

PHARMACEUTICAL COMPOUNDS

FIELD OF INVENTION

- 5 The present invention concerns inhibitors of ubiquitin specific protease 19 (USP19) and methods of use thereof.

BACKGROUND

- 10 Over the past decade, protein ubiquitination has emerged as an important post-translational modification with roles in a plethora of cellular processes including amongst others proteolysis, gene expression, DNA repair, immune response, metabolism or cell cycle regulation. Dysregulation of the Ubiquitin Proteasome System (UPS) has also been implicated in the pathogenesis of multiple human diseases including but not limited to
- 15 cancer (Hoeller D. *et al.*, *Nat. Rev. Cancer* (2006), 6, 776-788), viral infection (Gao *et al.*, *Can. J. Physiol., Pharmacol.* (2006), 84, 5-14), metabolic or neurodegenerative disorders (van Loosdregt J. *et al.*, *Immunity* (2013), 39, 259-271; Rubinsztein D., *et al.*, *Nature* (2006), 443, 780-786) as well as immune and inflammatory-related medical conditions (Wang J. *et al.*, *Cell Mol. Immunol.* (2006), 3, 255-261; Corn J. *et al.*, *Nat. Struct. Mol. Biol.*
- 20 (2014), 21, 297-300; Nicholson B. *et al.*, *Cell Biochem. Biophys.* (2011), 60, 61-68).

- The approval and clinical success of the proteasome inhibitors Velcade® (bortezomib) or Kyprolis® (carfilzomib) for the treatment of mantel cell lymphoma (MCL) and multiple myeloma (MM) have validated the UPS as a cancer target amenable for pharmacological
- 25 intervention. Although effective, their clinical utility has however been severely limited due to poor selectivity and acute toxicity issues. By inhibiting the 26S proteasome, the current proteasome inhibitors indiscriminately impair proteolysis in both cancer and normal cells and are characterised by a low therapeutic index. To circumvent this issue, a promising alternative approach may be to target the UPS upstream of the proteasome. Interfering
- 30 with the ubiquitin (Ub) conjugation / deconjugation machinery, for instance at the level of the Ubiquitin Specific Proteases (USPs), would allow for the development of improved therapeutics with enhanced specificity and reduced toxicity profiles.

- USPs are the largest subfamily of the deubiquitinating enzymes (DUBs) family with over 60
- 35 family members reported to date (Komander D. *et al.*, *Nat. Rev. Mol. Cell Biol.* (2009), 10,

550-563; Clague M. *et al.*, *Physiol. Rev.* (2013), 93, 1289-1315). USPs are typically cysteine proteases that catalyse the removal of Ub from specific target substrates thus preventing their induced degradation by the proteasome, or regulating their activation and/or subcellular localization (Daviet L. *et al.*, *Biochimie* (2008), 90, 270-283; Nicholson B. *et al.*, *Cell Biochem. Biophys.* (2011), 60, 61-68). It is now well established that USPs regulate the stability and activation of numerous proteins involved in the pathogenesis of human diseases including both oncogenes and tumour suppressors. As such, USPs represent an emerging and attractive target class for pharmacological intervention.

Amongst all USPs, USP19 is an important member due to its association with a number of important pathways with implications for pathological conditions including but not restricted to cancer, neurodegeneration and degenerative diseases as well as antiviral immune response. USP19 expresses as multiple isoforms varying in length from 71.09 kDa (isoform 2) to 156.03 kDa (isoform 5) with the canonical sequence (isoform 1) of 145.65 kDa in size (uniprot.org). The cellular localisation of USP19 may be cytosolic or bound to the endoplasmic reticulum (Lee J. *et al.*, *J. Biol. Chem.* (2014), 289, 3510-3517; Lee J. *et al.*, *Nat. Cell Biol.* (2016), 18, 765-776). Localised to the endoplasmic reticulum, USP19 is a key component of the endoplasmic reticulum-associated degradation (ERAD) pathway (Hassink B. *et al.*, *EMBO Rep.* (2009), 10, 755-761; Lee J. *et al.*, *J. Biol. Chem.* (2014), 289, 3510-3517; Lee J. *et al.*, *Nat. Cell Biol.* (2016), 18, 765-776). In particular, USP19 is involved in the latter steps of the protein quality-control machinery rescuing ERAD substrates that have been retro-translocated to the cytosol. USP19 has also been demonstrated to regulate the stability of the E3 ligases MARCH6 and HRD1 (Nakamura N. *et al.*, *Exp. Cell Res.* (2014), 328, 207-216; Harada K. *et al.*, *Int. J. Mol. Sci.* (2016), 17, 1829). In addition, USP19 has recently been implicated in the stabilisation of multiple and potentially important protein substrates. For instance, USP19 interacts with SIAH proteins to rescue HIF1 α from degradation under hypoxic conditions (Altun M. *et al.*, *J. Biol. Chem.* (2012), 287, 1962-1969; Velasco K. *et al.*, *Biochem. Biophys. Res. Commun.* (2013), 433, 390-395). USP19 also stabilises the KPC1 ubiquitin ligase which is involved in the regulation of the p27^{Kip1} cyclin-dependent kinase inhibitor (Lu Y. *et al.*, *Mol. Cell Biol.* (2009), 29, 547-558). Knock-out 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. In addition to some direct involvement in regulating hypoxia response and ER stress, USP19 has also been implicated recently as a positive regulator of autophagy and negative regulator of type I
5 interferon signalling (IFN, antiviral immune response) by deubiquitinating Beclin-1. USP19 was found to stabilise Beclin-1 at the post-translational level by removing the K11-linked ubiquitin chains of Beclin-1 at Lysine 437 (Jin S. *et al.*, *EMBO J.* (2016), 35, 866-880). USP19 negatively regulates type I IFN signalling pathway, by blocking RIG-I-MAVS
10 interaction in a Beclin-1 dependent manner. Depletion of either USP19 or Beclin-1 inhibits autophagic flux and promotes type I IFN signalling as well as cellular antiviral immunity (Jin S. *et al.*, *EMBO J.* (2016), 35, 866-880; Cui J. *et al.*, *Autophagy* (2016), 12, 1210-1211). Recent findings also indicate USP19 may negatively affect the cellular antiviral type I IFN signalling by regulating the TRAF3 substrate (Gu Z. *et al.*, *Future Microbiol.* (2017), 12, 767-779). USP19 has also been recently implicated in the Wnt signalling pathway by
15 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 addition to cancer and associated conditions, USP19 has been linked in gene knock-out
20 studies to muscle-wasting syndromes and other skeletal muscle atrophy disorders (Wing S., *Int. J. Biochem. Cell Biol.* (2013), 45, 2130-2135; Wing S., *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, each of which is incorporated herein by reference). Muscle wasting associated with conditions such as cachexia is known
25 to impair quality of life and response to therapy, which increase morbidity and mortality of cancer patients. 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.

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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.* (2018), 109B, 219-225). The
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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).

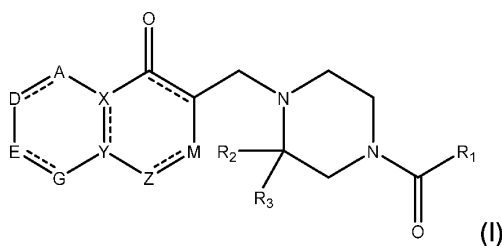
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WO 2022/200523 A1 discloses compounds that are useful as inhibitors of the activity of the ubiquitin specific protease USP19 and also relates to pharmaceutical compositions comprising these compounds and to methods of using these compounds in therapy.

10 The established 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. The identification of such inhibitors with drug-like potential is of prime importance and high priority.

15 SUMMARY OF INVENTION

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



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wherein

R¹ is optionally substituted C1-C6 alkyl, optionally substituted amino, optionally substituted 3 to 11 membered heterocycloalkyl, optionally substituted aryl, or optionally substituted 5 to 8 membered heteroaryl;

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R² and R³ are each independently selected from H and C1-C6 alkyl, or wherein R² and R³ together form C3-C8 cycloalkyl, C3-C8 cycloalkenyl or 3 to 8 membered heterocycloalkyl together with the carbon to which they are attached;

M is N or CR^a wherein R^a is H, halo, optionally substituted C3-C8 cycloalkyl, or optionally substituted C1-C6 alkyl;

A, D, E and G are absent and

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X is NR¹⁵ or CH;

Y is CR⁴ or N or absent;

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Z is CR⁵, NR⁶ or O;

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R⁴ is halo, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, 4 to 10 membered fused-ring heterocyclyl, optionally substituted C1-C6 alkylsulfanyl, sulfoxide, sulfone, sulfoximine, optionally substituted amino, optionally substituted 3 to 8 membered heterocycloalkyl, or OR²⁰; wherein R²⁰ is optionally substituted C1-C6 alkyl;

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R⁵ is H, optionally substituted C1-C6 alkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, optionally substituted 3 to 8 membered heterocycloalkyl, amido, sulfoximine, CN, halo, C(O)OR²¹, OR²², or NR²³R²⁴;

wherein R²¹ is selected from H and C1-C6 alkyl;

R²² is selected from H and C1-C6 alkyl;

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R²³ and R²⁴ are independently selected from H and optionally substituted C1-C6 alkyl;

R¹⁵ is H or C1-C6 alkyl;

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or R⁴ and R⁵ together form 3 to 8 membered heterocycloalkyl or aryl together with Y and Z to which they are attached;

or R⁴ and R¹⁵ together form 5 membered cycloalkyl, heterocycloalkyl, or heteroaryl together with X and Y to which they are attached;

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R⁶ is H, C1-C6 alkyl, optionally substituted aryl, or C3-C8 cycloalkyl;

or A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N and

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X is N or C;

Y is C;

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Z is CR²⁰, N, NR¹¹, or O,

wherein R¹¹ is H, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, or optionally substituted 5 to 8 membered heteroaryl;

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wherein R²⁰ is H, optionally substituted C1-C6 alkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, optionally substituted 3 to 8 membered heterocycloalkyl, amido, sulfoximine, CN, halo, C(O)OR²⁵, OR²⁶, or NR²⁷R²⁸;

wherein R²⁵ is selected from H and C1-C6 alkyl;

R²⁶ is selected from H and C1-C6 alkyl;

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R²⁷ and R²⁸ are independently selected from H and C1-C6 alkyl;

R⁷ is H, halo, C1-C6 alkyl, or OR¹⁹;

wherein R¹⁹ is optionally substituted C1-C6 alkyl;

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R¹² is H, halo, or C1-C6 alkyl;

R¹³ is H, halo, C1-C6 alkyl, OR¹⁶; or NR¹⁷R¹⁸;

wherein R¹⁶ is optionally substituted C1-C6 alkyl,

R¹⁷ and R¹⁸ are independently selected from H and C1-C6 alkyl or

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wherein R¹⁷ and R¹⁸ together form 5 to 6 membered heterocycloalkyl with the nitrogen atom to which they are attached; and

R¹⁴ is H, halo, or C1-C6 alkyl;

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

- 5 In a second aspect the invention provides a pharmaceutical composition comprising a compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to the first aspect, and a pharmaceutically acceptable carrier or diluent.
- 10 In a further aspect the invention provides the compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to the first aspect or the pharmaceutical composition according to the second aspect for use in therapy.
- In a further aspect the invention provides the compound, stereoisomer, tautomer, hydrate,
15 *N*-oxide derivative or pharmaceutically acceptable salt according to the first aspect or the pharmaceutical composition according to the second aspect for use as a medicament.
- In a further aspect the invention provides the compound, stereoisomer, tautomer, hydrate,
20 *N*-oxide derivative or pharmaceutically acceptable salt according to the first aspect or the pharmaceutical composition according to the second aspect for use in treating muscular atrophy, obesity, insulin resistance, or type II diabetes.
- In a further aspect the invention provides the compound, stereoisomer, tautomer, hydrate,
25 *N*-oxide derivative or pharmaceutically acceptable salt according to the first aspect or the pharmaceutical composition according to the second aspect for use in treating muscular atrophy, cachexia or sarcopenia, wherein the muscular atrophy, cachexia and sarcopenia are associated with or induced by cancer.
- 30 In a further aspect the invention provides a method of treating obesity, insulin resistance, type II diabetes, or muscular atrophy, comprising administering to a subject in need thereof an effective amount of a compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to the first aspect or a pharmaceutical composition according to the second aspect.

In a further aspect the invention provides a method of reducing loss of muscle mass in a subject comprising administering to a subject in need thereof an effective amount of a compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to the first aspect or a pharmaceutical composition according to the second aspect.

USP19 has been associated with a number of diseases and conditions including (but not limited to) cancer and neoplastic conditions. Knock-out 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).

It is further demonstrated herein that USP19 inhibitor compounds as described in relation to the first aspect exhibit cell permeability and potent target engagement in cancer cell lines. The cell permeability and target engagement in cancer cells is comparable to that observed in muscle cells. As demonstrated herein, USP19 inhibitors exhibit potent *in vivo* therapeutic effects on muscle wasting. Thus, by extension, since similar target engagement is seen in cancer cells, it is expected that pharmacological USP19 inhibitors will be effective at exerting therapeutic effects in cancer, due to the association of USP19 and oncogenic processes described above.

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.

These gene knock-out studies describe a connection between USP19 and obesity, as well as USP19 and insulin sensitivity. WO2020/115500 and WO2020/115501 describe *in vivo* studies demonstrating that pharmacological inhibitors of USP19 are an effective approach to the treatment of obesity and insulin resistance.

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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., *Int. J. Biochem. Cell Biol.* (2016), 79, 462-468; 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-E1290; Ogawa M. *et al.*, *J. Biol. Chem.* (2011), 286, 41455-41465; Ogawa M. *et al.*, *J. Endocrinol.* (2015), 225, 135-145).

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Knock-out 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 (Bédard N. *et al.*, *FASEB J.* (2015), 29, 3889-3898, which is incorporated herein by reference).

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As set out in the accompanying Examples, it is demonstrated herein that pharmacological treatment with a USP19 inhibitor can induce therapeutic effects in a wild-type *in vivo* model.

In particular, it is demonstrated that USP19 inhibitors reduce fat deposition in an *in vivo* model, indicating that USP19 inhibitors can be an effective treatment for obesity.

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Similarly, it is demonstrated herein that USP19 inhibitors can reduce loss of muscle mass in an *in vivo* model of muscular atrophy.

Similarly, it is demonstrated herein that USP19 inhibitors can treat the symptoms of insulin resistance, as indicated by an improved response to glucose.

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The compounds according to the invention are able to selectively inhibit USP19 activity. The Examples further demonstrate that compounds which potently inhibit USP19 activity can be effective therapeutic compounds. The compounds of the invention are therefore

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suitable for use in methods of treatment. Indications suitable for treatment with compounds of the invention 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.

Therefore, in a further aspect, is provided a compound, or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof, according to the first aspect, or a pharmaceutical composition according to the second aspect, for use in therapy.

In a further aspect, is provided a compound, or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof, according to the first aspect or a pharmaceutical composition according to the second aspect for use in a method of treating or preventing cancer. In certain preferred embodiments the cancer to be treated is breast cancer or neuroblastoma.

In a further aspect is provided a compound, or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof, according to the first aspect, or a pharmaceutical composition according to the second aspect for use in a method of treating or preventing muscular atrophy, optionally cachexia or sarcopenia.

In a further aspect is provided a compound, or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof, according to the first aspect, or a pharmaceutical composition according to the second aspect for use in a method of treating or preventing obesity.

In a further aspect is provided a compound, or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof, according to the first aspect, or a pharmaceutical composition according to the second aspect for use in a method of treating or preventing insulin resistance.

In a further aspect is provided a compound, or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof, according to the first aspect, or a pharmaceutical composition according to the second aspect for use in a method of treating or preventing type II diabetes.

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In a further aspect is provided a compound, or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof, according to the first aspect, or a pharmaceutical composition according to the second aspect for use in a method of treating or preventing Parkinson's Disease.

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In a further aspect is provided a method of treating cancer comprising administering to a subject an effective amount of a compound, or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof, according to the first aspect or a pharmaceutical composition according to the second aspect.

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In a further aspect is provided a method of treating muscular atrophy comprising administering to a subject an effective amount of a compound, or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof, according to the first aspect, or a pharmaceutical composition according to the second aspect.

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In a further aspect is provided a method of treating Parkinson's Disease comprising administering to a subject an effective amount of a compound, or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof, according to the first aspect, or a pharmaceutical composition according to the second aspect.

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The compounds, or stereoisomers, tautomers, hydrates, *N*-oxide derivatives or pharmaceutically acceptable salts thereof, may be used as monotherapy or as combination therapy with radiation and/or additional therapeutic agents.

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Without wishing to be bound by theory, it is thought that the compounds of the present invention tend to show the advantageous effects discussed above due, at least in part, to the presence of the carbon atom between position 'M' and the carbonyl group in formula (I).

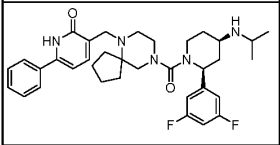
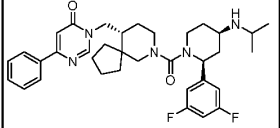
As shown in Table 1, compounds of the present invention exhibit improved *in vitro* physicochemical properties such as higher kinetic solubility (K_{sol}) and improved *in vitro*

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ADME properties such as higher metabolic stability (demonstrated by lower estimated intrinsic clearance, CL_{int}, using human liver microsome data) and lower CYP3A4 inhibition compared to analogues having the presence of a nitrogen atom between position 'M' and the carbonyl group.

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Table 1. Comparison of kinetic solubility (KSol), estimated intrinsic clearance (using human liver microsome data) and cytochrome P450 3A4 inhibition data between matched pairs.

Structure	Example	KSol (μM)	HLM CL _{int} (μL/min/mg)	CYP3A4 IC ₅₀ (μM)
	12	193	7.3	23
	WO2022200523 Example 192	62	15.3	14

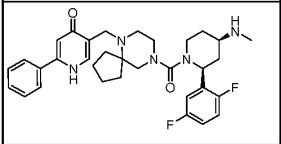
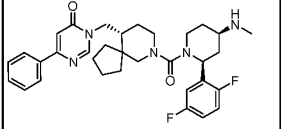
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As shown in Table 2, compounds of the present invention exhibit improved *in vitro* physicochemical properties such as higher kinetic solubility (KSol) and improved *in vitro* ADME properties such as lower hERG inhibition and lower CYP3A4 inhibition compared to analogues having the presence of a nitrogen atom between position 'M' and the carbonyl group.

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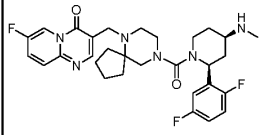
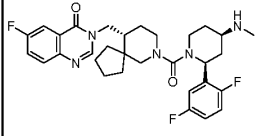
Table 2. Comparison of kinetic solubility (KSol), hERG inhibition and cytochrome P450 3A4 inhibition data between matched pairs.

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Structure	Example	KSol (μM)	hERG IC ₅₀ (μM)	CYP3A4 IC ₅₀ (μM)
	11	202	>100	>25
	WO2022200523 Example 78	179	4.6	14

As shown in Table 3, compounds of the present invention exhibit improved *in vitro* ADME properties such as higher metabolic stability (demonstrated by lower estimated intrinsic clearance, CL_{int}, using mouse or rat liver microsome data) and lower CYP3A4 inhibition compared to analogues having the presence of a nitrogen atom between position 'M' and the carbonyl group.

Table 3. Comparison of estimated intrinsic clearance (using mouse and rat liver microsome data) and cytochrome P450 3A4 inhibition data between matched pairs.

Structure	Example	MLM CLint (μL/min/mg)	RLM CLint (μL/min/mg)	CYP3A4 IC ₅₀ (μM)
	83	5.2	3.0	>50
	WO2022200523 Example 125	33.7	35.9	22.1

Other preferred embodiments 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.

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.

FIGURES

Figure 1: Effect of USP19 pharmacological inhibition on tibialis anterior mass. (A) Tibialis anterior mass (mg) from mice treated with vehicle or USP19 inhibitor compound ADC-141. Mass is given for the muscle from limb that had undergone sciatic nerve denervation (DEN) and also from the innervated limb (INN). (B) Percentage loss of tibialis anterior muscle mass as a result of denervation in vehicle and USP19 inhibitor (ADC-141) treated mice. Percentage calculated as a proportion of the mass of the muscle from the

innervated limb of the same mouse. (C) Loss of tibialis anterior muscle mass (in mg) as a result of denervation in vehicle treated and USP19 inhibitor (ADC-141) treated mice. $P < 0.025$.

- 5 **Figure 2:** Effect of USP19 pharmacological inhibition on gastrocnemius muscle mass. (A) gastrocnemius muscle mass (mg) from mice treated with vehicle or USP19 inhibitor compound ADC-141. Mass is given for the muscle from limb that had undergone sciatic nerve denervation (DEN) and also from the innervated limb (INN). (B) Percentage loss of gastrocnemius muscle mass as a result of denervation in vehicle and USP19 inhibitor
10 (ADC-141) treated mice. Percentage calculated as a proportion of the mass of the muscle from the innervated limb of the same mouse. (C) Loss of gastrocnemius muscle mass (in mg) as a result of denervation in vehicle treated and USP19 inhibitor (ADC-141) treated mice.
- 15 **Figure 3:** (A) Effect of USP19 pharmacological inhibition on fat mass. The epididymal fat pad was collected from vehicle and USP19 inhibitor (ADC-141) treated mice, with USP19 inhibitor treated mice showing a significant reduction in fat mass. (B) Effect of USP19 pharmacological inhibition on liver mass. The liver was collected from vehicle and USP19 inhibitor (ADC-141) treated mice. An increase in liver mass was observed, likely
20 due to accumulation of drug compound in the liver. (C) Percentage change in overall body weight in vehicle-treated control DIO mice. USP19 inhibitor 5 mg/kg i.p. BID, USP19 inhibitor 25 mg/kg i.p. BID, or positive control liraglutide 0.1 mg/kg s.c. BID (left to right bars, respectively); (D) Percentage change in overall lean mass and (E) percentage change in overall fat mass in vehicle, USP19 inhibitor 5 mg/kg, USP19 inhibitor 25 mg/kg,
25 and liraglutide treated mice (left to right, respectively). *** $p < 0.001$ vs vehicle

Figure 4: Cellular target engagement of USP19 inhibitor compound in breast cancer, neuroblastoma and skeletal muscle cell lines. EC_{50} was determined by densitometry.

- 30 **Figure 5:** Response to oral glucose tolerance test (OGTT) in obese mice. (A) Timeline of plasma glucose response in vehicle-treated control mice (circles), USP19 inhibitor 5 mg/kg i.p. BID (triangle), USP19 inhibitor 25 mg/kg i.p. BID (solid circle), or positive control liraglutide 0.1 mg/kg s.c. BID (diamond); (B) Glucose AUC (mM.h) and (C) insulin AUC (ng.h/mL) for vehicle, USP19 inhibitor 5 mg/kg, USP19 inhibitor 25 mg/kg, and liraglutide
35 (left to right, respectively). ** $p < 0.01$ vs vehicle; *** $p < 0.001$ vs vehicle.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of
5 ordinary skill in the art. The meaning and scope of the terms should be clear, however, in the event of any latent ambiguity, definitions provided herein take precedence over any dictionary or extrinsic definition.

As used in the specification and the appended claims, unless specified to the contrary, the
10 following terms have the meaning indicated:

The term "alkyl group" (alone or in combination with another term(s)) means a straight-or branched-chain saturated hydrocarbon substituent typically containing 1 to 15 carbon atoms, such as 1 to 10, 1 to 8, 1 to 6, or 1 to 4 carbon atoms. A "C_n alkyl" group refers to an
15 aliphatic group containing n carbon atoms. For example, a C₁-C₁₀ alkyl group contains 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms. Attachment to the alkyl group occurs through a carbon atom. Examples of such substituents include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl (branched or unbranched), hexyl (branched or unbranched), heptyl (branched or unbranched), octyl (branched or unbranched), nonyl
20 (branched or unbranched), and decyl (branched or unbranched).

The term "alkenyl group" (alone or in combination with another term(s)) means a straight-or branched-chain hydrocarbon substituent containing one or more double bonds and typically 2 to 15 carbon atoms; such as 2 to 10, 2 to 8, 2 to 6 or 2 to 4 carbon atoms. Examples of
25 such substituents include ethenyl (vinyl), 1-propenyl, 3-propenyl, 1,4-pentadienyl, 1,4-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, pentenyl and hexenyl.

The term "alkynyl group" (alone or in combination with another term(s)) means a straight-or branched-chain hydrocarbon substituent containing one or more triple bonds and typically 2
30 to 15 carbon atoms; such as 2 to 10, 2 to 8, 2 to 6 or 2 to 4 carbon atoms. Examples of such substituents include ethynyl, 1-propynyl, 3-propynyl, 1-butyne, 3-butyne and 4-butyne.

The term "heteroalkyl group" (alone or in combination with another term(s)) means a
35 straight-or branched-chain saturated hydrocarbon substituent typically containing 1 to 15

atoms, such as 1 to 10, 1 to 8, 1 to 6, or 1 to 4 atoms, wherein at least one of the atoms is a heteroatom (i.e. oxygen, nitrogen, or sulfur), with the remaining atoms being carbon atoms. A "C_n heteroalkyl" group refers to an aliphatic group containing n carbon atoms and one or more heteroatoms, for example one heteroatom. For example, a C₁-C₁₀ heteroalkyl group contains 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms in addition to one or more heteroatoms, for example one heteroatom. Attachment to the heteroalkyl group occurs through a carbon atom or through a heteroatom.

The term "heteroalkenyl group" (alone or in combination with another term(s)) means a straight-or branched-chain hydrocarbon substituent containing one or more carbon-carbon double bonds and typically 2 to 15 atoms; such as 2 to 10, 2 to 8, 2 to 6 or 2 to 4 atoms, wherein at least one of the atoms is a heteroatom (i.e. oxygen, nitrogen, or sulfur), with the remaining atoms being carbon atoms. A "C_n heteroalkenyl" group refers to an aliphatic group containing n carbon atoms and one or more heteroatoms, for example one heteroatom. For example, a C₂-C₁₀ heteroalkenyl group contains 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms in addition to one or more heteroatoms, for example one heteroatom. Attachment to the heteroalkenyl group occurs through a carbon atom or through a heteroatom.

The term "heteroalkynyl group" (alone or in combination with another term(s)) means a straight-or branched-chain hydrocarbon substituent containing one or more carbon-carbon triple bonds and typically 2 to 15 carbon atoms; such as 2 to 10, 2 to 8, 2 to 6 or 2 to 4 carbon atoms, wherein at least one of the atoms is a heteroatom (i.e. oxygen, nitrogen, or sulfur), with the remaining atoms being carbon atoms. A "C_n heteroalkynyl" group refers to an aliphatic group containing n carbon atoms and one or more heteroatoms, for example one heteroatom. For example, a C₂-C₁₀ heteroalkynyl group contains 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms in addition to one or more heteroatoms, for example one heteroatom. Attachment to the heteroalkynyl group occurs through a carbon atom or through a heteroatom.

The term "carbocyclyl group" (alone or in combination with another term(s)) means a saturated cyclic (i.e. "cycloalkyl"), partially saturated cyclic (i.e. "cycloalkenyl"), or completely unsaturated (i.e. "aryl") hydrocarbon substituent containing from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound together to form the ring or rings of a cyclic substituent). A carbocyclyl may be a single-ring (monocyclic) or polycyclic ring structure.

A carbocyclyl may be a single ring structure, which typically contains 3 to 8 ring atoms, more typically 3 to 7 ring atoms, and more typically 5 to 6 ring atoms. Examples of such single-ring carbocyclyls include cyclopropyl (cyclopropanyl), cyclobutyl (cyclobutanyl),
5 cyclopentyl (cyclopentanyl), cyclopentenyl, cyclopentadienyl, cyclohexyl (cyclohexanyl), cyclohexenyl, cyclohexadienyl, and phenyl. A carbocyclyl may alternatively be polycyclic (i.e. may contain more than one ring). Examples of polycyclic carbocyclyls include bridged, fused, and spirocyclic carbocyclyls. In a spirocyclic carbocyclyl, one atom is common to two different rings. An example of a spirocyclic carbocyclyl is spiropentanyl. In a bridged
10 carbocyclyl, the rings share at least two common non-adjacent atoms. Examples of bridged carbocyclyls include bicyclo[2.2.1]heptanyl, bicyclo[2.2.1]hept-2-enyl, and adamantanyl. For example, a bridged azepane may be 8-oxa-3-azabicyclo[3.2.1]octan-3-yl. In a fused-ring carbocyclyl system, two or more rings may be fused together, such that two rings share one common bond. Examples of two- or three-fused ring carbocyclyls include
15 naphthalenyl, tetrahydronaphthalenyl (tetralinyl), indenyl, indanyl (dihydroindenyl), anthracenyl, phenanthrenyl, and decalinyl.

The term "cycloalkyl group" (alone or in combination with another term(s)) means a saturated cyclic hydrocarbon substituent containing 3 to 14 carbon ring atoms. A cycloalkyl
20 may be a single carbon ring, which typically contains 3 to 8 carbon ring atoms and more typically 3 to 6 ring atoms. It is understood that attachment to a cycloalkyl group is via a ring atom of the cycloalkyl group. Examples of single-ring cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. A cycloalkyl may alternatively be polycyclic or contain more than one ring. Polycyclic cycloalkyls include bridged, fused, and spirocyclic
25 cycloalkyls.

The term "alkylcycloalkyl" refers to a cycloalkyl substituent attached via an alkyl chain. Examples of an alkylcycloalkyl substituent include cyclohexylethane, where the cyclohexane is attached via an ethane linker. Other examples include cyclopropylethane,
30 cyclobutylethane, cyclopentylethane, cycloheptylethane, cyclohexylmethane. In a "C_n" alkylcycloalkyl, C_n includes the carbon atoms in the alkyl chain and in the cycloalkyl ring. For example, cyclohexylethane is a C₈ alkylcycloalkyl.

The term "aryl group" (alone or in combination with another term(s)) means an aromatic carbocyclyl containing from 5 to 14 carbon ring atoms, optionally 5 to 8, 5 to 7, optionally 5
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to 6 carbon ring atoms. A "C_n aryl" group refers to an aromatic group containing n carbon atoms. For example, a C₆-C₁₀ aryl group contains 6, 7, 8, 9 or 10 carbon atoms.

Attachment to the aryl group occurs through a carbon atom. An aryl group may be monocyclic or polycyclic (i.e. may contain more than one ring). In the case of polycyclic aromatic rings, only one ring in the polycyclic system is required to be unsaturated while the remaining ring(s) may be saturated, partially saturated or unsaturated. Attachment to the aryl group occurs through a carbon atom contained in the ring. Examples of aryl groups include phenyl, naphthyl, acridinyl, indenyl, indanyl, and tetrahydronaphthyl.

10 The term "arylalkyl" refers to an aryl substituent attached via an alkyl chain. Examples of an arylalkyl substituent include benzyl and phenylethane/ethylbenzene, where the ethane chain links to a phenyl group to the point of attachment. In a "C_n" arylalkyl, C_n includes the carbon atoms in the alkyl chain and in the aryl group. For example, ethylbenzene is a C₈ arylalkyl.

15 The term "heterocyclyl group" (alone or in combination with another term(s)) means a saturated (i.e. "heterocycloalkyl"), partially saturated (i.e. "heterocycloalkenyl"), or completely unsaturated (i.e. "heteroaryl") ring structure containing a total of 3 to 14 ring atoms, wherein at least one of the ring atoms is a heteroatom (e.g. oxygen, nitrogen, or sulfur), with the remaining ring atoms being carbon atoms. A heterocyclyl group may, for example, contain one, two, three, four or five heteroatoms. Attachment to the heterocyclyl group may occur through a carbon atom and/or one or more heteroatoms that are contained in the ring. A heterocyclyl may be a single-ring (monocyclic) or polycyclic ring structure.

25 A heterocyclyl group may be a single ring, which typically contains from 3 to 7 ring atoms, more typically from 3 to 6 ring atoms, and even more typically 5 to 6 ring atoms. Examples of single-ring heterocyclyls include furanyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl (thiofuranyl), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, oxazolyl, oxazolidinyl, isoxazolidinyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl (furazanyl) or 1,3,4-oxadiazolyl), oxatriazolyl, dioxazolyl oxathiolyl, pyranyl, dihydropyranyl, tetrahydropyranyl, thiopyranyl, tetrahydrothiopyranyl, pyridinyl (azinyl), piperidinyl, diazinyl (including pyridazinyl (1,2-diazinyl), pyrimidinyl (1,3-diazinyl) or pyrazinyl (1,4-diazinyl)), piperazinyl, triazinyl

(including 1,3,5-triazinyl, 1,2,4-triazinyl and 1,2,3-triazinyl)), oxazinyl (including 1,2-oxazinyl, 1,3-oxazinyl or 1,4-oxazinyl)), oxadiazinyl (including 1,2,3-oxadiazinyl, 1,2,4-oxadiazinyl, 1,4,2-oxadiazinyl or 1,3,5-oxadiazinyl)), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

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A heterocyclyl group may alternatively be polycyclic (i.e. may contain more than one ring). Examples of polycyclic heterocyclyl groups include bridged, fused, and spirocyclic heterocyclyl groups. In a spirocyclic heterocyclyl group, one atom is common to two different rings. In a bridged heterocyclyl group, the rings share at least two common non-adjacent atoms. In a fused-ring heterocyclyl group, two or more rings may be fused together, such that two rings share one common bond. Examples of fused ring heterocyclyl groups containing two or three rings include indolizinyl, pyranopyrrolyl, 4*H*-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-*b*]-pyridinyl, pyrido[3,2-*b*]-pyridinyl, or pyrido[4,3-*b*]-pyridinyl), and pteridinyl. Other examples of fused-ring heterocyclyl groups include benzo-fused heterocyclyl groups, such as indolyl, isoindolyl (isobenzazolyl, pseudoisoindolyl), indoleninyl (pseudoindolyl), isoindazolyl (benzpyrazolyl), benzazinyl (including quinolinyl (1-benzazinyl) or isoquinolinyl (2-benzazinyl)), phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl (including cinnolinyl (1,2-benzodiazinyl) or quinazolinyl (1,3-benzodiazinyl)), benzopyranyl (including chromanyl or isochromanyl), and benzisoxazinyl (including 1,2-benzisoxazinyl or 1,4-benzisoxazinyl).

The term "heterocycloalkyl group" (alone or in combination with another term(s)) means a saturated heterocyclyl. An "x to y membered heterocycloalkyl" group refers to a cyclic aliphatic group containing x to y ring atoms, including at least one heteroatom (e.g. nitrogen), with the remainder being carbon atoms. For example, a 3 to 8 membered heterocycloalkyl group contains a total of 3 to 8 ring atoms, wherein at least one of the ring atoms is a heteroatom (e.g. nitrogen, oxygen, sulfur) with the remaining atoms being carbon atoms. Attachment to the heterocycloalkyl group occurs through a carbon atom or one of the at least one heteroatoms.

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The term "heteroaryl group" (alone or in combination with another term(s)) means an aromatic heterocyclyl containing from 5 to 14 ring atoms. An "x to y membered heteroaryl" group refers to an aromatic group containing x to y ring atoms, including at least one heteroatom (e.g. nitrogen), with the remainder being carbon atoms. For example, a 5 to 8 membered heteroaryl group contains a total of 5 to 8 ring atoms, wherein at least one of

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the ring atoms is a heteroatom (e.g. nitrogen, oxygen, sulfur) with the remaining atoms being carbon atoms. Attachment to the heteroaryl group occurs through a carbon atom or through a heteroatom. A heteroaryl group may be monocyclic or polycyclic. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of monocyclic heteroaryl groups

5 include 6-membered rings such as pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, and 1,3,5-, 1,2,4- or 1,2,3-triazinyl; 5-membered rings such as imidazolyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl. Polycyclic heteroaryl groups may be 2 or 3 fused rings. Examples of polycyclic heteroaryl groups include 6/5-membered fused ring groups such as benzothiofuranyl,

10 benzisoxazolyl, benzoxazolyl, and purinyl; and 6/6-membered fused ring groups such as benzopyranyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and benzoxazinyl. In the case of polycyclic heteroaryl groups, only one ring in the polycyclic system is required to be unsaturated while the remaining ring(s) may be saturated, partially saturated or unsaturated.

15 The term "amino group" refers to the -NR'R" group. The amino group can be optionally substituted. In an unsubstituted amino group, R' and R" are hydrogen. In a substituted amino group R' and R" each independently may be, but are not limited to, hydrogen, an alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, alkylcycloalkyl, alkylheterocycloalkyl, alkoxy,

20 sulfonyl, alkenyl, alkanoyl, aryl, arylalkyl, or a heteroaryl group, provided R' and R" are not both hydrogen. In a substituted amino group R' and R" may cyclise to form a cyclic amino group, e.g. a pyrrolidine group or a piperidine group. Such a cyclic amino group may incorporate other heteroatoms, for example to form a piperazine or morpholine group. Such a cyclic amino group may be optionally substituted, e.g. with an amino group, a hydroxyl

25 group or an oxo group.

The term "alkylamino" group refers to the -R^aNR'R" group, wherein R^a is an alkyl chain as defined above and NR'R" is an optionally substituted amino group as defined above. "C_n alkylamino" group refers to a group containing n carbon atoms. For example, a C₁-C₁₀

30 alkylamino group contains 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms. When the amino group of the alkylamino group is a substituted amino group, the number of carbon atoms includes any carbon atoms in the substituent groups. Attachment to the alkylamino group occurs through a carbon atom of the R^a alkyl group. Examples of alkylamino substituents include methylamine, ethylamine, methylaminomethyl, dimethylaminomethyl,

35 methylaminoethyl, dimethylaminoethyl, methylpyrrolidine, and ethylpyrrolidine

The term "amido group" refers to the -C(=O)-NR- group. Attachment may be through the carbon or nitrogen atom. For example, the amido group may be attached as a substituent via the carbon atom only, in which case the nitrogen atom has two R groups attached (-C(=O)-NR_2). The amido group may be attached by the nitrogen atom only, in which case the carbon atom has an R group attached (-NR-C(=O)R).

The term "alkylsulfanyl" refers to the -SR^a group, wherein R^a is an alkyl chain as defined above. " C_n alkylsulfanyl" group refers to a group containing n carbon atoms. For example, a $\text{C}_1\text{-C}_{10}$ alkylsulfanyl group contains 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms. Attachment to the alkylsulfanyl group occurs through the sulfur atom of the SR^a group. The alkylsulfanyl group may be optionally substituted. Examples of the alkylsulfanyl substituents include SMe (a methylsulfanyl group), an ethylsulfanyl group, a propylsulfanyl group and a benzylsulfanyl group.

The term "sulfoximine" refers to sulfoximine substituents that are either S-linked or N-linked - that is, attachment may be through the sulfur or nitrogen atom. For example, the sulfoximine group may be attached as a substituent via the sulfur atom, in which case the sulfur has a single R group in addition to the oxo group and the sulfur-bound nitrogen atom has one R group attached - that is the group is -S(O)(R)NR' . By way of further example, the sulfoximine group may be attached as a substituent via the nitrogen atom, in which case the sulfur atom has two attached R groups in addition to the oxo group - that is, the group is -NS(O)RR' . In unsubstituted sulfoximine groups, each of R and R' are H. Alternatively, the sulfoximine group may be substituted at one or both of R and R', for example to form a dimethyl sulfoximine, where both R and R' are methyl.

The term "ether" refers to an -O-alkyl group or an -alkyl-O-alkyl group, for example a methoxy group, a methoxymethyl group or an ethoxyethyl group. The alkyl chain(s) of an ether can be linear, branched or cyclic chains. The ether group can be optionally substituted (a "substituted ether") with one or more substituents. A C_n ether refers to an ether group having n carbons in all alkyl chains of the ether group. For example, a $\text{CH(CH}_3\text{)-O-C}_6\text{H}_{11}$ ether is a C_8 ether group.

The term "alkoxy group" refers to an -O-alkyl group. The alkoxy group can refer to linear, branched, or cyclic, saturated or unsaturated oxy-hydrocarbon chains, including, for

example, methoxyl, ethoxyl, propoxyl, isopropoxyl, butoxyl, *t*-butoxyl and pentoxyl. The alkoxy group can be optionally substituted (a "substituted alkoxy") with one or more alkoxy group substituents.

- 5 The term "aryloxy group" refers to an -O-aryl group, for example a phenoxy group. An aryloxy substituent may itself be optionally substituted, for example with a halogen.

The term "alkylester" refers to a -C(O)OR group, where R is an alkyl group as defined herein. An example of an alkylester is ethyl methanoate – i.e. R is an ethyl group.

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The term "hydroxyl" refers to an -OH group.

- The term "oxo group" refers to the (=O) group, i.e. a substituent oxygen atom connected to another atom by a double bond. For example, a carbonyl group (-C(=O)-) is a carbon atom
15 connected by a double bond to an oxygen atom, i.e. an oxo group attached to a carbon atom. Examples of carbonyl substituents include aldehydes (-C(=O)H), acetyl (-C(=O)CH₃) and carboxyl/carboxylic acid groups (-C(=O)OH).

- The term "halo" refers to a substituent selected from chlorine, fluorine, bromine and iodine.
20 Preferably, the halo substituent is selected from chlorine, fluorine and bromine. More preferably, the halo substituent is selected from chlorine and fluorine.

- An alkyl, alkenyl, alkynyl, carbocyclyl (including cycloalkyl, cycloalkenyl and aryl), heterocyclyl (including heterocycloalkyl, heterocyloalkenyl, heteroaryl, nitrogen-containing heterocyclyl), amino, amido, ester, ether, alkoxy, or sulfonamide group can be optionally
25 substituted with one or more substituents, which can be the same or different. A substituent can be attached through a carbon atom and/or a heteroatom in the alkyl, alkenyl, alkynyl, carbocyclyl (including cycloalkyl, cycloalkenyl and aryl), heterocyclyl (including heterocycloalkyl, heterocyloalkenyl, heteroaryl, nitrogen-containing heterocyclyl, nitrogen-containing heteroaryl), amino, amido, ester, ether, alkoxy, or sulfonamide group. The term
30 "substituent" (or "radical") includes but is not limited to alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, aralkyl, substituted aralkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halo, hydroxyl, cyano, amino, amido, alkylamino, arylamino, carbocyclyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted
35 heterocycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl,

substituted heteroaryl, nitro, thio, alkanoyl, hydroxyl, aryloxy, alkoxy, alkylthio, arylthio, aralkyloxy, aralkylthio, carboxyl, alkoxycarbonyl, oxo, alkylsulfonyl, arylsulfonyl and sulfoximiny.

- 5 In certain aspects, the substituent is alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, halo, hydroxyl, cyano, amino, amido, alkylamino, arylamino, carbocycl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, nitro, thio, alkanoyl, hydroxyl, aryloxy, 10 alkoxy, alkylthio, arylthio, aralkyloxy, aralkylthio, carboxyl, alkoxycarbonyl, oxo, alkylsulfonyl and arylsulfonyl.

- If a group, for example an alkyl group, is "optionally substituted", it is understood that the group has one or more substituents attached (substituted) or does not have any 15 substituents attached (unsubstituted).

If a group is substituted with a further optionally substituted group, it is understood that the first substituent may itself be either unsubstituted or substituted.

- 20 For completeness, it is also noted that certain chemical formulae used herein define delocalized systems. This definition is known in the art as a definition of aromaticity and may indicate the presence of, for example, a planar mono-, di- or tri-cyclic system that contains $(4n+2)$ electrons where n is an integer. In other words, these systems may display Hückel aromaticity.

- 25 In whatever aspect, the compounds of the present invention may possess some aspect of stereochemistry. For example, the compounds may possess chiral centres and/or planes and/or axes of symmetry. As such, the compounds may be provided as single stereoisomers, single diastereomers, mixtures of stereoisomers or as racemic mixtures, 30 unless otherwise specified. Stereoisomers are known in the art to be molecules that have the same molecular formula and sequence of bonded atoms, but which differ in their spatial orientations of their atoms and/or groups.

- In addition, the compounds of the present invention may exhibit tautomerism. Each 35 tautomeric form is intended to fall within the scope of the invention.

In addition, the compounds of the present invention may be provided as a pro-drug. Pro-drugs are transformed, generally *in vivo*, from one form to the active forms of the drugs described herein.

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In addition, it will be understood that the elements described herein may be the common isotope or an isotope other than the common isotope. For example, a hydrogen atom may be ^1H , ^2H (deuterium) or ^3H (tritium).

10 In addition, the compounds of the present invention may be provided in the form of their pharmaceutically acceptable salts or as co-crystals.

The term “pharmaceutically acceptable salt” refers to ionic compounds formed by the addition of an acid to a base. The term refers to such salts that are considered in the art as
15 being suitable for use in contact with a patient, for example *in vivo* and pharmaceutically acceptable salts are generally chosen for their non-toxic, non-irritant characteristics.

The term “co-crystal” refers to a multi- component molecular crystal, which may comprise non-ionic interactions.

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Pharmaceutically acceptable salts and co-crystals may be prepared by ion exchange chromatography or by reacting the free base or acidic form of a compound with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in one or more suitable solvents, or by mixing the compound with another
25 pharmaceutically acceptable compound capable of forming a co-crystal.

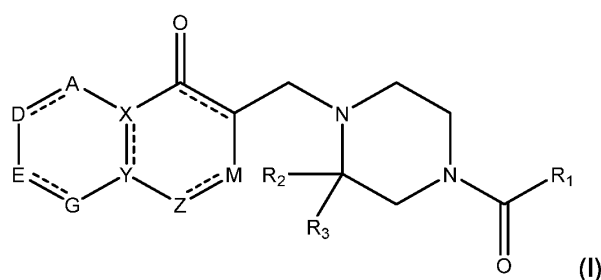
Salts known in the art to be generally suitable for use in contact with a patient include salts derived from inorganic and/or organic acids, including the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, oleate, palmitate, stearate, laurate, benzoate,
30 lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate and tartrate. These may include cations based on the alkali and alkaline earth metals, such as sodium, potassium, calcium and magnesium, as well as ammonium, tetramethylammonium, tetraethylammonium. Further reference is made to the number of literature sources that survey suitable pharmaceutically acceptable salts, for example the handbook of
35 pharmaceutical salts published by IUPAC.

In addition, the compounds of the present invention may sometimes exist as zwitterions, which are considered as part of the invention.

- 5 As used herein, a USP19 inhibitor refers to a compound which acts on USP19 so as to decrease the activity of the enzyme. Examples of USP19 inhibitors are exemplified compounds herein. Preferably a USP19 inhibitor exhibits an IC_{50} of less than 5 μM , preferably less than 0.5 μM .
- 10 As used herein, "obesity" refers to the medical condition characterised by excess body fat. Obesity can be characterised by, for example, a body mass index (BMI) of greater than 30. Treatment of obesity may be indicated by, for example, the reduction of body fat, in percentage and/or absolute mass terms. Treatment of obesity may also be exemplified by a reduction in the rate of body fat accumulation by a subject compared to before treatment.
- 15 As used herein, "insulin resistance" refers to the medical condition characterised by an abnormally weak response to insulin. Since insulin resistance is typically not treated by exogenous insulin treatment, the resistance is typically to insulin produced by the body of the subject, though the subject may also be resistant to exogenous insulin. "Insulin
- 20 resistance" encompasses the conditions "prediabetes" and Type II diabetes. Insulin resistance may be indicated, for example, by a glucose tolerance test (GTT) glycaemia of 7.8 mmol/L or greater. Type II diabetes is typically diagnosed following a glucose tolerance test (GTT) glycaemia of 11.1 mmol/L or greater.
- 25 Treatment of insulin resistance may be indicated by an improvement (i.e. reduction) in the subject's GTT glycaemia compared to before treatment. Treatment may also be indicated by a reduction in the subject's blood sugar concentration under normal conditions compared to before treatment.
- 30 As used herein, "muscular atrophy" and "muscle-wasting" are used interchangeably to refer to decrease in muscle mass in a subject, including in the context of cachexia or sarcopenia, for example. Muscular atrophy can be as a result of temporary or permanent disability, temporary or permanent immobilisation of a limb, extended bedrest, cachexia (for example as a result of cancer, heart failure, or COPD), or sarcopenia.

Treatment of muscular atrophy may be characterised as the slowing of the rate of atrophy – that is, treatment results in less muscle mass lost over a given period of time. Preferably, successful treatment results in no loss of muscle mass.

5 Accordingly, in a first aspect is provided a compound of formula (I):



wherein

10 R^1 is optionally substituted C1-C6 alkyl, optionally substituted amino, optionally substituted 3 to 11 membered heterocycloalkyl, optionally substituted aryl, or optionally substituted 5 to 8 membered heteroaryl;

15 R^2 and R^3 are each independently selected from H and C1-C6 alkyl, or wherein R^2 and R^3 together form C3-C8 cycloalkyl, C3-C8 cycloalkenyl or 3 to 8 membered heterocycloalkyl together with the carbon to which they are attached;

20 M is N or CR^a wherein R^a is H, halo, optionally substituted C3-C8 cycloalkyl, or optionally substituted C1-C6 alkyl;

A, D, E and G are absent and

X is NR^{15} or CH;

25 Y is CR^4 or N or absent;

Z is CR^5 , NR^6 or O;

30 R^4 is halo, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, optionally substituted 5 to 8 membered

heteroaryl, 4 to 10 membered fused-ring heterocyclyl, optionally substituted C1-C6 alkylsulfanyl (optionally SMe), sulfoxide, sulfone, sulfoximine, optionally substituted amino, optionally substituted 3 to 8 membered heterocycloalkyl, or OR²⁰;

5 wherein R²⁰ is optionally substituted C1-C6 alkyl;

R⁵ is H, optionally substituted C1-C6 alkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, optionally substituted 3 to 8 membered heterocycloalkyl, amido, sulfoximine, CN, halo, C(O)OR²¹, OR²², or NR²³R²⁴;

10

 wherein R²¹ is selected from H and C1-C6 alkyl;

 R²² is selected from H and C1-C6 alkyl;

 R²³ and R²⁴ are independently selected from H and optionally substituted C1-C6 alkyl;

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R¹⁵ is H or C1-C6 alkyl;

or R⁴ and R⁵ together form 3 to 8 membered heterocycloalkyl or aryl together with Y and Z to which they are attached;

20

or R⁴ and R¹⁵ together form 5 membered cycloalkyl, heterocycloalkyl, or heteroaryl together with X and Y to which they are attached;

R⁶ is H, C1-C6 alkyl, optionally substituted aryl or C3-C8 cycloalkyl;

25

or A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N and

X is N or C;

30

Y is C;

Z is CR²⁰, N, NR¹¹, or O,

 wherein R¹¹ is H, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, or optionally substituted 5 to 8 membered heteroaryl;

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wherein R^{20} is H, optionally substituted C1-C6 alkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, optionally substituted 3 to 8 membered heterocycloalkyl, amido, sulfoximine, CN, halo, C(O)OR²⁵, OR²⁶, or NR²⁷R²⁸;

5 wherein R^{25} is selected from H and C1-C6 alkyl;
 R^{26} is selected from H and C1-C6 alkyl;
 R^{27} and R^{28} are independently selected from H and C1-C6 alkyl;

R^7 is H, halo, C1-C6 alkyl, or OR¹⁹;

10 wherein R^{19} is optionally substituted C1-C6 alkyl;

R^{12} is H, halo, or C1-C6 alkyl;

R^{13} is H, halo, C1-C6 alkyl, OR¹⁶; or NR¹⁷R¹⁸;

15 wherein R^{16} is optionally substituted C1-C6 alkyl,
 R^{17} and R^{18} are independently selected from H and C1-C6 alkyl or
 wherein R^{17} and R^{18} together form 5 to 6 membered heterocycloalkyl
 with the nitrogen atom to which they are attached; and

20 R^{14} is H, halo, or C1-C6 alkyl;

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

25 Dotted lines in formula (I) indicate optional bonds. That is, the dotted lines indicate the ring including positions X, Y, Z, M can be aliphatic (for example saturated or partially unsaturated) or aromatic. Similarly, in formula (I) dotted lines indicate that, when present, the ring including positions A, D, E and G can be aliphatic (for example saturated or partially unsaturated) or aromatic.

30 For the avoidance of doubt, when A, D, E and G are absent and Y is absent, X is bonded directly to Z. Put another way, when A, D, E and G are absent and Y is absent, the ring containing X, Z and M is five-membered.

- For the compounds of formula (I), for each group that is optionally substituted, there is one or more independently selected optional substituent. In certain embodiments, each of the one or more optional substituents is independently selected from alkyl, alkoxy, oxo, halo, cycloalkyl, heterocycloalkyl, aryl, aryl substituted by one or more halo, aryl substituted by halo and alkyl, aryl substituted by halo and alkoxy, heteroaryl, hydroxyl, $\text{CR}^8\text{R}^9\text{R}^{10}$, NR^8 , NR^8R^9 , $\text{NHC}(\text{O})\text{R}^8$, $\text{NHCR}^8\text{R}^9\text{R}^{10}$, $\text{NHCH}_2\text{CR}^8\text{R}^9\text{R}^{10}$ and $\text{NHCH}_2\text{C}(\text{O})\text{R}^8$, wherein R^8 , R^9 and R^{10} are each independently selected from H, halo, hydroxyl, alkyl, cycloalkyl, cycloalkyl substituted by one or more halo or alkyl, heterocycloalkyl substituted by one or more alkyl or oxo, heteroaryl, alkoxy, CH_2OH and $\text{CH}_2\text{CH}_2\text{OH}$.
- In certain embodiments, R^1 is optionally substituted C1-C6 alkyl, optionally substituted amino, optionally substituted 3 to 8 membered heterocycloalkyl, optionally substituted aryl, or optionally substituted 5 to 8 membered heteroaryl.
- In certain preferred embodiments R^1 is optionally substituted 3 to 11 membered heterocycloalkyl. More preferably, R^1 is optionally substituted 3 to 8 membered heterocycloalkyl. More preferably, R^1 is optionally substituted 5 to 8 membered heterocycloalkyl. More preferably still R^1 is optionally substituted 5 to 6 membered heterocycloalkyl.
- In certain preferred embodiments R^1 is optionally substituted morpholine, bridged azepane, diazepane, thiomorpholine, pyrrolidine, piperazine, or piperidine. In preferred such embodiments R^1 is optionally substituted morpholine, thiomorpholine, pyrrolidine, piperazine, or piperidine. Preferably R^1 is optionally substituted piperidine.
- In certain preferred embodiments R^1 is substituted by one or more alkyl, oxo, cycloalkyl, heterocycloalkyl, aryl, aryl substituted by one or more halo, heteroaryl, NR^8 , NR^8R^9 , $\text{NHC}(\text{O})\text{R}^8$, $\text{NHCR}^8\text{R}^9\text{R}^{10}$, $\text{NHCH}_2\text{CR}^8\text{R}^9\text{R}^{10}$ and $\text{NHCH}_2\text{C}(\text{O})\text{R}^8$, wherein R^8 , R^9 and R^{10} are each independently selected from H, halo, hydroxyl, alkyl, cycloalkyl, cycloalkyl substituted by one or more halo or alkyl, heterocycloalkyl substituted by one or more alkyl or oxo, heteroaryl, and alkoxy.

In certain preferred embodiments R^1 is substituted by NR^8R^9 , $\text{NHC}(\text{O})\text{R}^8$, or $\text{NHCH}_2\text{CR}^8\text{R}^9\text{R}^{10}$, wherein R^8 , R^9 and R^{10} are each independently selected from H,

optionally substituted C1-C6 alkyl, C1-C6 alkoxy, CH₂OH, CH₂CH₂OH, and optionally substituted C3-C6 cycloalkyl.

In certain preferred embodiments R¹ is substituted by NR⁸R⁹, NHC(O)R⁸, or
5 NHCH₂CR⁸R⁹R¹⁰, wherein R⁸, R⁹ and R¹⁰ are each independently selected from H, C1-C6 alkyl, fluoro-substituted C1-C6 alkyl, C1-C6 alkoxy, CH₂OH, CH₂CH₂OH, fluoro-substituted C3-C6 cycloalkyl, C3-C6 cycloalkyl substituted by C1-C6 alkyl, and pyridine-substituted C1-C6 alkyl.

10 In certain preferred embodiments R¹ is substituted by phenyl or phenyl substituted by one or more halo, and wherein R¹ is optionally substituted with one or more further substituents.

In certain preferred embodiments R¹ is substituted by phenyl or phenyl substituted by one or more fluoro, wherein R¹ is optionally substituted with one or more further substituents. In
15 certain preferred embodiments R¹ is substituted by difluoro-phenyl.

In certain preferred embodiments R¹ is substituted by phenyl substituted by halo and C1-C6 alkyl, wherein R¹ is optionally substituted with one or more further substituents. In certain preferred embodiments R¹ is substituted by phenyl substituted by halo and C1-C6
20 alkoxy, wherein R¹ is optionally substituted with one or more further substituents. In certain preferred embodiments R¹ is substituted by phenyl substituted by fluoro and methyl, wherein R¹ is optionally substituted with one or more further substituents. In certain preferred embodiments R¹ is substituted by phenyl substituted by fluoro and methoxy, wherein R¹ is optionally substituted with one or more further substituents.

25 In certain preferred embodiments R¹ is substituted by NR⁸R⁹, NHC(O)R⁸, or NHCH₂CR⁸R⁹R¹⁰, and wherein R¹ is optionally substituted with one or more further substituents. In certain preferred embodiments R¹ is further substituted by phenyl or phenyl substituted by one or more halo. In certain preferred embodiments R¹ is further substituted
30 by phenyl or phenyl substituted by one or more fluoro. In certain preferred embodiments R¹ is further substituted by difluoro-phenyl.

In certain preferred embodiments R¹ is optionally substituted C1-C6 alkyl. Preferably, each optional substituent is selected from halo, alkoxy, cycloalkyl, and hydroxyl.

In certain preferred embodiments R^1 is optionally substituted 6 membered heteroaryl, preferably pyridinyl substituted by phenyl.

5 In certain preferred embodiments R^1 is optionally substituted amino. More preferably, R^1 is amino substituted with phenyl substituted by one or more halo or benzyl substituted by one or more halo.

10 In certain preferred embodiments of the compound of formula (I) R^1 is NR^bR^c or $NR^bCH_2R^c$, wherein R^b and R^c 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 each of the one or more optional substituents are independently selected from halo, methyl, cyclopropyl and CN,
15 optionally wherein R^1 is $NR^aCH_2R^b$ and the methylene group is substituted with CF_3 .

In certain embodiments R^1 is NR^bR^c and R^b and R^c together form an optionally substituted C3-C9 heterocycle together with the N to which they are attached.

20 In certain embodiments, R^1 is NR^bR^c and R^b and R^c together form an optionally substituted C3-C9 heterocycle together with the N to which they are attached, wherein each of the one or more optional substituents is selected from OH, oxo, C1-C3 alkyl optionally substituted with OH and/or halo, optionally substituted phenyl, optionally substituted benzyl, C1-C3 alkoxy, NR^mR^n , $NHC(O)R^m$, and $NHCH_2R^n$,
25 wherein R^m and R^n are independently selected from H; C1-C3 alkyl optionally substituted with OH, methoxy or halo; C3-C4 cycloalkyl optionally substituted with methyl and/or halo; C3-C4 heterocycloalkyl optionally substituted with oxo, methyl or fluoro-methyl; C3-C5 heteroaryl optionally substituted with methyl; and Boc; and/or wherein R^n is further selected from CH_2OCH_3 , $COOH$ and $COOCH_3$,
30 or wherein R^m and R^n form a C3-C5 heterocyclyl group together with the N to which they are attached, optionally wherein R^m and R^n form a morpholinyl group together with the N to which they are attached.

35 In certain embodiments, R^1 is NR^bR^c and R^b and R^c together form an optionally substituted C3-C9 heterocycle together with the N to which they are attached, wherein each of the one

or more optional substituents is selected from optionally halo-substituted phenyl, NR^mR^n , NHC(O)R^m , and NHCH_2R^n ,

wherein R^m and R^n are independently selected from H; C1-C3 alkyl optionally substituted with OH, methoxy or halo; C3-C4 cycloalkyl optionally substituted with methyl and/or halo; C3-C4 heterocycloalkyl optionally substituted with oxo, methyl or fluoro-methyl; C3-C5 heteroaryl optionally substituted with methyl; and Boc; and/or wherein R^n is further selected from CH_2OCH_3 , COOH and COOCH_3 ,

or wherein R^m and R^n form a C3-C5 heterocyclyl group together with the N to which they are attached, optionally wherein R^m and R^n form a morpholinyl group together with the N to which they are attached.

In certain embodiments, R^1 is NR^bR^c and R^b and R^c together form a substituted C3-C9 heterocycle together with the N to which they are attached, wherein each of the one or more substituents is selected from OH, CH_2OH , CH_2OCH_3 , oxo, NH_2 , C1-C3 aminoalkyl, amino-thietane dioxide, methyl, ethyl, propyl, CF_3 , phenyl, substituted phenyl, and benzyl.

In certain embodiments, R^1 is NR^bR^c and R^b and R^c form an optionally substituted heterocycle together with the N to which they are attached, wherein the heterocycle is selected from pyrrolidinyl, pyrimidinyl, piperidinyl, morpholino, piperazinyl, and thiomorpholino. In certain such embodiments, the heterocycle is optionally substituted with one or more substituents independently selected from methyl, spiro-cyclopropyl, C1-C3 aminoalkyl, NH_2 , CH_2OH , CH_2CF_3 , oxo, thiophene, phenyl optionally substituted with F or CF_3 , and OH provided the same ring carbon is not also substituted with methyl.

In certain embodiments, R^1 is NR^bR^c and R^b and R^c form a heterocycle together with the N to which they are attached, wherein the heterocycle is selected from pyrrolidinyl, piperidinyl, morpholino, piperazinyl, and thiomorpholino,

wherein the heterocycle is optionally substituted with one or more substituents independently selected from methyl, NH_2 , C1 or C2 aminoalkyl, CH_2CF_3 , oxo, thiophene, phenyl optionally substituted with F or CF_3 , and OH provided the same ring carbon is not also substituted with methyl.

In certain embodiments, R^1 is NR^bR^c and R^b and R^c form a heterocycle together with the N to which they are attached, wherein the heterocycle is selected from piperidinyl and piperazinyl,

wherein the heterocycle is optionally substituted with one or more substituents independently selected from methyl, NH₂, C1 or C2 aminoalkyl, CH₂CF₃, oxo, thiophene, phenyl optionally substituted with F or CF₃, and OH provided the same ring carbon is not also substituted with methyl.

5

In certain embodiments, R¹ is NR^bR^c and R^b and R^c form an optionally substituted heterocycle together with the N to which they are attached, wherein the heterocycle is selected from piperidinyl and piperazinyl.

10 Preferably R¹ forms a piperazinyl group substituted with fluoro-phenyl or difluorophenyl.

In certain embodiments, the piperazinyl group is optionally further substituted with methyl.

15 In certain embodiments, the piperazinyl group is optionally further substituted with CH₂OH or spiro-cyclopropyl.

In certain embodiments, R¹ is NR^bR^c and R^b and R^c form an optionally substituted heterocycle, wherein the heterocycle is a piperidinyl group substituted with phenyl, wherein the phenyl is optionally substituted with one or more halo (e.g. fluoro) substituents. In
20 certain preferred such embodiments the piperidinyl group is optionally further substituted with NH₂ or NHCH₃.

In certain embodiments, R¹ is NR^bR^c and R^b and R^c together with the N to which they are attached form a piperidinyl group optionally substituted with phenyl, fluoro-phenyl, or
25 difluoro-phenyl, and wherein the piperidinyl group is optionally further substituted with NR^mRⁿ, NHC(O)R^m, or NHCH₂Rⁿ,

wherein R^m and Rⁿ are independently selected from H; C1-C3 alkyl optionally substituted with OH, methoxy or halo; C3-C4 cycloalkyl optionally substituted with methyl and/or halo; C3-C4 heterocycloalkyl optionally substituted with oxo, methyl or fluoro-methyl;
30 C3-C5 heteroaryl optionally substituted with methyl; and Boc; and/or wherein Rⁿ is further selected from CH₂OCH₃, COOH and COOCH₃,

or wherein R^m and Rⁿ form a C3-C5 heterocyclyl group together with the N to which they are attached, optionally wherein R^m and Rⁿ form a morpholinyl group together with the N to which they are attached.

35

In certain embodiments R^1 is NR^bR^c and R^b and R^c together with the N to which they are attached form a piperidinyl group optionally substituted with phenyl, fluoro-phenyl, or difluoro-phenyl, and wherein the piperidinyl group is optionally further substituted with NR^mR^n , $NHC(O)R^m$, or $NHCH_2R^n$,

5 wherein R^m is selected from H; C1-C3 alkyl optionally substituted with OH or halo; C3-C4 cycloalkyl optionally substituted with methyl and/or halo; C3-C4 heterocycloalkyl optionally substituted with oxo, methyl or fluoro-methyl; C3-C5 heteroaryl optionally substituted with methyl; and Boc; and

 wherein R^n is selected from H; C1-C3 alkyl optionally substituted with OH or halo;
10 C3-C4 cycloalkyl optionally substituted with methyl and/or halo; C3-C4 heterocycloalkyl optionally substituted with oxo, methyl or fluoro-methyl; C3-C5 heteroaryl optionally substituted with methyl; Boc; COOH and COOCH₃.

In certain preferred embodiments, the piperidinyl ring formed by R^1 is substituted with
15 NR^mR^n , wherein R^m and R^n are independently selected from H; C1-C3 alkyl optionally substituted with OH or halo (preferably F); C3-C4 cycloalkyl optionally substituted with methyl and/or halo (preferably F); C3-C4 heterocycloalkyl optionally substituted with oxo, methyl or fluoro-methyl; C3-C5 heteroaryl optionally substituted with methyl; and Boc.

20 In certain preferred embodiments where R^1 is substituted with NR^mR^n , R^m is H.

In certain preferred embodiments, R^m is H and R^n is selected from: H; methyl; ethyl
optionally substituted with fluoro or OH; propyl (including isopropyl); cyclopropyl optionally
substituted with methyl; cyclobutyl optionally substituted with fluoro; and oxetanyl optionally
25 substituted with methyl or fluoro-methyl.

In certain preferred embodiments, the piperidinyl ring formed by R^1 is substituted with
 $NHC(O)R^m$, wherein R^m is selected from H; C1-C3 alkyl optionally substituted with OH or
halo (preferably F); C3-C4 cycloalkyl optionally substituted with methyl and/or halo
30 (preferably F); C3-C4 heterocycloalkyl optionally substituted with oxo, methyl or fluoro-methyl; C3-C5 heteroaryl optionally substituted with methyl; and Boc.

In certain preferred embodiments wherein R^1 is substituted with $NHC(O)R^m$, R^m is selected
from C1-C3 alkyl, C3-C4 cycloalkyl, and C4-C5 heteroaryl, for example pyridine.

35

In certain embodiments, R^1 is NR^bR^c and R^b and R^c together with the N to which they are attached form a piperidinyl group optionally substituted with phenyl, fluoro-phenyl, or difluoro-phenyl, and wherein the piperidinyl group is optionally further substituted with NR^mR^n ,

5 wherein R^m and R^n form a C3-C5 heterocyclyl group together with the N to which they are attached. In certain such embodiments R^m and R^n form a morpholinyl group together with the N to which they are attached.

10 In certain embodiments, R^1 is NR^bR^c and R^b and R^c together with the N to which they are attached form a piperidinyl group optionally substituted with phenyl, fluoro-phenyl, or difluoro-phenyl, and wherein the piperidinyl group is optionally further substituted with NH_2 , $NHCH_3$ or $NHCH_2CH_3$.

15 In certain embodiments wherein the heterocycle formed by R^1 is substituted, it is substituted at the *para* position (4 position).

In certain embodiments wherein the heterocycle formed by R^1 is substituted, it is substituted at the *ortho* position (2 position).

20 In certain such embodiments the heterocycle formed by R^1 is substituted at the *ortho* position and the *para* position (2,4 position).

25 In certain embodiments, the heterocycle formed by R^1 is substituted at the *meta* position (3 position). In certain such embodiments, the heterocycle formed by R^1 is substituted at the *ortho* position and the *meta* position (2,3 position).

In certain embodiments, the heterocycle formed by R^1 is substituted at the 3,5 position.

30 In certain preferred embodiments, R^1 is NR^bR^c and R^b and R^c together with the N to which they are attached form a piperidinyl group, wherein the piperidinyl group is substituted at the 4 position with NR^mR^n , $NHC(O)R^m$, and $NHCH_2R^n$, and is further substituted at the 2 position with phenyl, fluoro-phenyl, or difluoro-phenyl. In such embodiments, R^m and R^n are as defined above and elsewhere herein.

In preferred such embodiments where R¹ is a heterocycle substituted (e.g. by phenyl) at the *ortho* or 2 position and is chiral, the compound is the (*R*)-configuration at this position. In preferred embodiments where R¹ is substituted (e.g. by phenyl) at the *ortho* or 2 position and is chiral, the compound is the (*S*)-configuration at this position.

5

In certain preferred embodiments where R¹ is a heterocycle substituted at the *ortho* or 2 position and at the *meta* or 3 position and is chiral, the compound is the (*S*)-configuration at the *ortho* position and the (*S*)-configuration at the *meta* position. In certain preferred embodiments where R¹ is substituted at the *ortho* or 2 position and at the *meta* or 3
10 position and is chiral, the compound is the (*R*)-configuration at the *ortho* position and the (*R*)-configuration at the *meta* position.

In certain preferred embodiments, R¹ is a heterocycle substituted at the 3,4 position. In preferred such embodiments, and where R¹ is chiral, the compound is the (*R*)-configuration
15 at the 3 position and the (*R*)-configuration at the 4 position.

In certain preferred embodiments, R¹ is a heterocycle substituted at the 3,5 position. In preferred such embodiments, and where R¹ is chiral, the compound is the (*R*)-configuration
20 at the 3 position and the (*S*)-configuration at the 5 position.

20

In certain preferred embodiments, R¹ is a heterocycle substituted at the 1,2,5 position. In preferred such embodiments, and where R¹ is chiral, the compound is the (*S*)-configuration at the 1 position, the (*R*)-configuration at the 2 position and the (*R*)-configuration at the 5
position.

25

In preferred such embodiments where R¹ is a heterocycle substituted (e.g. by NH₂ or C1-C2 alkylamino) at the *ortho* or 2 position and at the *para* or 4-position and is chiral, the compound is the (*R*)-configuration at the *para* position and the (*S*)-configuration at the *ortho* position. In preferred such embodiments where R¹ is substituted (e.g. by NH₂ or C1-C2 alkylamino) at the *ortho* or 2 position and at the *para* or 4-position and is chiral, the
30 compound is the (*S*)-configuration at the *para* position and the (*R*)-configuration at the *ortho* position.

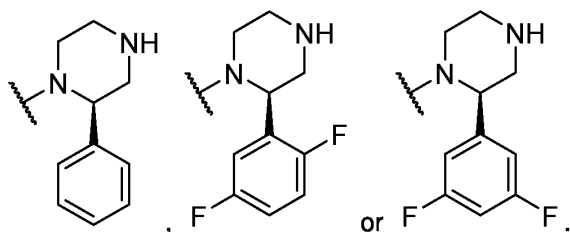
In certain preferred embodiments, R¹ forms a piperazinyl group substituted with phenyl, fluoro-phenyl, difluoro-phenyl, or thiophenyl. In certain preferred embodiments, R¹ forms a
35

- 4-aminopiperidinyl group substituted with phenyl, fluoro-phenyl, difluoro-phenyl, or thiophenyl. Preferably R¹ forms a piperazinyl or 4-aminopiperidinyl group substituted with phenyl. Preferably R¹ forms a piperazinyl or 4-aminopiperidinyl group substituted with fluoro-phenyl. Preferably R¹ forms a piperazinyl or 4-aminopiperidinyl group substituted with difluoro-phenyl.

In preferred embodiments where R¹ is substituted with difluoro-phenyl, the substituent is 2,5 difluoro-phenyl or 3,5 difluoro-phenyl.

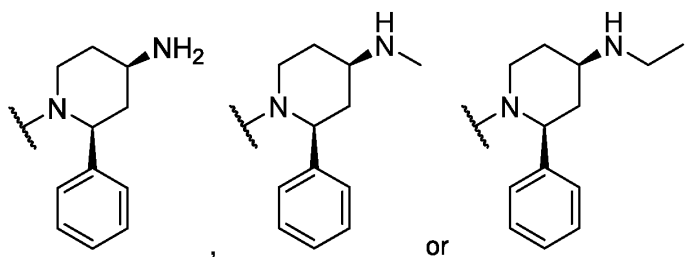
- 10 In certain embodiments, the piperazinyl or 4-aminopiperidinyl group is optionally further substituted with one or two, preferably one, *N*-alkyl groups, such as methyl or ethyl.

In certain preferred embodiments, R¹ is:

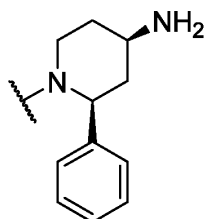


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In certain preferred embodiments, R¹ is:

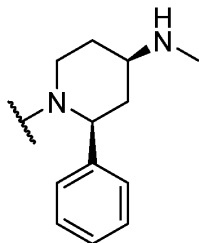


In certain preferred embodiments, R¹ is:



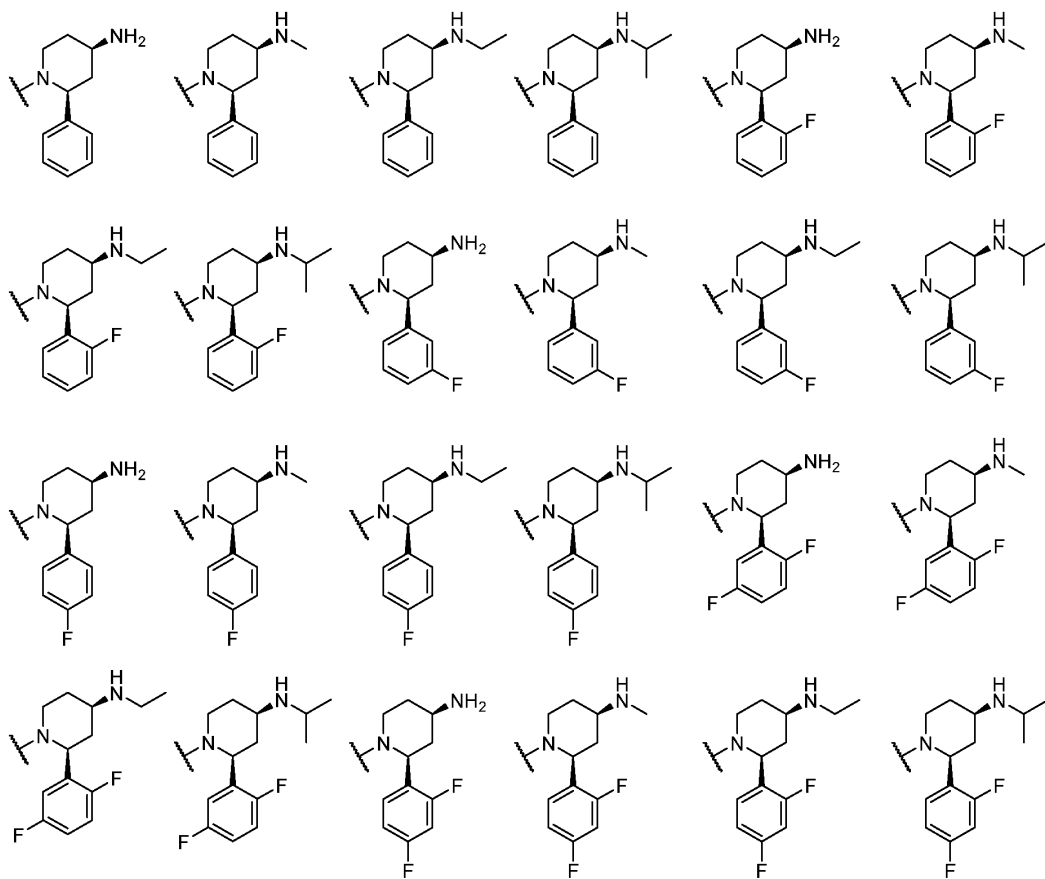
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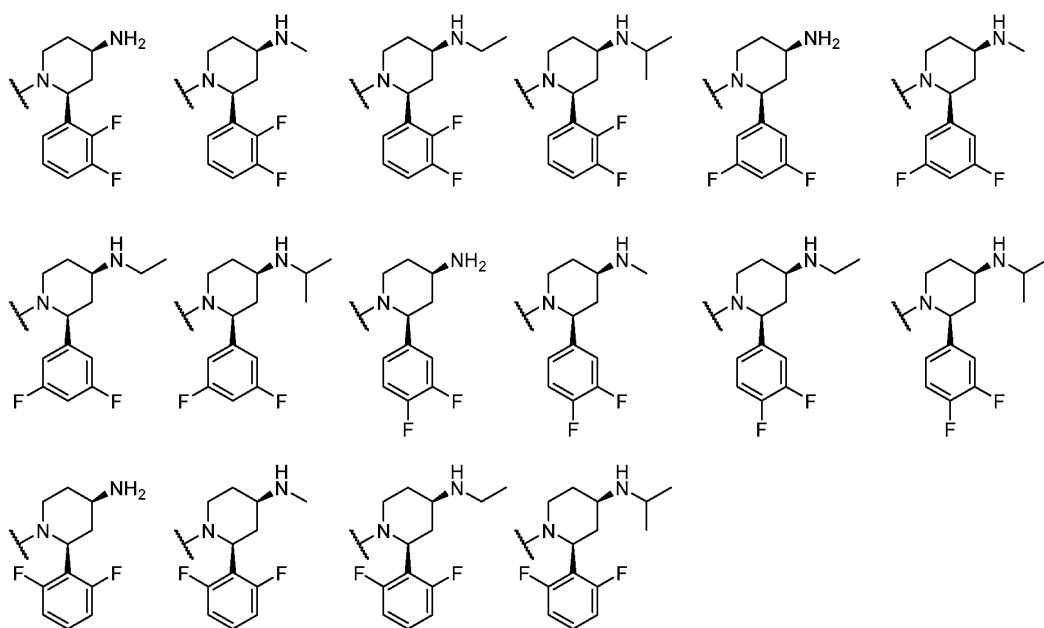
In certain preferred embodiments, R¹ is:



In certain preferred such embodiments, the phenyl ring is mono- or di-substituted with
5 fluoro.

In certain preferred embodiments, R¹ is selected from:





- In certain preferred embodiments of the compound of formula (I), R^1 is NR^bR^c or $NR^bCH_2R^c$, wherein R^b and R^c are independently selected from H, methyl, ethyl, propyl, CF_3 , cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, benzyl, pyridinyl, pyrazole, imidazole, or wherein R^b and R^c together form a C3-C5 heterocycle together with the N to which they are attached, optionally substituted with OH, CH_2OH , CH_2OCH_3 , methyl, ethyl, propyl, CF_3 , phenyl, or benzyl.
- 5
- 10 In certain preferred embodiments, R^1 is $NR^bCH_2R^c$, wherein R^b is H or methyl and R^c 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 CF_3 .
- 15 In certain preferred such embodiments, R^c is phenyl or fluoro-substituted phenyl.

- In certain preferred embodiments R^2 and R^3 are each independently H or methyl, or R^2 and R^3 together form C3-C6 cycloalkyl, cyclopentenyl or 4 to 6 membered heterocycloalkyl together with the carbon to which they are attached. In certain such embodiments, R^2 and R^3 together form cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, oxetanyl or oxanyl together with the carbon to which they are attached. More preferably, R^2 and R^3 are
- 20

each independently H or methyl, or R² and R³ together form cyclopentyl. More preferably, R² and R³ together form cyclopentyl together with the carbon to which they are attached.

5 In certain preferred embodiments M is N or CR^a wherein R^a is H, halo, cyclopropyl, or optionally substituted C1-C6 alkyl.

In certain preferred embodiments M is N or CR^a wherein R^a is H, fluoro, chloro, cyclopropyl, or C1-C6 alkyl optionally substituted with one or more halo groups.

10 In certain preferred embodiments M is N or CR^a wherein R^a is H, fluoro, chloro, cyclopropyl, CF₃ or C1-C6 alkyl.

In certain preferred embodiments M is N or CR^a wherein R^a is H, or optionally substituted C1-C6 alkyl. More preferably, M is N or CR^a wherein R^a is H, or C1-C6 alkyl.

15

In certain preferred embodiments M is CR^a. In certain such embodiments, R^a is H, cyclopropyl, CF₃ or methyl.

In certain preferred embodiments R^a is H or methyl. More preferably, R^a is H.

20

In certain preferred embodiments M is N.

In certain preferred embodiments R¹⁵ is H or methyl.

25 In certain preferred embodiments:

A, D, E and G are absent and

X is NR¹⁵ or CH;

30

Y is CR⁴, N or absent;

Z is CR⁵, NR⁶ or O;

R⁴ is halo, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, 4 to 10 membered fused-ring heterocyclyl or C1-C6 alkylsulfanyl;

5 R⁵ is H, optionally substituted C1-C6 alkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, optionally substituted 3 to 8 membered heterocycloalkyl, amido, sulfoximine, CN or halo;

10 or R⁴ and R⁵ together form 3 to 8 membered heterocycloalkyl or aryl together with Y and Z to which they are attached;

R⁶ is H, C1-C6 alkyl, aryl or C3-C8 cycloalkyl;

15 R¹⁵ is H or C1-C6 alkyl;

or R⁴ and R¹⁵ together form 5 membered heterocycloalkyl, or heteroaryl together with X and Y to which they are attached, optionally wherein R⁴ and R¹⁵ together form dihydrothiazole with X and Y to which they are attached;

20 or A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N and

X is N or C;

Y is C;

25

Z is CH, N, NR¹¹, or O,

wherein R¹¹ is H, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, or optionally substituted 5 to 8 membered heteroaryl;

30

R⁷ is H, halo, C1-C6 alkyl;

R¹² is H, halo, or C1-C6 alkyl;

35

R¹³ is H, halo, C1-C6 alkoxy, or C1-C6 alkyl; and

R^{14} is H, halo, or C1-C6 alkyl;

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

In certain preferred embodiments:

A, D, E and G are absent and

X is NH or CH;

Y is CR^4 or N.

In certain preferred embodiments:

A, D, E and G are absent and

X is NH or CH;

Y is CR^4 or N;

Z is CR^5 , NR^6 or O;

R^4 is halo, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, 4 to 10 membered fused-ring heterocyclyl, C1-C6 alkylsulfanyl (optionally SMe), sulfoxide, sulfone, sulfoximine, optionally substituted amino, or optionally substituted 3 to 8 membered heterocycloalkyl;

R^5 is H, optionally substituted C1-C6 alkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, optionally substituted 3 to 8 membered heterocycloalkyl, amido, sulfoximine, CN, or halo;

or R⁴ and R⁵ together form 3 to 8 membered heterocycloalkyl or aryl together with Y and Z to which they are attached; and

R⁶ is H, C1-C6 alkyl, or C3-C8 cycloalkyl.

5

In certain preferred embodiments, when A, D, E and G are absent, Z is CR⁵ or NR⁶.

In certain preferred embodiments, when A, D, E and G are absent, R⁶ is H or C1-C6 alkyl.

10 In certain preferred embodiments, when A, D, E and G are absent, R⁴ is halo, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, 4 to 10 membered fused-ring heterocyclyl, SMe, sulfoxide, sulfone, sulfoximine, optionally substituted amino, optionally substituted pyrrolidine, optionally substituted piperidine, optionally substituted morpholine,
15 or optionally substituted piperazine. More preferably, when A, D, E and G are absent, R⁴ is halo, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, or 4 to 10 membered fused-ring heterocyclyl.

20 In certain preferred embodiments, when A, D, E and G are absent, R⁵ is H.

In certain preferred embodiments, when A, D, E and G are absent, Y is CR⁴.

In certain preferred embodiments, when A, D, E and G are absent, Y is N.

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In certain preferred embodiments, when A, D, E and G are absent, X is NH.

In certain preferred embodiments, when A, D, E and G are absent, X is CH.

30 In certain preferred embodiments, when A, D, E and G are absent, R⁴ is C1-C6 alkyl, C1-C6 alkyl substituted by one or more halo groups, halo, cycloalkyl, cycloalkyl substituted by one or more C1-C6 alkyl, heteroaryl, heteroaryl substituted by C1-C6 alkyl, dihydrobenzofuran, phenyl, or phenyl substituted by one or more C1-C6 alkyl, alkoxy (optionally C1-C6 alkoxy), or halo. More preferably, when A, D, E and G are absent, R⁴ is
35 methyl, CF₃, CHF₂, chloro, cyclopropyl, methyl substituted cyclopropyl, thiophene, methyl

substituted pyrazole, 2,3-dihydrobenzofuran, phenyl, or phenyl substituted by methyl, methoxy, or fluoro.

5 In certain preferred embodiments, when A, D, E and G are absent, R⁴ is phenyl or phenyl substituted by methyl, methoxy, or fluoro.

In certain preferred embodiments, when A, D, E and G are absent, R⁴ and R⁵ together form 6 membered heterocycloalkyl or aryl together with Y and Z to which they are attached.

10 In certain preferred embodiments, when A, D, E and G are absent, Z is CH.

In certain preferred embodiments, when A, D, E and G are absent, Z is NR⁶.

15 In certain preferred embodiments, when A, D, E and G are absent, R⁶ is H, methyl or cyclopropyl. More preferably, when A, D, E and G are absent, R⁶ is H or methyl.

In certain preferred embodiments, Y is CR⁴ wherein R⁴ is C1-C6 alkylsulfanyl, preferably SMe, and Z is CR⁵ wherein R⁵ is CN.

20 In certain preferred embodiments M is N, X is CH, Y is CR⁴ and Z is NH. In preferred such embodiments, R⁴ is phenyl.

In certain preferred embodiments:

25 A, D, E and G are absent;
X is CH;
Y is CR⁴;
Z is NR⁶; and
M is CR^a or N,
wherein R^a, R⁴ and R⁶ are as defined herein above.

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In certain preferred embodiments:

35 A, D, E and G are absent;
X is NH;
Y is CR⁴;
Z is CR⁵; and

M is CR^a,
wherein R^a, R⁴ and R⁵ are as defined herein above.

In certain preferred embodiments:

- 5 A, D, E and G are absent;
 X is NH;
 Y is CR⁴;
 M is CR^a; and
 Z is N,
10 wherein R^a and R⁴ are as defined herein above.

In certain preferred embodiments:

- 15 A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N and
 X is N or C;
 Y is C;
20 Z is CH, N, NR¹¹, or O, wherein R¹¹ is H, optionally substituted C1-C6 alkyl,
 optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, or
 optionally substituted 5 to 8 membered heteroaryl;
 R⁷ is H, halo, or C1-C6 alkyl;
25 R¹² is H, halo, or C1-C6 alkyl;
 R¹³ is H, halo, C1-C6 alkoxy, or C1-C6 alkyl; and
30 R¹⁴ is H, halo, or C1-C6 alkyl.

In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N, Z is CH, N, or NR¹¹.

In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N, Z is CH, N, or O.

5 In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N, Z is CH or N.

In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N, R⁷ is H, methyl or halo.

10 In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N, R¹² is H.

In certain preferred embodiments, A is CR¹² or N, D is CR⁷, E is CR¹³ or N and G is CR¹⁴ or N.

15 In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ and G is CR¹⁴ or N.

20 In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N, R¹³ is H.

In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴.

25 In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N, R¹⁴ is H.

In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N, X is N.

30 In certain preferred embodiments, A is CH, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N.

In certain preferred embodiments, A is N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N.

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In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N, R⁷ is H or halo, optionally fluoro.

5 In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N, Z is CH.

In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N, Z is N.

10 In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N, Z is O.

In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N, Z is NR¹¹.

15 In certain preferred embodiments, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N, G is CR¹⁴ or N, and Z is NR¹¹, R¹¹ is H, C1-C6 alkyl, C3-C6 cycloalkyl, phenyl, or 5 to 7 membered heteroaryl. More preferably, when A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N, G is CR¹⁴ or N, and Z is NR¹¹, R¹¹ is methyl. More preferably, when A is CR¹² or N, D is
20 CR⁷ or N, E is CR¹³ or N, G is CR¹⁴ or N, and Z is NR¹¹, R¹¹ is H.

In certain preferred embodiments, X is N; Y is C; Z is N; M is CR^a; A and G are each CH; D is CR⁷; and E is CR¹³, wherein R^a, R⁷ and R¹¹ are as defined herein above.

25 In certain preferred embodiments, X and Y are each C; Z is O; A, E, G and M are each CH; and D is CR⁷, wherein R⁷ is as defined herein above.

In certain preferred embodiments, X and Y are each C; Z is NR¹¹; A, E, G and M are each CH; and D is N, wherein R¹¹ is as defined herein above.

30 In certain preferred embodiments, X and Y are each C; Z is NH; E is N; and A, D, G and M are each CH.

In certain preferred embodiments, A, D, E and G are absent; X is NR¹⁵; Y is CR⁴; Z is N; M is CH; and R⁴ and R¹⁵ together form 5 membered heterocycloalkyl with X and Y to which
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they are attached. In certain preferred embodiments, R⁴ and R¹⁵ together form dihydrothiazole with X and Y to which they are attached.

In certain preferred embodiments:

- 5 A, D, E and G are absent,
 X is NH or CH;
 Y is CR⁴;
 Z is CR⁵ or NR⁶;
 R¹ is optionally substituted piperidine or piperazine,
10 R² and R³ together form cyclopentyl together with the carbon to which they are
 attached,
 R⁴ is phenyl,
 R⁵ is H, and
 R⁶ is H or methyl,
15 wherein each optional substituent is selected from phenyl, difluoro-phenyl, NHCH₃,
 NHCH₂CH₃, NHCH(CH₃)₂, NHC(O)CH₃, N(CH₃)₂, NHCH₂CHF₂, NHCH₂CH₂F,
 NHCH₂CH₂OH and NHCH₂CH₂OCH₃.

In certain preferred embodiments:

- 20 A, D, E and G are absent;
 X is NH or CH;
 Y is CR⁴;
 Z is CR⁵ or NR⁶;
 R¹ is piperidine or piperazine each substituted by difluoro-phenyl and further
25 substituted by amino optionally substituted by one or more C₁-C₃ alkyl, oxo-
 substituted C₁-C₃ alkyl, fluoro-substituted C₁-C₃ alkyl, CH₂CH₂OH, C₁-C₃ alkoxy,
 fluoro-substituted C₃-C₆ cycloalkyl, C₃-C₆ cycloalkyl substituted by C₁-C₃ alkyl, or
 pyridine-substituted C₁-C₃ alkyl;
 R² and R³ are each methyl, or together form cyclopropyl, cyclobutyl, cyclopentyl,
30 cyclopentenyl, cyclohexyl, oxetanyl or oxanyl together with the carbon to which they
 are attached;
 R⁴ is methyl, dihydrobenzofuran, phenyl, phenyl substituted by methyl, phenyl
 substituted by F, phenyl substituted by OMe, phenyl substituted by SMe, phenyl
 substituted by OH, or thiophene;
35 R⁵ is H, methyl or CN; and

R⁶ is H or methyl.

In certain preferred embodiments:

- 5 X is N or C;
Y is C;
Z is N, NR¹¹ or O, wherein R¹¹ is H or methyl;
M is CR^a wherein R^a is H, methyl or cyclopropyl;
A is C;
D is CR⁷, wherein R⁷ is H, methyl, F, Cl, Br;
10 E is N or CR¹³, wherein R¹³ is H, Cl or OMe;
G is C;
R¹ is piperidine or piperazine each substituted by difluoro-phenyl and further substituted by amino optionally substituted by one or more C1-C3 alkyl, fluoro-substituted C1-C3 alkyl, CH₂CH₂OH, C1-C3 alkoxy; and
15 R² and R³ are each methyl, or together form cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, oxetanyl or oxanyl together with the carbon to which they are attached.

In certain preferred embodiments there is provided a compound selected from:

- 20 (*R*)-6-Phenyl-3-((4-(3-phenylmorpholine-4-carbonyl)piperazin-1-yl)methyl)pyridin-2(1*H*)-one;
(*R*)-3-((2,2-Dimethyl-4-(3-phenylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
25 3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)quinolin-2(1*H*)-one;
N-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-1-(6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)acetamide;
30 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1,5,7,8-tetrahydro-2*H*-pyrano[4,3-*b*]pyridin-2-one;
N-(2,4-Difluorobenzyl)-6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxamide;

- (*R*)-6-Phenyl-3-((9-(4,4,4-trifluoro-2-methylbutanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1*H*)-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 5 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-phenylpyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 10 3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-methoxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 15 3-((9-((2*S*,4*R*)-4-(Methylamino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 20 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- (*R*)-3-((9-(2-(2,5-Difluorophenyl)piperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 6-Phenyl-3-((9-((3*R*,4*R*)-3-phenylpiperidine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1*H*)-one;
- 25 3-((9-((2*S*,4*R*)-4-((3,3-Difluorocyclobutyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- (*S*)-6-Phenyl-3-((9-(4,4,4-trifluoro-2-(methoxymethyl)butanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1*H*)-one;
- (*R*)-3-((9-(3-Cyclohexyl-2-methylpropanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 30 6-Phenyl-3-((9-(3-phenylisonicotinoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1*H*)-one;
- 3-((9-((2*S*,4*R*)-4-((2-Hydroxyethyl)amino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

- 5-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 5-((7-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 5 6-Phenyl-3-((9-((2*S*,4*R*)-2-phenyl-4-((pyridin-2-ylmethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(3,4-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 10 (*R*)-3-((9-(2-Methyl-2-phenylpiperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 15 (*R*)-5-((9-(3-(2,5-Difluorophenyl)morpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- (*S*)-5-((9-(3-(2,5-Difluorophenyl)morpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 20 5-((9-((2*S*,4*R*)-2-(2,3-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-4-(Methylamino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 25 5-((9-((2*S*,4*R*)-4-(Cyclopropylamino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- (*R*)-5-((9-(2-(2,5-Difluorophenyl)-1,4-diazepane-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- (*S*)-5-((9-(2-(2,5-Difluorophenyl)-1,4-diazepane-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 30 5-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- (*R*)-5-((9-(3-(2,5-Difluorophenyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

- (*S*)-5-((9-(3-(2,5-Difluorophenyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,6-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,4-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
3-((9-((3*R*,5*S*)-3-(2,5-Difluorophenyl)-5-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-methoxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
5-((8-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
5-((8-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2-oxa-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
5-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
5-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
3-((7-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
3-((9-((2*S*,4*R*)-4-Amino-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
3-((8-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
3-((8-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2-oxa-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

- 3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(pyrrolidin-1-yl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 5 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(1-methyl-1*H*-pyrazol-5-yl)pyridin-4(1*H*)-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-methyl-5-phenylpyridin-2(1*H*)-one;
- 10 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-2-yl)pyridin-4(1*H*)-one;
- (*R*)-3-((9-(3-Cyclohexyl-2-methylpropanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 15 5-((9-((2*S*,4*R*)-4-((2,2-Difluoroethyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-4-Morpholino-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-fluorophenyl)pyridin-4(1*H*)-one;
- 20 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(*o*-tolyl)pyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-methoxyphenyl)pyridin-4(1*H*)-one;
- 25 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-chromen-4-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-4*H*-chromen-4-one;
- (*R*)-3-((9-(3-Cyclohexyl-2-methylpropanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-chromen-4-one;
- 30 4*H*-chromen-4-one;
- (*R*)-3-((9-(3-Cyclohexyl-2-methylpropanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-4*H*-chromen-4-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2,3-dihydrobenzofuran-7-yl)pyridin-4(1*H*)-one;

- (*R*)-3-((9-(2-(2,5-Difluorophenyl)piperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-4*H*-chromen-4-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(1-methyl-1*H*-pyrazol-3-yl)pyridin-4(1*H*)-one;
- 5 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 1-Cyclopropyl-5-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-methylpyridin-4(1*H*)-one;
- 10 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-5,6-dimethylpyridin-2(1*H*)-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrimido[1,2-*b*]pyridazin-4-one;
- 15 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoroquinolin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-hydroxyphenyl)pyridin-4(1*H*)-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-methyl-2-propylpyridin-4(1*H*)-one;
- 20 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-5-(trifluoromethyl)pyridin-2(1*H*)-one;
- 25 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(*o*-tolyl)pyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2,3-dihydrobenzofuran-7-yl)pyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-methoxyphenyl)pyridin-4(1*H*)-one;
- 30 (*R*)-5-((9-(2-(2,5-Difluorophenyl)piperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- (*R*)-3-((9-(2-(2,5-Difluorophenyl)piperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(4-fluorophenyl)pyridin-4(1*H*)-one;
- 5 3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(3-fluorophenyl)pyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(*m*-tolyl)pyridin-4(1*H*)-one;
- 10 5-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-methoxyphenyl)pyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2,3-dihydrobenzofuran-7-yl)pyridin-4(1*H*)-one;
- 15 5-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(*o*-tolyl)pyridin-4(1*H*)-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(*m*-tolyl)pyridin-2(1*H*)-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(3-fluorophenyl)pyridin-2(1*H*)-one;
- 20 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(4-fluorophenyl)pyridin-2(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(3-Fluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 25 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(methylthio)-6-oxo-1,6-dihydropyridine-3-carbonitrile;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyrimidin-4(3*H*)-one;
- 30 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1,7-naphthyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyrimidin-4(3*H*)-one;
- 5-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
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- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-2-yl)pyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-2-yl)pyridin-4(1*H*)-one;
- 5 5-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2,6-dimethylpyridin-4(1*H*)-one;
- 3-((9-((2*S*,4*R*)-4-((2,2-Difluoroethyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 10 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-methoxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((9-((2*S*,5*R*)-5-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 15 (R)-6-Phenyl-3-((4-(3-phenylmorpholine-4-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)pyridin-2(1*H*)-one;
- (R)-3-((4-(3-(4-Fluorophenyl)morpholine-4-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 20 3-((4-((2*R*,5*R*)-5-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2-Fluoro-5-methylphenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 25 5-((9-((2*S*,4*R*)-2-(2-Fluoro-5-methoxyphenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 5-((9-((2*S*,5*R*)-5-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyrimidin-4(3*H*)-one;
- 30 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

- N*-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-1-(6-((7-fluoro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl)piperidin-4-yl)acetamide;
N-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-1-(6-((7-fluoro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl)piperidin-4-yl)cyclopropanecarboxamide;
- 5 3-((9-((2*S*,4*R*)-4-((1,1-Dioxidothietan-3-yl)amino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
3-((9-((2*S*,4*R*)-4-((2,2-Difluoroethyl)amino)-2-(3,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 10 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(thiophen-3-yl)pyridin-4(1*H*)-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
(*S*)-6-(2-Methoxyphenyl)-3-((9-(2-phenylpyrrolidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1*H*)-one;
- 15 (*S*)-6-Phenyl-3-((7-(2-phenylpyrrolidine-1-carbonyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)pyridin-2(1*H*)-one;
(*S*)-6-Phenyl-3-((4-(2-phenylpyrrolidine-1-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)pyridin-2(1*H*)-one;
- 20 5-((9-((2*R*,5*R*)-5-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
(*S*)-3-((4-(2-(2,5-Difluorophenyl)pyrrolidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-6-(1-methyl-1*H*-pyrazol-5-yl)pyridin-2(1*H*)-one;
(*S*)-3-((2,2-Dimethyl-4-(2-phenylpyrrolidine-1-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 25 (*S*)-6-Phenyl-3-((8-(2-phenylpyrrolidine-1-carbonyl)-2-oxa-5,8-diazaspiro[3.5]nonan-5-yl)methyl)pyridin-2(1*H*)-one;
3-((4-((1*S*,2*R*,5*R*)-2-(2,5-Difluorophenyl)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 30 3-((9-((1*S*,2*R*,5*R*)-2-(2,5-Difluorophenyl)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
5-((9-((1*S*,2*R*,5*R*)-2-(2,5-Difluorophenyl)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-fluorophenyl)pyridin-4(1*H*)-one;
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- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-1-methylquinolin-4(1*H*)-one;
3-((9-((2*R*,3*R*)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
5 3-((9-((2*S*,3*S*)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(1-methyl-1*H*-pyrazol-5-yl)pyridin-4(1*H*)-one;
10 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(trifluoromethyl)pyridin-2(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(trifluoromethyl)pyridin-4(1*H*)-one;
3-((4-((2*R*,3*R*)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
15 3-((4-((2*S*,3*S*)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
5-((9-((2*R*,3*R*)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
20 5-((9-((2*S*,3*S*)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
3-((9-((2*R*,4*R*)-4-Amino-2-ethylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
3-((9-((2*R*,4*R*)-2-Ethyl-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
25 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(1-methyl-1*H*-pyrazol-3-yl)pyridin-4(1*H*)-one;
30 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-hydroxypiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(1-methyl-1*H*-pyrazol-3-yl)pyridin-4(1*H*)-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropyl(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-methoxyethyl)(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-hydroxypiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one;
- 3-(((*S*)-4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-2-methylpiperazin-1-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 7-Chloro-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-(((*R*)-4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-2-methylpiperazin-1-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 5-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(thiophen-3-yl)pyridin-4(1*H*)-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethyl(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-8-methoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 5 5-((9-((2*S*,4*S*)-4-Amino-2-phenylpyrrolidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 5-((9-((2*S*,4*S*)-4-(Isopropylamino)-2-phenylpyrrolidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 10 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7,8-dihydropyrrolo[1,2-*a*]pyrimidin-4(6*H*)-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7,8-dihydropyrrolo[1,2-*a*]pyrimidin-4(6*H*)-one;
- 3-((9-(5-Amino-2',5'-difluoro-[1,1'-biphenyl]-2-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
- 15 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-fluoroethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 20 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-fluoroethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
- 7-Fluoro-3-((9-((2*S*,4*S*)-4-(isopropylamino)-2-phenylpyrrolidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 25 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 30 4-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-phenyl-1,2-dihydro-3*H*-pyrazol-3-one;
- 4-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-methyl-1-phenyl-1,2-dihydro-3*H*-pyrazol-3-one;
- 7-Chloro-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

- 3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 5 7-Chloro-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 6-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one;
- 6-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one;
- 10 7-Fluoro-3-((9-((2*S*,4*R*)-4-((3-methyloxetan-3-yl)amino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 15 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 2-Cyclopropyl-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 20 2-Cyclopropyl-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridazin-4(1*H*)-one;
- 25 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridazin-4(1*H*)-one;
- 3-((9-((2*S*,4*R*)-4-Amino-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 30 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]dec-2-en-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 7-Bromo-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 8-Chloro-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 35

- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 5 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
- 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-1,6-naphthyridin-4(1*H*)-one;
- 10 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((1-methylcyclopropyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one; and
- 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(1-methylcyclopropyl)pyridin-4(1*H*)-one;
- 15 or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof.

In certain embodiments there is provided a compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt as described above that is an inhibitor of USP19, preferably human USP19.

20

In a second aspect the invention provides a pharmaceutical composition comprising a compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to the first aspect, and a pharmaceutically acceptable carrier or diluent.

25

Pharmaceutical compositions may be formulated according to their particular use and purpose by mixing, for example, excipient, binding agent, lubricant, disintegrating agent, coating material, emulsifier, suspending agent, solvent, stabilizer, absorption enhancer and/or ointment base. The composition may be suitable for oral, injectable, rectal or topical administration.

30

Suitable pharmaceutically acceptable excipients would be known by the person skilled in the art, for example: fats, water, physiological saline, alcohol (e.g. ethanol), glycerol, polyols, aqueous glucose solution, extending agent, disintegrating agent, binder, lubricant,

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wetting agent, stabilizer, emulsifier, dispersant, preservative, sweetener, colorant, seasoning agent or aromatizer, concentrating agent, diluent, buffer substance, solvent or solubilizing agent, chemical for achieving storage effect, salt for modifying osmotic pressure, coating agent or antioxidant, saccharides such as lactose or glucose; starch of
5 corn, wheat or rice; fatty acids such as stearic acid; inorganic salts such as magnesium metasilicate aluminate or anhydrous calcium phosphate; synthetic polymers such as polyvinylpyrrolidone or polyalkylene glycol; alcohols such as stearyl alcohol or benzyl alcohol; synthetic cellulose derivatives such as methylcellulose, carboxymethylcellulose, ethylcellulose or hydroxypropylmethylcellulose; and other conventionally used additives
10 such as gelatin, talc, plant oil and gum arabic.

For example, the pharmaceutical composition may be administered orally, such as in the form of tablets, coated tablets, hard or soft gelatine capsules, solutions, emulsions, or suspensions. Administration can also be carried out rectally, for example using
15 suppositories, locally or percutaneously, for example using ointments, creams, gels or solution, or parenterally, for example using injectable solutions.

For the preparation of tablets, coated tablets or hard gelatine capsules, the compounds of the present invention may be admixed with pharmaceutically inert, inorganic or organic
20 excipients. Examples of suitable excipients include lactose, maize starch or derivatives thereof, talc or stearic acid or salts thereof. Suitable excipients for use with soft gelatine capsules include, for example, vegetable oils, waxes, fats and semi-solid or liquid polyols.

For the preparation of solutions and syrups, excipients include, for example, water, polyols, saccharose, invert sugar and glucose.
25

For injectable solutions, excipients include, for example, water, alcohols, polyols, glycerine and vegetable oil.

30 For suppositories and for local and percutaneous application, excipients include, for example, natural or hardened oils, waxes, fats and semi-solid or liquid polyols.

The pharmaceutical compositions may also contain preserving agents, solubilizing agents, stabilizing agents, wetting agents, emulsifiers, sweeteners, colorants, odorants, buffers, coating agents and/or antioxidants.
35

For combination therapies, the second drug may be provided in pharmaceutical composition with the present invention or may be provided separately.

Thus, a pharmaceutical formulation for oral administration may, for example, be granule,
5 tablet, sugar-coated tablet, capsule, pill, suspension or emulsion. For parenteral injection
for, for example, intravenous, intramuscular or subcutaneous use, a sterile aqueous
solution may be provided that may contain other substances including, for example, salts
and/or glucose to make to solution isotonic. The anti-cancer agent may also be
administered in the form of a suppository or pessary, or may be applied topically in the form
10 of a lotion, solution, cream, ointment or dusting powder.

In a further aspect the invention provides a compound according to the first aspect,
including a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically
acceptable salt thereof, for use in therapy.

15

In a further aspect the invention provides a pharmaceutical composition according to the
second aspect for use in therapy.

In a further aspect the invention provides a compound according to any embodiment of the
20 first aspect, or a stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically
acceptable salt thereof, for use in the treatment and/or prevention of cancer.

In a further aspect the invention provides a pharmaceutical composition according to the
second aspect for use in the treatment and/or prevention of cancer.

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In a further aspect the invention provides a method of treating or preventing cancer
comprising administering to a subject a compound, including a stereoisomer, tautomer,
hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof, according to any
embodiment of the first aspect of the invention or a pharmaceutical composition according
30 to any embodiment of the second aspect of the invention.

In a further aspect the invention provides a use of a compound, including a stereoisomer,
tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt thereof,
according to any embodiment of the first aspect in the manufacture of a medicament for
35 treating or preventing cancer.

Cancers or neoplastic conditions suitable to be treated with the compounds or compositions according to the invention include, for example: prostate cancer, colon cancer, breast cancer, lung cancer, kidney cancer, CNS cancers (e.g. neuroblastomas, glioblastomas), osteosarcoma, haematological malignancies (e.g. leukaemia, multiple myeloma and mantle cell lymphoma). In certain preferred embodiments the cancer is associated with p53 dysregulation. In certain preferred embodiments, the cancer is selected from a haematological malignancy (e.g. mantle cell lymphoma, multiple myeloma), prostate cancer, a neuroblastoma, or a glioblastoma. In certain preferred embodiments, the cancer is neuroblastoma or breast cancer.

10

It is demonstrated herein that the potent USP19 inhibitory compounds effectively reduce fat accumulation *in vivo*. Gene knockout studies have described a possible association between USP19 and fat accumulation (Coyne *et al.*, *Diabetologia*, 2019, 62, 136-146, incorporated herein by reference). However, the effects seen in these studies need to be considered alongside the possible confounding factors inherent in knockout studies such as altered developmental or underlying physiological processes. For these reasons, acute or chronic pharmacological inhibition of an enzyme does not always result in similar physiological outcomes to genetic ablation.

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The data provided herein demonstrates that pharmacological inhibition of USP19 can reduce fat accumulation in a wild-type background. Taken together, the *in vitro* and *in vivo* data demonstrate that compounds which potently inhibit USP19 activity can effectively treat obesity.

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In a further aspect is provided a compound according to the first aspect, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in a method of treating obesity.

30

In a further aspect is provided a pharmaceutical composition according to the second aspect for use in a method of treating obesity.

Also provided in accordance with the invention is a method of treating obesity comprising administering to a subject in need thereof an effective amount of a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative according

to the first aspect, or an effective amount of a pharmaceutical composition according to the second aspect.

5 It is further demonstrated herein that the potent USP19 inhibitory compounds provided herein can effectively treat insulin resistance. Gene knockout studies have described an association between USP19 and insulin sensitivity (Coyne *et al.*, *supra*). Coyne *et al.* describe an improvement in insulin sensitivity in USP19 knockout mice but, as noted above, it could not be assumed that the effects would translate to pharmacological inhibition of USP19 in wild-type subjects.

10 The data provided herein demonstrates that pharmacological inhibition of USP19 can effectively treat insulin resistance (e.g. type II diabetes).

15 In a further aspect is provided a compound as defined in relation to the first aspect of the invention, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in a method of treating insulin resistance.

20 In a further aspect of the invention is provided a compound as defined in relation to the first aspect of the invention, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in a method of treating type II diabetes.

In a further aspect of the invention is provided a pharmaceutical composition according to the second aspect for use in a method of treating insulin resistance.

25 In a further aspect of the invention is provided a pharmaceutical composition according to the second aspect for use in a method of treating type II diabetes.

30 Also provided in accordance with the invention is a method of treating insulin resistance comprising administering to a subject in need thereof an effective amount of a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in relation to the first aspect of the invention, or an effective amount of a pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in relation to the first aspect of the invention.

Also provided in accordance with the invention is a method of treating type II diabetes comprising administering to a subject in need thereof an effective amount of a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in relation to the first aspect of the invention, or an effective amount of a pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in relation to the first aspect of the invention.

It is demonstrated in the accompanying Examples that compounds provided herein are potent USP19 inhibitors and further that potent USP19 inhibitory compounds effectively treat muscle loss in an *in vivo* disease model. Taken together, the *in vitro* and *in vivo* data demonstrate that compounds which potently inhibit USP19 activity can effectively treat muscular atrophy.

In a further aspect is provided a compound as defined in relation to the first aspect of the invention, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in a method of treating muscular atrophy.

In a further aspect the invention provides a compound as defined in relation to the first aspect, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in a method of treating cachexia or sarcopenia.

In a further aspect of the invention is provided a pharmaceutical composition according to the second aspect for use in a method of treating muscular atrophy.

In a further aspect of the invention is provided a pharmaceutical composition according to the second aspect for use in a method of treating cachexia or sarcopenia.

Also provided in accordance with the invention is a method of treating muscular atrophy comprising administering to a subject in need thereof an effective amount of a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in relation to the first aspect of the invention, or an effective amount of a pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in relation to the first aspect of the invention.

Also provided in accordance with the invention is a method of treating cachexia or sarcopenia comprising administering to a subject in need thereof an effective amount of a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in relation to the first aspect of the invention, or an effective amount of a pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in relation to the first aspect of the invention.

Muscle atrophy, cachexia or sarcopenia may be associated with or induced by HIV infection/AIDS, heart failure, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, multiple sclerosis, motor neuron disease (MND), Parkinson's disease, dementia, or cancer.

In a further aspect, the invention provides a compound or composition according to any embodiment of the first aspect or second aspect for use in the treatment and/or prevention of Parkinson's Disease. In a further aspect, the invention provides a method of treating or preventing Parkinson's Disease comprising administering an effective amount of a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, or pharmaceutical composition according to the invention to a subject. In a further aspect, the invention provides the use of a compound according to the invention, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, in the manufacture of a medicament for the treatment of Parkinson's Disease.

The compound or composition of the invention may be used in monotherapy and/or a combination modality. Suitable agents to be used in such combination modalities with compounds or compositions according to the invention include one or more of anti-cancer agents, anti-inflammatory agents, immuno-modulatory agents, for example immuno-suppressive agents, neurological agents, anti-diabetic agents, anti-viral agents, anti-bacterial agents and/or radiation therapy.

Agents used in combination with the compounds of the present invention may target the same or a similar biological pathway to that targeted by the compounds of the present invention or may act on a different or unrelated pathway.

Depending on the disease to be treated, a variety of combination partners may be coadministered with the compounds of the present invention. The second active ingredient may include, but is not restricted to: alkylating agents, including cyclophosphamide, ifosfamide, thiotepa, melphalan, chloroethylnitrosourea and bendamustine; platinum derivatives, including cisplatin, oxaliplatin, carboplatin and satraplatin; antimetabolic agents, including vinca alkaloids (vincristine, vinorelbine and vinblastine), taxanes (paclitaxel, docetaxel), epothilones and inhibitors of mitotic kinases including aurora and polo kinases; topoisomerase inhibitors, including anthracyclines, epipodophyllotoxins, camptothecin and analogues of camptothecin; antimetabolites, including 5-fluorouracil, capecitabine, cytarabine, gemcitabine, 6-mercaptopurine, 6-thioguanine, fludarabine, methotrexate and premetrexed; protein kinase inhibitors, including imatinib, gefitinib, sorafenib, sunitinib, erlotinib, dasatinib, and lapatinib; proteasome inhibitors, including bortezomib; histone deacetylase inhibitors, including valproate and SAHA; antiangiogenic drugs, including bevacizumab; monoclonal antibodies, including trastuzumab, rituximab, alemtuzumab, tositumomab, cetuximab, panitumumab; conjugates of monoclonal antibodies, including Gemtuzumab ozogamicin, Ibritumomab tiuxetan; hormonal therapies, including antiestrogens (tamoxifen, raloxifen, anastrozole, letrozole, exemestane) antiandrogens (Flutamide, Bicalutamide) and Luteinising Hormone Analogues or antagonists.

In regard to aspects of the invention relating to therapeutic use of compounds according to the invention, the compounds may be administered to the subject in need of treatment in an "effective amount". The term "effective amount" refers to the amount or dose of a compound which, upon single or multiple dose administration to a subject, provides therapeutic efficacy in the treatment of disease. Therapeutically effective amounts of a compound according to the invention can comprise an amount in the range of from about 0.1 mg/kg to about 20 mg/kg per single dose. A therapeutic effective amount for any individual patient can be determined by the healthcare professional by methods understood by the skilled person. The amount of compound administered at any given time point may be varied so that optimal amounts of the compound, whether employed alone or in combination with any other therapeutic agent, are administered during the course of treatment. It is also contemplated to administer compounds according to the invention, or pharmaceutical compositions comprising such compounds, in combination with any other cancer treatment, as a combination therapy.

For combination therapies, the second drug may be provided in pharmaceutical composition with the present invention or may be provided separately.

Routes of administration

- 5 In certain preferred embodiments, treatment according to the invention comprises administering the therapeutic agent (that is, the compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative, or pharmaceutical composition for use according to the invention) parenterally.
- 10 In certain preferred embodiments, the therapeutic agent is administered orally.

In certain preferred embodiments the therapeutic agent is administered intravenously. In certain preferred embodiments, the therapeutic agent is administered intraperitoneally. In certain preferred embodiments, the therapeutic agent is administered subcutaneously.

15

Dosage regimen

- In certain preferred embodiments of the invention, treatment comprises administering the therapeutic agent (that is, the compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative, or pharmaceutical composition for use according to the invention) at a dose in the range of from 10 to 150 mg/kg. In such embodiments, the dose refers to the amount of the active ingredient administered to the subject per single administration.

20

- In certain preferred embodiments, treatment comprises administering the therapeutic agent at a dose in the range of from 25 to 125 mg/kg. In certain preferred embodiments, treatment comprises administering the therapeutic agent at a dose in the range of from 50 to 100 mg/kg.

25

- In certain preferred embodiments, the method comprises administering the therapeutic agent at a dose of 75 mg/kg.

30

In certain preferred embodiments, treatment comprises administering the therapeutic agent (that is, the compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative, or pharmaceutical composition for use according to the invention) 1, 2, 3

or 4 times daily. In certain preferred embodiments, the therapeutic agent is administered once or twice daily, most preferably twice daily.

5 In certain preferred embodiments, the therapeutic agent is administered at a daily dosage in the range of from 10 to 300 mg/kg. That is, the total amount of active agent administered to the subject in one day is in the range of from 10-300 mg/kg. In such embodiments, the therapeutic agent may be administered once or multiple times per day as described herein, provided the total daily dosage is in the indicated range.

10 In certain preferred embodiments, the therapeutic agent is administered at a daily dosage in the range of from 50 to 250 mg/kg. In certain preferred embodiments, the therapeutic agent is administered at a daily dosage in the range of from 75 to 250 mg/kg. In certain preferred embodiments, the therapeutic agent is administered at a daily dosage in the range of from 100 to 200 mg/kg. In certain preferred embodiments, the therapeutic agent is
15 administered at a daily dosage of 150 mg/kg.

In certain preferred embodiments, the therapeutic agent (for example a compound as provided herein) is administered at a dose of 75 mg/kg twice daily.

20 In regard to aspects of the invention relating to therapeutic use of compounds according to the invention, in preferred embodiments the subject to be treated is human.

In a further aspect the invention provides the compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to the first aspect or the
25 pharmaceutical composition according the second aspect for use as a medicament.

In a further aspect the invention provides the compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to the first aspect or the pharmaceutical composition according to the second aspect for use in treating muscular
30 atrophy, obesity, insulin resistance, or type II diabetes.

In a further aspect the invention provides a method of treating obesity, insulin resistance, type II diabetes, or muscular atrophy, comprising administering to a subject in need thereof an effective amount of a compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or

pharmaceutically acceptable salt according to the first aspect or a pharmaceutical composition according to the second aspect.

- In a further aspect the invention provides a method of reducing loss of muscle mass in a subject comprising administering to a subject in need thereof an effective amount of a compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to according to the first aspect or a pharmaceutical composition according to the second aspect.
- When introducing elements of the present disclosure or the preferred embodiments(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.
- The foregoing detailed description has been provided by way of explanation and illustration, and is not intended to limit the scope of the appended claims. Many variations in the presently preferred embodiments illustrated herein will be apparent to one of ordinary skill in the art, and remain within the scope of the appended claims and their equivalents.

EXAMPLES

The present invention will now be described in relation to several examples.

- The examples indicated below were synthesised according to the methods described subsequently. IC₅₀ values were determined as described below and are represented in the following table:

Example Number	USP19 IC ₅₀ activity	Example Number	USP19 IC ₅₀ activity	Example Number	USP19 IC ₅₀ activity	Example Number	USP19 IC ₅₀ activity
1	**	61	****	121	****	181	*
2	***	62	*	122	****	182	**
3	****	63	***	123	***	183	****
4	***	64	*	124	***	184	****

5	****	65	****	125	*	185	****
6	***	66	****	126	****	186	****
7	**	67	****	127	***	187	***
8	*	68	***	128	***	188	***
9	****	69	****	129	**	189	**
10	****	70	*	130	*	190	****
11	****	71	**	131	**	191	****
12	****	72	****	132	***	192	****
13	****	73	**	133	**	193	****
14	****	74	****	134	**	194	****
15	****	75	****	135	*	195	****
16	****	76	****	136	***	196	****
17	****	77	***	137	***	197	****
18	****	78	****	138	**	198	****
19	**	79	**	139	****	199	****
20	****	80	****	140	****	200	***
21	*	81	****	141	**	201	****
22	***	82	***	142	***	202	****
23	*	83	****	143	***	203	****
24	****	84	***	144	**	204	***
25	****	85	****	145	*		
26	***	86	****	146	*		
27	****	87	****	147	***		
28	****	88	***	148	**		
29	****	89	**	149	****		
30	**	90	****	150	****		
31	****	91	****	151	***		
32	***	92	***	152	****		
33	***	93	****	153	***		
34	****	94	****	154	**		
35	****	95	****	155	**		
36	***	96	***	156	**		
37	***	97	***	157	***		
38	***	98	****	158	****		
39	**	99	****	159	***		

40	****	100	****	160	****		
41	****	101	***	161	****		
42	***	102	****	162	***		
43	****	103	****	163	**		
44	****	104	****	164	****		
45	***	105	****	165	****		
46	****	106	****	166	***		
47	****	107	****	167	***		
48	****	108	***	168	****		
49	****	109	***	169	****		
50	****	110	***	170	***		
51	****	111	****	171	***		
52	****	112	****	172	**		
53	****	113	***	173	**		
54	****	114	**	174	*		
55	****	115	**	175	***		
56	****	116	**	176	****		
57	**	117	***	177	****		
58	****	118	**	178	***		
59	****	119	***	179	****		
60	***	120	****	180	****		

Table 4. USP19 inhibition by exemplified compounds. The USP19 inhibitory activities are classified as the following:

	****	***	**	*
USP19 IC ₅₀ [μM]	IC ₅₀ <0.01	0.01≤IC ₅₀ <0.1	0.1≤IC ₅₀ <1	1≤IC ₅₀ <10

5

USP19 activity was determined in a fluorescence polarisation (FP) homogeneous assay using the isopeptide Ubiquitin-Lys-TAMRA substrate (either AUB-101, Almac Sciences Scotland Limited, or U-558, Boston Biochem, both of which gave identical results). Full-length USP19 was purchased from Boston Biochem (E-576). Unless otherwise stated, all other reagents were purchased from Sigma. Enzymatic reactions were conducted in black flat bottom polystyrene 384-well plates (Nunc) and 30 μL total volume. USP19 (2.5 nM, 10

10

μL) was incubated in assay buffer (50 mM HEPES (pH 7.4), 150 mM NaCl, 5 mM DTT, 0.05% BSA (w/v), 0.05% CHAPS) in the presence or absence of inhibitor (10 μL). Inhibitors were stored as 10 mM DMSO stocks in an inert environment (low humidity, dark, low oxygen, rt) using the StoragePod® system (Roylan Developments) and serial dilutions were prepared in buffer just prior to the assay (from 200 μM to 2 pM, 8-18 data point curve). Following incubation at rt for 30 min, the enzymatic reactions were initiated by dispensing the Ub substrate (500 nM, 10 μL). FP was measured every 15 min over a period of 90 min (within the linear range of the assay) using a Synergy 4 plate reader (BioTek) exciting at 530 nm and measuring the amount of parallel and perpendicular light at 575 nm. The FP signal was subsequently normalised to the no compound control. Data were plotted and fitted, and the concentrations resulting in 50% inhibition (IC₅₀) were calculated using the non-linear regression curve fitting model using Prism (GraphPad). IC₅₀ values for the inhibitors of the invention are compiled in Table 4 and represent the average of at least two duplicate experiments.

15

Cellular target engagement using western blotting

Cells from a breast cancer cell line, a neuroblastoma cell line and a mouse skeletal muscle cell line were treated with a USP19 inhibitor compound (ADC-141) for 2 h, lysed (lysis buffer: 50 mM Tris pH 7.4; 150 mM NaCl; 5 mM MgCl₂; 0.5 mM EDTA; 0.5% NP-40; 10% glycerol; 2 mM DTT) and ubiquitin-propargylamine (Ub-PA; UbiQ) or ubiquitin-vinyl methyl ester (Ub-VME; Almac Sciences Scotland Limited) was then added. Samples were analysed by western blotting probing for USP19 (EC₅₀ determined by densitometry). In each cell line, the USP19 inhibitor compound showed good cell permeability and exhibited a low nanomolar EC₅₀. The results for each cell line are shown in Figure 4.

25

Kinetic solubility (KSol) assay

Test compounds (5 μL of 10 mM DMSO stock) were added to 245 μL of phosphate-buffered saline (PBS) buffer solution at pH 7.4 (Dulbecco A) in a MultiScreen® Solubility filter plate (Millipore) and mixed at 300 rpm at rt on a plate shaker for 90 min. Meanwhile 5-point calibration curves for each compound were established in a mixture of acetonitrile/PBS buffer (top concentration 200 μM). After filtration and matrix match, the calibration and assay plates were analysed on a BioTek Synergy 4 plate reader (240-400 nm). Final concentration of the test compound in the filtrate was calculated using the slope of the calibration curve.

35

Determination of intrinsic clearance in human/mouse/rat liver microsomes (HLM/MLM/RLM)

Test compounds (final concentration = 1 μ M; final DMSO concentration = 0.1%v/v) were incubated in 0.1 M PBS buffer solution at pH 7.4 (Dulbecco A) with human, mouse or rat liver microsomes (0.5 mg of protein/mL), as required, at 37 °C. Reactions were started by addition of NADPH in 0.1 M PBS buffer solution at pH 7.4 (Dulbecco A) (final concentration = 1 mM). 40 μ L aliquots were removed at 2, 5, 10, 15, 20, 30, 40, and 50 min time points. Reactions were quenched with 80 μ L of ice-cold methanol. Samples were subsequently frozen overnight, then centrifuged at 3500 rpm for 20 min at 4 °C. The supernatants were removed and transferred into analytical plates and analysed by LC/MS/MS.

LC/MS/MS method:

All samples were analysed on a Waters ACQUITY I-Class UPLC coupled to a Waters Xevo TQD mass spectrometer. A Waters BEH C18 column (2.1 x 50 mm, 1.7 μ m) was used and the mobile phases were water and methanol containing 0.1%v/v formic acid as a modifier.

Analysis was by multiple reaction monitoring and conditions were optimised for each test compound.

Data analyses:

From a plot of ln peak area against time, the gradient of the line was determined.

Subsequently, half-life and intrinsic clearance are calculated using the equations below:

Eliminated rate constant (k) = (- gradient)

$$\text{Half life } (t_{1/2}) \text{ (min)} = \frac{0.693}{k}$$

$$\text{Intrinsic Clearance } (CL_{\text{int}}) \text{ } (\mu\text{L/min/million cells}) = \frac{V \times 0.693}{t_{1/2}}$$

where V = Incubation volume (μ L)/number of cells

Cytochrome P450 (CYP) inhibition assay

CYP inhibition was assessed simultaneously for 5 major isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) using a commercially available mixture of the isoforms heterogeneously expressed in *E. coli* (Cypex). The method was adapted from Weaver R. *et al.*, *Drug Metab. Dispos.* (2003), 31, 955-966. Activity of each isoform was assessed by measuring the appearance of an isoform-specific metabolite using a selective and FDA accepted substrate for each isoform at a concentration around its published K_m . Test compounds were assayed over a range of 8 concentrations (half-log dilutions) typically in

the range of 50 µM to 0.023 µM final concentration. Test compounds at 4x the desired final concentration in 0.1 M PBS buffer solution at pH 7.4 (Dulbecco A) were incubated at 37 °C for 3 min with a 2x mixture of CYP isoforms and substrate mix. 4 mM NADPH solution in 0.1 M PBS buffer solution at pH 7.4 (Dulbecco A) was then added to start the reaction.

- 5 After 10 min incubation, the reaction was stopped by the addition of methanol containing an internal standard and 0.1%v/v formic acid. Metabolites for each CYP substrate were quantified by LC/MS/MS using a Waters ACQUITY I-Class coupled to a Waters Xevo TQD mass spectrometer. A Waters BEH C18 column (2.1 x 50 mm, 1.7 µm) was used and mobile phases were water and methanol containing 0.1%v/v formic acid as a modifier.
- 10 Analysis was by multiple reaction monitoring and conditions were optimised for each metabolite.

Data analyses:

- The CYP activities for test compounds at each concentration were converted to % of control activity (CA) and the log (concentration) vs activity was plotted and used to generate a pseudo-Hill plot. The slope and y axis intercept were used to calculate the IC₅₀ values for test compounds against each CYP isoform according to the following equation:
- 15

$$IC_{50} = 10^{\frac{\text{intercept}}{\text{slope}}}$$

20 hERG ion channel inhibition assay

- Test compounds were assayed at an external provider for human Ether-a-go-go-Related Gene (hERG) inhibition using the QPatch II (Sophion Bioscience) automated patch-clamp. Six-point concentration-response curves were generated with serial dilutions from a 100 µM maximum concentration of test compound to allow for IC₅₀ value determination after curve fitting. Each data point is plotted from a minimum of n = 3 cells.
- 25

In vivo activity

- The following data from an *in vivo* model demonstrates that a USP19 inhibitor can be used to treat muscle loss, to reduce fat deposition and to improve insulin sensitivity. These data demonstrate that compounds which potently inhibit USP19 activity can effectively treat muscular atrophy, obesity and/or insulin resistance.
- 30

Methods:

- To induce muscle wasting, a 1 cm segment of the sciatic nerve in the thigh was removed from mice (male C57bl/6 mice at 8-10 weeks of age; n=10 per group) under isoflurane
- 35

anaesthesia and analgesia with carprofen. A sham operation was carried out in the opposite leg as a control.

5 Mice were randomised into Vehicle or Test groups, with all animals weighed to ensure a similar mean weight in each group. ADC-141, a USP19 inhibitory compound at 75 mg/kg or Vehicle was administered i.p. twice daily starting from the evening post-operation.

10 Mice were sacrificed 14 days later. Fat pads, liver, gastrocnemius and tibialis anterior muscles were harvested. Tissue masses were measured in both groups.

To assess obesity and insulin resistance, a diet-induced obesity mouse model was used. The diet-induced obese (DIO) mouse is a well characterised model of obesity which exhibits increased adiposity, insulin resistance and glucose intolerance.

15 Male C57BL6/J mice were continuously provided with high-fat diet (D12451, 45% kcal as fat; Research Diets, New Jersey, USA) and filtered tap water *ad libitum* for the duration of the study. From day 0, mice were administered vehicle i.p. BID, USP19 inhibitor (ADC-141) i.p. BID at 5 mg/kg or 25 mg/kg, or positive control liraglutide 0.1 mg/kg s.c. BID.

20 Body weight was measured daily. On Day 13, body composition was be assessed by DEXA. On Day 15, fasting glucose and insulin levels were measured before and during an oral glucose tolerance test (OGTT) to assess improvements in glucose control. The OGTT was performed following an overnight fast. Hence, on Day 14 food (but not water) was removed beginning at approximately 16:45, immediately after the PM dose. An OGTT was performed the following morning (~16 h post fast). Mice were dosed with vehicle or test compound (starting at 08.45) to a timed schedule 30 min prior to the administration of the glucose challenge (2.0 g/kg p.o.). Blood samples were taken immediately prior to dosing (B1), immediately prior to glucose administration (B2) and 15, 30, 60 and 120 min after glucose administration.

30 ADC-141 is 1-(((S)-7-((R)-3-cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1H)-one, corresponding to exemplary compound 212 provided in WO2018/020242. Both ADC-141 and the compounds provided herein are shown to have USP19 inhibitory activity using the fluorescence polarisation assay described above. It is therefore expected that the USP19

35

inhibitor compounds provided herein will show levels of efficacy similar to that described below for ADC-141.

Results:

5 *Muscular atrophy*

As shown in Figure 1, mice receiving a USP19 inhibitor had a significantly lower loss of muscle mass in the tibialis anterior muscle compared to mice receiving vehicle only. The sparing of muscle atrophy was evident both in terms of percentage mass (Figure 1B) and absolute muscle mass (Figure 1C).

10

Muscle wasting was also reduced in the gastrocnemius muscle (Figure 2), though the trend did not reach significance. Again, mice receiving a USP19 inhibitor exhibited less muscle wasting both in terms of percentage mass (Figure 2B) and absolute muscle mass (Figure 2C).

15

These data demonstrate the pharmacological inhibition of USP19 *in vivo* can reduce muscular atrophy. The data indicate that pharmacological inhibition of USP19 will be especially effective at reducing muscle wasting as a result of inactivity, immobilisation or other disuse. On the basis of the results provided herein, pharmacological USP19 inhibition is also expected to be effective in treating muscular atrophy as a result of cachexia or sarcopenia.

20

Obesity

Figure 3A shows the mass of the epididymal fat pad in mice following 2 weeks of receiving a USP19 inhibitor or vehicle alone. As shown in Figure 3, mice which received the USP19 inhibitor had significantly smaller fat pads compared to vehicle treated mice.

25

Figure 3B shows an increase in liver mass in mice treated with a USP19 inhibitor. This is thought to be as a result of drug accumulation in the liver.

30

Figure 3C shows that mice receiving USP19 inhibitor exhibited a reduction in overall body weight gain when on a high-fat diet. Figures 3D and 3E show that this is due to a reduction in fat mass, but that lean body mass is preserved. DIO mice treated with USP19 inhibitor also exhibited a reduction in cumulative food intake compared to vehicle control mice.

35

The data shown in Figure 3 demonstrates that pharmacological inhibition of USP19 can reduce fat accumulation in a wild-type background. Gene knockout studies have described a possible association between USP19 and fat accumulation (Coyne E. *et al.*, *Diabetologia* (2019), 62, 136-146, incorporated herein by reference). However, acute or chronic
5 pharmacological inhibition of an enzyme does not always result in similar physiological outcomes to genetic ablation.

The *in vivo* pharmacological inhibition data provided herein demonstrate that compounds which potently inhibit USP19 activity can effectively treat obesity.

10

Insulin resistance

Figure 5 shows the results of an oral glucose tolerance test (OGTT) in mice with diet-induced obesity. Untreated mice exhibit the symptoms of insulin-resistance characterised by elevated plasma glucose and plasma insulin levels. Mice treated with a USP19 inhibitor
15 exhibit a dose-dependent improvement in OGTT response characterised by decreased plasma glucose and decreased plasma insulin.

The data shown in Figure 5 demonstrates that pharmacological inhibition of USP19 can reduce insulin resistance in a wild-type background. Gene knockout studies have also
20 described an association between USP19 and insulin sensitivity (Coyne E. *et al.*, *supra*). Coyne *et al.* describe an improvement in insulin sensitivity in USP19 knockout mice but, as noted above, it could not be assumed that the effects would translate to pharmacological inhibition of USP19 in wild-type subjects.

25 The data provided herein demonstrates that pharmacological inhibition of USP19 effectively treats insulin resistance.

The data presented herein demonstrates the therapeutic effects of pharmacological inhibition of USP19. Accordingly, the USP19 inhibitor compounds provided herein can
30 effectively treat muscular atrophy, obesity and/or insulin resistance.

EXPERIMENTAL SECTION

Abbreviations and Acronyms

AcOH: acetic acid; aq: aqueous; atm: atmosphere(s); Boc: *tert*-butoxycarbonyl; br: broad;
5 Cbz: carboxybenzyl; d: doublet (spectral); DCM: dichloromethane; Dess-Martin
periodinane: 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one; DIPEA:
diisopropylethylamine; DMF: *N,N*-dimethylformamide; DMS: dimethylsulfide; DMSO:
dimethylsulfoxide; dpm: dipivaloylmethanato; dppf: 1,1'-bis(diphenylphosphino)ferrocene;
EDA: ethane-1,2-diamine; equiv.: equivalents; EtOAc: ethyl acetate; EtOH: ethanol; ESI:
10 electrospray ionisation; h: hour(s); HATU: *N*[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-
b]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; hept:
heptet (spectral); HPLC: high pressure liquid chromatography; IPA: 2-propanol; LC: liquid
chromatography; LCMS: liquid chromatography mass spectrometry; M: molar; *m/z*: mass-
to-charge ratio; MeCN: acetonitrile; MeOH: methanol; min: minute(s); mmol: millimole(s);
15 MS: mass spectrometry; MTBE: methyl *tert*-butyl ether; m: multiplet (spectral); NBS: *N*-
bromosuccinimide; NMR: nuclear magnetic resonance; pent: pentet (spectral); ppm: parts
per million; q: quartet (spectral); R_T: retention time; rt: room temperature; s: singlet; SCX:
strong cation exchange; sept: septet (spectral); SFC: supercritical fluid chromatography;
TBAF: tetra-*n*-butylammonium fluoride; TBDMS: *tert*-butyldimethylsilyl; Teoc: 2-
20 (trimethylsilyl)ethoxycarbonyl; TFA: trifluoroacetic acid; THF: tetrahydrofuran; t: triplet; UV:
ultraviolet; v/v: volume per unit volume; wt%: weight percent; w/v: weight per unit volume;
w/w: weight per unit weight; XPhos-Pd-G2: chloro(2-dicyclohexylphosphino-2',4',6'-
triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II).

25 General Experimental Conditions

Solvents and reagents

Common organic solvents that were used in reactions (e.g. THF, DMF, DCM, and MeOH)
were purchased anhydrous from Sigma-Aldrich® in Sure/Seal™ bottles and were handled
30 appropriately under nitrogen. Water was deionised using an Elga PURELAB Option-Q. All
other solvents used (i.e. for work-up procedures and purification) were generally HPLC
grade and were used as supplied from various commercial sources. Unless otherwise
stated, all starting materials used were purchased from commercial suppliers and used as
supplied.

35

Automated synthesis

Automated experiments were carried out using a Synple 2 instrument. The system uses reagent cartridges that allow for the appropriate reactant(s) to be subjected to various synthetic reaction procedures (including *N*-heterocycle formation, reductive amination, Mitsunobu, amide formation, deoxyfluorination, Suzuki, among others) in an automated manner that includes reaction, work-up and purification steps to give the desired reaction products. The system gives good reproducibility and allows for modification of some reaction parameters (e.g. time and temperature).

10 *Microwave synthesis*

Microwave experiments were carried out using a Biotage Initiator™ Eight instrument. The system gives good reproducibility and control at temperature ranges from 60-250 °C and pressures of up to a maximum of 20 bar.

15 *Flash chromatography*

Purification of compounds by flash chromatography was achieved using a Biotage Isolera Four system. Unless otherwise stated, Biotage Sfär Silica D cartridge columns (10-340 g) or Grace GraceResolv cartridge columns (4-330 g) were used along with the stated solvent system and an appropriate solvent gradient depending on compound polarity. In the case of some more polar and basic compounds, Biotage Sfär KP-Amino D cartridge columns (11-28 g) were used.

NMR spectroscopy

¹H NMR spectra were recorded at ambient temperature using a Bruker Avance III (400 MHz) or Bruker Ascend (500 MHz) spectrometer. All chemical shifts (δ) are expressed in ppm. Residual solvent signals were used as an internal standard and the characteristic solvent peaks were corrected to the reference data outlined in *J. Org. Chem.*, 1997, 62, p7512-7515; in other cases, NMR solvents contained tetramethylsilane, which was used as an internal standard.

30

Liquid Chromatography Mass Spectrometry (LCMS)

Liquid Chromatography Mass Spectrometry (LCMS) experiments to determine retention times (*R*_T) and associated mass ions were performed using the following methods:

- 5 Method A: The system consisted of an Agilent Technologies 6140 single quadrupole mass spectrometer linked to an Agilent Technologies 1290 Infinity LC system with UV diode array detector and autosampler. The spectrometer consisted of a multimode ionization source (electrospray and atmospheric pressure chemical ionizations) operating in positive and negative ion mode. LCMS experiments were performed on each sample submitted using the following conditions: LC Column: Zorbax Eclipse Plus C18 RRHD, 1.8 μ m, 50 x 2.1 mm maintained at 40 °C. Mobile phases: A) 0.1% (v/v) formic acid in water; B) 0.1% (v/v) formic acid in MeCN.

<u>Gradient Time (min)</u>	<u>Flow (mL/min)</u>	<u>%A</u>	<u>%B</u>
0.00	1.0	95	5
1.80	1.0	0	100
2.20	1.0	0	100
2.21	1.0	95	5
2.50	1.0	95	5

10

- 15 Method B: The system consisted of an Agilent Technologies 6130 quadrupole mass spectrometer linked to an Agilent Technologies 1290 Infinity LC system with UV diode array detector and autosampler. The spectrometer consisted of an electrospray ionization source operating in positive and negative ion mode. LCMS experiments were performed on each sample submitted using the following conditions: LC Column: Agilent Eclipse Plus C18 RRHD, 1.8 μ m, 50 x 2.1 mm maintained at 40 °C. Mobile phases: A) 0.1% (v/v) formic acid in water; B) 0.1% (v/v) formic acid in MeCN.

<u>Gradient Time (min)</u>	<u>Flow (mL/min)</u>	<u>%A</u>	<u>%B</u>
0.00	0.5	80	20
1.80	0.5	0	100
2.20	0.5	0	100
2.50	0.5	80	20
3.00	0.5	80	20

- 20 Method C: The system consisted of a Waters ACQUITY QDa mass spectrometer linked to a Waters ACQUITY I-Class UPLC system with TUV detector. The spectrometer consisted of an electrospray ionization source operating in positive and negative ion mode. LCMS experiments were performed on each sample submitted using the following conditions: LC

Column: Zorbax Eclipse Plus C18 RRHD, 1.8 μ m, 50 x 2.1 mm maintained at 40 °C. Mobile phases: A) 0.1% (v/v) formic acid in water; B) 0.1% (v/v) formic acid in MeCN.

<u>Gradient Time (min)</u>	<u>Flow (mL/min)</u>	<u>%A</u>	<u>%B</u>
0.00	0.8	95	5
1.80	0.8	0	95
2.20	0.8	0	95
2.30	0.8	95	5
2.50	0.8	95	5

- 5 Method D: The system consisted of either an Agilent Technologies 1100 Series LC/MSD system with UV diode array detector and evaporative light scattering detector (DAD/ELSD) and Agilent LC/MSD VL (G1956A), SL (G1956B) mass spectrometer or an Agilent 1200 Series LC/MSD system with DAD/ELSD and Agilent LC/MSD SL (G6130A), SL (G6140A) mass spectrometer. All of the LCMS data were obtained using the atmospheric pressure
- 10 chemical ionization mode with positive and negative ion mode switching with a scan range of m/z 80-1000. LCMS experiments were performed on each sample submitted using the following conditions: LC Column: Zorbax SB-C18 RRHD, 1.8 μ m, 4.6 x 15 mm. Mobile phases: A) 0.1% (v/v) formic acid in water; B) 0.1% (v/v) formic acid in MeCN.

<u>Gradient Time (min)</u>	<u>Flow (mL/min)</u>	<u>%A</u>	<u>%B</u>
0.00	3.0	100	0
1.50	3.0	0	100
1.80	3.0	0	100
1.81	3.0	100	0

15

- Method E: The system consisted of Shimadzu Prominence HPLC/Applied Biosystem LCMS/MS API 2000 instruments. Spectrometer ionization technique: ESI using API source operating in positive ion mode. LCMS experiments were performed on each sample submitted using the following conditions: LC Column: XBridge C18, 5 μ m, 4.6 x 50 mm
- 20 maintained at 25 °C. Mobile phases: A) 10 mM ammonium acetate (aq); B) MeCN.

<u>Gradient Time (min)</u>	<u>Flow (mL/min)</u>	<u>%A</u>	<u>%B</u>
0.01	1.2	90	10
1.50	1.2	70	30

3.00	1.2	10	90
4.00	1.2	10	90
5.00	1.2	90	10

Method F: The system consisted of a Waters ACQUITY SQD 2 mass spectrometer linked to a Waters ACQUITY H-Class UPLC system with TUV detector. The spectrometer consisted of an electrospray ionization source operating in positive and negative ion mode.

- 5 LCMS experiments were performed on each sample submitted using the following conditions: LC Column: XBridge C18, 3.5 μ m, 3.0 x 50 mm maintained at 50 °C. Mobile phases: A) 5 mM ammonium acetate (aq); B) 5 mM ammonium acetate in 9:1 MeCN/water.

<u>Gradient Time (min)</u>	<u>Flow (mL/min)</u>	<u>%A</u>	<u>%B</u>
0.00	1.2	95	5
0.75	1.2	95	5
1.00	1.2	70	30
2.00	1.2	2	98
2.50	1.2	2	98
2.75	1.2	95	5
3.00	1.2	95	5

10 *Preparative High Pressure Liquid Chromatography*

The system consisted of an Agilent Technologies 6120 single quadrupole mass spectrometer linked to an Agilent Technologies 1200 Preparative LC system with multiple wavelength detector and autosampler. The mass spectrometer used a multimode ionization source (electrospray and atmospheric pressure chemical ionizations) operating in positive and negative ion mode. Fraction collection was mass-triggered (multimode positive and negative ion). Purification experiments, unless otherwise stated, were performed under basic conditions at an appropriate solvent gradient that was typically determined by the retention time found using an appropriate LCMS method. In cases where the basic conditions were unsuccessful, acidic conditions were employed.

20

Basic conditions: LC Column: Waters XBridge™ Prep C18 5 μ m OBD™ 30 x 100 mm column at rt. Mobile phase: A) 0.1% (v/v) ammonium hydroxide in water; B) 0.1% (v/v) ammonium hydroxide in 95:5, MeCN/water. Total experiment time was ca. 10 min and a generic method is shown:

<u>Gradient Time (min)</u>	<u>Flow (mL/min)</u>	<u>%A</u>	<u>%B</u>
0.00	20.0	50	50
3.00	20.0	12	88
5.00	20.0	12	88
7.00	20.0	0	100
8.0	20.0	0	100
8.20	20.0	50	50

Chiral separation of stereoisomers by supercritical fluid chromatography (SFC)

5 The separation of mixtures of stereoisomers was performed using the following general procedure. The mixture of stereoisomers was dissolved to 50 mg/mL in MeOH and purified by SFC under the stated conditions. Combined fractions of each of stereoisomer were evaporated to near dryness using a rotary evaporator, transferred into final vessels using DCM, which was removed under a stream of compressed air at 40 °C, before being stored in a vacuum oven at 40 °C and 5 mbar for 16 h.

10

Chiral separation of stereoisomers by HPLC

The separation of mixtures of stereoisomers was performed using the following general procedure. The mixture of stereoisomers was dissolved to 66 mg/mL in MeOH and purified by HPLC under the stated conditions. Combined fractions of each of stereoisomer were
15 evaporated to near dryness using a rotary evaporator, transferred into final vessels using MeOH, which was removed under a stream of compressed air at 35 °C, before being stored in a vacuum oven at 35 °C and 5 mbar for 16 h.

Chiral purity analysis

20 After chiral separation of mixtures of stereoisomers, each stereoisomer was analysed to determine chiral purity using appropriate analytical SFC or HPLC methods under the stated conditions.

Nomenclature

25 Unless otherwise indicated, the nomenclature of structures was determined using the 'Convert Structure to Name' function of ChemDraw Professional 21.0 (CambridgeSoft/PerkinElmer). Stereochemical configuration for the Examples was determined by inferring from the intermediate precursors used to prepare them for which

either the absolute stereochemistry was already known (i.e. commercial reagents) or it was inferred from previous work (e.g. WO 2022/200523 intermediates). In the cases where new intermediates were used, the relative potency of the enantiomeric pairs allowed for assignment by comparing with similar analogues from previous work. However, it should be noted that for some or all of the Examples herein, it may be the case that they have been assigned with the incorrect configuration due to an error in this process and therefore, it is possible that these compounds have the opposite configuration to that stated. In any case, the most potent stereoisomers are preferred and expressly included herein.

10 General procedures

General Procedure 1: Boc deprotection to free base

The Boc protected amine (1 equiv.) was dissolved in DCM. TFA or 4 M HCl in 1,4-dioxane was added (as stated). The reaction was stirred at rt for 1-24 h. The mixture was loaded onto a pre-equilibrated SCX-2 cartridge. The column was washed with a 4:1 mixture of DCM/MeOH and the basic compound was eluted using a 4:1 mixture of DCM/7 M NH₃ in MeOH. The ammoniacal fractions were concentrated *in vacuo* to give the desired product that was used directly in the next step or repurified under the stated conditions, as necessary.

General Procedure 2: Automated synthesis using Synple 2 for N-heterocycle formation

This procedure utilised the Synple 2 integrated console for "capsule-based automated organic synthesis" (*Chem. Sci.*, 2021, 12, 6977-6982) for the purpose of *N*-heterocycle formation using the Sn amine protocol (SnAP) chemistry (*Org. Lett.*, 2014, 16, 1236-1239).

The appropriate aldehyde and a stirring bar were placed in the reaction vial and the line cap was attached. The appropriate reagent cartridge was scanned to load the reaction procedure and conditions, placed into the cartridge holder and locked into place. The solvents used for the procedure were attached to the appropriate solvent lines: DCM (S1), hexafluoroisopropanol (S2), MeOH (S3), 35:65 diisopropylamine/THF (S4). Nitrogen flow was applied. The reaction procedure was started using the standard conditions (unless otherwise stated) by pressing "Start". At the end of the sequence, the resultant product solution was analysed by LCMS to determine if further purification (i.e. flash chromatography or preparative HPLC) was required. The solvents were removed *in vacuo* to give the desired product that was used directly in the next step or repurified under the stated conditions, as necessary.

General Procedure 3: Urea formation via a carbamoyl chloride intermediate

To a solution of triphosgene (0.3-0.6 equiv.) in MeCN at 0 °C was added pyridine or DIPEA (2-5 equiv.) and the solution stirred for 10 min. A solution of the appropriate first amine (1 equiv.) in MeCN was added and the reaction stirred while warming to rt for 1-24 h. The mixture was added to the appropriate second amine (1 equiv.) followed by addition of DIPEA (2-5 equiv.) and stirred for a further 1-24 h. Saturated NaHCO_{3(aq)} was added. The resulting mixture was extracted with DCM (x 3) using a phase separator, the combined organic phase was concentrated under reduced pressure, and the residue was purified by flash chromatography to give the desired product.

General Procedure 4: Trifluoroacetamide deprotection to free base

The appropriate trifluoroacetamide (1 equiv.) was dissolved in a 10:1 mixture of MeOH/water and potassium carbonate (5-10 equiv.) was added. The resulting mixture was stirred at rt or up to 50 °C for 1-18 h, as required. The solvents were removed *in vacuo* and the remaining residue was partitioned between DCM and water or DCM and saturated NaHCO_{3(aq)} solution, the resultant biphasic mixture was separated, the aqueous phase was extracted using further DCM (x 2), and the combined organic phase was concentrated *in vacuo*. [Alternatively, the reaction mixture was diluted with DCM and loaded onto a pre-equilibrated SCX-2 cartridge. The column was washed with a 4:1 mixture of DCM/MeOH and the basic compound was eluted using a 4:1 mixture of DCM/7 M NH₃ in MeOH. The ammoniacal fractions were concentrated *in vacuo*]. The residue was purified by flash chromatography to give the desired product.

General Procedure 5: HATU coupling

The appropriate amine (1 equiv.), carboxylic acid (1.0-1.5 equiv.) and HATU (1-1.5 equiv.) were dissolved in DCM and DIPEA (1-4 equiv.) was added. The reaction was stirred for 1-24 h, as required, before being quenched by the addition of saturated NaHCO_{3(aq)}. The resulting mixture was extracted with DCM (x 3) using a phase separator. The combined organic extracts were concentrated under reduced pressure and the remaining residue was purified by flash chromatography to give the desired product.

General Procedure 6: Carbamoyl chloride formation

To a stirred solution of triphosgene (1 equiv.) in DCM was added pyridine (10 equiv.) dropwise at 0 °C. After 30 min, a solution of the appropriate amine (1 equiv.) in DCM, or

amine salt (1 equiv.) and DIPEA (1.5 equiv.) in DCM, was added dropwise at 0 °C. The temperature was allowed to increase to rt and stirred for 1-18 h, as required. The reaction mixture was quenched by addition of 1 M HCl_(aq) and the resultant mixture was extracted with DCM (x 3) using a phase separator. The combined organic phase was concentrated *in vacuo* to give the desired product that was typically used in the next step without further purification.

General Procedure 7: Urea formation using a carbamoyl chloride intermediate

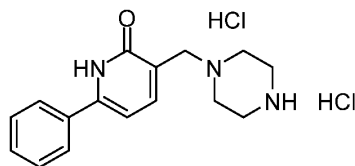
The appropriate carbamoyl chloride (1-2 equiv.), amine or amine.HCl salt (1-3 equiv.) and DIPEA (2-6 equiv.) were stirred in the stated solvent at rt for 1-18 h, as required, before quenching with 0.5 M HCl_(aq) and extracted with DCM (x 3) using a phase separator. The combined organic phases were concentrated *in vacuo* and the residue was purified by flash chromatography to give the desired product.

General Procedure 8: Reductive alkylation of amine

A solution of the amine (1 equiv.) and appropriate aldehyde or ketone (5 equiv.) in MeOH was stirred at rt. After 2 h, sodium triacetoxyborohydride (10 equiv.) was added. After a further 1 h, reaction progression was checked by LCMS. Depending on reaction progression, further portion(s) of aldehyde/ketone and sodium triacetoxyborohydride may be added until reaction completion. The reaction mixture was diluted with MeOH and loaded onto a pre-equilibrated SCX-2 cartridge. The column was washed with a 4:1 mixture of DCM/MeOH and the basic compound was eluted using a 4:1 mixture of DCM/7 M NH₃ in MeOH. The ammoniacal fractions were concentrated *in vacuo* and further purified by flash chromatography (typically 0-20% MeOH in DCM or 0-20% MeOH in EtOAc) to give the desired product.

General Procedure 9: Cbz deprotection to free base using H-Cube® Pro

The Cbz protected amine (e.g. 1.0 mmol) was dissolved in EtOAc (20 mL)/EtOH (20 mL) and the solution was passed through an H-Cube® Pro hydrogenation flow reactor containing a 10%w/w Pd/C cartridge with a flow rate of 1 mL/min at 60 °C and using the "controlled mode" setting for 1 bar of hydrogen. Reaction completion was determined by LCMS and the material was passed through the system again, if necessary, until complete reaction. The solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography to give the desired product.

Intermediate 1: 6-Phenyl-3-(piperazin-1-ylmethyl)pyridin-2(1H)-one dihydrochloride

Step 1: 3-(Hydroxymethyl)-6-phenylpyridin-2(1H)-one: To a solution of 2-oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid (53.3 g, 248 mmol) [commercially available] in THF (1200 mL) was added 1 M borane.DMS complex in THF solution (991 mL, 991 mmol), and the suspension was stirred at rt. After 18 h, MeOH was slowly added until gas evolution ceased. The reaction mixture was partitioned between EtOAc and brine, separated, the organic phase was dried (Na₂SO₄), filtered, and evaporated to dryness and purified by flash chromatography (0-5% MeOH in DCM) to give the title compound (33.1 g, 66%). LCMS (Method D): R_T = 0.69 min, *m/z* = 202 [M+H]⁺.

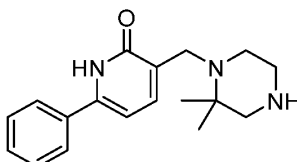
Step 2: 2-Oxo-6-phenyl-1,2-dihydropyridine-3-carbaldehyde: To a stirred solution of 3-(hydroxymethyl)-6-phenylpyridin-2(1H)-one (8.0 g, 40 mmol) in DCM (250 mL) at 0 °C was added Dess-Martin periodinane (22.0 g, 52 mmol). After 10 h, 2 M Na₂CO_{3(aq)} (300 mL) was added. After 2 h, the resultant precipitate was filtered and dried under vacuum to give the title compound (7.2 g, 90%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.61 (s, 1H), 10.14 (s, 1H), 8.05 – 7.96 (m, 4H), 7.70 (m, 1H), 7.55 (m, 1H), 6.80 (m, 1H).

Step 3: *tert*-Butyl 4-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)piperazine-1-carboxylate: To a stirred solution of 2-oxo-6-phenyl-1,2-dihydropyridine-3-carbaldehyde (1.5 g, 7.5 mmol) in DCM (50 mL) was added *tert*-butyl piperazine-1-carboxylate (2.1 g, 11.2 mmol) followed by sodium triacetoxyborohydride (4.8 g, 22.5 mmol). After 3 h, the reaction mixture was heated to 55 °C. After a further 10 h, saturated NaHCO_{3(aq)} (150 mL) was added with care and stirred for an additional 30 min. The resultant biphasic mixture was separated, the organic phase was dried (Na₂SO₄), filtered, evaporated to dryness, and purified by flash chromatography (0-5% MeOH in DCM) to give the title compound (1.6 g, 58%). LCMS (Method D): R_T = 0.85 min, *m/z* = 370 [M+H]⁺.

Step 4: 6-Phenyl-3-(piperazin-1-ylmethyl)pyridin-2(1H)-one dihydrochloride: Prepared according to General Procedure 1 using *tert*-butyl 4-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)piperazine-1-carboxylate (50.0 mg, 0.14 mmol), 4 M HCl in 1,4-dioxane (3 mL) and DCM (4 mL) but without SCX-2 purification to give the title compound (46.3 mg,

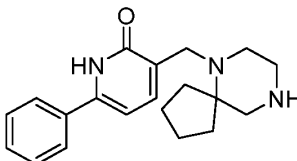
quantitative) [assumed dihydrochloride salt]. LCMS (Method A): $R_T = 0.41$ min, $m/z = 270$ $[M+H]^+$.

Intermediate 2: 3-((2,2-Dimethylpiperazin-1-yl)methyl)-6-phenylpyridin-2(1H)-one



5 The title compound was prepared similarly to 6-phenyl-3-(piperazin-1-ylmethyl)pyridin-2(1H)-one (Intermediate 1) except using *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate [commercially available] instead of *tert*-butyl piperazine-1-carboxylate (Step 3) and using TFA instead of 4 M HCl in 1,4-dioxane and including SCX-2 purification (Step 4) to give the
10 title compound as the free base. LCMS (Method A): $R_T = 0.44$ min, $m/z = 298$ $[M+H]^+$.

Intermediate 3: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1H)-one

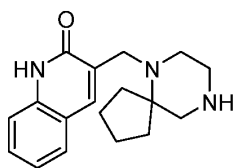


15 *Step 1: 3-(Chloromethyl)-6-phenylpyridin-2(1H)-one*: To a stirred solution of 3-(hydroxymethyl)-6-phenylpyridin-2(1H)-one (33.0 g, 165 mmol) in DCM (1200 mL) was added thionyl chloride (200 mL, 2.78 mol). The reaction mixture was heated to 40 °C. After 24 h, the volatiles were removed *in vacuo* using MeCN to assist with coevaporation to give the title compound (36.2 g, quantitative) that was used directly in the next step without purification.

20 *Step 2: tert-Butyl 6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)-methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate*: To a solution of 3-(chloromethyl)-6-phenylpyridin-2(1H)-one (8.5 g, 39 mmol) in MeCN (300 mL) was added DIPEA (15 g, 116 mmol) and *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate (9.3 g, 39 mmol) [commercially
25 available] and the suspension was stirred at 80 °C for 18 h. The reaction mixture was concentrated and partitioned between DCM and brine, separated, the organic phase was dried (Na_2SO_4), filtered, evaporated to dryness, and purified by flash chromatography (0-5% MeOH in DCM) to give the title compound (10.1 g, 61%). LCMS (Method D): $R_T = 0.64$ min, $m/z = 424$ $[M+H]^+$.

Step 3: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1H)-one: Prepared according to General Procedure 1 using *tert*-butyl 6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (100.0 mg, 0.24 mmol), TFA (1.1 mL) and anhydrous DCM (1 mL) to give the title compound (75.5 mg, 99%). LCMS (Method A): $R_T = 0.50$ min, $m/z = 324$ $[M+H]^+$.

Intermediate 4: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)quinolin-2(1H)-one



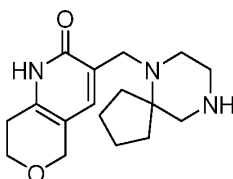
Step 1: *tert*-Butyl 6-((2-oxo-1,2-dihydroquinolin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate: To a solution of 2-oxo-1,2-dihydroquinoline-3-carbaldehyde [commercially available] (1.50 g, 8.7 mmol) in 1,2-dichloroethane (50 mL) was added *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate (3.10 g, 13.5 mmol) followed by portionwise addition of sodium triacetoxyborohydride (5.50 g, 26.1 mmol) and the suspension was stirred at 60 °C. After 18 h, the solvents were removed *in vacuo* and the remaining residue was partitioned between EtOAc and brine, and separated. The organic phase was washed using saturated $\text{NaHCO}_3(\text{aq})$, dried (Na_2SO_4), filtered, evaporated to dryness, and purified by flash chromatography (0-5% MeOH in DCM) to give the title compound (0.50 g, 14%). LCMS (Method D): $R_T = 0.75$ min, $m/z = 398$ $[M+H]^+$.

20

Step 2: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)quinolin-2(1H)-one: Prepared according to General Procedure 1 using *tert*-butyl 6-((2-oxo-1,2-dihydroquinolin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (100.0 mg, 0.25 mmol), TFA (0.5 mL) and anhydrous DCM (1 mL) to give the title compound (75.1 mg, quantitative). LCMS (Method A): $R_T = 0.47$ min, $m/z = 298$ $[M+H]^+$.

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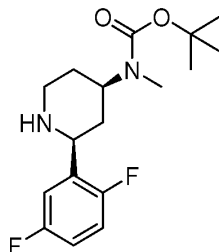
Intermediate 5: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1,5,7,8-tetrahydro-2H-pyrano[4,3-b]pyridin-2-one



Step 1: tert-Butyl 6-((2-oxo-1,5,7,8-tetrahydro-2H-pyrano[4,3-b]pyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate: To a solution of 2-oxo-2,5,7,8-tetrahydro-1H-pyrano[4,3-b]pyridine-3-carbaldehyde [commercially available] (0.50 g, 2.8 mmol) in 1,2-dichloroethane (30 mL) was added *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate (1.00 g, 4.2 mmol) followed by portionwise addition of sodium triacetoxyborohydride (1.80 g, 8.4 mmol) and the suspension was stirred at 60 °C. After 18 h, the solvents were removed *in vacuo* and the remaining residue was partitioned between EtOAc and brine, and separated. The organic phase was washed using saturated NaHCO_{3(aq)}, dried (Na₂SO₄), filtered, evaporated to dryness, and purified by flash chromatography (0-10% MeOH in DCM) to give the title compound (0.10 g, 9%). LCMS (Method D): R_T = 1.01 min, *m/z* = 404 [M+H]⁺.

Step 2: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1,5,7,8-tetrahydro-2H-pyrano[4,3-b]pyridin-2-one: Prepared according to General Procedure 1 using *tert*-butyl 6-((2-oxo-1,5,7,8-tetrahydro-2H-pyrano[4,3-b]pyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (100 mg, 0.25 mmol), TFA (0.5 mL) and DCM (1 mL) to give the title compound (30 mg, 40%). LCMS (Method B): R_T = 0.27 min (solvent front), *m/z* = 304 [M+H]⁺.

Intermediate 6: *tert*-Butyl ((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)(methyl)carbamate



Step 1: 2-(2,5-Difluorophenyl)isonicotinic acid: To a solution of methyl 2-bromoisonicotinate (250 g, 1.16 mol) and (2,5-difluorophenyl)boronic acid (200 g, 1.27 mol) in 1,4-dioxane (8.0 L) and water (2.6 L) was added Pd(dppf)Cl₂ (47.5 g, 5 mol%) and potassium phosphate tribasic (735 g, 3.46 mol). The reaction mixture was refluxed for 16 h and evaporated to dryness. The residue was dissolved in hot water (4 L) and filtered. The pH of the filtrate was adjusted to pH 3 using HCl_(aq), the precipitate was filtered, washed with water (2 L), and dried in a vacuum oven to give the title compound (260 g, 95%). LCMS (Method D): R_T = 1.15 min, *m/z* = 236 [M+H]⁺.

*Step 2: rac-(2*S*,4*R*)-2-(2,5-Difluorophenyl)piperidine-4-carboxylic acid:* To a well stirred suspension of 2-(2,5-difluorophenyl)isonicotinic acid (60.0 g, 0.255 mol) in MeOH (2.4 L)

was added 10% w/w Pd/C (6.0 g, 10%w/w) and the resultant mixture was reacted with hydrogen (50 atm) at 50 °C in an autoclave. After the reaction was complete (determined by ¹H NMR sampling of the reaction mixture to monitor for starting material consumption), the solvent was evaporated to dryness to give crude title compound (65.3 g, assumed
5 0.255 mol, contaminated with residual Pd/C catalyst) that was used in the next step without further purification.

Step 3: rac-(2S,4R)-1-((Benzyloxy)carbonyl)-2-(2,5-difluorophenyl)piperidine-4-carboxylic acid: To a suspension of *rac-(2S,4R)-2-(2,5-difluorophenyl)piperidine-4-carboxylic acid*
10 (284 g, assumed 1.11 mol, contaminated with Pd/C) in 1,4-dioxane (5.0 L) and water (2.5 L) added NaOH (221 g, 5.54 mol). The reaction mixture was cooled to 0 °C followed by dropwise addition of benzyl chloroformate (282 g, 1.66 mol). After 16 h, the resultant mixture was evaporated to dryness, the residue dissolved in water (5 L) and extracted using MTBE (2 L). The aqueous phase was made acidic (pH = 3) using HCl_(aq) and
15 extracted with ethyl acetate (3 L). The organic phase was dried (Na₂SO₄), filtered, and evaporated to dryness to give the title compound (313 g, 75.3%) as white solid. LCMS (Method D): R_T = 1.27 min, *m/z* = 374 [M-H]⁺.

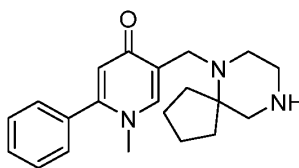
Step 4: rac-Benzyl (2S,4R)-2-(2,5-difluorophenyl)-4-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)piperidine-1-carboxylate: To a suspension of *rac-(2S,4R)-1-((benzyloxy)carbonyl)-2-(2,5-difluorophenyl)piperidine-4-carboxylic acid* (313 g,
20 0.834 mol) in toluene (4.0 L) was added triethylamine (253 g, 2.50 mol), followed by DPPA (298 g, 1.08 mol). The reaction mixture heated at 75 °C for 4 h until gas evolution ceased, followed by addition of 2-(trimethylsilyl)ethanol (296 g, 2.50 mol). The reaction mixture was
25 heated at 110 °C for 24 h. The reaction mixture was extracted using 15% w/v NaOH_(aq) (2 x 2 L), the organic phase was dried (Na₂SO₄), filtered, and evaporated to dryness to give the title compound (375 g, 92%). ¹H NMR (400 MHz, CDCl₃): δ 7.31 – 7.16 (m, 5H), 6.99 – 6.84 (m, 3H), 5.28 (m, 1H), 5.08 (m, 2H), 4.46 (m, 1H), 4.16 – 4.07 (m, 3H), 3.90 (m, 1H), 3.50 (m, 1H), 2.29 – 2.09 (m, 3H), 1.64 (m, 1H), 0.90 (m, 1H), 0.04 (s, 9H).

30
Step 5: rac-Benzyl (2S,4R)-4-((tert-butoxycarbonyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate: To a solution of *rac-benzyl (2S,4R)-2-(2,5-difluorophenyl)-4-(((2-(trimethylsilyl)ethoxy)carbonyl)amino)piperidine-1-carboxylate* (375 g, 0.764 mol) in THF (3.0 L) was added 1M TBAF in THF solution (2292 mL, 2.29 mol) and the resultant mixture
35 was heated at 55 °C for 48 h. The reaction mixture was concentrated *in vacuo*, the

- remaining residue was partitioned between EtOAc (3 L) and 15% w/v $\text{NH}_4\text{Cl}_{(\text{aq})}$ (2 L) and separated. The organic phase was washed using water (1 L) followed by brine (1 L), dried (Na_2SO_4), filtered, and the solvent was concentrated to dryness. The resultant crude *rac*-benzyl (2*S*,4*R*)-4-amino-2-(2,5-difluorophenyl)piperidine-1-carboxylate material was
- 5 dissolved in MeOH (2.5 L), cooled to 0 °C, and Boc_2O (200 g, 0.917 mol) was added dropwise at rt. After 24 h, the solvent was evaporated and the remaining residue was purified by flash chromatography (0-20% EtOAc in hexane) to give the title compound (250 g, 74%). LCMS (Method D): $R_T = 1.32$ min, $m/z = 347$ [M-Boc+H] $^+$.
- 10 *Step 6: rac-(2S,4R)-Benzyl 4-((tert-butoxycarbonyl)(methyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate*: To a stirred solution of *rac*-benzyl (2*S*,4*R*)-4-((tert-butoxycarbonyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate (25 g, 56 mmol) in DMF (200 mL) at 0 °C was added NaH (55% in mineral oil, 2.7 g, 61.7 mmol). After 3 h, iodomethane (9.6 g, 67.3 mmol) was added and the temperature was allowed to increase
- 15 to rt. After a further 24 h, the reaction mixture was partitioned between EtOAc (400 mL) and 15% w/v $\text{NH}_4\text{Cl}_{(\text{aq})}$ (500 mL), separated, the organic phase was washed with water (500 mL) and brine (500 mL), dried (Na_2SO_4), and the solvents were removed *in vacuo*. The remaining residue was purified by flash chromatography (0-20% EtOAc in hexane) to give the title compound (22.1 g, 86%). LCMS (Method D): $R_T = 1.61$ min, $m/z = 361$ [M-Boc+H] $^+$.
- 20 *Step 7: Benzyl (2S,4R)-4-((tert-butoxycarbonyl)(methyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate*: *rac*-(2*S*,4*R*)-benzyl 4-((tert-butoxycarbonyl)(methyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate (18.0 g) was resolved into the single stereoisomers by chiral HPLC using a CHIRALCEL® OJ-H (20 mm x 250 mm, 5 μm) column with isocratic solvent conditions: 90:5:5 hexane/IPA/MeOH. The first eluted material ($R_T = 16.12$ min) afforded the title compound (6.95 g). LCMS (Method D): $R_T = 1.61$ min, $m/z = 361$ [M-Boc+H] $^+$; and the second eluted material ($R_T = 24.90$ min) afforded benzyl (2*R*,4*S*)-4-((tert-butoxycarbonyl)(methyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate (7.74 g). LCMS (Method D): $R_T = 1.61$ min, $m/z =$
- 25 361 [M-Boc+H] $^+$.
- 30 *Step 8: tert-Butyl ((2S,4R)-2-(2,5-difluorophenyl)piperidin-4-yl)(methyl)carbamate*: Benzyl (2*S*,4*R*)-4-((tert-butoxycarbonyl)(methyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate (6.95 g, 15.1 mmol) was dissolved in MeOH (150 mL) and to this solution was
- 35 added 10%w/w Pd/C (0.7 g) and the reaction mixture was hydrogenated (~1 atm, balloon)

at rt. After 24 h, the reaction mixture was filtered through a pad of silica and evaporated to dryness to give the title compound (4.59 g, 93%). Chiral HPLC (CHIRALCEL® OJ-H (4.6 mm x 250 mm, 5 µm) column with isocratic solvent conditions: 95:2.5:2.5 hexane/IPA/MeOH): $R_T = 9.05$ min. LCMS (Method D): $R_T = 1.04$ min, $m/z = 327$ $[M+H]^+$.
5 $[\alpha]_D^{21} = +34.6$ (c 0.25 in $CHCl_3$).

Intermediate 7: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-phenylpyridin-4(1H)-one



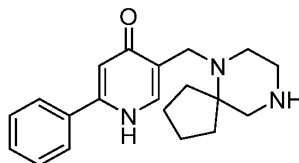
- 10 **Step 1: 5-(Hydroxymethyl)-2-phenylpyridin-4(1H)-one:** To a solution of ethyl 4-oxo-6-phenyl-1,4-dihydropyridine-3-carboxylate (30.4 g, 125 mmol) [prepared according to *Chem.Pharm.Bull.*, 1995, 43, p450-460] in THF (1100 mL) was added 1.0 M borane.DMS complex in THF solution (485 mL, 485 mmol), and the suspension was stirred at rt. After 18 h, MeOH was slowly added until gas evolution ceased. The resulting mixture was
- 15 partitioned between EtOAc and brine, and the organic layer was dried (Na_2SO_4). The solvents were removed under vacuum and the residue was purified by flash chromatography (0-10% EtOAc in hexane) to give the title compound (16.5 g, 66%). LCMS (Method D): $R_T = 0.59$ min, $m/z = 202$ $[M+H]^+$.
- 20 **Step 2: 5-(Chloromethyl)-2-phenylpyridin-4(1H)-one:** To a solution of 5-(hydroxymethyl)-2-phenylpyridin-4(1H)-one (16.3 g, 82 mmol) in DCM (600 mL) was added thionyl chloride (100 mL, 1.39 mol) and the suspension was stirred at 40 °C. After 24 h, the volatiles were removed *in vacuo* using MeCN to assist with coevaporation to give the title compound (18.0 g, quantitative) that was used directly in the next step without purification.
- 25 **Step 3: tert-Butyl 6-((4-oxo-6-phenyl-1,4-dihydropyridin-3-yl)-methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate:** To a solution of 5-(chloromethyl)-2-phenylpyridin-4(1H)-one (8.5 g, 39 mmol) in MeCN (300 mL) was added DIPEA (15 g, 116 mmol) and tert-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate (9.3 g, 39 mmol), and the resulting
- 30 suspension was stirred at 80 °C. After 24 h, the solvents were removed *in vacuo* and the remaining residue was partitioned between DCM and brine, separated, and the organic phase was dried (Na_2SO_4). The solvents were removed *in vacuo* and the residue was

purified by flash chromatography (0-5% MeOH in DCM) to give the title compound (11.4 g, 69%). LCMS (Method D): $R_T = 0.93$ min, $m/z = 424$ $[M+H]^+$.

5 *Step 4: tert-Butyl 6-((1-methyl-4-oxo-6-phenyl-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate*: To a solution of *tert*-butyl 6-((4-oxo-6-phenyl-1,4-dihydropyridin-3-yl)-methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (0.212 mg, 0.5 mmol) in DMF (2 mL) under argon was added sodium hydride (55% in mineral oil, 28 mg, 0.65 mmol). After 1 h, iodomethane (92 mg, 0.65 mmol) was added. After 4 h, the solvents were removed *in vacuo* and the residue was partitioned between DCM and brine, separated, and
10 the organic phase was dried (Na_2SO_4). The solvents were removed *in vacuo* and the remaining residue was purified by reversed phase preparative HPLC (C18 column) to give the title compound (11.4 g, 69%). LCMS (Method D): $R_T = 1.09$ min, $m/z = 438$ $[M+H]^+$.

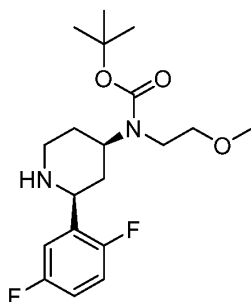
Step 5: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-phenylpyridin-4(1H)-one:
15 Prepared according to General Procedure 1 using *tert*-butyl 6-((1-methyl-4-oxo-6-phenyl-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (60.2 mg, 0.14 mmol), TFA (0.5 mL) and anhydrous DCM (1 mL) to give the title compound (49.5 mg, quantitative). LCMS (Method A): $R_T = 0.44$ min, $m/z = 338$ $[M+H]^+$.

20 Intermediate 8: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1H)-one



Prepared according to General Procedure 1 using *tert*-butyl 6-((4-oxo-6-phenyl-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (30 mg, 70.8 μmol), TFA (0.5 mL) and DCM (1 mL) to give the title compound (20 mg, 87%). LCMS (Method C):
25 $R_T = 0.43$ min, $m/z = 324$ $[M+H]^+$.

Intermediate 9: *tert*-Butyl ((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)(2-methoxyethyl)carbamate



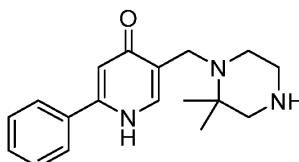
Step 1: *rac*-Benzyl (2*S*,4*R*)-4-((*tert*-butoxycarbonyl)(2-methoxyethyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate: To a solution of *rac*-benzyl (2*S*,4*R*)-4-((*tert*-butoxycarbonyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate (4.50 g, 10.2 mmol) in DMF (120 mL) at 0 °C was added sodium hydride (55% in mineral oil, 0.78 g, 13.3 mmol). After 3 h, 1-iodo-2-methoxyethane (4.20 g, 22.4 mmol) was added. After a further 24 h, the reaction mixture was partitioned between EtOAc (200 mL) and 15% NH₄Cl_(aq) (300 mL), and separated. The organic phase was washed using water (300 mL), followed by brine (300 mL) and was dried (Na₂SO₄). The solvents were removed *in vacuo* and the residue was purified by flash chromatography (0-40% CHCl₃ in hexane) to give the title compound (3.01 g, 59%). LCMS (Method D): R_T = 1.58 min, *m/z* = 405 [M-Boc+H]⁺.

Step 2: Benzyl (2*S*,4*R*)-4-((*tert*-butoxycarbonyl)(2-methoxyethyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate: *rac*-Benzyl (2*S*,4*R*)-4-((*tert*-butoxycarbonyl)(2-methoxyethyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate (2.98 g) was resolved into the single stereoisomers by chiral HPLC using a CHIRALPAK® AD-H (4.6 mm x 250 mm, 5 μm) column with isocratic solvent conditions: 95:2.5:2.5 hexane/IPA/MeOH. The first eluted material (R_T = 19.25 min) afforded the title compound (1.21 g). LCMS (Method D): R_T = 1.58 min, *m/z* = 405 [M-Boc+H]⁺; and the second eluted material (R_T = 25.65 min) afforded benzyl (2*R*,4*S*)-4-((*tert*-butoxycarbonyl)(2-methoxyethyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate (1.16 g). LCMS (Method D): R_T = 1.58 min, *m/z* = 405 [M-Boc+H]⁺.

Step 3: *tert*-Butyl ((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)(2-methoxyethyl)carbamate: Benzyl (2*S*,4*R*)-4-((*tert*-butoxycarbonyl)(2-methoxyethyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate (1.21 g, 2.4 mmol) was dissolved in MeOH (50 mL) and 10%w/w Pd/C (0.12 g) and the reaction mixture was hydrogenated (~1 atm, balloon) at rt. After 24 h, the reaction mixture was filtered through a pad of silica and evaporated to dryness to give the title compound (0.88 g, 99%). Chiral HPLC (CHIRALPAK® IC, 4.6 mm x

250 mm, 5 μ m) column with isocratic solvent conditions: 98:1:1 hexane (0.1% EDA)/IPA/MeOH): R_T = 7.12 min. LCMS (Method D): R_T = 1.12 min, m/z = 371 $[M+H]^+$.

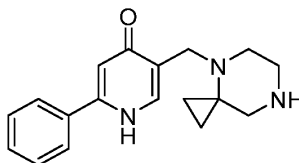
Intermediate 10: 5-((2,2-Dimethylpiperazin-1-yl)methyl)-2-phenylpyridin-4(1H)-one



5
Step 1: *tert*-Butyl 3,3-dimethyl-4-((4-oxo-6-phenyl-1,4-dihydropyridin-3-yl)methyl)piperazine-1-carboxylate: The title compound was prepared similarly to *tert*-butyl 6-((4-oxo-6-phenyl-1,4-dihydropyridin-3-yl)-methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (Intermediate 7, Steps 1 to 3) except using *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate instead of *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate. LCMS (Method D): R_T = 1.01 min, m/z = 398 $[M+H]^+$.

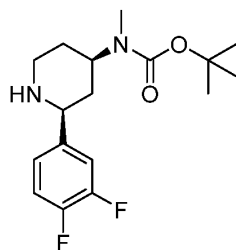
15
Step 2: 5-((2,2-Dimethylpiperazin-1-yl)methyl)-2-phenylpyridin-4(1H)-one: Prepared according to General Procedure 1 using *tert*-butyl 3,3-dimethyl-4-((4-oxo-6-phenyl-1,4-dihydropyridin-3-yl)methyl)piperazine-1-carboxylate (60.0 mg, 151 μ mol), TFA (0.13 mL) and DCM (2 mL) to give the title compound (44.0 mg, 98%). LCMS (Method A): R_T = 0.38 min, m/z = 298 $[M+H]^+$.

Intermediate 11: 5-((4,7-Diazaspiro[2.5]octan-4-yl)methyl)-2-phenylpyridin-4(1H)-one



20
The title compound was prepared similarly to 5-((2,2-dimethylpiperazin-1-yl)methyl)-2-phenylpyridin-4(1H)-one (Intermediate 10) except using *tert*-butyl 4,7-diazaspiro[2.5]octane-7-carboxylate [commercially available] instead of *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate to give the title compound. LCMS (Method A): R_T = 0.44 min, m/z = 296 $[M+H]^+$.

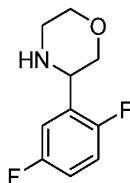
Intermediate 12: *tert*-Butyl ((2*S*,4*R*)-2-(3,4-difluorophenyl)piperidin-4-yl)(methyl)carbamate



The title compound was prepared similarly to *tert*-butyl ((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)(methyl)carbamate (Intermediate 6) except using (3,4-difluorophenyl)boronic acid instead of (2,5-difluorophenyl)boronic acid (Step 1) and a
 5 CHIRALPAK® AD-H (4.6 mm x 250 mm, 5 µm) column with isocratic solvent conditions: 70:15:15 hexane/IPA/MeOH for the chiral HPLC separation of enantiomers (Step 7) to give the title compound. Chiral HPLC (CHIRALPAK® AD-H (4.6 mm x 250 mm, 5 µm) column with isocratic solvent conditions: 5:5:90 hexane with 0.1%v/v EDA/IPA/MeOH): $R_T = 6.19$ min. LCMS (Method D): $R_T = 0.80$ min, $m/z = 327$ $[M+H]^+$. $[\alpha]_D^{21} = +25.3$ (c 0.50 in $CHCl_3$).

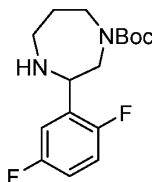
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Intermediate 13: 3-(2,5-difluorophenyl)morpholine



2,5-Difluorobenzaldehyde (0.05 mL, 0.50 mmol) was reacted using SnAP chemistry according to General Procedure 2 using the *N*-heterocycle formation "Morpholine" cartridge
 15 (H101) under the full sequence conditions (11 h) to afford material that required further purification by flash chromatography to give the title compound (35 mg, 35%) [assumed racemate, 1:1 mixture of enantiomers]. LCMS (Method A): $R_T = 0.42$ min, $m/z = 200$ $[M+H]^+$.

Intermediate 14: *tert*-Butyl 3-(2,5-difluorophenyl)-1,4-diazepane-1-carboxylate

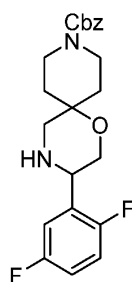


2,5-Difluorobenzaldehyde (0.05 mL, 0.50 mmol) was reacted using SnAP chemistry according to General Procedure 2 using the *N*-heterocycle formation "Diazepane" cartridge

(H106) under the full sequence conditions (11 h) to afford material that required further purification by flash chromatography to give the title compound (18 mg, 12%) [assumed racemate, 1:1 mixture of enantiomers]. LCMS (Method A): $R_T = 0.77$ min, $m/z = 257$ [M-butene+H]⁺.

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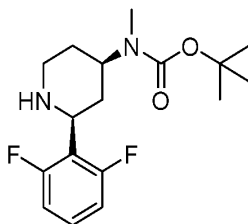
Intermediate 15: Benzyl 3-(2,5-difluorophenyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate



2,5-Difluorobenzaldehyde (0.05 mL, 0.50 mmol) was reacted using SnAP chemistry according to General Procedure 2 using the *N*-heterocycle formation “Morpholine-2-spiro-(4-Pip)” cartridge (H111) under the full sequence conditions (11 h) to afford material that required further purification by flash chromatography to give the title compound (66 mg, 33%) [assumed racemate, 1:1 mixture of enantiomers]. LCMS (Method A): $R_T = 0.91$ min, $m/z = 403$ [M+H]⁺.

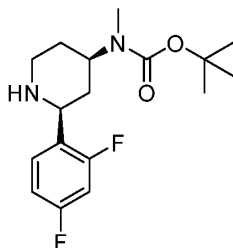
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Intermediate 16: *tert*-Butyl ((2*S*,4*R*)-2-(2,6-difluorophenyl)piperidin-4-yl)(methyl)carbamate

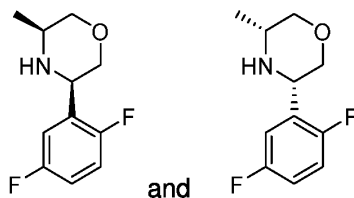


The title compound was prepared similarly to *tert*-butyl ((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)(methyl)carbamate (Intermediate 6) except using (2,6-difluorophenyl)boronic acid instead of (2,5-difluorophenyl)boronic acid (Step 1) and a CHIRALCEL® AD-H (4.6 mm x 250 mm, 5 μm) column with isocratic solvent conditions: 70:15:15 hexane/IPA/MeOH for the chiral HPLC separation of enantiomers (Step 7) to give the title compound. Chiral HPLC (CHIRALCEL® OJ-H (4.6 mm x 250 mm, 5 μm) column with isocratic solvent conditions: 90:5:5 hexane/IPA/MeOH): $R_T = 7.80$ min. LCMS (Method D): $R_T = 0.76$ min, $m/z = 327$ [M+H]⁺. $[\alpha]_D^{21} = +42.9$ (c 0.20 in CHCl₃).

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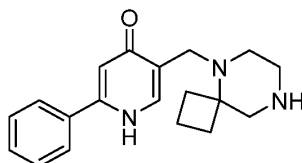
Intermediate 17: *tert*-Butyl ((2*S*,4*R*)-2-(2,4-difluorophenyl)piperidin-4-yl)(methyl)carbamate

The title compound was prepared similarly to *tert*-butyl ((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)(methyl)carbamate (Intermediate 6) except using (2,4-difluorophenyl)boronic acid instead of (2,5-difluorophenyl)boronic acid (Step 1) and a CHIRALPAK® IJ (4.6 mm x 250 mm, 5 μm) column with isocratic solvent conditions: 80:10:10 hexane/IPA/MeOH for the chiral HPLC separation of enantiomers (Step 7) to give the title compound. Chiral HPLC (CHIRALCEL® OD-H (4.6 mm x 250 mm, 5 μm) column with isocratic solvent conditions: 98:1:1 hexane/IPA/MeOH): $R_T = 6.39$ min. LCMS (Method D): $R_T = 1.07$ min, $m/z = 327$ $[M+H]^+$. $[\alpha]_D^{21} = +24.9$ (c 0.25 in $CHCl_3$).

Intermediate 18: *rac*-(3*R*,5*S*)-3-(2,5-Difluorophenyl)-5-methylmorpholine

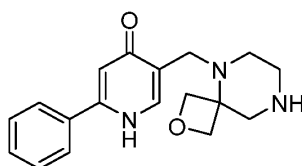
2,5-Difluorobenzaldehyde (0.05 mL, 0.50 mmol) was reacted using SnAP chemistry according to General Procedure 2 using the *N*-heterocycle formation “3-Methylmorpholine” cartridge (H107) under the full sequence conditions (11 h) to give the title compound (35 mg, 33%) that was used in the next step without further purification. LCMS (Method A): $R_T = 0.379$ min, $m/z = 214$ $[M+H]^+$. 1H NMR (500 MHz, $CDCl_3$): δ 7.31 (ddd, 1H), 6.97 (td, 1H), 6.93 – 6.87 (m, 1H), 4.37 – 4.30 (m, 1H), 3.89 (dd, 1H), 3.83 – 3.74 (m, 1H), 3.20 (t, 1H), 3.16 – 3.10 (m, 2H), 1.06 – 1.01 (m, 3H). [Note: NMR data suggested only *cis* stereoisomers present, i.e. no *trans* stereoisomers observed].

Intermediate 19: 5-((5,8-Diazaspiro[3.5]nonan-5-yl)methyl)-2-phenylpyridin-4(1*H*)-one



The title compound was prepared similarly to 5-((2,2-dimethylpiperazin-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one (Intermediate 10) except using *tert*-butyl 5,8-diazaspiro[3.5]nonane-8-carboxylate [commercially available] instead of *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate to give the title compound. LCMS (Method C): $R_T = 0.41$ min, $m/z = 310$ $[M+H]^+$.

Intermediate 20: 5-((2-Oxa-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-2-phenylpyridin-4(1*H*)-one

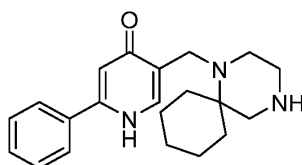


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The title compound was prepared similarly to 5-((2,2-dimethylpiperazin-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one (Intermediate 10) except using *tert*-butyl 2-oxa-5,8-diazaspiro[3.5]nonane-8-carboxylate [commercially available] instead of *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate to give the title compound. LCMS (Method C): $R_T = 0.42$ min, $m/z = 312$ $[M+H]^+$.

15

Intermediate 21: 5-((1,4-Diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one

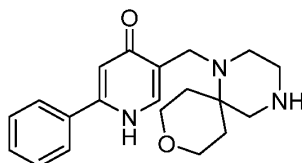


The title compound was prepared similarly to 5-((2,2-dimethylpiperazin-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one (Intermediate 10) except using *tert*-butyl 1,4-diazaspiro[5.5]undecane-4-carboxylate [commercially available] instead of *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate to give the title compound. LCMS (Method C): $R_T = 0.47$ min, $m/z = 338$ $[M+H]^+$.

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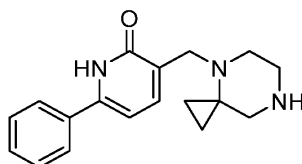
Intermediate 22: 5-((9-Oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one

25



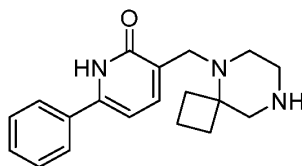
The title compound was prepared similarly to 5-((2,2-dimethylpiperazin-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one (Intermediate 10) except using *tert*-butyl 9-oxa-1,4-diazaspiro[5.5]undecane-4-carboxylate [commercially available] instead of *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate to give the title compound. LCMS (Method C): $R_T = 0.42$ min, $m/z = 340$ $[M+H]^+$.

Intermediate 23: 3-((4,7-Diazaspiro[2.5]octan-4-yl)methyl)-6-phenylpyridin-2(1*H*)-one



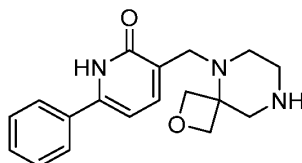
The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (Intermediate 3) except using *tert*-butyl 4,7-diazaspiro[2.5]octane-7-carboxylate [commercially available] instead of *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate to give the title compound. LCMS (Method C): $R_T = 0.58$ min, $m/z = 296$ $[M+H]^+$.

Intermediate 24: 3-((5,8-Diazaspiro[3.5]nonan-5-yl)methyl)-6-phenylpyridin-2(1*H*)-one



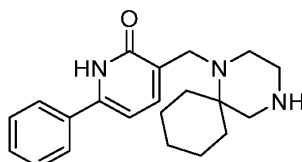
The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (Intermediate 3) except using *tert*-butyl 5,8-diazaspiro[3.5]nonane-8-carboxylate [commercially available] instead of *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate to give the title compound. LCMS (Method C): $R_T = 0.50$ min, $m/z = 310$ $[M+H]^+$.

Intermediate 25: 3-((2-Oxa-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-6-phenylpyridin-2(1*H*)-one



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (Intermediate 3) except using *tert*-butyl 2-oxa-5,8-diazaspiro[3.5]nonane-8-carboxylate [commercially available] instead of *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate to give the title compound. LCMS (Method C): R_T = 0.55 min, m/z = 312 $[M+H]^+$.

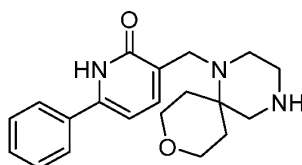
Intermediate 26: 3-((1,4-Diazaspiro[5.5]undecan-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (Intermediate 3) except using *tert*-butyl 1,4-diazaspiro[5.5]undecane-4-carboxylate [commercially available] instead of *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate to give the title compound. LCMS (Method C): R_T = 0.55 min, m/z = 338 $[M+H]^+$.

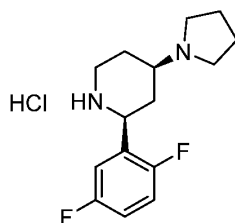
15

Intermediate 27: 3-((9-Oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (Intermediate 3) except using *tert*-butyl 9-oxa-1,4-diazaspiro[5.5]undecane-4-carboxylate [commercially available] instead of *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate to give the title compound. LCMS (Method C): R_T = 0.55 min, m/z = 340 $[M+H]^+$.

25 Intermediate 28: (2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(pyrrolidin-1-yl)piperidine hydrochloride

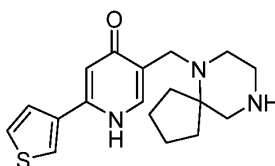


Step 1: *tert*-Butyl (2*S*)-2-(2,5-difluorophenyl)-4-(pyrrolidin-1-yl)piperidine-1-carboxylate: To a stirred solution of *tert*-butyl (2*S*)-2-(2,5-difluorophenyl)-4-oxopiperidine-1-carboxylate (1.5 g, 4.82 mmol) [prepared according to WO2022200523 Intermediate 19, Step 5] in MeOH (10 mL) were added acetic acid (3 drops) and pyrrolidine (0.6 mL, 7.23 mmol) at rt. After 2 h, NaBH₃CN (0.9 g, 14.5 mmol) was added. After a further 16 h, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography to give the title compound (1.6 g, 91%). LCMS (Method E): R_T = 3.15 min, *m/z* = 367 [M+H]⁺.

Step 2: *tert*-Butyl (2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(pyrrolidin-1-yl)piperidine-1-carboxylate: *tert*-Butyl (2*S*)-2-(2,5-difluorophenyl)-4-(pyrrolidin-1-yl)piperidine-1-carboxylate (1.6 g) was separated into the single stereoisomers by reversed phase preparative HPLC (C18 column) to give *tert*-butyl (2*S*,4*S*)-2-(2,5-difluorophenyl)-4-(pyrrolidin-1-yl)piperidine-1-carboxylate (first eluting isomer: 200 mg). LCMS (Method E): R_T = 3.15 min, *m/z* = 367 [M+H]⁺; and the title compound (second eluting isomer: 750 mg). LCMS (Method E): R_T = 3.15 min, *m/z* = 367 [M+H]⁺.

Step 3: (2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(pyrrolidin-1-yl)piperidine hydrochloride: To a stirred solution of *tert*-butyl (2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(pyrrolidin-1-yl)piperidine-1-carboxylate (890 mg 2.43 mmol) in DCM (10 mL) was added 4 M HCl in 1,4-dioxane (6 mL) at rt. After 3 h, the solvent was evaporated under reduced pressure and residue was triturated with DCM and pentane followed by lyophilization to yield the title compound (770 mg, quantitative). LCMS (Method E): R_T = 1.26 min, *m/z* = 267 [M+H]⁺.

Intermediate 29: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one



Step 1: Methyl 4-oxo-6-(thiophen-3-yl)-1,4-dihydropyridine-3-carboxylate: To a solution of (Z)-ethyl 2-(aminomethylene)-3-oxobutanoate (13.6 g, 87 mmol) in THF (400 mL) was added sodium hydride (55% in mineral oil, 10.0 g, 226 mmol) at 0 °C under argon atmosphere. After 1 h, methyl thiophene-3-carboxylate (25.0 g, 174 mmol) was slowly added and the resultant mixture was stirred at 60 °C. After 4 h, the solvents were removed *in vacuo* and the residue was dissolved in anhydrous MeOH (300 mL) followed by dropwise addition of thionyl chloride (31 g, 261 mmol). The reaction mixture was refluxed for 10 h. The solvents were removed *in vacuo* and the residue was partitioned between DCM and saturated NaHCO_{3(aq)}. The resultant biphasic mixture was separated, the organic layer was dried (Na₂SO₄), the solvents were removed *in vacuo*, and the residue was purified by flash chromatography (0-10% EtOAc in hexane) to give the title compound (7.1 g, 34%). LCMS (Method D): R_T = 0.70 min, *m/z* = 236 [M+H]⁺.

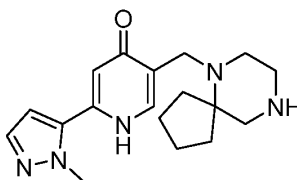
Step 2: 5-(Hydroxymethyl)-2-(thiophen-3-yl)pyridin-4(1H)-one: To a stirred solution of methyl 4-oxo-6-(thiophen-3-yl)-1,4-dihydropyridine-3-carboxylate (6.6 g, 28 mmol) in THF (250 mL) was added borane.DMS complex (6.4 g, 84 mmol) at rt. After 30 h, MeOH was slowly added until gas evolution ceased, the solvents were removed *in vacuo* using further MeOH to assist with coevaporation to give the title compound (5.8 g, quantitative). LCMS (Method D): R_T = 0.51 min, *m/z* = 208 [M+H]⁺.

Step 3: 5-(Chloromethyl)-2-(thiophen-3-yl)pyridin-4(1H)-one: To a stirred solution of 5-(hydroxymethyl)-2-(thiophen-3-yl)pyridin-4(1H)-one (6.0 g, 29 mmol) in DCM (200 mL) was added thionyl chloride (40 mL, 0.55 mol) at 40 °C. After 24 h, the solvents were removed *in vacuo* using MeCN to assist with coevaporation to give the title compound (6.5 g, quantitative) that was used directly in the next step without further purification.

Step 4: tert-Butyl 6-((4-oxo-6-(thiophen-3-yl)-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate: To a solution of 5-(chloromethyl)-2-(thiophen-3-yl)pyridin-4(1H)-one (2.1 g, 9.3 mmol) in MeCN (90 mL) was added DIPEA (3.6 g, 28 mmol) and *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate (2.7 g, 11 mmol) and the suspension was stirred at 80 °C. After 24 h, the solvents were removed *in vacuo* and the residue was partitioned between DCM and brine, separated, the organic phase was dried (Na₂SO₄), the solvents were removed *in vacuo*, and the residue was purified by flash chromatography (0-5% MeOH in DCM) to give the title compound (1.9 g, 47%). LCMS (Method D): R_T = 0.85 min, *m/z* = 430 [M+H]⁺.

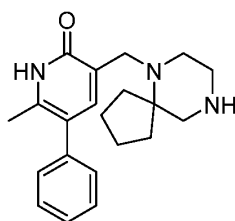
Step 5: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1H)-one:

Prepared according to General Procedure 1 using *tert*-butyl 6-((4-oxo-6-(thiophen-3-yl)-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carboxylate (60 mg, 140 μ mol),
 5 TFA (0.3 mL) and DCM (1.5 mL) to give the title compound (46.0 mg, quantitative). LCMS (Method A): R_T = 0.42 min, m/z = 330 $[M+H]^+$.

Intermediate 30: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(1-methyl-1H-pyrazol-5-yl)pyridin-4(1H)-one

10

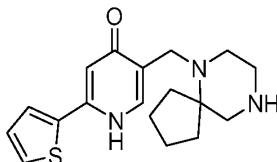
The title compound was prepared similarly to 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1H)-one (Intermediate 29) except using methyl 1-methyl-1H-pyrazole-5-carboxylate instead of methyl thiophene-3-carboxylate to give the title compound (via *tert*-butyl 6-((6-(1-methyl-1H-pyrazol-5-yl)-4-oxo-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carboxylate). LCMS (Method A): R_T = 0.34 min, m/z = 328 $[M+H]^+$.
 15

Intermediate 31: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-methyl-5-phenylpyridin-2(1H)-one

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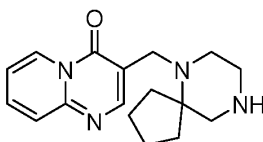
The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1H)-one (Intermediate 3) except using 3-(hydroxymethyl)-6-methyl-5-phenylpyridin-2(1H)-one (prepared similarly to 3-(hydroxymethyl)-6-phenylpyridin-2(1H)-one except using 6-methyl-2-oxo-5-phenyl-1,2-dihydropyridine-3-carboxylic acid [commercially available] instead of 2-oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid) instead of 3-(hydroxymethyl)-6-phenylpyridin-2(1H)-one to give the title compound. LCMS (Method A): R_T = 0.57 min, m/z = 338 $[M+H]^+$.
 25

Intermediate 32: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-2-yl)pyridin-4(1H)-one



- 5 The title compound was prepared similarly to 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1H)-one (Intermediate 29) except using methyl thiophene-2-carboxylate instead of methyl thiophene-3-carboxylate to give the title compound. LCMS (Method A): $R_T = 0.43$ min, $m/z = 330$ $[M+H]^+$.

10 Intermediate 33: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-4H-pyrido[1,2-a]pyrimidin-4-one



- Step 1: 3-Bromo-4H-pyrido[1,2-a]pyrimidin-4-one:* To a stirred solution of 4H-pyrido[1,2-a]pyrimidin-4-one (6.00 g, 41 mmol) [commercially available] in DCM (200 mL) was added NBS (8.05 g, 45 mmol, 1.1 eq.) portionwise at rt. After 10 h, 1 M sodium carbonate (aq) solution (150 mL) was added. After a further 2 h, the biphasic mixture was separated, the organic phase was dried (Na_2SO_4), and the solvents were removed *in vacuo* to give the title compound (6.2 g, 69%). ^1H NMR (400 MHz, CDCl_3): δ 9.07 (d, 1H), 8.55 (s, 1H), 7.78 (t, 1H), 7.67 (d, 1H), 7.22 (t, 1H).

- 20 *Step 2: 3-(Hydroxymethyl)-4H-pyrido[1,2-a]pyrimidin-4-one:* To a stirred solution of 3-bromo-4H-pyrido[1,2-a]pyrimidin-4-one (4.40 g, 19 mmol) in 1,4-dioxane (250 mL) was added tributylstannylmethanol (9.25 g, 29 mmol) and XPhos-Pd-G2 (1.62 g, 2.0 mmol). The reaction mixture degassed and back-filled with argon and then heated at 100 °C. After 48 h, the solvents were removed *in vacuo* and the residue was triturated using diethyl ether
25 (150 mL) and filtered to give the crude title compound (3.2 g, 68%) [contaminated with 4H-pyrido[1,2-a]pyrimidin-4-one]. LCMS (Method D): $R_T = 0.43$ min, $m/z = 177$ $[M+H]^+$.

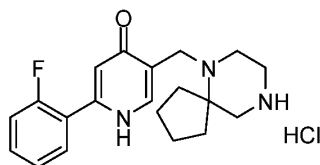
Step 3: 3-(Chloromethyl)-4H-pyrido[1,2-a]pyrimidin-4-one: To a stirred solution of 3-(hydroxymethyl)-4H-pyrido[1,2-a]pyrimidin-4-one (3.0 g, 17 mmol) in DCM (200 mL) was

added thionyl chloride (40 mL, 0.55 mol) at 40 °C. After 24 h, the solvents were removed *in vacuo* using MeCN to assist with coevaporation to give the title compound (3.2 g, quantitative) that was used directly in the next step without further purification.

- 5 **Step 4: *tert*-Butyl 6-((4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carboxylate:** To a stirred solution of 3-(chloromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (3.0 g, 16 mmol) in MeCN (150 mL) was added DIPEA (6.2 g, 48 mmol) and *tert*-butyl 6,9-diazaspiro[4.5]decan-9-carboxylate (3.4 g, 16 mmol) at 80 °C. After 18 h, solvents were removed *in vacuo* and the residue partitioned between DCM and
10 brine, and separated. The organic phase was dried (Na₂SO₄), the solvents were removed *in vacuo* and the residue was purified by flash chromatography (0-5% MeOH in DCM) to give the title compound (1.1 g, 27%). LCMS (Method D): R_T = 0.81 min, *m/z* = 399 [M+H]⁺.

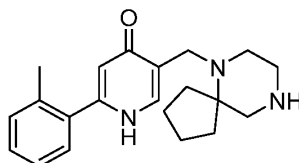
- Step 5: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one:**
15 Prepared according to General Procedure 1 using *tert*-butyl 6-((4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carboxylate (120 mg, 300 μmol), TFA (0.7 mL) and DCM (1.5 mL) to give the title compound (85.0 mg, 95%). LCMS (Method A): R_T = 0.41 min, *m/z* = 299 [M+H]⁺.

- 20 Intermediate 34: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(2-fluorophenyl)pyridin-4(1*H*)-one hydrochloride



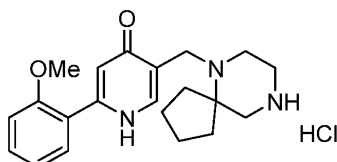
- The title compound was prepared similarly to 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one (Intermediate 29) except using methyl 2-fluorobenzoate
25 instead of methyl thiophene-3-carboxylate in Step 1 and using 4M HCl in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in Step 5 to give the title compound. LCMS (Method A): R_T = 0.43 min, *m/z* = 342 [M+H]⁺.

Intermediate 35: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(*o*-tolyl)pyridin-4(1*H*)-one



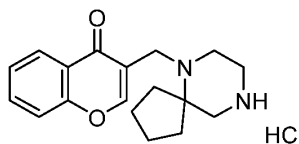
The title compound was prepared similarly to 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one (Intermediate 29) except using methyl 2-methylbenzoate instead of methyl thiophene-3-carboxylate to give the title compound. LCMS (Method A): R_T = 0.45 min, m/z = 338 $[M+H]^+$.

Intermediate 36: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(2-methoxyphenyl)pyridin-4(1*H*)-one hydrochloride



The title compound was prepared similarly to 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one (Intermediate 29) except using methyl 2-methoxybenzoate instead of methyl thiophene-3-carboxylate in Step 1 and using 4M HCl in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in Step 5 to give the title compound. LCMS (Method A): R_T = 0.55 min, m/z = 354 $[M+H]^+$. [Note: In Step 4, a 2:1 mixture of *tert*-butyl 6-((6-(2-methoxyphenyl)-4-oxo-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate/*tert*-butyl 6-((6-(2-hydroxyphenyl)-4-oxo-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate was obtained that required RP preparative HPLC purification].

Intermediate 37: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-4*H*-chromen-4-one hydrochloride



Step 1: 3-(Hydroxymethyl)-4*H*-chromen-4-one: To a stirred solution of 4-oxo-4*H*-chromene-3-carbaldehyde (500 mg, 2.87 mmol) [commercially available] in DCM (12 mL) was added NaBH(OAc)₃ (1.80 g, 8.61 mmol) at 0 °C and the resultant mixture was allowed to warm to rt. After 16 h, the reaction mixture was diluted with water and extracted with DCM (2 x 100

mL). The combined organic phase was washed with brine (100 mL), dried (Na_2SO_4), solvents were removed *in vacuo*, and the remaining residue was purified by flash chromatography (0-50% EtOAc in hexane) to give the title compound (300 mg, 59%). LCMS (Method E): $R_T = 2.07$ min, $m/z = 177$ $[\text{M}+\text{H}]^+$.

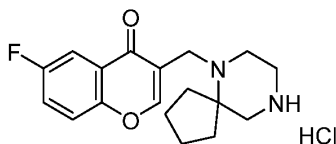
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Step 2: 3-(Chloromethyl)-4H-chromen-4-one: To a stirred solution of 3-(hydroxymethyl)-4H-chromen-4-one (1.00 g, 5.67 mmol) in DCM (20 mL) was added dropwise SOCl_2 (1.2 mL, 17.0 mmol) at 0 °C and the resultant mixture was allowed to warm to rt. After 3 h, the reaction mixture was diluted with water and extracted with DCM (2 x 200 mL). The combined organic phase was washed with brine (200 mL), dried (Na_2SO_4) and the solvents were removed *in vacuo* to give the title compound (640 mg, 58%) which was used next step without further purification. LCMS (Method E): $R_T = 2.93$ min, $m/z = 195$ $[\text{M}+\text{H}]^+$.

Step 3: tert-Butyl 6-((4-oxo-4H-chromen-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate: To a stirred of 3-(chloromethyl)-4H-chromen-4-one (640 mg, 3.28 mmol) in MeCN (20 mL) were added *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate (869 mg, 3.61 mmol) followed by addition of Cs_2CO_3 (2.10 g, 6.57 mmol) at rt. The resultant mixture was heated to 90 °C. After 3 h, the reaction mixture was filtered through Celite®, the filtrate was evaporated under reduced pressure and the remaining residue was purified by flash chromatography (0-30% EtOAc in hexane) to give the title compound (900 mg, 69%). LCMS (Method E): $R_T = 10.22$ min, $m/z = 399$ $[\text{M}+\text{H}]^+$.

Step 4: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-4H-chromen-4-one hydrochloride: Prepared according to General Procedure 1 using *tert*-butyl 6-((4-oxo-4H-chromen-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (60.0 mg, 151 μmol), 4M HCl in 1,4-dioxane (0.38 mL) and 1,4-dioxane (1 mL) and omitting the SCX-2 purification to give the title compound (50 mg, 99%). LCMS (Method A): $R_T = 0.56$ min, $m/z = 299$ $[\text{M}+\text{H}]^+$.

Intermediate 38: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-4H-chromen-4-one hydrochloride

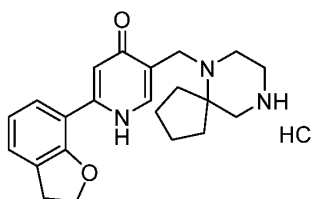


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The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-chromen-4-one hydrochloride (Intermediate 37) except using 6-fluoro-4-oxo-4*H*-chromene-3-carbaldehyde instead of 4-oxo-4*H*-chromene-3-carbaldehyde to give the title compound. LCMS (Method A): $R_T = 0.62$ min, $m/z = 317$ $[M+H]^+$.

5

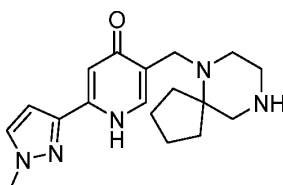
Intermediate 39: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(2,3-dihydrobenzofuran-7-yl)pyridin-4(1*H*)-one hydrochloride



The title compound was prepared similarly to 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one (Intermediate 29) except using methyl 2,3-dihydrobenzofuran-7-carboxylate instead of methyl thiophene-3-carboxylate in Step 1 and using 4M HCl in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in Step 5 to give the title compound. LCMS (Method A): $R_T = 0.59$ min, $m/z = 366$ $[M+H]^+$.

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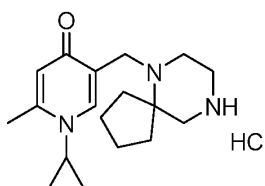
Intermediate 40: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(1-methyl-1*H*-pyrazol-3-yl)pyridin-4(1*H*)-one



The title compound was prepared similarly to 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one (Intermediate 29) except using methyl 1-methyl-1*H*-pyrazole-3-carboxylate instead of methyl thiophene-3-carboxylate to give the title compound. LCMS (Method A): $R_T = 0.38$ min, $m/z = 328$ $[M+H]^+$.

Intermediate 41: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1-cyclopropyl-2-methylpyridin-4(1*H*)-one hydrochloride

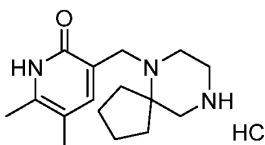
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The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (Intermediate 3) except using 1-cyclopropyl-5-(hydroxymethyl)-2-methylpyridin-4(1*H*)-one (prepared similarly to 3-(hydroxymethyl)-6-phenylpyridin-2(1*H*)-one except using 1-cyclopropyl-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid [commercially available] instead of 2-oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid) instead of 3-(hydroxymethyl)-6-phenylpyridin-2(1*H*)-one and using 4M HCl in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in the final step to give the title compound. LCMS (Method A): $R_T = 0.34$ min, $m/z = 302$ $[M+H]^+$.

10

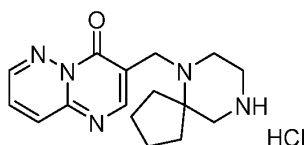
Intermediate 42: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-5,6-dimethylpyridin-2(1*H*)-one hydrochloride



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (Intermediate 3) except using 3-(hydroxymethyl)-5,6-dimethylpyridin-2(1*H*)-one (prepared similarly to 3-(hydroxymethyl)-6-phenylpyridin-2(1*H*)-one except using 5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid [commercially available] instead of 2-oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid) instead of 3-(hydroxymethyl)-6-phenylpyridin-2(1*H*)-one and using 4M HCl in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in the final step to give the title compound. LCMS (Method A): $R_T = 0.36$ min, $m/z = 276$ $[M+H]^+$.

20

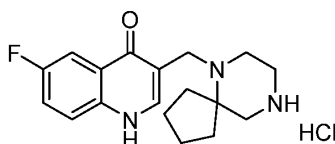
Intermediate 43: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrimido[1,2-*b*]pyridazin-4-one hydrochloride



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (Intermediate 3) except using 3-(hydroxymethyl)-4*H*-pyrimido[1,2-*b*]pyridazin-4-one (prepared similarly to 3-(hydroxymethyl)-6-phenylpyridin-2(1*H*)-one except using 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazine-3-carboxylic acid [commercially available] instead of 2-oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid) instead of 3-(hydroxymethyl)-6-phenylpyridin-2(1*H*)-one and using 4*M* HCl in 1,4-dioxane/DCM instead of TFA/DCM and omitting the SCX-2 purification in the final step to give the title compound. LCMS (Method A): R_T = 0.35 min, m/z = 300 $[M+H]^+$.

10

Intermediate 44: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-fluoroquinolin-4(1*H*)-one hydrochloride



*Step 1: 6-Fluoro-3-(hydroxymethyl)quinolin-4(1*H*)-one:* To a stirred solution of ethyl 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (1.5 g, 6.38 mmol) [commercially available] in dimethoxyethane (45 mL) was added a 2*M* solution of LiAlH_4 in THF (3.2 mL, 6.4 mmol) at rt. The reaction mixture was heated to 75 °C. After 2 h, the reaction mixture was cooled, quenched with saturated $\text{Na}_2\text{SO}_4(\text{aq})$ solution (50 mL) and filtered using Celite®. The filtrate was extracted with 3:2 EtOAc/THF (2 x 50 mL). The combined organic phase was dried (Na_2SO_4) and the solvents were removed *in vacuo* to give title compound (640 mg, 52%). LCMS (Method E): R_T = 1.52 min, m/z = 194 $[M+H]^+$.

*Step 2: 3-(Chloromethyl)-6-fluoroquinolin-4(1*H*)-one:* To a stirred solution of 6-fluoro-3-(hydroxymethyl)quinolin-4(1*H*)-one (100 mg, 0.52 mmol) in DCM (6 mL) was added SOCl_2 (0.11 mL, 1.55 mmol) at 0 °C. The reaction mixture was heated to 50 °C. After 16 h, the solvents were removed *in vacuo* to give title compound (101 mg, 92%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.21 (s, 1H), 8.29 – 8.27 (m, 1H), 7.79 – 7.76 (m, 1H), 7.64 – 7.59 (m, 2H), 4.66 (s, 2H).

Step 3: tert-Butyl 6-((6-fluoro-4-oxo-1,4-dihydroquinolin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate: To a stirred solution of 3-(chloromethyl)-6-fluoroquinolin-4(1*H*)-one (380 mg, 1.79 mmol) in MeCN (76 mL) were added *tert*-butyl 6,9-

diazaspiro[4.5]decane-9-carboxylate (647 mg, 2.96 mmol) and Cs_2CO_3 (1.17 g, 3.59 mmol) at rt. After 2 h, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with brine (50 mL), dried (Na_2SO_4), the solvents were removed *in vacuo*, and the remaining residue was

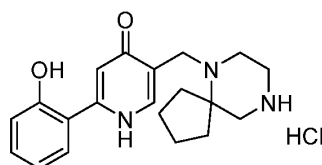
5 purified by flash chromatography (0-30% EtOAc in hexane), followed by RP preparative HPLC to give the title compound (80 mg, 11%). LCMS (Method E): $R_T = 2.50$ min, $m/z = 416$ $[\text{M}+\text{H}]^+$.

Step 4: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-fluoroquinolin-4(1H)-one hydrochloride:

10 Prepared according to General Procedure 1 using *tert*-butyl 6-((6-fluoro-4-oxo-1,4-dihydroquinolin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (58 mg, 140 μmol), 4M HCl in 1,4-dioxane (0.42 mL) and DCM (1.0 mL) but without SCX-2 purification to give the title compound (49 mg, quantitative). LCMS (Method A): $R_T = 0.41$ min, $m/z = 316$ $[\text{M}+\text{H}]^+$.

15

Intermediate 45: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(2-hydroxyphenyl)pyridin-4(1H)-one hydrochloride

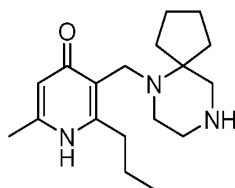


tert-Butyl 6-((6-(2-hydroxyphenyl)-4-oxo-1,4-dihydropyridin-3-yl)methyl)-6,9-

20 diazaspiro[4.5]decane-9-carboxylate (50 mg, 114 μmol) [obtained as a byproduct in the preparation of *tert*-butyl 6-((6-(2-methoxyphenyl)-4-oxo-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate: Step 4 in the synthetic procedure for 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-methoxyphenyl)pyridin-4(1H)-one hydrochloride (Intermediate 36)] was *N*-Boc deprotected according to General Procedure 1 using 4M HCl

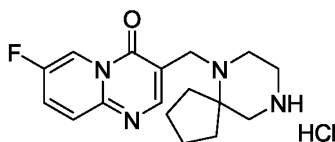
25 in 1,4-dioxane (0.43 mL) and 1,4-dioxane (1 mL) but without SCX-2 purification to give the title compound (42 mg, 98%). LCMS (Method A): $R_T = 0.45$ min, $m/z = 340$ $[\text{M}+\text{H}]^+$.

Intermediate 46: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-methyl-2-propylpyridin-4(1H)-one



The title compound was prepared similarly to 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1H)-one (Intermediate 29) except omitting Step 1 and using methyl 6-methyl-4-oxo-2-propyl-1,4-dihydropyridine-3-carboxylate [commercially available] instead
 5 of methyl 4-oxo-6-(thiophen-3-yl)-1,4-dihydropyridine-3-carboxylate in Step 2 to give the title compound. LCMS (Method A): $R_T = 0.40$ min, $m/z = 304$ $[M+H]^+$.

Intermediate 47: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride



10

Step 1: 3-Bromo-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one: To a stirred solution of 7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one (4.50 g, 27 mmol) [commercially available] in DCM (120 mL) was added NBS (5.37 g, 30 mmol) portionwise at rt. After 10 h, 1 M sodium carbonate (aq) solution (150 mL) was added. After a further 2 h, the biphasic mixture was separated,
 15 the organic phase was dried (Na_2SO_4), and the solvents were removed *in vacuo* to give the title compound (4.9 g, 75%). ^1H NMR (400 MHz, CDCl_3): δ 8.98 (m, 1H), 8.67 (s, 1H), 8.15 (m, 1H), 7.86 (m, 1H).

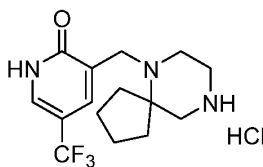
Step 2: 3-Hydroxymethyl-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one: To a stirred solution of 3-bromo-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one (4.40 g, 18 mmol) in 1,4-dioxane (250 mL) was added (tributylstannyl)methanol (9.25 g, 29 mmol) and XPhos-Pd-G2 (1.62 g, 2.0 mmol). The reaction mixture was degassed and back-filled with argon and then heated at 100 °C. After 48 h, the solvents were removed *in vacuo* and the residue was triturated using diethyl ether (150 mL) and filtered to give the crude title compound (3.2 g crude, 1:2
 25 mixture with 7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one determined by ^1H NMR analysis) that was used in the next step without further purification. LCMS (Method D): $R_T = 0.51$ min, $m/z = 195$ $[M+H]^+$.

Step 3: 3-Chloromethyl-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one: To a stirred solution of 3-hydroxymethyl-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one [contaminated with 7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one] (3.2 g crude, assumed 6 mmol) in DCM (200 mL) was added thionyl chloride (40 mL, 0.55 mol) at 40 °C. After 24 h, the solvents were removed *in vacuo* using MeCN to assist with coevaporation to give the crude title compound (3.2 g crude) that was used directly in the next step without further purification.

Step 4: tert-Butyl 6-((7-fluoro-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate: To a stirred solution of 3-chloromethyl-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one (3.0 g, assumed 6 mmol) in MeCN (150 mL) was added DIPEA (2.3 g, 18 mmol) and *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate (1.28 g, 6 mmol) at 80 °C. After 18 h, the solvents were removed *in vacuo*, the residue was partitioned between DCM and brine, and the resulting biphasic mixture was separated. The organic phase was dried (Na₂SO₄), the solvents were removed *in vacuo* and the remaining residue was purified by RP preparative HPLC to give the title compound (0.5 g, 7% over 3 steps). LCMS (Method D): R_T = 0.81 min, *m/z* = 417 [M+H]⁺.

Step 5: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride: Prepared according to General Procedure 1 using *tert*-butyl 6-((7-fluoro-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (60 mg, 144 μmol), 4M HCl in 1,4-dioxane (0.36 mL) and 1,4-dioxane (2 mL) but without SCX-2 purification to give the title compound (51 mg, 97%). LCMS (Method A): R_T = 0.45 min, *m/z* = 317 [M+H]⁺.

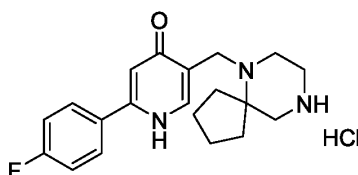
Intermediate 48: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-5-(trifluoromethyl)pyridin-2(1H)-one hydrochloride



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1H)-one (Intermediate 3) except using 3-(hydroxymethyl)-5-(trifluoromethyl)pyridin-2(1H)-one (prepared similarly to 3-(hydroxymethyl)-6-phenylpyridin-2(1H)-one except using 2-oxo-5-(trifluoromethyl)-1,2-dihydropyridine-3-carboxylic acid [commercially available] instead of 2-oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid)

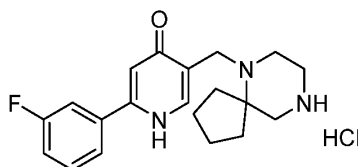
instead of 3-(hydroxymethyl)-6-phenylpyridin-2(1*H*)-one and using 4M HCl in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in the final step to give the title compound. LCMS (Method A): $R_T = 0.50$ min, $m/z = 316$ $[M+H]^+$.

5 Intermediate 49: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(4-fluorophenyl)pyridin-4(1*H*)-one hydrochloride



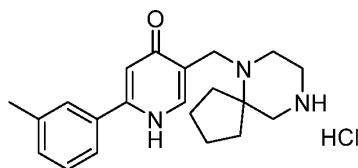
The title compound was prepared similarly to 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one (Intermediate 29) except using methyl 4-fluorobenzoate instead of methyl thiophene-3-carboxylate in Step 1 and using 4M HCl in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in Step 5 to give the title compound. LCMS (Method A): $R_T = 0.45$ min, $m/z = 342$ $[M+H]^+$.

15 Intermediate 50: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(3-fluorophenyl)pyridin-4(1*H*)-one hydrochloride



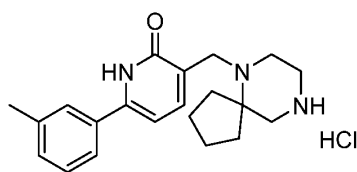
The title compound was prepared similarly to 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one (Intermediate 29) except using methyl 3-fluorobenzoate instead of methyl thiophene-3-carboxylate in Step 1 and using 4M HCl in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in Step 5 to give the title compound. LCMS (Method A): $R_T = 0.45$ min, $m/z = 342$ $[M+H]^+$.

20 Intermediate 51: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(*m*-tolyl)pyridin-4(1*H*)-one hydrochloride



The title compound was prepared similarly to 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one (Intermediate 29) except using methyl 3-methylbenzoate instead of methyl thiophene-3-carboxylate in Step 1 and using 4M HCl in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in Step 5 to give the title compound. LCMS (Method A): $R_T = 0.49$ min, $m/z = 338$ $[M+H]^+$.

Intermediate 52: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-(*m*-tolyl)pyridin-2(1*H*)-one hydrochloride



10

Step 1: 2-Oxo-6-(*m*-tolyl)-1,2-dihydropyridine-3-carboxylic acid: To a solution of 6-bromo-2-oxo-1,2-dihydropyridine-3-carboxylic acid (3.3 g, 15 mmol) in 1,4-dioxane (150 mL) and water (50 mL) was added *m*-tolylboronic acid (2.3 g, 16.5 mmol), Pd(dppf)Cl₂ (0.62 g, 0.8 mmol) and sodium carbonate (4.8 g, 45.6 mmol). The reaction mixture was degassed and backfilled with argon before heating to reflux. After 24 h, the solvents were evaporated. The remaining residue was dissolved in hot water (200 mL), filtered and acidified with HCl_(aq) to ~pH 3. The resulting precipitate was filtered, washed with water and dried under vacuum to give the title compound (3.0 g, 86%) as a grey solid. LCMS (Method D): $R_T = 0.87$ min, $m/z = 230$ $[M+H]^+$.

20

Step 2: 3-(Hydroxymethyl)-6-(*m*-tolyl)pyridin-2(1*H*)-one: To a stirred solution of 2-oxo-6-(*m*-tolyl)-1,2-dihydropyridine-3-carboxylic acid (2.9 g, 12.6 mmol) in THF (120 mL) was added 1 M borane.DMS complex in THF solution (39 mL, 39 mmol) at rt. After 18 h, MeOH was slowly added until gas evolution ceased. The resulting solution was partitioned between EtOAc and brine, separated, the organic phase was dried (Na₂SO₄), and the solvents were removed *in vacuo*. The remaining residue was purified by flash chromatography (0-5% MeOH in DCM) to give the title compound (2.6 g, 96%) as pale yellow solid that was used directly in the next step. LCMS (Method D): $R_T = 1.03$ min, $m/z = 216$ $[M+H]^+$.

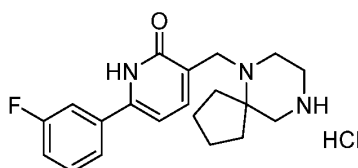
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Step 3: 3-(Chloromethyl)-6-(*m*-tolyl)pyridin-2(1*H*)-one: To a solution of 3-(hydroxymethyl)-6-(*m*-tolyl)pyridin-2(1*H*)-one (2.5 g, 11.6 mmol) in DCM (100 mL) was added thionyl chloride (20 mL, 0.278 mol), and the suspension was stirred at 40 °C. After 24 h, the solvents were

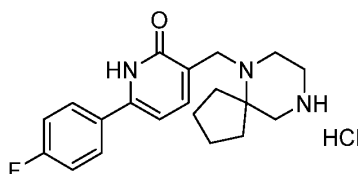
removed under vacuum, the residue was dissolved in MeCN and reevaporated to give the title compound (2.5 g, 92%) as a brown solid that was used directly in the next step without further purification.

- 5 **Step 4: *tert*-Butyl 6-((2-oxo-6-(*m*-tolyl)-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate:** To a solution of 3-(chloromethyl)-6-(*m*-tolyl)pyridin-2(1*H*)-one (2.4 g, 10 mmol) in MeCN (100 mL) was added DIPEA (3.9 g, 30 mmol) and *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate (2.4 g, 10 mmol). The resultant suspension was stirred at 80 °C. After 18 h, reaction mixture was evaporated, partitioned
10 between DCM and brine, separated, the organic phase was dried (Na₂SO₄), and the solvents were removed *in vacuo*. The remaining residue was purified by flash chromatography (0-5% MeOH in DCM) to give the title compound (1.2 g, 27%) as pale yellow solid. LCMS (Method D): R_T = 1.00 min, *m/z* = 438 [M+H]⁺.
- 15 **Step 5: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-(*m*-tolyl)pyridin-2(1*H*)-one hydrochloride:** Prepared according to General Procedure 1 using *tert*-butyl 6-((2-oxo-6-(*m*-tolyl)-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (60 mg, 137 μmol), 4M HCl in 1,4-dioxane (0.411 mL) and DCM (1.0 mL) but without SCX-2 purification to give the title compound (51 mg, 99%). LCMS (Method A): R_T = 0.59 min, *m/z* = 338
20 [M+H]⁺.

Intermediate 53: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-(3-fluorophenyl)pyridin-2(1*H*)-one hydrochloride



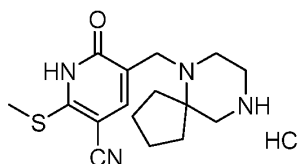
- 25 The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(*m*-tolyl)pyridin-2(1*H*)-one hydrochloride (Intermediate 52) except using 3-fluorophenylboronic acid instead of *m*-tolylboronic acid in Step 1 to give the title compound. LCMS (Method A): R_T = 0.54 min, *m/z* = 342 [M+H]⁺.
- 30 Intermediate 54: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-(4-fluorophenyl)pyridin-2(1*H*)-one hydrochloride



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(*m*-tolyl)pyridin-2(1*H*)-one hydrochloride (Intermediate 52) except using 4-fluorophenylboronic acid instead of *m*-tolylboronic acid in Step 1 to give the title compound.

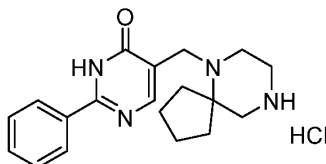
5 LCMS (Method A): $R_T = 0.53$ min, $m/z = 342$ $[M+H]^+$.

Intermediate 55: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(methylthio)-6-oxo-1,6-dihydropyridine-3-carbonitrile hydrochloride



10 The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (Intermediate 3) except using 5-(hydroxymethyl)-2-(methylthio)-6-oxo-1,6-dihydropyridine-3-carbonitrile (prepared similarly to 3-(hydroxymethyl)-6-phenylpyridin-2(1*H*)-one except using 5-cyano-6-(methylthio)-2-oxo-1,2-dihydropyridine-3-carboxylic acid [commercially available] instead of 2-oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid) instead of 3-(hydroxymethyl)-6-phenylpyridin-2(1*H*)-one and using 4M HCl
15 in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in the final step to give the title compound. LCMS (Method A): $R_T = 0.54$ min, $m/z = 319$ $[M+H]^+$.

20 Intermediate 56: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyrimidin-4(3*H*)-one hydrochloride

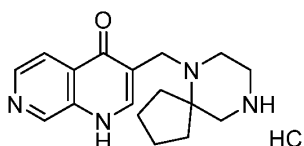


The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (Intermediate 3) except using 5-(hydroxymethyl)-2-phenylpyrimidin-4(3*H*)-one (prepared similarly to 3-(hydroxymethyl)-6-phenylpyridin-2(1*H*)-one except using 6-oxo-2-phenyl-1,6-dihydropyrimidine-5-carboxylic acid [commercially
25

available] instead of 2-oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid) instead of 3-(hydroxymethyl)-6-phenylpyridin-2(1*H*)-one and using 4M HCl in 1,4-dioxane/DCM instead of TFA/DCM and omitting the SCX-2 purification in the final step to give the title compound. LCMS (Method A): $R_T = 0.49$ min, $m/z = 325$ $[M+H]^+$.

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Intermediate 57: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1,7-naphthyridin-4(1*H*)-one hydrochloride

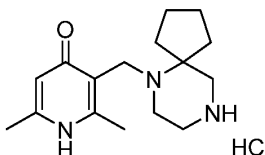


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The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (Intermediate 33) except using 1,7-naphthyridin-4(1*H*)-one [commercially available] instead of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one in Step 1 and using 4M HCl in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in the final step to give the title compound. LCMS (Method C): $R_T = 0.32$ min, $m/z = 299$ $[M+H]^+$.

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Intermediate 58: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2,6-dimethylpyridin-4(1*H*)-one hydrochloride

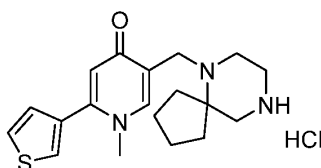


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The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (Intermediate 33) except using 2,6-dimethylpyridin-4(1*H*)-one [commercially available] instead of 4*H*-pyrido[1,2-*a*]pyrimidin-4-one in Step 1 and using 4M HCl in 1,4-dioxane/DCM instead of TFA/DCM and omitting the SCX-2 purification in the final step to give the title compound. LCMS (Method A): $R_T = 0.24$ min, $m/z = 276$ $[M+H]^+$.

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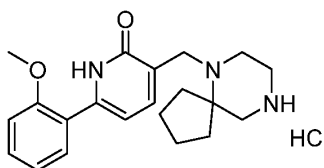
Intermediate 59: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(thiophen-3-yl)pyridin-4(1*H*)-one hydrochloride



Step 1: *tert*-Butyl 6-((1-methyl-4-oxo-6-(thiophen-3-yl)-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate: To a solution of *tert*-butyl 6-((4-oxo-6-(thiophen-3-yl)-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (429 mg, 1 mmol) in DMF (2 mL) under argon was added 55% sodium hydride in mineral oil (56 mg, 1.3 mmol). After 1 h, iodomethane (184 mg, 1.3 mmol) was added and the solution was stirred at rt. After 14 h, the solvents were removed *in vacuo*, the remaining residue was partitioned between DCM and brine, separated, the organic phase was dried (Na₂SO₄). The solvents were removed *in vacuo* and the remaining residue was purified by preparative HPLC to give the title compound (0.2 g, 48%) as white solid. LCMS (Method D): R_T = 1.05 min, *m/z* = 444 [M+H]⁺.

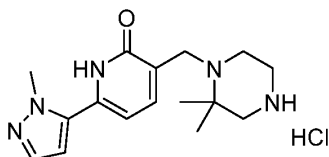
Step 2: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(thiophen-3-yl)pyridin-4(1*H*)-one hydrochloride: Prepared according to General Procedure 1 using *tert*-butyl 6-((1-methyl-4-oxo-6-(thiophen-3-yl)-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (50 mg, 113 μmol), 4M HCl in 1,4-dioxane (0.338 mL) and DCM (1.0 mL) but without SCX-2 purification to give the title compound (42 mg, 98%). LCMS (Method A): R_T = 0.42 min, *m/z* = 344 [M+H]⁺.

Intermediate 60: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-(2-methoxyphenyl)pyridin-2(1*H*)-one hydrochloride



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(*m*-tolyl)pyridin-2(1*H*)-one hydrochloride (Intermediate 52) except using 2-methoxyphenylboronic acid [commercially available] instead of *m*-tolylboronic acid in Step 1 and using 4M HCl in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in Step 5 to give the title compound. LCMS (Method A): R_T = 0.55 min, *m/z* = 354 [M+H]⁺.

Intermediate 61: 3-((2,2-Dimethylpiperazin-1-yl)methyl)-6-(1-methyl-1H-pyrazol-5-yl)pyridin-2(1H)-one hydrochloride

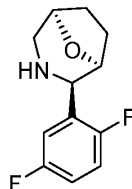


Step 1: tert-Butyl 4-((6-chloro-2-(2-(trimethylsilyl)ethoxy)pyridin-3-yl)methyl)-3,3-dimethylpiperazine-1-carboxylate: To a stirred solution of (6-chloro-2-(2-(trimethylsilyl)ethoxy)pyridin-3-yl)methanol (260 mg, 1.00 mmol) [prepared according to WO2018195321] in DCM (10 mL) under an atmosphere of N₂ at 0 °C were sequentially added triethylamine (167 µL, 1.20 mmol) and methanesulfonyl chloride (85.7 µL, 1.10 mmol). After stirring at 0 °C for 30 min, the ice-bath was removed and the reaction was stirred at rt for 3 h. The reaction was cooled to 0 °C before further triethylamine (167 µL, 1.20 mmol) and methanesulfonyl chloride (85.7 µL, 1.10 mmol) were sequentially added. After stirring at 0 °C for 30 min the ice-bath was removed and the reaction was stirred at rt for 19 h. The reaction was cooled to 0 °C before further triethylamine (167 µL, 1.20 mmol) and methanesulfonyl chloride (85.7 µL, 1.10 mmol) were sequentially added. After stirring at 0 °C for 30 min, the ice-bath was removed and the reaction was stirred at rt for 3 h before the reaction mixture was washed sequentially with water (10 mL), 1 M NaOH_(aq) solution (10 mL) and brine (10 mL) using a phase separator. The organic layer was concentrated under reduced pressure before MeCN (1 mL), *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate (236 mg, 1.10 mmol) and DIPEA (227 µL, 1.30 mmol) were added. After stirring the resulting suspension at rt for 4 days, the temperature was increased to 40 °C to give a solution which was stirred for a further 2 days at 40 °C. Upon cooling to rt, water (15 mL) was added, and the resulting mixture was extracted with DCM (3 x 10 mL) using a phase separator. The combined organic phase was concentrated under reduced pressure and the residue was purified by flash chromatography to give the title compound (322 mg, 70%) as a colourless oil. LCMS (Method A): R_T = 1.26 min, *m/z* = 456, 457 [M+H]⁺.

Step 2: tert-Butyl 3,3-dimethyl-4-((6-(1-methyl-1H-pyrazol-5-yl)-2-(2-(trimethylsilyl)ethoxy)pyridin-3-yl)methyl)piperazine-1-carboxylate: A sealed 2-5 mL microwave vial charged with *tert*-butyl 4-((6-chloro-2-(2-(trimethylsilyl)ethoxy)pyridin-3-yl)methyl)-3,3-dimethylpiperazine-1-carboxylate (96.6 mg, 0.212 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (88.1 mg, 0.424 mmol),

- potassium phosphate (135 mg, 0.635 mmol), Pd(dppf)Cl₂.DCM (9 mg, 0.0106 mmol), 1,4-dioxane (1.5 mL) and water (0.5 mL) was 'degassed' by evacuating and refilling the vessel three times with N₂. The reaction was heated under microwave irradiation at 120 °C for 30 min. Upon cooling to rt, the reaction mixture was poured into a mixture of brine (20 mL) and
- 5 water (40 mL) and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic phase was dried (phase separator) and concentrated under reduced pressure. The residue was purified by flash chromatography to give the title compound (91.3 mg, 85%). LCMS (Method A): R_T = 1.15 min, *m/z* = 502 [M+H]⁺.
- 10 **Step 3: 3-((2,2-Dimethylpiperazin-1-yl)methyl)-6-(1-methyl-1H-pyrazol-5-yl)pyridin-2(1H)-one hydrochloride:** A mixture of *tert*-butyl 3,3-dimethyl-4-((6-(1-methyl-1H-pyrazol-5-yl)-2-(2-(trimethylsilyl)ethoxy)pyridin-3-yl)methyl)piperazine-1-carboxylate (91.3 mg, 0.182 mmol), 4 M HCl in 1,4-dioxane (908 µL, 3.63 mmol) and DCM (1.8 mL) was stirred at rt for 16 h. The resulting suspension was filtered, the solids were washed with DCM (3 x 2 mL)
- 15 and dried in a vacuum oven at 50 °C to give title compound (56 mg, 82%) as yellow solid. LCMS (Method A): R_T = 0.33 min, *m/z* = 302 [M+H]⁺.

Intermediate 62: (1*S*,2*R*,5*R*)-2-(2,5-Difluorophenyl)-8-oxa-3-azabicyclo[3.2.1]octane



- 20 **Step 1: (R)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)dihydrofuran-2(3*H*)-one:** To a stirred solution of (*R*)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (1.00 g, 8.61 mmol) and imidazole (1.17 g, 17.2 mmol) in DMF (10 mL) at 0 °C was added *tert*-butylchlorodiphenylsilane (2.91 mL, 11.2 mmol). The reaction mixture was allowed to warm to rt. After 16 h, EtOAc (50 mL) was added, the resulting mixture was washed with 1:1 brine/water (3 x 50 mL), the organic
- 25 phase was dried (MgSO₄), and concentrated under reduced pressure. The remaining residue was purified by flash chromatography to give title compound (2.74 g, 89%). LCMS (Method A): R_T = 1.70 min, *m/z* = 277 [M-Ph]⁺. ¹H NMR (500 MHz, CDCl₃): δ 7.70 – 7.61 (m, 4H), 7.48 – 7.34 (m, 6H), 4.66 – 4.56 (m, 1H), 3.88 (dd, 1H), 3.69 (dd, 1H), 2.67 (ddd, 1H), 2.51 (ddd, 1H), 2.37 – 2.15 (m, 2H), 1.06 (s, 9H).

Step 2: (5R)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-ol: To a stirred solution of (*R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)dihydrofuran-2(3*H*)-one (2.74 g, 7.72 mmol) in diethyl ether (40 mL) at -78 °C under nitrogen and was added a 1M solution of diisobutylaluminium hydride in DCM (11.6 mL, 11.6 mmol). After 5 h at -78 °C, the reaction mixture was quenched by the addition of MeOH (5 mL). After a further 15 min at -78 °C, the reaction mixture was warmed to rt, diluted with diethyl ether (150 mL) and washed using 0.2 M sodium tartrate_(aq) solution (3 x 100 mL) and brine. The organic phase was dried (MgSO₄), filtered, and concentrated under reduced pressure to give the title compound (2.75 g, quantitative). LCMS (Method A): R_T = 1.69 min, *m/z* = 339 [M-OH]⁺.

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Step 3: (R)-tert-Butyl((2,3-dihydrofuran-2-yl)methoxy)diphenylsilane: To a stirred solution of (*5R*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)tetrahydrofuran-2-ol (2.75 g, 7.71 mmol) and triethylamine (4.09 mL, 29.3 mmol) in DCM (50 mL) at -50 °C under nitrogen was added methanesulfonyl chloride (748 µL, 9.64 mmol). After 3 h at -50 °C, the reaction mixture was warmed to rt and subsequently stirred at reflux for a further 18 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure and the remaining residue was purified by flash chromatography to give title compound (1.37 g, 52%). ¹H NMR (500 MHz, CDCl₃): δ 7.74 – 7.65 (m, 4H), 7.45 – 7.34 (m, 6H), 6.27 (q, 1H), 4.85 (q, 1H), 4.71 – 4.58 (m, 1H), 3.75 (dd, 1H), 3.68 (dd, 1H), 2.64 (ddt, 1H), 2.47 (ddt, 1H), 1.06 (s, 9H).

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Step 4: (R)-(2,3-Dihydrofuran-2-yl)methyl 4-methylbenzenesulfonate: To (*R*)-*tert*-butyl((2,3-dihydrofuran-2-yl)methoxy)diphenylsilane (1.37 g, 4.05 mmol) was added a 1M TBAF in THF solution (4.05 mL, 4.05 mmol) and the resulting mixture was stirred at rt for 1 h. The reaction mixture was diluted with DCM (25 mL) and cooled to 0 °C before triethylamine (5.64 mL, 40.5 mmol) and 4-methylbenzenesulfonyl chloride (3.86 g, 20.3 mmol) were added. The reaction mixture was stirred for 19 h and allowed to warm to rt. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in EtOAc (50 mL) and washed with 1:1 brine/water (2 x 50 mL). The organic layer was dried (MgSO₄), filtered, concentrated under reduced pressure, and the remaining residue was purified by flash chromatography to give title compound (858 mg, 83%). LCMS (Method B): R_T = 1.40 min, *m/z* = 255 [M+H]⁺.

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Step 5: (R)-2-((2,3-Dihydrofuran-2-yl)methyl)isoindoline-1,3-dione: A mixture of (*R*)-(2,3-dihydrofuran-2-yl)methyl 4-methylbenzenesulfonate (858 mg, 3.74 mmol) and potassium 1,3-dioxoisoindolin-2-ide (937 mg, 5.06 mmol) in DMF (13 mL) under nitrogen was stirred

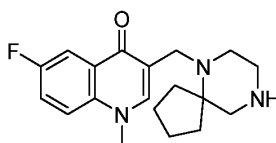
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at 75 °C for 19 h. Upon cooling to rt, the reaction mixture was diluted with EtOAc (50 mL) and washed with 1:1 brine/water (3 x 50 mL). The organic layer was dried (MgSO₄), filtered, and concentrated under reduced pressure. The remaining residue was purified by flash chromatography to give title compound (623 mg, 80%). LCMS (Method A): R_T = 1.10 min, *m/z* = 230 [M+H]⁺.

Step 6: (R)-(2,3-Dihydrofuran-2-yl)methanamine: To (*R*)-2-((2,3-dihydrofuran-2-yl)methyl)isoindoline-1,3-dione (310 mg, 1.35 mmol) in MeOH (5.5 mL) was added hydrazine monohydrate (250 µL, 8.1 mmol) and the resulting mixture was heated at 60 °C for 2 h. Upon cooling to rt, a 2M sodium hydroxide_(aq) solution (10 mL) was added and the resulting mixture was extracted using DCM (3 x 20 mL). The combined phase was washed using brine (50 mL), dried (MgSO₄), filtered, and concentrated at reduced pressure (41 °C, 220 mbar) to give the title compound (140 mg, crude) that was used in the next step without purification.

Step 7: (1S,2R,5R)-2-(2,5-Difluorophenyl)-8-oxa-3-azabicyclo[3.2.1]octane: To crude (*R*)-2-((2,3-dihydrofuran-2-yl)methanamine (134 mg, 1.35 mmol) and 2,5-difluorobenzaldehyde (192 mg, 1.35 mmol) in DCM (1.4 mL) was added 3Å molecular sieves (300 mg) at rt. After 16 h, the reaction mixture was filtered (syringe filter) and the volatiles were evaporated under reduced pressure (40 °C, 210 mbar). The resultant crude imine was transferred to a 20 mL MW vial and dissolved in 2-propanol (13 mL). Mn(dpm)₃ (40.9 mg, 0.068 mmol) was added and the vial was capped. PhSiH₃ (0.33 mL, 2.71 mmol) was added and the reaction was heated at 85 °C for 5 h. Due to incomplete reaction, further PhSiH₃ (0.33 mL, 2.71 mmol) was added and the reaction was continued at 85 °C for 16 h. Due to incomplete reaction, further PhSiH₃ (0.33 mL, 2.71 mmol) was added and the reaction was continued at 85 °C for 4 h. The reaction mixture was cooled to rt and evaporated under reduced pressure. The remaining residue was purified by flash chromatography (20-100% EtOAc in cyclohexane) to give the title compound (57 mg, 19%). LCMS (Method C): R_T = 0.50 min, *m/z* = 226 [M+H]⁺.

Intermediate 63: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-1-methylquinolin-4(1*H*)-one



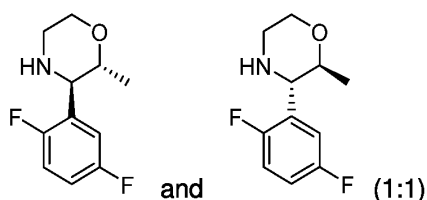
Step 1: 6-Fluoro-3-(hydroxymethyl)-1-methylquinolin-4(1H)-one: To a stirred solution of 6-fluoro-3-(hydroxymethyl)quinolin-4(1H)-one (965 mg, 5.00 mmol) in water (40 mL) were added NaOH (260 mg, 6.49 mmol), followed by dimethyl sulfate (1.40 mL, 19.0 mmol) at rt.
 5 After 3 h, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the title compound (0.79 g, 76%) as an off-white solid. LCMS (Method E): $R_T = 1.80$ min, $m/z = 208$ $[M+H]^+$.

Step 2: 3-(Chloromethyl)-6-fluoro-1-methylquinolin-4(1H)-one: To a stirred solution of 6-fluoro-3-(hydroxymethyl)-1-methylquinolin-4(1H)-one (300 mg, 1.45 mmol) in DCM (10 mL) was added $SOCl_2$ (0.31 mL, 4.34 mmol) at 50 °C. After 16 h, the solvents were evaporated under reduced pressure to yield the title compound (0.32 g, 98%) that was used in the next step without further purification. 1H NMR (400 MHz, $DMSO-d_6$): δ 8.38 (s, 1H), 7.97 – 7.85 (m, 1H), 7.82 – 7.79 (m, 1H), 7.72 – 7.68 (m, 1H), 4.64 (s, 2H), 3.87 (s, 3H).
 10

Step 3: tert-Butyl 6-((6-fluoro-1-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate: To a stirred solution of 3-(chloromethyl)-6-fluoro-1-methylquinolin-4(1H)-one (0.32 g, 1.42 mmol) in MeCN (40 mL) were added *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate (0.511 g, 2.13 mmol) and DIPEA (0.74 mL, 4.25 mmol) at rt. After 2 h, the reaction mixture was concentrated under reduced pressure to get crude product which was purified by preparative HPLC to give the title compound (0.1 g, 16%) as an off-white solid. LCMS (Method F): $R_T = 2.68$ min, $m/z = 430$ $[M+H]^+$.
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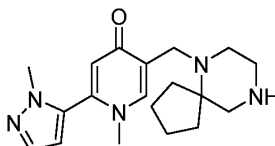
Step 4: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-1-methylquinolin-4(1H)-one: Prepared according to General Procedure 1 using *tert*-butyl 6-((6-fluoro-1-methyl-4-oxo-1,4-dihydroquinolin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (50 mg, 116 μ mol), TFA (0.5 mL) and DCM (1.0 mL) to give the title compound (35.7 mg, 93%). LCMS (Method C): $R_T = 0.46$ min, $m/z = 330$ $[M+H]^+$.
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30 Intermediate 64: *rac*-(2*R*,3*R*)-3-(2,5-difluorophenyl)-2-methylmorpholine



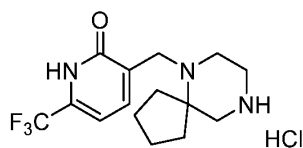
To 2-vinyloxyethanamine (100 mg, 1.15 mmol) and 2,5-difluorobenzaldehyde (163 mg, 1.15 mmol) in DCM (1.4 mL) was added 3Å molecular sieves (300 mg) at rt. After 16 h, the reaction mixture was filtered (syringe filter) and evaporated under reduced pressure (40 °C, 210 mbar). The resultant crude imine was transferred to a 20 mL MW vial and dissolved in 2-propanol (12 mL). Mn(dpm)₃ (34.8 mg, 0.0575 mmol) was added and the vial was capped. PhSiH₃ (0.28 mL, 2.30 mmol) was added and the reaction was heated at 85 °C for 5 h. Due to incomplete reaction, further PhSiH₃ (0.28 mL, 2.30 mmol) was added and the reaction was continued at 85 °C for 16 h. Due to incomplete reaction, further PhSiH₃ (0.28 mL, 2.30 mmol) was added and the reaction was continued at 85 °C for 4 h. The reaction mixture was cooled to rt and evaporated under reduced pressure. The remaining residue was purified by flash chromatography (20-100% EtOAc in cyclohexane) to give the title compound (22 mg, 9%). LCMS (Method C): R_T = 0.52 min, *m/z* = 214 [M+H]⁺.

Intermediate 65: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(1-methyl-1*H*-pyrazol-5-yl)pyridin-4(1*H*)-one



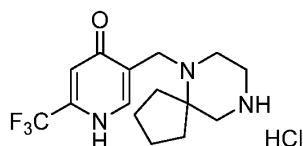
The title compound was prepared similarly to 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(thiophen-3-yl)pyridin-4(1*H*)-one hydrochloride (Intermediate 59) except using *tert*-butyl 6-((6-(1-methyl-1*H*-pyrazol-5-yl)-4-oxo-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate instead of *tert*-butyl 6-((1-methyl-4-oxo-6-(thiophen-3-yl)-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate in Step 1 and using TFA/DCM instead of 4M HCl in 1,4-dioxane/DCM and including the SCX-2 purification in the final step to give the title compound. LCMS (Method C): R_T = 0.38 min, *m/z* = 342 [M+H]⁺.

Intermediate 66: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-(trifluoromethyl)pyridin-2(1*H*)-one hydrochloride



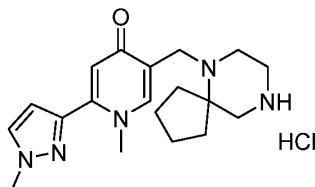
The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-4H-pyrido[1,2-a]pyrimidin-4-one (Intermediate 33) except omitting Step 1 and using 3-bromo-6-(trifluoromethyl)pyridin-2(1H)-one [commercially available] instead of 3-bromo-4H-pyrido[1,2-a]pyrimidin-4-one in Step 2 and using 4M HCl in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in the final step to give the title compound. LCMS (Method A): $R_T = 0.51$ min, $m/z = 316$ $[M+H]^+$.

Intermediate 67: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(trifluoromethyl)pyridin-4(1H)-one hydrochloride



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-4H-pyrido[1,2-a]pyrimidin-4-one (Intermediate 33) except omitting Step 1 and using 5-bromo-2-(trifluoromethyl)pyridin-4(1H)-one [commercially available] instead of 3-bromo-4H-pyrido[1,2-a]pyrimidin-4-one in Step 2 and using 4M HCl in 1,4-dioxane/1,4-dioxane instead of TFA/DCM and omitting the SCX-2 purification in the final step to give the title compound. LCMS (Method A): $R_T = 0.55$ min, $m/z = 316$ $[M+H]^+$.

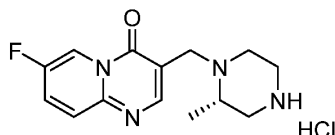
Intermediate 68: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(1-methyl-1H-pyrazol-3-yl)pyridin-4(1H)-one hydrochloride



The title compound was prepared similarly to 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(thiophen-3-yl)pyridin-4(1H)-one hydrochloride (Intermediate 59) except using *tert*-butyl 6-((6-(1-methyl-1H-pyrazol-3-yl)-4-oxo-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate instead of *tert*-butyl 6-((1-methyl-4-oxo-6-(thiophen-3-

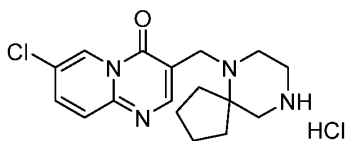
yl)-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate in Step 1 to give the title compound. LCMS (Method A): $R_T = 0.37$ min, $m/z = 342$ $[M+H]^+$.

Intermediate 69: (S)-7-Fluoro-3-((2-methylpiperazin-1-yl)methyl)-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride



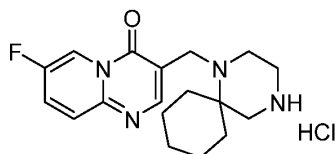
The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (Intermediate 47) except using *tert*-butyl (S)-3-methylpiperazine-1-carboxylate [commercially available] instead of *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate in Step 4 to give the title compound. LCMS (Method A): $R_T = 0.31$ min, $m/z = 277$ $[M+H]^+$.

Intermediate 70: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-7-chloro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (Intermediate 47) except using 7-chloro-4H-pyrido[1,2-a]pyrimidin-4-one [commercially available] instead of 7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one in Step 1 to give the title compound. LCMS (Method A): $R_T = 0.53$ min, $m/z = 333$ $[M+H]^+$.

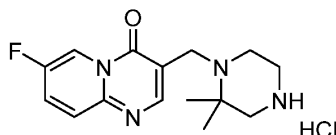
Intermediate 71: 3-((1,4-Diazaspiro[5.5]undecan-1-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (Intermediate 47) except using *tert*-butyl 1,4-diazaspiro[5.5]undecane-4-carboxylate [commercially available] instead of *tert*-

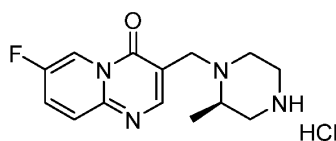
butyl 6,9-diazaspiro[4.5]decane-9-carboxylate in Step 4 to give the title compound. LCMS (Method A): $R_T = 0.48$ min, $m/z = 331$ $[M+H]^+$.

Intermediate 72: 3-((2,2-Dimethylpiperazin-1-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride



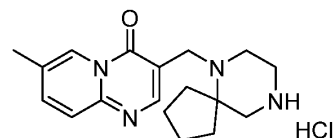
The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (Intermediate 47) except using *tert*-butyl 3,3-dimethylpiperazine-1-carboxylate [commercially available] instead of *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate in Step 4 to give the title compound. LCMS (Method A): $R_T = 0.36$ min, $m/z = 291$ $[M+H]^+$.

Intermediate 73: (*R*)-7-Fluoro-3-((2-methylpiperazin-1-yl)methyl)-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (Intermediate 47) except using *tert*-butyl (*R*)-3-methylpiperazine-1-carboxylate [commercially available] instead of *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate in Step 4 to give the title compound. LCMS (Method A): $R_T = 0.26$ min, $m/z = 277$ $[M+H]^+$.

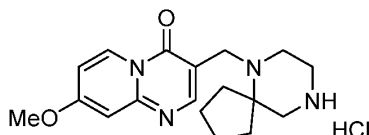
Intermediate 74: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-7-methyl-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (Intermediate 47) except using 7-methyl-4H-pyrido[1,2-a]pyrimidin-4-one [commercially available] instead of 7-fluoro-4H-

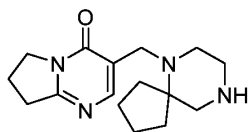
pyrido[1,2-*a*]pyrimidin-4-one in Step 1 to give the title compound. LCMS (Method A): R_T = 0.46 min, m/z = 313 $[M+H]^+$.

5 Intermediate 75: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-8-methoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one hydrochloride



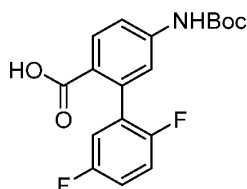
To a stirred solution of 4-methoxy-2-aminopyridine (15.8 g, 127 mmol) in EtOH (300 mL) was added 2,2-dimethyl-1,3-dioxane-4,6-dione (20.1 g, 140 mmol) and triethyl orthoformate (20.7 g, 140 mmol) at rt. The reaction mixture was stirred at reflux for 24 h, evaporated to dryness, the residue was dissolved in diphenylether (100 mL) and heated to 240 °C for 3 h. After cooling to rt, the reaction mixture was poured into hexane (1.5 L), the resultant precipitate was filtered and washed with hexane to give 8-methoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (11.1 g, 50%). LCMS (Method D): R_T = 0.72 min, m/z = 177 $[M+H]^+$. Subsequently, the title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one hydrochloride (Intermediate 47) except using 8-methoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one instead of 7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in Step 1 to give the title compound. LCMS (Method A): R_T = 0.44 min, m/z = 329 $[M+H]^+$.

20 Intermediate 76: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-7,8-dihydropyrrolo[1,2-*a*]pyrimidin-4(6*H*)-one



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one hydrochloride (Intermediate 47) except using 7,8-dihydropyrrolo[1,2-*a*]pyrimidin-4(6*H*)-one [commercially available] instead of 7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in Step 1 and using TFA/DCM instead of 4M HCl in 1,4-dioxane/1,4-dioxane and including SCX-2 purification in the final step to give the title compound. LCMS (Method C): R_T = 0.42 min, m/z = 289 $[M+H]^+$.

Intermediate 77: 5-((*tert*-Butoxycarbonyl)amino)-2',5'-difluoro-[1,1'-biphenyl]-2-carboxylic acid

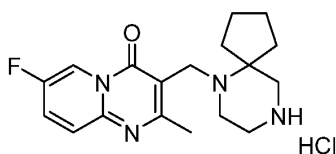


Step 1: 5-amino-2',5'-difluoro-[1,1'-biphenyl]-2-carboxylic acid: 2',5'-Difluoro-5-nitro-[1,1'-biphenyl]-2-carboxylic acid (0.1 g, 0.35 mmol) [commercially available] was dissolved in MeOH (3 mL) and the solution was passed through an H-Cube® Pro hydrogenation flow reactor containing a 10%w/w Pd/C cartridge with a flow rate of 1 mL/min at 30 °C. After one cycle, the solvents were removed *in vacuo* to give the title compound (0.09 g, 98%). LCMS (Method A): $R_T = 0.90$ min, $m/z = 250$ $[M+H]^+$.

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Step 2: 5-((*tert*-Butoxycarbonyl)amino)-2',5'-difluoro-[1,1'-biphenyl]-2-carboxylic acid: To a stirred solution 5-amino-2',5'-difluoro-[1,1'-biphenyl]-2-carboxylic acid (0.09 g, 0.35 mmol) and triethylamine (0.15 mL, 1.06 mmol) in 1,4-dioxane (4 mL)/water (2 mL) was added Boc_2O (0.16 mL, 0.71 mmol). The reaction mixture was stirred at rt for 24 h. The solvents were removed *in vacuo* and a 3 M $\text{HCl}_{(\text{aq})}$ solution (10 mL) was added dropwise to the remaining residue. The resultant precipitate was filtered, washed using water and dried under vacuum to give the title compound (0.076 g, 61%). LCMS (Method A): $R_T = 1.31$ min, $m/z = 348$ $[M-H]^-$.

20 Intermediate 78: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one hydrochloride



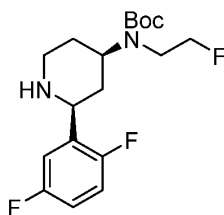
To a stirred solution of 5-fluoro-2-aminopyridine (10.0 g, 89 mmol) in EtOH (200 mL) was added 2,2-dimethyl-1,3-dioxane-4,6-dione (14.1 g, 98 mmol) and triethyl orthoacetate (15.9 g, 98 mmol) at rt. The reaction mixture was stirred at reflux for 24 h, evaporated to dryness, the residue was dissolved in diphenylether (90 mL) and heated to 240 °C for 3 h. After cooling to rt, the reaction mixture was poured into hexane (1.0 L), the resultant precipitate was filtered and washed with hexane to give 7-fluoro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (6.2 g, 39%). Subsequently, the title compound was prepared similarly to 3-((6,9-

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diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one hydrochloride (Intermediate 47) except using 7-fluoro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one instead of 7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in Step 1 to give the title compound. LCMS (Method A): $R_T = 0.47$ min, $m/z = 331$ $[M+H]^+$.

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Intermediate 79: *tert*-Butyl ((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)(2-fluoroethyl)carbamate



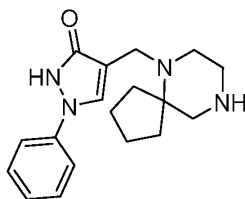
*Step 1: Benzyl (2*S*,4*R*)-4-((*tert*-butoxycarbonyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate:* To a stirred solution of *tert*-butyl *N*-[(2*S*,4*R*)-2-(2,5-difluorophenyl)-4-piperidyl]carbamate (0.3 g, 0.96 mmol) in THF (2 mL) was added benzyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.28 g, 1.15 mmol) followed by a solution of sodium bicarbonate (0.16 g, 192 mmol) in water (2 mL). After 24 h, the reaction mixture was partitioned between EtOAc (10 mL) and brine (10 mL) and separated. The organic phase was washed using water (10 mL), followed by brine (10 mL). The solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography (0-60% EtOAc in cyclohexane) to give the title compound (0.31 g, 59%). LCMS (Method A): $R_T = 1.56$ min, $m/z = 347$ $[M-Boc+H]^+$.

*Step 2: Benzyl (2*S*,4*R*)-4-((*tert*-butoxycarbonyl)(2-fluoroethyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate:* To a stirred solution of benzyl (2*S*,4*R*)-4-((*tert*-butoxycarbonyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate (0.3 g, 0.67 mmol) in DMF (3 mL) was added 55% sodium hydride dispersion in mineral oil (0.035 g, 0.87 mmol) at 0 °C. After 30 min, 1-fluoro-2-iodoethane (0.07 mL, 0.80 mmol) was added. After 24 h, further 1-fluoro-2-iodoethane (0.07 mL, 0.80 mmol) and sodium hydride (55% in mineral oil, 0.035 g, 0.87 mmol) were added. After a further 24 h, the reaction mixture was partitioned between EtOAc (30 mL) and 15% $NH_4Cl_{(aq)}$ solution (10 mL), separated, the organic phase was washed using water (10 mL), followed by brine (10 mL), and dried (Mg_2SO_4). The solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography (0-40% EtOAc in cyclohexane) to give the title compound (0.1 g, 30%). LCMS (Method A): $R_T = 1.68$ min, $m/z = 393$ $[M-Boc+H]^+$.

Step 3: tert-Butyl ((2S,4R)-2-(2,5-difluorophenyl)piperidin-4-yl)(2-fluoroethyl)carbamate:

Benzyl (2S,4R)-4-((*tert*-butoxycarbonyl)(2-fluoroethyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carboxylate (0.08 g, 0.16 mmol) was dissolved in MeOH (3 mL) and the solution was passed through an H-Cube® Pro hydrogenation flow reactor containing a 10%w/w Pd/C cartridge with a flow rate of 1 mL/min at 50 °C. After one cycle, the solvents were removed *in vacuo* to give the title compound (0.05 g, 85%). LCMS (Method A): $R_T = 0.778$ min, $m/z = 359$ $[M+H]^+$.

10 Intermediate 80: 4-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1-phenyl-1,2-dihydro-3H-pyrazol-3-one



Step 1: Ethyl 3-oxo-1-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate: To a solution of *N*-phenylacetohydrazide (10.0 g, 66.6 mmol) in POCl₃ (37.4 mL, 400 mmol) was added diethyl 2-(ethoxymethylene)malonate (14.8 g, 73.2 mmol) at rt and the resultant reaction mixture was heated at 70 °C. After 3 h, the reaction mixture was cooled and quenched using ice cold water. The resultant precipitate was filtered and washed using water. The residual solid was dissolved in EtOAc (200 mL), washed with brine (100 mL), dried (Na₂SO₄) and the solvents were removed *in vacuo* to give the title compound (15.4 g, 16%). LCMS (Method E): $R_T = 3.02$ min, $m/z = 233$ $[M+H]^+$.

Step 2: Ethyl 3-methoxy-1-phenyl-1H-pyrazole-4-carboxylate: To a stirred solution of ethyl 3-oxo-1-phenyl-2,3-dihydro-1H-pyrazole-4-carboxylate (300 mg, 1.29 mmol) and K₂CO₃ (250 mg, 1.80 mmol) in DMF (5 mL) was added iodomethane (96.5 μ L, 1.55 mmol) at rt. After 4 h, the reaction mixture was diluted with ice cold water and extracted using EtOAc (50 mL). The organic phase was washed using brine (20 mL), dried (Na₂SO₄), the solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography (0-20% EtOAc in hexane) to give title compound (220 mg, 69.1%). LCMS (Method E): $R_T = 3.48$ min, $m/z = 247$ $[M+H]^+$.

Step 3: (3-Methoxy-1-phenyl-1H-pyrazol-4-yl)methanol: To a stirred solution of ethyl 3-methoxy-1-phenyl-1H-pyrazole-4-carboxylate (100 mg, 0.41 mmol) in diethyl ether (2 mL) was added 1M DIBAL-H in toluene (0.046 mL, 1.22 mmol) at -78 °C. The temperature of the reaction mixture was allowed to increase to -10 °C and held at this temperature. After 4 h, the reaction mixture was quenched using saturated NH₄Cl_(aq) solution, and extracted using EtOAc (20 mL). The organic phase was washed using brine (20 mL), dried (Na₂SO₄), the solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography (0-50% EtOAc in hexane) to give the title compound (60 mg, 72%). LCMS (Method E): R_T = 2.78 min, *m/z* = 205 [M+H]⁺.

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Step 4: 4-(Bromomethyl)-3-methoxy-1-phenyl-1H-pyrazole: To a stirred solution of (3-methoxy-1-phenyl-1H-pyrazol-4-yl)methanol (570 mg, 2.79 mmol) in DCM (85 mL) was added triphenylphosphine (806 mg, 3.07 mmol) and CBr₄ (1.0 g, 3.07 mmol) at rt. After 16 h, the reaction mixture was concentrated *in vacuo* to give the title compound (crude, 570 mg) that was used in the next step without further purification.

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Step 5: tert-Butyl 6-((3-methoxy-1-phenyl-1H-pyrazol-4-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate: To a stirred solution of 4-(bromomethyl)-3-methoxy-1-phenyl-1H-pyrazole (570 mg, 2.13 mmol) in MeCN (45 mL) was added Cs₂CO₃ (1.39 g, 4.26 mmol) at rt. After 30 min, *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate (1.02 g, 4.26 mmol) was added. After 16 h, the reaction mixture was concentrated *in vacuo*, diluted with EtOAc (100 mL), washed using brine (50 mL), dried (Na₂SO₄). The solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography (0-5% MeOH in DCM) to give the title compound (700 mg, 59% over 2 steps). LCMS (Method E): R_T = 4.18 min, *m/z* = 427 [M+H]⁺.

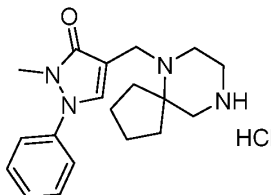
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Step 6: 4-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1-phenyl-1,2-dihydro-3H-pyrazol-3-one: A slurry of *tert*-butyl 6-((3-methoxy-1-phenyl-1H-pyrazol-4-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (670 mg, 1.57 mmol) in 33% HBr in AcOH (4 mL) was heated at 100 °C. After 2 h, the reaction mixture was concentrated under reduced pressure and the remaining residue was triturated with diethyl ether (3 x 20 mL) to give crude product material (800 mg) of which 150 mg was purified by preparative HPLC to give the title compound (52 mg, 35% recovery) and the rest of the material (650 mg) was held for use in a subsequent reaction without further purification. LCMS (Method E): R_T = 1.97 min, *m/z* = 313 [M+H]⁺.

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Intermediate 81: 4-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-methyl-1-phenyl-1,2-dihydro-3H-pyrazol-3-one hydrochloride

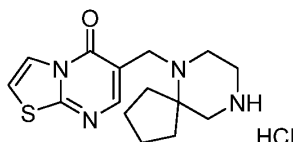


- 5 *Step 1: tert-Butyl 6-((3-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-4-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate*: To a stirred solution of 4-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-phenyl-1,2-dihydro-3H-pyrazol-3-one (180 mg, 0.46 mmol) in DCM (4 mL) was added triethylamine (0.4 mL, 2.29 mmol) at rt, followed by Boc₂O (0.09 mL, 0.41 mmol). After 2 h, the reaction mixture was diluted with water and was extracted using 9:1
- 10 DCM/MeOH (3 x 20 mL). The combined organic phase was washed using water (10 mL), followed by brine (10 mL) and dried (Na₂SO₄). The solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography (0-5% MeOH in DCM) to give the title compound (90 mg, 47%). LCMS (Method E): R_T = 1.90 min, *m/z* = 413 [M+H]⁺.
- 15 *Step 2: tert-Butyl 6-((2-methyl-3-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-4-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate*: To a stirred solution of *tert*-butyl 6-((3-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-4-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (150 mg, 0.36 mmol) in 1:1 DCM/MeOH (5 mL) was added trimethylsilyldiazomethane (0.12 mL, 1.09 mmol) at rt. After 5 h, the reaction mixture was diluted with water (20 mL) and was
- 20 extracted using 9:1 DCM/MeOH (3 x 20 mL). The combined organic phase was washed using brine (20 mL), dried (Na₂SO₄), the solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography (0-15% EtOAc in hexane, then 10% MeOH in DCM) to give *tert*-butyl 6-((3-methoxy-1-phenyl-1H-pyrazol-4-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (25 mg, 16.8%, first eluting): LCMS (Method E): R_T =
- 25 3.56 min, *m/z* = 427 [M+H]⁺; and the title compound (35 mg, 21%, second eluting): LCMS (Method E): R_T = 2.60 min, *m/z* = 427 [M+H]⁺.

- Step 3: 4-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-methyl-1-phenyl-1,2-dihydro-3H-pyrazol-3-one hydrochloride*: Prepared according to General Procedure 1 using *tert*-butyl 6-((2-methyl-3-oxo-1-phenyl-2,3-dihydro-1H-pyrazol-4-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (32 mg, 75.0 μmol), 4M HCl in 1,4-dioxane (0.375 mL) and 1,4-dioxane (3.0
- 30

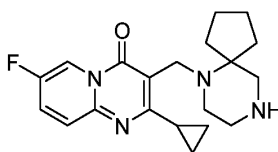
mL) to give the title compound (28.0 mg, quantitative). LCMS (Method A): $R_T = 0.42$ min, $m/z = 327$ $[M+H]^+$.

Intermediate 82: 6-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-5H-thiazolo[3,2-a]pyrimidin-5-one hydrochloride



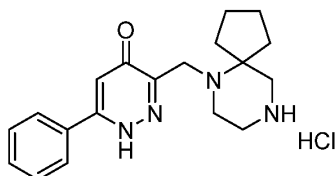
The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (Intermediate 47) except using 5H-thiazolo[3,2-a]pyrimidin-5-one [commercially available] instead of 7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one in Step 1 to give the title compound. LCMS (Method A): $R_T = 0.39$ min, $m/z = 305$ $[M+H]^+$.

Intermediate 83: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-cyclopropyl-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one



5-Fluoro-2-aminopyridine (5.0 g, 45 mmol), ethyl 3-cyclopropyl-3-oxopropanoate (16.4 g, 90 mmol) and bismuth(III) chloride (0.7 g, 2.2 mmol) were stirred at reflux for 24 h. The reaction mixture was evaporated to dryness, dissolved in diphenylether (100 mL) and heated to 100 °C for 24 h. After cooling to rt, the reaction mixture was purified by flash chromatography to give 2-cyclopropyl-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one (4.1 g, 43%). LCMS (Method D): $R_T = 0.87$ min, $m/z = 205$ $[M+H]^+$. Subsequently, the title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (Intermediate 47) except using 2-cyclopropyl-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one instead of 7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one in Step 1 and dissolving the HCl salt in the final step and washing with saturated sodium bicarbonate_(aq) to give the title compound as the free base. LCMS (Method A): $R_T = 0.59$ min, $m/z = 357$ $[M+H]^+$.

Intermediate 84: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridazin-4(1H)-one hydrochloride



Step 1: 4-Methoxy-6-phenylpyridazin-3(2H)-one: To a stirred solution of 4-methoxy-6-chloropyridazin-3(2H)-one (6.0 g, 37.5 mmol) [commercially available] in 1,4-dioxane (130 mL)/water (45 mL) were added phenylboronic acid (5.0 g, 41 mmol), Pd(dppf)Cl₂ (1.5 g, 5 mol%) and potassium phosphate tribasic (24.0 g, 112 mmol). The reaction mixture was degassed and backfilled using argon and heated to reflux. After 24 h, the solvents were removed *in vacuo* and the remaining residue was dissolved in hot water (200 mL), filtered, and acidified using HCl_(aq) to ~pH 3. The resultant precipitate was filtered, washed with water, and dried under vacuum to give the title compound (7.1 g, 94%). LCMS (Method D): R_T = 0.98 min, *m/z* = 203 [M+H]⁺.

Step 2: 3-Chloro-4-methoxy-6-phenylpyridazine: 4-Methoxy-6-phenylpyridazin-3(2H)-one (6.5 g, 62 mmol) was suspended in POCl₃ (80 mL) and stirred at reflux for 4 h. After evaporation of excess POCl₃, iced water was added to the remaining residue. After 1 h, the aqueous mixture was extracted using DCM. The combined organic phase was concentrated under reduced pressure and the resultant residue was dissolved in MeCN and reevaporated to give the title compound (4.4 g, 98%). LCMS (Method D): R_T = 1.16 min, *m/z* = 221 [M+H]⁺.

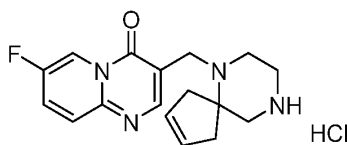
Step 3: (4-Methoxy-6-phenylpyridazin-3-yl)methanol: To a stirred solution of 3-chloro-4-methoxy-6-phenylpyridazine (3.6 g, 16 mmol) in 1,4-dioxane (90 mL) were added tributylstannylmethanol (6.94 g, 24 mmol) and XPhos Pd G4 (0.9 g, 10 mol%). The reaction mixture was degassed and purged with argon and heated to 60 °C. After 48 h, the solvents were removed *in vacuo*, the remaining residue was triturated in diethyl ether (70 mL), filtered, and purified by flash chromatography to give the title compound (0.4 g, 43%). LCMS (Method D): R_T = 0.60 min, *m/z* = 251 [M+Cl]⁻.

Step 4: tert-Butyl 6-((4-oxo-6-phenyl-1,4-dihydropyridazin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate: To a stirred solution of (4-methoxy-6-phenylpyridazin-3-yl)methanol (0.38 g, 1.8 mmol) in DCM (20 mL) was added thionyl chloride (3.0 mL) at rt. After 4 h, the solvents were removed *in vacuo* and the remaining residue was dissolved in MeCN (100 mL), followed by the addition of DIPEA (0.7 g, 5.4 mmol) and *tert*-butyl 6,9-

diazaspiro[4.5]decane-9-carboxylate (0.45 g, 1.9 mmol). The resultant suspension was stirred at 80 °C for 24 h. The reaction mixture was concentrated under reduced pressure and the remaining residue was partitioned between DCM and brine, separated, and the organic phase was dried (Na₂SO₄). The solvents were removed *in vacuo* and the remaining residue was dissolved in 40% HBr_(aq) (15 mL) and heated at 80 °C. After 48 h, the reaction mixture was concentrated under reduced pressure and the remaining residue was suspended in MeCN (25 mL) and triethylamine (1.5 mL). After cooling to 0 °C, Boc₂O (0.42 g, 1.9 mmol) was added dropwise. The solvents were removed *in vacuo* and the remaining residue was washed using water and purified by preparative HPLC to give the title compound (0.10 g, 22%). LCMS (Method D): R_T = 0.86 min, *m/z* = 425 [M+H]⁺.

Step 5: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridazin-4(1H)-one hydrochloride: Prepared according to General Procedure 1 using *tert*-butyl 6-((4-oxo-6-phenyl-1,4-dihydropyridazin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (109 mg, 257 μmol), 4M HCl in 1,4-dioxane (1.28 mL) and 1,4-dioxane (4.0 mL) to give the title compound (71 mg, 77%). LCMS (Method A): R_T = 0.51 min, *m/z* = 325 [M+H]⁺.

Intermediate 85: 3-((6,9-Diazaspiro[4.5]dec-2-en-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-*a*]pyrimidin-4-one hydrochloride



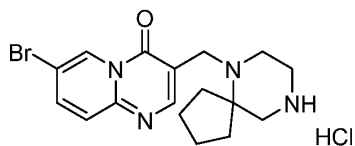
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Step 1: tert-Butyl 3,3-diallylpiperazine-1-carboxylate: To a stirred solution of *tert*-butyl 3-oxopiperazine-1-carboxylate (6.0 g, 30 mmol) in THF (80 mL) was added triallylborane (16.4 g, 90 mmol). The reaction mixture was stirred at 70 °C. After 14 h, the solvents were removed *in vacuo* and the remaining residue was partitioned between DCM (100 mL) and 2M NaOH_(aq) (100 mL). The resultant biphasic mixture was separated, extracted (3 x DCM), dried (Na₂SO₄), the solvents were removed *in vacuo*, and the remaining residue was purified by flash chromatography to give the title compound (5.1 g, 49%). ¹H NMR (500 MHz, CDCl₃): δ 5.78 (m, 2H), 5.11 (m, 4H), 3.37 (m, 2H), 3.20 (s, 2H), 2.79 (m, 2H), 2.16 (m, 4H), 1.45 (s, 9H).

30

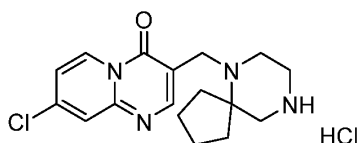
- Step 2: *tert*-Butyl 3,3-diallyl-4-(2,2,2-trifluoroacetyl)piperazine-1-carboxylate: To a stirred solution of *tert*-butyl 3,3-diallylpiperazine-1-carboxylate (5.50 g, 19 mmol) in DCM (100 mL) at 0 °C was added triethylamine (2.4 g, 23 mmol), followed by dropwise addition of trifluoroacetic anhydride (4.3 g, 20.5 mmol). After 24 h, the reaction mixture was partitioned between DCM and water, separated, the organic phase was washed several times using water, dried (Na₂SO₄), and the solvents were removed *in vacuo* to give the title compound (6.9 g, 99%). ¹H NMR (500 MHz, CDCl₃): δ 5.67 (m, 2H), 5.12 (m, 4H), 3.64 (m, 4H), 3.45 (m, 2H), 2.94 (m, 2H), 2.43 (m, 2H), 1.45 (d, 9H).
- Step 3: *tert*-Butyl 6,9-diazaspiro[4.5]dec-2-ene-9-carboxylate: To a pre-degassed (bubbling argon for 15 min) and stirred solution of *tert*-butyl 3,3-diallyl-4-(2,2,2-trifluoroacetyl)piperazine-1-carboxylate (6.90 g, 19 mmol) in DCM (200 mL) was added Grubbs Catalyst® M204 (0.6 g, 5 mol%) at rt. After 48 h, 2M NaOH_(aq) solution was added and the resultant mixture was heated at 40 °C. After a further 24 h, the organic phase was decanted, dried (Na₂SO₄), the solvents were removed *in vacuo*, and the remaining residue was purified by flash chromatography to give the title compound (3.2 g, 71%). ¹H NMR (500 MHz, CDCl₃): δ 5.68 (m, 2H), 3.42 (m, 2H), 3.27 (s, 2H), 2.85 (m, 2H), 2.40 (m, 2H), 2.25 (m, 2H), 1.81 (br s, 1H), 1.46 (s, 9H).
- Step 4: *tert*-Butyl 6-((7-fluoro-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]dec-2-ene-9-carboxylate: To a stirred solution of 3-chloromethyl-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one (0.70 g, 3.3 mmol) and DIPEA (1.7 g, 13.2 mmol) in MeCN (30 mL) was added *tert*-butyl 6,9-diazaspiro[4.5]dec-2-ene-9-carboxylate (0.94 g, 4 mmol). The resultant suspension was stirred at 80 °C. After 18 h, the solvents were removed *in vacuo*, and the remaining residue was partitioned between DCM and brine, separated, and extracted using DCM. The combined organic phase was dried (Na₂SO₄), the solvents were removed *in vacuo*, and the remaining residue was purified by flash chromatography to give the title compound (0.53 g, 39%). LCMS (Method D): R_T = 0.67 min, *m/z* = 415 [M+H]⁺.
- Step 5: 3-((6,9-Diazaspiro[4.5]dec-2-en-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride: Prepared according to General Procedure 1 using *tert*-butyl 6-((7-fluoro-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]dec-2-ene-9-carboxylate (50 mg, 121 μmol), 4M HCl in 1,4-dioxane (0.25 mL) and DCM (0.25 mL) to give the title compound (42.2 mg, quantitative). LCMS (Method C): R_T = 0.49 min, *m/z* = 315 [M+H]⁺.

Intermediate 86: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-7-bromo-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride



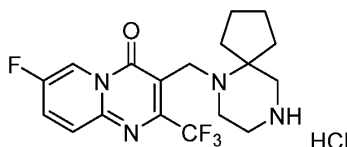
The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (Intermediate 47) except using 7-bromo-4H-pyrido[1,2-a]pyrimidin-4-one [commercially available] instead of 7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one in Step 1 to give the title compound. LCMS (Method C): $R_T = 0.57$ min, $m/z = 377$ $[M+H]^+$.

Intermediate 87: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-8-chloro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride



The title compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride (Intermediate 47) except using 8-chloro-4H-pyrido[1,2-a]pyrimidin-4-one [commercially available] instead of 7-fluoro-4H-pyrido[1,2-a]pyrimidin-4-one in Step 1 to give the title compound. LCMS (Method C): $R_T = 0.52$ min, $m/z = 333$ $[M+H]^+$.

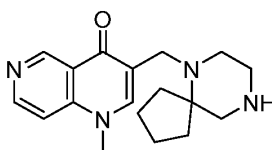
Intermediate 88: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin-4-one hydrochloride



5-Fluoro-2-aminopyridine (5.0 g, 45 mmol), ethyl 4,4,4-trifluoro-3-oxobutanoate (16.4 g, 90 mmol) and bismuth(III) chloride (0.7 g, 2.2 mmol) were stirred at reflux for 24 h. The reaction mixture was evaporated to dryness, dissolved in diphenylether (100 mL), and heated to 100 °C for 24 h. After cooling to rt, the reaction mixture was purified by flash chromatography to give 7-fluoro-2-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin-4-one (5.1 g, 49%). LCMS (Method D): $R_T = 1.13$ min, $m/z = 233$ $[M+H]^+$. Subsequently, the title

compound was prepared similarly to 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one hydrochloride (Intermediate 47) except using 7-fluoro-2-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one instead of 7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one in Step 1 to give the title compound. LCMS (Method C): $R_T = 0.78$ min, $m/z = 385$ $[M+H]^+$.

Intermediate 89: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-1,6-naphthyridin-4(1*H*)-one



Step 1: Ethyl 1-methyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylate: To a stirred solution ethyl 4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylate (1.50 g, 6.87 mmol) [commercially available] in DMF (20 mL) was added K_2CO_3 (1.90 g, 13.8 mmol) and iodomethane (0.26 mL, 3.43 mmol) at rt. After 16 h, the reaction mixture was concentrated *in vacuo*, the remaining residue was diluted with 9:1 DCM/MeOH (75 mL) and washed using water (30 mL) and brine (30 mL). The organic phase was dried (Na_2SO_4), the solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography (10% MeOH in DCM) to give the title compound (720 mg, 45%). LCMS (Method E): $R_T = 1.59$ min, $m/z = 233$ $[M+H]^+$.

Step 2: 1-Methyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid: To a stirred solution of ethyl 1-methyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylate (0.4 g, 1.72 mmol) in 4:1 THF/water (10 mL) was added $LiOH \cdot H_2O$ (0.18 g, 4.31 mmol) at 0 °C. The reaction mixture was stirred at rt for 16 h. The solvents were removed *in vacuo* and the remaining residue was diluted with water (30 mL) and acidified with glacial acetic acid to ~pH 2. The resultant precipitate was filtered and dried under vacuum to give the title compound (200 mg, 57%). LCMS (Method E): $R_T = 0.59$ min, $m/z = 205$ $[M+H]^+$.

Step 3: 3-Bromo-1-methyl-1,6-naphthyridin-4(1*H*)-one: To a stirred solution of 1-methyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid (0.2 g, 0.98 mmol) in 5:1 DMF/water (6 mL) were added lithium acetate (0.078 g, 1.17 mmol) and NBS (0.74 g, 4.11 mmol). The reaction mixture was heated under microwave irradiation at 85 °C for 10 min. The reaction mixture was diluted with water (10 mL), 5M sodium carbonate_(aq) solution (20 mL) was

added, and stirred for 30 min. The resultant biphasic mixture was separated, the aqueous phase was extracted using EtOAc (50 mL) and the combined organic phase was dried (Na₂SO₄). The solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography (0-80% EtOAc in hexane) to give the title compound (100 mg, 43%).

5 LCMS (Method E): R_T = 1.49 min, *m/z* = 239 [M+H]⁺.

Step 4: 3-(((tert-Butyldimethylsilyl)oxy)methyl)-1-methyl-1,6-naphthyridin-4(1H)-one: A

stirred solution of 3-bromo-1-methyl-1,6-naphthyridin-4(1H)-one (0.14 g, 0.58 mmol) in 1,4-dioxane (5 mL) was degassed by bubbling argon for 20 min. *tert*-

10 butyldimethyl[(tributylstannyl)methoxy]silane (0.25 g, 0.58 mmol) and XPhos Pd G2 (0.046 g, 0.06 mmol) were added and the reaction mixture was stirred at 80 °C for 24 h. The reaction mixture was filtered through Celite®, the filtrate was concentrated *in vacuo* and the remaining residue was purified by flash chromatography (0-30% EtOAc in hexane) to give the title compound (80 mg, 45%). LCMS (Method E): R_T = 1.28 min, *m/z* = 305 [M+H]⁺.

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Step 5: 3-(Hydroxymethyl)-1-methyl-1,6-naphthyridin-4(1H)-one: To a stirred solution of 3-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-methyl-1,6-naphthyridin-4(1H)-one (0.07 g, 0.23 mmol) in THF (3 mL) was added TBAF (0.09 mL, 0.35 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with water (10 mL) and washed

20 using EtOAc (20 mL). The aqueous phase was concentrated *in vacuo* and dried under vacuum to give the title compound (40 mg, crude) and used in the next step without further purification. LCMS (Method F): R_T = 0.66 min, *m/z* = 191 [M+H]⁺.

Step 6: 3-(Chloromethyl)-1-methyl-1,6-naphthyridin-4(1H)-one: To a stirred solution of 3-

25 (hydroxymethyl)-1-methyl-1,6-naphthyridin-4(1H)-one (100 mg, 0.52 mmol) in DCM (5 mL) was added SOCl₂ (0.11 mL, 1.55 mmol) at 0 °C. The reaction mixture was stirred at 50 °C for 4 h. The reaction mixture was concentrated *in vacuo* to give the title compound (100 mg, crude) that was used in the next step without further purification.

Step 7: tert-Butyl 6-((1-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-3-yl)methyl)-6,9-

diazaspiro[4.5]decane-9-carboxylate: To a stirred solution of 3-(chloromethyl)-1-methyl-1,6-naphthyridin-4(1H)-one (100 mg, assumed 0.48 mmol) in MeCN (5 mL) were added *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate (0.14 g, 0.57 mmol) and Cs₂CO₃ (0.31 g, 0.96 mmol) at rt. After 2 h, the reaction mixture was diluted with water (25 mL) and

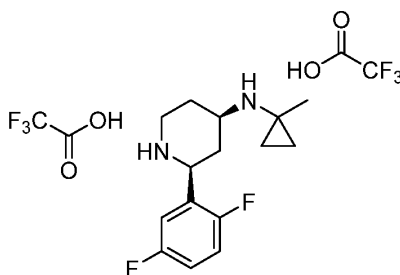
35 extracted using EtOAc (3 x 30 mL). The combined organic phase was washed using brine

(30 mL), dried (Na₂SO₄), the solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography (0-5% MeOH in DCM) to give the title compound (15 mg, 7% over 2 steps). LCMS (Method E): R_T = 2.43 min, *m/z* = 413 [M+H]⁺.

- 5 **Step 8: 3-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-1,6-naphthyridin-4(1H)-one:**
Prepared according to General Procedure 1 using *tert*-butyl 6-((1-methyl-4-oxo-1,4-dihydro-1,6-naphthyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (10.5 mg, 121 μmol), TFA (0.1 mL) and DCM (0.4 mL) to give the title compound (4.0 mg, 50%). LCMS (Method C): R_T = 0.36 min, *m/z* = 313 [M+H]⁺.

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Intermediate 90: (2*S*,4*R*)-2-(2,5-Difluorophenyl)-*N*-(1-methylcyclopropyl)piperidin-4-amine bis(2,2,2-trifluoroacetate)



- Step 1: *tert*-Butyl (2*S*)-2-(2,5-difluorophenyl)-4-((1-methylcyclopropyl)amino)piperidine-1-carboxylate:** To a stirred solution of *tert*-butyl (2*S*)-2-(2,5-difluorophenyl)-4-oxopiperidine-1-carboxylate (1 g, 3.21 mmol) [prepared according to WO2022200523 Intermediate 19, Step 5] in MeOH (20 mL) was added 1-methylcyclopropan-1-amine.HCl (0.52 g, 4.82 mmol) at rt. After 2 h, NaBH₃CN (0.61 g, 9.64 mmol) was added portionwise. After 16 h, the solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography (0-50% EtOAc in hexane) to give the title compound (0.7 g, 59%). LCMS (Method E): R_T = 1.73 min, *m/z* = 367 [M+H]⁺.

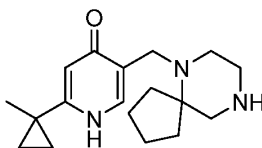
- Step 2: *tert*-Butyl (2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(2,2,2-trifluoro-*N*-(1-methylcyclopropyl)acetamido)piperidine-1-carboxylate:** To a stirred solution of *tert*-butyl (2*S*)-2-(2,5-difluorophenyl)-4-((1-methylcyclopropyl)amino)piperidine-1-carboxylate (0.6 g, 1.63 mmol) and triethylamine (1.14 mL, 8.19 mmol) in DCM (10 mL) was added trifluoroacetic anhydride (0.43 mL, 3.11 mmol) at 0 °C. The reaction mixture was stirred at rt for 16 h. The solvents were removed *in vacuo* and the remaining crude mixture of diastereoisomers was purified and separated by flash chromatography (0-20% EtOAc in hexane) to give *tert*-butyl (2*S*,4*S*)-2-(2,5-difluorophenyl)-4-(2,2,2-trifluoro-*N*-(1-

methylcyclopropyl)acetamido)piperidine-1-carboxylate (140 mg, 18%, de = 99%) as first eluting trans diastereoisomer. LCMS (Method E): $R_T = 4.01$ min, $m/z = 463$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6 @ 100 °C): δ 7.25 – 7.16 (m, 2 H), 7.01 (s, 1H), 5.55 (s, 1H), 4.10 – 4.07 (m, 1H), 3.67 (br s, 1H), 3.25 – 3.19 (m, 1H), 2.66 (br s, 1H), 2.31 – 2.16 (m, 2H), 1.90 – 1.87 (m, 1H), 1.36 – 1.32 (m, 12H), 1.19 – 0.75 (m, 4H); and the title compound (130 mg, 17%, de = 98%) as the second eluting cis diastereoisomer. LCMS (Method E): $R_T = 4.01$ min, $m/z = 463$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6 @ 100 °C): δ 7.16 – 7.15 (m, 1H), 7.07 – 7.05 (m, 2 H), 4.93 – 4.90 (m, 1H), 3.93 (br s, 2H), 3.62 – 3.57 (t, 1H), 2.66 – 2.57 (m, 1H), 2.16 (br s, 1H), 1.95 – 1.87 (m, 2H), 1.41 (s, 3H), 1.23 (s, 9H), 1.12 – 1.07 (m, 2H), 0.84 (br s, 2H). [Note: cis and trans stereochemistry was assigned by comparison of NMR data with closely related analogues].

Step 3: tert-Butyl (2S,4R)-2-(2,5-difluorophenyl)-4-((1-methylcyclopropyl)amino)piperidine-1-carboxylate: To a stirred solution of *tert*-butyl (2S,4R)-2-(2,5-difluorophenyl)-4-[(1-methylcyclopropyl)-(2,2,2-trifluoroacetyl)amino]piperidine-1-carboxylate (30 mg, 0.065 mmol) in MeOH (0.50 mL) were added K_2CO_3 (72 mg, 0.52 mmol) and water (0.10 mL). The reaction mixture was heated under microwave irradiation at 100 °C for 3 h. The solvents were removed *in vacuo* and the remaining residue was partitioned between water and DCM, separated, the aqueous phase was extracted (2 x DCM), and the combined organic phase was dried (phase separator). The solvents were removed *in vacuo* and the remaining residue was dissolved in DCM and loaded onto a pre-equilibrated SCX-2 cartridge. The column was washed with a 4:1 mixture of DCM/MeOH and the basic compound was eluted using a 4:1 mixture of DCM/7M NH_3 in MeOH. The ammoniacal fractions were concentrated *in vacuo* to give the title compound (12 mg, 50%) that was used directly in the next step without further purification. LCMS (Method A): $R_T = 0.90$ min, $m/z = 311$ $[M-butene+H]^+$.

Step 4: (2S,4R)-2-(2,5-Difluorophenyl)-N-(1-methylcyclopropyl)piperidin-4-amine bis(2,2,2-trifluoroacetate): To a stirred solution of *tert*-butyl (2S,4R)-2-(2,5-difluorophenyl)-4-[(1-methylcyclopropyl)amino]piperidine-1-carboxylate (12 mg, 0.033 mmol) in DCM (0.5 mL) was added TFA (0.13 mL, 1.64 mmol) at rt. After 4 h, the solvents were removed *in vacuo* to give the title compound (16 mg, 98%) that was used directly in the next step without further purification. LCMS (Method A): $R_T = 0.17$ min, $m/z = 267$ $[M+H]^+$.

Intermediate 91: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(1-methylcyclopropyl)pyridin-4(1H)-one



Step 1: 4-Methoxy-6-(prop-1-en-2-yl)nicotinic acid: To a stirred solution of 6-chloro-4-methoxynicotinic acid (15.3 g, 80 mmol) in 1,4-dioxane (350 mL)/water (120 mL) were added potassium trifluoro(prop-1-en-2-yl)borate (13.3 g, 88 mmol), Pd(dppf)Cl₂ (3.06 g, 5 mol%) and potassium phosphate tribasic (52.0 g, 240 mmol) at rt. The resultant mixture was degassed and backfilled using argon and heated to reflux. After 24 h, the solvents were removed *in vacuo*, the remaining residue was dissolved in hot water (200 mL), filtered, and acidified using HCl_(aq) to ~pH 3. The resultant precipitate was filtered, washed using water and dried under vacuum to give the title compound (14.0 g, 91%). LCMS (Method D): R_T = 0.59 min, *m/z* = 194 [M+H]⁺.

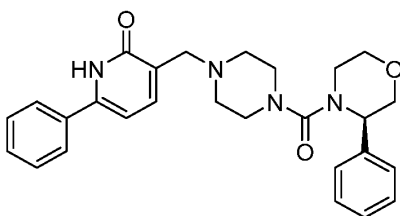
Step 2: (4-Methoxy-6-(1-methylcyclopropyl)pyridin-3-yl)methanol: To a stirred solution of 4-methoxy-6-(prop-1-en-2-yl)nicotinic acid (12 g, 62 mmol) in MTBE (300 mL) was added a 2M solution of diazomethane in diethyl ether (300 mL). The reaction mixture was stirred at reflux for 24 h. After cooling, the reaction mixture was concentrated *in vacuo* and the remaining residue was dissolved in THF (250 mL). Borane.DMS complex (11 g, 186 mmol) was added and the suspension was stirred at rt. After 48 h, MeOH was added slowly until gas evolution ceased. The reaction mixture was partitioned between EtOAc and brine, separated, extracted, the combined organic phase was dried (NaSO₄), the solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography (0-10% EtOAc in hexane) to give the title compound (2.5 g, 98%). LCMS (Method D): R_T = 0.50 min, *m/z* = 194 [M+H]⁺.

Step 3: 5-(Chloromethyl)-4-methoxy-2-(1-methylcyclopropyl)pyridine: To a stirred solution of (4-methoxy-6-(1-methylcyclopropyl)pyridin-3-yl)methanol (8.6 g, 44 mmol) in DCM (170 mL) was added thionyl chloride (23.7 g, 186 mmol). The resultant suspension was stirred at 40 °C. After 24 h, the solvents were removed *in vacuo* and the remaining residue was dissolved in MeCN and reevaporated to give the title compound (2.6 g, 99%) that was used directly in the next step without further purification.

Step 4: tert-Butyl 6-((6-(1-methylcyclopropyl)-4-oxo-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate: To a stirred solution of 5-(chloromethyl)-4-methoxy-2-(1-methylcyclopropyl)pyridine (4.0 g, 19 mmol) and DIPEA (7.3 g, 57 mmol) in MeCN (150 mL) was added *tert*-butyl 6,9-diazaspiro[4.5]decane-9-carboxylate (4.5 g, 19 mmol). The resultant suspension was stirred at 80 °C. After 24 h, the solvents were removed *in vacuo* and the remaining residue was partitioned between DCM and brine, separated, extracted, and the combined organic phase was dried (Na₂SO₄). The solvents were removed *in vacuo* and the remaining residue was dissolved in 40% HBr_(aq) solution (100 mL) and the resultant solution was stirred at 80 °C. After 48 h, the reaction mixture was evaporated under reduced pressure and the remaining residue was suspended in MeCN (250 mL) and triethylamine (15 mL). After cooling to 0 °C, Boc₂O (4.2 g, 19 mmol) was added dropwise. The solvents were removed *in vacuo* and the remaining residue was washed using water, dried under vacuum, and purified by flash chromatography to give the title compound containing material (1.0 g, 13% by mass recovered) [Caution: see below]. LCMS (Method D): R_T = 0.94 min, *m/z* = 402 [M+H]⁺.

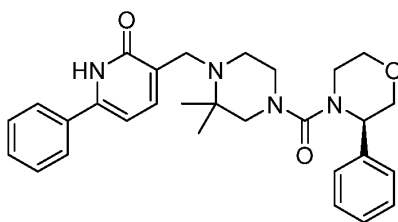
Step 5: 5-((6,9-Diazaspiro[4.5]decan-6-yl)methyl)-2-(1-methylcyclopropyl)pyridin-4(1H)-one: Prepared according to General Procedure 1 using *tert*-butyl 6-((6-(1-methylcyclopropyl)-4-oxo-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxylate (100 mg, 249 μmol), TFA (0.50 mL) and DCM (1.0 mL) to give the title compound containing material (82 mg, quantitative by mass recovered). [Note: that the material was subsequently found to contain only 6% of the title compound along with two alkene containing side products at 85% and 9%, respectively, that were carried through from the previous step due to potential cyclopropyl decomposition but nevertheless was used in the next step to successfully prepare the desired product after purification to remove the unwanted alkene products]. LCMS (Method C): R_T = 0.45 min, *m/z* = 302 [M+H]⁺.

Example 1: (*R*)-6-Phenyl-3-((4-(3-phenylmorpholine-4-carbonyl)piperazin-1-yl)methyl)pyridin-2(1H)-one



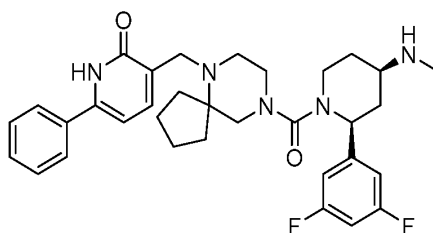
Prepared according to General Procedure 3 using triphosgene (20.1 mg, 0.068 mmol), pyridine (54 μ L, 0.68 mmol) and anhydrous MeCN (0.5 mL) at 0 °C then (*R*)-3-phenylmorpholine (26.5 mg, 0.16 mmol) [commercially available] and anhydrous MeCN (0.5 mL) then 6-phenyl-3-(piperazin-1-ylmethyl)pyridin-2(1*H*)-one dihydrochloride (46.3 mg, 0.14 mmol) [Intermediate 1] and DIPEA (165 μ L, 0.95 mmol) to give the title compound (23.8 mg, 38%). LCMS (Method A): R_T = 0.73 min, m/z = 459 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6): δ 11.78 (br s, 1H), 7.81 – 7.67 (m, 2H), 7.54 – 7.42 (m, 4H), 7.38 – 7.26 (m, 4H), 7.25 – 7.16 (m, 1H), 6.60 (br s, 1H), 4.51 (t, 1H), 3.83 (dd, 1H), 3.74 (dd, 1H), 3.72 – 3.68 (m, 1H), 3.67 – 3.61 (m, 1H), 3.37 (s, 2H), 3.36 – 3.32 (m, 2H), 3.28 – 3.22 (m, 2H), 3.17 – 3.06 (m, 2H), 2.45 – 2.37 (m, 4H).

Example 2: (*R*)-3-((2,2-Dimethyl-4-(3-phenylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one



Prepared according to General Procedure 3 using triphosgene (18.1 mg, 0.061 mmol), pyridine (49 μ L, 0.61 mmol) and anhydrous MeCN (0.5 mL) at 0 °C then (*R*)-3-phenylmorpholine (23.8 mg, 0.15 mmol) and anhydrous MeCN (0.5 mL); then 3-((2,2-dimethylpiperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one (36.2 mg, 0.12 mmol) [Intermediate 2] and DIPEA (128 μ L, 0.73 mmol) to give the title compound (10.5 mg, 17%). LCMS (Method A): R_T = 0.76 min, m/z = 487 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6): δ 11.75 (br s, 1H), 7.81 (m, 2H), 7.57 (s, 1H), 7.52 – 7.40 (m, 3H), 7.38 – 7.28 (m, 4H), 7.23 (t, 1H), 6.58 (br s, 1H), 4.48 (t, 1H), 3.86 – 3.60 (m, 4H), 3.42 – 3.34 (m, 2H), 3.20 – 2.99 (m, 4H), 2.48 – 2.40 (m, 4H), 1.00 (s, 3H), 0.97 (s, 3H).

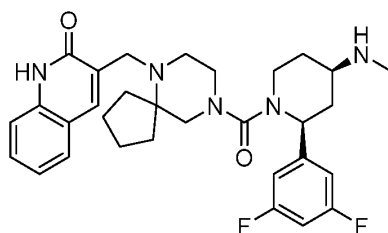
Example 3: 3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one



Step 1: *N*-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-1-(6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl)piperidin-4-yl)-2,2,2-trifluoro-*N*-methylacetamide: Prepared according to General Procedure 3 using triphosgene (13.1 mg, 0.044 mmol), pyridine (44 μ L, 0.55 mmol) and anhydrous MeCN (0.5 mL) at 0 $^{\circ}$ C; then *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoro-*N*-methylacetamide hydrochloride (39.5 mg, 0.11 mmol) [prepared according to WO2022200523], DIPEA (28.8 μ L, 0.17 mmol) and anhydrous MeCN (0.5 mL); then 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (35.6 mg, 0.11 mmol) [Intermediate 3] and DIPEA (96 μ L, 0.55 mmol) to give the title compound (18.2 mg, 25%). LCMS (Method A): R_T = 0.99 min, m/z = 672 $[M+H]^+$.

Step 2: 3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one: Prepared according to General Procedure 4 using *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)-1-(6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl)piperidin-4-yl)-2,2,2-trifluoro-*N*-methylacetamide (18.2 mg, 0.027 mmol), potassium carbonate (18.7 mg, 0.14 mmol), MeOH (0.25 mL) and water (0.025 mL) to give the title compound (13.4 mg, 85%). LCMS (Method A): R_T = 0.63 min, m/z = 576 $[M+H]^+$. 1H (500 MHz, DMSO- d_6): δ 7.73 (d, 2H), 7.56 (d, 1H), 7.50 – 7.41 (m, 3H), 7.00 (tt, 1H), 6.95 – 6.88 (m, 2H), 6.60 (d, 1H), 4.02 (dd, 1H), 3.62 – 3.40 (m, 2H), 3.36 – 3.32 (m, 2H), 3.29 – 3.22 (m, 3H), 3.11 – 2.92 (m, 1H), 2.70 – 2.62 (m, 1H), 2.46 – 2.38 (m, 3H), 2.24 (s, 3H), 1.96 (d, 1H), 1.89 (d, 1H), 1.66 – 1.38 (m, 6H), 1.38 – 1.27 (m, 2H), 1.27 – 1.10 (m, 2H).

Example 4: 3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)quinolin-2(1*H*)-one



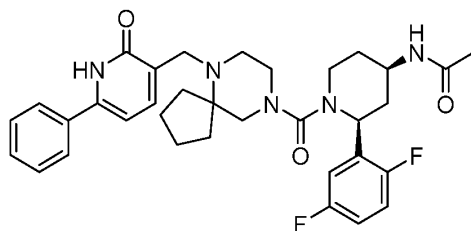
Step 1: N-((2S,4R)-2-(3,5-Difluorophenyl)-1-(6-((2-oxo-1,2-dihydroquinolin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)-2,2,2-trifluoro-N-methylacetamide:

Prepared according to General Procedure 3 using triphosgene (15.5 mg, 0.052 mmol),
 5 pyridine (52 μ L, 0.65 mmol) and anhydrous MeCN (0.5 mL) at 0 °C then *N-((2S,4R)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoro-N-methylacetamide hydrochloride* (46.7 mg, 0.13 mmol) [prepared according to WO2022200523], DIPEA (34 μ L, 0.20 mmol) and anhydrous MeCN (0.5 mL); then 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)quinolin-2(1*H*)-one (38.7 mg, 0.13 mmol) [Intermediate 4] and DIPEA (114 μ L, 0.65 mmol) to give the title
 10 compound (16.8 mg, 20%). LCMS (Method A): R_T = 1.00 min, m/z = 646 [M+H]⁺.

Step 2: 3-((9-((2S,4R)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)quinolin-2(1H)-one: Prepared according to General

Procedure 4 using *N-((2S,4R)-2-(3,5-difluorophenyl)-1-(6-((2-oxo-1,2-dihydroquinolin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)-2,2,2-trifluoro-N-*
 15 *methylacetamide* (16.8 mg, 0.026 mmol), potassium carbonate (18.0 mg, 0.13 mmol), MeOH (0.25 mL) and water (0.025 mL) to give the title compound (6.1 mg, 39%). LCMS (Method A): R_T = 0.60 min, m/z = 550 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.77 (br s, 1H), 7.90 (s, 1H), 7.67 (d, 1H), 7.45 (dt, 1H), 7.30 (d, 1H), 7.16 (dt, 1H), 7.00 (tt, 1H), 6.91 (dd, 2H), 4.02 (dd, 1H), 3.61 – 3.52 (m, 1H), 3.51 – 3.436 (m, 1H), 3.42 – 3.33 (m, 2H),
 20 3.30 – 3.22 (m, 2H), 3.09 – 2.94 (m, 1H), 2.71 – 2.61 (m, 1H), 2.48 – 2.38 (m, 3H), 2.24 (s, 3H), 1.96 (d, 1H), 1.89 (d, 1H), 1.70 – 1.39 (m, 7H), 1.39 – 1.27 (m, 2H), 1.27 – 1.20 (m, 1H), 1.20 – 1.11 (m, 1H).

25 Example 5: *N-((2S,4R)-2-(2,5-Difluorophenyl)-1-(6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)acetamide*



Step 1: N-((2S,4R)-2-(2,5-Difluorophenyl)-1-(6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)-2,2,2-trifluoroacetamide:

Prepared according to General Procedure 3 using triphosgene (13.8 mg, 0.047 mmol),
 5 pyridine (47 μ L, 0.58 mmol) and anhydrous MeCN (0.5 mL) at 0 °C then *N-((2S,4R)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride* (40.2 mg, 0.12 mmol) [prepared according to WO2022200523], DIPEA (30.5 μ L, 0.17 mmol) and anhydrous MeCN (0.5 mL); then 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (37.7 mg, 0.12 mmol) and DIPEA (102 μ L, 0.58 mmol) to give the title compound (41.2 mg,
 10 54%). LCMS (Method A): R_T = 0.93 min, m/z = 658 [M+H]⁺.

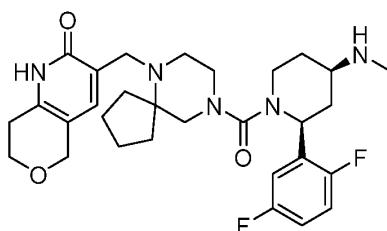
Step 2: 3-((9-((2S,4R)-4-Amino-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1H)-one: Prepared according to General Procedure 4 using *N-((2S,4R)-2-(2,5-difluorophenyl)-1-(6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)-2,2,2-trifluoroacetamide* (41.2 mg, 0.063 mmol), potassium carbonate (43.3 mg, 0.31 mmol), MeOH (0.6 mL) and water (0.060 mL) to give the title compound (36.0 mg, 99%). LCMS (Method A): R_T = 0.62 min, m/z = 562 [M+H]⁺.

Step 3: N-((2S,4R)-2-(2,5-Difluorophenyl)-1-(6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)acetamide: To a stirred solution of 3-((9-((2S,4R)-4-amino-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (36.0 mg, 0.062 mmol) in anhydrous DCM (0.5 mL) was added acetic anhydride (6.5 μ L, 0.068 mmol) and DIPEA (33
 25 μ L, 0.19 mmol). After 2 h, the residue was partitioned between saturated NaHCO_{3(aq)} (1 mL) and DCM (1 mL), separated, and extracted using DCM (3 x 1 mL). The combined organic phase was dried (phase separator), the solvents were removed *in vacuo* and the residue was purified by flash chromatography (0-20% MeOH in DCM) and freeze-dried to give the title compound (29.8 mg, 77%). LCMS (Method A): R_T = 0.80 min, m/z = 604
 30 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.68 (br s, 1H), 7.80 (d, 1H), 7.77 – 7.67 (m,

2H), 7.56 (d, 1H), 7.51 – 7.41 (m, 3H), 7.16 (td, 1H), 7.10 – 6.97 (m, 2H), 6.58 (br s, 1H), 4.28 (d, 1H), 3.76 – 3.65 (m, 1H), 3.64 – 3.48 (m, 1H), 3.48 – 3.41 (m, 1H), 3.41 – 3.35 (m, 1H), 3.28 – 3.20 (m, 2H), 3.09 – 2.92 (m, 1H), 2.72 (t, 1H), 2.47 – 2.37 (m, 3H), 1.95 – 1.82 (m, 2H), 1.76 (s, 3H), 1.67 – 1.48 (m, 6H), 1.48 – 1.29 (m, 3H), 1.25 – 1.13 (m, 1H).

5

Example 6: 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1,5,7,8-tetrahydro-2*H*-pyrano[4,3-*b*]pyridin-2-one



- Step 1: tert-Butyl ((2*S*,4*R*)-1-(chlorocarbonyl)-2-(2,5-difluorophenyl)piperidin-4-yl)(methyl)carbamate:* A reaction vial containing a solution of triphosgene (136 mg, 0.46 mmol) in DCM (3 mL) was cooled to 0 °C before adding pyridine (0.37 mL, 4.60 mmol) and stirring for 10 min. A solution of *tert*-butyl ((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)(methyl)carbamate (150.0 mg, 0.46 mmol) in DCM (1 mL) was slowly added to the cooled solution and the reaction mixture was left to stir at rt overnight. The reaction mixture was then quenched with 0.5 M HCl_(aq) and the resulting mixture was extracted with DCM (x 3) using a phase separator. The combined organic phases were concentrated *in vacuo* to give the title compound (178 mg, quantitative) that was used in the next step without further purification.
- Step 2: tert-Butyl ((2*S*,4*R*)-2-(2,5-difluorophenyl)-1-(6-((2-oxo-1,5,7,8-tetrahydro-2*H*-pyrano[4,3-*b*]pyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)(methyl)carbamate:* Prepared according to General Procedure 7 using 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-1,5,7,8-tetrahydro-2*H*-pyrano[4,3-*b*]pyridin-2-one (30 mg, 98.9 μmol) [Intermediate 5], *tert*-butyl ((2*S*,4*R*)-1-(chlorocarbonyl)-2-(2,5-difluorophenyl)piperidin-4-yl)(methyl)carbamate (46 mg, 0.119 mmol) and DIPEA (86 μL, 0.494 mmol) in DCM (2 mL) to give the title compound (41 mg, 63%). LCMS (Method B): R_T = 0.98 min, *m/z* = 656 [M+H]⁺.

*Step 3: 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1,5,7,8-tetrahydro-2*H*-pyrano[4,3-*b*]pyridin-2-one:*

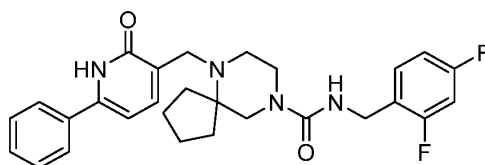
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Prepared according to General Procedure 1 using *tert*-butyl ((2*S*,4*R*)-2-(2,5-difluorophenyl)-1-(6-((2-oxo-1,5,7,8-tetrahydro-2*H*-pyrano[4,3-*b*]pyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)(methyl)carbamate (41 mg, 62.5 μ mol) and TFA (0.5 mL) in DCM (2 mL) to give the title compound (27 mg, 74%). LCMS (Method A):

5 R_T = 0.50 min (solvent front), m/z = 556 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6): δ 11.46 (s, 1H), 7.22 – 7.12 (m, 2H), 7.03 (dddd, 2H), 4.40 (s, 2H), 4.28 – 4.21 (m, 1H), 3.81 (t, 2H), 3.52 (s, 1H), 3.40 (s, 1H), 3.29 – 3.09 (m, 4H, obscured by HDO), 2.95 (d, 1H), 2.69 – 2.61 (m, 1H), 2.52 (d, 2H), 2.47 – 2.37 (m, 2H), 2.35 – 2.29 (m, 1H), 2.24 (s, 3H), 1.98 – 1.86 (m, 2H), 1.70 – 1.22 (m, 9H), 1.16 (dd, 2H).

10

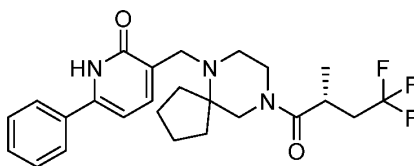
Example 7: *N*-(2,4-Difluorobenzyl)-6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxamide



To a stirred solution of 3-((6,9-diazaspiro[4.5]decane-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (30.7 mg, 0.095 mmol) in anhydrous DCM (1 mL) was added DIPEA (33 μ L, 0.19 mmol) followed by a solution of 2,4-difluoro-1-(isocyanatomethyl)benzene (16.1 mg, 0.095 mmol) in anhydrous DCM (1 mL) at rt. After 2 h, the mixture was partitioned with saturated NaHCO_{3(aq)} (2 mL), separated, and extracted using DCM (2 x 1 mL). The combined organic phase was dried (phase separator), the solvents were removed *in vacuo* and the residue was purified by flash chromatography (0-100% EtOAc in cyclohexane) followed by RP preparative HPLC and freeze-dried to give the title compound (14.8 mg, 31%). LCMS (Method A): R_T = 0.81 min, m/z = 493 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6): δ 11.73 (br s, 1H), 7.82 – 7.64 (m, 2H), 7.56 (d, 1H), 7.51 – 7.38 (m, 3H), 7.34 (dt, 1H), 7.17 (dt, 1H), 7.10 – 7.00 (m, 2H), 6.60 (br s, 1H), 4.24 (d, 2H), 3.41 – 3.32 (m, 4H), 3.22 – 3.15 (m, 2H), 2.39 (t, 2H), 1.70 – 1.54 (m, 6H), 1.49 – 1.38 (m, 2H).

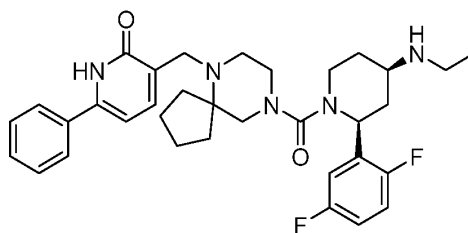
25

Example 8: (*R*)-6-Phenyl-3-((9-(4,4,4-trifluoro-2-methylbutanoyl)-6,9-diazaspiro[4.5]decane-6-yl)methyl)pyridin-2(1*H*)-one



Prepared according to General Procedure 5 using 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (25.0 mg, 0.077 mmol), (*R*)-4,4,4-trifluoro-2-methylbutanoic acid (12.1 mg, 0.077 mmol) [prepared according to WO2020115501], HATU (35.3 mg, 0.093 mmol), DIPEA (41 μ L, 0.23 mmol) and anhydrous DCM (1 mL). The crude material was purified by RP preparative HPLC to give the title compound (21.5 mg, 57%). LCMS (Method A): R_T = 0.81 min, m/z = 462 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6): δ 11.75 (br s, 1H), 7.78 – 7.67 (m, 2H), 7.62 – 7.54 (m, 1H), 7.52 – 7.40 (m, 3H), 6.77 – 6.42 (m, 1H), 3.60 – 3.49 (m, 1H), 3.43 (t, 1H), 3.38 – 3.33 (m, 2H), 3.24 (d, 1H), 3.18 – 3.06 (m, 1H), 2.80 – 2.68 (m, 1H), 2.46 – 2.44 (m, 2H), 2.40 – 2.20 (m, 2H), 1.78 – 1.32 (m, 8H), 1.16 – 1.04 (m, 3H).

Example 9: 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one

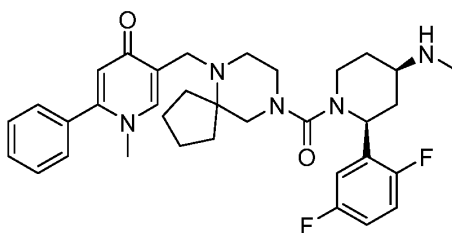


Step 1: (2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(*N*-ethyl-2,2,2-trifluoroacetamido)piperidine-1-carbonyl chloride: Prepared according to General Procedure 6 using triphosgene (11.9 mg, 0.040 mmol), pyridine (32 μ L, 0.40 mmol) and anhydrous DCM (1 mL) at 0 $^{\circ}$ C; then *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-*N*-ethyl-2,2,2-trifluoroacetamide hydrochloride (30.0 mg, 0.081 mmol) [prepared according to WO2022200523], DIPEA (21.1 μ L, 0.12 mmol) and anhydrous DCM (1 mL) to give the title compound (32.8 mg, quantitative) that was used in the next step without further purification.

Step 2: *N*-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-1-(6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl)piperidin-4-yl)-*N*-ethyl-2,2,2-trifluoroacetamide: Prepared according to General Procedure 7 using 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (28.6 mg, 0.089 mmol), (2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(*N*-ethyl-2,2,2-trifluoroacetamido)piperidine-1-carbonyl chloride (32.8 mg, 0.080 mmol), DIPEA (70.2 μ L, 0.40 mmol) and anhydrous DCM (1 mL) to give the title compound (39.4 mg, 71%). LCMS (Method A): R_T = 1.06 min, m/z = 686 $[M+H]^+$.

Step 3: 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one: Prepared according to General Procedure 4 using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)-1-(6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl)piperidin-4-yl)-*N*-ethyl-2,2,2-trifluoroacetamide (39.4 mg, 0.058 mmol), potassium carbonate (39.7 mg, 0.29 mmol), MeOH (0.5 mL) and water (0.05 mL) to give the title compound (27.8 mg, 81%). LCMS (Method A): R_T = 0.64 min, m/z = 590 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6): δ 7.78 – 7.66 (m, 2H), 7.56 (d, 1H), 7.51 – 7.38 (m, 3H), 7.20 – 7.10 (m, 1H), 7.10 – 6.98 (m, 2H), 6.60 (d, 1H), 4.26 (d, 1H), 3.66 – 3.40 (m, 2H), 3.38 – 3.33 (m, 2H), 3.28 – 3.18 (m, 3H), 3.07 – 2.92 (m, 1H), 2.67 (t, 1H), 2.61 – 2.54 (m, 3H), 2.46 – 2.32 (m, 3H), 1.92 (t, 2H), 1.67 – 1.26 (m, 8H), 1.26 – 1.14 (m, 2H), 0.97 (t, 3H).

Example 10: 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-phenylpyridin-4(1*H*)-one



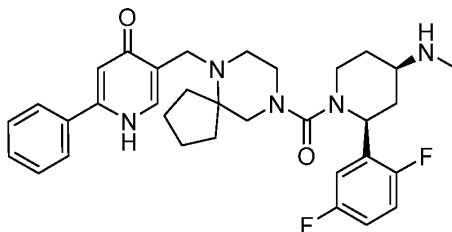
Step 1: (2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(2,2,2-trifluoro-*N*-methylacetamido)piperidine-1-carbonyl chloride: Prepared according to General Procedure 6 using triphosgene (9.6 mg, 0.032 mmol), pyridine (26.1 μ L, 0.32 mmol) and anhydrous DCM (0.5 mL) at 0 °C; then *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoro-*N*-methylacetamide hydrochloride (23.2 mg, 0.065 mmol) [prepared according to WO2022200523], DIPEA (13.8 μ L, 0.078 mmol) and anhydrous DCM (0.5 mL) to give the title compound (24.9 mg, quantitative) that was used in the next step without further purification.

Step 2: *N*-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-1-(6-((1-methyl-4-oxo-6-phenyl-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl)piperidin-4-yl)-2,2,2-trifluoro-*N*-methylacetamide: Prepared according to General Procedure 7 using 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-phenylpyridin-4(1*H*)-one (24.4 mg, 0.068 mmol), (2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(2,2,2-trifluoro-*N*-methylacetamido)piperidine-1-carbonyl chloride (24.9 mg, 0.065 mmol), DIPEA (56.5 μ L, 0.32 mmol) and anhydrous DCM

(1.5 mL) to give the title compound (17.5 mg, 39%). LCMS (Method B): R_T = 0.96 min, m/z = 686 $[M+H]^+$.

Step 3: 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-phenylpyridin-4(1*H*)-one: Prepared according to General Procedure 4 using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)-1-(6-((1-methyl-4-oxo-6-phenyl-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl)piperidin-4-yl)-2,2,2-trifluoro-*N*-methylacetamide (17.5 mg, 0.026 mmol), potassium carbonate (17.6 mg, 0.13 mmol), MeOH (0.25 mL) and water (0.025 mL) to give the title compound (10.1 mg, 67%). LCMS (Method B): R_T = 0.22 & 0.30 min (product peak is split across solvent front), m/z = 590 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6): δ 7.71 (s, 1H), 7.55 – 7.49 (m, 3H), 7.49 – 7.44 (m, 2H), 7.15 (td, 1H), 7.10 – 6.97 (m, 2H), 5.96 (s, 1H), 4.26 (d, 1H), 3.63 – 3.45 (m, 2H), 3.44 (s, 3H), 3.30 – 3.22 (m, 3H), 3.22 – 3.13 (m, 1H), 3.10 – 2.88 (m, 1H), 2.72 – 2.64 (m, 1H), 2.47 – 2.37 (m, 3H), 2.25 (s, 3H), 1.94 (t, 2H), 1.88 – 1.47 (m, 6H), 1.47 – 1.27 (m, 3H), 1.26 – 1.12 (m, 2H).

Example 11: 5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one

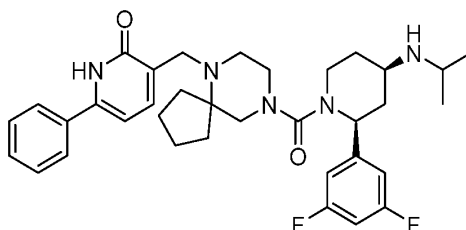


Step 1: *N*-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-1-(6-((4-oxo-6-phenyl-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl)piperidin-4-yl)-2,2,2-trifluoro-*N*-methylacetamide: To a stirring solution of triphosgene (18.4 mg, 61.8 μ mol) in DCM (1 mL) at 0 °C was added pyridine (50 μ L, 0.618 mmol). The resulting mixture was stirred for 15 min before adding a solution of *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoro-*N*-methylacetamide (26.6 mg, 74.2 μ mol) [prepared according to WO2022200523] in DCM (1 mL). The reaction was stirred at 0 °C for 4 h before quenching with 1 M HCl_(aq). The mixture was extracted with DCM (x 3) using a phase separator and the combined organic phases were concentrated *in vacuo*. To the resulting residue was added a solution of 5-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one (20 mg, 61.8 μ mol) in DCM (1 mL), to which was added DIPEA (54 μ L, 0.309 mmol). The resulting mixture was

stirred at rt for 18 h before quenching with 1 M HCl_(aq). The mixture was extracted with DCM (x 3) using a phase separator and the combined organic phases were concentrated *in vacuo*. The resulting residue was purified by flash chromatography (10-100% EtOAc in cyclohexane) to give the title compound (28 mg, 67%). LCMS (Method C): R_T = 0.96 min, *m/z* = 672 [M+H]⁺.

Step 2: 5-((9-((2S,4R)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1H)-one: Prepared according to General Procedure 4 using *N*-((2S,4R)-2-(2,5-difluorophenyl)-1-(6-((4-oxo-6-phenyl-1,4-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl)piperidin-4-yl)-2,2,2-trifluoro-*N*-methylacetamide (28 mg, 41.7 μmol), potassium carbonate (57.6 mg, 0.417 mmol) in MeOH (1 mL) and water (0.1 mL) to give the title compound (17.7 mg, 73%). LCMS (Method C): R_T = 0.56 min, *m/z* = 576 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.54 (br s, 0.4H), 8.30 (br s, 0.4H), 7.97 (s, 1H), 7.66 (d, 1H), 7.49 (s, 3H), 7.23 (br s, 0.4H), 7.16 (td, 1.4H), 7.04 (tq, 2H), 6.38 (br s, 0.4H), 4.26 (d, 1H), 3.76–2.90 (m, 9H, obscured by HDO), 2.71 – 2.63 (m, 1H), 2.47 – 2.37 (m, 3H, obscured by DMSO signal), 2.25 (s, 3H), 1.93 (t, 2H), 1.73 (s, 1H), 1.56 (s, 4H), 1.44 (s, 1H), 1.34 (tt, 2H), 1.19 (q, 2H).

Example 12: 3-((9-((2S,4R)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1H)-one



Step 1: (2S,4R)-2-(3,5-Difluorophenyl)-4-(2,2,2-trifluoroacetamido)piperidine-1-carbonyl chloride: Prepared according to General Procedure 6 using triphosgene (21.5 mg, 0.073 mmol), pyridine (58.4 μL, 0.73 mmol) and anhydrous DCM (0.5 mL) at 0 °C; then *N*-((2S,4R)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride (50.0 mg, 0.15 mmol) [prepared according to WO2022200523], DIPEA (31.0 μL, 0.17 mmol) and anhydrous DCM (0.5 mL) to give the title compound (56.3 mg, quantitative) that was used in the next step without further purification.

Step 2: *N*-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-1-(6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl)piperidin-4-yl)-2,2,2-trifluoroacetamide:

Prepared according to General Procedure 7 using 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (49.3 mg, 0.15 mmol), (2*S*,4*R*)-2-(3,5-difluorophenyl)-4-(2,2,2-trifluoroacetamido)piperidine-1-carbonyl chloride (56.3 mg, 0.15 mmol), DIPEA (127 μ L, 0.73 mmol) and anhydrous DCM (1 mL) to give the title compound (66.1 mg, 69%). LCMS (Method C): R_T = 0.96 min, m/z = 658 [M+H]⁺.

Step 3: 3-((9-((2*S*,4*R*)-4-Amino-2-(3,5-difluorophenyl)piperidine-1-carbonyl)-6,9-

diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one: Prepared according to General Procedure 4 using *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)-1-(6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl)piperidin-4-yl)-2,2,2-trifluoroacetamide (66.1 mg, 0.10 mmol), potassium carbonate (69.5 mg, 0.50 mmol), MeOH (0.9 mL) and water (0.09 mL) to give the title compound (56.1 mg, 99%). LCMS (Method C): R_T = 0.59 min, m/z = 562 [M+H]⁺.

Step 4: 3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one: Prepared according to

General Procedure 8 using 3-((9-((2*S*,4*R*)-4-amino-2-(3,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one (27.0 mg, 0.048 mmol), acetone (17.8 μ L, 0.24 mmol) and MeOH (0.5 mL); then sodium triacetoxyborohydride (102 mg, 0.48 mmol) to give the title compound (18.2 mg, 59%). LCMS (Method C): R_T = 0.63 min, m/z = 604 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.78-7.68 (m, 2H), 7.56 (d, 1H), 7.51 – 7.41 (m, 3H), 7.02 (t, 1H), 6.96 – 6.86 (m, 2H), 6.66 – 6.54 (m, 1H), 4.05 (dd, 1H), 3.59 – 3.41 (m, 2H), 3.38 – 3.34 (m, 2H), 3.29 – 3.21 (m, 4H), 3.09 – 2.91 (m, 2H), 2.91 – 2.74 (m, 1H), 2.69 (t, 1H), 2.47 – 2.37 (m, 2H), 1.99 (d, 1H), 1.92 (d, 1H), 1.68 – 1.48 (m, 5H), 1.48 – 1.37 (m, 2H), 1.37 – 1.30 (m, 1H), 1.30 – 1.17 (m, 2H), 1.13 – 0.88 (m, 6H).

Example 13 was prepared from 3-((9-((2*S*,4*R*)-4-amino-2-(3,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one [Example 12, Step 3] according to General Procedure 8 using excess formaldehyde (37% w/w in water). Example 14 was prepared similarly to Example 6 except using Intermediate 3 instead of Intermediate 5 and using Intermediate 9 instead of Intermediate 6. Example 15 was

prepared similarly to Example 9 except using 2,2,2-trifluoro-*N*-methyl-*N*-((2*S*,4*R*)-2-phenylpiperidin-4-yl)acetamide hydrochloride [prepared according to WO2022200523 Intermediate 6] instead of *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-*N*-ethyl-2,2,2-trifluoroacetamide hydrochloride. Example 16 was prepared similarly to Example 6 except
5 using Intermediate 3 instead of Intermediate 5. Example 17 was prepared from Example 16 according to General Procedure 8 using excess formaldehyde (37% w/w in water). Example 18 was prepared similarly to Example 6 except using Intermediate 3 instead of Intermediate 5 and *tert*-butyl (*R*)-3-(2,5-difluorophenyl)piperazine-1-carboxylate [prepared according to WO2022200523 Intermediate 3] instead of Intermediate 6. Example 19 was
10 prepared similarly to Example 8 except using (3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-phenylpiperidine-4-carboxylic acid [WO2009072643] instead of (*R*)-4,4,4-trifluoro-2-methylbutanoic acid and followed by *N*-Boc deprotection according to General Procedure 1 using TFA. Example 20 was prepared similarly to Example 9 except using *N*-(3,3-difluorocyclobutyl)-*N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide
15 [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-*N*-ethyl-2,2,2-trifluoroacetamide hydrochloride. Example 21 was prepared similarly to Example 8 except using (*S*)-4,4,4-trifluoro-2-(methoxymethyl)butanoic acid [prepared according to WO2022200523] instead of (*R*)-4,4,4-trifluoro-2-methylbutanoic acid. Example 22 was prepared similarly to Example 8
20 except using (*R*)-3-cyclohexyl-2-methylpropanoic acid [prepared according to WO2018020242] instead of (*R*)-4,4,4-trifluoro-2-methylbutanoic acid. Example 23 was prepared similarly to Example 8 except using 3-phenylisonicotinic acid [commercially available] instead of (*R*)-4,4,4-trifluoro-2-methylbutanoic acid. Example 24 was prepared similarly to Example 6 except using Intermediate 3 instead of Intermediate 5 and *N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2,2-trifluoro-*N*-((2*S*,4*R*)-2-phenylpiperidin-4-yl)acetamide [prepared according to WO2022200523] instead of Intermediate 6 with an
25 extra step to remove the *N*-trifluoroacetyl group according to General Procedure 4 ahead of the final deprotection step removing the *O*-TBDMS group instead of the *N*-Boc group. Example 25 was prepared similarly to Example 6 except using Intermediate 10 instead of Intermediate 5. Example 26 was prepared similarly to Example 6 except using Intermediate 11 instead of Intermediate 5. Example 27 was prepared similarly to Example 9 except
30 using 2,2,2-trifluoro-*N*-((2*S*,4*R*)-2-phenylpiperidin-4-yl)-*N*-(pyridin-2-ylmethyl)acetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-*N*-ethyl-2,2,2-trifluoroacetamide hydrochloride. Example 28
35 was prepared similarly to Example 3 except using Intermediate 8 instead of Intermediate 3.

Example 29 was prepared similarly to Example 6 except using Intermediate 8 instead of Intermediate 5 and Intermediate 12 instead of Intermediate 6. Example 30 was prepared similarly to Example 6 except using Intermediate 3 instead of Intermediate 5 and *tert*-butyl (*R*)-3-methyl-3-phenylpiperazine-1-carboxylate [prepared according to WO2020115501] instead of Intermediate 6. Example 31 was prepared similarly to Example 9 except using Intermediate 8 instead of Intermediate 3. Example 32 was prepared similarly to Example 2 except using Intermediate 8 instead of Intermediate 2 and Intermediate 13 instead of (*R*)-3-phenylmorpholine. Example 33 was prepared from Example 11 according to General Procedure 8 using excess formaldehyde (37% w/w in water). Example 34 was prepared similarly to Example 9 except using Intermediate 8 instead of Intermediate 3 and *N*-((2*S*,4*R*)-2-(2,3-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoro-*N*-methylacetamide hydrochloride [prepared according to WO2022200523 Intermediate 40] instead of *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-*N*-ethyl-2,2,2-trifluoroacetamide hydrochloride. Example 35 was prepared similarly to Example 15 except using Intermediate 8 instead of Intermediate 3. Example 36 was prepared similarly to Example 6 except using Intermediate 8 instead of Intermediate 5 and *tert*-butyl cyclopropyl((2*S*,4*R*)-2-phenylpiperidin-4-yl)carbamate [prepared according to WO2022200523 Intermediate 20] instead of Intermediate 6. Example 37 was prepared similarly to Example 2 except using Intermediate 8 instead of Intermediate 2 and Intermediate 14 instead of (*R*)-3-phenylmorpholine and the *N*-Boc protecting group was removed according to General Procedure 1. Example 38 was prepared similarly to Example 12 except using Intermediate 8 instead of Intermediate 3. Example 39 was prepared similarly to Example 2 except using Intermediate 8 instead of Intermediate 2 and Intermediate 15 instead of (*R*)-3-phenylmorpholine and the *N*-Cbz protecting group was removed according to General Procedure 9. Example 40 was prepared similarly to Example 6 except using Intermediate 8 instead of Intermediate 5 and Intermediate 16 instead of Intermediate 6. Example 41 was prepared similarly to Example 6 except using Intermediate 8 instead of Intermediate 5 and Intermediate 17 instead of Intermediate 6. Example 42 was prepared similarly to Example 2 except using Intermediate 3 instead of Intermediate 2 and Intermediate 18 instead of (*R*)-3-phenylmorpholine followed by chiral preparative HPLC separation using a Phenomenex Lux i-Cellulose-5 (10 mm x 250 mm, 5 μ m) column with isocratic solvent conditions: MeOH + 0.2% NH₃, flow rate: 1 mL/min and 30 min run time for the chiral HPLC separation of enantiomers (16 mg) to give the title compound (2nd eluting, R_T = 15.9 min: 6 mg). Example 43 was prepared similarly to Example 6 except using Intermediate 8 instead of Intermediate 5 and using Intermediate 9 instead Intermediate 6. Example 44 was prepared

similarly to Example 11 except using Intermediate 19 instead of Intermediate 8. Example 45 was prepared similarly to Example 11 except using Intermediate 20 instead of Intermediate 8. Example 46 was prepared similarly to Example 11 except using Intermediate 21 instead of Intermediate 8. Example 47 was prepared similarly to Example 12 except using Intermediate 8 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 48 was prepared similarly to Example 12 except using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 49 was prepared similarly to Example 11 except using Intermediate 22 instead of Intermediate 8. Example 50 was prepared similarly to Example 11 except using Intermediate 2 instead of Intermediate 8. Example 51 was prepared similarly to Example 11 except using Intermediate 23 instead of Intermediate 8. Example 52 was prepared similarly to Example 9 except using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-*N*-ethyl-2,2,2-trifluoroacetamide hydrochloride. Example 53 was prepared similarly to Example 11 except using Intermediate 24 instead of Intermediate 8. Example 54 was prepared similarly to Example 11 except using Intermediate 25 instead of Intermediate 8. Example 55 was prepared similarly to Example 11 except using Intermediate 26 instead of Intermediate 8. Example 56 was prepared similarly to Example 11 except using Intermediate 27 instead of Intermediate 8. Example 57 was prepared similarly to Example 2 except using Intermediate 8 instead of Intermediate 2 and Intermediate 28 instead of (*R*)-3-phenylmorpholine. Example 58 was prepared similarly to Example 11 except using Intermediate 29 instead of Intermediate 8. Example 59 was prepared similarly to Example 11 except using Intermediate 30 instead of Intermediate 8. Example 60 was prepared similarly to Example 11 except using Intermediate 31 instead of Intermediate 8. Example 61 was prepared similarly to Example 11 except using Intermediate 32 instead of Intermediate 8. Example 62 was prepared similarly to Example 8 except using Intermediate 33 instead of Intermediate 3 and (*R*)-3-cyclohexyl-2-methylpropanoic acid [prepared according to WO2018020242] instead of (*R*)-4,4,4-trifluoro-2-methylbutanoic acid. Example 63 was prepared similarly to Example 9 except using Intermediate 8 instead of Intermediate 3 and *N*-(2,2-difluoroethyl)-*N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to

WO2022200523 Intermediate 42] instead of *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-*N*-ethyl-2,2,2-trifluoroacetamide hydrochloride. Example 64 was prepared similarly to Example 9 except using Intermediate 8 instead of Intermediate 3 and 4-((2*S*,4*R*)-2-phenylpiperidin-4-yl)morpholine hydrochloride [prepared according to WO2022200523

5 Intermediate 32] instead of *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-*N*-ethyl-2,2,2-trifluoroacetamide hydrochloride and no final deprotection step was required. Example 65 was prepared similarly to Example 6 except using Intermediate 34 instead of Intermediate 5. Example 66 was prepared similarly to Example 6 except using Intermediate 35 instead of Intermediate 5. Example 67 was prepared similarly to Example 6 except using

10 Intermediate 36 instead of Intermediate 5. Example 68 was prepared similarly to Example 6 except using Intermediate 37 instead of Intermediate 5. Example 69 was prepared similarly to Example 6 except using Intermediate 38 instead of Intermediate 5. Example 70 was prepared similarly to Example 8 except using Intermediate 37 instead of Intermediate 3 and (*R*)-3-cyclohexyl-2-methylpropanoic acid [prepared according to WO2018020242] instead

15 of (*R*)-4,4,4-trifluoro-2-methylbutanoic acid. Example 71 was prepared similarly to Example 8 except using Intermediate 38 instead of Intermediate 3 and (*R*)-3-cyclohexyl-2-methylpropanoic acid [prepared according to WO2018020242] instead of (*R*)-4,4,4-trifluoro-2-methylbutanoic acid. Example 72 was prepared similarly to Example 6 except using Intermediate 39 instead of Intermediate 5. Example 73 was prepared similarly to Example 6

20 except using Intermediate 38 instead of Intermediate 5 and *tert*-butyl (*R*)-3-(2,5-difluorophenyl)piperazine-1-carboxylate [prepared according to WO2022200523 Intermediate 3] instead of Intermediate 6. Example 74 was prepared similarly to Example 6 except using Intermediate 40 instead of Intermediate 5. Example 75 was prepared similarly to Example 6 except using Intermediate 33 instead of Intermediate 5. Example 76 was

25 prepared similarly to Example 6 except using Intermediate 2 instead of Intermediate 5. Example 77 was prepared similarly to Example 6 except using Intermediate 41 instead of Intermediate 5. Example 78 was prepared similarly to Example 6 except using Intermediate 42 instead of Intermediate 5. Example 79 was prepared similarly to Example 6 except using Intermediate 43 instead of Intermediate 5. Example 80 was prepared similarly to

30 Example 6 except using Intermediate 44 instead of Intermediate 5. Example 81 was prepared similarly to Example 6 except using Intermediate 45 instead of Intermediate 5. Example 82 was prepared similarly to Example 6 except using Intermediate 46 instead of Intermediate 5. Example 83 was prepared similarly to Example 6 except using Intermediate 47 instead of Intermediate 5. Example 84 was prepared similarly to Example 6 except

35 using Intermediate 48 instead of Intermediate 5. Example 85 was prepared similarly to

Example 12 except using Intermediate 35 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 86 was prepared similarly to Example 12

5 except using Intermediate 39 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 87 was prepared similarly to Example 12 except

10 using Intermediate 36 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 88 was prepared similarly to Example 6 except

15 using Intermediate 8 instead of Intermediate 5 and *tert*-butyl (*R*)-3-(2,5-difluorophenyl)piperazine-1-carboxylate [prepared according to WO2022200523 Intermediate 3] instead of Intermediate 6. Example 89 was prepared similarly to Example 6 except using Intermediate 33 instead of Intermediate 5 and *tert*-butyl (*R*)-3-(2,5-difluorophenyl)piperazine-1-carboxylate [prepared according to WO2022200523

20 Intermediate 3] instead of Intermediate 6. Example 90 was prepared similarly to Example 12 except using Intermediate 47 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 91 was prepared similarly to Example 6 except

25 using Intermediate 49 instead of Intermediate 5. Example 92 was prepared similarly to Example 12 except using Intermediate 47 instead of Intermediate 3. Example 93 was prepared similarly to Example 6 except using Intermediate 50 instead of Intermediate 5. Example 94 was prepared similarly to Example 6 except using Intermediate 51 instead of Intermediate 5. Example 95 was prepared similarly to Example 3 except using Intermediate

30 36 instead of Intermediate 3. Example 96 was prepared similarly to Example 12 except using Intermediate 39 instead of Intermediate 3. Example 97 was prepared similarly to Example 12 except using Intermediate 35 instead of Intermediate 3. Example 98 was prepared similarly to Example 6 except using Intermediate 52 instead of Intermediate 5. Example 99 was prepared similarly to Example 6 except using Intermediate 53 instead of Intermediate 5. Example 100 was prepared similarly to Example 6 except using

35 Intermediate 54 instead of Intermediate 5. Example 101 was prepared similarly to Example 12 except using Intermediate 8 instead of Intermediate 3 and using 2,2,2-trifluoro-*N*-

((2*S*,4*R*)-2-(3-fluorophenyl)piperidin-4-yl)acetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride and using preparative HPLC (acidic conditions) for the final purification instead of flash chromatography that resulted in the formation of the formic acid salt. Example 102 was prepared similarly to Example 6 except using Intermediate 55 instead of Intermediate 5. Example 103 was prepared similarly to Example 6 except using Intermediate 56 instead of Intermediate 5. Example 104 was prepared similarly to Example 6 except using Intermediate 57 instead of Intermediate 5. Example 105 was prepared similarly to Example 12 except using Intermediate 56 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 106 was prepared similarly to Example 12 except using Intermediate 21 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 107 was prepared similarly to Example 12 except using Intermediate 32 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 108 was prepared from Example 61 according to General Procedure 8 using excess formaldehyde (37% w/w in water). Example 109 was prepared from Example 46 according to General Procedure 8 using excess formaldehyde (37% w/w in water). Example 110 was prepared similarly to Example 6 except using Intermediate 58 instead of Intermediate 5. Example 111 was prepared similarly to Example 9 except using Intermediate 47 instead of Intermediate 3 and *N*-(2,2-difluoroethyl)-*N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523 Intermediate 42] instead of *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-*N*-ethyl-2,2,2-trifluoroacetamide hydrochloride. Example 112 was prepared similarly to Example 6 except using Intermediate 47 instead of Intermediate 5 and using Intermediate 9 instead of Intermediate 6. Example 113 was prepared similarly to Example 1 except using (2*S*,5*R*)-5-(2,5-difluorophenyl)-2-methylmorpholine [prepared according to WO2022200523 Intermediate 61] instead of (*R*)-3-phenylmorpholine. Example 114 was prepared similarly to Example 1 except using Intermediate 27 instead of Intermediate 1. Example 115 was prepared similarly to Example 1 except using (*R*)-3-(4-fluorophenyl)morpholine

[commercially available] instead of (*R*)-3-phenylmorpholine and Intermediate 27 instead of Intermediate 1. Example 116 was prepared similarly to Example 1 except using (2*R*,5*R*)-2-methyl-5-phenylmorpholine [commercially available] instead of (*R*)-3-phenylmorpholine. Example 117 was prepared similarly to Example 12 except using Intermediate 8 instead of

5 Intermediate 3 and using *tert*-butyl ((2*S*,4*R*)-2-(2-fluoro-5-methylphenyl)piperidin-4-yl)carbamate [prepared similarly to *tert*-butyl ((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)(methyl)carbamate (Intermediate 6) except using (2-fluoro-5-methylphenyl)boronic acid instead of (2,5-difluorophenyl)boronic acid in Step 1 and omitting Step 6. Data: LCMS

10 (Method D): $R_T = 0.83$ min, $m/z = 309$ $[M+H]^+$. $[\alpha]_D^{21} = +19.7$ (c 0.25 in $CHCl_3$) instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride and using General Procedure 1 instead of General Procedure 4 in Step 3. Example 118 was prepared similarly to Example 12 except using Intermediate 8 instead of Intermediate 3 and using *tert*-butyl ((2*S*,4*R*)-2-(2-fluoro-5-methoxyphenyl)piperidin-4-yl)carbamate [prepared

15 similarly to *tert*-butyl ((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)(methyl)carbamate (Intermediate 6) except using (2-fluoro-5-methoxyphenyl)boronic acid instead of (2,5-difluorophenyl)boronic acid in Step 1 and omitting Step 6. Data: LCMS (Method D): $R_T = 0.81$ min, $m/z = 325$ $[M+H]^+$. $[\alpha]_D^{21} = +44.9$ (c 0.25 in $CHCl_3$) instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride, using General

20 Procedure 1 instead of General Procedure 4 in Step 3 and using preparative HPLC (acidic conditions) for the final purification instead of flash chromatography that resulted in the formation of the formic acid salt. Example 119 was prepared similarly to Example 1 except using Intermediate 8 instead of Intermediate 1 and using (2*S*,5*R*)-5-(2,5-difluorophenyl)-2-methylmorpholine [prepared according to WO2022200523 Intermediate 61] instead of (*R*)-3-phenylmorpholine. Example 120 was prepared similarly to Example 12 except using

25 Intermediate 56 instead of Intermediate 3. Example 121 was prepared similarly to Example 6 except using Intermediate 3 instead of Intermediate 5 and *N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-*N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide [prepared similarly to *N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2,2-trifluoro-*N*-((2*S*,4*R*)-2-phenylpiperidin-4-yl)acetamide in WO2022200523 Intermediate 51

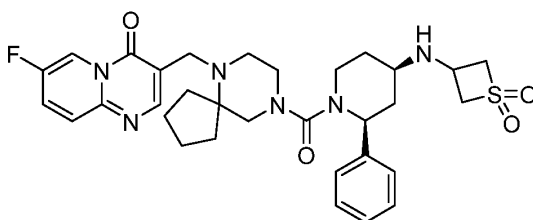
30 except using *tert*-butyl (*S*)-2-(2,5-difluorophenyl)-4-oxopiperidine-1-carboxylate WO2022200523 Intermediate 19 Step 5 instead of *tert*-butyl (*S*)-4-oxo-2-phenylpiperidine-1-carboxylate] instead of Intermediate 6 with an extra step to remove the *N*-trifluoroacetyl group according to General Procedure 4 ahead of the final deprotection step removing the *O*-TBDMS group instead of the *N*-Boc group. Example 122 was prepared similarly to

35 Example 121 except using Intermediate 8 instead of Intermediate 3. Example 123 was

prepared similarly to Example 5 except using Intermediate 47 instead of Intermediate 3.
 Example 124 was prepared similarly to Example 5 except using Intermediate 47 instead of Intermediate 3 in Step 1 and using an amide coupling with cyclopropanecarboxylic acid according to General Procedure 5 instead of the acylation using acetic anhydride in Step 3.

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Example 125: 3-((9-((2*S*,4*R*)-4-((1,1-Dioxidothietan-3-yl)amino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one



*Step 1: 6-((7-Fluoro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl chloride:* To a stirred solution of bis(trichloromethyl)carbonate (28.6 mg, 0.0963 mmol) in DCM (2.0 mL) at 0 °C was added pyridine (0.02 mL, 0.190 mmol). After 10 min, a solution of 3-((6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-pyrido[1,2-*a*]pyrimidin-4-one (75.0 mg, 0.193 mmol) in DCM (2.0 mL) was added. After a further 16 h, the solvents were removed *in vacuo* to give the title compound (90 mg, crude) that was used without further purification. LCMS (Method C): R_T = 0.65 min, m/z = 379 $[M+H]^+$.

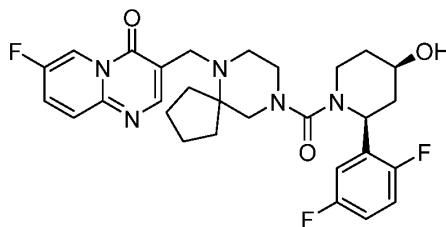
*Step 2: 3-((9-((2*S*,4*R*)-4-((1,1-Dioxidothietan-3-yl)amino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one:*
 To a stirred solution of 6-((7-fluoro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]decan-9-carbonyl chloride (40.0 mg, 0.106 mmol) in DCM (2.0 mL) was added DIPEA (111 μ L, 0.634 mmol) followed by 3-(((2*S*,4*R*)-2-phenylpiperidin-4-yl)amino)thietane 1,1-dioxide hydrochloride [prepared according to WO2022200523 Intermediate 7] (37.3 mg, 0.106 mmol) at rt. After 16 h, the solvents were removed *in vacuo* and the remaining residue was purified by flash chromatography using a KP-NH column (0-20% MeOH in EtOAc) to give the title compound (9.0 mg, 14%). LCMS (Method A): R_T = 0.59 min, m/z = 623 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6): δ 9.00 – 8.89 (m, 1H), 8.39 (s, 1H), 8.12 – 8.01 (m, 1H), 7.84 – 7.73 (m, 1H), 7.29 – 7.23 (m, 2H), 7.23 – 7.19 (m, 2H), 7.19 – 7.14 (m, 1H), 4.35 – 4.21 (m, 2H), 3.94 (dd, 1H), 3.91 – 3.76 (m, 2H), 3.73 – 3.58 (m, 1H), 3.51 – 3.34 (m, 4H), 3.28 – 3.18 (m, 2H), 3.14 – 2.95 (m, 1H), 2.68 – 2.61 (m, 1H), 2.60 – 2.53 (m, 1H), 2.49 – 2.45 (m, 1H), 2.45 – 2.39 (m, 2H), 1.97 – 1.83 (m, 2H), 1.79 –

1.68 (m, 1H), 1.68 – 1.49 (m, 4H), 1.48 – 1.40 (m, 1H), 1.39 – 1.28 (m, 2H), 1.30 – 1.12 (m, 2H).

Example 126 was prepared similarly to Example 9 except using *N*-(2,2-difluoroethyl)-*N*-
5 ((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride
[prepared similarly to *N*-(2,2-difluoroethyl)-*N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-
2,2,2-trifluoroacetamide hydrochloride in WO2022200523 Intermediate 42 except using
tert-butyl (*S*)-2-(3,5-difluorophenyl)-4-oxopiperidine-1-carboxylate prepared according to
WO2022200523 Intermediate 30 instead of *tert*-butyl (*S*)-2-(2,5-difluorophenyl)-4-
10 oxopiperidine-1-carboxylate] instead of *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-*N*-
ethyl-2,2,2-trifluoroacetamide hydrochloride. Example 127 was prepared similarly to
Example 11 except using Intermediate 59 instead of Intermediate 8, followed by a reductive
alkylation according to General Procedure 8 using excess formaldehyde (37% w/w in
water). Example 128 was prepared from Example 83 according to General Procedure 8
15 using excess formaldehyde (37% w/w in water). Example 129 was prepared similarly to
Example 1 except using Intermediate 60 instead of Intermediate 1 and (*S*)-2-
phenylpyrrolidine instead of (*R*)-3-phenylmorpholine. Example 130 was prepared similarly
to Example 1 except using Intermediate 23 instead of Intermediate 1 and (*S*)-2-
phenylpyrrolidine instead of (*R*)-3-phenylmorpholine. Example 131 was prepared similarly
20 to Example 1 except using Intermediate 27 instead of Intermediate 1 and (*S*)-2-
phenylpyrrolidine instead of (*R*)-3-phenylmorpholine. Example 132 was prepared similarly
to Example 1 except using Intermediate 8 instead of Intermediate 1 and (2*R*,5*R*)-2-methyl-
5-phenylmorpholine [commercially available] instead of (*R*)-3-phenylmorpholine. Example
133 was prepared similarly to Example 1 except using Intermediate 61 instead of
25 Intermediate 1 and (*S*)-2-(2,5-difluorophenyl)pyrrolidine [commercially available] instead of
(*R*)-3-phenylmorpholine. Example 134 was prepared similarly to Example 2 except using
(*S*)-2-phenylpyrrolidine instead of (*R*)-3-phenylmorpholine. Example 135 was prepared
similarly to Example 1 except using Intermediate 25 instead of Intermediate 1 and (*S*)-2-
phenylpyrrolidine instead of (*R*)-3-phenylmorpholine. Example 136 was prepared similarly
30 to Example 1 except using Intermediate 62 instead of (*R*)-3-phenylmorpholine. Example
137 was prepared similarly to Example 1 except using Intermediate 3 instead of
Intermediate 1 and Intermediate 62 instead of (*R*)-3-phenylmorpholine. Example 138 was
prepared similarly to Example 1 except using Intermediate 8 instead of Intermediate 1 and
Intermediate 62 instead of (*R*)-3-phenylmorpholine. Example 139 was prepared similarly to
35 Example 12 except using Intermediate 34 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-

2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 140 was prepared similarly to Example 6 except using Intermediate 63 instead of Intermediate 5. Example 141 was prepared similarly to Example 1 except using Intermediate 3 instead of Intermediate 1 and Intermediate 64 instead of (*R*)-3-phenylmorpholine. Example 142 was prepared similarly to Example 6 except using Intermediate 65 instead of Intermediate 5. Example 143 was prepared similarly to Example 6 except using Intermediate 66 instead of Intermediate 5. Example 144 was prepared similarly to Example 6 except using Intermediate 67 instead of Intermediate 5. Example 145 was prepared similarly to Example 1 except using Intermediate 64 instead of (*R*)-3-phenylmorpholine. Example 146 was prepared similarly to Example 1 except using Intermediate 8 instead of Intermediate 1 and Intermediate 64 instead of (*R*)-3-phenylmorpholine. Example 147 was prepared similarly to Example 6 except using Intermediate 3 instead of Intermediate 5 and using 2-(trimethylsilyl)ethyl ((2*R*,4*R*)-2-ethylpiperidin-4-yl)carbamate [prepared according to WO2022200523 Intermediate 13] instead of Intermediate 6 with the *N*-Teoc protecting group removal occurring under same conditions as the *N*-Boc protecting group removal in the final step. Example 148 was prepared from Example 147 according to General Procedure 8 using excess acetone. Example 149 was prepared from Example 121 according to General Procedure 8 using excess formaldehyde (37% w/w in water). Example 150 was prepared similarly to Example 6 except using Intermediate 68 instead of Intermediate 5. Example 151 was prepared from Example 58 according to General Procedure 8 using excess formaldehyde (37% w/w in water). Example 152 was prepared similarly to Example 9 except using Intermediate 47 instead of Intermediate 3.

Example 153: 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-hydroxypiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one



Step 1: tert-Butyl (2S,4R)-2-(2,5-difluorophenyl)-4-hydroxypiperidine-1-carboxylate: To a stirred solution of *tert*-butyl (*S*)-2-(2,5-difluorophenyl)-4-oxopiperidine-1-carboxylate (1.5 g, 4.81 mmol) [prepared according to WO2022200523 Intermediate 19, Step 5] in MeOH (30

- mL) was added CeCl_3 (1.18 g, 4.82 mmol) at rt. After 2 h, NaBH_4 (0.219 g, 5.78 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at rt for 16 h. The solvents were removed *in vacuo*, the remaining residue was partitioned between EtOAc and water, separated, extracted using EtOAc (2 x 30 mL), the combined organic phase was washed using brine (20 mL), and dried (Na_2SO_4). The solvents were removed *in vacuo* and the remaining crude mixture of diastereoisomers (1.2 g) was purified and resolved into the single stereoisomers by chiral SFC using a (*R,R*) Whelk-O® 1 (21.1 mm x 250 mm, 5 μm) column with isocratic solvent conditions: 50:40:10 hexane/IPA/MeOH. The first eluted material ($R_T = 1.92$ min) afforded the title compound (640 mg, cis isomer, de = 100%).
- LCMS (Method E): $R_T = 3.30$ min, $m/z = 314$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.18 – 7.15 (m, 1H), 7.08 – 7.00 (m, 2H), 5.02 (t, 1H), 4.62 (d, 1H), 3.89 – 3.88 (m, 1H), 3.80 – 3.75 (m, 1H), 3.51 – 3.47 (m, 1H), 2.04 – 1.99 (m, 1H), 1.98 – 1.75 (m, 2H), 1.58 – 1.56 (m, 1H), 1.22 (s, 9H); and the second eluted material ($R_T = 2.15$ min) afforded *tert*-butyl (2*S*,4*S*)-2-(2,5-difluorophenyl)-4-hydroxypiperidine-1-carboxylate (270 mg, trans isomer, de = 97%). LCMS (Method E): $R_T = 3.27$ min, $m/z = 314$ $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.28 – 7.12 (m, 2H), 6.94 – 6.89 (m, 1H), 5.40 (t, 1H), 4.81 (d, 1H), 4.02 – 3.98 (m, 1H), 3.59 – 3.53 (m, 1H), 3.17 – 3.10 (m, 1H), 2.12 – 2.09 (m, 1H), 1.88 – 1.85 (m, 1H), 1.74 – 1.66 (m, 1H), 1.38 – 1.28 (m, 1H), 1.22 (s, 9H). [Note: the stereoisomers were confirmed by comparison of ^1H NMR nOe data].
- Step 2: (2S,4R)-2-(2,5-Difluorophenyl)piperidin-4-ol*: Prepared according to General Procedure 1 using *tert*-butyl (2*S*,4*R*)-2-(2,5-difluorophenyl)-4-hydroxypiperidine-1-carboxylate (200 mg, 0.638 mmol) and TFA (1.5 mL) in DCM (3 mL) to give the title compound (140 mg, 100%). LCMS (Method A): $R_T = 0.27$ min, $m/z = 214$ $[\text{M}+\text{H}]^+$.
- Step 3: (2S,4R)-4-((tert-Butyldiphenylsilyl)oxy)-2-(2,5-difluorophenyl)piperidine*: To a stirred solution of (2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-ol (140 mg, 0.657 mmol) and imidazole (89 mg, 1.31 mmol) in DMF (0.65 mL) was added *tert*-butylchlorodiphenylsilane (0.22 mL, 0.85 mmol) at 0 °C. The reaction mixture was stirred at rt for 1.5 h, diluted with EtOAc and washed using a 1:1 brine/water solution (x 3). The organic phase was dried (MgSO_4), filtered (phase separator), the solvents were removed *in vacuo*, and the remaining residue was purified by flash chromatography to give the title compound (0.280 g, 94%). LCMS (Method A): $R_T = 1.20$ min, $m/z = 452$ $[\text{M}+\text{H}]^+$.

Step 4: 3-((9-((2*S*,4*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one:

Prepared according to General Procedure 3 using the free base of Intermediate 47 (30 mg, 0.095 mmol), (2*S*,4*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(2,5-difluorophenyl)piperidine (51.4 mg, 0.114 mmol), triphosgene (16.9 mg, 0.057 mmol), pyridine (46 μ L, 0.569 mmol) and DIPEA (66 μ L, 0.379 mmol) to give the title compound (65 mg, 86%). LCMS (Method A): R_T = 1.43 min, m/z = 794 $[M+H]^+$.

Step 5: 3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-hydroxypiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one: 3-((9-((2*S*,4*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (65 mg, 0.082 mmol) was stirred in 3 M HCl in MeOH solution (3 mL) for 18 h. The volatiles were removed *in vacuo* and the remaining residue was quenched using with saturated $\text{NaHCO}_3(\text{aq})$ solution. The resultant aqueous suspension was extracted using DCM (x 3), dried (phase separator), the combined organic phase was concentrated *in vacuo*, and the remaining residue was purified by flash chromatography to give the title compound (27 mg, 59%). LCMS (Method A): R_T = 0.70 min, m/z = 556 $[M+H]^+$. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 8.93 (dd, 1H), 8.38 (s, 1H), 8.05 (ddd, 1H), 7.79 (dd, 1H), 7.15 (td, 1H), 7.08 – 7.01 (m, 2H), 4.83 (d, 1H), 4.27 (dt, 1H), 3.64 – 3.55 (m, 1H), 3.55 – 3.42 (m, 2H), 3.42 – 3.33 (m, 2H), 3.29 – 3.20 (m, 2H), 2.97 (d, 1H), 2.71 – 2.64 (m, 1H), 2.47 – 2.43 (m, 1H), 2.43 – 2.37 (m, 1H), 1.94 – 1.81 (m, 2H), 1.81 – 1.70 (m, 1H), 1.68 – 1.28 (m, 8H), 1.27 – 1.12 (m, 1H).

Example 154 was prepared from Example 150 according to General Procedure 8 using excess formaldehyde (37% w/w in water). Example 155 was prepared from Example 90 according to General Procedure 8 using excess formaldehyde (37% w/w in water). Example 156 was prepared from Example 112 according to General Procedure 8 using excess formaldehyde (37% w/w in water). Example 157 was prepared similarly to Example 153 except using Intermediate 8 instead of the free base of Intermediate 47. Example 158 was prepared similarly to Example 12 except using Intermediate 29 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 159 was prepared similarly to Example 12 except using Intermediate 69 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide

hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 160 was prepared similarly to Example 12 except using Intermediate 70 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 161 was prepared similarly to Example 12 except using Intermediate 71 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 162 was prepared similarly to Example 12 except using Intermediate 72 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 163 was prepared similarly to Example 12 except using Intermediate 73 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 164 was prepared similarly to Example 12 except using Intermediate 59 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 165 was prepared similarly to Example 6 except using Intermediate 47 instead of Intermediate 5 and *N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-*N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide [prepared similarly to *N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2,2,2-trifluoro-*N*-((2*S*,4*R*)-2-phenylpiperidin-4-yl)acetamide in WO2022200523 Intermediate 51 except using *tert*-butyl (*S*)-2-(2,5-difluorophenyl)-4-oxopiperidine-1-carboxylate WO2022200523 Intermediate 19 Step 5 instead of *tert*-butyl (*S*)-4-oxo-2-phenylpiperidine-1-carboxylate] instead of Intermediate 6 with an extra step to remove the *N*-trifluoroacetyl group according to General Procedure 4 ahead of the final deprotection step removing the *O*-TBDMS group instead of the *N*-Boc group. Example 166 was prepared from Example 165 according to General Procedure 8 using excess formaldehyde (37% w/w in water). Example 167 was prepared from Example 152 according to General Procedure 8 using excess formaldehyde (37% w/w in water). Example 168 was prepared similarly to Example 12 except using Intermediate 74 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-

difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 169 was prepared similarly to Example 12 except using Intermediate 75 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-

5 difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 170 was prepared similarly to Example 6 except using Intermediate 8 instead of Intermediate 5 and *tert*-butyl ((3*S*,5*S*)-5-phenylpyrrolidin-3-yl)carbamate [prepared according to WO2022200523 Intermediate 15] instead of

10 Intermediate 6. Example 171 was prepared from Example 170 according to General Procedure 8 using excess acetone. Example 172 was prepared similarly to Example 6 except using Intermediate 76 instead of Intermediate 5. Example 173 was prepared similarly to Example 12 except using Intermediate 76 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride

15 [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 174 was prepared similarly to Example 8 except using Intermediate 77 instead of (*R*)-4,4,4-trifluoro-2-methylbutanoic acid. Example 175 was prepared similarly to Example 12 except using Intermediate 78 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-

20 difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 176 was prepared similarly to Example 6 except using Intermediate 47 instead of Intermediate 5 and using Intermediate 79 instead

Intermediate 6. Example 177 was prepared similarly to Example 6 except using

25 Intermediate 8 instead of Intermediate 5 and using Intermediate 79 instead Intermediate 6. Example 178 was prepared similarly to Example 6 except using Intermediate 47 instead of Intermediate 5 and *tert*-butyl ((3*S*,5*S*)-5-phenylpyrrolidin-3-yl)carbamate [prepared according to WO2022200523 Intermediate 15] instead of Intermediate 6 and including an additional final reductive alkylation step according to General Procedure 8 using excess

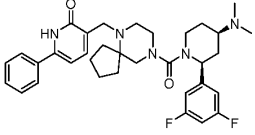
30 acetone. Example 179 was prepared similarly to Example 6 except using Intermediate 74 instead of Intermediate 5. Example 180 was prepared similarly to Example 6 except using Intermediate 78 instead of Intermediate 5. Example 181 was prepared similarly to Example 12 except using Intermediate 80 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to

35 WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-

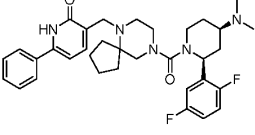
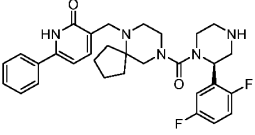
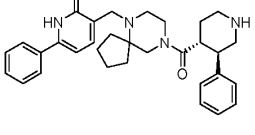
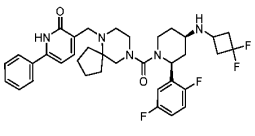
trifluoroacetamide hydrochloride. Example 182 was prepared similarly to Example 12 except using Intermediate 81 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 183 was prepared similarly to Example 6 except using Intermediate 70 instead of Intermediate 5. Example 184 was prepared similarly to Example 6 except using Intermediate 71 instead of Intermediate 5. Example 185 was prepared similarly to Example 9 except using Intermediate 71 instead of Intermediate 3. Example 186 was prepared similarly to Example 9 except using Intermediate 70 instead of Intermediate 3. Example 187 was prepared similarly to Example 6 except using Intermediate 82 instead of Intermediate 5. Example 188 was prepared similarly to Example 12 except using Intermediate 82 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 189 was prepared similarly to Example 125 except using (2*S*,4*R*)-*N*-(3-methyloxetan-3-yl)-2-phenylpiperidin-4-amine 2,2,2-trifluoroacetate [prepared according to WO2022200523 Intermediate 33] instead of 3-(((2*S*,4*R*)-2-phenylpiperidin-4-yl)amino)thietane 1,1-dioxide hydrochloride and using preparative HPLC (acidic conditions) for the final purification instead of flash chromatography that resulted in the formation of the formic acid salt. Example 190 was prepared similarly to Example 9 except using Intermediate 74 instead of Intermediate 3. Example 191 was prepared similarly to Example 9 except using Intermediate 78 instead of Intermediate 3. Example 192 was prepared similarly to Example 6 except using Intermediate 83 instead of Intermediate 5. Example 193 was prepared similarly to Example 12 except using Intermediate 83 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 194 was prepared similarly to Example 6 except using Intermediate 84 instead of Intermediate 5. Example 195 was prepared similarly to Example 12 except using Intermediate 84 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 196 is prepared as an intermediate in the penultimate step in the synthesis of Example 90. Example 197 was prepared similarly to Example 12 except using Intermediate 85 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-

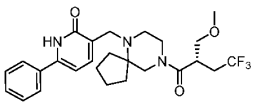
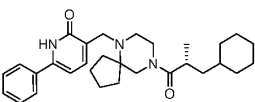
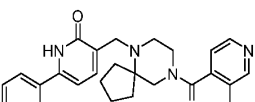
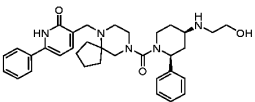
2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 198 was prepared similarly to Example 12 except using Intermediate 86 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 199 was prepared similarly to Example 12 except using Intermediate 87 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 200 was prepared similarly to Example 12 except using Intermediate 88 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride. Example 201 was prepared similarly to Example 6 except using Intermediate 88 instead of Intermediate 5. Example 202 was prepared similarly to Example 6 except using Intermediate 89 instead of Intermediate 5. Example 203 was prepared similarly to Example 125 except using Intermediate 90 instead of 3-(((2*S*,4*R*)-2-phenylpiperidin-4-yl)amino)thietane 1,1-dioxide hydrochloride. Example 204 was prepared similarly to Example 12 except using Intermediate 91 instead of Intermediate 3 and using *N*-((2*S*,4*R*)-2-(2,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride [prepared according to WO2022200523] instead of *N*-((2*S*,4*R*)-2-(3,5-difluorophenyl)piperidin-4-yl)-2,2,2-trifluoroacetamide hydrochloride.

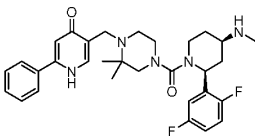
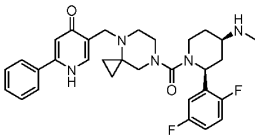
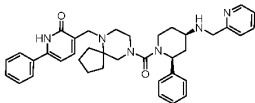
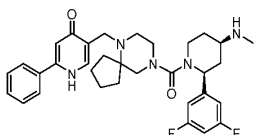
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Example	Structure	Name	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆): δ	LCMS (Method): R _T , <i>m/z</i>
13		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(3,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	11.71 (br s, 1H), 7.73 (d, 2H), 7.56 (d, 1H), 7.50 – 7.41 (m, 3H), 7.00 (tt, 1H), 6.97 – 6.90 (m, 2H), 6.68 – 6.52 (m, 1H), 3.99 (dd, 1H), 3.65 – 3.49 (m, 1H), 3.49 – 3.40 (m, 1H), 3.37 – 3.32 (m, 2H), 3.29 – 3.21 (m, 2H), 3.01 (d, 1H), 2.64 (t, 1H), 2.47 – 2.37 (m, 2H), 2.35 – 2.28	(Method C) R _T = 0.60 min, <i>m/z</i> 590 [M+H] ⁺

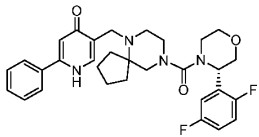
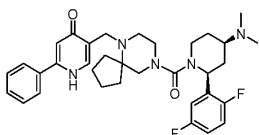
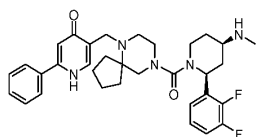
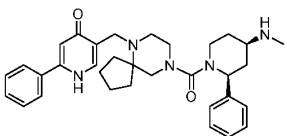
			(m, 1H), 2.16 (s, 6H), 1.88 (d, 1H), 1.81 (d, 1H), 1.65 – 1.38 (m, 7H), 1.38 – 1.26 (m, 2H), 1.26 – 1.16 (m, 1H).	
14		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-((2-methoxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	7.72-7.61 (m, 2H), 7.50 (d, 1H), 7.45 – 7.34 (m, 3H), 7.13 – 7.04 (m, 1H), 7.02 – 6.92 (m, 2H), 6.54 (s, 1H), 4.23 – 4.14 (m, 1H), 3.54 – 3.26 (m, 6H, overlapping HDO), 3.23-3.16 (m, 2H, overlapping HDO), 3.15 (s, 3H), 3.03 – 2.82 (m, 1H), 2.67 – 2.47 (m, 4H), 2.40 – 2.70 (m, 2H), 1.86 (t, 2H), 1.60 – 1.21 (m, 8H), 1.21 – 1.04 (m, 2H).	(Method A) R _T = 0.65 min, <i>m/z</i> 620 [M+H] ⁺
15		3-((9-((2 <i>S</i> ,4 <i>R</i>)-4-(Methylamino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	7.76 – 7.70 (m, 2H), 7.56 (d, 1H), 7.50 – 7.40 (m, 3H), 7.28 – 7.19 (m, 4H), 7.19 – 7.12 (m, 1H), 6.60 (d, 1H), 3.96 (dd, 1H), 3.56 – 3.37 (m, 2H), 3.28 – 3.19 (m, 3H), 3.04 (d, 1H), 2.74 – 2.64 (m, 1H), 2.53 – 2.51 (m, 1H), 2.47 – 2.38 (m, 3H), 2.24 (s, 3H), 1.95 – 1.87 (m, 2H), 1.65 – 1.13 (m, 11H)	(Method A) R _T = 0.59 min, <i>m/z</i> 540 [M+H] ⁺
16		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	7.70 – 7.61 (m, 2H), 7.50 (d, 1H), 7.44 – 7.34 (m, 3H), 7.12 – 7.05 (m, 1H), 7.02 – 6.92 (m, 2H), 6.53 (d, 1H), 4.24 – 4.13 (m, 1H), 3.61 – 3.27 (m, 3H), 3.23 – 3.08 (m, 3H, overlapping HDO), 3.03 – 2.81 (m, 1H), 2.67 – 2.54 (m, 1H), 2.41 – 2.26 (m, 3H), 2.18 (s, 3H), 1.93 – 1.78 (m, 2H), 1.65 – 1.21 (m, 8H), 1.19 – 1.03 (m, 2H).	(Method A) R _T = 0.61 min, <i>m/z</i> 576 [M+H] ⁺

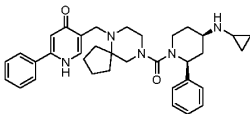
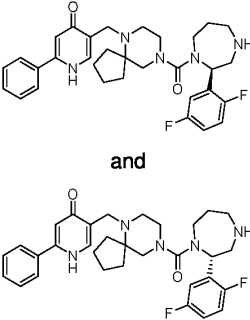
17		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	11.65 (s, 1H), 7.73 – 7.62 (m, 2H), 7.51 (d, 1H), 7.45-7.34 (m, 3H), 7.14 – 7.06 (m, 1H), 7.05 – 6.95 (m, 2H), 6.63 – 6.47 (m, 1H), 4.23 – 4.14 (m, 1H), 3.63 – 3.34 (m, 2H), 3.33 – 3.08 (m, 4H, overlapping HDO), 3.01 – 2.83 (m, 1H), 2.67 – 2.55 (m, 1H), 2.42 – 2.24 (m, 3H), 2.11 (s, 6H), 1.84 – 1.71 (m, 2H), 1.63 – 1.04 (m, 10H).	(Method A) R _T = 0.62 min, <i>m/z</i> 590 [M+H] ⁺
18		(<i>R</i>)-3-((9-(2-(2,5-Difluorophenyl)piperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	11.72 (s, 1H), 7.76 – 7.63 (m, 2H), 7.51 – 7.39 (m, 3H), 7.22 – 7.10 (m, 2H), 7.12 – 7.04 (m, 1H), 6.60 (s, 1H), 4.42 (dd, 1H), 3.44 (s, 2H), 3.30 (s, 1H), 3.24 (d, 1H), 3.20 – 3.13 (m, 1H), 3.00 (d, 1H), 2.91 (dd, 1H), 2.86 – 2.76 (m, 3H), 2.68 – 2.64 (m, 1H), 2.54 – 2.51 (m, 2H), 2.46 – 2.38 (m, 2H), 1.64 – 1.41 (m, 6H), 1.39 – 1.20 (m, 3H).	(Method A) R _T = 0.61 min, <i>m/z</i> 548 [M+H] ⁺
19		6-Phenyl-3-((9-((3 <i>R</i> ,4 <i>R</i>)-3-phenylpiperidine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1 <i>H</i>)-one	7.70 – 7.59 (m, 2H), 7.48 – 7.32 (m, 4H), 7.22 – 7.05 (m, 5H), 6.58 – 6.45 (m, 1H), 3.54 – 3.27 (m, 2H), 3.20 – 2.97 (m, 4H), 2.95 – 2.75 (m, 4H), 2.65 – 2.48 (m, 2H), 2.28 – 2.15 (m, 1H), 2.05 – 1.89 (m, 1H), 1.67 – 1.12 (m, 8.3H), 1.11 – 1.00 (m, 0.7H), 1.01 – 0.93 (m, 0.3H), 0.70 – 0.59 (m, 0.7H).	(Method A) R _T = 0.58 min, <i>m/z</i> 511 [M+H] ⁺
20		3-((9-((2 <i>S</i> ,4 <i>R</i>)-4-((3,3-Difluorocyclobutyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	11.77 (s, 1H), 7.88 – 7.64 (m, 2H), 7.57 (d, 1H), 7.52 – 7.39 (m, 3H), 7.23 – 7.11 (m, 1H), 7.11 – 6.98 (m, 2H), 6.57 (br s, 1H), 4.29 – 4.21 (m, 1H), 3.71 – 3.35 (m, 3H, overlapping HDO), 3.30 – 3.12 (m, 3H, overlapping HDO), 3.10 – 2.86 (m, 1H), 2.82 – 2.55 (m, 5H), 2.48 – 2.35 (m, 2H), 2.35 – 2.13 (m, 2H), 1.96 –	(Method A) R _T = 0.65 min, <i>m/z</i> 652 [M+H] ⁺

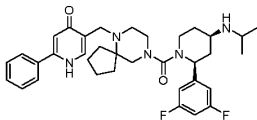
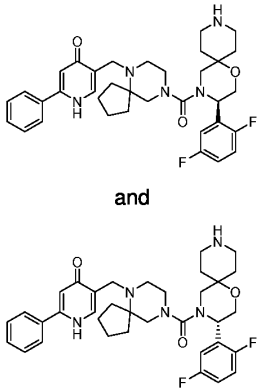
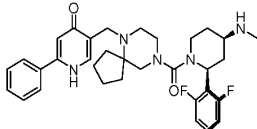
			1.79 (m, 2H), 1.72 – 1.11 (m, 10H).	
21		(<i>S</i>)-6-Phenyl-3-((9-(4,4,4-trifluoro-2-(methoxymethyl)butanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1 <i>H</i>)-one	11.76 (s, 1H), 7.73 (d, 2H), 7.58 (dd, 1H), 7.50 – 7.38 (m, 3H), 6.60 (s, 1H), 3.56 (q, 1H), 3.48 – 3.31 (m, 7H), 3.27 (m, 1H), 3.24 (s, 3H), 2.76 – 2.64 (m, 1H), 2.54 – 2.51 (m, 1H), 2.48 – 2.34 (m, 2H), 1.73 – 1.46 (m, 7H), 1.41 (dt, 1H).	(Method A) R _T = 0.81 min, <i>m/z</i> 492 [M+H] ⁺
22		(<i>R</i>)-3-((9-(3-Cyclohexyl-2-methylpropanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	11.76 (s, 1H), 7.73 (d, 2H), 7.57 (dd, 1H), 7.53 – 7.36 (m, 3H), 6.59 (s, 1H), 3.69 – 3.52 (m, 1H), 3.53 – 3.32 (m, 3H), 3.28 – 3.17 (m, 2H), 2.94 – 2.79 (m, 1H), 2.53 – 2.51 (m, 1H), 2.42 – 2.38 (d, 1H), 1.80 – 1.32 (m, 14H), 1.24 – 1.02 (m, 5H), 0.96 (d, 3H), 0.90 – 0.76 (m, 2H).	(Method A) R _T = 1.00 min, <i>m/z</i> 476 [M+H] ⁺
23		6-Phenyl-3-((9-(3-phenylisonicotinoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1 <i>H</i>)-one	11.72 (br s, 1H), 8.73 – 8.62 (m, 2H), 7.69 (s, 2H), 7.54 – 7.37 (m, 10H), 6.51 (br s, 1H), 3.97 – 2.97 (m, 4H, overlapping HDO signal), 2.91 – 2.71 (m, 1H), 2.58 – 2.31 (m, 2H, overlapping solvent signal), 2.30 – 2.16 (m, 1H), 1.87 – 0.67 (m, 8H).	(Method A) R _T = 0.77 min, <i>m/z</i> 505 [M+H] ⁺
24		3-((9-((2 <i>S</i> ,4 <i>R</i>)-4-((2-Hydroxyethyl)amino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	7.70 – 7.61 (m, 2H), 7.49 (d, 1H), 7.44 – 7.34 (m, 3H), 7.21 – 7.11 (m, 4H), 7.11 – 7.09 (m, 1H), 6.53 (d, 1H), 4.34 (s, 1H), 3.90 (dd, 1H), 3.52 – 3.29 (m, 4H), 3.22 – 3.10 (m, 4H), 3.04 – 2.89 (m, 1H), 2.66 – 2.58 (m, 1H), 2.56 – 2.47 (m, 3H), 2.38 – 2.31 (m, 2H), 1.90 – 1.79 (m, 2H), 1.61 – 1.22 (m, 8H), 1.21 – 1.04 (m, 2H).	(Method A) R _T = 0.60 min, <i>m/z</i> 570 [M+H] ⁺

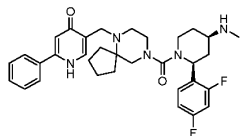
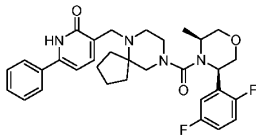
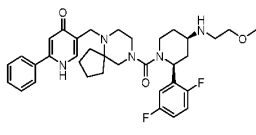
25		5-((4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.99 (s, 1H), 7.73 – 7.66 (m, 2H), 7.57 – 7.50 (m, 3H), 7.14 – 7.08 (m, 1H), 7.08 – 6.99 (m, 1H), 6.97 – 6.89 (m, 1H), 6.72 (s, 1H), 4.43 – 4.36 (m, 1H), 3.77 – 3.34 (m, 6H), 3.17 – 3.06 (m, 1H), 2.85 – 2.76 (m, 1H), 2.68 – 2.54 (m, 3H), 2.39 (s, 3H), 2.13 – 2.01 (m, 2H), 1.51 (qd, 1H), 1.38 (q, 1H), 1.10 (s, 3H), 0.94 (s, 3H).	(Method A) R _T = 0.51 min, <i>m/z</i> 550 [M+H] ⁺
26		5-((7-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.81 (s, 1H), 7.72 – 7.64 (m, 2H), 7.57 – 7.49 (m, 3H), 7.13 – 6.99 (m, 2H), 6.98 – 6.90 (m, 1H), 6.71 (s, 1H), 4.39 (d, 1H), 3.98 – 3.78 (m, 2H), 3.76 – 3.61 (m, 2H), 3.53 – 3.39 (m, 2H), 3.39 – 3.32 (m, 1H), 2.96 – 2.85 (m, 2H), 2.85 – 2.75 (m, 1H), 2.68 – 2.58 (m, 1H), 2.39 (s, 3H), 2.08 (t, 2H), 1.55 – 1.43 (m, 1H), 1.37 (q, 1H), 0.73 – 0.66 (m, 1H), 0.66 – 0.54 (m, 2H), 0.48 – 0.39 (m, 1H)	(Method A) R _T = 0.54 min, <i>m/z</i> 548 [M+H] ⁺
27		6-Phenyl-3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-phenyl-4-((pyridin-2-ylmethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1 <i>H</i>)-one	11.75 (s, 1H), 8.49 (d, 1H), 7.73 (s, 3H), 7.56 (d, 1H), 7.51 – 7.40 (m, 4H), 7.29 – 7.20 (m, 5H), 7.20 – 7.14 (m, 1H), 6.67 – 6.39 (m, 1H), 4.07 – 3.73 (m, 2H), 3.60 – 3.38 (m, 2H), 3.24 (d, 3H), 3.10 – 2.94 (m, 1H), 2.73 – 2.65 (m, 1H), 2.53 – 2.52 (m, 1H), 2.41 (s, 2H), 2.07 – 1.88 (m, 2H), 1.69 – 1.11 (m, 13H).	(Method A) R _T = 0.65 min, <i>m/z</i> 617 [M+H] ⁺
28		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.98 (s, 1H), 7.73 – 7.66 (m, 2H), 7.58 – 7.50 (m, 3H), 6.94 – 6.86 (m, 2H), 6.80 – 6.73 (m, 1H), 6.72 (s, 1H), 4.05 (dd, 1H), 3.69 (br s, 1H), 3.62 –	(Method A) R _T = 0.61 min, <i>m/z</i> 576 [M+H] ⁺

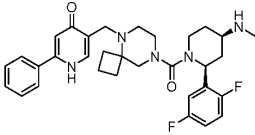
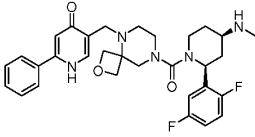
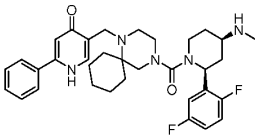
		phenylpyridin-4(1 <i>H</i>)-one	3.37 (m, 5H), 3.19 – 3.07 (m, 1H), 2.79 (td, 1H), 2.66 – 2.53 (m, 3H), 2.38 (s, 3H), 2.12 – 2.01 (m, 2H), 1.78 – 1.23 (m, 10H).	
29		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(3,4-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.98 (s, 1H), 7.73 – 7.66 (m, 2H), 7.58 – 7.50 (m, 3H), 7.23 – 7.13 (m, 2H), 7.12 – 7.07 (m, 1H), 6.72 (s, 1H), 4.02 (dd, 1H), 3.68 (br s, 1H), 3.60 – 3.35 (m, 5H), 3.13 (d, 1H), 2.79 (td, 1H), 2.65 – 2.49 (m, 3H), 2.38 (s, 3H), 2.10 – 1.99 (m, 2H), 1.77 – 1.17 (m, 10H).	(Method A) R _T = 0.62 min, <i>m/z</i> 576 [M+H] ⁺
30		(<i>R</i>)-3-((9-(2-Methyl-2-phenylpiperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	11.73 (br s, 1H), 7.73 (d, 2H), 7.57 (d, 1H), 7.51 – 7.42 (m, 3H), 7.38 (d, 2H), 7.27 (t, 2H), 7.16 (t, 1H), 6.60 (br s, 1H), 3.57 – 3.33 (m, 3H), 3.27 – 3.15 (m, 2H), 3.14 – 3.03 (m, 2H), 2.98 – 2.82 (m, 2H), 2.81 – 2.67 (m, 2H), 2.48 – 2.40 (m, 4H), 1.73 (s, 3H), 1.68 – 1.30 (m, 8H).	(Method C) R _T = 0.55 min, <i>m/z</i> 526 [M+H] ⁺
31		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	11.55 (br s, 0.4H), 8.28 (br s, 0.4H), 8.12 – 7.58 (m, 2.4 H), 7.58 – 7.36 (m, 3H), 7.30 – 7.10 (m, 1.4H), 7.08 – 6.99 (m, 2H), 6.38 (br s, 0.4H), 4.26 (d, 1H), 3.84-3.41 (m, 5H), 3.25 – 3.10 (m, 3H), 3.10 – 2.93 (m, 1H), 2.67 (t, 1H), 2.62 – 2.52 (m, 3H), 3.48 – 2.37 (m, 3H), 1.98 – 1.87 (m, 2H), 1.79 – 1.49 (m, 5H), 1.49 – 1.42 (m, 1H), 1.42 – 1.28 (m, 2H), 1.28 – 1.15 (m, 2H).	(Method C) R _T = 0.56 min, <i>m/z</i> 590 [M+H] ⁺
32		(<i>R</i>)-5-((9-(3-(2,5-Difluorophenyl)morpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.98 (s, 1H), 7.74 – 7.63 (m, 2H), 7.59 – 7.48 (m, 3H), 7.28 (ddd, 1H), 7.09 (td, 1H), 7.05 – 6.98 (m, 1H), 6.70	(Method A) R _T = 0.84 min, <i>m/z</i> 549 [M+H] ⁺

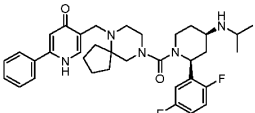
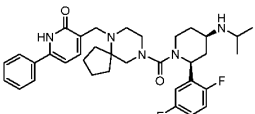
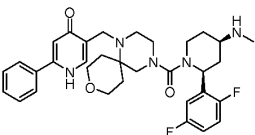
	 [~1:1 mixture of enantiomers]	phenylpyridin-4(1 <i>H</i>)-one and (<i>S</i>)-5-((9-(3-(2,5-Difluorophenyl)morpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	(s, 1H), 4.77 (dd, 1H), 3.88 (dd, 1H), 3.84 – 3.78 (m, 2H), 3.72 (dd, 1H), 3.63 – 3.43 (m, 4H), 3.39 – 3.31 (m, 2H overlapping solvent), 3.18 – 3.03 (m, 2H), 2.59 (q, 2H), 1.88 – 1.36 (m, 8H).	
33		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.99 (s, 1H), 7.73 – 7.68 (m, 2H), 7.54 (dd, 3H), 7.11 – 7.02 (m, 2H), 7.00 – 6.91 (m, 1H), 6.72 (s, 1H), 4.44 – 4.31 (m, 1H), 3.71 (s, 1H), 3.62 – 3.42 (m, 5H), 3.17 – 3.06 (m, 1H), 2.80 (td, 1H), 2.66 – 2.54 (m, 2H), 2.53 – 2.41 (m, 1H), 2.32 (s, 6H), 2.12 – 1.97 (m, 2H), 1.84 – 1.39 (m, 10H), 1.37 – 1.25 (m, 1H).	(Method A) R _T = 0.59 min, <i>m/z</i> 590 [M+H] ⁺
34		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,3-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.88 (s, 1H), 7.69 – 7.56 (m, 2H), 7.52 – 7.39 (m, 3H), 7.12 – 6.93 (m, 3H), 6.63 (s, 1H), 4.34 (dd, 1H), 3.59 (s, 1H), 3.51 – 3.27 (m, 4H), 3.01 (d, 1H), 2.72 (td, 1H), 2.63 – 2.41 (m, 3H), 2.30 (s, 3H), 2.05 – 1.92 (m, 2H), 1.69 – 1.37 (m, 9H), 1.38 – 1.28 (m, 2H), 1.30 – 1.07 (m, 2H).	(Method A) R _T = 0.59 min, <i>m/z</i> 576 [M+H] ⁺
35		5-((9-((2 <i>S</i> ,4 <i>R</i>)-4-(Methylamino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.88 (s, 1H), 7.65 – 7.52 (m, 2H), 7.48 – 7.39 (m, 3H), 7.22 – 7.15 (m, 4H), 7.14 – 7.06 (m, 1H), 6.63 (s, 1H), 3.94 (dd, 1H), 3.60 (s, 1H), 3.49 – 3.34 (m, 3H), 3.34 – 3.25 (m,	(Method A) R _T = 0.56 min, <i>m/z</i> 540 [M+H] ⁺

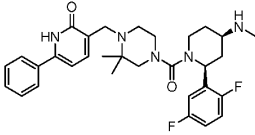
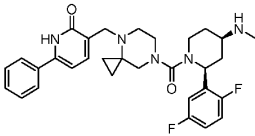
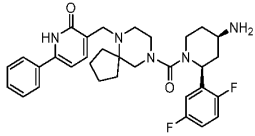
		phenylpyridin-4(1 <i>H</i>)-one	2H), 3.03 (d, 1H), 2.72 (td, 1H), 2.59 – 2.40 (m, 3H), 2.29 (s, 3H), 2.03 – 1.89 (m, 2H), 1.65 – 1.38 (m, 8H), 1.38 – 1.26 (m, 3H), 1.17 – 1.07 (m, 1H).	
36		5-((9-((2 <i>S</i> ,4 <i>R</i>)-4-(Cyclopropylamino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.93 – 7.82 (m, 1H), 7.64 – 7.56 (m, 2H), 7.48 – 7.30 (m, 3H), 7.27 – 7.12 (m, 4H), 7.08 (td, 1H), 6.81 – 6.28 (m, 1H), 4.09 – 3.83 (m, 1H), 3.59 (s, 1H), 3.52 – 3.33 (m, 3H), 3.33 – 3.23 (m, 2H), 3.10 – 2.94 (m, 1H), 2.85 – 2.60 (m, 2H), 2.53 – 2.37 (m, 2H), 2.10 – 1.90 (m, 3H), 1.67 – 1.25 (m, 10H), 1.27 – 1.01 (m, 2H), 0.44 – 0.32 (m, 2H), 0.30 – 0.13 (m, 2H).	(Method A) R _T = 0.58 min, <i>m/z</i> 566 [M+H] ⁺
37	 and [~1:1 mixture of enantiomers]	(<i>R</i>)-5-((9-(2-(2,5-Difluorophenyl)-1,4-diazepane-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one and (<i>S</i>)-5-((9-(2-(2,5-Difluorophenyl)-1,4-diazepane-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.95 (s, 1H), 7.74 – 7.64 (m, 2H), 7.56 – 7.49 (m, 3H), 7.15 – 7.05 (m, 2H), 7.04 – 6.97 (m, 1H), 6.70 (s, 1H), 5.34 (dd, 1H), 3.96 (dd, 1H), 3.63 – 3.41 (m, 3H), 3.40 – 3.32 (m, 2H), 3.21 – 3.11 (m, 1H), 3.11 – 2.99 (m, 3H), 2.92 (dd, 1H), 2.73 – 2.64 (m, 1H), 2.58 – 2.48 (m, 2H), 1.95 – 1.78 (m, 2H), 1.76 – 1.56 (m, 4H), 1.56 – 1.37 (m, 3H), 1.36 – 1.24 (m, 1H).	(Method A) R _T = 0.56 min, <i>m/z</i> 562 [M+H] ⁺

38		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.01 (s, 1H), 7.75 – 7.69 (m, 2H), 7.59 – 7.52 (m, 3H), 6.96 – 6.90 (m, 2H), 6.79 (tt, 1H), 6.74 (s, 1H), 4.08 (dd, 1H), 3.78 – 3.65 (m, 1H), 3.64 – 3.54 (m, 2H), 3.53 – 3.41 (m, 3H), 3.20 – 3.12 (m, 1H), 3.09 – 3.00 (m, 1H), 2.89 (t, 1H), 2.82 (t, 1H), 2.68 – 2.56 (m, 2H), 2.08 (t, 2H), 1.79 – 1.51 (m, 7H), 1.50 – 1.43 (m, 1H), 1.39 (q, 1H), 1.36 – 1.28 (m, 1H), 1.14 – 1.08 (t, 6H).	(Method C) R _T = 0.60 min, <i>m/z</i> 604 [M+H] ⁺
39	 and [~1:1 mixture of enantiomers]	(<i>R</i>)-5-((9-(3-(2,5-Difluorophenyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one and (<i>S</i>)-5-((9-(3-(2,5-Difluorophenyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.98 (s, 1H), 7.73 – 7.66 (m, 2H), 7.57 – 7.49 (m, 3H), 7.37 – 7.29 (m, 1H), 7.17 – 6.98 (m, 2H), 6.72 (s, 1H), 4.96 – 4.89 (m, 1H), 4.00 – 3.85 (m, 2H), 3.65 – 3.52 (m, 2H), 3.52 – 3.42 (m, 1H), 3.39 – 3.25 (m, 2H, overlapping solvent), 3.21 (d, 1H), 3.12 (d, 1H), 3.06 – 2.90 (m, 3H), 2.90 – 2.79 (m, 2H), 2.65 – 2.52 (m, 2H), 2.04 (d, 1H), 1.90 (d, 1H), 1.81 – 1.21 (m, 10H).	(Method A) R _T = 0.62 min, <i>m/z</i> 618 [M+H] ⁺
40		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,6-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.97 (s, 1H), 7.73 – 7.63 (m, 2H), 7.57 – 7.47 (m, 3H), 7.29-7.18 (m, 1H), 6.89 (t, 2H), 6.72 (s, 1H), 4.53 (d, 1H), 3.71 – 3.34 (m, 6H), 3.07 (d, 1H), 2.81 (t, 1H), 2.67 – 2.56 (m,	(Method A) R _T = 0.56 min, <i>m/z</i> 576 [M+H] ⁺

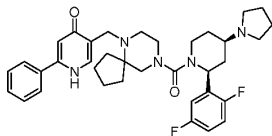
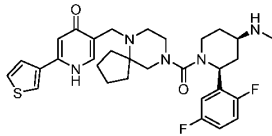
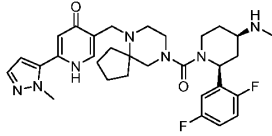
		phenylpyridin-4(1 <i>H</i>)-one	1H), 2.56 – 2.45 (m, 2H), 2.39 (s, 3H), 2.04 (t, 2H), 1.81 (q, 1H), 1.74 – 1.45 (m, 7H), 1.44 – 1.32 (m, 1H), 1.31 – 1.16 (m, 1H).	
41		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,4-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.98 (s, 1H), 7.75 – 7.65 (m, 2H), 7.59 – 7.48 (m, 3H), 7.42 – 7.32 (m, 1H), 6.97 – 6.81 (m, 2H), 6.72 (s, 1H), 4.37 (d, 1H), 3.69 (s, 1H), 3.59 – 3.35 (m, 5H), 3.10 (d, 1H), 2.80 (t, 1H), 2.67 – 2.48 (m, 3H), 2.38 (s, 3H), 2.05 (d, 2H), 1.79 – 1.35 (m, 9H), 1.30 – 1.16 (m, 1H).	(Method A) R _T = 0.58 min, <i>m/z</i> 576 [M+H] ⁺
42		3-((9-((3 <i>R</i> ,5 <i>S</i>)-3-(2,5-Difluorophenyl)-5-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.65 (d, 1H), 7.57 (d, 2H), 7.40 (d, 3H), 7.16 (q, 1H), 7.01 (dq, 2H), 6.56 (d, 1H), 4.42 – 4.33 (m, 1H), 4.11 (s, 1H), 3.77 – 3.61 (m, 3H), 3.45 (d, 2H), 3.36 (q, 2H), 3.12 (d, 1H), 3.04 (t, 1H), 2.84 (d, 1H), 2.49 – 2.39 (m, 1H), 2.25 (t, 1H), 1.73 – 1.61 (m, 1H), 1.50 (q, 3H), 1.40 – 1.10 (m, 3H), 0.93 (d, 3H), 0.61 (s, 1H).	(Method A) R _T = 0.85 min, <i>m/z</i> 563 [M+H] ⁺
43		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-((2-methoxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.98 (s, 1H), 7.74 – 7.66 (m, 2H), 7.58 – 7.49 (m, 3H), 7.12 – 6.99 (m, 2H), 6.97 – 6.90 (m, 1H), 6.72 (s, 1H), 4.44 – 4.36 (m, 1H), 3.71 (s, 1H), 3.62 – 3.37 (m, 7H), 3.34 (s, 3H), 3.12 (d, 1H), 2.86 – 2.69 (m, 4H), 2.65 – 2.52 (m, 2H), 2.13 – 1.99 (m, 2H), 1.80 – 1.22 (m, 10H).	(Method A) R _T = 0.60 min, <i>m/z</i> 620 [M+H] ⁺

44		5-((8-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.99 (s, 1H), 7.75 – 7.69 (m, 2H), 7.60 – 7.53 (m, 3H), 7.12 – 7.02 (m, 2H), 6.98 – 6.92 (m, 1H), 6.75 (s, 1H), 4.45 – 4.39 (m, 1H), 3.87 – 3.69 (m, 3H), 3.64 – 3.53 (m, 2H), 3.52 – 3.43 (m, 1H), 3.26 (d, 1H), 2.88 – 2.79 (m, 1H), 2.69 – 2.57 (m, 3H), 2.41 (s, 3H), 2.24 – 2.02 (m, 4H), 1.82 – 1.65 (m, 3H), 1.59 – 1.45 (m, 2H), 1.40 (q, 1H).	(Method A) R _T = 0.54 min, <i>m/z</i> 562 [M+H] ⁺
45		5-((8-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2-oxa-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.96 (s, 1H), 7.73 – 7.67 (m, 2H), 7.59 – 7.52 (m, 3H), 7.09 – 7.03 (m, 2H), 6.99 – 6.93 (m, 1H), 6.72 (s, 1H), 4.74 (d, 1H), 4.64 (d, 1H), 4.44 – 4.38 (m, 1H), 4.28 (d, 1H), 4.07 (d, 1H), 3.99 (dd, 2H), 3.77 – 3.63 (m, 2H), 3.59 – 3.41 (m, 3H), 2.84 (td, 1H), 2.72 – 2.62 (m, 2H), 2.61 – 2.53 (m, 1H), 2.41 (s, 3H), 2.15 – 2.03 (m, 2H), 1.54 (qd, 1H), 1.41 (q, 1H).	(Method A) R _T = 0.57 min, <i>m/z</i> 564 [M+H] ⁺
46		5-((4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.02 (s, 1H), 7.73 – 7.67 (m, 2H), 7.58 – 7.50 (m, 3H), 7.10 (ddd, 1H), 7.04 (td, 1H), 6.98 – 6.90 (m, 1H), 6.72 (s, 1H), 4.41 – 4.34 (m, 1H), 3.92 – 3.64 (m, 3H), 3.62 – 3.49 (m, 2H), 3.49 – 3.39 (m, 1H), 3.27 – 3.08 (m, 1H), 2.85 – 2.58 (m, 4H), 2.39 (s, 3H), 2.09 (t, 2H), 1.72 – 1.26 (m, 11H), 1.24 – 1.11 (m, 1H).	(Method A) R _T = 0.61 min, <i>m/z</i> 590 [M+H] ⁺

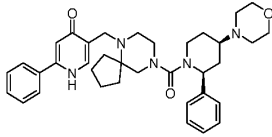
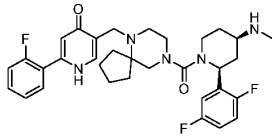
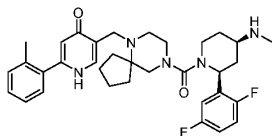
47		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.99 (s, 1H), 7.72 – 7.66 (m, 2H), 7.56 – 7.52 (m, 3H), 7.10 – 7.00 (m, 2H), 6.97 – 6.91 (m, 1H), 6.72 (s, 1H), 4.40 (d, 1H), 3.68 (s, 1H), 3.56 (d, 2H), 3.49 (s, 1H), 3.44 – 3.40 (m, 1H), 3.15 – 3.09 (m, 1H), 3.02 (hept, 1H), 2.91 – 2.78 (m, 2H), 2.64 – 2.54 (m, 2H), 2.06 (t, 2H), 1.76 – 1.60 (m, 5H), 1.59 – 1.48 (m, 2H), 1.47 – 1.38 (m, 2H), 1.35 – 1.30 (m, 1H), 1.29 – 1.25 (m, 1H), 1.09 (dd, 6H).	(Method A) R _T = 0.60 min, <i>m/z</i> 604 [M+H] ⁺
48		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.79 (d, 1H), 7.69 – 7.65 (m, 2H), 7.53 – 7.41 (m, 3H), 7.11 – 7.02 (m, 2H), 7.00 – 6.92 (m, 1H), 6.66 (d, 1H), 4.41 (d, 1H), 3.71 (s, 1H), 3.63 – 3.35 (m, 5H), 3.14 – 3.05 (m, 2H), 3.01 – 2.89 (m, 1H), 2.81 (td, 1H), 2.61 – 2.49 (m, 2H), 2.17 – 2.01 (m, 2H), 1.79 – 1.38 (m, 9H), 1.28 – 1.23 (m, 1H), 1.12 (dd, 6H).	(Method A) R _T = 0.59 min, <i>m/z</i> 604 [M+H] ⁺
49		5-((4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.00 (d, 1H), 7.73 – 7.67 (m, 2H), 7.58 – 7.52 (m, 3H), 7.14 – 7.01 (m, 2H), 6.99 – 6.92 (m, 1H), 6.71 (s, 1H), 4.41 – 4.34 (m, 1H), 4.10 – 3.74 (m, 4H), 3.61 – 3.36 (m, 6H), 3.20 – 3.04 (m, 1H), 2.85 – 2.75 (m, 2H), 2.74 – 2.67 (m, 1H), 2.67 – 2.57 (m, 1H), 2.39 (s, 3H), 2.14 – 2.02 (m, 2H), 1.99 – 1.88 (m, 1H), 1.71 – 1.59 (m, 1H), 1.58 – 1.46 (m, 1H), 1.46 – 1.30 (m, 2H), 1.18 (d, 1H).	(Method A) R _T = 0.52 min, <i>m/z</i> 592 [M+H] ⁺

50		3-((4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.80 (d, 1H), 7.70 – 7.64 (m, 2H), 7.54 – 7.45 (m, 3H), 7.12 (ddd, 1H), 7.04 (td, 1H), 6.96 – 6.90 (m, 1H), 6.67 (d, 1H), 4.42 – 4.36 (m, 1H), 3.70 (bs, 1H), 3.59 – 3.48 (m, 2H), 3.48 – 3.34 (m, 3H), 3.16 – 3.03 (m, 1H), 2.84 – 2.75 (m, 1H), 2.66 – 2.51 (m, 3H), 2.39 (s, 3H), 2.12 – 2.01 (m, 2H), 1.56 – 1.45 (m, 1H), 1.37 (q, 1H), 1.10 (s, 3H), 0.93 (s, 3H).	(Method A) R _T = 0.54 min, <i>m/z</i> 550 [M+H] ⁺
51		3-((7-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.69 – 7.61 (m, 3H), 7.53 – 7.45 (m, 3H), 7.10 (ddd, 1H), 7.05 (td, 1H), 6.97 – 6.91 (m, 1H), 6.63 (d, 1H), 4.43 – 4.34 (m, 1H), 3.94 – 3.78 (m, 2H), 3.77 – 3.64 (m, 2H), 3.51 – 3.39 (m, 2H), 3.38 – 3.32 (m, 1H), 2.97 – 2.84 (m, 2H), 2.81 (td, 1H), 2.62 (tt, 1H), 2.39 (s, 3H), 2.13 – 2.01 (m, 2H), 1.50 (qd, 1H), 1.36 (q, 1H), 0.76 – 0.68 (m, 1H), 0.68 – 0.60 (m, 1H), 0.60 – 0.52 (m, 1H), 0.50 – 0.37 (m, 1H).	(Method A) R _T = 0.59 min, <i>m/z</i> 548 [M+H] ⁺
52		3-((9-((2 <i>S</i> ,4 <i>R</i>)-4-Amino-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.78 (d, 1H), 7.67 (dd, 2H), 7.55 – 7.45 (m, 3H), 7.10 – 7.00 (m, 2H), 6.96 – 6.88 (m, 1H), 6.66 (d, 1H), 4.38 (d, 1H), 3.71 (s, 1H), 3.60 – 3.34 (m, 5H), 3.10 (d, 1H), 2.88 (s, 1H), 2.79 (t, 1H), 2.64 – 2.49 (m, 2H), 2.04 – 1.93 (m, 2H), 1.78 – 1.52 (m, 7H), 1.46 – 1.38 (m, 2H), 1.32 – 1.23 (m, 1H).	(Method A) R _T = 0.59 min, <i>m/z</i> 562 [M+H] ⁺

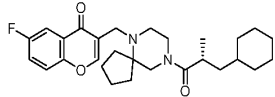
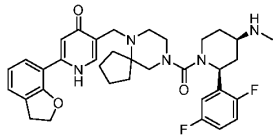
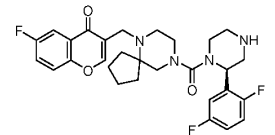
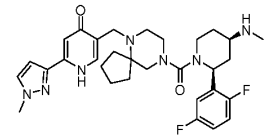
53		3-((8-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.77 (d, 1H), 7.69 – 7.64 (m, 2H), 7.53 – 7.46 (m, 3H), 7.10 – 7.00 (m, 2H), 6.96 – 6.89 (m, 1H), 6.66 (d, 1H), 4.43 – 4.37 (m, 1H), 3.84 – 3.64 (m, 3H), 3.60 – 3.48 (m, 2H), 3.48 – 3.39 (m, 1H), 3.23 (d, 1H), 2.85 – 2.76 (m, 1H), 2.67 – 2.53 (m, 3H), 2.39 (s, 3H), 2.20 (q, 1H), 2.13 – 2.01 (m, 3H), 1.78 – 1.62 (m, 3H), 1.57 – 1.42 (m, 2H), 1.38 (q, 1H).	(Method A) R _T = 0.56 min, <i>m/z</i> 562 [M+H] ⁺
54		3-((8-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2-oxa-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.76 (d, 1H), 7.72 – 7.64 (m, 2H), 7.56 – 7.46 (m, 3H), 7.11 – 7.02 (m, 2H), 7.01 – 6.92 (m, 1H), 6.66 (d, 1H), 4.77 (d, 1H), 4.65 (d, 1H), 4.41 (d, 1H), 4.28 (d, 1H), 4.06 (d, 1H), 3.99 (dd, 2H), 3.77 – 3.62 (m, 2H), 3.59 – 3.38 (m, 3H), 2.89 – 2.77 (m, 1H), 2.73 – 2.59 (m, 2H), 2.59 – 2.51 (m, 1H), 2.39 (s, 3H), 2.08 (t, 2H), 1.52 (qd, 1H), 1.40 (q, 1H).	(Method A) R _T = 0.69 min, <i>m/z</i> 564 [M+H] ⁺
55		3-((4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.84 (d, 1H), 7.70 – 7.63 (m, 2H), 7.53 – 7.45 (m, 3H), 7.10 (ddd, 1H), 7.04 (td, 1H), 6.97 – 6.90 (m, 1H), 6.67 (d, 1H), 4.41 – 4.34 (m, 1H), 3.89 – 3.38 (m, 6H), 3.26 – 3.06 (m, 1H), 2.84 – 2.57 (m, 4H), 2.39 (s, 3H), 2.09 (t, 2H), 1.71 – 1.26 (m, 11H), 1.22 – 1.09 (m, 1H).	(Method A) R _T = 0.66 min, <i>m/z</i> 590 [M+H] ⁺
56		3-((4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.83 (d, 1H), 7.69 – 7.63 (m, 2H), 7.54 – 7.46 (m, 3H), 7.14 – 7.00 (m, 2H), 6.98 – 6.91 (m, 1H), 6.66 (d, 1H), 4.41	(Method A) R _T = 0.55 min, <i>m/z</i> 592 [M+H] ⁺

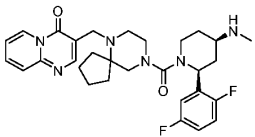
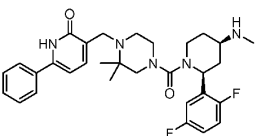
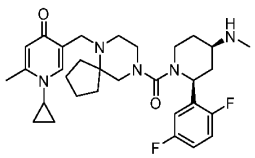
		diazaspiro[5.5]undecan-1-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	– 4.33 (m, 1H), 4.02 (d, 1H), 3.95 – 3.72 (m, 3H), 3.61 – 3.35 (m, 6H), 3.17 – 3.00 (m, 1H), 2.84 – 2.57 (m, 4H), 2.39 (s, 3H), 2.14 – 2.02 (m, 2H), 2.01 – 1.90 (m, 1H), 1.70 – 1.57 (m, 1H), 1.57 – 1.46 (m, 1H), 1.45 – 1.30 (m, 2H), 1.22 – 1.10 (m, 1H).	
57		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(pyrrolidin-1-yl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.03 (s, 1H), 7.79 – 7.69 (m, 2H), 7.62 – 7.54 (m, 3H), 7.17 – 7.06 (m, 2H), 7.02 – 6.96 (m, 1H), 6.76 (s, 1H), 4.47 – 4.39 (m, 1H), 3.85 – 3.43 (m, 5H), 3.20 – 3.10 (m, 1H), 2.90 – 2.78 (m, 1H), 2.77 – 2.54 (m, 6H), 2.46 – 2.33 (m, 1H), 2.16 (t, 2H), 1.93 – 1.29 (m, 15H).	(Method A) R _T = 0.60 min, <i>m/z</i> 616 [M+H] ⁺
58		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.99 (dd, 1H), 7.97 (s, 1H), 7.66 (dd, 1H), 7.55 (dd, 1H), 7.15 – 7.05 (m, 2H), 7.02 – 6.95 (m, 1H), 6.79 (s, 1H), 4.47 – 4.39 (m, 1H), 3.90 – 3.41 (m, 6H), 3.21 – 3.07 (m, 1H), 2.84 (td, 1H), 2.72 – 2.55 (m, 3H), 2.43 (s, 3H), 2.18 – 2.05 (m, 2H), 1.82 – 1.26 (m, 10H).	(Method A) R _T = 0.56 min, <i>m/z</i> 582 [M+H] ⁺
59		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(1-methyl-1 <i>H</i> -pyrazol-5-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.16 (s, 1H), 7.57 (d, 1H), 7.16 – 7.05 (m, 2H), 7.03 – 6.96 (m, 1H), 6.78 (s, 1H), 6.61 (d, 1H), 4.47 – 4.41 (m, 1H), 4.03 (s, 3H), 3.86 – 3.44 (m, 6H), 3.25 – 3.10 (m, 1H), 2.89 – 2.79 (m, 1H), 2.76 – 2.57 (m, 3H), 2.45 (s, 3H), 2.18 – 2.07 (m, 2H), 1.90 – 1.27 (m, 10H).	(Method A) R _T = 0.50 min, <i>m/z</i> 580 [M+H] ⁺

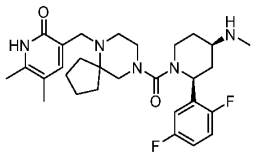
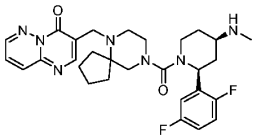
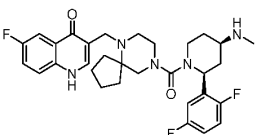
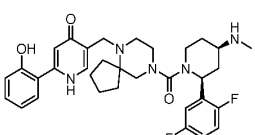
60		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-methyl-5-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.63 (s, 1H), 7.46 – 7.40 (m, 2H), 7.39 – 7.32 (m, 1H), 7.32 – 7.28 (m, 2H), 7.10 – 6.99 (m, 2H), 6.97 – 6.90 (m, 1H), 4.41 – 4.34 (m, 1H), 3.73 – 3.61 (m, 1H), 3.56 – 3.34 (m, 5H), 3.06 (d, 1H), 2.81 – 2.74 (m, 1H), 2.69 – 2.63 (m, 1H), 2.61 – 2.50 (m, 2H), 2.41 (s, 3H), 2.26 (s, 3H), 2.13 – 2.01 (m, 2H), 1.80 – 1.71 (m, 1H), 1.71 – 1.36 (m, 8H), 1.27 – 1.20 (m, 1H).	(Method A) R _T = 0.67 min, <i>m/z</i> 590 [M+H] ⁺
61		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-2-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.96 (s, 1H), 7.62 – 7.57 (m, 2H), 7.18 (dd, 1H), 7.11 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 6.82 (s, 1H), 4.39 (dd, 1H), 3.70 (s, 1H), 3.68 – 3.50 (m, 3H), 3.50 – 3.39 (m, 2H), 3.16 – 3.07 (m, 1H), 2.80 (td, 1H), 2.69 – 2.53 (m, 3H), 2.40 (s, 3H), 2.15 – 2.01 (m, 2H), 1.82 – 1.73 (m, 1H), 1.72 – 1.58 (m, 4H), 1.58 – 1.42 (m, 3H), 1.39 (q, 1H), 1.30 – 1.24 (m, 1H).	(Method A) R _T = 0.56 min, <i>m/z</i> 582 [M+H] ⁺
62		(<i>R</i>)-3-((9-(3-Cyclohexyl-2-methylpropanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.12 (d, 1H), 8.48 (s, 1H), 7.98 (td, 1H), 7.73 (d, 1H), 7.41 (td, 1H), 3.82 – 3.39 (m, 6H), 3.09 – 2.93 (m, 1H), 2.73 – 2.51 (m, 2H), 2.09 – 1.51 (m, 14H), 1.38 – 1.16 (m, 5H), 1.11 (d, 3H), 1.01 – 0.86 (m, 2H).	(Method A) R _T = 0.91 min, <i>m/z</i> 451 [M+H] ⁺
63		5-((9-((2 <i>S</i> ,4 <i>R</i>)-4-((2,2-Difluoroethyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-2-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.98 (s, 1H), 7.76 – 7.63 (m, 2H), 7.61 – 7.49 (m, 3H), 7.12 – 6.99 (m, 2H), 6.98 – 6.89 (m, 1H), 6.71 (s, 1H), 5.87 (tt, 1H), 4.43 – 4.35 (m, 1H), 3.82-3.36 (m, 6H), 3.19 – 3.05 (m, 1H).	(Method A) R _T = 0.59 min, <i>m/z</i> 626 [M+H] ⁺

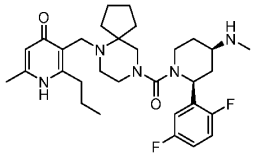
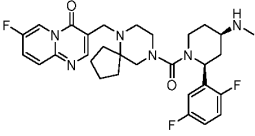
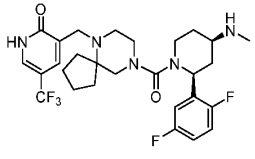
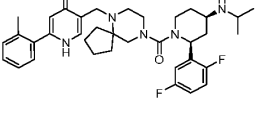
		6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	(m, 1H), 2.98 (td, 2H), 2.86 – 2.69 (m, 2H), 2.66 – 2.52 (m, 2H), 2.14 – 2.00 (m, 2H), 1.82 – 1.23 (m, 10H).	
64		5-((9-((2 <i>S</i> ,4 <i>R</i>)-4-Morpholino-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.97 (s, 1H), 7.78 – 7.63 (m, 2H), 7.60 – 7.48 (m, 3H), 7.33 – 7.24 (m, 4H), 7.23 – 7.15 (m, 1H), 6.70 (s, 1H), 4.03 (dd, 1H), 3.76 – 3.61 (m, 5H), 3.60 – 3.34 (m, 5H), 3.19 – 3.05 (m, 1H), 2.87 – 2.77 (m, 1H), 2.66 – 2.50 (m, 6H), 2.50 – 2.40 (m, 1H), 2.09 – 1.99 (m, 2H), 1.78 – 1.15 (m, 10H).	(Method A) R _T = 0.58 min, <i>m/z</i> 596 [M+H] ⁺
65		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-fluorophenyl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.04 (s, 1H), 7.63 (td, 1H), 7.61 – 7.55 (m, 1H), 7.37 (td, 1H), 7.34 – 7.29 (m, 1H), 7.11 – 7.05 (m, 2H), 7.00 – 6.93 (m, 1H), 6.68 (s, 1H), 4.42 (d, 1H), 3.73 (s, 1H), 3.66 – 3.54 (m, 2H), 3.55 – 3.42 (m, 3H), 3.15 (d, 1H), 2.83 (td, 1H), 2.69 – 2.56 (m, 3H), 2.41 (s, 3H), 2.15 – 2.04 (m, 2H), 1.81 – 1.60 (m, 5H), 1.60 – 1.28 (m, 5H).	(Method A) R _T = 0.56 min, <i>m/z</i> 594 [M+H] ⁺
66		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(<i>o</i> -tolyl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.96 (d, 1H), 7.44 – 7.29 (m, 4H), 7.11 – 7.29 (m, 2H), 6.95 (ddt, 1H), 6.39 (s, 1H), 4.43 – 4.37 (m, 1H), 3.86 – 3.36 (m, 6H), 3.19 – 3.03 (m, 1H), 2.85 – 2.76 (m, 1H), 2.68 – 2.54 (m, 3H), 2.39 (s, 3H), 2.31 (s, 3H), 2.14 – 2.03 (m, 2H), 1.79 – 1.21 (m, 10H).	(Method A) R _T = 0.59 min, <i>m/z</i> 590 [M+H] ⁺

67		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-methoxyphenyl)pyridine-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.97 (s, 1H), 7.52 (dd, 1H), 7.47 (dd, 1H), 7.19 (dd, 1H), 7.14 – 7.04 (m, 3H), 6.96 (m, 1H), 6.60 (s, 1H), 4.45 – 4.39 (m, 1H), 3.91 (s, 3H), 3.82 – 3.36 (m, 6H), 3.21 – 3.07 (m, 1H), 2.82 (t, 1H), 2.67 – 2.56 (m, 3H), 2.40 (s, 3H), 2.10 (t, 2H), 1.81 – 1.19 (m, 10H).	(Method A) R _T = 0.59 min, <i>m/z</i> 606 [M+H] ⁺
68		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -chromen-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.26 (s, 1H), 8.16 (dd, 1H), 7.78 (ddd, 1H), 7.59 (dd, 1H), 7.48 (ddd, 1H), 7.10 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 4.4 – 4.35 (m, 1H), 3.83 – 3.33 (m, 6H), 3.18 – 2.98 (m, 1H), 2.79 (td, 1H), 2.66 – 2.50 (m, 3H), 2.38 (s, 3H), 2.13 – 2.00 (m, 2H), 1.90 – 1.78 (m, 1H), 1.76 – 1.19 (m, 9H).	(Method A) R _T = 0.58 min, <i>m/z</i> 551 [M+H] ⁺
69		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-4 <i>H</i> -chromen-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.27 (s, 1H), 7.78 (dd, 1H), 7.66 (dd, 1H), 7.57 (ddd, 1H), 7.10 – 7.00 (m, 2H), 6.97 – 6.89 (m, 1H), 4.39 (d, 1H), 3.80 – 3.33 (m, 6H), 3.14 – 3.00 (m, 1H), 2.83 – 2.74 (m, 1H), 2.66 – 2.49 (m, 3H), 2.39 (s, 3H), 2.15 – 1.97 (m, 2H), 1.89 – 1.77 (m, 1H), 1.74 – 1.19 (m, 9H).	(Method A) R _T = 0.61 min, <i>m/z</i> 569 [M+H] ⁺
70		(<i>R</i>)-3-((9-((3-Cyclohexyl-2-methylpropanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -chromen-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.27 (s, 1H), 8.16 (dd, 1H), 7.78 (ddd, 1H), 7.59 (dd, 1H), 7.48 (ddd, 1H), 3.78 – 3.34 (m, 6H), 3.04 – 2.90 (m, 1H), 2.67 – 2.47 (m, 2H), 1.99 – 1.44 (m, 14H), 1.39 – 1.11 (m, 5H), 1.06 (dd, 3H), 0.96 – 0.85 (m, 2H).	(Method A) R _T = 1.01 min, <i>m/z</i> 451 [M+H] ⁺

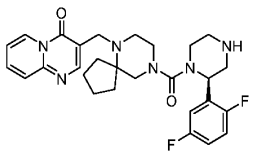
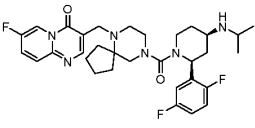
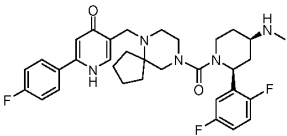
71		(<i>R</i>)-3-((9-(3-cyclohexyl-2-methylpropanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-4 <i>H</i> -chromen-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.28 (s, 1H), 7.78 (dd, 1H), 7.66 (dd, 1H), 7.57 (ddd, 1H), 3.81 – 3.33 (m, 6H), 3.04 – 2.90 (m, 1H), 2.67 – 2.47 (m, 2H), 1.98 – 1.43 (m, 14H), 1.38 – 1.11 (m, 5H), 1.06 (dd, 3H), 0.97 – 0.82 (m, 2H).	(Method A) R _T = 1.06 min, <i>m/z</i> 469 [M+H] ⁺
72		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2,3-dihydrobenzofuran-7-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.01 (s, 1H), 7.45 (d, 1H), 7.39 (d, 1H), 7.13 – 7.00 (m, 3H), 7.00 – 6.92 (m, 1H), 6.86 (s, 1H), 4.74 (t, 2H), 4.45 – 4.38 (m, 1H), 3.72 (s, 1H), 3.63 – 3.51 (m, 2H), 3.46 (d, 3H), 3.37 (m, 1H), 3.31 – 3.29 (m, 1H), 3.14 (d, 1H), 2.83 (t, 1H), 2.68 – 2.55 (m, 3H), 2.41 (d, 3H), 2.10 (t, 2H), 1.77 – 1.26 (m, 10H).	(Method A) R _T = 0.63 min, <i>m/z</i> 618 [M+H] ⁺
73		(<i>R</i>)-3-((9-(2-(2,5-difluorophenyl)piperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-4 <i>H</i> -chromen-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.29 (t, 1H), 7.80 (dd, 1H), 7.68 (dd, 1H), 7.62 – 7.56 (m, 1H), 7.20 – 7.14 (m, 1H), 7.13 – 7.06 (m, 1H), 7.05 – 6.96 (m, 1H), 4.55 (dd, 1H), 3.71 – 3.59 (m, 1H), 3.58 – 3.34 (m, 5H), 3.12 (d, 1H), 3.09 – 2.91 (m, 4H), 2.79 (dd, 1H), 2.65 – 2.53 (m, 2H), 1.90 – 1.79 (m, 1H), 1.77 – 1.55 (m, 5H), 1.49 – 1.42 (m, 1H), 1.40 – 1.30 (m, 1H).	(Method A) R _T = 0.63 min, <i>m/z</i> 541 [M+H] ⁺
74		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.92 (s, 1H), 7.69 (d, 1H), 7.10 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 6.80 (s, 1H), 6.76 (d, 1H), 4.43 – 4.36 (m, 1H), 3.98 (s, 3H), 3.82 – 3.35 (m, 6H), 3.19 – 3.04 (m, 1H), 2.80 (td, 1H), 2.67 – 2.50 (m, 3H),	(Method A) R _T = 0.52 min, <i>m/z</i> 580 [M+H] ⁺

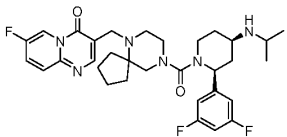
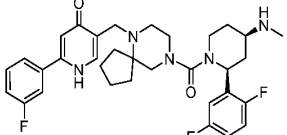
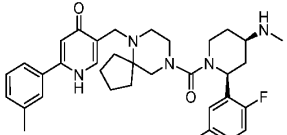
			2.39 (s, 3H), 2.14 – 2.01 (m, 2H), 1.77 – 1.19 (m, 10H).	
75		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.09 – 9.05 (m, 1H), 8.43 (s, 1H), 7.97 – 7.90 (m, 1H), 7.71 – 7.67 (m, 1H), 7.36 (td, 1H), 7.11 – 7.01 (m, 2H), 6.98 – 6.90 (m, 1H), 4.42 – 4.36 (m, 1H), 3.77 – 3.58 (m, 2H), 3.58 – 3.37 (m, 4H), 3.10 (d, 1H), 2.79 (td, 1H), 2.67 – 2.52 (m, 3H), 2.38 (s, 3H), 2.13 – 2.01 (m, 2H), 1.95 – 1.84 (m, 1H), 1.80 – 1.23 (m, 9H).	(Method A) R _T = 0.51 min, <i>m/z</i> 551 [M+H] ⁺
76		3-((4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.80 (d, 1H), 7.70 – 7.64 (m, 2H), 7.54 – 7.45 (m, 3H), 7.12 (ddd, 1H), 7.04 (td, 1H), 6.96 – 6.90 (m, 1H), 6.67 (d, 1H), 4.42 – 4.36 (m, 1H), 3.70 (br s, 1H), 3.59 – 3.48 (m, 2H), 3.48 – 3.34 (m, 3H), 3.16 – 3.03 (m, 1H), 2.84 – 2.75 (m, 1H), 2.66 – 2.51 (m, 3H), 2.39 (s, 3H), 2.12 – 2.01 (m, 2H), 1.56 – 1.45 (m, 1H), 1.37 (q, 1H), 1.10 (s, 3H), 0.93 (s, 3H).	(Method A) R _T = 0.54 min, <i>m/z</i> 550 [M+H] ⁺
77		1-Cyclopropyl-5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-methylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.92 (s, 1H), 7.09 – 7.00 (m, 2H), 6.97 – 6.91 (m, 1H), 6.32 (d, 1H), 4.43 – 4.36 (m, 1H), 3.68 (br s, 1H), 3.59 – 3.34 (m, 6H), 3.16 – 3.03 (m, 1H), 2.84 – 2.74 (m, 1H), 2.67 – 2.57 (m, 1H), 2.57 – 2.45 (m, 5H), 2.39 (s, 3H), 2.13 – 2.02 (m, 2H), 1.74 – 1.17 (m, 12H), 1.14 – 1.04 (m, 2H).	(Method A) R _T = 0.50 min, <i>m/z</i> 554 [M+H] ⁺

78		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-5,6-dimethylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.52 (s, 1H), 7.09 – 7.00 (m, 2H), 6.97 – 6.90 (m, 1H), 4.42 – 4.35 (m, 1H), 3.82 – 3.35 (m, 5H), 3.16 – 3.00 (m, 1H), 2.84 – 2.74 (m, 1H), 2.68 – 2.44 (m, 3H), 2.39 (s, 3H), 2.24 (s, 3H), 2.14 – 2.00 (m, 5H), 1.82 – 1.16 (m, 11H).	(Method A) R _T = 0.52 min, <i>m/z</i> 528 [M+H] ⁺
79		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -pyrimido[1,2- <i>b</i>]pyridazin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.77 (dd, 1H), 8.46 (s, 1H), 8.00 (dd, 1H), 7.69 (dd, 1H), 7.12 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 4.43 – 4.35 (m, 1H), 3.78 – 3.37 (m, 6H), 3.16 – 3.04 (m, 1H), 2.84 – 2.74 (m, 1H), 2.68 – 2.53 (m, 3H), 2.38 (s, 3H), 2.13 – 2.01 (m, 2H), 1.91 – 1.81 (m, 1H), 1.79 – 1.19 (m, 9H).	(Method A) R _T = 0.48 min, <i>m/z</i> 552 [M+H] ⁺
80		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoroquinolin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.12 (s, 1H), 7.89 (dd, 1H), 7.64 (dd, 1H), 7.54 – 7.47 (m, 1H), 7.11 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 4.43 – 4.35 (m, 1H), 3.79 – 3.35 (m, 6H), 3.18 – 3.04 (m, 1H), 2.85 – 2.74 (m, 1H), 2.67 – 2.51 (m, 3H), 2.39 (s, 3H), 2.14 – 2.01 (m, 2H), 1.89 – 1.77 (m, 1H), 1.77 – 1.20 (m, 9H).	(Method A) R _T = 0.58 min, <i>m/z</i> 568 [M+H] ⁺
81		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-hydroxyphenyl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.05 (s, 1H), 7.61 (d, 1H), 7.30 – 7.23 (m, 1H), 7.11 – 7.01 (m, 2H), 6.99 – 6.92 (m, 2H), 6.92 – 6.84 (m, 2H), 4.44 – 4.37 (m, 1H), 3.82 – 3.63 (m, 2H), 3.63 – 3.51 (m, 2H), 3.51 – 3.38 (m, 2H), 3.19 – 3.06 (m, 1H), 2.81 (t, 1H), 2.76 – 2.67 (m, 1H), 2.68 – 2.54 (m, 2H), 2.44 (s, 3H), 2.16 – 2.03 (m, 2H),	(Method A) R _T = 0.57 min, <i>m/z</i> 592 [M+H] ⁺

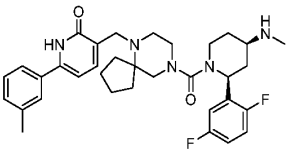
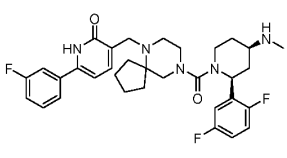
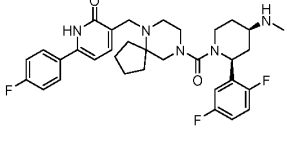
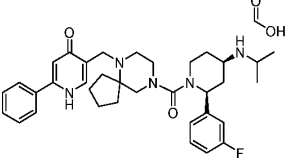
			1.84 – 1.36 (m, 9H), 1.34 – 1.23 (m, 1H).	
82		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-methyl-2-propylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.07 – 6.99 (m, 2H), 6.96 – 6.89 (m, 1H), 6.17 (s, 1H), 4.40 – 4.33 (m, 1H), 3.65 – 3.32 (m, 6H), 3.07 (d, 1H), 2.82 – 2.69 (m, 3H), 2.61 (tt, 1H), 2.42 (t, 2H), 2.38 (s, 3H), 2.29 (s, 3H), 2.12 – 2.00 (m, 2H), 1.99 – 1.89 (m, 1H), 1.87 – 1.19 (m, 11H), 1.03 (t, 3H).	(Method A) R _T = 0.57 min, <i>m/z</i> 556 [M+H] ⁺
83		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.05 – 8.96 (m, 1H), 8.47 (s, 1H), 8.02 – 7.91 (m, 1H), 7.78 (dd, 1H), 7.16 – 7.02 (m, 2H), 7.01 – 6.93 (m, 1H), 4.40 (d, 1H), 3.66 (d, 2H), 3.61 – 3.40 (m, 4H), 3.12 (d, 1H), 2.81 (d, 1H), 2.68 – 2.54 (m, 3H), 2.40 (s, 3H), 2.15 – 2.01 (m, 2H), 1.89 (dd, 1H), 1.84 – 1.20 (m, 9H).	(Method A) R _T = 0.54 min, <i>m/z</i> 569 [M+H] ⁺
84		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-5-(trifluoromethyl)pyridine-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.85 – 7.83 (m, 1H), 7.80 – 7.78 (m, 1H), 7.16 – 7.01 (m, 2H), 7.00 – 6.88 (m, 1H), 4.41 (s, 1H), 3.73 (s, 1H), 3.61 – 3.53 (m, 1H), 3.52 – 3.35 (m, 4H), 3.18 – 3.06 (m, 1H), 2.81 (t, 1H), 2.70 – 2.59 (m, 1H), 2.60 – 2.50 (m, 2H), 2.41 (s, 3H), 2.10 (t, 2H), 1.77 – 1.19 (m, 11H).	(Method A) R _T = 0.57 min, <i>m/z</i> 568 [M+H] ⁺
85		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.98 (s, 1H), 7.47 – 7.40 (m, 1H), 7.38 (dt, 1H), 7.36 – 7.31 (m, 2H), 7.12 – 7.04 (m, 2H), 6.96 (ddt, 1H), 6.41 (s, 1H),	(Method A) R _T = 0.62 min, <i>m/z</i> 618 [M+H] ⁺

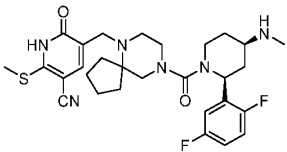
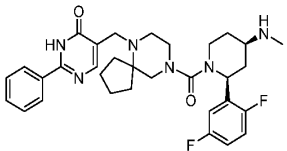
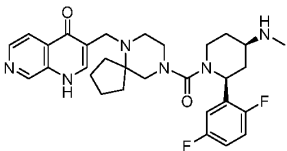
		6-yl)methyl)-2-(<i>o</i> -tolyl)pyridin-4(1 <i>H</i>)-one	4.44 – 4.39 (m, 1H), 3.72 (s, 1H), 3.63 – 3.53 (m, 2H), 3.53 – 3.42 (m, 3H), 3.14 (d, 1H), 3.04 (hept, 1H), 2.94 – 2.79 (m, 2H), 2.66 – 2.55 (m, 2H), 2.33 (s, 3H), 2.12 – 2.03 (m, 2H), 1.81 – 1.50 (m, 7H), 1.50 – 1.27 (m, 3H), 1.10 (t, 6H).	
86		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2,3-dihydrobenzofuran-7-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.01 (s, 1H), 7.45 (d, 1H), 7.39 (dq, 1H), 7.12 – 7.00 (m, 3H), 7.00 – 6.94 (m, 1H), 6.86 (s, 1H), 4.74 (t, 2H), 4.44 – 4.39 (m, 1H), 3.72 (s, 1H), 3.64 – 3.50 (m, 2H), 3.50 – 3.42 (m, 3H), 3.35 – 3.34 (m, 1H), 3.32 – 3.30 (m, 1H), 3.14 (d, 1H), 3.04 (hept, 1H), 2.93 – 2.78 (m, 2H), 2.65 – 2.53 (m, 2H), 2.13 – 2.04 (m, 2H), 1.78 – 1.51 (m, 7H), 1.50 – 1.27 (m, 3H), 1.11 (dd, 6H).	(Method A) R _T = 0.65 min, <i>m/z</i> 646 [M+H] ⁺
87		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-methoxyphenyl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.97 (s, 1H), 7.54 – 7.51 (m, 1H), 7.47 (dd, 1H), 7.19 (dd, 1H), 7.14 – 7.04 (m, 3H), 7.00 – 6.93 (m, 1H), 6.60 (s, 1H), 4.42 (d, 1H), 3.91 (s, 3H), 3.72 (s, 1H), 3.65 – 3.39 (m, 5H), 3.14 (d, 1H), 3.03 (hept, 1H), 2.94 – 2.78 (m, 2H), 2.68 – 2.55 (m, 2H), 2.12 – 2.03 (m, 2H), 1.78 – 1.50 (m, 7H), 1.49 – 1.37 (m, 2H), 1.36 – 1.27 (m, 1H), 1.10 (dd, 6H).	(Method A) R _T = 0.62 min, <i>m/z</i> 634 [M+H] ⁺
88		(<i>R</i>)-5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)piperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.01 (s, 1H), 7.75 – 7.70 (m, 2H), 7.60 – 7.54 (m, 3H), 7.21 (ddd, 1H), 7.15 (td, 1H), 7.11 – 7.05 (m, 1H), 6.75 (s, 1H), 4.71 (dd, 1H), 3.79 – 3.68 (m, 1H), 3.68 – 3.54 (m, 1H), 3.54 – 3.42 (m, 3H), 3.14 (d, 1H), 3.04 (hept, 1H), 2.94 – 2.78 (m, 2H), 2.68 – 2.55 (m, 2H), 2.12 – 2.03 (m, 2H), 1.78 – 1.50 (m, 7H), 1.49 – 1.37 (m, 2H), 1.36 – 1.27 (m, 1H), 1.10 (dd, 6H).	(Method C) R _T = 0.56 min, <i>m/z</i> 548 [M+H] ⁺

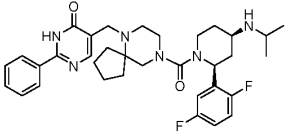
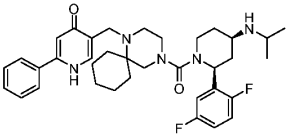
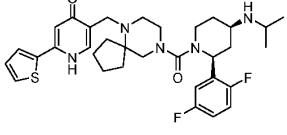
			3H), 3.53 – 3.43 (m, 2H), 3.31 – 3.27 (m, 2H), 3.27 – 3.23 (m, 1H), 3.23 – 3.17 (m, 1H), 3.15 – 3.03 (m, 2H), 2.75 – 2.62 (m, 2H), 1.86 – 1.56 (m, 6H), 1.53 – 1.45 (m, 1H), 1.41 – 1.29 (m, 1H).	
89		(<i>R</i>)-3-((9-(2-(2,5-Difluorophenyl)piperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.09 (ddd, 1H), 8.45 (s, 1H), 7.95 (dddd, 1H), 7.71 (ddd, 1H), 7.38 (dt, 1H), 7.17 (ddd, 1H), 7.09 (td, 1H), 7.05 – 6.96 (m, 1H), 7.56 (dd, 1H), 3.71 – 3.60 (m, 2H), 3.60 – 3.50 (m, 2H), 3.42 (d, 1H), 3.38 – 3.34 (m, 1H), 3.14 (m, 1H), 3.10 – 2.92 (m, 4H), 2.80 (dd, 1H), 2.68 – 2.55 (m, 2H), 1.96 – 1.87 (m, 1H), 1.84 – 1.56 (m, 5H), 1.52 – 1.44 (m, 1H), 1.42 – 1.33 (m, 1H).	(Method C) R _T = 0.50 min, <i>m/z</i> 523 [M+H] ⁺
90		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.99 (ddd, 1H), 8.45 (s, 1H), 7.94 (ddd, 1H), 7.78 – 7.73 (m, 1H), 7.11 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 4.43 – 4.35 (m, 1H), 3.83 – 3.58 (m, 2H), 3.58 – 3.47 (m, 2H), 3.47 – 3.36 (m, 2H), 3.17 – 3.05 (m, 1H), 3.01 (hept, 1H), 2.89 – 2.74 (m, 2H), 2.66 – 2.51 (m, 2H), 2.11 – 1.99 (m, 2H), 1.93 – 1.82 (m, 1H), 1.79 – 1.33 (m, 8H), 1.33 – 1.22 (m, 1H), 1.08 (t, 6H).	(Method A) R _T = 0.57 min, <i>m/z</i> 597 [M+H] ⁺
91		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(4-fluorophenyl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.01 (s, 1H), 7.83 – 7.74 (m, 2H), 7.33 – 7.27 (m, 2H), 7.12 – 7.04 (m, 2H), 7.00 – 6.93 (m, 1H), 6.73 (s, 1H), 4.42 (d, 1H), 3.72 (s, 1H), 3.64 – 3.55 (m, 2H), 3.54 – 3.42 (m, 3H), 3.14 (d, <i>J</i> = 12.8 Hz, 1H), 2.83	(Method A) R _T = 0.59 min, <i>m/z</i> 594 [M+H] ⁺

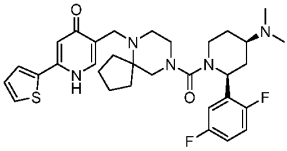
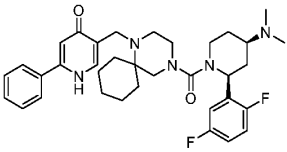
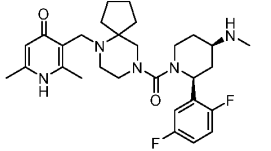
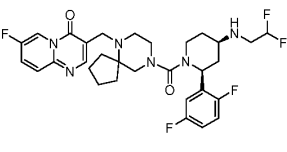
			(t, J = 12.4, 2.3 Hz, 1H), 2.69 – 2.54 (m, 3H), 2.41 (s, 3H), 2.15 – 2.05 (m, 2H), 1.90 – 1.22 (m, 10H).	
92		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.02 – 8.96 (m, 1H), 8.45 (s, 1H), 7.94 (ddd, 1H), 7.76 (dd, 1H), 6.94 – 6.87 (m, 2H), 6.77 (tt, 1H), 4.05 (dd, 1H), 3.81 – 3.58 (m, 2H), 3.58 – 3.47 (m, 2H), 3.47 – 3.36 (m, 2H), 3.19 – 3.06 (m, 1H), 3.01 (sept, 1H), 2.90 – 2.73 (m, 2H), 2.66 – 2.51 (m, 2H), 2.11 – 1.98 (m, 2H), 1.95 – 1.81 (m, 1H), 1.79 – 1.23 (m, 9H), 1.08 (t, 6H).	(Method A) R _T = 0.58 min, <i>m/z</i> 597 [M+H] ⁺
93		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(3-fluorophenyl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.04 (s, 1H), 7.57 (td, 2H), 7.54 – 7.50 (m, 1H), 7.33 – 7.25 (m, 1H), 7.13 – 7.03 (m, 2H), 7.01 – 6.94 (m, 1H), 6.80 (s, 1H), 4.42 (d, 1H), 3.72 (s, 1H), 3.67 – 3.41 (m, 5H), 3.14 (d, 1H), 2.83 (t, 1H), 2.71 – 2.55 (m, 3H), 2.42 (s, 3H), 2.16 – 2.05 (m, 2H), 1.85 – 1.23 (m, 10H).	(Method A) R _T = 0.59 min, <i>m/z</i> 594 [M+H] ⁺
94		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(<i>m</i> -tolyl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.99 (s, 1H), 7.55 (s, 1H), 7.50 (d, 1H), 7.44 (t, 1H), 7.38 (d, 1H), 7.14 – 7.02 (m, 2H), 7.01 – 6.92 (m, 1H), 6.72 (s, 1H), 4.44 – 4.38 (m, 1H), 3.68 (s, 1H), 3.64 – 3.39 (m, 5H), 3.14 (d, 1H), 2.83 (td, 1H), 2.70 – 2.55 (m, 3H), 2.46 (s, 3H), 2.41 (s, 3H), 2.14 – 2.04 (m, 2H), 1.80 – 1.22 (m, 10H).	(Method A) R _T = 0.59 min, <i>m/z</i> 590 [M+H] ⁺

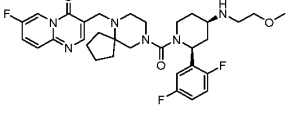
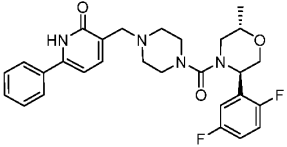
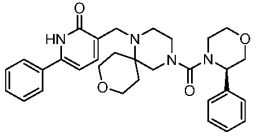
95		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-methoxyphenyl)pyridine-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.97 (s, 1H), 7.52 (ddd, 1H), 7.47 (dd, 1H), 7.20 (dd, 1H), 7.11 (td, 1H), 6.96 – 6.90 (m, 2H), 6.81 (tt, 1H), 6.60 (s, 1H), 4.10 (dd, 1H), 3.91 (s, 3H), 3.78 – 3.65 (m, 1H), 3.65 – 3.39 (m, 5H), 3.20 – 3.11 (m, 1H), 2.91 – 2.80 (m, 2H), 2.69 – 2.55 (m, 2H), 2.53 (s, 3H), 2.20 – 2.10 (m, 2H), 1.83 – 1.52 (m, 7H), 1.52 – 1.42 (m, 2H), 1.38 – 1.19 (m, 1H).	(Method A) R _T = 0.59 min, <i>m/z</i> 606 [M+H] ⁺
96		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2,3-dihydrobenzofuran-7-yl)pyridine-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.99 (s, 1H), 7.46 – 7.40 (m, 1H), 7.39 – 7.34 (m, 1H), 7.00 (t, 1H), 6.94 – 6.87 (m, 2H), 6.84 (s, 1H), 6.77 (tt, 1H), 4.72 (t, 2H), 4.06 (dd, 1H), 3.79 – 3.36 (m, 6H), 3.34 – 3.28 (m, 2H overlapping solvent), 3.21 – 3.08 (m, 1H), 3.02 (sept, 1H), 2.90 – 2.75 (m, 2H), 2.64 – 2.53 (m, 2H), 2.11 – 1.99 (m, 2H), 1.79 – 1.23 (m, 10H), 1.08 (dd, 6H).	(Method A) R _T = 0.63 min, <i>m/z</i> 646 [M+H] ⁺
97		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(<i>o</i> -tolyl)pyridine-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.96 (s, 1H), 7.44 – 7.38 (m, 1H), 7.37 – 7.33 (m, 1H), 7.34 – 7.30 (m, 2H), 6.94 – 6.88 (m, 2H), 6.80 – 6.73 (m, 1H), 6.39 (s, 1H), 4.09 – 4.03 (m, 1H), 3.80 – 3.35 (m, 6H), 3.21 – 3.08 (m, 1H), 3.07 – 2.97 (m, 1H), 2.91 – 2.75 (m, 2H), 2.67 – 2.53 (m, 2H), 2.31 (s, 3H), 2.05 (t, 2H), 1.80 – 1.23 (m, 10H), 1.13 – 1.05 (m, 6H).	(Method A) R _T = 0.63 min, <i>m/z</i> 618 [M+H] ⁺

98		3-((9-((2S,4R)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(<i>m</i> -tolyl)pyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.78 (dd, 1H), 7.51 – 7.48 (m, 1H), 7.48 – 7.43 (m, 1H), 7.38 (t, 1H), 7.33 – 7.29 (m, 1H), 7.11 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 6.65 (d, 1H), 4.43 – 4.36 (m, 1H), 3.71 (s, 1H), 3.61 – 3.36 (m, 5H), 3.11 (d, 1H), 2.84 – 2.75 (m, 1H), 2.67 – 2.50 (m, 3H), 2.42 (s, 3H), 2.39 (s, 3H), 2.14 – 2.03 (m, 2H), 1.82 – 1.19 (m, 10H).	(Method A) R _T = 0.65 min, <i>m/z</i> 590 [M+H] ⁺
99		3-((9-((2S,4R)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(3-fluorophenyl)pyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.81 – 7.76 (m, 1H), 7.55 – 7.49 (m, 2H), 7.49 – 7.43 (m, 1H), 7.26 – 7.19 (m, 1H), 7.11 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 6.71 (d, 1H), 4.43 – 4.35 (m, 1H), 3.71 (s, 1H), 3.61 – 3.36 (m, 5H), 3.11 (d, 1H), 2.80 (td, 1H), 2.65 – 2.50 (m, 3H), 2.38 (s, 3H), 2.13 – 2.02 (m, 2H), 1.80 – 1.21 (m, 10H).	(Method A) R _T = 0.60 min, <i>m/z</i> 594 [M+H] ⁺
100		3-((9-((2S,4R)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(4-fluorophenyl)pyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.79 – 7.75 (m, 1H), 7.73 – 7.68 (m, 2H), 7.27 – 7.21 (m, 2H), 7.10 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 6.63 (d, 1H), 4.42 – 4.36 (m, 1H), 3.71 (s, 1H), 3.61 – 3.35 (m, 5H), 3.11 (d, 1H), 2.85 – 2.75 (m, 1H), 2.67 – 2.50 (m, 3H), 2.39 (s, 3H), 2.13 – 2.02 (m, 2H), 1.81 – 1.19 (m, 10H).	(Method A) R _T = 0.60 min, <i>m/z</i> 594 [M+H] ⁺
101		5-((9-((2S,4R)-2-(3-Fluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one formate	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.54 (s, 1H), 8.00 (s, 1H), 7.75 – 7.69 (m, 2H), 7.57 (dd, 3H), 7.36 (td, 1H), 7.20 – 7.15 (m, 1H), 7.09 (dt, 1H), 7.00 (td, 1H), 6.75 (s, 1H), 4.17 (dd, 1H), 3.75 (s, 1H), 3.64 – 3.43 (m, 7H), 3.17 (dd, 1H), 2.91 (td,	(Method A) R _T = 0.62 min, <i>m/z</i> 586 [M+H] ⁺

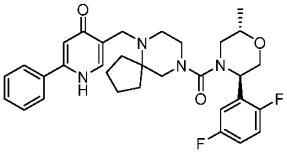
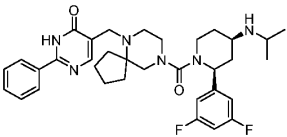
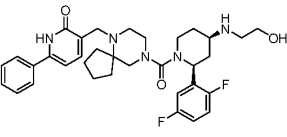
			1H), 2.68 – 2.55 (m, 2H), 2.28 – 2.18 (m, 2H), 1.84 – 1.51 (m, 8H), 1.47 (dd, 1H), 1.36 (t, 6H), 1.24 (dd, 1H).	
102		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(methylthio)-6-oxo-1,6-dihydropyridine-3-carbonitrile	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.66 (s, 1H), 7.13 – 7.06 (m, 2H), 7.04 – 6.96 (m, 1H), 4.47 – 4.41 (m, 1H), 3.76 (s, 1H), 3.70 – 3.62 (m, 1H), 3.61 – 3.47 (m, 4H), 3.27 – 3.19 (m, 1H), 3.19 – 3.10 (m, 1H), 2.86 (td, 1H), 2.68 (s, 3H), 2.68 – 2.64 (m, 1H), 2.63 – 2.60 (m, 1H), 2.58 (s, 3H), 2.26 – 2.17 (m, 2H), 1.87 – 1.79 (m, 1H), 1.78 – 1.60 (m, 6H), 1.59 – 1.51 (m, 1H), 1.49 – 1.42 (m, 1H), 1.35 – 1.24 (m, 1H).	(Method A) R _T = 0.62 min, <i>m/z</i> 571 [M+H] ⁺
103		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyrimidin-4(3 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.15 (d, 1H), 8.06 – 8.00 (m, 2H), 7.62 – 7.52 (m, 3H), 7.12 – 7.04 (m, 2H), 7.00 – 6.94 (m, 1H), 4.44 – 4.39 (m, 1H), 3.73 (s, 1H), 3.61 – 3.37 (m, 5H), 3.12 (d, 1H), 2.82 (t, 1H), 2.74 – 2.56 (m, 3H), 2.44 (s, 3H), 2.16 – 2.07 (m, 2H), 1.85 – 1.79 (m, 1H), 1.75 – 1.61 (m, 4H), 1.61 – 1.49 (m, 2H), 1.49 – 1.37 (m, 2H), 1.34 – 1.24 (m, 1H).	(Method A) R _T = 0.55 min, <i>m/z</i> 577 [M+H] ⁺
104		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1,7-naphthyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.03 (s, 1H), 8.47 (d, 1H), 8.29 (s, 1H), 8.14 (dd, 1H), 7.15 – 7.04 (m, 2H), 7.01 – 6.91 (m, 1H), 4.47 – 4.36 (m, 1H), 3.76 – 3.50 (m, 4H), 3.49 – 3.40 (m, 2H), 3.14 (d, 1H), 2.82 (td, 1H), 2.72 – 2.53 (m, 3H), 2.43 (s, 3H), 2.17 – 2.05 (m, 2H),	(Method A) R _T = 0.50 min, <i>m/z</i> 551 [M+H] ⁺

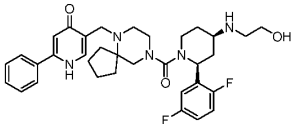
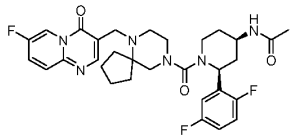
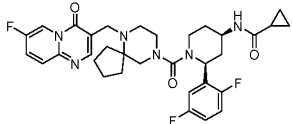
			1.85 (dt, 1H), 1.77 – 1.25 (m, 9H).	
105		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyrimidin-4(3 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.03 (s, 1H), 7.97 – 7.90 (m, 2H), 7.54 – 7.42 (m, 3H), 7.05 – 6.92 (m, 2H), 6.91 – 6.83 (m, 1H), 4.36 – 4.26 (m, 1H), 3.60 (s, 1H), 3.51 – 3.26 (m, 5H), 3.05 – 2.92 (m, 2H), 2.91 – 2.80 (m, 1H), 2.72 (td, 1H), 2.61 – 2.42 (m, 2H), 1.99 (t, 2H), 1.71 (dd, 1H), 1.63 – 1.51 (m, 4H), 1.51 – 1.41 (m, 2H), 1.39 – 1.29 (m, 2H), 1.26 – 1.12 (m, 1H), 1.03 (t, 6H).	(Method A) R _T = 0.58 min, <i>m/z</i> 605 [M+H] ⁺
106		5-((4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.02 (s, 1H), 7.74 – 7.67 (m, 2H), 7.58 – 7.50 (m, 3H), 7.10 (ddd, 1H), 7.04 (td, 1H), 6.97 – 6.91 (m, 1H), 6.72 (s, 1H), 4.40 – 4.35 (m, 1H), 3.74 (d, 3H), 3.63 – 3.49 (m, 2H), 3.48 – 3.39 (m, 1H), 3.26 – 3.13 (m, 1H), 3.03 (sept, 1H), 2.92 – 2.65 (m, 4H), 2.14-2.00 (m, 2H), 1.71 – 1.25 (m, 11H), 1.24 – 1.14 (m, 1H), 1.09 (t, 6H).	(Method A) R _T = 0.64 min, <i>m/z</i> 618 [M+H] ⁺
107		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-2-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.96 (s, 1H), 7.62 – 7.56 (m, 2H), 7.18 (dd, 1H), 7.10 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 6.82 (s, 1H), 4.43 – 4.37 (m, 1H), 3.80 – 3.38 (m, 6H), 3.19 – 3.07 (m, 1H), 3.03 (hept, 1H), 2.93 – 2.76 (m, 2H), 2.66 – 2.52 (m, 2H), 2.11 – 2.01 (m, 2H), 1.82 – 1.35 (m, 9H), 1.35 – 1.23 (m, 1H), 1.09 (t, 6H).	(Method A) R _T = 0.59 min, <i>m/z</i> 610 [M+H] ⁺

108		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-2-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.96 (s, 1H), 7.64 – 7.56 (m, 2H), 7.18 (dd, 1H), 7.13 – 7.02 (m, 2H), 6.99 – 6.92 (m, 1H), 6.82 (s, 1H), 4.43 – 4.35 (m, 1H), 3.82 – 3.39 (m, 6H), 3.19 – 3.05 (m, 1H), 2.85 – 2.75 (m, 1H), 2.67 – 2.44 (m, 3H), 2.32 (s, 6H), 2.10 – 1.98 (m, 2H), 1.84 – 1.39 (m, 9H), 1.36 – 1.22 (m, 1H).	(Method A) R _T = 0.56 min, <i>m/z</i> 596 [M+H] ⁺
109		5-((4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.02 (s, 1H), 7.74 – 7.67 (m, 2H), 7.58 – 7.51 (m, 3H), 7.12 (ddd, 1H), 7.05 (td, 1H), 6.98 – 6.91 (m, 1H), 6.72 (s, 1H), 4.39 – 4.33 (m, 1H), 3.91 – 3.65 (m, 3H), 3.61 – 3.43 (m, 3H), 3.23 – 3.10 (m, 1H), 2.84 – 2.66 (m, 3H), 2.53 – 2.43 (m, 1H), 2.32 (s, 6H), 2.11 – 1.99 (m, 2H), 1.74 – 1.25 (m, 11H), 1.24 – 1.10 (m, 1H).	(Method A) R _T = 0.63 min, <i>m/z</i> 604 [M+H] ⁺
110		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2,6-dimethylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.07 – 6.99 (m, 2H), 6.96 – 6.89 (m, 1H), 6.18 (s, 1H), 4.40 – 4.34 (m, 1H), 3.63 – 3.33 (m, 6H), 3.08 (d, 1H), 2.77 (td, 1H), 2.67 – 2.58 (m, 1H), 2.46 (s, 3H), 2.43 (t, 2H), 2.39 (s, 3H), 2.28 (s, 3H), 2.13 – 1.91 (m, 3H), 1.88 – 1.77 (m, 1H), 1.76 – 1.43 (m, 5H), 1.42 – 1.17 (m, 3H).	(Method C) R _T = 0.50 min, <i>m/z</i> 528 [M+H] ⁺
111		3-((9-((2 <i>S</i> ,4 <i>R</i>)-4-((2,2-Difluoroethyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.99 (ddd, 1H), 8.45 (s, 1H), 7.94 (ddd, 1H), 7.76 (ddd, 1H), 7.11 – 7.00 (m, 2H), 6.97 – 6.91 (m, 1H), 5.87 (tt, 1H), 4.41 – 4.35 (m, 1H), 3.78 – 3.59 (m, 2H), 3.56 – 3.47 (m, 2H), 3.47 – 3.37 (m, 2H),	(Method A) R _T = 0.55 min, <i>m/z</i> 619 [M+H] ⁺

		4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	3.16 – 3.04 (m, 1H), 3.03 – 2.93 (m, 2H), 2.82 – 2.70 (m, 2H), 2.66 – 2.52 (m, 2H), 2.12 – 2.01 (m, 2H), 1.93 – 1.82 (m, 1H), 1.76 – 1.60 (m, 4H), 1.60 – 1.48 (m, 2H), 1.48 – 1.33 (m, 2H), 1.33 – 1.27 (m, 1H).	
112		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-((2-methoxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.01 (ddd, 1H), 8.47 (s, 1H), 7.96 (ddd, 1H), 7.78 (ddd, 1H), 7.13 – 7.03 (m, 2H), 6.99 – 6.93 (m, 1H), 4.45 – 4.38 (m, 1H), 3.81 – 3.61 (m, 2H), 3.59 – 3.40 (m, 6H), 3.36 (s, 3H), 3.17 – 3.04 (m, 1H), 2.87 – 2.71 (m, 4H), 2.67 – 2.53 (m, 2H), 2.14 – 2.02 (m, 2H), 1.94 – 1.83 (m, 1H), 1.79 – 1.36 (m, 8H), 1.35 – 1.25 (m, 1H).	(Method A) R _T = 0.55 min, <i>m/z</i> 613 [M+H] ⁺
113		3-((4-((2 <i>S</i> ,5 <i>R</i>)-5-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	11.78 (s, 1H), 7.74 (d, 2H), 7.53 – 7.42 (m, 4H), 7.19 (td, 1H), 7.13 – 7.04 (m, 2H), 6.57 (s, 1H), 4.33 – 4.27 (m, 1H), 3.80 (dt, 1H), 3.74 (dd, 1H), 3.48 (dt, 2H), 3.43 – 3.32 (m, 5H), 3.30 – 3.23 (m, 2H), 2.40 – 2.30 (m, 4H), 1.13 (d, 3H).	(Method A) R _T = 0.80 min, <i>m/z</i> = 509 [M+H] ⁺
114		(<i>R</i>)-6-Phenyl-3-((4-(3-phenylmorpholine-4-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)pyridin-2(1 <i>H</i>)-one	11.74 (s, 1H), 7.80 – 7.67 (m, 2H), 7.60 (d, 1H), 7.52 – 7.40 (m, 3H), 7.38 – 7.28 (m, 4H), 7.29 – 7.18 (m, 1H), 6.59 (s, 1H), 4.41 (t, 1H), 3.81 – 3.66 (m, 5H), 3.64 – 3.56 (m, 1H), 3.54 – 3.32 (m, 7H), 3.30 – 3.25 (m, 1H), 3.20 – 3.12 (m, 1H), 3.08 – 2.99 (m, 1H), 2.61 (q, 2H), 1.79 – 1.56 (m, 2H), 1.36 – 1.16 (m, 2H).	(Method A) R _T = 0.76 min, <i>m/z</i> 529 [M+H] ⁺

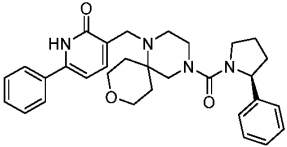
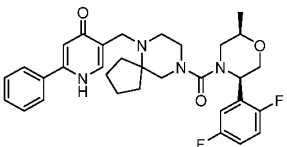
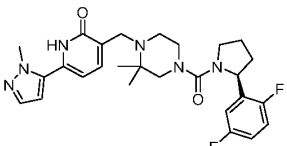
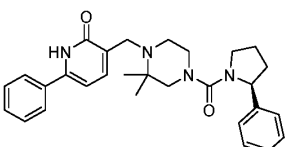
115		(<i>R</i>)-3-((4-(3-(4-Fluorophenyl)morpholine-4-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	11.74 (s, 1H), 7.80 – 7.67 (m, 2H), 7.60 (d, 1H), 7.52 – 7.41 (m, 3H), 7.41 – 7.33 (m, 2H), 7.19 – 7.09 (m, 2H), 6.59 (s, 1H), 4.46 – 4.36 (m, 1H), 3.81 – 3.66 (m, 5H), 3.65 – 3.58 (m, 1H), 3.57 – 3.32 (m, 7H), 3.30 – 3.21 (m, 1H), 3.19 – 3.10 (m, 1H), 3.06 – 2.96 (m, 1H), 2.63 – 2.56 (m, 2H), 1.78 – 1.54 (m, 2H), 1.37 – 1.16 (m, 2H).	(Method A) R _T = 0.79 min, <i>m/z</i> 547 [M+H] ⁺
116		3-((4-((2 <i>R</i> ,5 <i>R</i>)-5-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	11.77 (s, 1H), 7.82 – 7.66 (m, 2H), 7.56 – 7.44 (m, 4H), 7.40 (ddd, 1H), 7.29 – 7.21 (m, 1H), 7.22 – 7.12 (m, 1H), 6.58 (s, 1H), 5.07 (s, 1H), 4.18 (dd, 1H), 3.87 (dd, 1H), 3.61 – 3.52 (m, 1H), 3.46 – 3.33 (m, 2H), 3.29 – 3.19 (m, 3H), 3.09 (s, 2H), 2.86 (dd, 1H), 2.47 – 2.30 (m, 4H), 1.09 (d, 3H).	(Method A) R _T = 0.79 min, <i>m/z</i> = 509 [M+H] ⁺
117		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2-Fluoro-5-methylphenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.01 (s, 1H), 7.76 – 7.69 (m, 2H), 7.60 – 7.54 (m, 3H), 7.17 (dd, 1H), 7.05 – 7.00 (m, 1H), 6.92 (dd, 1H), 6.74 (s, 1H), 4.40 (dd, 1H), 3.77 (s, 1H), 3.62 – 3.40 (m, 5H), 3.15 – 3.01 (m, 2H), 2.94 – 2.86 (m, 1H), 2.87 – 2.77 (m, 1H), 2.68 – 2.55 (m, 2H), 2.33 (s, 3H), 2.11 – 2.04 (m, 2H), 1.77 – 1.39 (m, 9H), 1.29 (dd, 1H), 1.12 (t, 6H).	(Method A) R _T = 0.62 min, <i>m/z</i> 600 [M+H] ⁺
118		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2-Fluoro-5-methoxyphenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one formate	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.56 (s, 1H), 7.99 (s, 1H), 7.72 – 7.66 (m, 2H), 7.55 (dd, 3H), 6.99 (dd, 1H), 6.88 (dd, 1H), 6.81 (dt, 1H), 6.73 (s, 1H), 4.43 (dd, 1H), 3.80 – 3.70 (m, 4H), 3.61 – 3.39 (m, 7H), 3.09 (d, 1H), 2.89 (td, 1H), 2.60 (q, 2H), 2.26 – 2.16 (m, 2H), 1.81 –	(Method A) R _T = 0.59 min, <i>m/z</i> 616 [M+H] ⁺

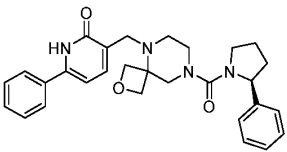
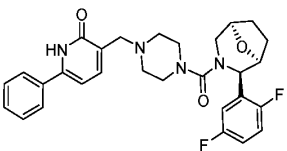
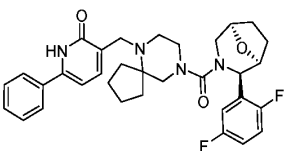
			1.48 (m, 8H), 1.44 (dd, 1H), 1.31 (dd, 6H), 1.28 – 1.18 (m, 1H).	
119		5-((9-((2 <i>S</i> ,5 <i>R</i>)-5-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: a drop of TFA was added to the DMSO- <i>d</i> ₆ solution] 8.61 (s, 1H), 7.86 – 7.77 (m, 2H), 7.69 – 7.58 (m, 3H), 7.40 (s, 1H), 7.22 – 7.04 (m, 3H), 4.51 – 4.11 (m, 3H), 4.09 – 3.71 (m, 4H), 3.69 – 2.95 (m, 7H), 2.56 – 2.52 (m, 2H), 2.23 – 1.50 (m, 8H), 1.13 (d, 3H).	(Method A) R _T = 0.88 min, <i>m/z</i> 563 [M+H] ⁺
120		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyrimidin-4(3 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.12 (s, 1H), 8.02 – 7.98 (m, 2H), 7.59 – 7.50 (m, 3H), 6.94 – 6.88 (m, 2H), 6.78 (t, 1H), 4.07 (dd, 1H), 3.70 (s, 1H), 3.62–3.35 (m, 5H), 3.18 – 3.05 (m, 2H), 2.99 – 2.89 (m, 1H), 2.85 – 2.76 (m, 1H), 2.68 – 2.52 (m, 2H), 2.13 – 2.02 (m, 2H), 1.86 – 1.49 (m, 7H), 1.48 – 1.35 (m, 2H), 1.33 – 1.23 (m, 1H), 1.12 (t, 6H).	(Method A) R _T = 0.60 min, <i>m/z</i> 605 [M+H] ⁺
121		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.81 – 7.77 (m, 1H), 7.69 – 7.64 (m, 2H), 7.54 – 7.46 (m, 3H), 7.13 – 7.01 (m, 2H), 6.99 – 6.91 (m, 1H), 6.66 (d, 1H), 4.44 – 4.37 (m, 1H), 3.80 – 3.62 (m, 3H), 3.61 – 3.35 (m, 5H), 3.18 – 3.05 (m, 1H), 2.86 – 2.72 (m, 4H), 2.65 – 2.50 (m, 2H), 2.15 – 2.02 (m, 2H), 1.83 – 1.48 (m, 7H), 1.48 – 1.36 (m, 2H), 1.35 – 1.20 (m, 1H).	(Method A) R _T = 0.59 min, <i>m/z</i> 606 [M+H] ⁺

122		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)amino)pyridine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.99 (s, 1H), 7.74 – 7.67 (m, 2H), 7.58 – 7.51 (m, 3H), 7.12 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 6.72 (s, 1H), 4.44 – 4.37 (m, 1H), 3.71 (s, 1H), 3.65 (t, 2H), 3.62 – 3.38 (m, 5H), 3.12 (d, 1H), 2.87 – 2.72 (m, 4H), 2.66 – 2.53 (m, 2H), 2.15 – 2.03 (m, 2H), 1.80 – 1.49 (m, 7H), 1.49 – 1.37 (m, 2H), 1.35 – 1.24 (m, 1H).	(Method A) R _T = 0.55 min, <i>m/z</i> 606 [M+H] ⁺
123		<i>N</i> -((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-1-(6-((7-fluoro-4-oxo-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)acetamide	8.96 – 8.91 (m, 1H), 8.39 (s, 1H), 8.05 (ddd, 1H), 7.83 – 7.75 (m, 2H), 7.17 (td, 1H), 7.09 – 6.96 (m, 2H), 4.27 (dd, 1H), 3.76 – 3.64 (m, 1H), 3.49 (d, 2H), 3.76 – 3.64 (d, 2H), 3.29 – 3.22 (m, 1H), 3.05 – 2.89 (m, 1H), 2.75 – 2.66 (m, 1H), 2.47 – 2.37 (m, 3H (obscured by DMSO signal)), 1.93 – 1.81 (m, 2H), 1.76 (s, 4H), 1.68 – 1.50 (m, 5H), 1.49 – 1.39 (m, 1H), 1.39 – 1.29 (m, 2H), 1.26 – 1.14 (m, 1H).	(Method A) R _T = 0.71 min, <i>m/z</i> = 597 [M+H] ⁺
124		<i>N</i> -((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-1-(6-((7-fluoro-4-oxo-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)cyclopropanecarboxamide	8.94 (ddd, 1H), 8.39 (s, 1H), 8.10 – 7.97 (m, 2H), 7.79 (ddd, 1H), 7.17 (td, 1H), 7.11 – 6.98 (m, 2H), 4.27 (dd, 1H), 3.78 – 3.66 (m, 1H), 3.49 (d, 2H), 3.38 (d, 2H), 3.29 – 3.19 (m, 1H), 3.06 – 2.89 (m, 1H), 2.76 – 2.66 (m, 1H), 2.47 – 2.38 (m, 3H (obscured by DMSO signal)), 1.89 (dd, 2H), 1.83 – 1.71 (m, 1H), 1.68 – 1.50 (m, 5H), 1.50 – 1.29 (m, 4H), 1.25 – 1.13 (m, 1H), 0.69 – 0.55 (m, 4H).	(Method A) R _T = 0.78 min, <i>m/z</i> = 623 [M+H] ⁺

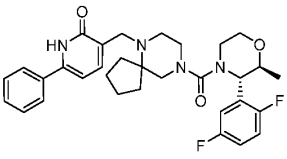
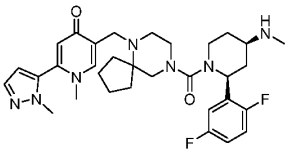
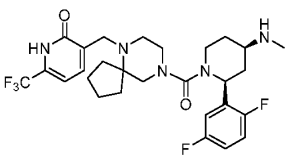
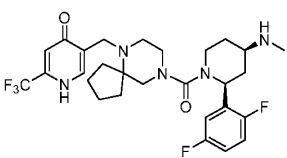
125		3-((9-((2 <i>S</i> ,4 <i>R</i>)-4-((1,1-Dioxidothietan-3-yl)amino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	9.00 – 8.89 (m, 1H), 8.39 (s, 1H), 8.12 – 8.01 (m, 1H), 7.84 – 7.73 (m, 1H), 7.29 – 7.23 (m, 2H), 7.23 – 7.19 (m, 2H), 7.19 – 7.14 (m, 1H), 4.35 – 4.21 (m, 2H), 3.94 (dd, 1H), 3.91 – 3.76 (m, 2H), 3.73 – 3.58 (m, 1H), 3.51 – 3.34 (m, 4H), 3.28 – 3.18 (m, 2H), 3.14 – 2.95 (m, 1H), 2.68 – 2.61 (m, 1H), 2.60 – 2.53 (m, 1H), 2.49 – 2.45 (m, 1H), 2.45 – 2.39 (m, 2H), 1.97 – 1.83 (m, 2H), 1.79 – 1.68 (m, 1H), 1.68 – 1.49 (m, 4H), 1.48 – 1.40 (m, 1H), 1.39 – 1.28 (m, 2H), 1.30 – 1.12 (m, 2H).	(Method A) R _T = 0.59 min, <i>m/z</i> 623 [M+H] ⁺
126		3-((9-((2 <i>S</i> ,4 <i>R</i>)-4-((2,2-Difluoroethyl)amino)-2-(3,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.79 (d, 1H), 7.70 – 7.64 (m, 2H), 7.54 – 7.45 (m, 3H), 6.94 – 6.87 (m, 2H), 6.76 (tt, 1H), 6.66 (d, 1H), 5.87 (tt, 1H), 4.05 (dd, 1H), 3.70 (s, 1H), 3.61 – 3.36 (m, 5H), 3.13 (d, 1H), 2.98 (td, 2H), 2.82 – 2.69 (m, 2H), 2.64 – 2.50 (m, 2H), 2.13 – 2.00 (m, 2H), 1.83 – 1.21 (m, 10H).	(Method A) R _T = 0.63 min, <i>m/z</i> 626 [M+H] ⁺
127		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(thiophen-3-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.96 (d, 1H), 7.71 (dd, 1H), 7.64 (dd, 1H), 7.27 (dd, 1H), 7.13 – 7.00 (m, 2H), 6.99 – 6.91 (m, 1H), 6.42 (s, 1H), 4.44 – 4.35 (m, 1H), 3.71 (s, 1H), 3.68 (s, 3H), 3.63 – 3.54 (m, 1H), 3.54 – 3.37 (m, 4H), 3.13 (d, 1H), 2.85 – 2.75 (m, 1H), 2.66 – 2.53 (m, 2H), 2.52 – 2.42 (m, 1H), 2.32 (s, 6H), 2.11 – 1.98 (m, 2H), 1.78 – 1.37 (m, 9H), 1.36 – 1.21 (m, 1H).	(Method A) R _T = 0.55 min, <i>m/z</i> 610 [M+H] ⁺

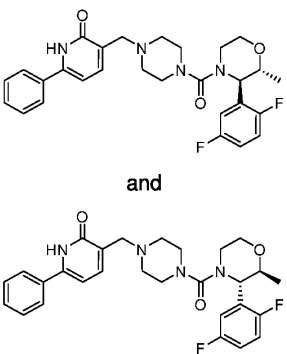
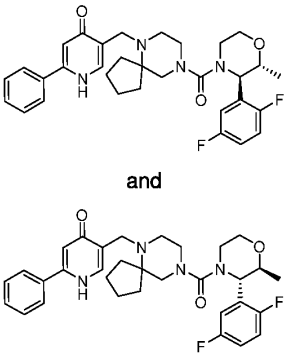
128		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	8.96 – 8.90 (m, 1H), 8.38 (s, 1H), 8.05 (ddd, 1H), 7.79 (ddd, 1H), 7.15 (td, 1H), 7.06 (qd, 2H), 4.24 (d, 1H), 3.48 (d, 2H), 3.43 – 3.34 (m, 2H), 3.05 – 2.89 (m, 1H), 2.68 – 2.61 (m, 2H), 2.47 – 2.30 (m, 4H (obscured by HDO signal)), 2.16 (s, 6H), 1.86 – 1.69 (m, 3H), 1.66 – 1.49 (m, 5H), 1.49 – 1.27 (m, 3H), 1.28 – 1.14 (m, 1H).	(Method A) $R_T = 0.53$ min, $m/z = 583$ [M+H] ⁺
129		(<i>S</i>)-6-(2-Methoxyphenyl)-3-((9-(2-phenylpyrrolidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1 <i>H</i>)-one	11.43 (s, 1H), 7.50 (d, 1H), 7.42 (ddd, 1H), 7.37 – 7.31 (m, 1H), 7.31 – 7.21 (m, 4H), 7.21 – 7.17 (m, 1H), 7.11 (dd, 1H), 7.01 (td, 1H), 6.24 (s, 1H), 4.92 (dd, 1H), 3.79 (s, 3H), 3.64 (td, 1H), 3.48 (t, 1H), 3.42 (d, 1H), 3.33 (s, 1H), 3.16 (d, 1H), 3.10 – 2.98 (m, 3H), 2.43 – 2.33 (m, 2H), 2.29 (ddt, 1H), 1.92 – 1.85 (m, 1H), 1.83 – 1.72 (m, 1H), 1.69 – 1.42 (m, 8H), 1.38 – 1.29 (m, 1H).	(Method A) $R_T = 0.87$ min, $m/z = 527$ [M+H] ⁺
130		(<i>S</i>)-6-Phenyl-3-((7-(2-phenylpyrrolidine-1-carbonyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)pyridin-2(1 <i>H</i>)-one	11.71 (s, 1H), 7.72 (d, 2H), 7.49 – 7.43 (m, 3H), 7.41 (d, 1H), 7.32 – 7.27 (m, 2H), 7.26 – 7.22 (m, 2H), 7.22 – 7.17 (m, 1H), 6.54 (s, 1H), 4.92 (dd, 1H), 3.71 (d, 1H), 3.60 (td, 2H), 3.50 – 3.43 (m, 1H), 3.43 – 3.36 (m, 1H), 3.34 (s, 1H), 3.17 (ddd, 1H), 2.96 (d, 1H), 2.78 (ddd, 1H), 2.68 (ddd, 1H), 2.28 (ddd, 1H), 1.91 – 1.81 (m, 1H), 1.76 (ddt, 1H), 1.57 (tdd, 1H), 0.66 – 0.59 (m, 1H), 0.56 (q, 2H), 0.43 (dq, 1H).	(Method A) $R_T = 0.80$ min, $m/z = 469$ [M+H] ⁺

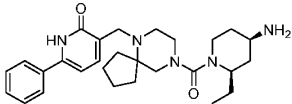
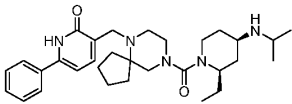
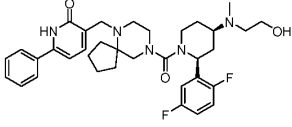
131		(<i>S</i>)-6-Phenyl-3-((4-(2-phenylpyrrolidine-1-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)pyridin-2(1 <i>H</i>)-one	11.71 (s, 1H), 7.72 (d, 2H), 7.59 (d, 1H), 7.49 – 7.41 (m, 3H), 7.29 (t, 2H), 7.25 – 7.21 (m, 2H), 7.19 (ddt, 1H), 6.57 (s, 1H), 4.92 (dd, 1H), 3.75 – 3.63 (m, 3H), 3.56 – 3.42 (m, 4H), 3.42 – 3.34 (m, 2H), 3.34 – 3.27 (m, 2H (obscured by HDO signal)), 3.24 (d, 1H), 3.18 – 3.08 (m, 1H), 2.60 (td, 1H), 2.30 (ddt, 1H), 1.95 – 1.85 (m, 1H), 1.84 – 1.69 (m, 2H), 1.67 – 1.55 (m, 2H), 1.36 (d, 1H), 1.25 (d, 1H).	(Method A) $R_T = 0.78$ min, $m/z = 513$ [M+H] ⁺
132		5-((9-((2 <i>R</i> ,5 <i>R</i>)-5-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	7.57 – 7.37 (m, 4H), 7.32 – 7.14 (m, 2H), 5.07 (d, 1H), 4.16 (dd, 1H), 3.88 (dd, 1H), 3.56 (ddt, 1H), 3.41 (d, 3H), 3.32 – 3.26 (m, 6H (obscured by HDO)), 3.12 – 2.85 (m, 4H), 2.45 (s, 2H (obscured by DMSO signal)), 1.73 (s, 1H), 1.68 – 1.42 (m, 5H), 1.38 (d, 2H), 1.11 (d, 3H).	(Method A) $R_T = 0.84$ min, $m/z = 563$ [M+H] ⁺
133		(<i>S</i>)-3-((4-(2-(2,5-Difluorophenyl)pyrrolidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-6-(1-methyl-1 <i>H</i> -pyrazol-5-yl)pyridin-2(1 <i>H</i>)-one	11.72 (s, 1H), 7.61 (d, 1H), 7.47 (d, 1H), 7.19 (td, 1H), 7.15 – 7.03 (m, 2H), 6.58 (d, 1H), 6.58 (br s, 1H), 5.12 (dd, 1H), 3.94 (s, 3H), 3.69 (td, 1H), 3.54 – 3.38 (m, 3H), 3.29 – 3.23 (m, 1H (signal overlaps with HDO)), 3.16 – 2.99 (m, 3H), 2.48 – 2.28 (m, 3H), 1.95 – 1.88 (m, 1H), 1.86 – 1.75 (m, 1H), 1.58 (tdd, 1H), 1.08 (s, 3H), 0.98 (s, 3H).	(Method A) $R_T = 0.73$ min, $m/z = 511$ [M+H] ⁺
134		(<i>S</i>)-3-((2,2-Dimethyl-4-(2-phenylpyrrolidine-1-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	11.64 (s, 1H), 7.66 (s, 2H), 7.49 (d, 1H), 7.42 – 7.33 (m, 3H), 7.24 – 7.19 (m, 2H), 7.19 – 7.15 (m, 2H), 7.14 – 7.09 (m, 1H), 6.51 (s, 1H), 4.85 (dd, 1H), 3.59 (td, 1H), 3.43 (t, 1H), 3.37 – 3.26 (m, 2H), 3.22 – 3.13 (m, 1H), 3.02 – 2.91 (m, 3H), 2.40 – 2.30 (m, 2H), 2.22 (dtd, 1H), 1.85 –	(Method A) $R_T = 0.79$ min, $m/z = 471$ [M+H] ⁺

			1.77 (m, 1H), 1.76 – 1.65 (m, 1H), 1.57 – 1.46 (m, 1H), 1.00 (s, 3H), 0.89 (s, 3H).	
135		(S)-6-Phenyl-3-((8-(2-phenylpyrrolidine-1-carbonyl)-2-oxa-5,8-diazaspiro[3.5]nonan-5-yl)methyl)pyridin-2(1H)-one	11.79 (s, 1H), 7.73 (d, 2H), 7.54 (d, 1H), 7.50 – 7.41 (m, 3H), 7.32 – 7.27 (m, 2H), 7.27 – 7.22 (m, 2H), 7.22 – 7.16 (m, 1H), 6.57 (s, 1H), 4.93 (dd, 1H), 4.63 (d, 1H), 4.56 (d, 1H), 4.30 (d, 1H), 4.10 (d, 1H), 3.80 (d, 1H), 3.70 (td, 1H), 3.59 (d, 1H), 3.49 (dd, 2H), 3.41 (d, 1H), 3.37 – 3.32 (m, 1H), 3.03 (ddd, 1H), 2.48 – 2.38 (m, 2H), 2.31 (dtd, 1H), 1.94 – 1.85 (m, 1H), 1.85 – 1.72 (m, 1H), 1.66 – 1.57 (m, 1H).	(Method A) R _T = 0.95 min, <i>m/z</i> = 485 [M+H] ⁺
136		3-((4-((1S,2R,5R)-2-(2,5-Difluorophenyl)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1H)-one	11.73 (s, 1H), 7.74 (d, 2H), 7.54 – 7.42 (m, 4H), 7.27 – 7.18 (m, 1H), 7.14 – 7.06 (m, 1H), 7.03 – 6.96 (m, 1H), 6.60 (s, 1H), 4.55 (d, 1H), 4.42 (d, 1H), 4.16 (dd, 1H), 3.56 – 3.33 (m, 7H), 3.12 (dd, 1H), 2.87 (dd, 1H), 2.46 – 2.37 (m, 3H), 2.07 – 1.94 (m, 1H), 1.94 – 1.81 (m, 2H), 1.54 – 1.41 (m, 1H).	(Method A) R _T = 0.79 min, <i>m/z</i> = 521 [M+H] ⁺
137		3-((9-((1S,2R,5R)-2-(2,5-Difluorophenyl)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1H)-one	11.75 (s, 1H), 7.75 (d, 2H), 7.59 (d, 1H), 7.53 – 7.41 (m, 3H), 7.28 – 7.20 (m, 1H), 7.18 – 7.09 (m, 1H), 7.05 – 6.95 (m, 1H), 6.72 – 6.47 (m, 1H), 4.60 – 4.52 (m, 1H), 4.44 (d, 1H), 4.19 (dd, 1H), 3.96 – 3.36 (m, 4H), 3.24 (s, 1H), 3.12 (d, 1H), 3.05 – 2.88 (m, 1H), 2.86 (dd, 1H), 2.62 – 2.53 (m, 1H), 2.49 – 2.44 (m, 1H), 2.05 – 1.93 (m, 1H), 1.93 – 1.81 (m, 2H), 1.78 – 1.28 (m, 9H).	(Method A) R _T = 0.87 min, <i>m/z</i> = 575 [M+H] ⁺

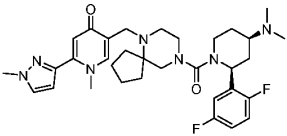
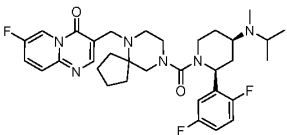
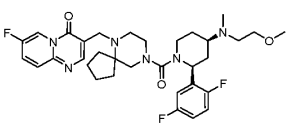
138		5-((9-((1 <i>S</i> ,2 <i>R</i> ,5 <i>R</i>)-2-(2,5-Difluorophenyl)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: a drop of TFA was added to the DMSO- <i>d</i> ₆ solution] 8.64 (s, 1H), 7.89 – 7.78 (m, 2H), 7.71 – 7.59 (m, 3H), 7.42 (s, 1H), 7.26 – 7.17 (m, 1H), 7.15 – 7.01 (m, 2H), 4.62 – 4.56 (m, 1H), 4.51 – 4.28 (m, 3H), 4.19 (dd, 1H), 4.10 – 3.51 (m, 2H), 3.46 – 3.03 (m, 3H), 2.93 (d, 1H), 2.36 – 2.20 (m, 1H), 2.20 – 1.44 (m, 15H).	(Method A) R _T = 0.84 min, <i>m/z</i> 575 [M+H] ⁺
139		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-fluorophenyl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.04 (s, 1H), 7.63 (t, 1H), 7.60 – 7.55 (m, 1H), 7.37 (t, 1H), 7.35 – 7.29 (m, 1H), 7.14 – 7.04 (m, 2H), 6.99 – 6.93 (m, 1H), 6.68 (s, 1H), 4.42 (d, 1H), 3.73 (s, 1H), 3.64 – 3.41 (m, 5H), 3.18 – 3.11 (m, 1H), 3.05 (hept, 1H), 2.94 – 2.78 (m, 2H), 2.68 – 2.56 (m, 2H), 2.08 (t, 2H), 1.79 – 1.37 (m, 9H), 1.36 – 1.30 (m, 1H), 1.12 (td, 6H).	(Method A) R _T = 0.59 min, <i>m/z</i> 622 [M+H] ⁺
140		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-1-methylquinolin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.16 (s, 1H), 8.00 (dd, 1H), 7.84 (dd, 1H), 7.62 (ddd, 1H), 7.12-7.04 (m, 2H), 6.97 (tt, 1H), 4.42 (d, 1H), 4.02 (s, 3H), 3.78-3.64 (m, 1H), 3.63-3.53 (m, 2H), 3.53-3.40 (m, 3H), 3.14 (d, 1H), 2.82 (td, 1H), 2.68 (tt, 1H), 2.65-2.54 (m, 2H), 2.43 (s, 3H), 2.16-2.05 (m, 2H), 1.92-1.82 (m, 1H), 1.78-1.62 (m, 4H), 1.62-1.50 (m, 2H), 1.50-1.44 (m, 1H), 1.40 (q, 1H), 1.35-1.26 (m, 1H).	(Method C) R _T = 0.58 min, <i>m/z</i> 582 [M+H] ⁺
141		3-((9-((2 <i>R</i> ,3 <i>R</i>)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-1-methylquinolin-4(1 <i>H</i>)-one	11.74 (s, 1H), 7.79 – 7.66 (m, 2H), 7.56 (d, 1H), 7.51 – 7.40 (m, 3H), 7.24 – 7.06 (m, 3H), 6.60 (s, 1H), 4.02 (dd, 1H), 3.95 – 3.84 (m, 1H), 3.80 (td, 1H), 3.53 (dq, 3H), 3.29 – 2.89 (m, 1H).	(Method A) R _T = 0.89 min, <i>m/z</i> 563 [M+H] ⁺

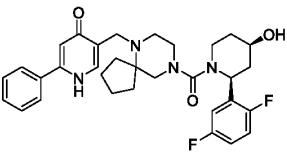
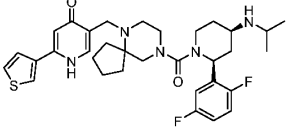
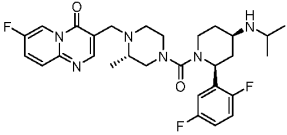
	 (assumed 1:1 mixture)	phenylpyridin-2(1<i>H</i>)-one and 3-((9-((2<i>S</i>,3<i>S</i>)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1<i>H</i>)-one	5H), 2.78 (td, 1H), 2.45 – 2.32 (m, 2H), 1.71 – 1.39 (m, 6H), 1.36 – 1.22 (m, 1H), 1.17 – 1.07 (m, 1H), 0.91 (dd, 3H).	
142		5-((9-((2<i>S</i>,4<i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(1-methyl-1<i>H</i>-pyrazol-5-yl)pyridin-4(1<i>H</i>)-one	[Note: methanol-<i>d</i>₄ instead of DMSO-<i>d</i>₆] 8.06 (s, 1H), 7.64 (d, 1H), 7.14 – 7.02 (m, 2H), 7.02 – 6.91 (m, 1H), 6.56 (d, 1H), 6.45 (s, 1H), 4.42 (d, 1H), 3.81 (s, 3H), 3.79 – 3.67 (m, 1H), 3.65 – 3.61 (m, 1H), 3.58 (s, 3H), 3.56 – 3.41 (m, 4H), 3.15 (d, 1H), 2.84 (t, 1H), 2.72 – 2.54 (m, 3H), 2.42 (s, 3H), 2.15 – 2.03 (m, 2H), 1.78 – 1.51 (m, 7H), 1.51 – 1.34 (m, 3H).	(Method C) R_T = 0.50 min, <i>m/z</i> 594 [M+H]⁺
143		3-((9-((2<i>S</i>,4<i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(trifluoromethyl)pyridin-2(1<i>H</i>)-one	[Note: methanol-<i>d</i>₄ instead of DMSO-<i>d</i>₆] 7.81 – 7.74 (m, 1H), 7.10 – 7.01 (m, 3H), 6.95 (ddt, 1H), 4.40 (ddd, 1H), 3.70 (d, 2H), 3.65 – 3.52 (m, 2H), 3.51 – 3.41 (m, 2H), 3.15 – 3.09 (m, 1H), 2.81 (dd, 1H), 2.72 – 2.51 (m, 3H), 2.41 (s, 3H), 2.13 – 2.04 (m, 2H), 1.78 – 1.38 (m, 9H), 1.28 (t, 1H).	(Method A) R_T = 0.56 min, <i>m/z</i> 568 [M+H]⁺
144		5-((9-((2<i>S</i>,4<i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(trifluoromethyl)pyridin-4(1<i>H</i>)-one	[Note: methanol-<i>d</i>₄ instead of DMSO-<i>d</i>₆] 8.25 (s, 1H), 7.13 – 7.06 (m, 2H), 7.02 – 6.96 (m, 1H), 6.96 (s, 1H), 4.43 (dd, 1H), 3.86 (d, 1H), 3.73 (d, 2H), 3.65 – 3.43 (m, 3H), 3.19 – 3.11 (m, 1H), 2.92 – 2.78 (m, 2H), 2.72 –	(Method A) R_T = 0.61 min, <i>m/z</i> 568 [M+H]⁺

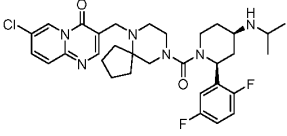
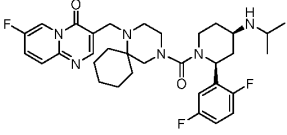
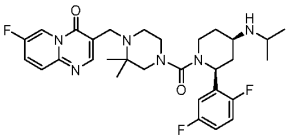
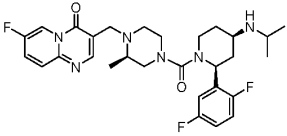
		(trifluoromethyl)pyridin-4(1 <i>H</i>)-one	2.58 (m, 2H), 2.51 (s, 3H), 2.20 – 2.10 (m, 2H), 1.91 – 1.82 (m, 1H), 1.78 – 1.44 (m, 8H), 1.33 – 1.27 (m, 1H).	
145	 and (assumed 1:1 mixture)	3-((4-((2<i>R</i>,3<i>R</i>)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1<i>H</i>)-one and 3-((4-((2<i>S</i>,3<i>S</i>)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1<i>H</i>)-one	11.71 (s, 1H), 7.81 – 7.68 (m, 2H), 7.57 – 7.40 (m, 4H), 7.25 – 7.12 (m, 2H), 7.11 – 7.02 (m, 1H), 6.70 – 6.50 (m, 1H), 4.01 (dd, 1H), 3.93 – 3.84 (m, 1H), 3.80 (td, 1H), 3.50 (dq, 1H), 3.47 – 3.34 (m, 4H), 3.30 – 3.15 (m, 3H), 2.87 – 2.75 (m, 1H), 2.31 (s, 4H), 0.91 (dd, 3H).	(Method A) R_T = 0.74 min, <i>m/z</i> 509 [M+H]⁺
146	 and (assumed 1:1 mixture)	5-((9-((2<i>R</i>,3<i>R</i>)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1<i>H</i>)-one and 5-((9-((2<i>S</i>,3<i>S</i>)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1<i>H</i>)-one	[Note: a drop of TFA was added to the DMSO-<i>d</i>₆ solution] 10.45 – 9.56 (m, 1H), 8.63 (s, 1H), 7.85 – 7.76 (m, 2H), 7.70 – 7.59 (m, 3H), 7.44 (s, 1H), 7.24 – 7.12 (m, 2H), 7.12 – 7.04 (m, 1H), 4.49 – 3.99 (m, 4H), 3.91 – 3.75 (m, 3H), 3.68 – 2.95 (m, 7H), 2.91 – 2.80 (m, 1H), 2.02 – 1.39 (m, 8H), 0.96 – 0.85 (m, 3H).	(Method A) R_T = 0.85 min, <i>m/z</i> 563 [M+H]⁺

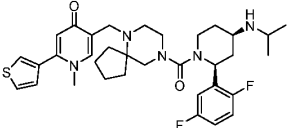
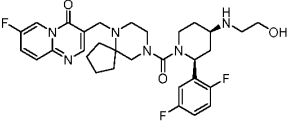
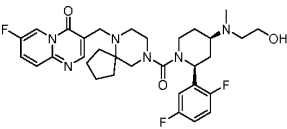
147		3-((9-((2 <i>R</i> ,4 <i>R</i>)-4-Amino-2-ethylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.81 (d, 1H), 7.72 – 7.65 (m, 2H), 7.56 – 7.47 (m, 3H), 6.68 (d, 1H), 3.60 – 3.48 (m, 4H), 3.39 – 3.35 (m, 1H), 3.32 – 3.28 (m, 1H), 3.00 – 2.94 (m, 1H), 2.93 – 2.82 (m, 2H), 2.59 (t, 2H), 1.97 – 1.92 (m, 1H), 1.92 – 1.63 (m, 9H), 1.63 – 1.53 (m, 3H), 1.49 – 1.30 (m, 2H), 0.91 (t, 3H).	(Method C) R _T = 0.54 min, <i>m/z</i> 478 [M+H] ⁺
148		3-((9-((2 <i>R</i> ,4 <i>R</i>)-2-Ethyl-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.81 (d, 1H), 7.72 – 7.66 (m, 2H), 7.56 – 7.46 (m, 3H), 6.68 (d, 1H), 3.59 – 3.45 (m, 4H), 3.38 – 3.34 (m, 1H), 3.32 – 3.27 (m, 2H), 3.11 – 3.03 (sept, 1H), 3.03 – 2.95 (m, 1H), 2.91 – 2.76 (m, 2H), 2.59 (t, 2H), 2.01 – 1.90 (m, 2H), 1.87 – 1.64 (m, 7H), 1.63 – 1.51 (m, 3H), 1.41 – 1.28 (m, 2H), 1.10 (d, 6H), 0.91 (t, 3H).	(Method C) R _T = 0.56 min, <i>m/z</i> 520 [M+H] ⁺
149		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.81 (d, 1H), 7.71 – 7.67 (m, 2H), 7.56 – 7.48 (m, 3H), 7.11 (ddd, 1H), 7.06 (td, 1H), 7.00 – 6.93 (m, 1H), 6.68 (d, 1H), 4.41 (d, 1H), 3.82 – 3.69 (m, 1H), 3.65 (t, 2H), 3.61 – 3.47 (m, 3H), 3.47 – 3.38 (m, 2H), 3.12 (d, 1H), 2.81 (td, 1H), 2.74 (tt, 1H), 2.67 (t, 2H), 2.65 – 2.54 (m, 2H), 2.35 (s, 3H), 2.06 – 1.95 (m, 2H), 1.83 – 1.73 (m, 2H), 1.73 – 1.61 (m, 4H), 1.61 – 1.50 (m, 2H), 1.48 – 1.40 (m, 1H), 1.36 – 1.25 (m, 1H).	(Method C) R _T = 0.62 min, <i>m/z</i> 620 [M+H] ⁺

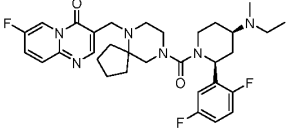
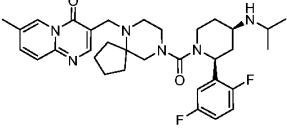
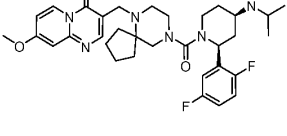
150		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.96 (s, 1H), 7.73 (d, 1H), 7.10 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 6.59 (d, 1H), 6.58 (s, 1H), 4.43 – 4.36 (m, 1H), 3.99 (s, 3H), 3.86 (s, 3H), 3.71 (s, 1H), 3.63 – 3.54 (m, 1H), 3.54 – 3.36 (m, 4H), 3.13 (d, 1H), 2.85 – 2.77 (m, 1H), 2.71 – 2.51 (m, 3H), 2.41 (s, 3H), 2.14 – 2.04 (m, 2H), 1.77 – 1.23 (m, 10H).	(Method A) R _T = 0.51 min, <i>m/z</i> 594 [M+H] ⁺
151		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.95 (dd, 1H), 7.93 (s, 1H), 7.62 (dd, 1H), 7.51 (dd, 1H), 7.13 – 7.02 (m, 2H), 6.99 – 6.91 (m, 1H), 6.75 (s, 1H), 4.43 – 4.35 (m, 1H), 3.71 (s, 1H), 3.63 – 3.36 (m, 5H), 3.11 (d, 1H), 2.80 (td, 1H), 2.66 – 2.53 (m, 2H), 2.52 – 2.43 (m, 1H), 2.32 (s, 6H), 2.10 – 1.97 (m, 2H), 1.78 – 1.37 (m, 9H), 1.35 – 1.23 (m, 1H).	(Method A) R _T = 0.56 min, <i>m/z</i> 596 [M+H] ⁺
152		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.99 (ddd, 1H), 8.45 (s, 1H), 7.94 (ddd, 1H), 7.76 (ddd, 1H), 7.11 – 7.00 (m, 2H), 6.98 – 6.91 (m, 1H), 4.43 – 4.36 (m, 1H), 3.78 – 3.58 (m, 2H), 3.57 – 3.37 (m, 4H), 3.10 (d, 1H), 2.85 – 2.65 (m, 4H), 2.65 – 2.51 (m, 2H), 2.13 – 2.01 (m, 2H), 1.94 – 1.82 (m, 1H), 1.79 – 1.36 (m, 8H), 1.34 – 1.22 (m, 1H), 1.13 (t, 3H).	(Method A) R _T = 0.56 min, <i>m/z</i> 583 [M+H] ⁺
153		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-hydroxypiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-	8.93 (dd, 1H), 8.38 (s, 1H), 8.05 (ddd, 1H), 7.79 (dd, 1H), 7.15 (td, 1H), 7.08 – 7.01 (m, 2H), 4.83 (d, 1H), 4.27 (dt, 1H), 3.64 – 3.55 (m, 1H), 3.55 – 3.42 (m, 2H), 3.42 – 3.33 (m, 2H), 3.29 –	(Method A) R _T = 0.70 min, <i>m/z</i> = 556 [M+H] ⁺

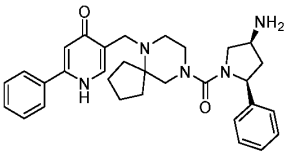
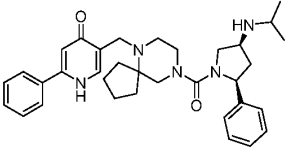
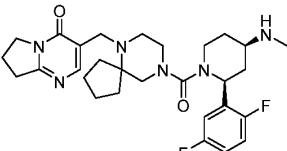
		4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	3.20 (m, 2H), 2.97 (d, 1H), 2.71 – 2.64 (m, 1H), 2.47 – 2.43 (m, 1H), 2.43 – 2.37 (m, 1H), 1.94 – 1.81 (m, 2H), 1.81 – 1.70 (m, 1H), 1.68 – 1.28 (m, 8H), 1.27 – 1.12 (m, 1H).	
154		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.96 (s, 1H), 7.73 (d, 1H), 7.12 – 7.02 (m, 2H), 6.99 – 6.92 (m, 1H), 6.59 (d, 1H), 6.58 (s, 1H), 4.42 – 4.35 (m, 1H), 3.99 (s, 3H), 3.86 (s, 3H), 3.72 (s, 1H), 3.63 – 3.54 (m, 1H), 3.54 – 3.38 (m, 4H), 3.12 (d, 1H), 2.84 – 2.76 (m, 1H), 2.64 – 2.44 (m, 3H), 2.32 (s, 6H), 2.10 – 1.99 (m, 2H), 1.78 – 1.38 (m, 9H), 1.35 – 1.23 (m, 1H).	(Method A) R _T = 0.53 min, <i>m/z</i> 608 [M+H] ⁺
155		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropyl(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.01 (dd, 1H), 8.47 (s, 1H), 8.00 – 7.92 (m, 1H), 7.78 (ddd, 1H), 7.15 – 7.03 (m, 2H), 7.01 – 6.94 (m, 1H), 4.44 – 4.38 (m, 1H), 3.67 (d, 2H), 3.58 – 3.42 (m, 4H), 3.17 – 3.05 (m, 2H), 2.86 – 2.76 (m, 2H), 2.69 – 2.53 (m, 2H), 2.24 (s, 3H), 2.04 (t, 2H), 1.95 – 1.85 (m, 1H), 1.77 – 1.51 (m, 7H), 1.51 – 1.43 (m, 1H), 1.37 – 1.27 (m, 1H), 1.10 (dd, 6H).	(Method A) R _T = 0.57 min, <i>m/z</i> 611 [M+H] ⁺
156		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-((2-methoxyethyl)(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.01 (dd, 1H), 8.47 (s, 1H), 7.99 – 7.94 (m, 1H), 7.78 (dd, 1H), 7.13 – 7.04 (m, 2H), 6.99 – 6.93 (m, 1H), 4.42 – 4.34 (m, 1H), 3.66 (d, 2H), 3.59 – 3.41 (m, 6H), 3.35 (s, 3H), 3.11 (d, 1H), 2.80 (td, 1H), 2.76 – 2.68 (m, 3H), 2.66 – 2.53 (m, 2H), 2.34 (s, 3H), 2.05 – 1.85 (m, 3H), 1.77 – 1.51 (m, 7H),	(Method A) R _T = 0.54 min, <i>m/z</i> 627 [M+H] ⁺

			1.50 – 1.42 (m, 1H), 1.36 – 1.26 (m, 1H).	
157		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-hydroxypiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	11.55 (s, 0.5H), 8.31 (s, 0.5H), 8.02 – 7.94 (m, 1H), 7.72 – 7.68 (m, 1H), 7.63 (d, 0.5H), 7.54 (d, 1.5H), 7.47 (t, 1H), 7.41 (t, 0.5H), 7.24 (s, 0.5H), 7.16 (dt, 1H), 7.06 (td, 2H), 6.38 (s, 0.5H), 4.85 (d, 1H), 4.29 (d, 1H), 3.74 (d, 0.5H), 3.68 – 3.56 (m, 2H), 3.57 – 3.41 (m, 2H), 3.28 – 3.15 (m, 3H), 3.10 – 2.90 (m, 1H), 2.69 (t, 1H), 2.46 – 2.38 (m, 2H), 1.95 – 1.83 (m, 2H), 1.67 – 1.28 (m, 9H), 1.28 – 1.13 (m, 1H).	(Method A) R _T = 0.74 min, <i>m/z</i> = 563 [M+H] ⁺
158		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1 <i>H</i>)-one	8.06 (t, 1H), 7.66 (s, 1H), 7.60 (d, 1H), 7.15 (td, 1H), 7.03 (qd, 2H), 4.26 (dd, 1H), 3.75 – 3.30 (m, 9H (obscured by HDO)), 3.03 (s, 1H), 2.84 (pent, 1H), 2.71 – 2.61 (m, 2H), 2.46 – 2.37 (m, 2H), 1.89 (t, 2H), 1.73 – 1.49 (m, 5H), 1.49 – 1.10 (m, 6H), 0.93 (t, 6H).	(Method A) R _T = 0.56 min, <i>m/z</i> = 610 [M+H] ⁺
159		3-(((<i>S</i>)-4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-2-methylpiperazin-1-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	8.95 (ddd, 1H), 8.36 (s, 1H), 8.07 (ddd, 1H), 7.81 (ddd, 1H), 7.11 (td, 1H), 7.00 – 6.90 (m, 2H), 4.28 – 4.19 (m, 1H), 3.81 (d, 1H), 3.66 – 3.53 (m, 2H), 3.39 (d, 1H), 3.29 – 3.24 (m, 1H), 3.16 (t, 1H), 2.83 (s, 1H), 2.78 – 2.69 (m, 2H), 2.69 – 2.63 (m, 2H), 2.29 (s, 1H), 2.08 (td, 1H), 1.92 – 1.84 (m, 2H), 1.38 – 1.27 (m, 1H), 1.24 (s, 1H), 1.16 (q, 1H), 1.08 (d, 3H), 0.92 (dd, 6H).	(Method A) R _T = 0.47 min, <i>m/z</i> = 557 [M+H] ⁺

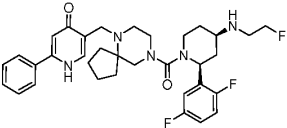
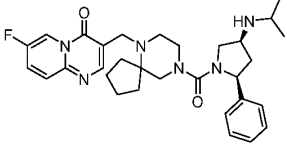
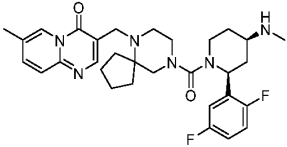
160		7-Chloro-3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	8.95 (dd, 1H), 8.38 (s, 1H), 7.96 (dd, 1H), 7.71 (dd, 1H), 7.15 (td, 1H), 7.03 (dddd, 2H), 4.25 (d, 1H), 3.55 – 3.34 (m, 4H), 3.29 – 3.19 (m, 2H), 3.00 (s, 1H), 2.84 (pent, 1H), 2.71 – 2.65 (m, 2H), 2.45 – 2.37 (m, 2H), 1.89 (t, 2H), 1.74 (s, 1H), 1.67 – 1.50 (m, 4H), 1.45 (s, 1H), 1.39 – 1.13 (m, 5H), 0.93 (dd, 6H).	(Method A) R _T = 0.60 min, <i>m/z</i> = 613 [M+H] ⁺
161		3-((4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.01 – 8.92 (m, 1H), 8.50 (s, 1H), 7.93 (ddd, 1H), 7.75 (ddd, 1H), 7.13 – 7.08 (m, 1H), 7.07 – 7.01 (m, 1H), 6.97 – 6.91 (m, 1H), 4.40 – 4.35 (m, 1H), 3.88 – 3.69 (m, 3H), 3.60 (d, 1H), 3.56 – 3.48 (m, 1H), 3.46 – 3.39 (m, 1H), 3.02 (hept, 1H), 2.91 – 2.66 (m, 4H), 2.12 – 2.02 (m, 2H), 1.78 – 1.27 (m, 12H), 1.24 – 1.13 (m, 1H), 1.08 (t, 6H).	(Method A) R _T = 0.62 min, <i>m/z</i> = 611 [M+H] ⁺
162		3-((4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.99 (m, 1H), 8.46 (s, 1H), 7.94 (dd, 1H), 7.76 (dd, 1H), 7.15 – 7.09 (m, 1H), 7.08 – 6.99 (m, 1H), 6.97 – 6.89 (m, 1H), 4.41 – 4.34 (m, 1H), 3.68 (d, 2H), 3.56 – 3.46 (m, 2H), 3.46 – 3.35 (m, 2H), 3.12 – 3.07 (m, 1H), 3.01 (hept, 1H), 2.89 – 2.74 (m, 2H), 2.66 – 2.54 (m, 2H), 2.11 – 1.98 (m, 2H), 1.58 – 1.46 (m, 1H), 1.39 (q, 1H), 1.15 (s, 3H), 1.08 (t, 6H), 0.96 (s, 3H).	(Method A) R _T = 0.51 min, <i>m/z</i> = 571 [M+H] ⁺
163		3-(((<i>R</i>)-4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-2-	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.95 (dd, 1H), 8.37 (s, 1H), 8.07 (dd, 1H), 7.81 (dd, 1H), 7.13 (td, 1H), 7.05 – 6.94 (m, 2H), 4.27 – 4.21 (m, 1H),	(Method A) R _T = 0.51 min, <i>m/z</i> = 557 [M+H] ⁺

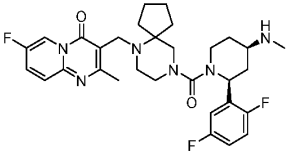
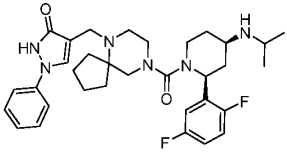
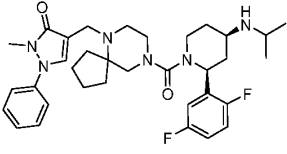
		methylpiperazin-1-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	3.78 (d, 1H), 3.61 – 3.51 (m, 2H), 3.39 (d, 1H), 3.30 – 3.25 (m, 1H), 3.12 (s, 1H), 2.99 (dd, 1H), 2.85 (hept, 1H), 2.72 – 2.65 (m, 3H), 2.42 (s, 1H), 2.12 – 2.03 (m, 1H), 1.94 – 1.84 (m, 2H), 1.41 – 1.32 (m, 1H), 1.22 – 1.15 (m, 1H), 1.03 (d, 3H), 0.94 (dd, 6H).	
164		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(thiophen-3-yl)pyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.98 (s, 1H), 7.73 (dd, 1H), 7.66 (dd, 1H), 7.29 (dd, 1H), 7.13 – 7.03 (m, 2H), 6.97 (tt, 1H), 6.44 (s, 1H), 4.42 (d, 1H), 3.82 – 3.66 (m, 4H), 3.66 – 3.56 (m, 1H), 3.56 – 3.39 (m, 4H), 3.15 (d, 1H), 3.02 (sept, 1H), 2.95 – 2.79 (m, 2H), 2.66 – 2.54 (m, 2H), 2.08 (t, 2H), 1.80 – 1.50 (m, 7H), 1.49 – 1.37 (m, 2H), 1.36 – 1.27 (m, 1H), 1.11 (t, 6H).	(Method C) R _T = 0.62 min, <i>m/z</i> 624 [M+H] ⁺
165		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.01 (dd, 1H), 8.47 (s, 1H), 7.96 (ddd, 1H), 7.77 (dd, 1H), 7.16 – 7.02 (m, 2H), 7.02 – 6.92 (m, 1H), 4.42 (d, 1H), 3.81 – 3.61 (m, 4H), 3.59 – 3.50 (m, 2H), 3.50 – 3.40 (m, 2H), 3.12 (d, 1H), 2.86 – 2.72 (m, 4H), 2.68 – 2.53 (m, 2H), 2.10 (t, 2H), 1.95 – 1.84 (m, 1H), 1.79 – 1.62 (m, 4H), 1.62 – 1.50 (m, 2H), 1.50 – 1.38 (m, 2H), 1.38 – 1.23 (m, 1H).	(Method C) R _T = 0.58 min, <i>m/z</i> 599 [M+H] ⁺
166		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.02 (dd, 1H), 8.47 (s, 1H), 7.96 (ddd, 1H), 7.77 (dd, 1H), 7.15 – 7.02 (m, 2H), 7.01 – 6.92 (m, 1H), 4.40 (d, 1H), 3.81 – 3.61 (m, 4H), 3.59 – 3.50 (m, 2H), 3.50 – 3.42 (m, 2H), 3.11	(Method C) R _T = 0.58 min, <i>m/z</i> 613 [M+H] ⁺

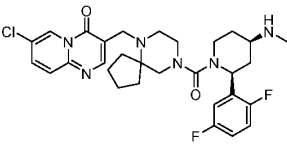
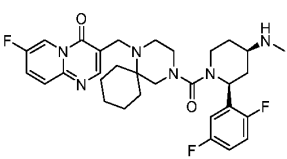
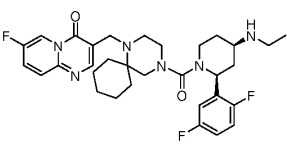
		4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	(d, 1H), 2.86 – 2.70 (m, 2H), 2.70 – 2.53 (m, 4H), 2.35 (s, 3H), 2.07 – 1.94 (m, 2H), 1.94 – 1.84 (m, 1H), 1.80 – 1.62 (m, 5H), 1.62 – 1.52 (m, 2H), 1.50 – 1.42 (m, 1H), 1.35 – 1.28 (m, 1H).	
167		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(ethyl(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.99 (d, 1H), 8.45 (s, 1H), 7.94 (ddd, 1H), 7.76 (dd, 1H), 7.13 – 7.02 (m, 2H), 6.98 – 6.92 (m, 1H), 4.41 – 4.36 (m, 1H), 3.75 – 3.60 (m, 2H), 3.56 – 3.40 (m, 4H), 3.09 (d, 1H), 2.83 – 2.75 (m, 1H), 2.75 – 2.67 (m, 1H), 2.65 – 2.52 (m, 4H), 2.28 (s, 3H), 2.03 – 1.92 (m, 2H), 1.92 – 1.83 (m, 1H), 1.77 – 1.61 (m, 5H), 1.60 – 1.49 (m, 2H), 1.48 – 1.40 (m, 1H), 1.33 – 1.24 (m, 1H), 1.09 (t, 3H).	(Method A) R _T = 0.58 min, <i>m/z</i> 597 [M+H] ⁺
168		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-methyl-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.93 – 8.88 (m, 1H), 8.42 (s, 1H), 7.86 (dd, 1H), 7.64 (d, 1H), 7.13 – 7.03 (m, 2H), 7.02 – 6.91 (m, 1H), 4.43 – 4.38 (m, 1H), 3.75 – 3.61 (m, 2H), 3.56 – 3.49 (m, 2H), 3.48 – 3.39 (m, 2H), 3.12 (d, 1H), 3.04 (hept, 1H), 2.93 – 2.85 (m, 1H), 2.81 (td, 1H), 2.65 – 2.54 (m, 2H), 2.49 (d, 3H), 2.12 – 2.03 (m, 2H), 1.95 – 1.87 (m, 1H), 1.79 – 1.62 (m, 4H), 1.61 – 1.36 (m, 4H), 1.35 – 1.27 (m, 1H), 1.11 (t, 6H).	(Method A) R _T = 0.61 min, <i>m/z</i> 593 [M+H] ⁺
169		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-8-methoxy-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.97 (dd, 1H), 8.30 (s, 1H), 7.13 – 7.03 (m, 3H), 7.00 – 6.90 (m, 2H), 4.45 – 4.39 (m, 1H), 4.05 (s, 3H), 3.69 (s, 1H), 3.63 – 3.39 (m, 5H), 3.11 (d,	(Method A) R _T = 0.60 min, <i>m/z</i> 609 [M+H] ⁺

		methoxy-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	1H), 3.04 (hept, 1H), 2.94 – 2.85 (m, 1H), 2.81 (td, 1H), 2.69 – 2.52 (m, 2H), 2.13 – 2.02 (m, 2H), 1.99 – 1.87 (m, 1H), 1.81 – 1.62 (m, 4H), 1.63 – 1.36 (m, 4H), 1.33 – 1.25 (m, 1H), 1.11 (t, 6H).	
170		5-((9-((2 <i>S</i> ,4 <i>S</i>)-4-Amino-2-phenylpyrrolidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.97 (s, 1H), 7.73 – 7.67 (m, 2H), 7.54 (dd, 3H), 7.29 (d, 4H), 7.24 – 7.19 (m, 1H), 6.72 (s, 1H), 5.02 (dd, 1H), 3.73 (dd, 1H), 3.60 (d, 2H), 3.51 – 3.35 (m, 3H), 3.24 – 3.10 (m, 3H), 2.55 (dt, 3H), 1.84 – 1.54 (m, 8H), 1.46 – 1.37 (m, 1H).	(Method A) R _T = 0.54 min, <i>m/z</i> = 512 [M+H] ⁺
171		5-((9-((2 <i>S</i> ,4 <i>S</i>)-4-(Isopropylamino)-2-phenylpyrrolidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.97 (s, 1H), 7.70 (dd, 2H), 7.54 (dd, 3H), 7.30 (d, 4H), 7.21 (sept, 1H), 6.71 (s, 1H), 5.01 (dd, 1H), 3.82 – 3.74 (m, 1H), 3.58 (d, 2H), 3.50 – 3.35 (m, 3H), 3.23 – 3.10 (m, 3H), 2.92 (sept, 1H), 2.62 (dt, 1H), 2.54 (t, 2H), 1.84 – 1.54 (m, 8H), 1.45 – 1.36 (m, 1H), 1.11 (d, 6H).	(Method A) R _T = 0.56 min, <i>m/z</i> = 554 [M+H] ⁺
172		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7,8-dihydropyrrolo[1,2- <i>a</i>]pyrimidin-4(6 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.98 (s, 1H), 7.12 – 7.01 (m, 2H), 6.99 – 6.92 (m, 1H), 4.40 (d, 1H), 4.15 (t, 2H), 3.77 – 3.60 (m, 1H), 3.60 – 3.49 (m, 1H), 3.49 – 3.38 (m, 3H), 3.32 – 3.27 (m, 1H), 3.15 (t, 2H), 3.08 (d, 1H), 2.80 (t, 1H), 2.64 (tt, 1H), 2.60 – 2.48 (m, 2H), 2.41 (s, 3H), 2.29 (pent, 2H), 2.09 (t, 2H), 1.86 – 1.77 (m, 1H), 1.73 – 1.59 (m, 4H), 1.59 – 1.47 (m, 2H), 1.46 – 1.34 (m, 2H), 1.34 – 1.21 (m, 1H).	(Method C) R _T = 0.49 min, <i>m/z</i> = 541 [M+H] ⁺

173		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7,8-dihydropyrrolo[1,2- <i>a</i>]pyrimidin-4(6 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.98 (s, 1H), 7.11 – 7.03 (m, 2H), 6.99 – 6.93 (m, 1H), 4.41 (d, 1H), 4.15 (t, 2H), 3.76 – 3.62 (m, 1H), 3.57 – 3.49 (m, 1H), 3.46 – 3.40 (m, 2H), 3.32 – 3.27 (m, 1H), 3.15 (t, 2H), 3.12 – 3.01 (m, 2H), 2.96 – 2.86 (m, 1H), 2.81 (td, 1H), 2.61 – 2.48 (m, 2H), 2.30 (pent, 2H), 2.13 – 2.03 (m, 2H), 1.87 – 1.77 (m, 1H), 1.74 – 1.59 (m, 4H), 1.59 – 1.49 (m, 2H), 1.48 – 1.37 (m, 2H), 1.30 – 1.23 (m, 1H), 1.12 (t, 6H), 0.96 – 0.83 (m, 1H).	(Method C) R _T = 0.52 min, <i>m/z</i> = 569 [M+H] ⁺
174		3-((9-(5-Amino-2',5'-difluoro-[1,1'-biphenyl]-2-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1 <i>H</i>)-one	11.75 (s, 1H), 7.78 – 7.67 (m, 2H), 7.53 – 7.41 (m, 4H), 7.36 – 7.21 (m, 2H), 7.11 – 7.03 (m, 2H), 6.69 – 6.48 (m, 3H), 5.52 (s, 2H), 3.21 (d, 4H), 2.22 (s, 1H), 1.77 – 1.03 (m, 9H).	(Method A) R _T = 0.82 min, <i>m/z</i> = 555 [M+H] ⁺
175		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-methyl-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.93 (ddd, 1H), 7.92 (ddd, 1H), 7.68 (ddd, 1H), 7.09 – 7.00 (m, 2H), 6.98 – 6.91 (m, 1H), 4.42 – 4.33 (m, 1H), 3.76 (d, 1H), 3.68 (d, 1H), 3.58 (s, 1H), 3.48 – 3.35 (m, 3H), 3.14 – 2.99 (m, 2H), 2.88 (s, 1H), 2.82 – 2.72 (m, 1H), 2.63 (s, 3H), 2.48 (t, 2H), 2.05 (t, 3H), 1.94 – 1.79 (m, 1H), 1.78 – 1.18 (m, 8H), 1.09 (t, 6H).	(Method A) R _T = 0.59 min, <i>m/z</i> = 611 [M+H] ⁺
176		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-((2-fluoroethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-methyl-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.04 – 8.97 (m, 1H), 8.47 (s, 1H), 7.98 – 7.92 (m, 1H), 7.78 (ddd, 1H), 7.13 – 7.03 (m, 2H), 6.99 – 6.90 (m, 1H), 4.58 (t, 1H), 4.48 (t, 1H), 4.41 (dd, 1H), 3.66 (d, 2H), 3.57 –	(Method A) R _T = 0.59 min, <i>m/z</i> = 601 [M+H] ⁺

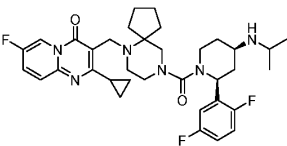
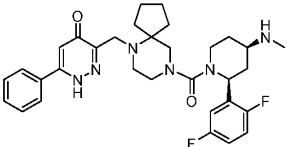
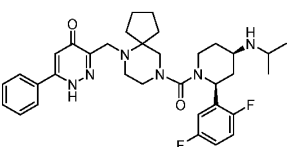
		4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	3.50 (m, 2H), 3.50 – 3.40 (m, 2H), 3.12 (d, 1H), 3.00 – 2.94 (m, 1H), 2.93 – 2.88 (m, 1H), 2.85 – 2.72 (m, 2H), 2.68 – 2.54 (m, 2H), 2.15 – 2.03 (m, 2H), 1.95 – 1.85 (m, 1H), 1.78 – 1.63 (m, 4H), 1.62 – 1.51 (m, 2H), 1.51 – 1.36 (m, 2H), 1.33 – 1.22 (m, 1H).	
177		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-((2-fluoroethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.01 (s, 1H), 7.75 – 7.68 (m, 2H), 7.59 – 7.51 (m, 3H), 7.16 – 7.04 (m, 2H), 7.00 – 6.92 (m, 1H), 6.73 (s, 1H), 4.58 (t, 1H), 4.49 (t, 1H), 4.45 – 4.40 (m, 1H), 3.73 (s, 1H), 3.59 (s, 2H), 3.54 – 3.41 (m, 3H), 3.14 (d, 1H), 3.01 – 2.88 (m, 2H), 2.86 – 2.74 (m, 2H), 2.67 – 2.55 (m, 2H), 2.11 (t, 2H), 1.80 – 1.52 (m, 7H), 1.49 – 1.41 (m, 2H), 1.37 – 1.24 (m, 1H).	(Method A) R _T = 0.62 min, <i>m/z</i> 608 [M+H] ⁺
178		7-Fluoro-3-((9-((2 <i>S</i> ,4 <i>S</i>)-4-(isopropylamino)-2-phenylpyrrolidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.03 – 8.97 (m, 1H), 8.45 (s, 1H), 7.95 (ddd, 1H), 7.76 (dd, 1H), 7.36 – 7.27 (m, 4H), 7.27 – 7.18 (m, 1H), 5.01 (dd, 1H), 3.83 – 3.74 (m, 1H), 3.71 (d, 1H), 3.58 (d, 1H), 3.52 – 3.40 (m, 3H), 3.20 (q, 2H), 3.15 – 3.06 (m, 1H), 2.93 (sept, 1H), 2.62 (pent, 1H), 2.59 – 2.48 (m, 2H), 1.97 (pent, 1H), 1.82 – 1.56 (m, 7H), 1.45 – 1.37 (m, 1H), 1.12 (d, 6H).	(Method C) R _T = 0.55 min, <i>m/z</i> 547 [M+H] ⁺
179		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-methyl-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.90 – 8.87 (m, 1H), 8.40 (s, 1H), 7.83 (dd, 1H), 7.62 (d, 1H), 7.11 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 4.43 – 4.36 (m, 1H), 3.81 – 3.57 (m, 2H), 3.57 – 3.36 (m, 4H), 3.10	(Method A) R _T = 0.57 min, <i>m/z</i> 565 [M+H] ⁺

		4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	(d, 1H), 2.79 (td, 1H), 2.68 – 2.51 (m, 3H), 2.47 (d, 3H), 2.39 (s, 3H), 2.13 – 2.01 (m, 2H), 1.96 – 1.83 (m, 1H), 1.80 – 1.21 (m, 9H).	
180		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-methyl-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.92 (ddd, 1H), 7.92 (ddd, 1H), 7.67 (ddd, 1H), 7.08 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 4.42 – 4.33 (m, 1H), 3.79 – 3.63 (m, 2H), 3.58 (s, 1H), 3.50 – 3.34 (m, 3H), 3.09 (d, 1H), 2.77 (td, 1H), 2.63 (s, 3H), 2.62 – 2.56 (m, 1H), 2.48 (t, 2H), 2.38 (s, 3H), 2.14 – 1.99 (m, 3H), 1.95 – 1.81 (m, 1H), 1.78 – 1.19 (m, 8H).	(Method A) R _T = 0.57 min, <i>m/z</i> 583 [M+H] ⁺
181		4-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-phenyl-1,2-dihydro-3 <i>H</i> -pyrazol-3-one	8.13 (s, 1H), 7.69 – 7.63 (m, 2H), 7.44 – 7.37 (m, 2H), 7.18 – 7.12 (m, 2H), 7.08 – 6.98 (m, 2H), 4.25 (d, 1H), 3.55 – 3.38 (m, 2H), 3.27 – 2.91 (m, 5H), 2.85 (hept, 1H), 2.71 – 2.66 (m, 1H), 2.45 – 2.38 (m, 1H), 1.90 (t, 2H), 1.79 – 1.68 (m, 1H), 1.65 – 1.51 (m, 5H), 1.50 – 1.12 (m, 8H), 0.94 (dd, 6H).	(Method A) R _T = 0.65 min, <i>m/z</i> 593 [M+H] ⁺
182		4-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-methyl-1-phenyl-1,2-dihydro-3 <i>H</i> -pyrazol-3-one	7.93 (s, 1H), 7.53 – 7.47 (m, 2H), 7.35 – 7.30 (m, 3H), 7.19 – 7.11 (m, 1H), 7.08 – 6.97 (m, 2H), 4.29 – 4.21 (m, 1H), 3.55 – 3.36 (m, 2H), 3.28 – 3.21 (m, 2H), 3.16 (s, 3H), 3.13 (s, 1H), 3.02 (d, 1H), 2.94 (s, 1H), 2.85 (hept, 1H), 2.73 – 2.65 (m, 2H), 2.43 – 2.38 (m, 1H), 1.89 (t, 2H), 1.75 – 1.66 (m, 1H), 1.57 (d, 4H), 1.48 – 1.09 (m, 7H), 0.94 (dd, 6H).	(Method A) R _T = 0.59 min, <i>m/z</i> 607 [M+H] ⁺

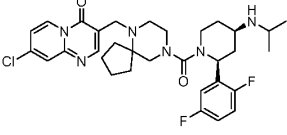
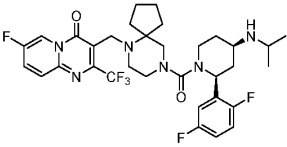
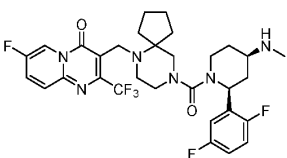
183		7-Chloro-3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.09 (dd, 1H), 8.45 (s, 1H), 7.92 (dd, 1H), 7.69 (dd, 1H), 7.14 – 7.02 (m, 2H), 6.96 (tt, 1H), 4.41 (dd, 1H), 3.81 – 3.60 (m, 2H), 3.58 – 3.49 (m, 2H), 3.48 – 3.39 (m, 2H), 3.12 (d, 1H), 2.81 (td, 1H), 2.70 – 2.53 (m, 3H), 2.41 (s, 3H), 2.15 – 2.04 (m, 2H), 1.95 – 1.85 (m, 1H), 1.79 – 1.62 (m, 4H), 1.62 – 1.24 (m, 4H), 1.34 – 1.25 (m, 1H).	(Method C) R _T = 0.60 min, <i>m/z</i> 585 [M+H] ⁺
184		3-((4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.00 (dd, 1H), 8.52 (s, 1H), 7.95 (ddd, 1H), 7.77 (dd, 1H), 7.12 (ddd, 1H), 7.06 (dt, 1H), 6.95 (tt, 1H), 4.39 (d, 1H), 3.9 – 3.68 (m, 3H), 3.61 (d, 1H), 3.53 (tt, 1H), 3.49 – 3.40 (m, 1H), 3.27 – 3.08 (m, 1H), 2.84 – 2.62 (m, 4H), 2.42 (s, 3H), 2.16 – 2.06 (m, 2H), 1.77 – 1.60 (m, 3H), 1.59 – 1.52 (m, 2H), 1.50 – 1.29 (m, 6H), 1.26 – 1.14 (m, 1H).	(Method C) R _T = 0.61 min, <i>m/z</i> 583 [M+H] ⁺
185		3-((4-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.03 – 8.95 (m, 1H), 8.50 (s, 1H), 7.93 (td, 1H), 7.75 (dd, 1H), 7.15 – 7.07 (m, 1H), 7.04 (td, 1H), 6.99 – 6.90 (m, 1H), 4.37 (d, 1H), 3.91 – 3.68 (m, 3H), 3.59 (d, 1H), 3.54 – 3.46 (m, 1H), 3.46 – 3.40 (m, 1H), 2.86 – 2.66 (m, 6H), 2.09 (t, 2H), 1.73 – 1.50 (m, 5H), 1.48 – 1.31 (m, 7H), 1.22 – 1.16 (m, 1H), 1.14 (t, 3H).	(Method A) R _T = 0.60 min, <i>m/z</i> 597 [M+H] ⁺

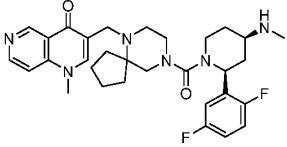
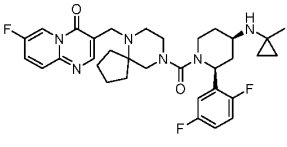
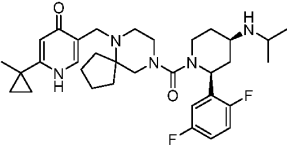
186		7-Chloro-3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.08 (dd, 1H), 8.43 (s, 1H), 7.90 (dd, 1H), 7.68 (dd, 1H), 7.10 – 7.02 (m, 2H), 6.98 – 6.91 (m, 1H), 4.39 (dd, 1H), 3.73 – 3.59 (m, 2H), 3.52 (s, 2H), 3.46 – 3.40 (m, 2H), 3.10 (d, 1H), 2.85 – 2.73 (m, 2H), 2.72 – 2.65 (m, 2H), 2.65 – 2.51 (m, 2H), 2.12 – 2.04 (m, 1H), 1.89 – 1.83 (m, 1H), 1.78 – 1.48 (m, 7H), 1.47 – 1.39 (m, 2H), 1.29 (s, 1H), 1.13 (t, 3H)	(Method A) R _T = 0.60 min, <i>m/z</i> 599 [M+H] ⁺
187		6-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyrimidin-5-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.18 (s, 1H), 8.07 (d, 1H), 7.47 (d, 1H), 7.11 – 7.03 (m, 2H), 6.96 (dq, 1H), 4.44 – 4.37 (m, 1H), 3.69 (s, 1H), 3.54 (q, 2H), 3.44 (m, 3H), 3.10 (d, 1H), 2.80 (td, 1H), 2.69 – 2.51 (m, 3H), 2.41 (s, 3H), 2.09 (tt, 2H), 1.89 (dd, 1H), 1.78 – 1.61 (m, 4H), 1.61 – 1.24 (m, 5H).	(Method A) R _T = 0.52 min, <i>m/z</i> 557 [M+H] ⁺
188		6-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-5 <i>H</i> -thiazolo[3,2- <i>a</i>]pyrimidin-5-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.16 (s, 1H), 8.05 (d, 1H), 7.45 (d, 1H), 7.10 – 6.99 (m, 2H), 6.98 – 6.90 (m, 1H), 4.41 – 4.36 (m, 1H), 3.67 (s, 1H), 3.60 – 3.47 (m, 2H), 3.46 – 3.36 (m, 3H), 3.09 (d, 1H), 3.01 (hept, 1H), 2.91 – 2.76 (m, 2H), 2.65 – 2.51 (m, 2H), 2.11 – 1.96 (m, 2H), 1.94 – 1.84 (m, 1H), 1.77 – 1.61 (m, 4H), 1.58 – 1.35 (m, 4H), 1.31 – 1.24 (m, 1H), 1.08 (t, 6H).	(Method A) R _T = 0.55 min, <i>m/z</i> 585 [M+H] ⁺
189		7-Fluoro-3-((9-((2 <i>S</i> ,4 <i>R</i>)-4-((3-methyloxetan-3-yl)amino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.02 (dd, 1H), 8.47 (d, 2H), 7.99 – 7.94 (m, 1H), 7.80 – 7.76 (m, 1H), 7.33 – 7.27 (m, 4H), 7.24 – 7.19 (m, 1H), 4.61 (d, 1H), 4.54 (d, 1H), 4.38	(Method A) R _T = 0.56 min, <i>m/z</i> 589 [M+H] ⁺

		diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	(d, 1H), 4.33 (d, 1H), 4.04 (dd, 1H), 3.65 (d, 2H), 3.56 (d, 2H), 3.20 – 3.17 (m, 1H), 3.14 (d, 1H), 2.94 (t, 1H), 2.87 – 2.77 (m, 1H), 2.69 – 2.65 (m, 1H), 2.64 – 2.53 (m, 2H), 2.02 – 1.92 (m, 1H), 1.91 – 1.82 (m, 3H), 1.82 – 1.76 (m, 1H), 1.75 – 1.61 (m, 5H), 1.59 (s, 3H), 1.56 – 1.43 (m, 2H).	
190		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidin-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-methyl-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.91 (s, 1H), 8.42 (s, 1H), 7.85 (dd, 1H), 7.64 (d, 1H), 7.14 – 7.03 (m, 2H), 7.01 – 6.88 (m, 1H), 4.41 (d, 1H), 3.77 – 3.61 (m, 2H), 3.57 – 3.48 (m, 2H), 3.49 – 3.39 (m, 2H), 3.12 (d, 1H), 2.87 – 2.72 (m, 2H), 2.72 – 2.66 (m, 2H), 2.66 – 2.55 (m, 2H), 2.49 (d, 3H), 2.13 – 2.04 (m, 2H), 1.95 – 1.87 (m, 1H), 1.79 – 1.62 (m, 4H), 1.61 – 1.52 (m, 2H), 1.51 – 1.24 (m, 4H), 1.15 (t, 3H).	(Method A) R _T = 0.62 min, <i>m/z</i> 579 [M+H] ⁺
191		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidin-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-methyl-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.92 (dd, 1H), 7.92 (dd, 1H), 7.67 (dd, 1H), 7.08 – 7.01 (m, 2H), 6.97 – 6.87 (m, 1H), 4.43 – 4.35 (m, 1H), 3.80 – 3.65 (m, 2H), 3.58 (s, 1H), 3.48 – 3.35 (m, 3H), 3.09 (d, 1H), 2.81 – 2.64 (m, 4H), 2.60 (s, 3H), 2.48 (t, 2H), 2.14 – 1.99 (m, 3H), 1.96 – 1.84 (m, 1H), 1.75 – 1.34 (m, 7H), 1.30 – 1.18 (m, 1H), 1.12 (t, 3H).	(Method A) R _T = 0.60 min, <i>m/z</i> 597 [M+H] ⁺
192		2-Cyclopropyl-3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-difluorophenyl)-4-(methylamino)piperidin-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.85 (dd, 1H), 7.82 (dd, 1H), 7.59 (dd, 1H), 7.10 – 7.04 (m, 2H), 7.00 – 6.93 (m, 1H), 4.40 (dd, 1H), 3.93 – 3.77 (m, 2H), 3.61 (s, 1H), 3.52 –	(Method A) R _T = 0.72 min, <i>m/z</i> 609 [M+H] ⁺

		6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	3.37 (m, 3H), 3.09 (d, 1H), 2.98 – 2.85 (m, 1H), 2.80 (td, 1H), 2.63 – 2.52 (m, 3H), 2.52 (s, 3H), 2.20 – 2.06 (m, 3H), 1.92 (s, 1H), 1.81 – 1.63 (m, 3H), 1.63 – 1.36 (m, 4H), 1.31 – 1.19 (m, 3H), 1.09 – 1.01 (m, 2H).	
193		2-Cyclopropyl-3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.85 (dd, 1H), 7.81 (dd, 1H), 7.58 (dd, 1H), 7.09 – 7.00 (m, 2H), 6.98 – 6.90 (m, 1H), 4.41 – 4.36 (m, 1H), 3.93 – 3.75 (m, 2H), 3.59 (s, 1H), 3.53 – 3.35 (m, 3H), 3.10 (d, 1H), 3.01 (hept, 1H), 2.88 – 2.81 (m, 1H), 2.77 (td, 1H), 2.63 – 2.46 (m, 3H), 2.18 – 1.99 (m, 3H), 1.91 (d, 1H), 1.79 – 1.53 (m, 4H), 1.54 – 1.33 (m, 3H), 1.29 – 1.20 (m, 3H), 1.07 (q, 8H).	(Method A) R _T = 0.72 min, <i>m/z</i> 637 [M+H] ⁺
194		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridazin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.14 – 8.11 (m, 1H), 8.03 – 7.98 (m, 2H), 7.60 – 7.50 (m, 3H), 7.11 – 7.01 (m, 2H), 6.98 – 6.91 (m, 1H), 4.44 – 4.36 (m, 1H), 3.71 (s, 1H), 3.59 – 3.34 (m, 5H), 3.10 (d, 1H), 2.80 (t, 1H), 2.69 (t, 1H), 2.66 – 2.53 (m, 2H), 2.43 (s, 3H), 2.15 – 2.03 (m, 2H), 1.87 – 1.74 (m, 1H), 1.74 – 1.49 (m, 6H), 1.48 – 1.36 (m, 2H), 1.31 – 1.24 (m, 1H).	(Method A) R _T = 0.57 min, <i>m/z</i> 577 [M+H] ⁺
195		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridazin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.12 (s, 1H), 8.03 – 7.98 (m, 2H), 7.59 – 7.50 (m, 3H), 7.07 (dtd, 2H), 6.99 – 6.92 (m, 1H), 4.43 – 4.38 (m, 1H), 3.69 (d, 1H), 3.59 – 3.35 (m, 5H), 3.09 (hept, 2H), 2.98 – 2.91 (m, 1H), 2.85 – 2.78 (m, 1H), 2.66 – 2.54 (m, 2H), 2.08 (t, 2H),	(Method A) R _T = 0.61 min, <i>m/z</i> 605 [M+H] ⁺

			1.80 (dd, 1H), 1.75 – 1.52 (m, 6H), 1.51 – 1.38 (m, 2H), 1.37 – 1.24 (m, 1H), 1.12 (t, 6H).	
196		3-((9-((2 <i>S</i> ,4 <i>R</i>)-4-Amino-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.01 (dd, 1H), 8.47 (s, 1H), 7.96 (ddd, 1H), 7.77 (dd, 1H), 7.14 – 7.02 (m, 2H), 7.00 – 6.92 (m, 1H), 4.39 (d, 1H), 3.83 – 3.61 (m, 2H), 3.60 – 3.49 (m, 2H), 3.49 – 3.37 (m, 2H), 3.12 (d, 1H), 2.88 (tt, 1H), 2.80 (td, 1H), 2.67 – 2.53 (m, 2H), 2.01 (d, 1H), 1.97 (d, 1H), 1.94 – 1.84 (m, 1H), 1.79 – 1.62 (m, 4H), 1.62 – 1.51 (m, 2H), 1.51 – 1.37 (m, 2H), 1.37 – 1.24 (m, 1H).	(Method C) R _T = 0.55 min, <i>m/z</i> 555 [M+H] ⁺
197		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.01 (dd, 1H), 8.46 (s, 1H), 7.96 (ddd, 1H), 7.77 (dd, 1H), 7.13 – 7.04 (m, 2H), 7.02 – 6.95 (m, 1H), 4.73 – 5.68 (m, 1H), 5.66 – 5.61 (m, 1H), 4.41 (d, 1H), 3.86 – 3.66 (m, 1H), 3.63 – 3.50 (m, 3H), 3.46 – 3.39 (m, 2H), 3.20 (d, 1H), 3.04 (sept, 1H), 2.89 (t, 1H), 2.82 (t, 1H), 2.76 – 2.65 (m, 2H), 2.65 – 2.59 (m, 1H), 2.55 (d, 1H), 2.17 (d, 1H), 2.08 (t, 2H), 1.95 (d, 1H), 1.52 (qd, 1H), 1.42 (q, 1H), 1.11 (t, 6H).	(Method C) R _T = 0.59 min, <i>m/z</i> 595 [M+H] ⁺
198		7-Bromo-3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.18 (d, 1H), 8.45 (s, 1H), 8.00 (dd, 1H), 7.62 (d, 1H), 7.12 – 7.03 (m, 2H), 6.97 (tt, 1H), 4.41 (d, 1H), 3.78 – 3.60 (m, 2H), 3.58 – 3.49 (m, 2H), 3.48 – 3.39 (m, 2H), 3.12 (d, 1H), 3.05 (sept, 1H), 2.89 (t, 1H), 2.81 (td, 1H), 2.67 – 2.54	(Method C) R _T = 0.63 min, <i>m/z</i> 657 [M+H] ⁺

			(m, 2H), 2.08 (t, 2H), 1.93 – 1.84 (m, 1H), 1.78 – 1.63 (m, 4H), 1.62 – 1.51 (m, 2H), 1.50 – 1.37 (m, 2H), 1.35 – 1.26 (m, 1H), 1.11 (t, 6H).	
199		8-Chloro-3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.03 (d, 1H), 8.41 (s, 1H), 7.73 (d, 1H), 7.36 (dd, 1H), 7.12 – 7.03 (m, 2H), 6.97 (tt, 1H), 4.41 (d, 1H), 3.76 – 3.59 (m, 2H), 3.57 – 3.48 (m, 2H), 3.48 – 3.40 (m, 2H), 3.12 (d, 1H), 3.05 (sept, 1H), 2.89 (t, 1H), 2.81 (t, 1H), 2.66 – 2.54 (m, 2H), 2.12 – 2.03 (m, 2H), 1.94 – 1.85 (m, 1H), 1.78 – 1.62 (m, 4H), 1.62 – 1.51 (m, 2H), 1.51 – 1.37 (m, 2H), 1.34 – 1.26 (m, 1H), 1.11 (t, 6H).	(Method C) R _T = 0.59 min, <i>m/z</i> 613 [M+H] ⁺
200		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-(trifluoromethyl)-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.02 (dd, 1H), 8.06 (ddd, 1H), 7.89 (dd, 1H), 7.10 – 7.03 (m, 2H), 6.96 (tt, 1H), 4.39 (d, 1H), 3.88 (d, 1H), 3.76 (d, 1H), 3.68 – 3.51 (m, 1H), 3.45 – 3.35 (m, 3H), 3.12 – 2.98 (m, 2H), 2.86 (t, 1H), 2.78 (td, 1H), 2.46 (t, 2H), 2.21 – 2.11 (m, 1H), 2.10 – 1.99 (m, 2H), 1.94 – 1.81 (m, 1H), 1.76 – 1.61 (m, 3H), 1.61 – 1.45 (m, 2H), 1.44 – 1.34 (m, 2H), 1.28 – 1.18 (m, 1H), 1.10 (t, 6H).	(Method C) R _T = 0.72 min, <i>m/z</i> 665 [M+H] ⁺
201		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-(trifluoromethyl)-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.02 (dd, 1H), 8.06 (ddd, 1H), 7.89 (dd, 1H), 7.10 – 7.02 (m, 2H), 7.01 – 6.93 (m, 1H), 4.39 (d, 1H), 3.88 (d, 1H), 3.76 (d, 1H), 3.68 – 3.52 (m, 1H), 3.45 – 3.36 (m, 3H), 3.06 (d, 1H), 2.78 (td, 1H), 2.71 – 2.62 (m, 1H), 2.50 – 2.43 (m,	(Method C) R _T = 0.68 min, <i>m/z</i> 637 [M+H] ⁺

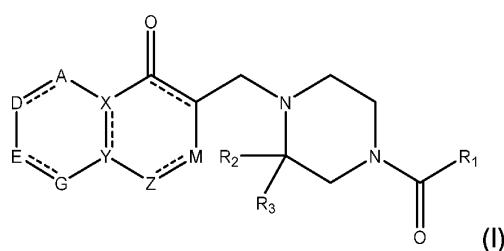
			2H), 2.42 (s, 3H), 2.21 – 2.02 (m, 3H), 1.94 – 1.80 (m, 1H), 1.76 – 1.61 (m, 3H), 1.61 – 1.54 (m, 1H), 1.50 (qd, 1H), 1.44 – 1.34 (m, 2H), 1.27 – 1.17 (m, 1H).	
202		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-1,6-naphthyridin-4(1 <i>H</i>)-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 9.43 (s, 1H), 8.69 (d, 1H), 8.17 (s, 1H), 7.67 (d, 1H), 7.13 – 7.04 (m, 2H), 7.01 – 6.95 (m, 1H), 4.42 (d, 1H), 3.96 (s, 3H), 3.76 – 3.65 (m, 1H), 3.62 – 3.53 (m, 2H), 3.50 – 3.40 (m, 3H), 3.14 (d, 1H), 2.83 (td, 1H), 2.79 – 2.70 (m, 1H), 2.66 – 2.53 (m, 2H), 2.46 (s, 3H), 2.12 (t, 2H), 1.88 – 1.80 (m, 1H), 1.76 – 1.64 (m, 3H), 1.62 – 1.50 (m, 2H), 1.50 – 1.39 (m, 2H), 1.35 – 1.27 (m, 2H).	(Method C) R _T = 0.48 min, <i>m/z</i> 565 [M+H] ⁺
203		3-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-((1-methylcyclopropyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4 <i>H</i> -pyrido[1,2- <i>a</i>]pyrimidin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 8.99 (dd, 1H), 8.45 (s, 1H), 7.94 (ddd, 1H), 7.76 (dd, 1H), 7.09 – 7.01 (m, 2H), 6.97 – 6.91 (m, 1H), 4.42 – 4.36 (d, 1H), 3.79 – 3.59 (m, 2H), 3.56 – 3.47 (m, 2H), 3.46 – 3.37 (m, 2H), 3.15 – 2.99 (m, 2H), 2.79 (td, 1H), 2.65 – 2.52 (m, 2H), 2.11 – 2.03 (m, 2H), 1.92 – 1.82 (m, 1H), 1.78 – 1.60 (m, 4H), 1.60 – 1.41 (m, 3H), 1.41 – 1.33 (m, 1H), 1.32 – 1.25 (m, 4H), 0.60 – 0.54 (m, 1H), 0.54 – 0.47 (m, 1H), 0.44 – 0.34 (m, 2H).	(Method A) R _T = 0.61 min, <i>m/z</i> 609 [M+H] ⁺
204		5-((9-((2 <i>S</i> ,4 <i>R</i>)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(1-methylcyclopropyl)-1 <i>H</i> -pyridin-4-one	[Note: methanol- <i>d</i> ₄ instead of DMSO- <i>d</i> ₆] 7.82 (s, 1H), 7.11 – 7.02 (m, 2H), 6.98 – 6.92 (m, 1H), 6.35 (s, 1H), 4.41 (d, 1H), 3.77 – 3.62 (m, 1H), 3.61 – 3.51 (m, 1H), 3.49 – 3.36 (m, 4H), 3.11 (d, 1H), 3.02 (sept, 1H),	(Method C) R _T = 0.56 min, <i>m/z</i> 582 [M+H] ⁺

		methyleycyclopropyl)pyr idin-4(1 <i>H</i>)-one	2.90 – 2.77 (m, 2H), 2.60 – 2.50 (m, 2H), 2.07 (t, 2H), 1.74 – 1.49 (m, 7H), 1.44 (s, 3H), 1.42 – 1.33 (m, 2H), 1.31 – 1.24 (m, 1H), 1.10 (t, 6H), 1.00 (t, 2H), 0.87 (t, 2H).	
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USP19 inhibitor compounds are also disclosed in WO2018/020242, WO2020/115500,
 WO2019/150119, WO2020/115501, and WO2022/200523 each of which is expressly
 5 incorporated herein by reference. Compounds according to formula (I) that are analogues
 of the compounds disclosed in WO2018/020242, WO2020/115500, WO2019/150119,
 WO2020/115501, and WO2022/200523 – i.e. analogues where the optionally substituted
 piperazine linker in (I) is present rather than an optionally substituted 4-piperidinol or
 piperidine moiety – are expressly incorporated herein and can be obtained by the skilled
 10 person following the synthesis protocols provided herein and in WO2018/020242,
 WO2020/115500, WO2019/150119, WO2020/115501, and WO2022/200523.

CLAIMS:

1. A compound of formula (I):



wherein

R¹ is optionally substituted C1-C6 alkyl, optionally substituted amino, optionally substituted 3 to 11 membered heterocycloalkyl, optionally substituted aryl, or optionally substituted 5 to 8 membered heteroaryl;

R² and R³ are each independently selected from H and C1-C6 alkyl, or wherein R² and R³ together form C3-C8 cycloalkyl, C3-C8 cycloalkenyl or 3 to 8 membered heterocycloalkyl together with the carbon to which they are attached;

M is N or CR^a wherein R^a is H, halo, optionally substituted C3-C8 cycloalkyl, or optionally substituted C1-C6 alkyl;

A, D, E and G are absent and

X is NR¹⁵ or CH;

Y is CR⁴ or N or absent;

Z is CR⁵, NR⁶ or O;

R⁴ is halo, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, 4 to 10 membered fused-ring heterocyclyl, optionally substituted C1-C6 alkylsulfanyl, sulfoxide, sulfone, sulfoximine, optionally substituted amino, optionally substituted 3 to 8 membered heterocycloalkyl, or OR²⁰;

wherein R²⁰ is optionally substituted C1-C6 alkyl;

R⁵ is H, optionally substituted C1-C6 alkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, optionally substituted 3 to 8 membered heterocycloalkyl, amido, sulfoximine, CN, halo, C(O)OR²¹, OR²², or NR²³R²⁴;

wherein R²¹ is selected from H and C1-C6 alkyl;

R²² is selected from H and C1-C6 alkyl;

R²³ and R²⁴ are independently selected from H and optionally substituted C1-C6 alkyl;

R¹⁵ is H or C1-C6 alkyl;

or R⁴ and R⁵ together form 3 to 8 membered heterocycloalkyl or aryl together with Y and Z to which they are attached;

or R⁴ and R¹⁵ together form 5 membered cycloalkyl, heterocycloalkyl, or heteroaryl together with X and Y to which they are attached;

R⁶ is H, C1-C6 alkyl, optionally substituted aryl, or C3-C8 cycloalkyl;

or A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N and

X is N or C;

Y is C;

Z is CR²⁰, N, NR¹¹, or O,

wherein R¹¹ is H, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, or optionally substituted 5 to 8 membered heteroaryl;

wherein R²⁰ is H, optionally substituted C1-C6 alkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, optionally substituted 3 to 8 membered heterocycloalkyl, amido, sulfoximine, CN, halo, C(O)OR²⁵, OR²⁶, or NR²⁷R²⁸;

wherein R²⁵ is selected from H and C1-C6 alkyl;
R²⁶ is selected from H and C1-C6 alkyl;
R²⁷ and R²⁸ are independently selected from H and C1-C6 alkyl;

R⁷ is H, halo, C1-C6 alkyl, or OR¹⁹;
wherein R¹⁹ is optionally substituted C1-C6 alkyl;

R¹² is H, halo, or C1-C6 alkyl;

R¹³ is H, halo, C1-C6 alkyl, OR¹⁶; or NR¹⁷R¹⁸;
wherein R¹⁶ is optionally substituted C1-C6 alkyl,
R¹⁷ and R¹⁸ are independently selected from H and C1-C6 alkyl or
wherein R¹⁷ and R¹⁸ together form 5 to 6 membered heterocycloalkyl
with the nitrogen atom to which they are attached; and

R¹⁴ is H, halo, or C1-C6 alkyl;

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 according to claim 1, wherein for each optionally substituted group, each one or more optional substituent is independently selected from alkyl, alkoxy, oxo, halo, cycloalkyl, heterocycloalkyl, aryl, aryl substituted by one or more halo, aryl substituted by halo and alkyl, aryl substituted by halo and alkoxy, heteroaryl, hydroxyl, CR⁸R⁹R¹⁰, NR⁸, NR⁸R⁹, NHC(O)R⁸, NHCR⁸R⁹R¹⁰, NHCH₂CR⁸R⁹R¹⁰ and NHCH₂C(O)R⁸,

wherein R⁸, R⁹ and R¹⁰ are each independently selected from H, halo, hydroxyl, alkyl, cycloalkyl, cycloalkyl substituted by one or more halo or alkyl, heterocycloalkyl substituted by one or more alkyl or oxo, heteroaryl, alkoxy, CH₂OH, and CH₂CH₂OH.

3. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to claim 1 or claim 2, wherein R¹ is optionally substituted 3 to 11 membered heterocycloalkyl.
4. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein R¹ is optionally substituted 5 to 8 membered heterocycloalkyl, optionally wherein R¹ is optionally substituted 5 to 6 membered heterocycloalkyl.
5. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein R¹ is optionally substituted morpholine, bridged azepane, diazepane, thiomorpholine, pyrrolidine, piperazine, or piperidine.
6. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein R¹ is optionally substituted piperidine.
7. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 3 to 6, wherein R¹ is substituted by one or more alkyl, oxo, cycloalkyl, heterocycloalkyl, aryl, aryl substituted by one or more halo, heteroaryl, NR⁸, NR⁸R⁹, NHC(O)R⁸, NHCR⁸R⁹R¹⁰, NHCH₂CR⁸R⁹R¹⁰ and NHCH₂C(O)R⁸, wherein R⁸, R⁹ and R¹⁰ are each independently selected from H, halo, hydroxyl, alkyl, cycloalkyl, cycloalkyl substituted by one or more halo or alkyl, heterocycloalkyl substituted by one or more alkyl or oxo, heteroaryl, and alkoxy.
8. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 3 to 7, wherein R¹ is substituted by phenyl or phenyl substituted by one or more halo, and wherein R¹ is optionally substituted with one or more further substituents.
9. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 3 to 8, wherein R¹ is

substituted by phenyl or phenyl substituted by one or more fluoro, and wherein R¹ is optionally substituted with one or more further substituents.

10. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 3 to 9, wherein R¹ is substituted by difluoro-phenyl.
11. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 3 to 10, wherein R¹ is substituted by NR⁸R⁹, NHC(O)R⁸, or NHCH₂CR⁸R⁹R¹⁰, and wherein R¹ is optionally substituted with one or more further substituents.
12. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 2 to 11, wherein R⁸, R⁹, and R¹⁰ are each independently selected from H, C1-C6 alkyl, fluoro-substituted C1-C6 alkyl, C1-C6 alkoxy, CH₂OH, CH₂CH₂OH, fluoro-substituted C3-C6 cycloalkyl, C3-C6 cycloalkyl substituted by C1-C6 alkyl, and pyridine-substituted C1-C6 alkyl.
13. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to claim 1 or claim 2, wherein R¹ is optionally substituted C1-C6 alkyl.
14. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to claim 13, wherein each optional substituent is selected from halo, C1-C6 alkoxy, cycloalkyl, and hydroxyl.
15. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 1-4, wherein R¹ is optionally substituted amino.
16. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to claim 15, wherein R¹ is amino substituted with phenyl substituted by one or more halo, or benzyl substituted by one or more halo.

17. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein R² and R³ are each independently H or methyl, or wherein R² and R³ together form C3-C6 cycloalkyl, cyclopentenyl or 4 to 6 membered heterocycloalkyl together with the carbon to which they are attached.
18. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein R² and R³ are each independently H or methyl, or wherein R² and R³ together form cyclopentyl.
19. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein R² and R³ together form oxetanyl or oxanyl together with the carbon to which they are attached.
20. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein M is CR^a.
21. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein R^a is H, cyclopropyl, CF₃ or methyl.
22. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein R^a is H.
23. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein:

A, D, E and G are absent and

X is NR¹⁵ or CH;

Y is CR⁴, N or absent;

Z is CR⁵, NR⁶ or O;

R⁴ is halo, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, 4 to 10 membered fused-ring heterocyclyl, or C1-C6 alkylsulfanyl;

R⁵ is H, optionally substituted C1-C6 alkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, optionally substituted 3 to 8 membered heterocycloalkyl, amido, sulfoximine, CN, or halo;

or R⁴ and R⁵ together form 3 to 8 membered heterocycloalkyl or aryl together with Y and Z to which they are attached;

R⁶ is H, C1-C6 alkyl, aryl, or C3-C8 cycloalkyl;

R¹⁵ is H or C1-C6 alkyl;

or R⁴ and R¹⁵ together form 5 membered heterocycloalkyl, or heteroaryl together with X and Y to which they are attached, optionally wherein R⁴ and R¹⁵ together form dihydrothiazole with X and Y to which they are attached;

or A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N and

X is N or C;

Y is C;

Z is CH, N, NR¹¹, or O,

wherein R¹¹ is H, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, or optionally substituted 5 to 8 membered heteroaryl;

R⁷ is H, halo, C1-C6 alkyl;

R¹² is H, halo, or C1-C6 alkyl;

R¹³ is H, halo, C1-C6 alkoxy, or C1-C6 alkyl; and

R¹⁴ is H, halo, or C1-C6 alkyl;

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

24. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein:

A, D, E and G are absent and

X is NH or CH;

Y is CR⁴ or N.

25. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein:

A, D, E and G are absent and

X is NH or CH;

Y is CR⁴ or N;

Z is CR⁵, NR⁶ or O;

R⁴ is halo, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, 4 to 10 membered fused-ring heterocyclyl, C1-C6 alkylsulfanyl, sulfoxide, sulfone, sulfoximine, optionally substituted amino, or optionally substituted 3 to 8 membered heterocycloalkyl;

R⁵ is H, optionally substituted C1-C6 alkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, optionally substituted 3 to 8 membered heterocycloalkyl, amido, sulfoximine, CN, or halo;

or R⁴ and R⁵ together form 3 to 8 membered heterocycloalkyl or aryl together with Y and Z to which they are attached; and

R⁶ is H, C1-C6 alkyl, or C3-C8 cycloalkyl.

26. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to claim 25, wherein Z is CR⁵ or NR⁶.
27. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to claim 25 or claim 26, wherein R⁶ is H or C1-C6 alkyl.
28. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25 to 27, wherein R⁴ is halo, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, 4 to 10 membered fused-ring heterocyclyl, SMe, sulfoxide, sulfone, sulfoximine, optionally substituted amino, optionally substituted pyrrolidine, optionally substituted piperidine, optionally substituted morpholine, or optionally substituted piperazine.
29. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25 to 28, wherein R⁴ is halo, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, optionally substituted 5 to 8 membered heteroaryl, or 4 to 10 membered fused-ring heterocyclyl.
30. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25 to 29, wherein R⁵ is H.

31. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25 to 30, wherein Y is CR⁴.
32. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25 to 31, wherein Y is N.
33. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25 to 32, wherein X is NH.
34. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25 to 32, wherein X is CH.
35. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25 to 34, wherein R⁴ is C1-C6 alkyl, C1-C6 alkyl substituted by one or more halo groups, halo, cycloalkyl, cycloalkyl substituted by one or more C1-C6 alkyl, heteroaryl, heteroaryl substituted by C1-C6 alkyl, dihydrobenzofuran, phenyl, or phenyl substituted by one or more C1-C6 alkyl, C1-C6 alkoxy, or halo.
36. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25 to 35, wherein R⁴ is methyl, CF₃, CHF₂, chloro, cyclopropyl, methyl substituted cyclopropyl, thiophene, methyl substituted pyrazole, 2,3-dihydrobenzofuran, phenyl, or phenyl substituted by methyl, methoxy, or fluoro.
37. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25 to 36, wherein R⁴ is phenyl or phenyl substituted by methyl, methoxy, or fluoro.
38. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25, 26, 31, 33 or 34, wherein R⁴ and R⁵ together form 6 membered heterocycloalkyl or aryl together with Y and Z to which they are attached.

39. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25, 26 or 28 to 38, wherein Z is CH.

40. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25 to 38, wherein Z is NR⁶.

41. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25 to 37 or 40, wherein R⁶ is H or methyl.

42. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25, 33 or 34, wherein Y is CR⁴ wherein R⁴ is C1-C6 alkylsulfanyl, optionally SMe, and wherein Z is CR⁵ wherein R⁵ is CN.

43. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 25, 28, 29, 35, 36 or 37, wherein M is N, X is CH, Y is CR⁴ and Z is NH, optionally wherein R⁴ is phenyl.

44. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 1 to 23, wherein:

A is CR¹² or N, D is CR⁷ or N, E is CR¹³ or N and G is CR¹⁴ or N and

X is N or C;

Y is C;

Z is CH, N, NR¹¹, or O, wherein R¹¹ is H, optionally substituted C1-C6 alkyl, optionally substituted C3-C8 cycloalkyl, optionally substituted aryl, or optionally substituted 5 to 8 membered heteroaryl;

R⁷ is H, halo, or C1-C6 alkyl;

R¹² is H, halo, or C1-C6 alkyl;

R¹³ is H, halo, C1-C6 alkoxy, or C1-C6 alkyl; and

R¹⁴ is H, halo, or C1-C6 alkyl.

45. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to claim 44, wherein Z is CH, N, or NR¹¹.
46. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to claim 44, wherein Z is CH, N, or O.
47. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to claim 44, wherein Z is CH or N.
48. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 47, wherein R⁷ is H, methyl or halo.
49. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 48, wherein R¹² is H.
50. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 49, wherein D is CR⁷.
51. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 50, wherein E is CR¹³.
52. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 51, wherein R¹³ is H.
53. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 52, wherein G is CR¹⁴.
54. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 53, wherein R¹⁴ is H.

55. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 54, wherein X is N.
56. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 55, wherein A is CH.
57. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 55, wherein A is N.
58. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 57, wherein R⁷ is halo.
59. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 58, wherein R⁷ is fluoro.
60. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 57, wherein R⁷ is H.
61. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 60, wherein Z is CH.
62. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44 to 60, wherein Z is N.
63. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44, 46 or 48 to 60, wherein Z is O.
64. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44, 45 or 48 to 60, wherein Z is NR¹¹.

65. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44, 45, 48 to 60 or 64, wherein R^{11} is H, C1-C6 alkyl, C3-C6 cycloalkyl, phenyl, or 5 to 7 membered heteroaryl.

66. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44, 45, 48 to 60, 64 or 65, wherein R^{11} is H.

67. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 44, 45, 48 to 60, 64 or 65, wherein R^{11} is methyl.

68. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 1 to 25, 27 to 29, 35 to 37 or 41, wherein:

A, D, E and G are absent;

M is CR^a or N;

X is CH;

Y is CR^4 ; and

Z is NR^6 .

69. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 1 to 25, 28 to 30, 35 to 39 or 42, wherein:

A, D, E and G are absent;

M is CR^a ;

X is NH;

Y is CR^4 ; and

Z is CR^5 .

70. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 1 to 25, 28, 29, 35, 36 or 37, wherein:

A, D, E and G are absent;

M is CR^a ;

X is NH;
Y is CR⁴; and
Z is N.

71. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 1 to 23, 44, 48, 52, 58, 59 or 60, wherein:

X is N;
Y is C;
Z is N;
M is CR^a;
A and G are each CH;
D is CR⁷; and
E is CR¹³.

72. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 1 to 23, 44, 48, 58, 59 or 60, wherein:

X and Y are each C;
Z is O;
A, E, G and M are each CH; and
D is CR⁷.

73. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 1 to 23, 44, 65, 66 or 67, wherein:

X and Y are each C;
Z is NR¹¹;
A, E, G and M are each CH; and
D is N.

74. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 1 to 23 or 44, wherein:

X and Y are each C;
Z is NH;

E is N; and

A, D, G and M are each CH.

75. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein the C1-C6 alkyl is C1-C3 alkyl, optionally methyl.

76. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 12, 14, 23, 35 or 44, wherein the C1-C6 alkoxy is methoxy or 2-methoxyethyl.

77. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, wherein the C1-C6 alkylsulfanyl is SMe.

78. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to claim 1, wherein:
A, D, E and G are absent,
X is NH or CH;
Y is CR⁴;
Z is CR⁵ or NR⁶;
R¹ is optionally substituted piperidine or piperazine,
R² and R³ together form cyclopentyl together with the carbon to which they are attached,
R⁴ is phenyl,
R⁵ is H, and
R⁶ is H or methyl,
wherein each optional substituent is selected from phenyl, difluoro-phenyl, NHCH₃, NHCH₂CH₃, NHCH(CH₃)₂, NHC(O)CH₃, N(CH₃)₂, NHCH₂CHF₂, NHCH₂CH₂F, NHCH₂CH₂OH, and NHCH₂CH₂OCH₃.

79. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to claim 1, wherein
A, D, E and G are absent;
X is NH or CH;

Y is CR⁴;

Z is CR⁵ or NR⁶;

R¹ is piperidine or piperazine each substituted by difluoro-phenyl and further substituted by amino optionally substituted by one or more C1-C3 alkyl, oxo-substituted C1-C3 alkyl, fluoro-substituted C1-C3 alkyl, CH₂CH₂OH, C1-C3 alkoxy, fluoro-substituted C3-C6 cycloalkyl, C3-C6 cycloalkyl substituted by C1-C3 alkyl, or pyridine-substituted C1-C3 alkyl;

R² and R³ are each methyl, or together form cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, oxetanyl or oxanyl together with the carbon to which they are attached;

R⁴ is methyl, dihydrobenzofuran, phenyl, phenyl substituted by methyl, phenyl substituted by F, phenyl substituted by OMe, phenyl substituted by SMe, phenyl substituted by OH, or thiophene;

R⁵ is H, methyl or CN; and

R⁶ is H or methyl.

80. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to claim 1, wherein

X is N or C;

Y is C;

Z is N, NR¹¹ or O, wherein R¹¹ is H or methyl;

M is CR^a wherein R^a is H, methyl or cyclopropyl;

A is C;

D is CR⁷, wherein R⁷ is H, methyl, F, Cl, Br;

E is N or CR¹³, wherein R¹³ is H, Cl or OMe;

G is C;

R¹ is piperidine or piperazine each substituted by difluoro-phenyl and further substituted by amino optionally substituted by one or more C1-C3 alkyl, fluoro-substituted C1-C3 alkyl, CH₂CH₂OH, C1-C3 alkoxy; and

R² and R³ are each methyl, or together form cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, oxetanyl or oxanyl together with the carbon to which they are attached.

81. A compound selected from:

(*R*)-6-Phenyl-3-((4-(3-phenylmorpholine-4-carbonyl)piperazin-1-yl)methyl)pyridin-2(1*H*)-one;

(*R*)-3-((2,2-Dimethyl-4-(3-phenylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)quinolin-2(1*H*)-one;

N-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-1-(6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)acetamide;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1,5,7,8-tetrahydro-2*H*-pyrano[4,3-*b*]pyridin-2-one;

N-(2,4-Difluorobenzyl)-6-((2-oxo-6-phenyl-1,2-dihydropyridin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carboxamide;

(*R*)-6-Phenyl-3-((9-(4,4,4-trifluoro-2-methylbutanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-methoxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((9-((2*S*,4*R*)-4-(Methylamino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

(*R*)-3-((9-(2-(2,5-Difluorophenyl)piperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
6-Phenyl-3-((9-((3*R*,4*R*)-3-phenylpiperidine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1*H*)-one;
3-((9-((2*S*,4*R*)-4-((3,3-Difluorocyclobutyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
(*S*)-6-Phenyl-3-((9-(4,4,4-trifluoro-2-(methoxymethyl)butanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1*H*)-one;
(*R*)-3-((9-(3-Cyclohexyl-2-methylpropanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
6-Phenyl-3-((9-(3-phenylisonicotinoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1*H*)-one;
3-((9-((2*S*,4*R*)-4-((2-Hydroxyethyl)amino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
5-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
5-((7-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
6-Phenyl-3-((9-((2*S*,4*R*)-2-phenyl-4-((pyridin-2-ylmethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(3,4-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
(*R*)-3-((9-(2-Methyl-2-phenylpiperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
(*R*)-5-((9-(3-(2,5-Difluorophenyl)morpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
(*S*)-5-((9-(3-(2,5-Difluorophenyl)morpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,3-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-4-(Methylamino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-4-(Cyclopropylamino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

(*R*)-5-((9-(2-(2,5-Difluorophenyl)-1,4-diazepane-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

(*S*)-5-((9-(2-(2,5-Difluorophenyl)-1,4-diazepane-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

(*R*)-5-((9-(3-(2,5-Difluorophenyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

(*S*)-5-((9-(3-(2,5-Difluorophenyl)-1-oxa-4,9-diazaspiro[5.5]undecane-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,6-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,4-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

3-((9-((3*R*,5*S*)-3-(2,5-Difluorophenyl)-5-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-methoxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((8-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((8-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2-oxa-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

5-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((7-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((9-((2*S*,4*R*)-4-Amino-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((8-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((8-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-2-oxa-5,8-diazaspiro[3.5]nonan-5-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(pyrrolidin-1-yl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(1-methyl-1*H*-pyrazol-5-yl)pyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-methyl-5-phenylpyridin-2(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-2-yl)pyridin-4(1*H*)-one;

(*R*)-3-((9-(3-Cyclohexyl-2-methylpropanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

5-((9-((2*S*,4*R*)-4-((2,2-Difluoroethyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-4-Morpholino-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-fluorophenyl)pyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(*o*-tolyl)pyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-methoxyphenyl)pyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-chromen-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-4*H*-chromen-4-one;

(*R*)-3-((9-(3-Cyclohexyl-2-methylpropanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-chromen-4-one;

(*R*)-3-((9-(3-Cyclohexyl-2-methylpropanoyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-4*H*-chromen-4-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2,3-dihydrobenzofuran-7-yl)pyridin-4(1*H*)-one;

(*R*)-3-((9-(2-(2,5-Difluorophenyl)piperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-4*H*-chromen-4-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(1-methyl-1*H*-pyrazol-3-yl)pyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

1-Cyclopropyl-5-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-methylpyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-5,6-dimethylpyridin-2(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrimido[1,2-*b*]pyridazin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoroquinolin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-hydroxyphenyl)pyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-methyl-2-propylpyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-5-(trifluoromethyl)pyridin-2(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(*o*-tolyl)pyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2,3-dihydrobenzofuran-7-yl)pyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-methoxyphenyl)pyridin-4(1*H*)-one;
(*R*)-5-((9-(2-(2,5-Difluorophenyl)piperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
(*R*)-3-((9-(2-(2,5-Difluorophenyl)piperazine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(4-fluorophenyl)pyridin-4(1*H*)-one;
3-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(3-fluorophenyl)pyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(*m*-tolyl)pyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-methoxyphenyl)pyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2,3-dihydrobenzofuran-7-yl)pyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(*o*-tolyl)pyridin-4(1*H*)-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(*m*-tolyl)pyridin-2(1*H*)-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(3-fluorophenyl)pyridin-2(1*H*)-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(4-fluorophenyl)pyridin-2(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(3-Fluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(methylthio)-6-oxo-1,6-dihydropyridine-3-carbonitrile;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyrimidin-4(3*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1,7-naphthyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyrimidin-4(3*H*)-one;

5-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-2-yl)pyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-2-yl)pyridin-4(1*H*)-one;

5-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2,6-dimethylpyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-4-((2,2-Difluoroethyl)amino)-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-methoxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((4-((2*S*,5*R*)-5-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

(*R*)-6-Phenyl-3-((4-(3-phenylmorpholine-4-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)pyridin-2(1*H*)-one;

(*R*)-3-((4-(3-(4-Fluorophenyl)morpholine-4-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((4-((2*R*,5*R*)-5-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2-Fluoro-5-methylphenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2-Fluoro-5-methoxyphenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
5-((9-((2*S*,5*R*)-5-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(3,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyrimidin-4(3*H*)-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
N-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-1-(6-((7-fluoro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)acetamide;
N-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-1-(6-((7-fluoro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)methyl)-6,9-diazaspiro[4.5]decane-9-carbonyl)piperidin-4-yl)cyclopropanecarboxamide;
3-((9-((2*S*,4*R*)-4-((1,1-Dioxidothietan-3-yl)amino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
3-((9-((2*S*,4*R*)-4-((2,2-Difluoroethyl)amino)-2-(3,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(thiophen-3-yl)pyridin-4(1*H*)-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
(*S*)-6-(2-Methoxyphenyl)-3-((9-(2-phenylpyrrolidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)pyridin-2(1*H*)-one;
(*S*)-6-Phenyl-3-((7-(2-phenylpyrrolidine-1-carbonyl)-4,7-diazaspiro[2.5]octan-4-yl)methyl)pyridin-2(1*H*)-one;
(*S*)-6-Phenyl-3-((4-(2-phenylpyrrolidine-1-carbonyl)-9-oxa-1,4-diazaspiro[5.5]undecan-1-yl)methyl)pyridin-2(1*H*)-one;
5-((9-((2*R*,5*R*)-5-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;
(*S*)-3-((4-(2-(2,5-Difluorophenyl)pyrrolidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-6-(1-methyl-1*H*-pyrazol-5-yl)pyridin-2(1*H*)-one;

(*S*)-3-((2,2-Dimethyl-4-(2-phenylpyrrolidine-1-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

(*S*)-6-Phenyl-3-((8-(2-phenylpyrrolidine-1-carbonyl)-2-oxa-5,8-diazaspiro[3.5]nonan-5-yl)methyl)pyridin-2(1*H*)-one;

3-((4-((1*S*,2*R*,5*R*)-2-(2,5-Difluorophenyl)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((9-((1*S*,2*R*,5*R*)-2-(2,5-Difluorophenyl)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

5-((9-((1*S*,2*R*,5*R*)-2-(2,5-Difluorophenyl)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(2-fluorophenyl)pyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-fluoro-1-methylquinolin-4(1*H*)-one;

3-((9-((2*R*,3*R*)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((9-((2*S*,3*S*)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(1-methyl-1*H*-pyrazol-5-yl)pyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-(trifluoromethyl)pyridin-2(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(trifluoromethyl)pyridin-4(1*H*)-one;

3-((4-((2*R*,3*R*)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((4-((2*S*,3*S*)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)piperazin-1-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

5-((9-((2*R*,3*R*)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,3*S*)-3-(2,5-Difluorophenyl)-2-methylmorpholine-4-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

3-((9-((2*R*,4*R*)-4-Amino-2-ethylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((9-((2*R*,4*R*)-2-Ethyl-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(1-methyl-1*H*-pyrazol-3-yl)pyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-hydroxypiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(dimethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(1-methyl-1*H*-pyrazol-3-yl)pyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropyl(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-methoxyethyl)(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-hydroxypiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(thiophen-3-yl)pyridin-4(1*H*)-one;

3-(((*S*)-4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-2-methylpiperazin-1-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

7-Chloro-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-2,2-dimethylpiperazin-1-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-(((*R*)-4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-2-methylpiperazin-1-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

5-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-2-(thiophen-3-yl)pyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-hydroxyethyl)(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethyl(methyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-8-methoxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

5-((9-((2*S*,4*S*)-4-Amino-2-phenylpyrrolidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

5-((9-((2*S*,4*S*)-4-(Isopropylamino)-2-phenylpyrrolidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7,8-dihydropyrrolo[1,2-*a*]pyrimidin-4(6*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7,8-dihydropyrrolo[1,2-*a*]pyrimidin-4(6*H*)-one;

3-((9-(5-Amino-2',5'-difluoro-[1,1'-biphenyl]-2-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridin-2(1*H*)-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-fluoroethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((2-fluoroethyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-phenylpyridin-4(1*H*)-one;

7-Fluoro-3-((9-((2*S*,4*S*)-4-(isopropylamino)-2-phenylpyrrolidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

4-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-phenyl-1,2-dihydro-3*H*-pyrazol-3-one;

4-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-methyl-1-phenyl-1,2-dihydro-3*H*-pyrazol-3-one;

7-Chloro-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((4-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-1,4-diazaspiro[5.5]undecan-1-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

7-Chloro-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

6-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one;

6-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one;

7-Fluoro-3-((9-((2*S*,4*R*)-4-((3-methyloxetan-3-yl)amino)-2-phenylpiperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(ethylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

2-Cyclopropyl-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

2-Cyclopropyl-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridazin-4(1*H*)-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-6-phenylpyridazin-4(1*H*)-one;
3-((9-((2*S*,4*R*)-4-Amino-2-(2,5-difluorophenyl)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]dec-2-en-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
7-Bromo-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
8-Chloro-3-((9-((2*S*,4*R*)-2-(2,5-difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-2-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(methylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-1-methyl-1,6-naphthyridin-4(1*H*)-one;
3-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-((1-methylcyclopropyl)amino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-7-fluoro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one; and
5-((9-((2*S*,4*R*)-2-(2,5-Difluorophenyl)-4-(isopropylamino)piperidine-1-carbonyl)-6,9-diazaspiro[4.5]decan-6-yl)methyl)-2-(1-methylcyclopropyl)pyridin-4(1*H*)-one;

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

82. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim that is an inhibitor of USP19, preferably human USP19.

83. A pharmaceutical composition comprising a compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any preceding claim, and a pharmaceutically acceptable carrier or diluent.
84. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 1-82 or the pharmaceutical composition according to claim 83 for use in therapy.
85. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any of claims 1-82 or the pharmaceutical composition according to claim 83 for use as a medicament.
86. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any one of claims 1-82 or the pharmaceutical composition according to claim 83 for use in treating muscular atrophy, obesity, insulin resistance, or type II diabetes.
87. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any one of claims 1-82 or the pharmaceutical composition according to claim 83 for use in treating muscular atrophy, cachexia or sarcopenia, wherein the muscular atrophy, cachexia and sarcopenia are associated with or induced by cancer.
88. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any one of claims 1-82 or the pharmaceutical composition according to claim 83 for use in treating cancer, preferably wherein the cancer is breast cancer or neuroblastoma.
89. The compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any one of claims 1-82 or the pharmaceutical composition according to claim 83 for use according to claim 88, wherein the use comprises treating muscular atrophy, cachexia and/or sarcopenia.
90. A method of treating obesity, insulin resistance, type II diabetes, or muscular atrophy, comprising administering to a subject in need thereof an effective amount of a

compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any one of claims 1-82 or a pharmaceutical composition according to claim 83.

91. A method of reducing loss of muscle mass in a subject comprising administering to a subject in need thereof an effective amount of a compound, stereoisomer, tautomer, hydrate, *N*-oxide derivative or pharmaceutically acceptable salt according to any one of claims 1-82 or a pharmaceutical composition according to claim 83.