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(54) Title: USP19 INHIBITORS FOR USE IN THERAPY

(57) Abstract: Provided are USP19 inhibitors, methods of treating obesity, metabolic syndrome and/or diabetes using the USP19 inhibitor compounds, as well as those compounds for use in methods of treating obesity, metabolic syndrome and/or diabetes. Also provided are methods of treating muscular atrophy, for example cachexia or sarcopenia with USP19 inhibitor compounds, plus those compounds for use in methods of treating muscular atrophy.

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USP19 INHIBITORS FOR USE IN THERAPY

FIELD OF INVENTION

The present invention is directed to a method of treating obesity, metabolic syndrome and/or diabetes. In particular, the invention provides methods of treating these metabolic disorders with USP19 inhibitor compounds, and further provides those compounds for use in methods of treating obesity, metabolic syndrome and/or diabetes. The present invention is also directed to a method of treating muscular atrophy, for example cachexia or sarcopenia. In particular, the invention provides methods of treating muscular atrophy with USP19 inhibitor compounds, plus those compounds for use in methods of treating muscular atrophy.

BACKGROUND

According to the World Health Organisation, the global obesity epidemic is a rapidly growing threat to public health. Obesity is associated with co-morbidities including cardiovascular diseases (e.g. coronary heart disease, hypertension and stroke), osteoarthritis, and pulmonary diseases (e.g. sleep apnoea). Obesity is also associated with metabolic disorders such as metabolic syndrome, type II diabetes and glucose intolerance.

The current primary treatments for obesity (diet and exercise) require behavioural change by the subject. However, maintaining such behavioural changes is frequently difficult and socio-economic factors can result in barriers to access. Bariatric surgery is effective, but not accessible or appropriate for many subjects. There is therefore a need to provide new therapies for obesity that can be used instead of or alongside existing interventions.

Insulin resistance is characterised by a reduced or refractory response to insulin produced by the body, resulting in symptoms such as hyperglycaemia, hyperlipidaemia and/or weight gain. Insulin resistance may be caused by obesity or viral infection, though is not confined to these conditions. Ultimately insulin resistance can progress to type II diabetes.

Management of insulin resistance is primarily through changes in diet and levels of activity. However, similarly to obesity, maintaining these behavioural changes can be challenging. In the context of type II diabetes, insulin resistance therapy with metformin or thiazolidinediones can lead to improvements in glycaemia, though efficacy is variable.

Accordingly, there is a need for new therapies for treating insulin resistance, for example in type II diabetes patients.

Muscle wasting is a common complication of many prevalent diseases (e.g. cancer, heart failure, chronic obstructive lung disease, kidney failure, stroke) and a prominent feature of aging. Muscle loss causes weakness and limits mobility, thereby burdening both caregivers and the health care system. Severe loss of muscle mass results in death. Muscle wasting is an independent predictor of mortality in many conditions regardless of disease severity. In gastrointestinal cancers, at initial presentation, it is already present in 41% of patients, but often masked by obesity. This muscle wastage predicts not only death, but increased dose limiting toxicity to chemotherapy as well as earlier relapse [7]. High quality animal studies have demonstrated that treatment of muscle wasting in cancer cachexia prolongs survival independently of any effect on tumor burden [9]. Treatment of muscle atrophy may therefore not only improve quality of life, but also survival.

Despite the wide prevalence of muscle wasting and its important medical and social consequences, there are no approved therapies. Such a therapeutic would have a major impact on quality and span of life as well as reduce costs for assisted living and institutionalized care. There is therefore a need for an effective therapy for muscular atrophy.

SUMMARY OF INVENTION

USPs are the largest subfamily of the deubiquitinating enzymes (DUBs) family with over 60 family members reported to date (Komander D. *et al.*, *Nat. Rev. Mol.* (2009), 10, 550-563; Claque M. *et al.*, *Physiol. Rev.* (2013), 93, 1289-1315).

Amongst all USPs, USP19 is an important member due to its implications in pathological conditions including but not restricted to muscle atrophy disorders, 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, 3510-3507; 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 J.* (2009), 10, 755-761; Lee J. *et al.*, *J. Biol. Chem.* (2014), 289, 3510-3507; 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, E1829). 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 HIF1α 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 L. *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 TNFα-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 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 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 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).

USP19 is also implicated in muscular atrophy, muscle-wasting syndromes and other skeletal muscle atrophy disorders (Wing S., *Int. J. Biochem. Cell Biol.* (2013), 45, 2130-2135; Wing S. *et al.*, *Int. J. Biochem. Cell Biol.* (2016), 79, 426-468; Wiles B. *et al.*, *Mol. Biol. Cell* (2015), 26, 913-923; Combaret L. *et al.*, *Am. J. Physiol. Endocrinol. Metab.* (2005), 288, E693-700). This was supported for instance by studies which demonstrated that USP19-silencing induced the expression of myofibrillar proteins and promoted myogenesis (Sundaram P. *et al.*, *Am. J. Physiol. Endocrinol. Metab.* (2009), 297, E1283-90; Ogawa M. *et al.*, *J. Biol. Chem.* (2011), 286, 41455-41465; Ogawa M. *et al.*, *J. Endocrinol.* (2015), 225, 135-145).

In vivo studies have 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.* 2018 Nov 1. doi: 10.1007/s00125-018-4754-4., 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. However, no *in vivo* studies have been described demonstrating that pharmacological inhibitors of USP19 are an effective approach to the treatment of obesity. Similarly, no *in vivo* studies have demonstrated that pharmacological inhibitors of USP19 can be effective in increasing insulin sensitivity.

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

These gene knock-out studies describe a connection between USP19 and muscular atrophy. However, no *in vivo* studies have been described demonstrating that pharmacological inhibitors of USP19 are an effective approach to the treatment of muscle-wasting conditions (e.g. cachexia and sarcopenia).

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

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

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

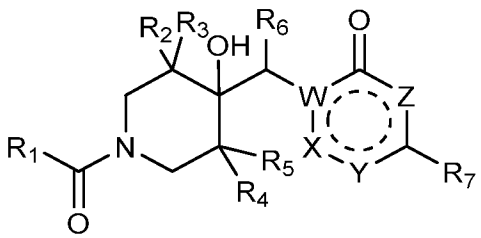
Similarly, it is demonstrated herein for the first time that USP19 inhibitors can treat the symptoms of insulin resistance, as indicated by an improved response to glucose.

WO2018/020242 provides for the first time a series of compounds which inhibit USP19, as determined by *in vitro* assay. The contents of WO2018/020242 are expressly incorporated herein by reference in its entirety, and particularly in relation to the compounds disclosed therein, their synthesis, methods of production and their *in vitro* inhibitory activity.

The Examples herein provide the first data demonstrating the efficacy of USP19 inhibitor compounds, for example those of WO2018/020242, in an *in vivo* model.

Thus, it is demonstrated in the accompanying Examples that the USP19 inhibitory compounds provided herein are capable of treating a number of disease conditions. Taken together, the *in vitro* and *in vivo* data demonstrate that compounds which potently inhibit USP19 activity can be effective therapeutic compounds.

Accordingly, in a first aspect the invention provides a compound, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in a method of therapy, wherein the compound is a compound according to formula (I):



(I)

wherein:

R_1 is an optionally substituted alkyl, alkenyl, alkynyl, ether, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, alkylheterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl group;

R_2 is H or an optionally substituted alkyl group,

R_3 is H or an optionally substituted alkyl group,

R_4 is H or an optionally substituted alkyl group,

R_5 is H or an optionally substituted alkyl group,

R_2 and R_4 may be joined to one another to form an optionally substituted cycloalkyl or heterocycloalkyl that includes the carbon to which they are attached,

R_4 and R_5 may be joined to one another to form an optionally substituted cycloalkyl or heterocycloalkyl that includes the carbon to which they are attached;

R_6 is H or an optionally substituted alkyl group;

W is C or N;

X is N or CR_8, wherein R_8 is H or optionally substituted C1-C6 alkyl,

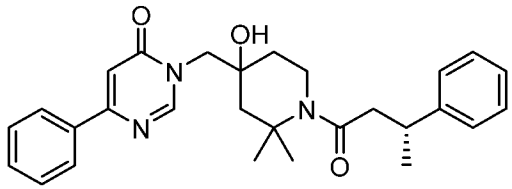
Y is N or CR_9

Z is CH, or NH,

wherein R_9 is H or optionally substituted alkyl, amido, amino, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, halo, carbonyl, ester, aminoalkyl, or cyano;

R_7 is hydrogen, halo, or an optionally substituted alkyl, alkenyl, alkynyl, amino, aryl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryl or heterocycloalkyl group;

or the compound



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

In a further aspect is provided 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 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 as defined

in relation to the first aspect, 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.

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 insulin resistance. 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.

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.

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 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.

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.

It is further demonstrated herein that USP19 inhibitor compound 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.

Accordingly, 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 cancer.

Also provided in accordance with the invention is a method of treating cancer 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.

In preferred such embodiments the cancer to be treated in accordance with the invention is breast cancer or neuroblastoma.

The data presented herein is the first demonstration of the efficacy of USP19 inhibitors as effective therapeutic drugs. This efficacy is shown in a variety of pathological conditions.

Accordingly, in a further aspect is provided a USP19 inhibitor for use in treating obesity. In a further aspect is provided a USP19 inhibitor for use in treating muscular atrophy. In a further aspect is provided a USP19 inhibitor for use in treating type II diabetes. In a further aspect is provided a USP19 inhibitor for use in treating cancer.

In a further aspect is provided a method of treating cancer, obesity, insulin resistance, type II diabetes and/or muscular atrophy comprising administering to a subject in need thereof an effective amount of a USP19 inhibitor.

Other preferred embodiments of the invention 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.

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

(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.

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 due to accumulation of drug compound in the liver. (C) Percentage change in overall body weight in vehicle-treated control DIO mice. USP19 inhibitor 5mg/kg ip BID, USP19 inhibitor 25mg/kg ip BID, or positive control liraglutide 0.1mg/kg sc 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 5mg/kg, USP19 inhibitor 25mg/kg, and liraglutide treated mice (left to right, respectively). ***p<0.001 vs vehicle.

Figure 4: Body composition analysis of mice in a dietary-induced obesity model, treated with USP19 inhibitor ACD-141 or liraglutide. All mice were fed a high-fat diet and treated as indicated. Results for total tissue mass, total body fat, and percentage body protein were determined. Percentage carcass ash was also determined. Means are adjusted for differences between treatment groups in Day 1 bodyweight. Error bars show SEM. *** p<0.001, ** p<0.01.

Figure 5: Cell target engagement of USP19 inhibitor compound in breast cancer, neuroblastoma and skeletal muscle cell lines. EC_{50} was determined by densitometry.

Figure 6: Response to oral glucose tolerance test (OGTT) in obese mice. (A) Timeline of plasma glucose response in vehicle-treated control mice (circles), USP19 inhibitor 5mg/kg ip BID (triangle), USP19 inhibitor 25mg/kg ip BID (solid circle), or positive control liraglutide 0.1mg/kg sc BID (diamond); (B) Glucose AUC (mM.hr) and (C) insulin AUC (ng.hr/ml) for vehicle, USP19 inhibitor 5mg/kg, USP19 inhibitor 25mg/kg, and liraglutide (left to right, respectively). ** p<0.01 vs vehicle; ***p<0.001 vs vehicle.

DETAILED DESCRIPTION

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 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 following terms have the meaning indicated:

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 5μM, preferably less than 0.5μM.

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.

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 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.

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.

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.

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 aliphatic group containing n carbon atoms. For example, a C_1-C_{10} 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 (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 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 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-butynyl, 3-butynyl and 4-butynyl.

The term "heteroalkyl group" (alone or in combination with another term(s)) means a straight-or branched-chain saturated hydrocarbyl 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 C_1-C_{10} 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 C_2-C_{10} 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 C_2-C_{10} 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), 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 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. 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 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 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 cycloalkyls.

The term “alkylcycloalkyl” refers to a cycloalkyl substituent attached via an alkyl chain. Examples of an alkylcycloalkyl substitent include cyclohexylethane, where the cyclohexane is attached via an ethane linker. Other examples include cyclopropylethane, 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 to 6 carbon ring atoms. A “C_n aryl” group refers to an aromatic group containing n carbon atoms. For example, a C_6-C_{10} 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 tetrahydronapthyl.

The term “arylalkyl” refers to an aryl substituent attached via an alkyl chain. Examples of an arylalkyl substitent include 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.
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 (i.e. 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.

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, 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.

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. A "C_n heterocycloalkyl" group refers to a cyclic aliphatic group containing n carbon atoms in addition to at least one heteroatom, for example nitrogen. For example, a C_1-C_{10} heterocycloalkyl group contains 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon ring atoms in addition to the at least one heteroatom. Attachment to the heterocycloalkyl group occurs through a carbon atom or one of the at least one heteroatoms.

The term "alkylheterocycloalkyl" refers to a heterocycloalkyl substituent attached via an alkyl chain. In a "C_n" alkylheterocycloalkyl, C_n includes the carbon atoms in the alkyl chain and in the heterocycloalkyl ring. For example, ethylpiperidine is a C7 alkylheterocycloalkyl.

The term "heteroaryl group" (alone or in combination with another term(s)) means an aromatic heterocyclyl containing from 5 to 14 ring atoms. A "C_n heteroaryl" group refers to an aromatic group containing n carbon atoms and at least one heteroatom. For example, a C_2-C_{10} aryl group contains 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms in addition to at least one heteroatom. 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 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, 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.

A nitrogen-containing heteroaryl group is a heteroaryl group in which at least one of the one or more heteroatoms in the ring is nitrogen.

The term “heteroarylalkyl” refers to a heteroaryl substituent attached via an alkyl chain. Examples of a heteroarylalkyl substitent include ethylpyridine, where the ethane chain links a pyridine group to the point of attachment.

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, 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 group or an oxo group.

The term “aminoalkyl” 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 aminoalkyl” group refers to a group containing n carbon atoms. For example, a C_1-C_{10} aminoalkyl group contains 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms. When the amino group of the aminoalkyl group is a substituted amino group, the number of carbon atoms includes any carbon atoms in the substituent groups. Attachment to the aminoalkyl group occurs through a carbon atom of the R^a alkyl group. Examples of aminoalkyl substituents include methylamine, ethylamine, methylaminomethyl, dimethylaminomethyl, methylaminoethyl, dimethylaminoethyl, methylpyrrolidine, and ethylpyrrolidine

The term “amido group” refers to the –C(=O)-NR- group. Attachment may be through the carbon and/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 “ether” refers to an 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 CH(CH3)-O-C6H11 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.

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.

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 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 group” refers to a group selected from chlorine, fluorine, bromine and iodine. Preferably, the halo group 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 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 "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 heterocycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, nitro, thio, alkanoyl, hydroxyl, aryloxyl, alkoxyl, alkylthio, arylthio, aralkyloxyl, aralkylthio, carboxyl, alkoxycarbonyl, oxo, alkylsulfonyl, arylsulfonyl and sulfoximinyl.

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, carbocyclyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, nitro, thio, alkanoyl, hydroxyl, aryloxyl, alkoxyl, alkylthio, arylthio, aralkyloxyl, 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 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.

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 (4*n*+2) electrons where *n* is an integer. In other words, these systems may display Hückel aromaticity.

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, 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 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.

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 ^{1}H, ^{2}H (deuterium) or ^{3}H (tritium).

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 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.

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

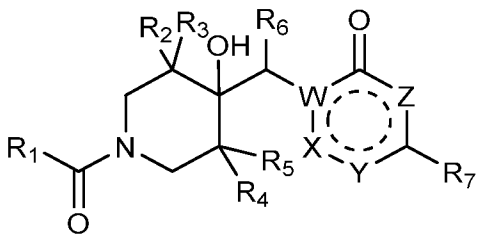
acid or base in one or more suitable solvents, or by mixing the compound with another pharmaceutically acceptable compound capable of forming a co-crystal.

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, 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 pharmaceutical salts published by IUPAC.

In addition, the compounds for use in accordance with the present invention may sometimes exist as zwitterions, which are considered as part 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 a number of disease conditions. Taken together, the *in vitro* and *in vivo* data demonstrate that compounds which potently inhibit USP19 activity can be effective therapeutic compounds.

Accordingly, in a first aspect the invention provides a compound, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in a method of therapy, wherein the compound is a compound according to formula (I):



(I)

wherein:

R_1 is an optionally substituted alkyl, alkenyl, alkynyl, ether, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, alkylheterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl group;

R_2 is H or an optionally substituted alkyl group,

R_3 is H or an optionally substituted alkyl group,

R_4 is H or an optionally substituted alkyl group,

R_5 is H or an optionally substituted alkyl group,

R_2 and R_4 may be joined to one another to form an optionally substituted cycloalkyl or heterocycloalkyl that includes the carbon to which they are attached,

R_4 and R_5 may be joined to one another to form an optionally substituted cycloalkyl or heterocycloalkyl that includes the carbon to which they are attached;

R_6 is H or an optionally substituted alkyl group;

W is C or N;

X is N or CR_8, wherein R_8 is H or optionally substituted C1-C6 alkyl,

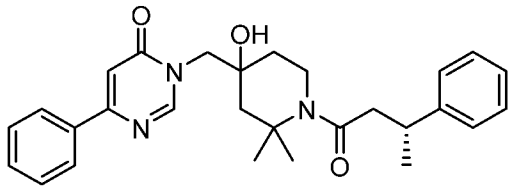
Y is N or CR_9

Z is CH, or NH,

wherein R_9 is H or optionally substituted alkyl, amido, amino, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, halo, carbonyl, ester, aminoalkyl, or cyano;

R_7 is hydrogen, halo, or an optionally substituted alkyl, alkenyl, alkynyl, amino, aryl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryl or heterocycloalkyl group;

or the compound



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

It is demonstrated herein that the potent USP19 inhibitory compounds provided herein effectively reduce fat accumulation *in vivo*. Gene knockout studies have described a possible association between USP19 and fat accumulation (Coyne *et al*, *Diabetologia*. 2018 Nov 1. doi: 10.1007/s00125-018-4754-4., 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.

The data provided herein is the first demonstration 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.

Accordingly, in a further aspect is provided a USP19 inhibitor for use in a method of treating obesity.

In a further aspect is provided 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 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 as defined in relation to the first aspect, 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.

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.

The data provided herein is the first demonstration that pharmacological inhibition of USP19 can effectively treat insulin resistance.

Accordingly, in a further aspect is provided a USP19 inhibitor for use in a method of treating insulin resistance. In a further aspect is provided a USP19 inhibitor for use in a method of treating type II diabetes.

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 insulin resistance. 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.

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.

Accordingly, in a further aspect is provided a USP19 inhibitor for use in a method of treating muscular atrophy.

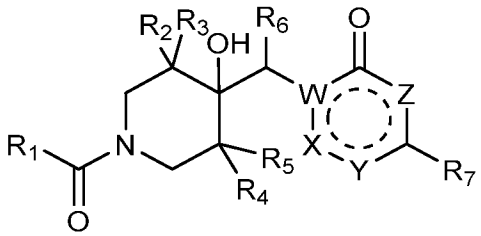
In a further aspect of the invention is provided a compound as defined in relation to the first aspect of the invention, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in a method of treating muscular atrophy. In a further aspect the invention provides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

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.

Compounds for use according to the invention

In all aspects, the compound (or pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof) for use in methods of therapy according to the invention is a compound according to formula (I):



(I)

wherein:

R_1 is an optionally substituted alkyl, alkenyl, alkynyl, ether, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, alkylheterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl group;

R_2 is H or an optionally substituted alkyl group,

R_3 is H or an optionally substituted alkyl group,

R_4 is H or an optionally substituted alkyl group,

R_5 is H or an optionally substituted alkyl group,

R_2 and R_4 may be joined to one another to form an optionally substituted cycloalkyl or heterocycloalkyl that includes the carbon to which they are attached,

R_4 and R_5 may be joined to one another to form an optionally substituted cycloalkyl or heterocycloalkyl that includes the carbon to which they are attached;

R_6 is H or an optionally substituted alkyl group;

W is C or N;

X is N or CR_8, wherein R_8 is H or optionally substituted C1-C6 alkyl,

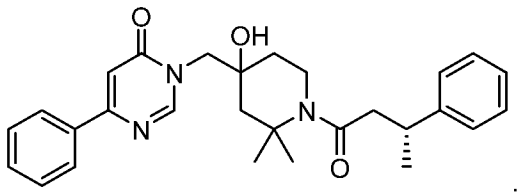
Y is N or CR_9

Z is CH, or NH,

wherein R_9 is H or optionally substituted alkyl, amido, amino, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, halo, carbonyl, ester, aminoalkyl, or cyano;

R_7 is hydrogen, halo, or an optionally substituted alkyl, alkenyl, alkynyl, amino, aryl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryl or heterocycloalkyl group;

or the compound



.

In certain embodiments of all aspects of the invention, R_1 is optionally substituted C1-C6 alkyl, optionally substituted C4-C10 alkylcycloalkyl, optionally substituted C7-C10 arylalkyl, optionally substituted C3-C6 cycloalkyl, optionally substituted C4-C5 heterocycloalkyl, or optionally substituted C3-C6 heteroaryl,

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

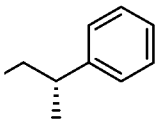
In certain embodiments, R_1 is optionally substituted C7-C10 cyclohexylalkane, optionally substituted C4-C6 cyclopropylalkane, optionally substituted C5-C6 cyclobutylalkane, optionally substituted C7-C10 alkylbenzene, optionally substituted 2,2 difluorobutane, or optionally substituted 3,3,3-trifluoropropane,

wherein each optional substituent is independently selected from C1-C6 alkyl, C2-C6 alkenyl, hydroxymethyl, hydroxyethyl, methoxymethyl, OH, or halo.

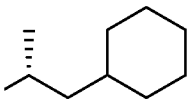
In certain embodiments, R_1 is substituted and the substituent is C1-C6 alkyl, optionally methyl.

In certain preferred embodiments, R_1 is methyl substituted cyclohexylethane or methyl substituted ethylbenzene.

In certain preferred embodiments, R_1 is:

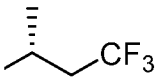


In certain preferred embodiments, R_1 is:

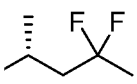


In certain preferred embodiments, R_1 is methyl substituted 2,2 difluorobutane, or methyl substituted 3,3,3-trifluoropropane.

In certain preferred embodiments, R_1 is:



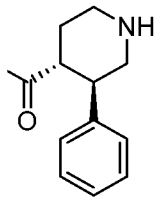
In certain preferred embodiments, R_1 is:



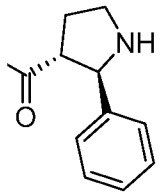
In certain preferred embodiments, R_1 is C4-C5 heterocycloalkyl, optionally substituted with phenyl.

In certain preferred embodiments R_1 is phenyl-substituted pyrrolidine or phenyl-substituted piperidine.

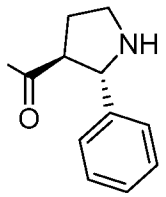
In certain preferred embodiments, R_1 forms the following group together with the carbonyl to which it is attached:



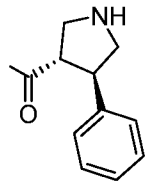
In certain preferred embodiments, R_1 forms the following group together with the carbonyl to which it is attached:



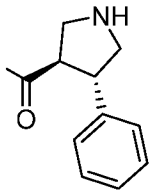
In certain preferred embodiments, R_1 forms the following group together with the carbonyl to which it is attached:



In certain preferred embodiments, R_1 forms the following group together with the carbonyl to which it is attached:



In certain preferred embodiments, R_1 forms the following group together with the carbonyl to which it is attached:



In certain embodiments of all aspects of the invention R_7 is optionally substituted C6-C10 aryl, C1-C12 heteroaryl, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, amino, C1-C3 alkoxy, or halo,

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

In certain preferred embodiments, R_7 is cyclopropyl, thiophene, or optionally substituted phenyl,

wherein the optional substituent is selected from C1-C6 alkyl, hydroxysubstituted C1-C6 alkyl, C1-C6 alkylamine, and halo.

In certain preferred embodiments, R_7 is phenyl.

In certain preferred embodiments, R_7 is fluoro-substituted phenyl. In certain preferred such embodiments, the phenyl has a single fluoro substituent. In certain preferred such embodiments, the fluoro substituent is in the *ortho* or *meta* position,

In certain embodiments of all aspects of the invention, R_2, R_3, R_4, R_5 are independently selected from H and C1-C6 alkyl.

In certain preferred embodiments, R_2 and R_3 are H, and R_4 and R_5 are methyl.

In certain preferred embodiments, R_4 and R_5 are joined to one another to form an optionally substituted C3-C6 cycloalkyl or C3-C6 heterocycloalkyl that includes the carbon to which they are attached and R_2 and R_3 are independently selected from H and C1-C6 alkyl.

In certain preferred embodiments, R_2 and R_3 are H and R_4 and R_5 are joined to one another to form a C3-C6 cycloalkyl that includes the carbon to which they are attached.

In certain preferred embodiments, R_4 and R_5 are joined to one another to form a C4 cycloalkyl that includes the carbon to which they are attached.

In certain preferred embodiments, R_4 and R_5 are joined to one another to form a C5 cycloalkyl that includes the carbon to which they are attached.

In certain preferred embodiments, R_6 is H or C1-C6 alkyl.

In certain embodiments, R_2 and R_4 are joined to one another to form a C5 cycloalkyl that includes the carbons to which they are attached, and wherein R_3, R_5 and R_6 are independently H or C1-C6 alkyl.

In certain preferred embodiments, W is N and X is CR_8, wherein R_8 is H or methyl.

In certain preferred embodiments, Y is N or CR_9, wherein R_9 is H, C1-C6 alkyl, NR'R'', C(O)NR'R'', cyano, carboxyl, halo, C1-C6 alkylamine, C3-C6 alkylester, optionally substituted C6-C10 aryl or optionally substituted C2-C6 heteroaryl, wherein the one or more heteroatoms are selected from N and O, and the one or more optional substituents of the aryl or heteroaryl are selected from C1-C6 alkyl, C1-C6 alkylamine, amido, and cyano,

wherein R' and R'' are independently selected from H, C1-C6 alkyl optionally substituted with OH, C3-C7 cycloalkyl, C1-C7 heterocycloalkyl, C4-C7 alkylcycloalkyl, C3-C7 alkylheterocycloalkyl, benzyl, phenyl, and methoxy, or wherein R' and R'' are joined to one another to form a C2-C7 heterocycle that includes the N to which they are attached, wherein the heterocycle is optionally hydroxyl-substituted, oxo-substituted, methyl-substituted, CH2OH-substituted, or acetyl-substituted.

In certain preferred embodiments, Y is N or CR_9, wherein R_9 is selected from: phenyl optionally substituted with amido, cyano or methyl amine; pyridine; oxazole; pyrazole; carboxyl; C(O)NR'R''; or NR'R'';

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

In a preferred embodiment of all aspects of the invention, the compound (or pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof) for use in methods according to the invention is a compound according to formula (I), wherein

R_1 is selected from optionally substituted ethylcyclohexane, optionally substituted ethylbenzene, optionally substituted 2,2 difluorobutane, and optionally substituted 3,3,3-trifluoropropane, wherein the optional substituent is one or more of methyl, ethyl, propyl, propenyl, hydroxymethyl and methoxymethyl, or wherein R_1 is phenyl-substituted pyrrolidine,

R_2 and R_3 are independently selected from H, methyl,

R_4 and R_5 are independently selected from H, methyl, or are joined to one another to form a C3-C6 cycloalkyl or heterocycloalkyl that includes the carbon to which they are attached, optionally a C4 or C5 cycloalkyl that includes the carbon to which they are attached

R_6 is H or methyl,

R_7 is selected from optionally substituted phenyl, indazole, thiophene, or pyrazole, wherein the optional substituent is selected from C1-C6 alkyl, hydroxysubstituted C1-C6 alkyl, C3-C6 cycloalkyl, C1-C6 heterocycloalkyl, C1-C6 alkoxy, halo-substituted C1-C6 alkoxy, C1-C6 alkylamine, amido, cyano or halo,

W is N or C

X is CH or N

Z is C or NH

Y is N or CR_9, wherein R_9 is selected from: phenyl optionally substituted with amido, cyano or methyl amine; pyridine; oxazole; pyrazole; C(O)NR'R''; or NR'R'';

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

In certain preferred embodiments of all aspects of the invention Y is CR_9, wherein R_9 is C(O)NR'R'' and wherein R' and R'' are joined to one another to form an optionally substituted pyrrolidine, piperidine, piperazine or morpholine that includes the N to which they are attached, wherein the piperidine, pyrrolidine, piperazine or morpholine is optionally hydroxyl-substituted, oxo-substituted, methyl-substituted, hydroxymethyl-substituted, or acetyl-substituted.

In certain preferred embodiments Y is CR_9, wherein R_9 is C(O)NR'R'' and wherein R' and R'' are joined to one another to form a piperazinyl ring.

In certain preferred embodiments, W is N and Y is N, such that the ring comprising W, X, Y, Z is a substituted pyrimidinone ring.

It will be appreciated by the skilled person that some compounds according to formula I for use according to the invention will be chiral at the carbon of the piperadinyl ring bound to the hydroxyl group. In certain preferred embodiments of all aspects of the invention, when the compound is chiral at this position, the compound is the *S* enantiomer. In certain alternative preferred embodiments of all aspects of the invention, when the compound is chiral at this position, the compound is the *R* enantiomer.

In certain embodiments of all aspects of the invention the compound is:

(*R*)-5-Bromo-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

6-(2-Fluorophenyl)-3-((4-hydroxy-1-(3-phenylpropanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

3-((1-(3-Cyclobutylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-((1-(3-Cyclopentylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(2-methyl-3-phenylpropanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*)-*N*-(3-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridin-3-yl)phenyl)acetamide;

(*R*)-3-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)6-oxo-4-phenyl-1,6-dihydropyridin-3-yl)benzamide;

(*R*)-5-(Furan-2-yl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-4-Chloro-1-((4-hydroxy-1(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenylpyridin-2(1*H*)-one;

(*R*)-4-(Dimethylamino)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenylpyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenyl-4-(prop-1-en-2-yl)pyridine-2(1*H*)-one;

(*R*)-Ethyl 1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate;

(*R,S*)-4-(2-Fluorophenyl)-1-((4-hydroxy-1-(2-methyl-1,2,3,4-tetrahydronaphthalene-2-carbonyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

(*R,S*)-1-((1-(3-Cyclobutyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-4-phenyl-5-(piperidine-1-carbonyl)pyridin-2(1*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(1-methyl-1*H*-indazol-7-yl)pyrimidin-4(3*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(2-methoxyphenyl)pyrimidin-4(3*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-2-methyl-6-phenylpyrimidin-4(3*H*)-one;

(*R*)-2-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5,6-diphenylpyridazin-3(2*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(naphthalen-1-yl)pyrimidin-4(3*H*)-one;

(*R*)-6-(3-(1,3-Dioxolan-2-yl)phenyl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(thiophen-3-yl)pyrimidin-4(3*H*)-one;

4-(2-Fluorophenyl)-1-((4-hydroxy-1-(1-methylcyclopentane-1-carbonyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

3-((1-(1-Ethylcyclohexane-1-carbonyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-((1-(2-(Cyclohexylmethyl)-3-methylbutanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-6-(Furan-2-yl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-6-(Cyclohex-1-en-1-yl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(prop-1-en-2-yl)pyrimidin-4(3*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(2-(trifluoromethoxy)phenyl)pyrimidin-4(3*H*)-one;

3-(((1*R*,5*S*)-3-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-8-hydroxy-3-azabicyclo[3.2.1]octan-8-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*)-5-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-2-phenylpyrimidin-4(3*H*)-one;

3-((4-Hydroxy-1-(3-phenylpropanoyl)piperidin-4-yl)methyl)-2-methyl-6-phenylpyrimidin-4(3*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(isobutylamino)pyrimidin-4(3*H*)-one;

(*R*)-1-((1-(3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-4-phenyl-5-(piperidine-1-carbonyl)pyridin-2(1*H*)-one;

(*R*)-2-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenylpyridazin-3(2*H*)-one;

(*R*)-4-(2-Cyanophenyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

(*R*)-3-((1-(3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-((1-(2-(Cyclohexylmethyl)butanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

rac-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(*cis*-2-phenylcyclopropanecarbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

6-(2-Fluorophenyl)-3-((4-hydroxy-1-(1-methylcyclohexanecarbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

3-((*S*)-1-(1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)propyl)-6-phenylpyrimidin-4(3*H*)-one;

3-((*R*)-1-(1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)propyl)-6-phenylpyrimidin-4(3*H*)-one;

(*R*,*S*)-3-((1-(3-Cyclohexyl-2-hydroxypropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carbaldehyde;

(*R*)-5-((Dimethylamino)methyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

3-((*R*)-1-(4-Hydroxy-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)ethyl)-6-phenylpyrimidin-4(3*H*)-one;

3-((*S*)-1-(4-Hydroxy-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)ethyl)-6-phenylpyrimidin-4(3*H*)-one;

(*R*)-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(4,4,4-trifluoro-3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-3-((1-(3-Cyclohexyl-2-fluoropropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

3-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

3-(((*R*)-6-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-9-hydroxy-6-azaspiro[3.5]nonan-9-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-(((*S*)-6-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-9-hydroxy-6-azaspiro[3.5]nonan-9-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-5-(3-(Aminomethyl)phenyl)-1-((1-(3-cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-4-(2-fluorophenyl)pyridin-2(1*H*)-one;

3-(((*S*)-4-Hydroxy-3,3-dimethyl-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

3-(((*R*)-4-Hydroxy-3,3-dimethyl-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

(*R*)-6-(4-Fluorophenoxy)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(2-oxopyrrolidin-1-yl)-4-phenylpyridin-2(1*H*)-one;

6-(2-Fluorophenyl)-3-((4-hydroxy-1-(1-methyl-4-methylenecyclohexanecarbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-3-((1-(3-Cyclobutyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-3-((1-(3-Cycloheptyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-((1-(3-Cyclobutyl-2,2-dimethylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

6-(2-Fluorophenyl)-3-(((1*R*,5*S*)-8-hydroxy-3-((*R*)-3-phenylbutanoyl)-3-azabicyclo[3.2.1]octan-8-yl)methyl)pyrimidin-4(3*H*)-one;

3-(((*R*)-4-Hydroxy-2,2-dimethyl-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

3-(((*S*)-4-Hydroxy-2,2-dimethyl-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(4-hydroxypiperidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(pyrrolidine-1-carbonyl)pyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(1,4-dioxa-8-azaspiro[4.5]decane-8-carbonyl)pyridin-2(1*H*)-one;

(*R*)-*N*-Cyclohexyl-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(*cis*-2-phenylcyclopropane-1-carbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-3-((1-(3-Cyclohexyl-1H-pyrazole-4-carbonyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(3-phenylpropanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(1-isobutyl cyclopropane-1-carbonyl)-3,3-dimethylpiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(3-methyl-3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*S*)-1-((1-(4,4-Difluoro-3-phenylbutanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((4-Hydroxy-1-(1-(thiophen-2-yl)cyclopropane-1-carbonyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(2-(hydroxymethyl)phenyl)pyrimidin-4(3*H*)-one;

(*R*)-*N*,*N*-Diethyl-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

3-((1-(3-Cyclohexylbutanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(morpholine-4-carbonyl)-4-phenylpyridin-2(1*H*)-one;

(*R*,*S*)-3-((1-(3-Cyclohexylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-1-((1-(3-Cyclobutylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*,*S*)-1-((1-(2-Ethylhexanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R,S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(1-methylcyclohexane-1-carbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

6-(2-Fluorophenyl)-3-((1-(3-(4-fluorophenyl)propanoyl)-4-hydroxypiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-3-((1-(3-Cyclopropylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

1-((1-(2,2-Dimethylbutanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-*N*-(2-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-1,6-dihydropyrimidin-4-yl)phenyl)acetamide;

(*R*)-5-(4-(Aminomethyl)phenyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-1-((1-(3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(piperidine-1-carbonyl)pyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-4-(2-methoxyphenyl)-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

(*R*)-4-(2-Fluorophenyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

(*R*)-1'-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4'-phenyl-[2,3'-bipyridin]-6'(1'*H*)-one;

1-((1-(3-Cyclohexylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-*tert*-Butyl 4-(1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carbonyl)piperazine-1-carboxylate;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-(*p*-tolyl)-1,6-dihydropyridine-3-carboxamide;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-methoxy-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4,5-diphenylpyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-[3,3'-bipyridin]-6(1*H*)-one;

(*R*)-5-(3-(Aminomethyl)phenyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-(*m*-tolyl)-1,6-dihydropyridine-3-carboxamide;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(pyrimidin-5-yl)pyridin-2(1*H*)-one;

(*R*)-*N*-(Cyclopropylmethyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-*N*-Benzyl-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-2-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridin-3-yl)benzonitrile;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-methyl-6-oxo-*N*,4-diphenyl-1,6-dihydropyridine-3-carboxamide;

3-(1-(1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)ethyl)-6-phenylpyrimidin-4(3*H*)-one;

(R)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(1-methyl-1H-pyrazol-4-yl)-4-phenylpyridin-2(1H)-one;

(*R*)-3-((1-(2-(Cyclohexylmethyl)pent-4-enoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-methyl-4-phenylpyridin-2(1*H*)-one;

(*R*)-6-(1,5-Dimethyl-1*H*-pyrazol-4-yl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

3-(((1*R*,5*S*)-3-(3-Cyclohexylpropanoyl)-8-hydroxy-3-azabicyclo[3.2.1]octan-8-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carbonitrile;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-(2-hydroxyethyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((4-Hydroxy-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-5-((*S*)-2-methylpyrrolidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(4-(hydroxymethyl)piperidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

3-((1-(2-(Cyclohexylmethyl)butanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenyl-5-(pyrrolidine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

3-((1-(2-(Cyclohexyloxy)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((1-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((1-((*R*)-3-Cyclopropyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-[4,5'-bipyrimidin]-6(1*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(1-methyl-1*H*-pyrazol-5-yl)pyrimidin-4(3*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(1*H*-pyrazol-4-yl)pyrimidin-4(3*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(1*H*-pyrazol-5-yl)pyrimidin-4(3*H*)-one;

3-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(thiophen-3-yl)pyrimidin-4(3*H*)-one;

1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(oxazol-2-yl)-4-phenylpyridin-2(1*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-(hydroxymethyl)phenyl)pyrimidin-4(3*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(3-(hydroxymethyl)phenyl)pyrimidin-4(3*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(4-(hydroxymethyl)phenyl)pyrimidin-4(3*H*)-one;

6-(4-(Aminomethyl)phenyl)-3-((1-((*R*)-3-cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

6-(2-(Aminomethyl)phenyl)-3-((1-((*R*)-3-cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(2,4,4-trimethylpentanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(4,4,4-trifluoro-2-methylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

4-Chloro-1-((7-((*R*)-3-cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(dimethylamino)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((1-((*S*)-3-(Benzyloxy)-2-(cyclohexylmethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

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

1-((7-((*R*)-3-Cyclopropyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(2-methyl-3-(1*H*-pyrazol-1-yl)propanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-(hydroxymethyl)phenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*S*)-3-Cyclohexyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*S*)-3-Cyclohexyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1'-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4'-(2-fluorophenyl)-[2,3'-bipyridin]-6'(1'*H*)-one;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-(thiophen-3-yl)-1,6-dihydropyridine-3-carboxamide;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(3-(hydroxymethyl)phenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((7-(3-Cyclohexyl-2-hydroxypropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((10-Hydroxy-7-(2-methyl-3-(piperidin-1-yl)propanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

6-(3-(Aminomethyl)phenyl)-3-((1-((*R*)-3-cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

1-(((*S*)-1-((*S*)-3-Cyclohexyl-2-(methoxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

4-(2-(Aminomethyl)phenyl)-1-((7-((*R*)-3-cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(4-(hydroxymethyl)phenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((10-Hydroxy-7-(2-methyl-3-morpholinopropanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*S*)-2-(Cyclohexylmethyl)-4-hydroxybutanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*S*)-2-(Cyclohexylmethyl)-4-hydroxybutanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*S*)-3-Cyclobutyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*S*)-3-Cyclobutyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(morpholine-4-carbonyl)-4-phenylpyridin-2(1*H*)-one;

5-(4-Acetylpiperazine-1-carbonyl)-1-((1-((*R*)-3-cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(4-methylpiperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

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

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

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

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

1-((7-(Cyclopropanecarbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

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

1-((7-(1-(2,2-Difluoroethyl)cyclopropane-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(Bicyclo[2.2.1]heptane-1-carbonyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-((*S*)-4,4-Difluoro-3-phenylbutanoyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-((*R*)-4,4-Difluoro-3-phenylbutanoyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(3-Ethoxypropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

1-((7-(3-(4-Fluorophenyl)propanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

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

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

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

1-((7-(3-Cyclohexyl-1*H*-pyrazole-4-carbonyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

1-((7-(Bicyclo[1.1.1]pentane-1-carbonyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((10-Hydroxy-7-(5-phenyloxazole-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(5-Cyclopropyloxazole-4-carbonyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(2-(Cyclohexyloxy)acetyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((10-Hydroxy-7-(spiro[2.2]pentane-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

1-((7-(2,4-Dimethylpentanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(1-Benzyl-1*H*-pyrrole-2-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(2-(Cyclohexyloxy)propanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

3-((1-((*S*)-3-Cyclobutyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

1-((7-(2-Cyclobutoxyacetyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

1-((10-Hydroxy-7-(2-hydroxy-3-phenylpropanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-4-Hydroxy-3,3-dimethyl-1-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)piperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

(*S*)-1-((4-Hydroxy-3,3-dimethyl-1-(4,4,4-trifluoro-2-(2,2,2-trifluoroethyl)butanoyl)piperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-((*S*)-2-(hydroxymethyl)piperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

1-(((*R*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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(1*H*)-one;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-((*R*)-3-methylpiperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

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

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

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

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

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-cyclopropyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

4-(2-Fluorophenyl)-1-(((*S*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

4-(2-Fluorophenyl)-1-(((*S*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(4-hydroxypiperidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

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

1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-((2-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-5-hydroxy-9-oxa-2-azaspiro[5.5]undecan-5-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-((2-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((2-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

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

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

1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylic acid;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-methoxy-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((7-(4,4-Difluoro-2-methylbutanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(4,4-Difluoro-2,2-dimethylbutanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((10-Hydroxy-7-(4-(trifluoromethyl)thiazole-2-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((10-Hydroxy-7-(2-(trifluoromethyl)thiazole-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

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

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

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

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

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

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

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenyl-5-(pyrrolidine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*R*)-1-((*S*)-3-Cyclohexyl-2-(methoxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-4-Hydroxy-3,3-dimethyl-1-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)piperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-3,3-dimethyl-1-(4,4,4-trifluoro-2-(2,2,2-trifluoroethyl)butanoyl)piperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-((*S*)-2-(hydroxymethyl)piperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-((*R*)-3-methylpiperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

1-(((*R*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

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

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

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

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

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-cyclopropyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*R*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

4-(2-Fluorophenyl)-1-(((*R*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

4-(2-Fluorophenyl)-1-(((*R*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*R*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

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

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(4-hydroxypiperidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

1-(((*R*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*R*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

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

1-(((*R*)-1-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

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

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

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

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

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

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

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

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

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

3-((10-Hydroxy-7-((3*R*,4*R*)-3-phenylpiperidine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

3-(((*S*)-10-Hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

6-(2-Fluorophenyl)-3-(((*S*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one;

6-(3-Fluorophenyl)-3-(((*S*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one;

3-(((*S*)-7-((*R*)-4,4-Difluoro-2-methylpentanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

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

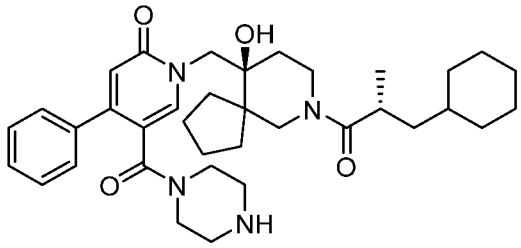
3-(((*S*)-10-Hydroxy-7-((3*R*,4*S*)-4-phenylpyrrolidine-3-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

3-(((*S*)-10-Hydroxy-7-((2*R*,3*R*)-2-phenylpyrrolidine-3-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

3-(((*S*)-10-Hydroxy-7-((2*S*,3*S*)-2-phenylpyrrolidine-3-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

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

In a preferred embodiment, the compound for use in the methods of treatment in accordance with the invention is the compound of Example 212 herein: 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:



This compound and its synthesis is provided as Example 212 of WO2018/020242 (page 217), which is expressly incorporated herein by reference.

In a further aspect is provided the compound 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(1*H*)-one for use in therapy.

In a further aspect is provided the compound 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(1*H*)-one for use in a method of treating muscular atrophy.

In a further aspect is provided the compound 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(1*H*)-one for use in a method of treating obesity.

In a further aspect is provided the compound 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(1*H*)-one for use in a method of treating insulin resistance.

In a further aspect is provided the compound 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(1*H*)-one for use in a method of treating type II diabetes.

In a further aspect is provided the compound 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(1*H*)-one for use in a method of treating cachexia or sarcopenia.

Compounds disclosed herein for use according to the invention are hereby also disclosed and provided in accordance with the invention as compounds *per se*.

Pharmaceutical compositions for use according to the invention

In a further aspect the present invention provides a pharmaceutical composition for use in a method of therapy, the pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined herein.

Also provided in accordance with the invention is a pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined herein, for use in a method of treating muscular atrophy.

Also provided in accordance with the invention is a pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined herein, for use in a method of obesity.

Also provided in accordance with the invention is a pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined herein, for use in a method of treating insulin resistance.

Also provided in accordance with the invention is a pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined herein, for use in a method of treating type II diabetes.

In certain embodiments of the invention, the pharmaceutical composition for use in methods of the invention further comprises a pharmaceutically acceptable diluent, excipient or carrier.

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.

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, 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 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 such as gelatin, talc, plant oil and gum arabic.

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.
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 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 excipients. Examples of suitable excipients include lactose, mize 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.

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

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, solublizing agents, stabilizing agents, wetting agents, emulsifiers, sweeteners, colorants, odorants, buffers, coating agents and/or antioxidants.

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

Routes of administration

In certain preferred embodiments, of the methods according to the invention, the method 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.

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.

Dosage regimen

In certain preferred embodiments of the methods 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) 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.

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

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

In certain preferred embodiments, the method 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.

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.

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 administered at a daily dosage of 150mg/kg.

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

In a preferred aspect of all aspects of the invention, the subject or patient to be treated is a human.

EXAMPLES

The compounds described herein were first described in WO2018/020242 and the content of this document describing the synthesis and activity of these compounds is expressly incorporated herein by reference.

In vitro activity

As described in WO2018/020242, the compounds were assessed *in vitro* for their ability to inhibit USP19 activity. The results are shown in Table 1.

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	*	67	**	133	***	199	**
2	*	68	**	134	**	200	***
3	*	69	**	135	****	201	**
4	*	70	**	136	***	202	*
5	**	71	**	137	***	203	***
6	**	72	*	138	****	204	***
7	***	73	****	139	****	205	****
8	**	74	*	140	***	206	****
9	**	75	***	141	****	207	**
10	*	76	***	142	*	208	****
11	*	77	***	143	**	209	**
12	**	78	***	144	****	210	**
13	*	79	***	145	****	211	****
14	***	80	**	146	***	212	****
15	**	81	*	147	*	213	****
16	**	82	*	148	**	214	****
17	**	83	*	149	****	215	****
18	**	84	*	150	*	216	****
19	**	85	*	151	**	217	****
20	**	86	**	152	****	218	***
21	**	87	***	153	**	219	***
22	**	88	***	154	**	220	***
23	**	89	***	155	****	221	***
24	**	90	***	156	****	222	****
25	***	91	***	157	****	223	***
26	*	92	***	158	*	224	****
27	*	93	**	159	***	225	***
28	*	94	***	160	****	226	****
29	*	95	**	161	**	227	****
30	*	96	**	162	****	228	****
31	***	97	**	163	**	229	**
32	**	98	**	164	****	230	***
33	**	99	**	165	**	231	***
34	*	100	**	166	****	232	****
35	*	101	**	167	**	233	****
36	***	102	***	168	****	234	***
37	*	103	**	169	****	235	***
38	*	104	**	170	****	236	****
39	**	105	**	171	*	237	****
40	**	106	**	172	**	238	****
41	**	107	**	173	*	239	****
42	**	108	***	174	****	240	****
43	**	109	*	175	*	241	***
44	**	110	***	176	**	242	***

45	*	**111**	*	**177**	*	**243**	**
46	*	**112**	*	**178**	*	**244**	**
47	*	**113**	*	**179**	*	**245**	**
48	*	**114**	**	**180**	**	**246**	**
49	*	**115**	**	**181**	***	**247**	****
50	****	**116**	***	**182**	**	**248**	****
51	***	**117**	***	**183**	**	**249**	****
52	***	**118**	***	**184**	***	**250**	****
53	***	**119**	****	**185**	***	**251**	****
54	*	**120**	****	**186**	*	**252**	****
55	**	**121**	****	**187**	*	**253**	****
56	**	**122**	*	**188**	*	**254**	****
57	**	**123**	****	**189**	***	**255**	****
58	**	**124**	****	**190**	*	**256**	****
59	**	**125**	**	**191**	*	**257**	****
60	**	**126**	*	**192**	**	**258**	****
61	*	**127**	***	**193**	**	**259**	****
62	***	**128**	***	**194**	**	**260**	****
63	***	**129**	**	**195**	**		
64	**	**130**	***	**196**	***		
65	**	**131**	***	**197**	****		
66	N.D.	**132**	**	**198**	**		

Table 1. *USP19 inhibition by exemplified compounds*

For representative examples in **Table 1**, USP19 inhibitory activities are classified as the following:

	****	***	**	*	N.D.
USP19 IC_{50} [μM]	IC_{50}<0.5	0.5≤IC_{50}<5	5≤IC_{50}<50	50≤IC_{50}<250	Not determined

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 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, room temperature) using the Storage Pod System 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 (IC_{50}) were calculated using the non-linear regression curve fitting model using GraphPad (Prism). IC_{50} values for the inhibitors of the invention are compiled in Table 1 and represent the average of at least two duplicate experiments.

Cell target engagement

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, corresponding to Example 212 provided herein) for 2 hrs, lysed (lysis buffer: 50mM Tris pH 7.4; 150mM NaCl; 5mM MgCl2; 0.5mM EDTA; 0.5% NP40; 10% Glycerol; 2mM 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 (EC_{50} determined by densitometry).

In each cell line, the USP19 inhibitor compound showed good cell permeability and exhibited a low nanomolar EC_{50}. The results for each cell line are shown in Figure 5.

In vivo activity

The *in vitro* activity data described in WO2018/020242 and reproduced above indicated that the compounds provided in that document and herein could have therapeutic utility due to their ability to inhibit USP19.

The following data from an *in vivo* model is the first demonstration 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.

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

Mice were randomised into Vehicle or Test groups, with all animals weighed to ensure a similar mean weight in each group. A USP19 inhibitory compound (ADC-141, which 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(1*H*)-one, corresponding to exemplary compound 212 provided herein) at 75 mg/kg or Vehicle was administered IP twice daily starting from the evening post-operation.

Mice were sacrificed 14 days later. Fat pads, liver, gastrocnemius and tibialis anterior muscles were harvested. Tissue mass 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.

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 5mg/kg or 25mg/kg, or positive control liraglutide 0.1mg/kg s.c. BID. Mice were allocated to treatment groups to balance the groups on the basis of body weight, food and water intake prior to the start of treatment.

Body weight was measured daily. On Day 13, body composition was 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 (approx. 16h post fast). Mice were dosed with vehicle or test compound (starting at 08.45) to a timed schedule 30 minutes prior to the administration of the glucose challenge (2.0 g/kg po). Blood samples were taken immediately prior to dosing (B1), immediately prior to glucose administration (B2) and 15, 30, 60 and 120 minutes after glucose administration.

After OGTT, mice were humanely killed and carcass composition was assessed. The carcass was weighed and stored frozen and the chemical composition of each carcass (fat, protein, water and ash) was determined using classical techniques. Carcass water was

determined by freeze-drying the carcasses to constant weight for 2 weeks. Carcass fat was determined on samples of the dry powdered carcasses using a modified Soxhlet extraction protocol (petroleum ether at 40-60°C) with a Tecator Soxtec 2050 system (Foss UK Ltd, Wheldrake, UK) according to the manufacturer's recommended protocol. Carcass protein was determined using a micro-Kjeldahl procedure on samples of the dry powdered carcasses using a Tecator 2012 digestion block and 2200 distilling unit (Foss UK Ltd). Residual carcass ash was determined by firing samples of the dry powdered carcasses at high temperatures using a muffle ashing furnace (Carbolite OAF 11/1). Repeat determinations of the chemical analysis parameters were performed if necessary (e.g. if the duplicate samples differed by more than 1%). Data for each body composition parameter (fat, protein, water and ash) was determined as g/carcass and % total. Final carcass weights were also analysed as a direct comparison.

Results:

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).

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).

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.

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.

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.

Figure 3C shows that mice receiving USP19 inhibitor exhibited a reduction in overall body weight gain when on a high-fat diet. Average weekly body weight gain was significantly decreased by USP19 inhibitor (25 mg/kg ip bid) in week 1 and 2 ($p<0.001$ and $p<0.01$ respectively). In contrast, Liraglutide significantly decreased body weight gain in week 1 ($p<0.001$) but not week 2 ($p>0.05$).

Figures 3D and 3E show USP19 inhibitor treated mice exhibited a reduction in fat mass by 24% compared to the vehicle treated controls ($p<0.001$), but that lean body mass does not change significantly (-3%; $p>0.05$. Similarly, Liraglutide (0.1 mg/kg sc bid) significantly reduced fat mass (g) by 19% compared to the vehicle treated controls ($p<0.001$), but in contrast it also significantly reduced lean mass (g) by 8% ($p<0.01$).

When fat and lean mass were expressed as a percentage of total tissue mass, USP19 inhibitor (25 mg/kg ip bid) significantly decreased fat mass % and increased lean mass % ($p<0.001$). In contrast, Liraglutide did not significantly change fat or lean mass % ($p=0.069$).

Thus, DEXA analysis showed that administration of a USP19 inhibitor (ADC-141) caused a significant reduction in total tissue mass, which was primarily attributed to a reduction in fat mass, with no significant change in lean mass.

Figure 4 shows body composition data determined based on carcass material. USP19 inhibitor (25 mg/kg ip bid) and Liraglutide (0.1 mg/kg sc bid) significantly decreased carcass weight compared to that of vehicle-treated controls (c. -12%; $p<0.001$). Reductions in carcass weight observed following two weeks administration of USP19 inhibitor (25 mg/kg ip bid) and Liraglutide (0.1 mg/kg sc bid) closely reflected differences in body weights on the final day of the study (c. 13%).

USP19 inhibitor (5 and 25 mg/kg ip bid) had no significant effect on carcass water content, whereas Liraglutide caused a significant reduction in carcass water content (g; -8.6%; $p<0.001$). When expressed as a percentage of total carcass mass, USP19 inhibitor (25 mg/kg ip bid) increased the relative water content of the carcass (+ 11.4%; $p<0.001$) whereas ADC-141 (5 mg/kg ip bid) and Liraglutide (0.1 mg/kg sc bid) had no effect on this parameter.

USP19 inhibitor ADC-141 (25 mg/kg ip bid) produced a 24.9% reduction in carcass fat (g; $p<0.001$) from controls. Liraglutide (0.1 mg/kg sc bid) produced a 17.4% reduction in carcass fat (g; $p<0.01$) (Figure 4). When expressed as a percentage, only ADC-141 (25 mg/kg ip bid) significantly reduced the carcass percentage fat (-14.6%; $p<0.001$). Overall, the loss of fat accounted for 79% of the total weight lost for ADC-141 (25 mg/kg ip bid) and 60% for Liraglutide (0.1 mg/kg sc bid).

Carcass protein content (g) was significantly decreased by USP19 inhibitor ADC-141 (25 mg/kg ip bid; -7.2%; $p<0.05$) and Liraglutide (0.1 mg/kg sc bid; -7.9%; $p<0.05$). However, when expressed as a percentage of total carcass mass, percent protein was significantly increased (6.0% and 5.7% respectively; $p<0.05$; Figure 4). The lowest dose of ADC-141 (5 mg/kg ip bid) produced no significant changes in carcass protein when compared to vehicle-treated animals.

Carcass ash content (g) was significantly reduced by USP19 inhibitor ADC-141 (25 mg/kg ip bid; -9.6%; $p<0.05$) and Liraglutide (0.1 mg/kg sc bid; -11.6%; $p<0.01$). However, when expressed as a percentage of total carcass mass, there was no significant difference in carcass ash for any of the treatment groups in comparison to control values (Figure 4).

DIO mice treated with USP19 inhibitor also exhibited a reduction in cumulative and average food intake compared to vehicle control mice ($p<0.001$).

In conclusion, administration of USP19 inhibitor (25 mg/kg ip bid) produced a marked reduction in carcass weight, which was primarily attributed to a significant loss of fat mass, with a small contribution from the loss of protein and ash. Effective weight loss agents typically produce weight loss consisting of 70-90% from fat, with the remainder consisting of a small compensatory decrease in protein, ash and water. Therefore, the effect of the USP19 inhibitor ADC-141 to target the loss of fat mass *per se* is consistent with the desirable effects of anti-obesity agents in the DIO mouse model.

The data shown in Figures 3 and 4 is the first demonstration 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 *et al*, *Diabetologia*. 2018 Nov 1. doi: 10.1007/s00125-018-4754-4., incorporated herein by reference). However, acute or chronic pharmacological inhibition of an enzyme does not always result in similar physiological outcomes to genetic ablation.

It is notable also that UP19 inhibition is able to reduce fat accumulation while preserving or increasing relative body protein and ash content.

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

Insulin resistance

Figure 6 shows the results of an oral glucose tolerance test (OGTT) in mice with diet-induced obesity.

Mice responded to the glucose load as expected, with a sharp increase in plasma glucose and insulin which diminished by 120 minutes post-glucose. USP19 inhibitor ADC-141 (25 mg/kg ip bid) significantly reduced plasma glucose at all time points pre- and post-glucose (Figure 6A) and glucose AUC (Figure 6B) and AUCB2 (0-120 minutes only), compared to the vehicle group. USP19 inhibitor ADC-141 (25 mg/kg ip bid) also reduced plasma insulin at 30, 60 and 120 minutes post-glucose, and insulin AUC (0-60 and 0-120 minutes; Figure 6C).

Following 2 weeks of treatment, USP19 inhibition was effective at decreasing fasting plasma glucose whilst maintaining plasma insulin levels similar to that of the controls, indicating improved insulin sensitivity. Consistent with these observations in the fasted state, when challenged with a glucose load USP19 inhibition led to improved glucose disposal and stimulated a diminished increase in plasma insulin (at 30, 60 and 120 minutes) compared to that of the controls. Therefore, treatment with a USP19 inhibitor was effective at improving insulin sensitivity and glucose tolerance in the DIO mouse model of insulin resistance.

The data shown in Figure 6 is the first demonstration that pharmacological inhibition of USP19 can reduce insulin resistance in a wild-type background. Gene knockout studies have also 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.

The data provided herein is the first demonstration that pharmacological inhibition of USP19 effectively treats insulin resistance.

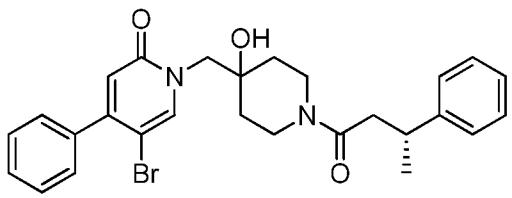
The data presented herein is the first demonstration of the therapeutic effects of pharmacological inhibition of USP19. Accordingly, USP19 inhibitors, for example those compounds provided herein and disclosed in WO2018/020242, can effectively treat muscular atrophy, obesity, insulin resistance and/or cancer.

Experimental

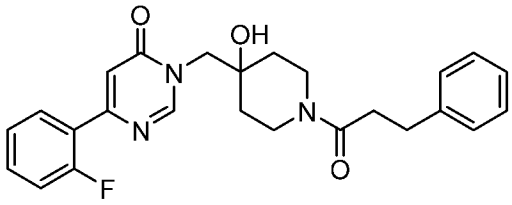
The content of WO2018/020242 is expressly incorporated herein by reference in its entirety.

The following USP19 inhibitory compounds were first described in WO2018/020242, where their synthesis is provided in detail. The Example numbers provided below correspond to the Examples of WO2018/020242. As well as the content of WO2018/020242 in general, the synthesis of the compounds below that is provided by pages 45 to 251 of WO2018/020242 is expressly incorporated herein by reference in particular.

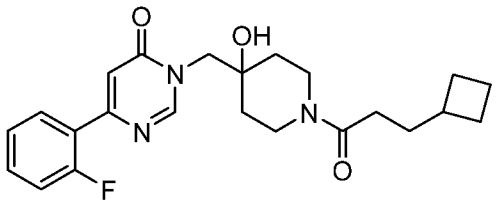
Example 1: (*R*)-5-Bromo-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one



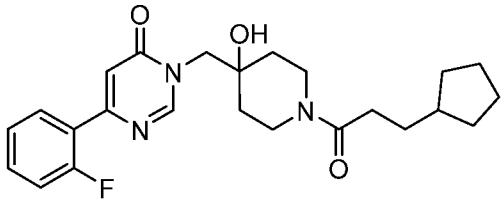
Example 2: 6-(2-Fluorophenyl)-3-((4-hydroxy-1-(3-phenylpropanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



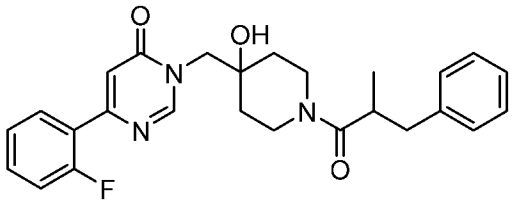
Example 3: 3-((1-(3-Cyclobutylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



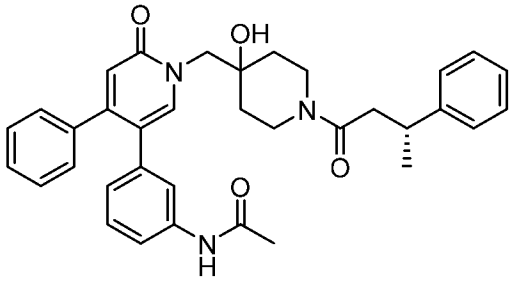
Example 4: 3-((1-(3-Cyclopentylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



Example 5: (*R,S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(2-methyl-3-phenylpropanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one

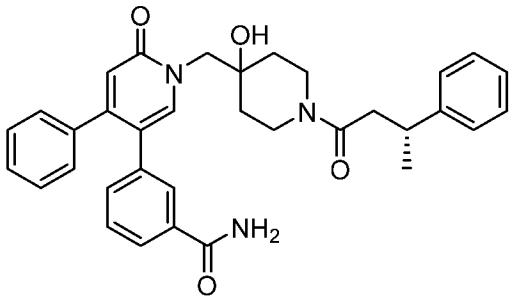


Example 6: (*R*)-*N*-(3-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridin-3-yl)phenyl)acetamide

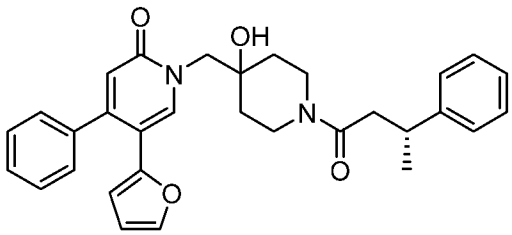


Example 7: (*R*)-3-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)6-oxo-4-phenyl-

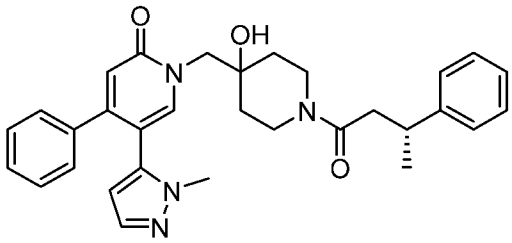
1,6-dihydropyridin-3-yl)benzamide



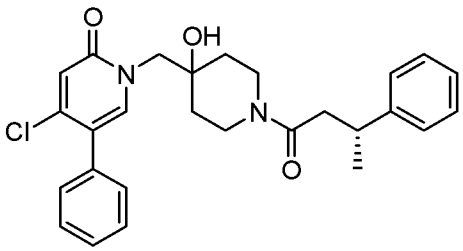
Example 8: (*R*)-5-(Furan-2-yl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one



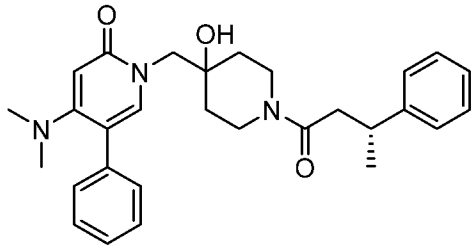
Example 9: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-4-phenylpyridin-2(1*H*)-one



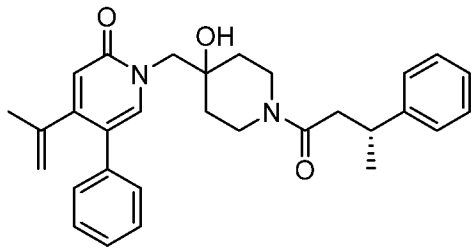
Example 10: (*R*)-4-Chloro-1-((4-hydroxy-1(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenylpyridin-2(1*H*)-one



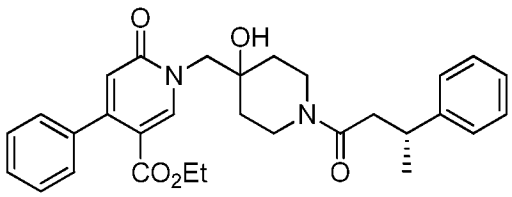
Example 11: (*R*)-4-(Dimethylamino)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenylpyridin-2(1*H*)-one



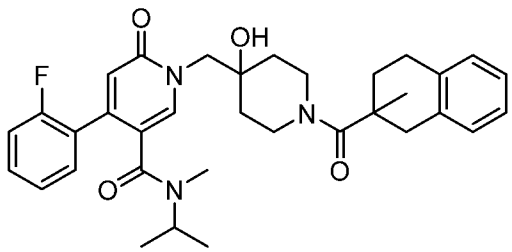
Example 12: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenyl-4-(prop-1-en-2-yl)pyridine-2(1*H*)-one



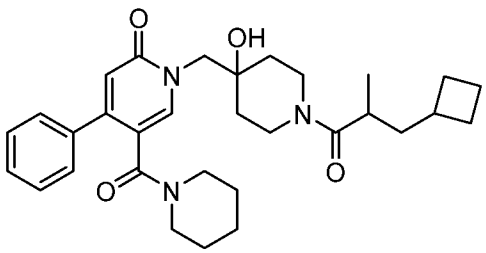
Example 13: (*R*)-Ethyl 1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate



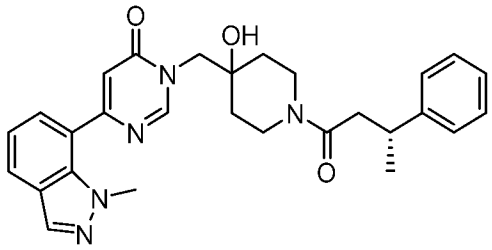
Example 14: (*R,S*)-4-(2-Fluorophenyl)-1-((4-hydroxy-1-(2-methyl-1,2,3,4-tetrahydronaphthalene-2-carbonyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide



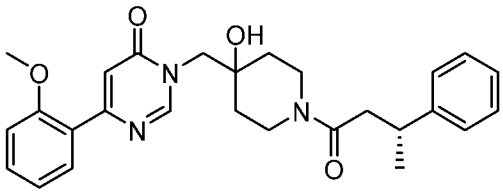
Example 15: (*R,S*)-1-((1-(3-Cyclobutyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-4-phenyl-5-(piperidine-1-carbonyl)pyridin-2(1*H*)-one



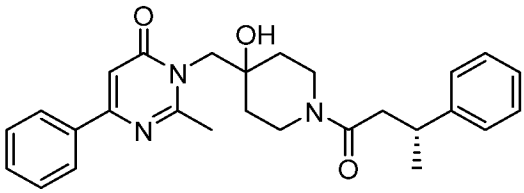
Example 16: (*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(1-methyl-1H-indazol-7-yl)pyrimidin-4(3*H*)-one



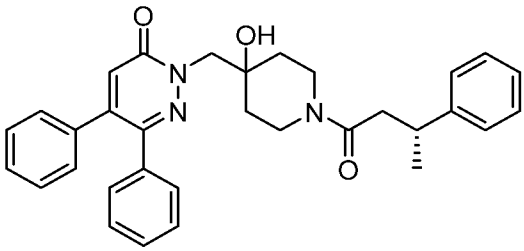
Example 17: (*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(2-methoxyphenyl)pyrimidin-4(3*H*)-one



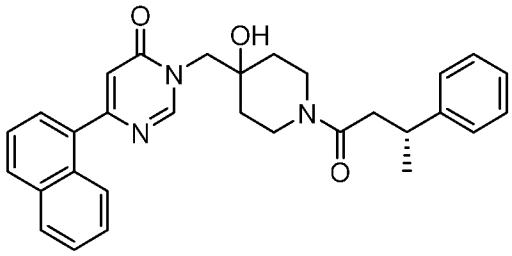
Example 18: (*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-2-methyl-6-phenylpyrimidin-4(3*H*)-one



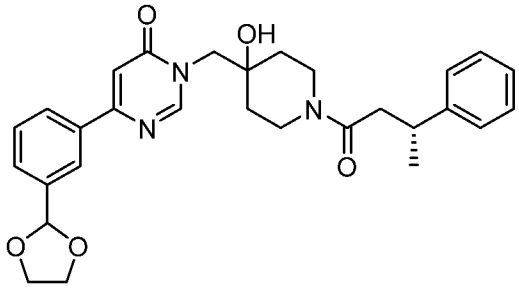
Example 19: (*R*)-2-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5,6-diphenylpyridazin-3(2*H*)-one



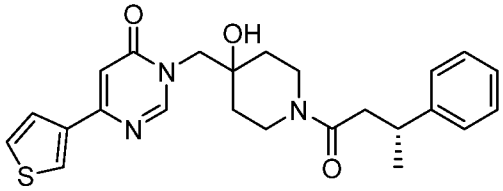
Example 20: (*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(naphthalen-1-yl)pyrimidin-4(3*H*)-one



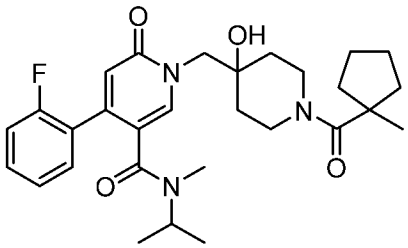
Example 21: (*R*)-6-(3-(1,3-Dioxolan-2-yl)phenyl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



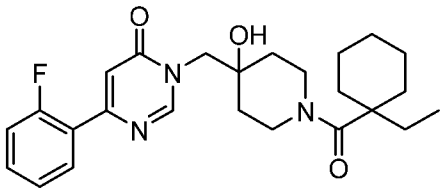
Example 22: (*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(thiophen-3-yl)pyrimidin-4(3*H*)-one



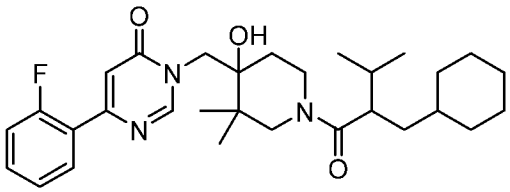
Example 23: 4-(2-Fluorophenyl)-1-((4-hydroxy-1-(1-methylcyclopentane-1-carbonyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide



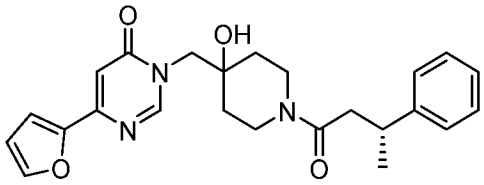
Example 24: 3-((1-(1-Ethylcyclohexane-1-carbonyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



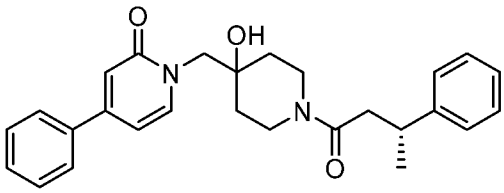
Example 25: 3-((1-(2-(Cyclohexylmethyl)-3-methylbutanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



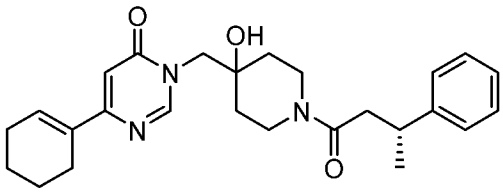
Example 26: (*R*)-6-(Furan-2-yl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



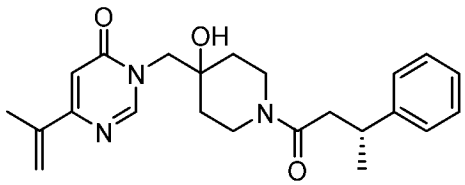
Example 27: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one



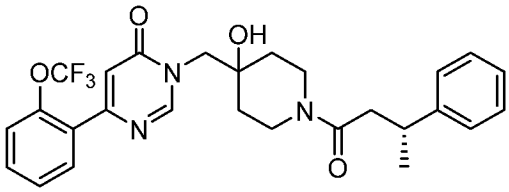
Example 28: (*R*)-6-(Cyclohex-1-en-1-yl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



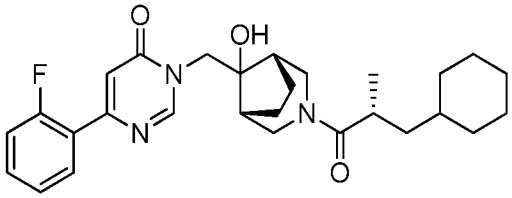
Example 29: (*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(prop-1-en-2-yl)pyrimidin-4(3*H*)-one



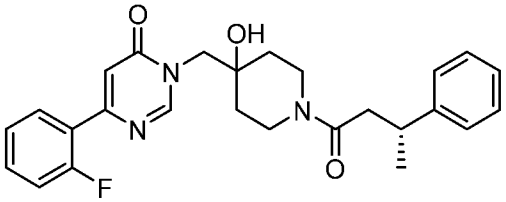
Example 30: (*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(2-(trifluoromethoxy)phenyl)pyrimidin-4(3*H*)-one



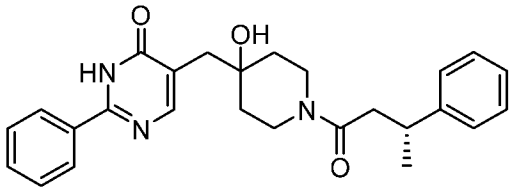
Example 31: 3-(((1*R*,5*S*)-3-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-8-hydroxy-3-azabicyclo[3.2.1]octan-8-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



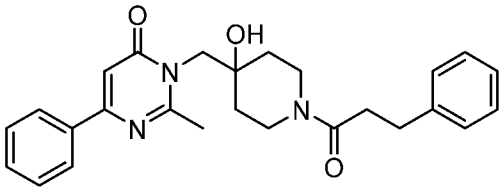
Example 32: (*R*)-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



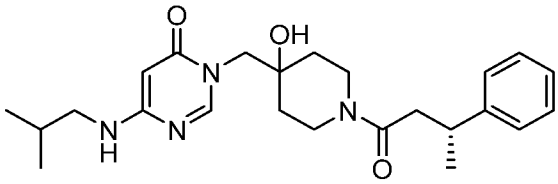
Example 33: (*R*)-5-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-2-phenylpyrimidin-4(3*H*)-one



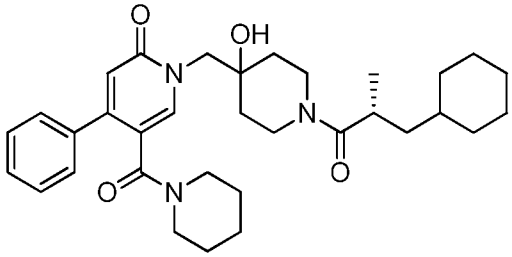
Example 34: 3-((4-Hydroxy-1-(3-phenylpropanoyl)piperidin-4-yl)methyl)-2-methyl-6-phenylpyrimidin-4(3*H*)-one



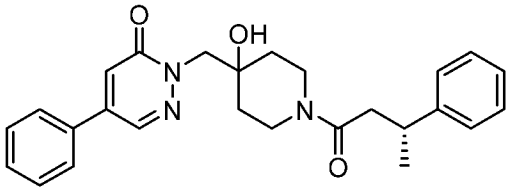
Example 35: (*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(isobutylamino)pyrimidin-4(3*H*)-one



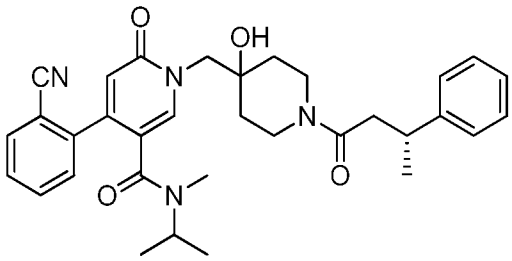
Example 36: (*R*)-1-((1-(3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-4-phenyl-5-(piperidine-1-carbonyl)pyridin-2(1*H*)-one



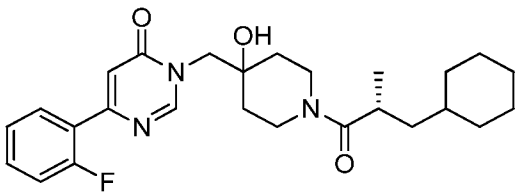
Example 37: (*R*)-2-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenylpyridazin-3(2*H*)-one



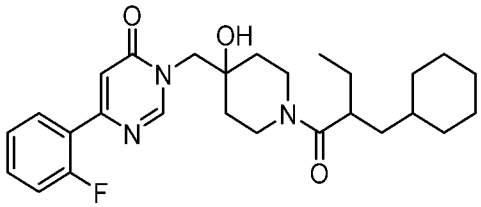
Example 38: (*R*)-4-(2-Cyanophenyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide



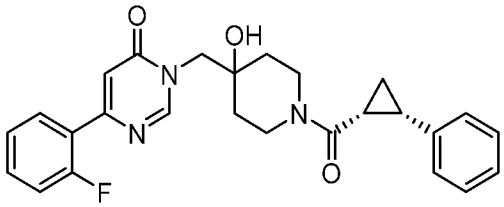
Example 39: (*R*)-3-((1-(3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



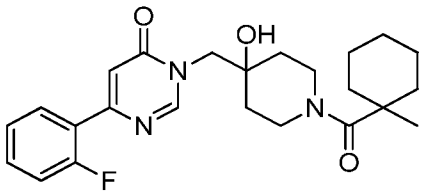
Example 40: 3-((1-(2-(Cyclohexylmethyl)butanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



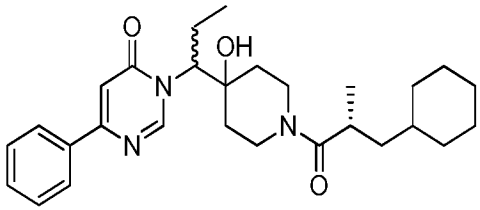
Example 41: *rac*-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(*cis*-2-phenylcyclopropanecarbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



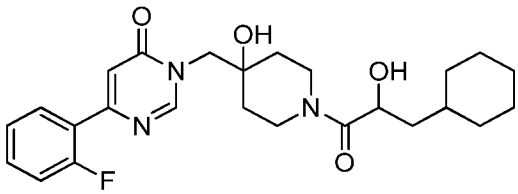
Example 42: 6-(2-Fluorophenyl)-3-((4-hydroxy-1-(1-methylcyclohexanecarbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



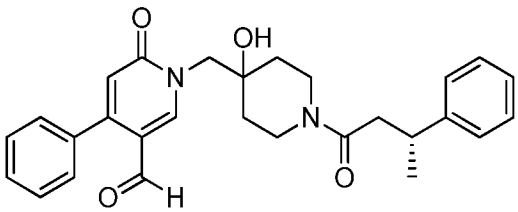
Example 43: 3-((*S*)-1-(1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)propyl)-6-phenylpyrimidin-4(3*H*)-one and 3-((*R*)-1-(1-((*R*)-3-cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)propyl)-6-phenylpyrimidin-4(3*H*)-one



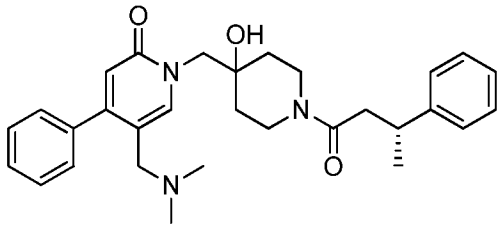
Example 44: (*R,S*)-3-((1-(3-Cyclohexyl-2-hydroxypropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



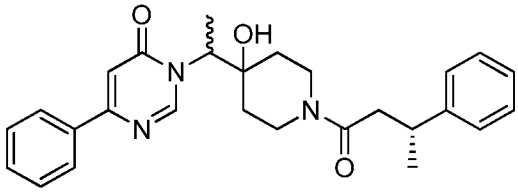
Example 45: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carbaldehyde



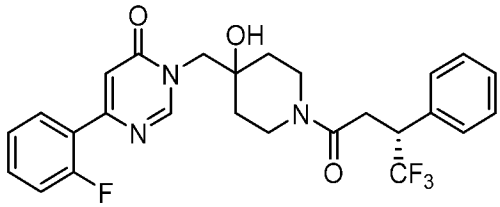
Example 46: (*R*)-5-((Dimethylamino)methyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one



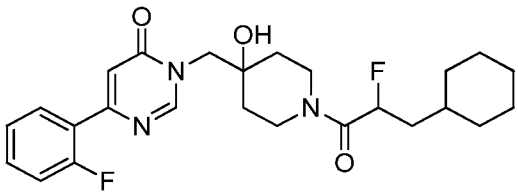
Example 47: 3-((*R*)-1-(4-Hydroxy-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)ethyl)-6-phenylpyrimidin-4(3*H*)-one and 3-((*S*)-1-(4-hydroxy-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)ethyl)-6-phenylpyrimidin-4(3*H*)-one



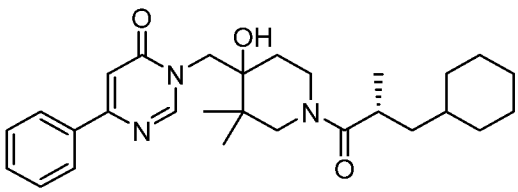
Example 48: (*R*)-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(4,4,4-trifluoro-3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



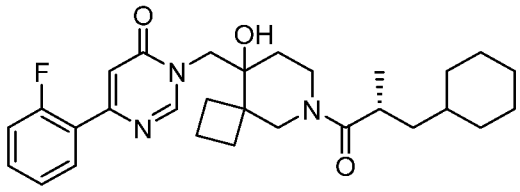
Example 49: (*R,S*)-3-((1-(3-Cyclohexyl-2-fluoropropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



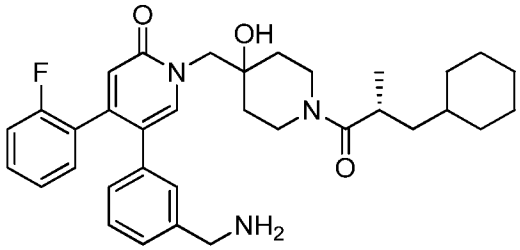
Example 50: 3-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one and 3-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one



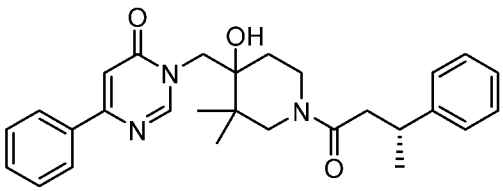
Example 51: 3-(((*R*)-6-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-9-hydroxy-6-azaspiro[3.5]nonan-9-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one and 3-(((*S*)-6-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-9-hydroxy-6-azaspiro[3.5]nonan-9-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



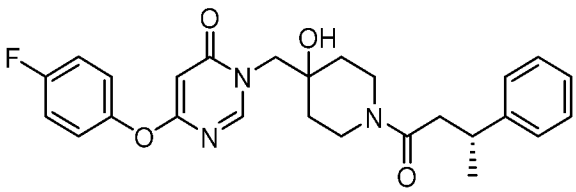
Example 52: (*R*)-5-(3-(Aminomethyl)phenyl)-1-((1-(3-cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-4-(2-fluorophenyl)pyridin-2(1*H*)-one



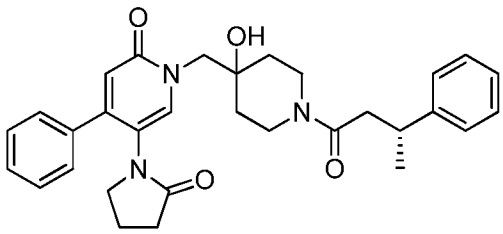
Example 53: 3-(((*S*)-4-Hydroxy-3,3-dimethyl-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one and 3-(((*R*)-4-hydroxy-3,3-dimethyl-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one



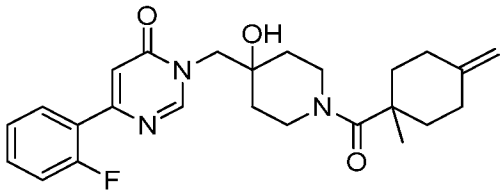
Example 54: (*R*)-6-(4-Fluorophenoxy)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



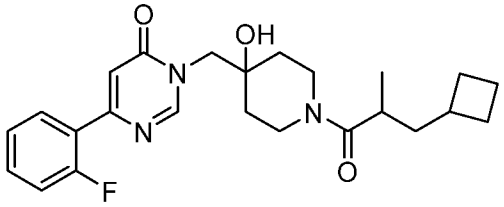
Example 55: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(2-oxopyrrolidin-1-yl)-4-phenylpyridin-2(1*H*)-one



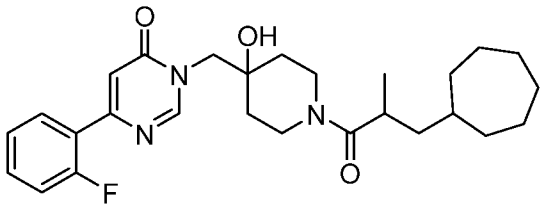
Example 56: 6-(2-Fluorophenyl)-3-((4-hydroxy-1-(1-methyl-4-methylenecyclohexanecarbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



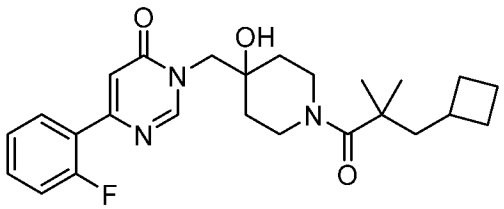
Example 57: (*R,S*)-3-((1-(3-Cyclobutyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



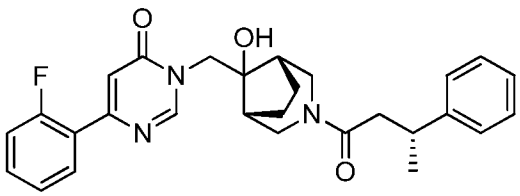
Example 58: (*R,S*)-3-((1-(3-Cycloheptyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



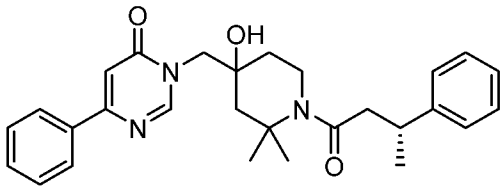
Example 59: 3-((1-(3-Cyclobutyl-2,2-dimethylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



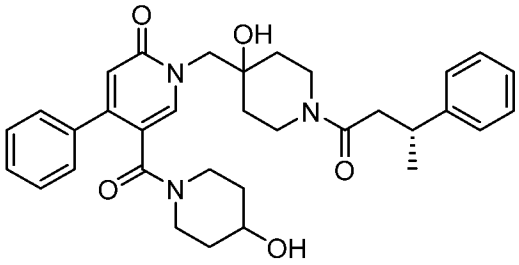
Example 60: 6-(2-Fluorophenyl)-3-(((1*R*,5*S*)-8-hydroxy-3-((*R*)-3-phenylbutanoyl)-3-azabicyclo[3.2.1]octan-8-yl)methyl)pyrimidin-4(3*H*)-one



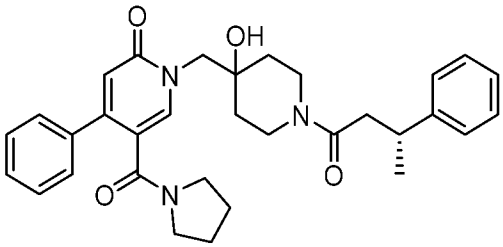
Example 61: 3-(((*R*)-4-Hydroxy-2,2-dimethyl-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one and 3-(((*S*)-4-Hydroxy-2,2-dimethyl-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one



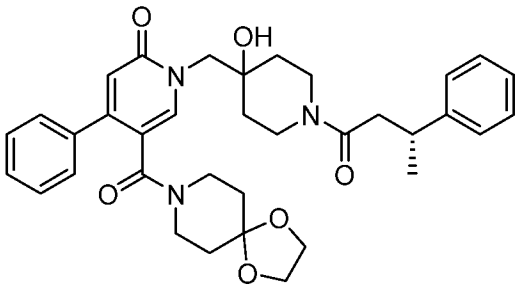
Example 62: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(4-hydroxypiperidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one



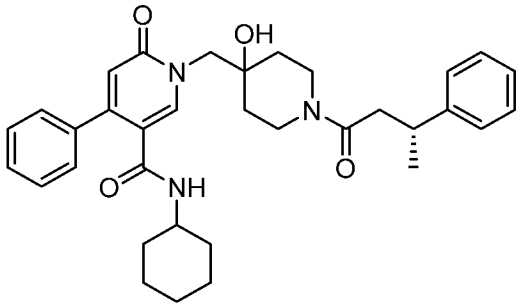
Example 63: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(pyrrolidine-1-carbonyl)pyridin-2(1*H*)-one



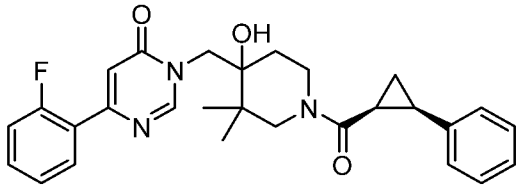
Example 64: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(1,4-dioxa-8-azaspiro[4.5]decane-8-carbonyl)pyridin-2(1*H*)-one



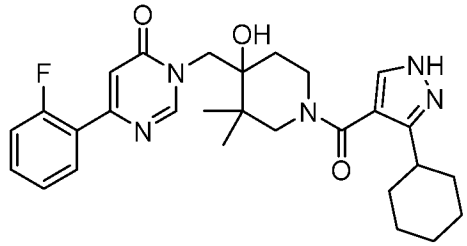
Example 65: (*R*)-*N*-Cyclohexyl-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



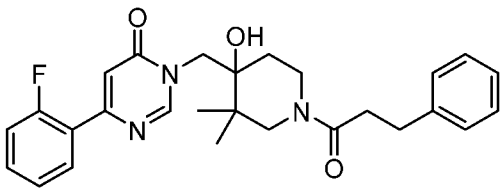
Example 66: 6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(*cis*-2-phenylcyclopropane-1-carbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



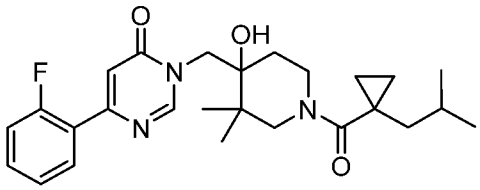
Example 67: (*R,S*)-3-((1-(3-Cyclohexyl-1*H*-pyrazole-4-carbonyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



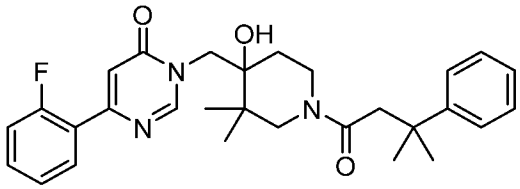
Example 68: (*R,S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(3-phenylpropanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



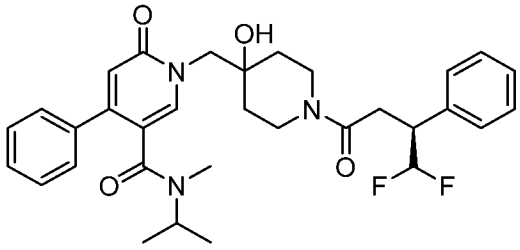
Example 69: (*R,S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(1-isobutyl cyclopropane-1-carbonyl)-3,3-dimethylpiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



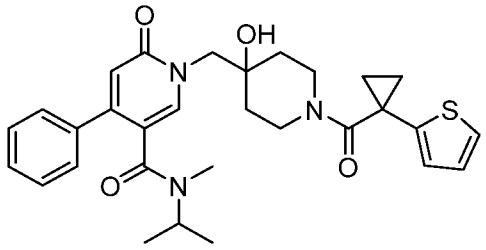
Example 70: (*R,S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(3-methyl-3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



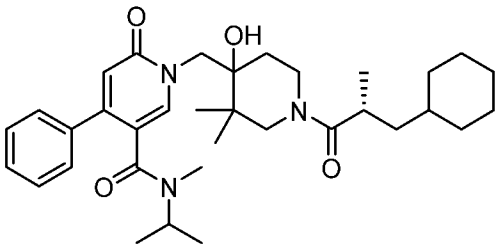
Example 71: (*S*)-1-((1-(4,4-Difluoro-3-phenylbutanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



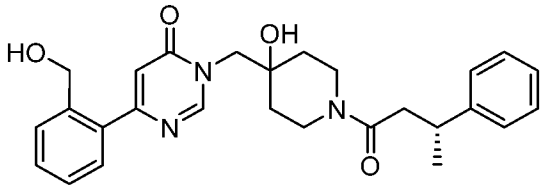
Example 72: 1-((4-Hydroxy-1-(1-(thiophen-2-yl)cyclopropane-1-carbonyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



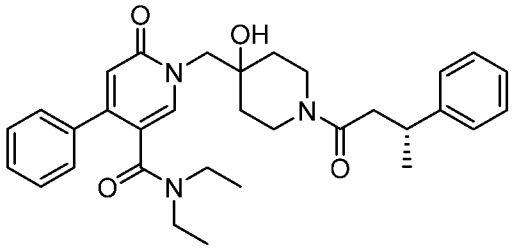
Example 73: 1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide and 1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



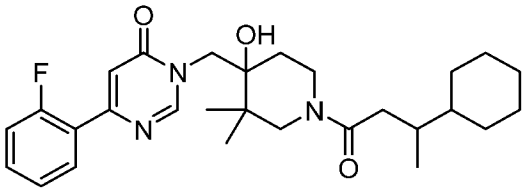
Example 74: (*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(2-(hydroxymethyl)phenyl)pyrimidin-4(3*H*)-one



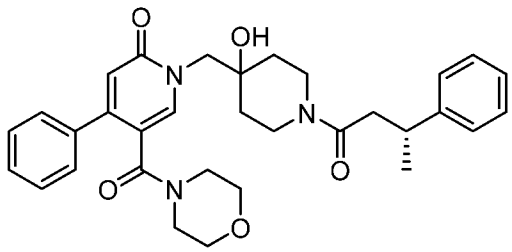
Example 75: (*R*)-*N*,*N*-Diethyl-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



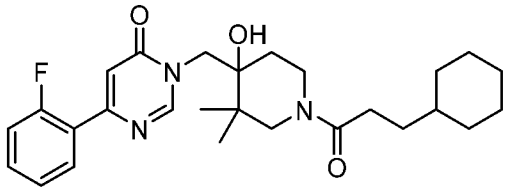
Example 76: 3-((1-(3-Cyclohexylbutanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



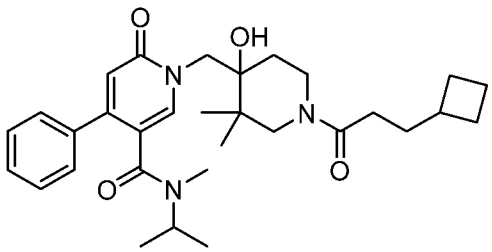
Example 77: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(morpholine-4-carbonyl)-4-phenylpyridin-2(1*H*)-one



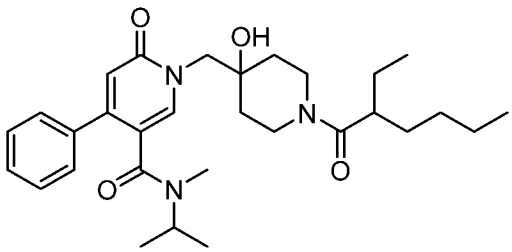
Example 78: (*R,S*)-3-((1-(3-Cyclohexylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



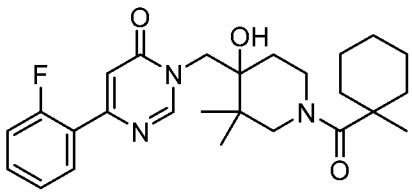
Example 79: (*R,S*)-1-((1-(3-Cyclobutylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



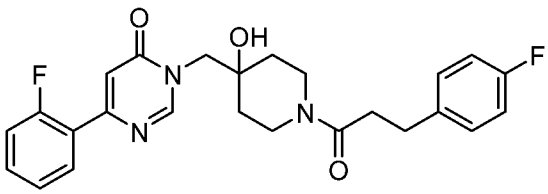
Example 80: (*R,S*)-1-((1-(2-Ethylhexanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



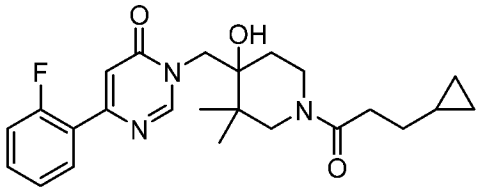
Example 81: (*R,S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(1-methylcyclohexane-1-carbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



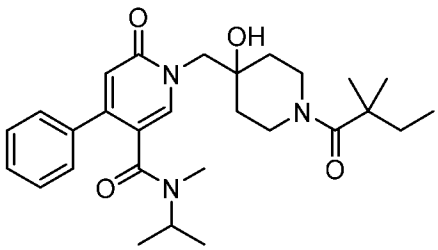
Example 82: 6-(2-Fluorophenyl)-3-((1-(3-(4-fluorophenyl)propanoyl)-4-hydroxypiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



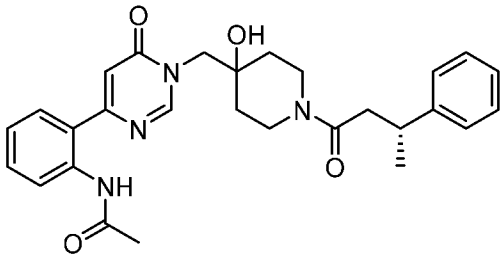
Example 83: (*R,S*)-3-((1-(3-Cyclopropylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



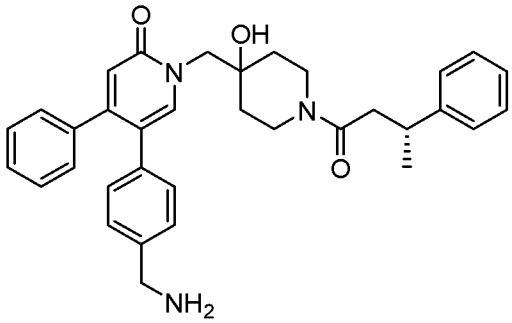
Example 84: 1-((1-(2,2-Dimethylbutanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



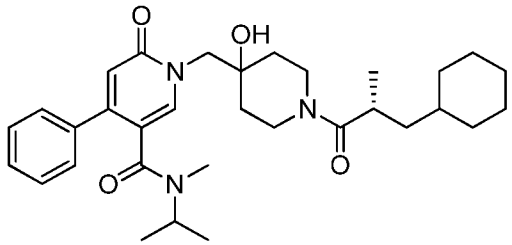
Example 85: (*R*)-*N*-(2-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-1,6-dihydropyrimidin-4-yl)phenyl)acetamide



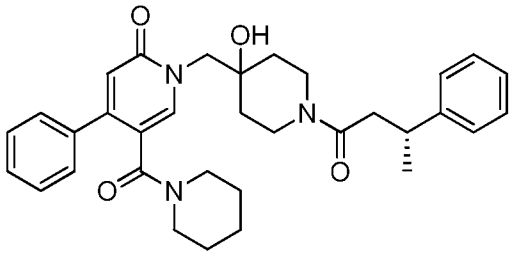
Example 86: (*R*)-5-(4-(Aminomethyl)phenyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one



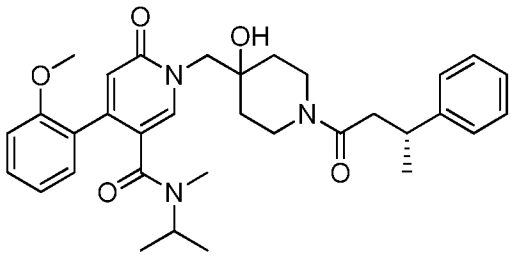
Example 87: (*R*)-1-((1-(3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



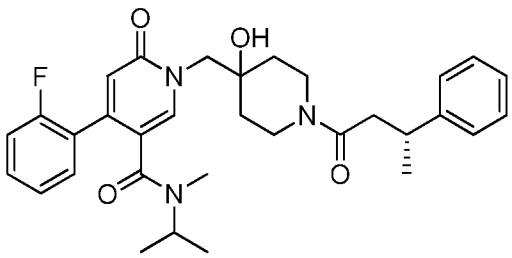
Example 88: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(piperidine-1-carbonyl)pyridin-2(1*H*)-one



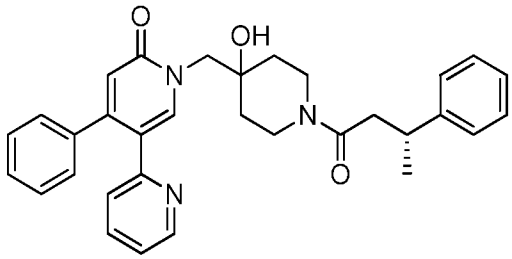
Example 89: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-4-(2-methoxyphenyl)-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide



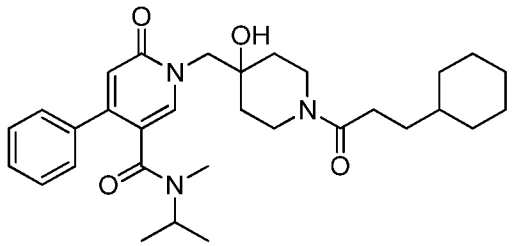
Example 90: (*R*)-4-(2-Fluorophenyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide



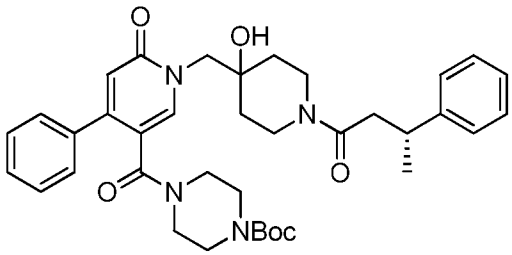
Example 91: (*R*)-1'-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4'-phenyl-[2,3'-bipyridin]-6'(1'*H*)-one



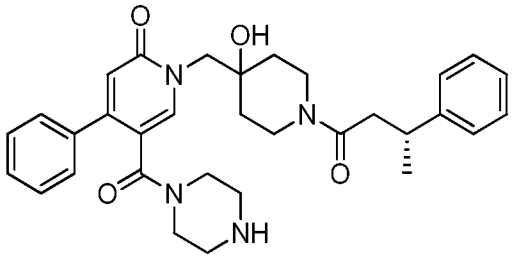
Example 92: 1-((1-(3-Cyclohexylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



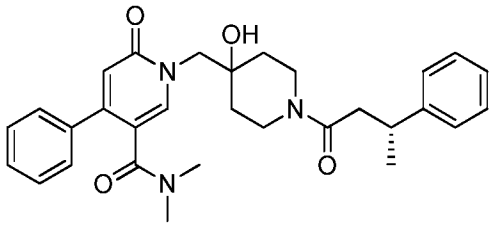
Example 93: (*R*)-*tert*-Butyl 4-(1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carbonyl)piperazine-1-carboxylate



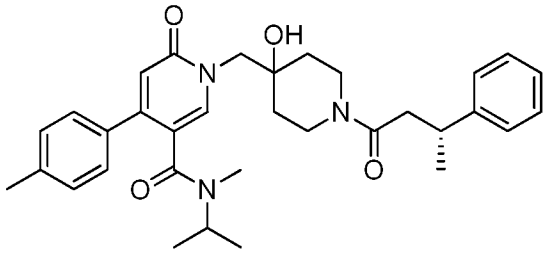
Example 94: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



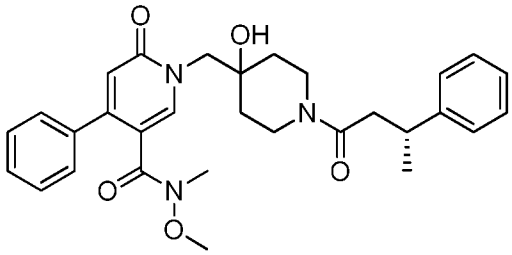
Example 95: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



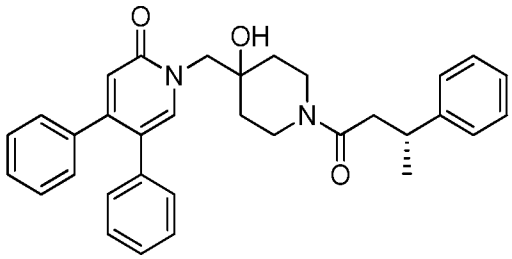
Example 96: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-(*p*-tolyl)-1,6-dihydropyridine-3-carboxamide



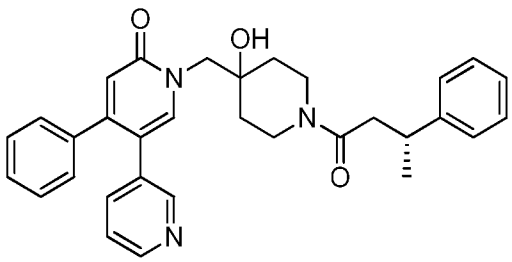
Example 97: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-methoxy-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



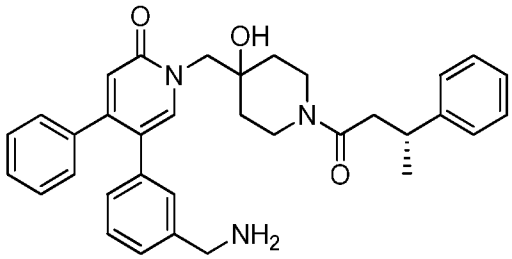
Example 98: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4,5-diphenylpyridin-2(1*H*)-one



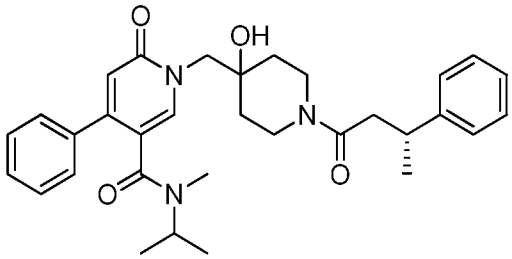
Example 99: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-[3,3'-bipyridin]-6(1*H*)-one



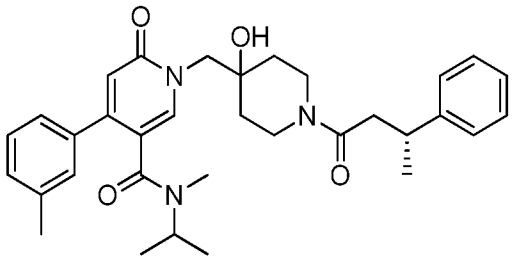
Example 100: (*R*)-5-(3-(Aminomethyl)phenyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one



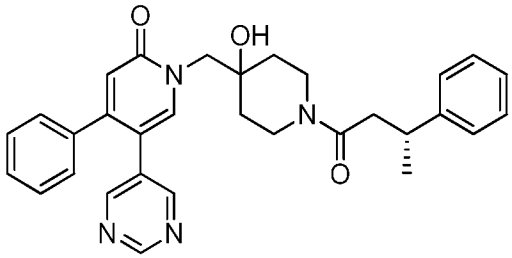
Example 101: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



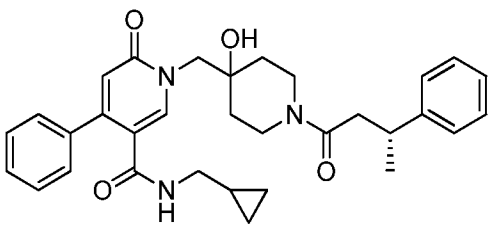
Example 102: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-(*m*-tolyl)-1,6-dihydropyridine-3-carboxamide



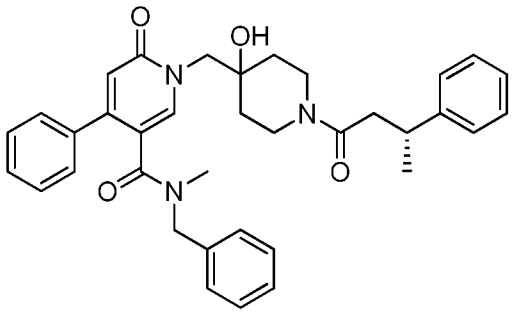
Example 103: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(pyrimidin-5-yl)pyridin-2(1*H*)-one



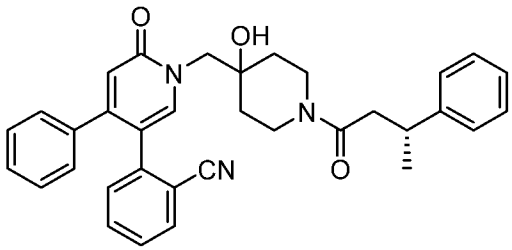
Example 104: (*R*)-*N*-(Cyclopropylmethyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



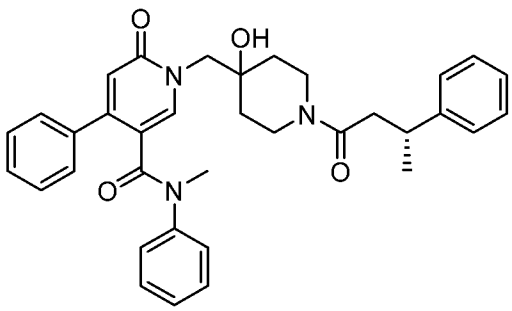
Example 105: (*R*)-*N*-Benzyl-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



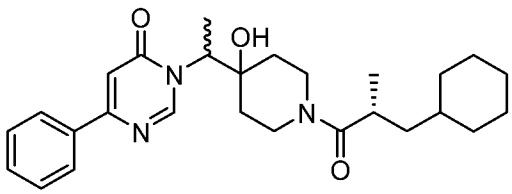
Example 106: (*R*)-2-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridin-3-yl)benzonitrile



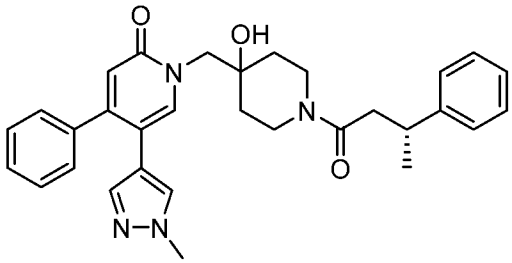
Example 107: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-methyl-6-oxo-*N*,4-diphenyl-1,6-dihydropyridine-3-carboxamide



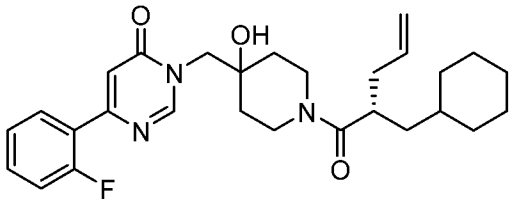
Example 108: 3-(1-(1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)ethyl)-6-phenylpyrimidin-4(3*H*)-one



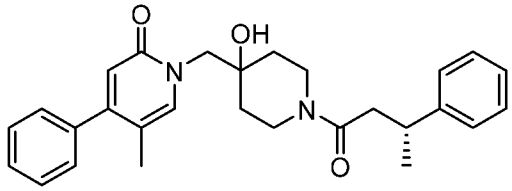
Example 109: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(1-methyl-1*H*-pyrazol-4-yl)-4-phenylpyridin-2(1*H*)-one



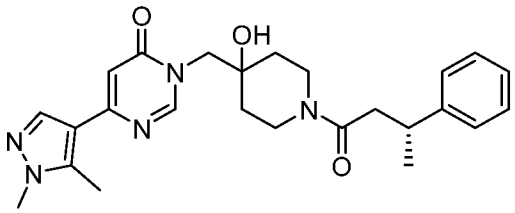
Example 110: (*R*)-3-((1-(2-(Cyclohexylmethyl)pent-4-enoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



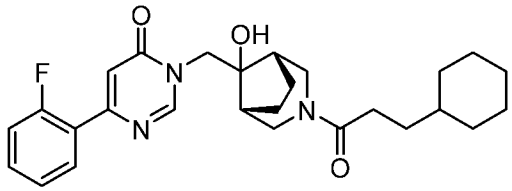
Example 111: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-methyl-4-phenylpyridin-2(1*H*)-one



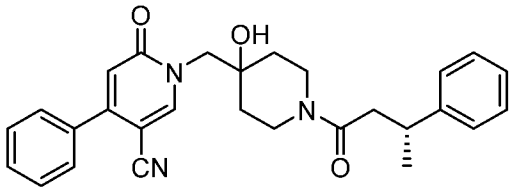
Example 112: (*R*)-6-(1,5-Dimethyl-1*H*-pyrazol-4-yl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



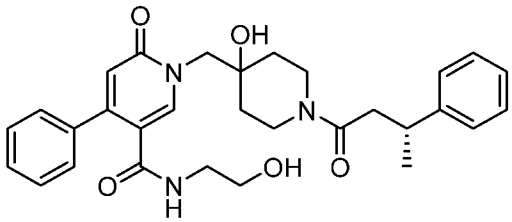
Example 113: 3-(((1*R*,5*S*)-3-(3-Cyclohexylpropanoyl)-8-hydroxy-3-azabicyclo[3.2.1]octan-8-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



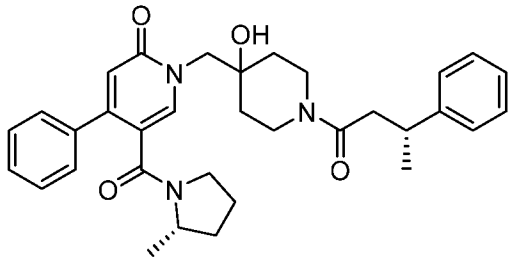
Example 114: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carbonitrile



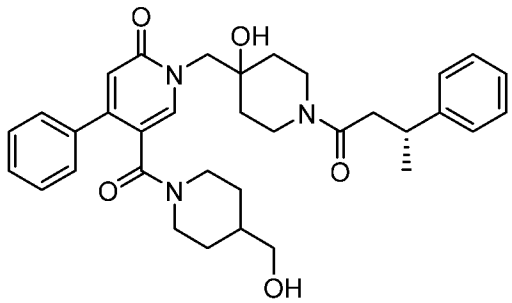
Example 115: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-(2-hydroxyethyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



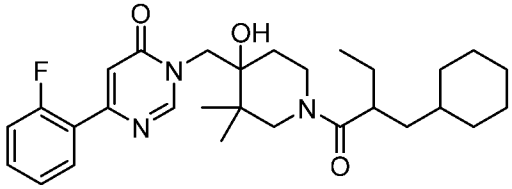
Example 116: 1-((4-Hydroxy-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-5-((*S*)-2-methylpyrrolidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one



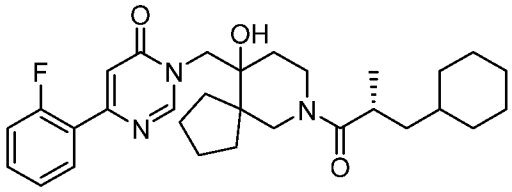
Example 117: (*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(4-(hydroxymethyl)piperidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one



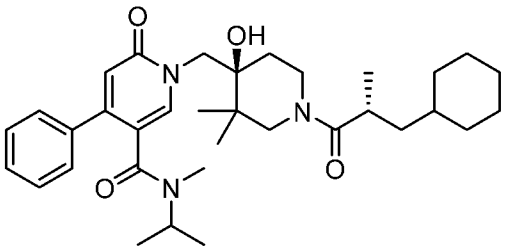
Example 118: 3-((1-(2-(Cyclohexylmethyl)butanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



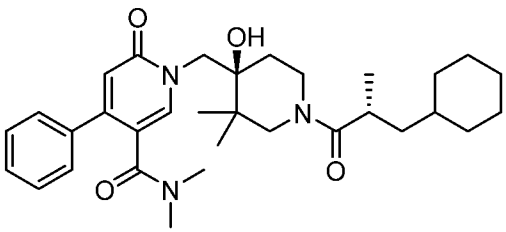
Example 119: 3-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



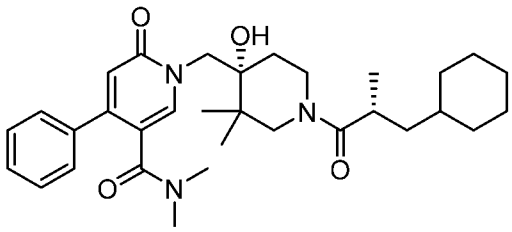
Example 120: 1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



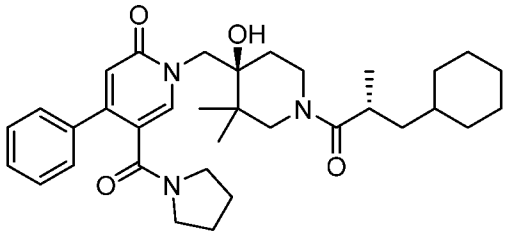
Example 121: 1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



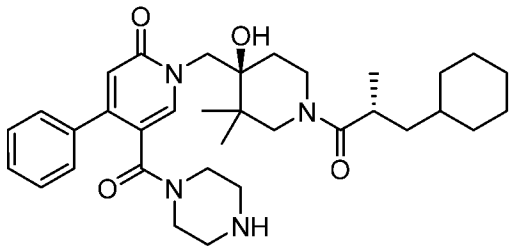
Example 122: 1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



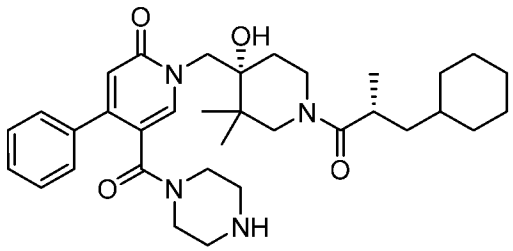
Example 123: 1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenyl-5-(pyrrolidine-1-carbonyl)pyridin-2(1*H*)-one



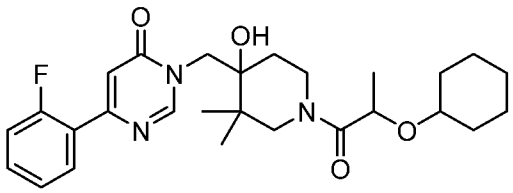
Example 124: 1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



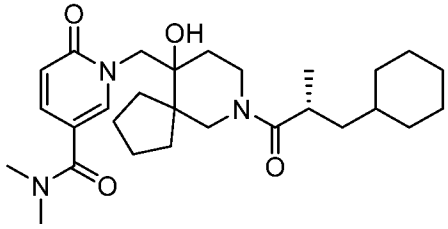
Example 125: 1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



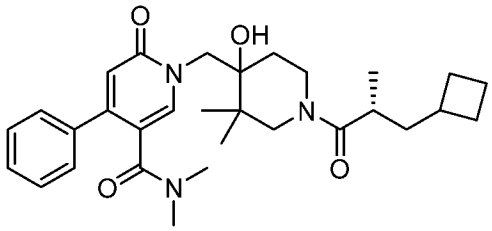
Example 126: 3-((1-(2-(Cyclohexyloxy)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



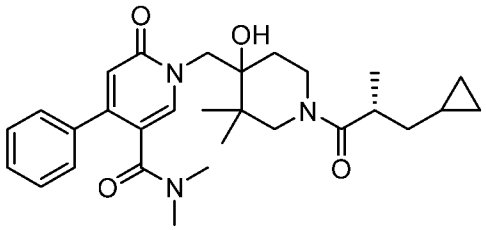
Example 127: 1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



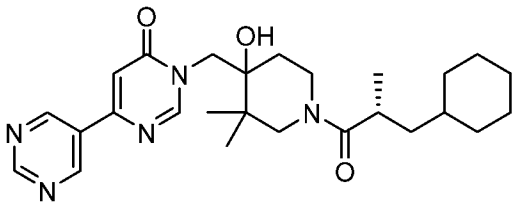
Example 128: 1-((1-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



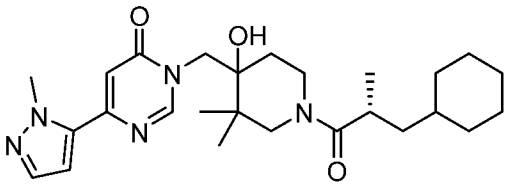
Example 129: 1-((1-((*R*)-3-Cyclopropyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



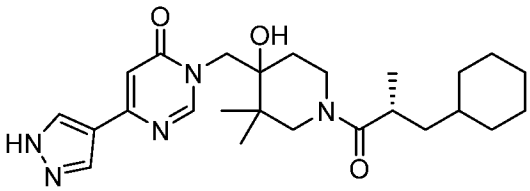
Example 130: 1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-[4,5'-bipyrimidin]-6(1*H*)-one



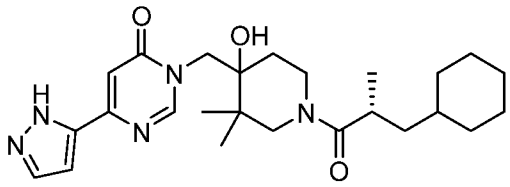
Example 131: 3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(1-methyl-1*H*-pyrazol-5-yl)pyrimidin-4(3*H*)-one



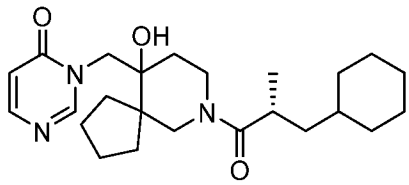
Example 132: 3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(1*H*-pyrazol-4-yl)pyrimidin-4(3*H*)-one



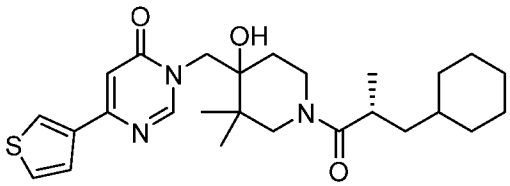
Example 133: 3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(1*H*-pyrazol-5-yl)pyrimidin-4(3*H*)-one



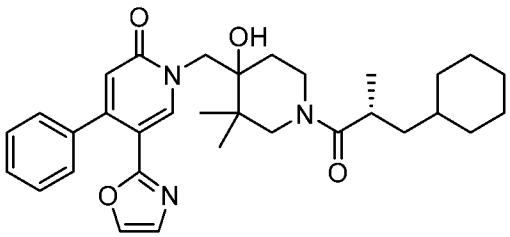
Example 134: 3-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one



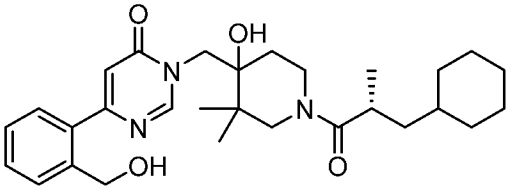
Example 135: 3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(thiophen-3-yl)pyrimidin-4(3*H*)-one



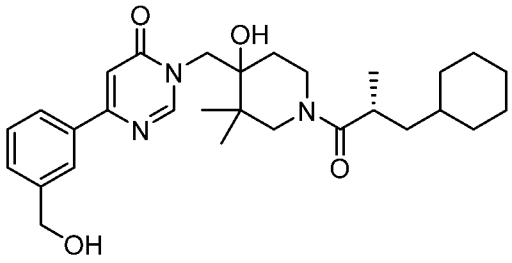
Example 136: 1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(oxazol-2-yl)-4-phenylpyridin-2(1*H*)-one



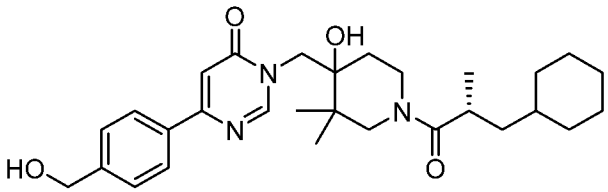
Example 137: 3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-(hydroxymethyl)phenyl)pyrimidin-4(3*H*)-one



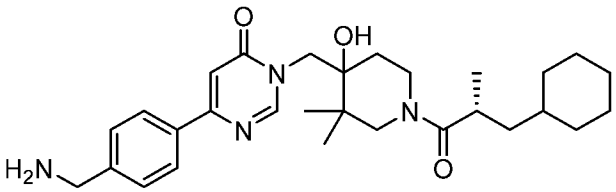
Example 138: 3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(3-(hydroxymethyl)phenyl)pyrimidin-4(3*H*)-one



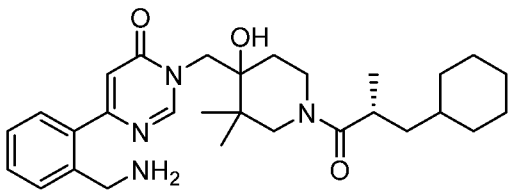
Example 139: 3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(4-(hydroxymethyl)phenyl)pyrimidin-4(3*H*)-one



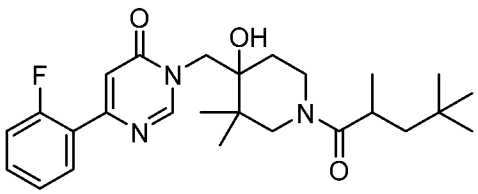
Example 140: 6-(4-(Aminomethyl)phenyl)-3-((1-((*R*)-3-cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



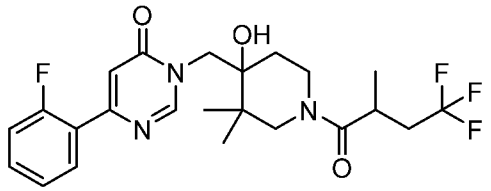
Example 141: 6-(2-(Aminomethyl)phenyl)-3-((1-((*R*)-3-cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



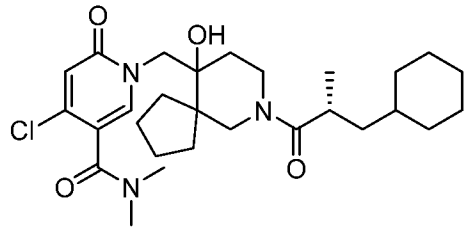
Example 142: 6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(2,4,4-trimethylpentanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



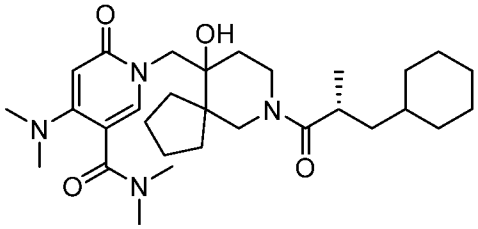
Example 143: 6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(4,4,4-trifluoro-2-methylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



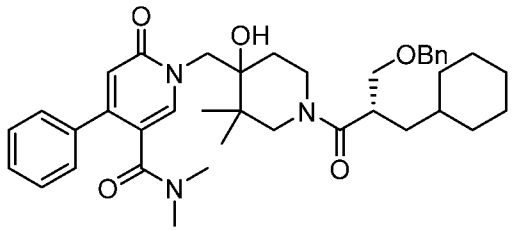
Example 144: 4-Chloro-1-((7-((*R*)-3-cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



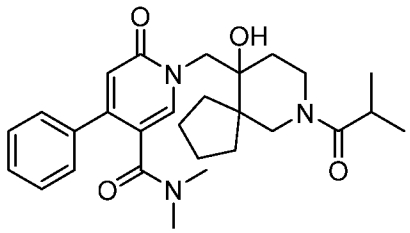
Example 145: 1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(dimethylamino)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



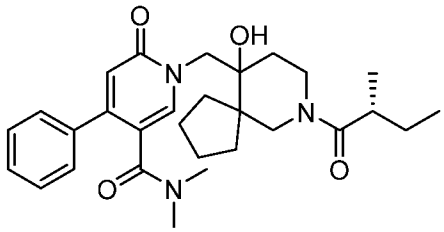
Example 146: 1-((1-((*S*)-3-(Benzyloxy)-2-(cyclohexylmethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



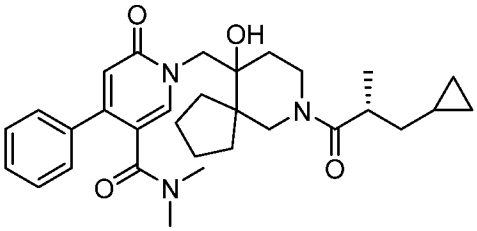
Example 147: 1-((10-Hydroxy-7-isobutyryl-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



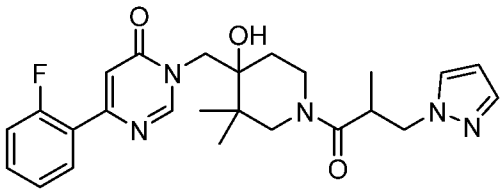
Example 148: 1-((10-Hydroxy-7-((*R*)-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



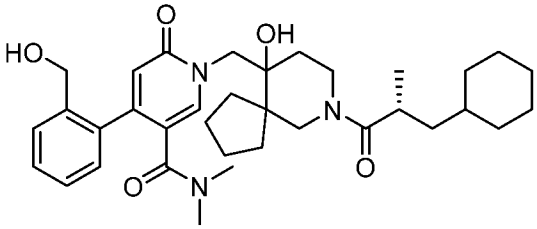
Example 149: 1-((7-((*R*)-3-Cyclopropyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



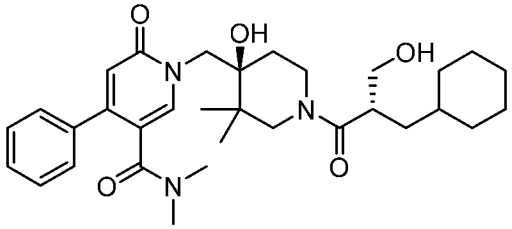
Example 150: 6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(2-methyl-3-(1*H*-pyrazol-1-yl)propanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one

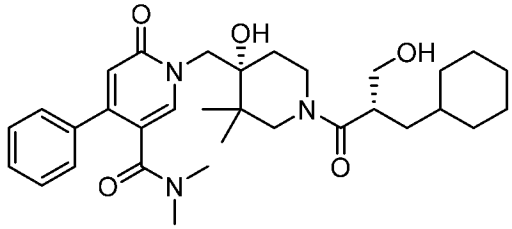


Example 151: 1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-(hydroxymethyl)phenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide

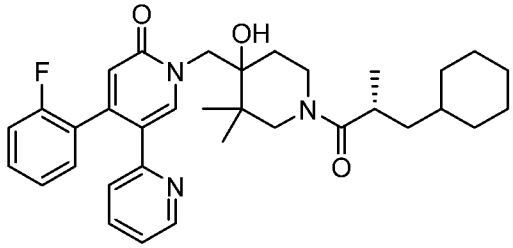


Example 152 and Example 153: 1-(((*S*)-1-((*S*)-3-Cyclohexyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide and 1-(((*R*)-1-((*S*)-3-Cyclohexyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide

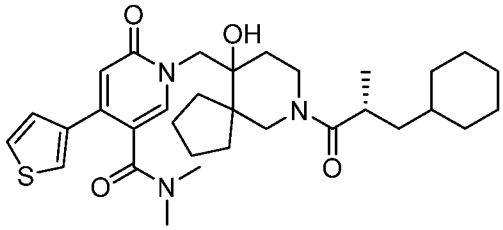




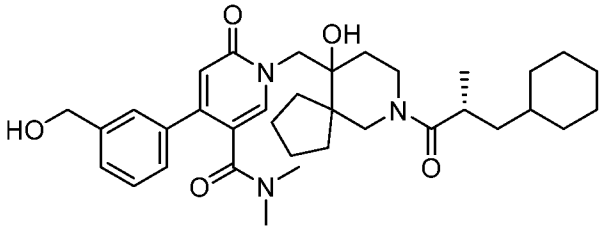
Example 154: 1'-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4'-(2-fluorophenyl)-[2,3'-bipyridin]-6'(1'*H*)-one



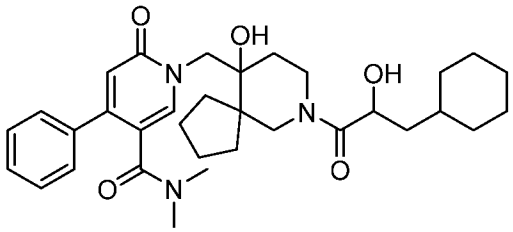
Example 155: 1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-(thiophen-3-yl)-1,6-dihydropyridine-3-carboxamide



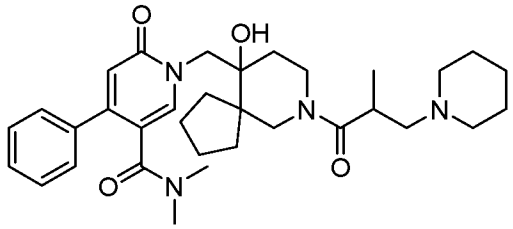
Example 156: 1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(3-(hydroxymethyl)phenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



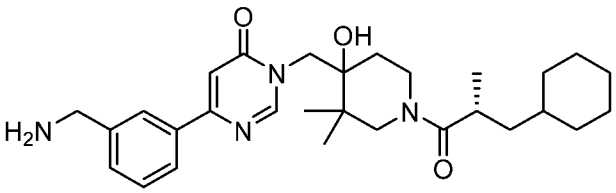
Example 157: 1-((7-(3-Cyclohexyl-2-hydroxypropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



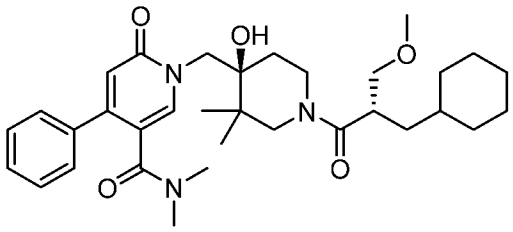
Example 158: 1-((10-Hydroxy-7-(2-methyl-3-(piperidin-1-yl)propanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



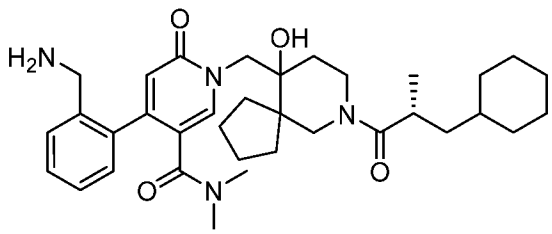
Example 159: 6-(3-(Aminomethyl)phenyl)-3-((1-((*R*)-3-cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one



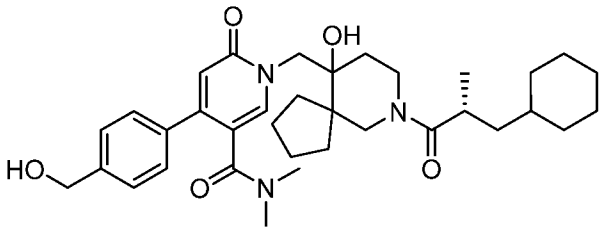
Example 160: 1-(((*S*)-1-((*S*)-3-Cyclohexyl-2-(methoxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



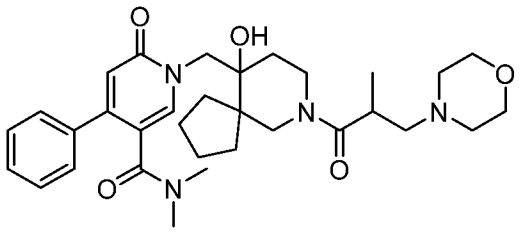
Example 161: 4-(2-(Aminomethyl)phenyl)-1-((7-((*R*)-3-cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



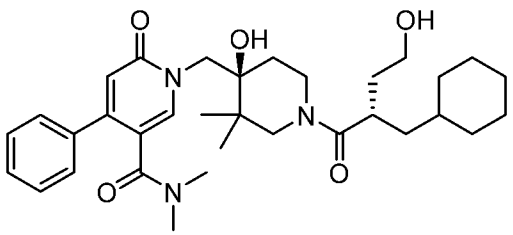
Example 162: 1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(4-(hydroxymethyl)phenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide

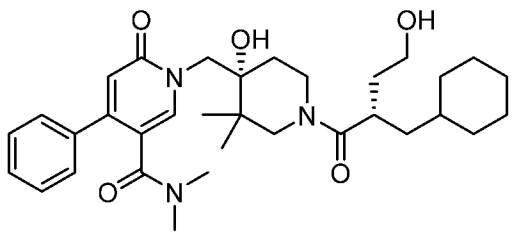


Example 163: 1-((10-Hydroxy-7-(2-methyl-3-morpholinopropanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide

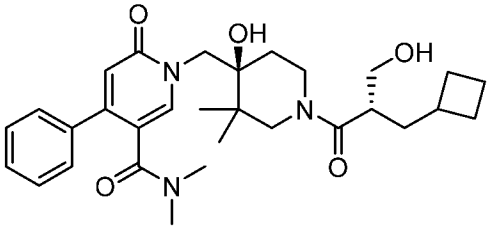


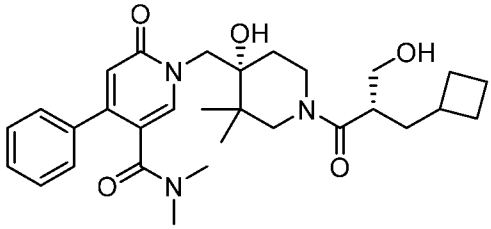
Example 164 and Example 165: 1-(((*S*)-1-((*S*)-2-(Cyclohexylmethyl)-4-hydroxybutanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide and 1-(((*R*)-1-((*S*)-2-(Cyclohexylmethyl)-4-hydroxybutanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



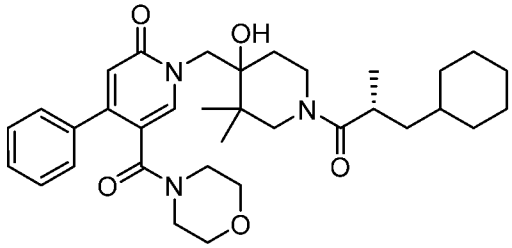


Example 166 and Example 167: 1-(((*S*)-1-((*S*)-3-Cyclobutyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide and 1-(((*R*)-1-((*S*)-3-Cyclobutyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide

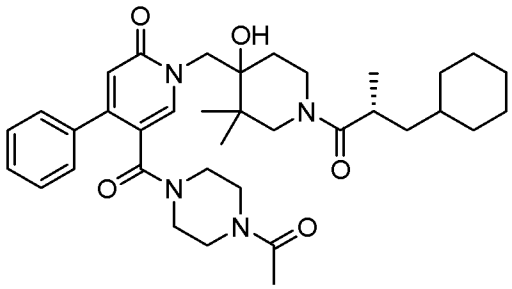




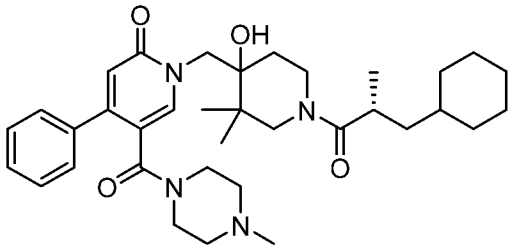
Example 168: 1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(morpholine-4-carbonyl)-4-phenylpyridin-2(1*H*)-one

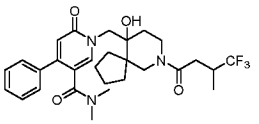
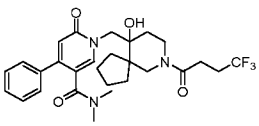
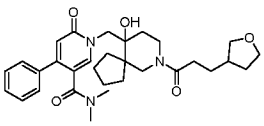
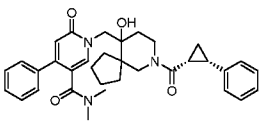
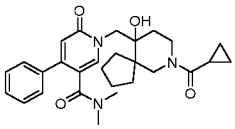
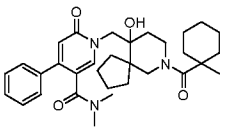
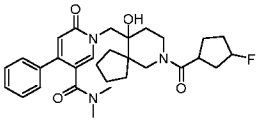


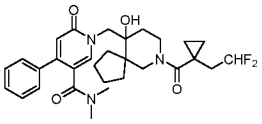
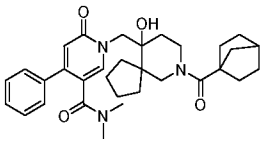
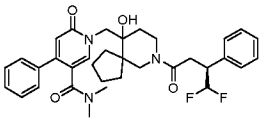
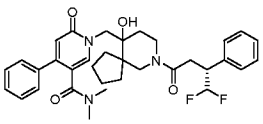
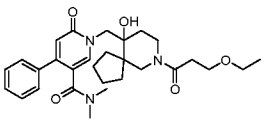
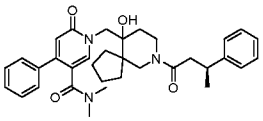
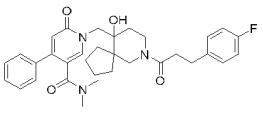
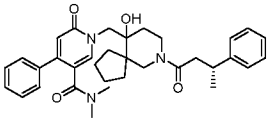
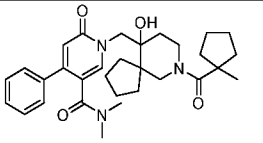
Example 169: 5-(4-Acetylpiperazine-1-carbonyl)-1-((1-((*R*)-3-cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one

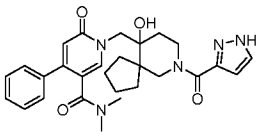
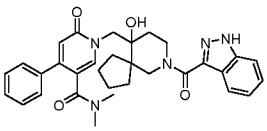
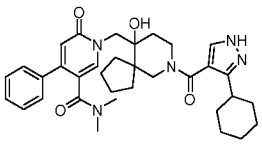
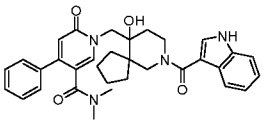
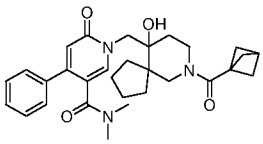
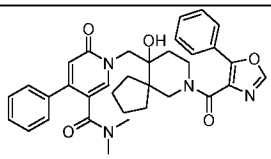
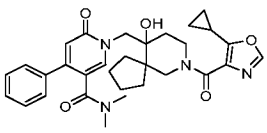
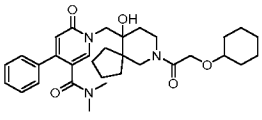


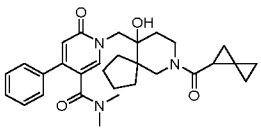
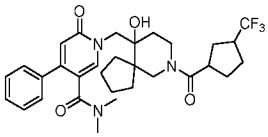
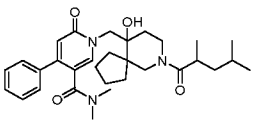
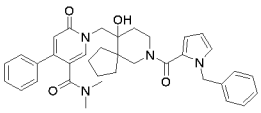
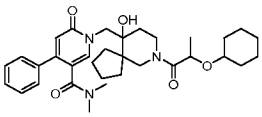
Example 170: 1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(4-methylpiperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one



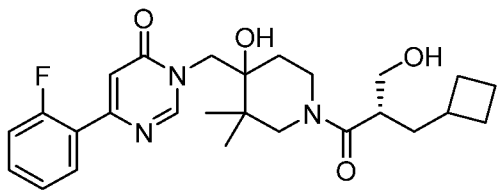
Example	Structure	Name	LCMS (Method A): R_T, *m/z*
171		1-((10-Hydroxy-7-(4,4,4-trifluoro-3-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.38 min, 548 $[M+H]^+$
172		1-((10-Hydroxy-7-(4,4,4-trifluorobutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.28 min, 534 $[M+H]^+$
173		1-((10-Hydroxy-7-(3-(tetrahydrofuran-3-yl)propanoyl)-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.05 min, 536 $[M+H]^+$
174		1-((10-Hydroxy-7-((1*R*,2*S*)-2-phenylcyclopropane-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.32 min, 554 $[M+H]^+$
175		1-((7-(Cyclopropanecarbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.09 min, 478 $[M+H]^+$
176		1-((10-Hydroxy-7-(1-methylcyclohexane-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.50 min, 534 $[M+H]^+$
177		1-((7-(3-Fluorocyclopentane-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.18 min, 524 $[M+H]^+$

178		1-((7-(1-(2,2-Difluoroethyl)cyclopropane-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.18 min, 542 $[M+H]^+$
179		1-((7-(Bicyclo[2.2.1]heptane-1-carbonyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.38 min, 532 $[M+H]^+$
180		1-((7-((*S*)-4,4-Difluoro-3-phenylbutanoyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.41 min, 592 $[M+H]^+$
181		1-((7-((*R*)-4,4-Difluoro-3-phenylbutanoyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.41 min, 592 $[M+H]^+$
182		1-((7-(3-Ethoxypropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.08 min, 510 $[M+H]^+$
183		1-((10-Hydroxy-7-((*S*)-3-phenylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.41 min, 556 $[M+H]^+$
184		1-((7-(3-(4-Fluorophenyl)propanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.38 min, 560 $[M+H]^+$
185		1-((10-Hydroxy-7-((*R*)-3-phenylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.41 min, 556 $[M+H]^+$
186		1-((10-Hydroxy-7-(1-methylcyclopentane-1-carbonyl)-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-	1.37 min, 520 $[M+H]^+$

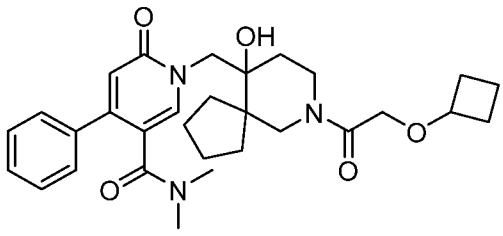
		1,6-dihydropyridine-3-carboxamide	
187		1-((10-Hydroxy-7-(1*H*-pyrazole-3-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	0.864 min, 504 $[M+H]^+$
188		1-((10-Hydroxy-7-(1*H*-indazole-3-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.09 min, 554 $[M+H]^+$
189		1-((7-(3-Cyclohexyl-1*H*-pyrazole-4-carbonyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.10 min, 586 $[M+H]^+$
190		1-((10-Hydroxy-7-(1*H*-indole-3-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.10 min, 553 $[M+H]^+$
191		1-((7-(Bicyclo[1.1.1]pentane-1-carbonyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.14 min, 504 $[M+H]^+$
192		1-((10-Hydroxy-7-(5-phenyloxazole-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.23 min, 581 $[M+H]^+$
193		1-((7-(5-Cyclopropyloxazole-4-carbonyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.11 min, 545 $[M+H]^+$
194		1-((7-(2-(Cyclohexyloxy)acetyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.30 min, 550 $[M+H]^+$

195		1-((10-Hydroxy-7-(spiro[2.2]pentane-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.14 min, 504 $[M+H]^+$
196		1-((10-Hydroxy-7-(3-(trifluoromethyl)cyclopentane-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.33 min, 574 $[M+H]^+$
197		1-((7-(2,4-Dimethylpentanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.37 min, 522 $[M+H]^+$
198		1-((7-(1-Benzyl-1*H*-pyrrole-2-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.41 min, 593 $[M+H]^+$
199		1-((7-(2-(Cyclohexyloxy)propanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide	1.32 min, 564 $[M+H]^+$

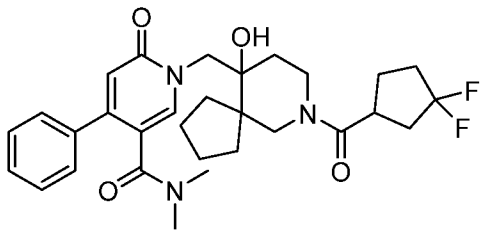
Example 200: 3-((1-((*S*)-3-Cyclobutyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one



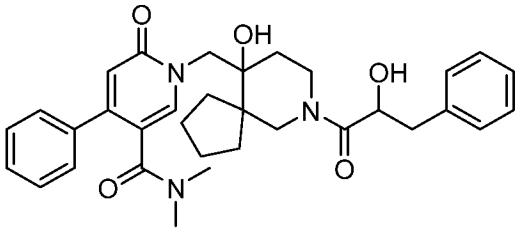
Example 201: 1-((7-(2-Cyclobutoxyacetyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



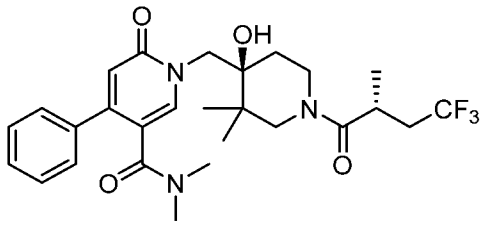
Example 202: 1-((7-(3,3-Difluorocyclopentane-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



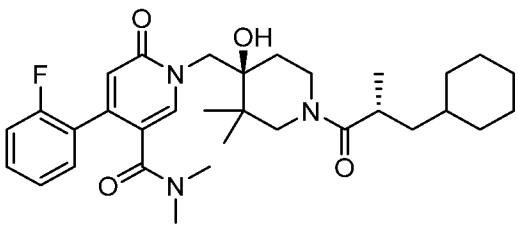
Example 203: 1-((10-Hydroxy-7-(2-hydroxy-3-phenylpropanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



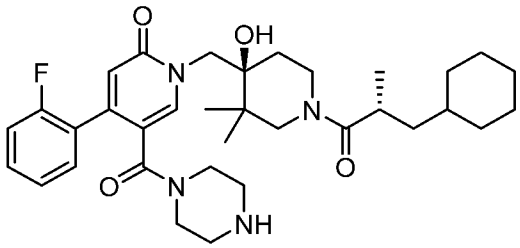
Example 204: 1-(((*S*)-4-Hydroxy-3,3-dimethyl-1-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)piperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



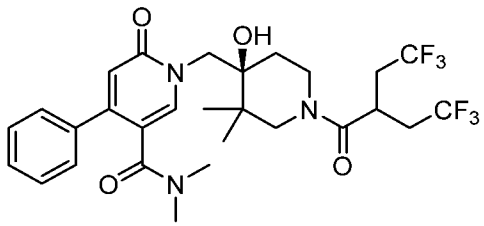
Example 205: 1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



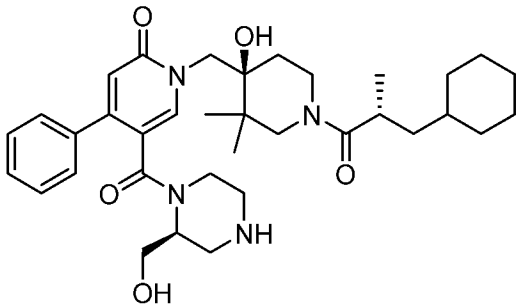
Example 206: 1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



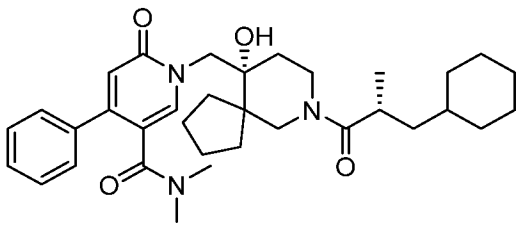
Example 207: (*S*)-1-((4-Hydroxy-3,3-dimethyl-1-(4,4,4-trifluoro-2-(2,2,2-trifluoroethyl)butanoyl)piperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



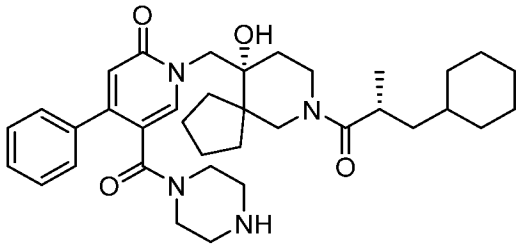
Example 208: 1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-((*S*)-2-(hydroxymethyl)piperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one



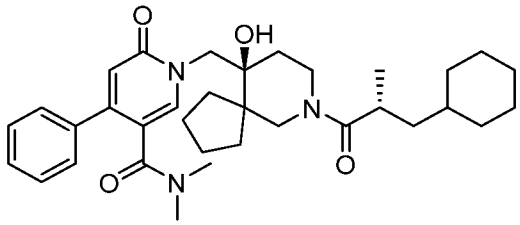
Example 209: 1-(((*R*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



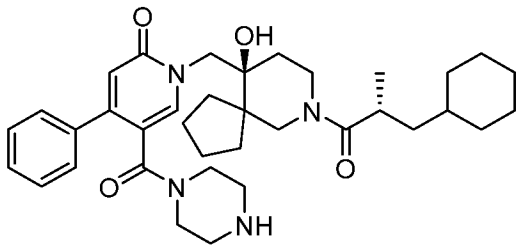
Example 210: 1-(((*R*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



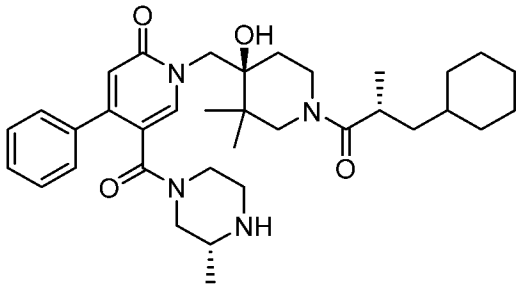
Example 211: 1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



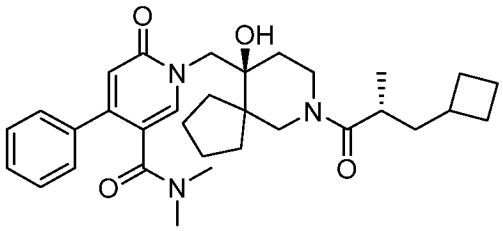
Example 212: 1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



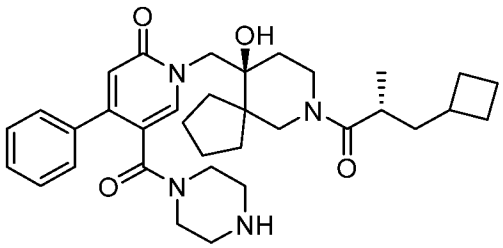
Example 213: 1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-((*R*)-3-methylpiperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one



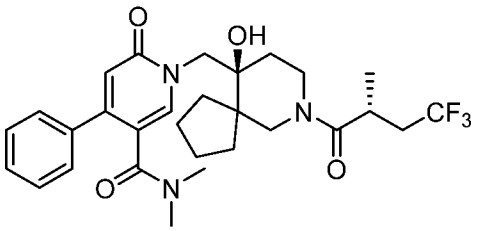
Example 214: 1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



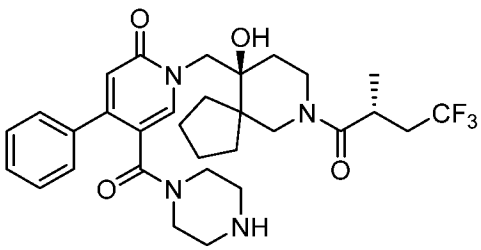
Example 215: 1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



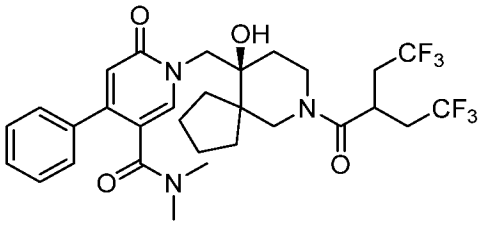
Example 216: 1-(((*S*)-10-Hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



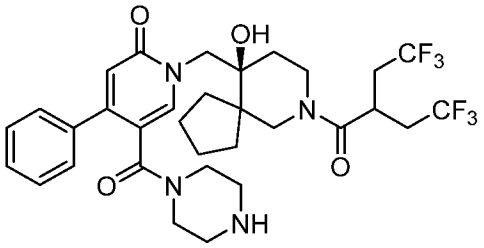
Example 217: 1-(((*S*)-10-Hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



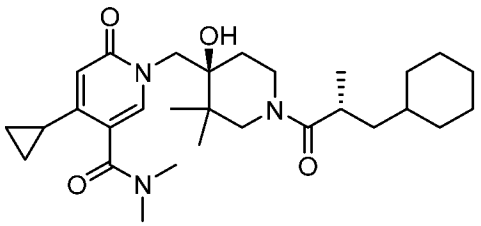
Example 218: (*S*)-1-((10-Hydroxy-7-(4,4,4-trifluoro-2-(2,2,2-trifluoroethyl)butanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



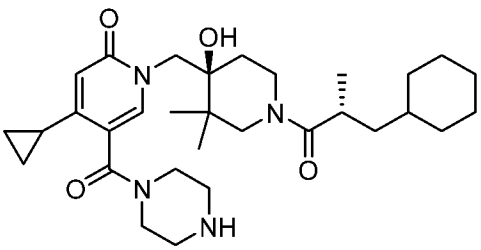
Example 219: (*S*)-1-((10-Hydroxy-7-(4,4,4-trifluoro-2-(2,2,2-trifluoroethyl)butanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



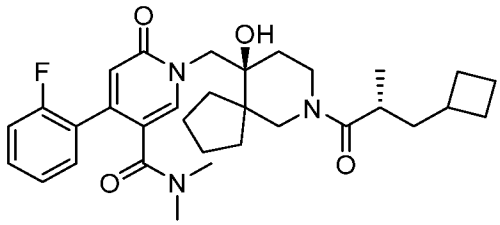
Example 220: 1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



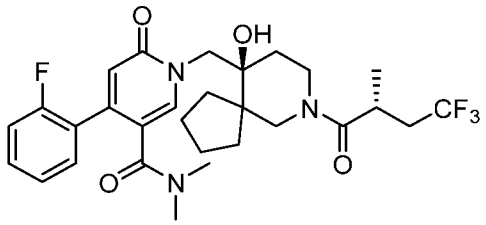
Example 221: 1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-cyclopropyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



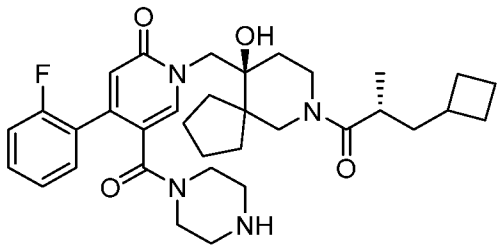
Example 222: 1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



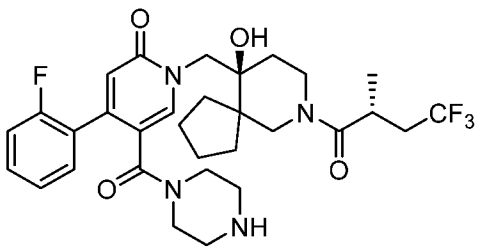
Example 223: 4-(2-Fluorophenyl)-1-(((*S*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



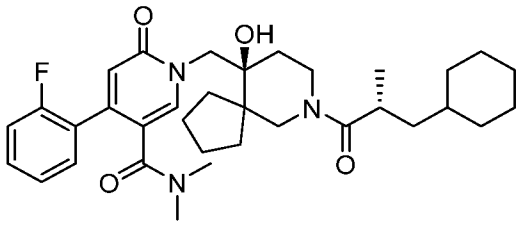
Example 224: 1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



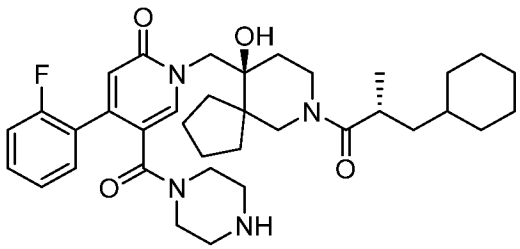
Example 225: 4-(2-Fluorophenyl)-1-(((*S*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



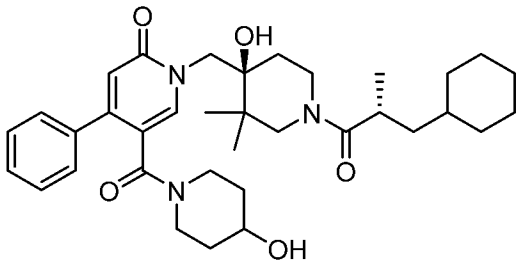
Example 226: 1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



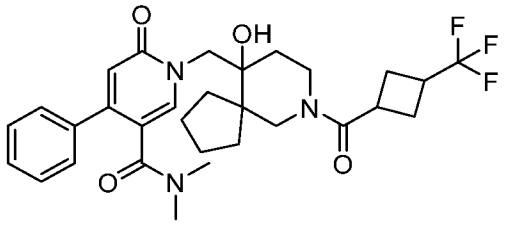
Example 227: 1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



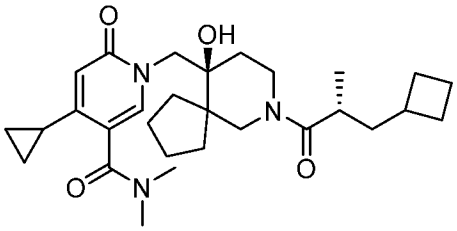
Example 228: 1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(4-hydroxypiperidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one



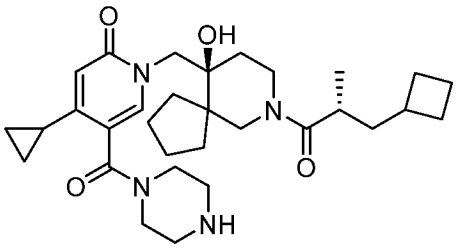
Example 229: 1-((10-Hydroxy-7-(3-(trifluoromethyl)cyclobutane-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



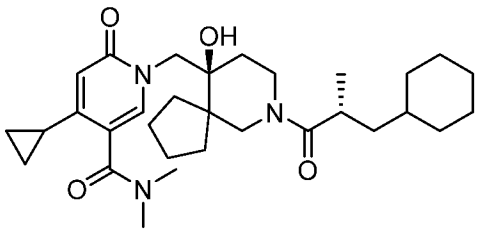
Example 230: 1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



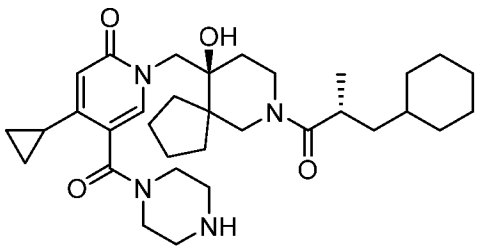
Example 231: 1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



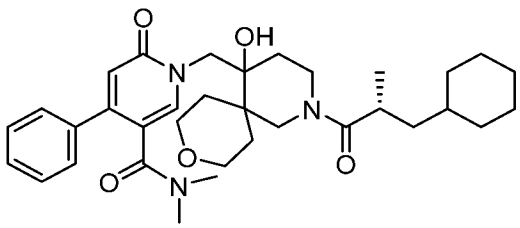
Example 232: 1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



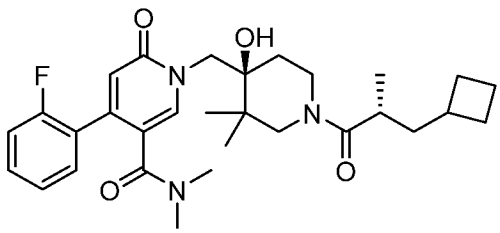
Example 233: 1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



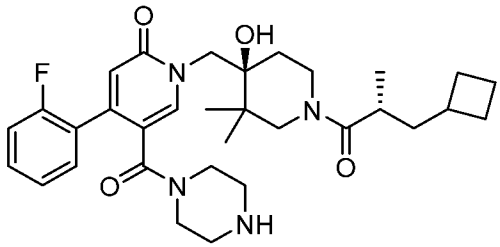
Example 234: 1-((2-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-5-hydroxy-9-oxa-2-azaspiro[5.5]undecan-5-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



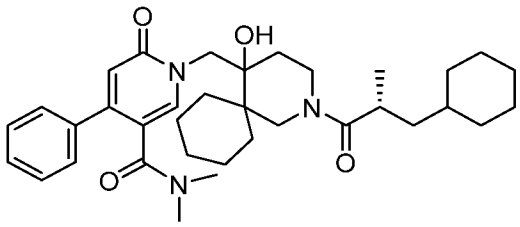
Example 235: 1-(((*S*)-1-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



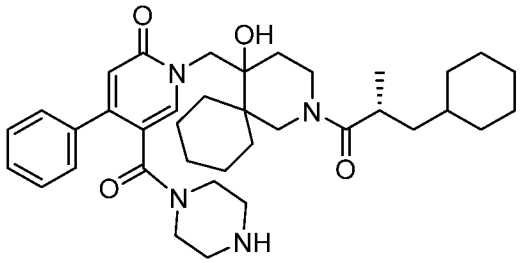
Example 236: 1-(((*S*)-1-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



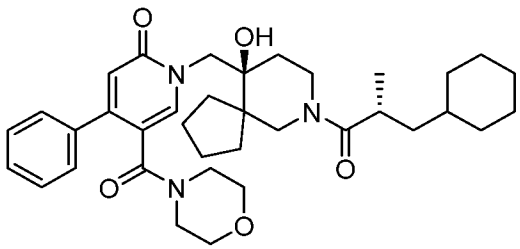
Example 237: 1-((2-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



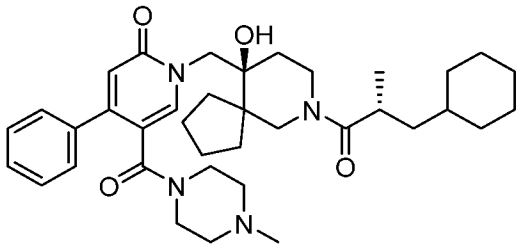
Example 238: 1-((2-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



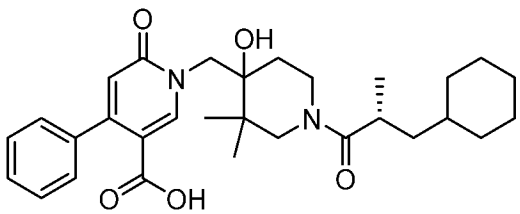
Example 239: 1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-5-(morpholine-4-carbonyl)-4-phenylpyridin-2(1*H*)-one



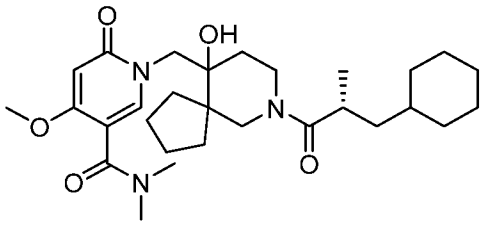
Example 240: 1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-5-(4-methylpiperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one



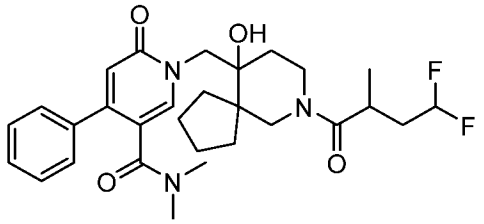
Example 241: 1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylic acid



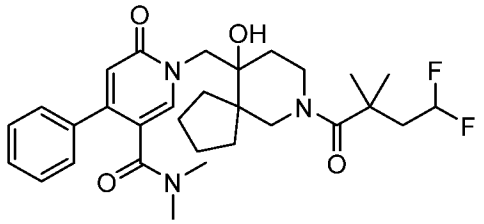
Example 242: 1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-methoxy-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide



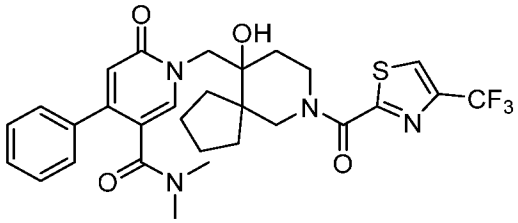
Example 243: 1-((7-(4,4-Difluoro-2-methylbutanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



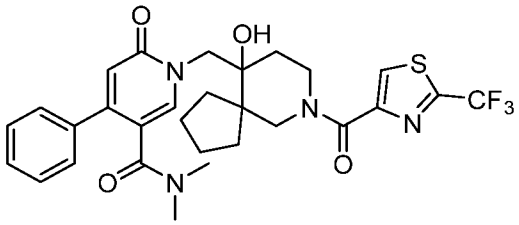
Example 244: 1-((7-(4,4-Difluoro-2,2-dimethylbutanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



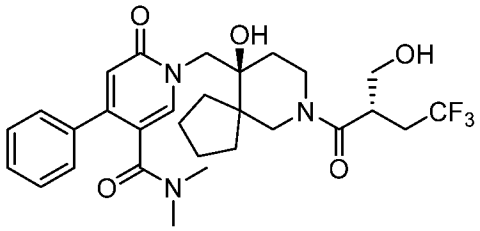
Example 245: 1-((10-Hydroxy-7-(4-(trifluoromethyl)thiazole-2-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



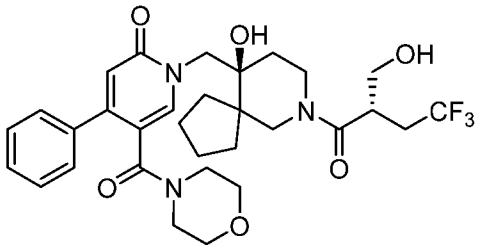
Example 246: 1-((10-Hydroxy-7-(2-(trifluoromethyl)thiazole-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



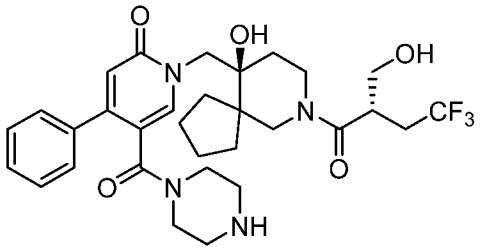
Example 247: 1-(((*S*)-10-Hydroxy-7-((*S*)-4,4,4-trifluoro-2-(hydroxymethyl)butanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide



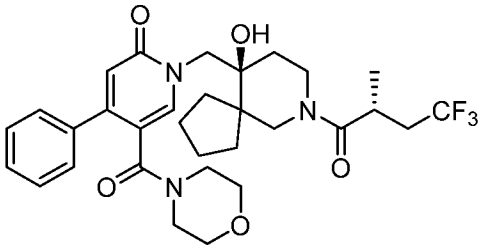
Example 248: 1-(((*S*)-10-Hydroxy-7-((*S*)-4,4,4-trifluoro-2-(hydroxymethyl)butanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(morpholine-4-carbonyl)-4-phenylpyridin-2(1*H*)-one



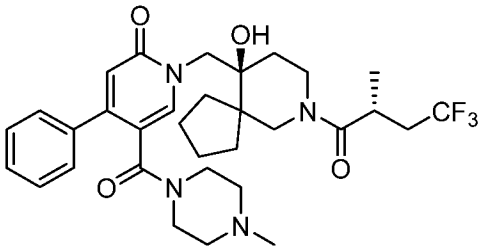
Example 249: 1-(((*S*)-10-Hydroxy-7-((*S*)-4,4,4-trifluoro-2-(hydroxymethyl)butanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one



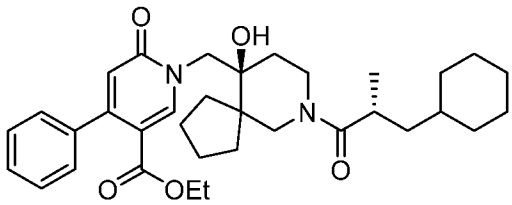
Example 250: 1-(((*S*)-10-Hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(morpholine-4-carbonyl)-4-phenylpyridin-2(1*H*)-one



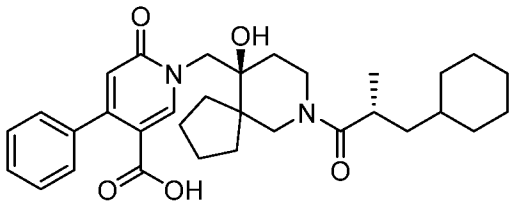
Example 251: 1-(((*S*)-10-Hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(4-methylpiperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one



Example 252: Ethyl 1-(((*S*)-7-((*R*)-3-cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate



Example 253: 1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylic acid

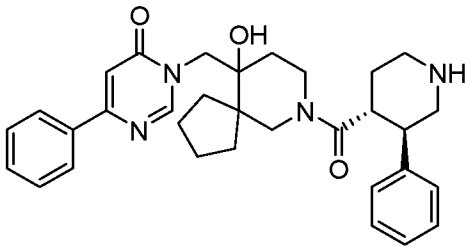


The following USP19 inhibitory compounds were prepared similarly to the above compounds first described in WO2018/020242 and in addition, in some cases using intermediates that were first described in WO2019/150119. Example 254 was prepared

using the intermediate described in WO2019/150119 Example 193, Step 3' and (3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-phenylpiperidine-4-carboxylic acid that is described in WO2009/072643.

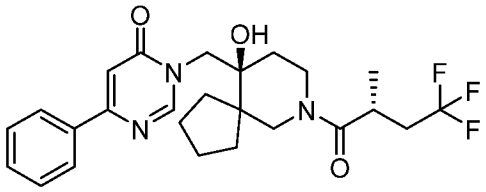
Examples 255, 258, 259 and 260 were prepared using the intermediate described in WO2019/150119 Example 210, Step 3'. Example 256 may be prepared using the intermediate (*S*)-6-(2-fluorophenyl)-3-((10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one that can be prepared similarly to the intermediate described in WO2019/150119 Example 210, Step 3', except using (2-fluorophenyl)boronic acid in Step 2. Example 257 may be prepared using the intermediate (*S*)-6-(3-fluorophenyl)-3-((10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one that can be prepared similarly to the intermediate described in WO2019/150119 Example 210, Step 3', except using (3-fluorophenyl)boronic acid in Step 2. In addition, Examples 255, 256 and 257 used WO2018/020242 'Acid 11' and Examples 258 used commercially available (*R*)-4,4-difluoro-2-methylpentanoic acid. In the cases of Example 259 and 260, commercially available *rel*-(3*R*,4*S*)-1-(*tert*-butoxycarbonyl)-4-phenylpyrrolidine-3-carboxylic acid and *rel*-(2*R*,3*R*)-1-(*tert*-butoxycarbonyl)-2-phenylpyrrolidine-3-carboxylic acid were used, respectively, followed by Boc protecting group removal after HATU coupling (e.g. as described in WO2018/020242 General Procedures 3 and 7). In all cases, the compounds were purified by flash chromatography and freeze-dried.

Example 254: 3-((10-Hydroxy-7-((3*R*,4*R*)-3-phenylpiperidine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one



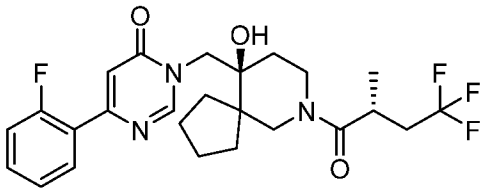
LCMS (Method B): R_T = 0.87 min, *m/z* = 527 $[M+H]^+$. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.45 – 8.38 (m, 1H), 8.14 – 7.99 (m, 2H), 7.61 – 7.40 (m, 3H), 7.35 – 7.05 (m, 5H), 6.99 – 6.92 (m, 1H), 4.83 – 4.68 (m, 1H), 4.62 – 4.55 (m, 1H), 4.39 – 4.33 (m, 1H), 3.76 – 3.60 (m, 1H), 3.60 – 3.46 (m, 1H), 3.42 – 3.16 (m, 2H (signals overlap with HDO)), 3.14 – 3.04 (m, 1H), 2.99 – 2.84 (m, 3H), 2.70 – 2.53 (m, 2H), 2.20 (br s, 1H), 1.83 – 1.18 (m, 9H), 1.11 – 0.86 (m, 2H), 0.66 – 0.47 (m, 1H).

Example 255: 3-(((*S*)-10-Hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one



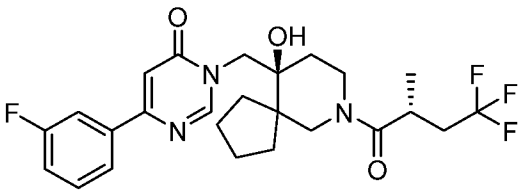
LCMS (Method A): R_T = 1.43 min, *m/z* = 478 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.18 – 7.99 (m, 2H), 7.63 – 7.35 (m, 3H), 6.99 (s, 0.4H), 6.98 (s, 0.6H), 4.92 (s, 0.4H), 4.90 (s, 0.6H), 4.60 (d, *J* = 13.6 Hz, 0.6H), 4.51 (d, *J* = 13.5 Hz, 0.4H), 4.00 – 3.92 (m, 0.4H), 3.76 – 3.67 (m, 1H), 3.64 (d, *J* = 13.6 Hz, 0.6H), 3.53 – 3.21 (m, 1.4H (signal overlaps with HDO)), 3.18 – 2.98 (m, 1.6H), 2.83 – 2.65 (m, 1H), 2.31 – 2.20 (m, 1H), 2.06 – 1.99 (m, 0.4H), 1.95 – 1.87 (m, 0.6H), 1.80 – 1.50 (m, 5H), 1.50 – 1.12 (m, 5H), 1.09 (d, *J* = 6.9 Hz, 1.8H), 1.07 (d, *J* = 6.8 Hz, 1.2H).

Example 256: 6-(2-Fluorophenyl)-3-(((*S*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one



LCMS (Method A): R_T = 1.45 min, *m/z* = 496 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6): δ 8.49 (s, 1H), 8.07 – 7.99 (m, 1H), 7.60 – 7.51 (m, 1H), 7.40 – 7.30 (m, 2H), 6.81 (s, 1H), 4.92 (s, 1H), 4.60 (d, *J* = 13.6 Hz, 0.6H), 4.50 (d, *J* = 13.7 Hz, 0.4H), 4.00 – 3.92 (m, 0.4H), 3.77 – 3.67 (m, 1H), 3.65 (d, *J* = 13.6 Hz, 0.6H), 3.53 – 3.22 (m, 1.4H (signal overlaps with HDO)), 3.19 – 3.00 (m, 1.6H), 2.83 – 2.65 (m, 1H), 2.32 – 2.19 (m, 1H), 2.05 – 1.98 (m, 0.4H), 1.94 – 1.87 (m, 0.6H), 1.79 – 1.20 (m, 9H), 1.20 – 1.12 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 1.8H), 1.07 (d, *J* = 6.9 Hz, 1.2H).

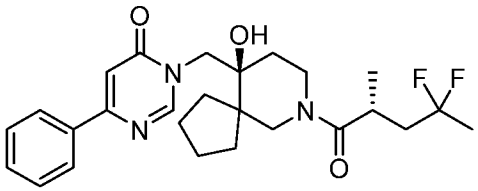
Example 257: 6-(3-Fluorophenyl)-3-(((*S*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one



LCMS (Method A): R_T = 1.48 min, *m/z* = 496 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6): δ 8.48 (s, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.92 – 7.86 (m, 1H), 7.60 – 7.50 (m, 1H), 7.39 – 7.29 (m,

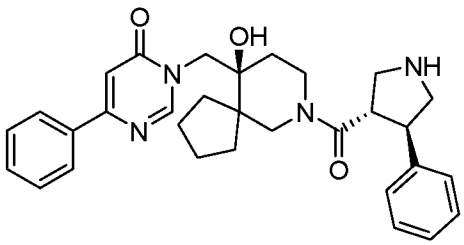
1H), 7.08 (s, 0.4H), 7.06 (s, 0.6H), 4.92 (s, 1H), 4.60 (d, *J* = 13.5 Hz, 0.6H), 4.51 (d, *J* = 13.5 Hz, 0.4H), 3.99 – 3.93 (m, 0.4H), 3.76 – 3.67 (m, 1H), 3.64 (d, *J* = 13.6 Hz, 0.6H), 3.54 – 3.21 (m, 1.4H (signals overlap with HDO)), 3.20 – 2.99 (m, 1.6H), 2.83 – 2.65 (m, 1H), 2.32 – 2.19 (m, 1H), 2.05 – 2.00 (m, 0.4H), 1.94 – 1.87 (m, 0.6H), 1.76 – 1.20 (m, 9H), 1.19 – 1.12 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 1.8H), 1.07 (d, *J* = 6.9 Hz, 1.2H).

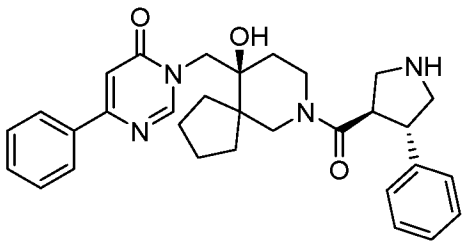
Example 258: 3-(((*S*)-7-((*R*)-4,4-Difluoro-2-methylpentanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one



LCMS (Method A): R_T = 1.38 min, *m/z* = 474 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.11 – 8.04 (m, 2H), 7.56 – 7.45 (m, 3H), 7.01 – 6.95 (m, 1H), 4.93 – 4.85 (m, 1H), 4.65 – 4.49 (m, 1H), 3.94 – 3.59 (m, 2H), 3.53 – 3.20 (m, 2H, overlapping HDO signal), 3.16 – 2.99 (m, 1H), 2.47 – 2.37 (m, 1H, overlapping solvent signal), 2.05 – 1.76 (m, 2H), 1.74 – 0.75 (m, 16H).

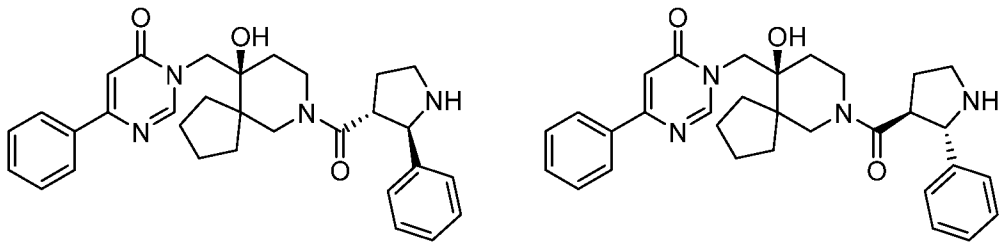
Example 259: 3-(((*S*)-10-Hydroxy-7-((3*S*,4*R*)-4-phenylpyrrolidine-3-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one and 3-(((*S*)-10-Hydroxy-7-((3*R*,4*S*)-4-phenylpyrrolidine-3-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one





LCMS (Method B): R_T = 0.84 min, *m/z* = 513 $[M+H]^+$. ^1H NMR (500 MHz, DMSO-d_6): δ 8.50 – 8.36 (m, 1H), 8.25 – 7.92 (m, 2H), 7.70 – 7.37 (m, 3H), 7.35 – 7.00 (m, 5H), 7.00 – 6.89 (m, 1H), 4.90 – 4.76 (m, 1H), 4.61 – 4.38 (m, 1H), 3.87 – 2.66 (m, 11H (signals overlap with HDO)), 1.94 – 1.79 (m, 1H), 1.75 – 1.38 (m, 4H), 1.36 – 1.20 (m, 2H), 1.18 – 0.99 (m, 2H), 0.91 – 0.70 (m, 1H). NH not visible.

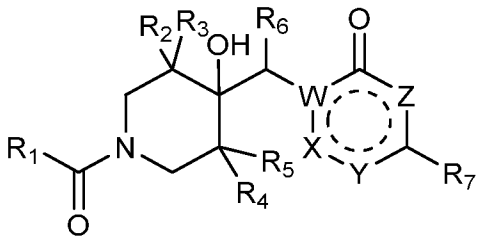
Example 260: 3-(((*S*)-10-Hydroxy-7-((2*R*,3*R*)-2-phenylpyrrolidine-3-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one and 3-(((*S*)-10-Hydroxy-7-((2*S*,3*S*)-2-phenylpyrrolidine-3-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one



LCMS (Method B): R_T = 0.84 min, *m/z* = 513 $[M+H]^+$. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.45 – 8.39 (m, 1H), 8.12 – 8.00 (m, 2H), 7.58 – 7.42 (m, 3H), 7.38 – 7.12 (m, 5H), 7.00 – 6.92 (m, 1H), 4.88 – 4.74 (m, 1H), 4.59 – 4.16 (m, 3H), 3.88 – 3.66 (m, 1H), 3.62 – 3.53 (m, 1H), 3.52 – 2.89 (m, 5H (signals overlap with HDO)), 2.69 (br s, 1H), 2.19 – 2.04 (m, 1H), 1.93 – 1.74 (m, 2H), 1.68 – 1.58 (m, 2H), 1.55 – 1.46 (m, 1H), 1.43 – 1.31 (m, 1H), 1.30 – 1.17 (m, 2H), 1.15 – 0.97 (m, 2H), 0.89 – 0.66 (m, 1H).

CLAIMS:

1. A compound, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in therapy, wherein the compound is a compound according to formula (I):



(I)

wherein:

R_1 is an optionally substituted alkyl, alkenyl, alkynyl, ether, cycloalkyl, alkylcycloalkyl, heterocycloalkyl, alkylheterocycloalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl group;

R_2 is H or an optionally substituted alkyl group,

R_3 is H or an optionally substituted alkyl group,

R_4 is H or an optionally substituted alkyl group,

R_5 is H or an optionally substituted alkyl group,

R_2 and R_4 may be joined to one another to form an optionally substituted cycloalkyl or heterocycloalkyl that includes the carbon to which they are attached,

R_4 and R_5 may be joined to one another to form an optionally substituted cycloalkyl or heterocycloalkyl that includes the carbon to which they are attached;

R_6 is H or an optionally substituted alkyl group;

W is C or N;

X is N or CR_8, wherein R_8 is H or optionally substituted C1-C6 alkyl,

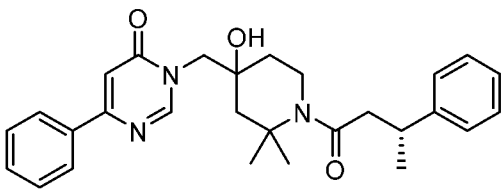
Y is N or CR_9

Z is CH, or NH,

wherein R_9 is H or optionally substituted alkyl, amido, amino, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, halo, carbonyl, ester, aminoalkyl, or cyano;

R_7 is hydrogen, halo, or an optionally substituted alkyl, alkenyl, alkynyl, amino, aryl, cycloalkyl, cycloalkenyl, alkoxy, aryloxy, heteroaryl or heterocycloalkyl group;

or the compound



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

2. A compound as defined in claim 1, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in a method of treating obesity.

3. A compound as defined in claim 1, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in a method of treating insulin resistance.

4. A compound as defined in claim 1, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in a method of treating type II diabetes.

5. A compound as defined in claim 1, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in a method of treating muscular atrophy.

6. A compound as defined in claim 1, or a pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use in a method of treating cachexia or sarcopenia.

7. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any of claims 1-6, wherein R_1 is optionally substituted C1-C6 alkyl, optionally substituted C4-C10 alkylcycloalkyl, optionally substituted C4-C5 heterocycloalkyl, optionally substituted C7-C10 arylalkyl, optionally substituted C3-C6 cycloalkyl, or optionally substituted C3-C6 heteroaryl,

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

8. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any of claims 1-4, wherein R_1 is optionally substituted C7-C10 cyclohexylalkane, optionally substituted C4-C6 cyclopropylalkane, optionally substituted C5-C6 cyclobutylalkane, optionally substituted C7-C10 alkylbenzene, optionally substituted 2,2 difluorobutane, or optionally substituted 3,3,3-trifluoropropane,

wherein each optional substituent is independently selected from C1-C6 alkyl, C2-C6 alkenyl, hydroxymethyl, hydroxyethyl, methoxymethyl, OH, or halo.

9. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any of claims 1-8 wherein R_1 is substituted and the substituent is C1-C6 alkyl, optionally methyl.

10. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any one of claims 1-9, wherein R_1 is methyl substituted cyclohexylethane or methyl substituted ethylbenzene.

11. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any one of claims 1-9, wherein R_1 is methyl substituted 2,2 difluorobutane, or methyl substituted 3,3,3-trifluoropropane.

12. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any one of claims 1-9, wherein R_1 is C4-C5 heterocycloalkyl, optionally substituted with phenyl.

13. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to claim 12, wherein R_1 is phenyl-substituted pyrrolidine or phenyl-substituted piperidine.

14. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any of claims 1-13, wherein R_7 is optionally substituted C6-C10 aryl, C1-C12 heteroaryl, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, amino, C1-C3 alkoxy, or halo,

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

15. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any one of claims 1-14, wherein R_7 is cyclopropyl, thiophene, or optionally substituted phenyl,

wherein the optional substituent is selected from C1-C6 alkyl, hydroxysubstituted C1-C6 alkyl, C1-C6 alkylamine, and halo.

16. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any one of claims 1-15, wherein R_7 is phenyl or fluoro-substituted phenyl.

17. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any of claims 1-16, wherein R_2, R_3, R_4, R_5 are independently selected from H and C1-C6 alkyl.

18. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any one of claims 1-17, wherein R_2 and R_3 are H, and R_4 and R_5 are methyl.

19. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any of claims 1-18 wherein R_4 and R_5 are joined to one another to form an optionally substituted C3-C6 cycloalkyl or C3-C6 heterocycloalkyl that includes the carbon to which they are attached and R_2 and R_3 are independently selected from H and C1-C6 alkyl.

20. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to claim 19, wherein R_2 and R_3 are H and R_4 and R_5 are joined to one another to form a C3-C6 cycloalkyl that includes the carbon to which they are attached.

21. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to claim 19 or 20, wherein R_4 and R_5 are joined to one another to form a C4 or C5 cycloalkyl that includes the carbon to which they are attached.

22. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any one of claims 1-21 wherein R_6 is H or C1-C6 alkyl.

23. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any of claims 1-16, wherein R_2 and R_4 are joined to one another to form a C5 cycloalkyl that includes the carbons to which they are attached, and wherein R_3, R_5 and R_6 are independently H or C1-C6 alkyl.

24. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any of claims 1-23, wherein W is N and X is CR_8, wherein R_8 is H or methyl.

25. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any of claims 1-24, wherein Y is N or CR_9, wherein R_9 is H, C1-C6 alkyl, NR'R'', C(O)NR'R'', cyano, carboxyl, halo, C1-C6 alkylamine, C3-C6 alkylester, optionally substituted C6-C10 aryl or optionally substituted C2-C6 heteroaryl, wherein the one or more heteroatoms are selected from N and O, and the one or more optional substituents of the aryl or heteroaryl are selected from C1-C6 alkyl, C1-C6 alkylamine, amido, and cyano,

wherein R' and R'' are independently selected from H, C1-C6 alkyl optionally substituted with OH, C3-C7 cycloalkyl, C1-C7 heterocycloalkyl, C4-C7 alkylcycloalkyl, C3-C7 alkylheterocycloalkyl, benzyl, phenyl, and methoxy, or wherein R' and R'' are joined to one another to form a C2-C7 heterocycle that includes the N to which they are attached, wherein the heterocycle is optionally hydroxyl-substituted, oxo-substituted, methyl-substituted, CH2OH-substituted, or acetyl-substituted.

26. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any of claims 1-25, wherein Y is N or CR_9, wherein R_9 is selected from: phenyl optionally substituted with amido, cyano or methyl amine; pyridine; oxazole; pyrazole; carboxyl; C(O)NR'R''; or NR'R'';

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

27. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to claim 1, wherein

R_1 is selected from optionally substituted ethylcyclohexane, optionally substituted ethylbenzene, optionally substituted 2,2 difluorobutane, and optionally substituted 3,3,3-trifluoropropane, wherein the optional substituent is one or more of methyl, ethyl, propyl, propenyl, hydroxymethyl and methoxymethyl, or wherein R_1 is phenyl-substituted pyrrolidine;

R_2 and R_3 are independently selected from H, methyl,

R_4 and R_5 are independently selected from H, methyl, or are joined to one another to form a C3-C6 cycloalkyl or heterocycloalkyl that includes the carbon to which they are attached, optionally a C4 or C5 cycloalkyl that includes the carbon to which they are attached

R_6 is H or methyl,

R_7 is selected from optionally substituted phenyl, indazole, thiophene, or pyrazole, wherein the optional substituent is selected from C1-C6 alkyl, hydroxysubstituted C1-C6 alkyl, C3-C6 cycloalkyl, C1-C6 heterocycloalkyl, C1-C6 alkoxy, halo-substituted C1-C6 alkoxy, C1-C6 alkylamine, amido, cyano or halo,

W is N or C

X is CH or N

Z is C or NH

Y is N or CR_9, wherein R_9 is selected from: phenyl optionally substituted with amido, cyano or methyl amine; pyridine; oxazole; pyrazole; C(O)NR'R''; or NR'R'';

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

28. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any one of claims 25-27, wherein Y is CR_9, wherein R_9 is C(O)NR'R'' and wherein R' and R'' are joined to one another to form an optionally substituted pyrrolidine, piperidine, piperazine or morpholine that includes the N to which they are attached, wherein the piperidine, pyrrolidine, piperazine or morpholine is optionally hydroxyl-substituted, oxo-substituted, methyl-substituted, hydroxymethyl-substituted, or acetyl-substituted.

29. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to claim 28, wherein Y is CR_9, wherein R_9 is C(O)NR'R'' and wherein R' and R'' are joined to one another to form a piperazinyl ring.

30. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any one of claims 1-27 wherein W is N and Y is N, such that the ring comprising W, X, Y, Z is a substituted pyrimidinone ring.

31. A compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative for use according to any one of claims 1-30 wherein when the compound is chiral at the hydroxyl position of formula (I), the compound is the *S* enantiomer.

32. A compound, or pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use according to any one of claims 1-6, wherein the compound is:

(*R*)-5-Bromo-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

6-(2-Fluorophenyl)-3-((4-hydroxy-1-(3-phenylpropanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

3-((1-(3-Cyclobutylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-((1-(3-Cyclopentylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(2-methyl-3-phenylpropanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*)-*N*-(3-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridin-3-yl)phenyl)acetamide;

(*R*)-3-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)6-oxo-4-phenyl-1,6-dihydropyridin-3-yl)benzamide;

(*R*)-5-(Furan-2-yl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-4-Chloro-1-((4-hydroxy-1(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenylpyridin-2(1*H*)-one;

(*R*)-4-(Dimethylamino)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenylpyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenyl-4-(prop-1-en-2-yl)pyridine-2(1*H*)-one;

(*R*)-Ethyl 1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylate;

(*R,S*)-4-(2-Fluorophenyl)-1-((4-hydroxy-1-(2-methyl-1,2,3,4-tetrahydronaphthalene-2-carbonyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

(*R,S*)-1-((1-(3-Cyclobutyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-4-phenyl-5-(piperidine-1-carbonyl)pyridin-2(1*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(1-methyl-1*H*-indazol-7-yl)pyrimidin-4(3*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(2-methoxyphenyl)pyrimidin-4(3*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-2-methyl-6-phenylpyrimidin-4(3*H*)-one;

(*R*)-2-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5,6-diphenylpyridazin-3(2*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(naphthalen-1-yl)pyrimidin-4(3*H*)-one;

(*R*)-6-(3-(1,3-Dioxolan-2-yl)phenyl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(thiophen-3-yl)pyrimidin-4(3*H*)-one;

4-(2-Fluorophenyl)-1-((4-hydroxy-1-(1-methylcyclopentane-1-carbonyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

3-((1-(1-Ethylcyclohexane-1-carbonyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-((1-(2-(Cyclohexylmethyl)-3-methylbutanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-6-(Furan-2-yl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-6-(Cyclohex-1-en-1-yl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(prop-1-en-2-yl)pyrimidin-4(3*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(2-(trifluoromethoxy)phenyl)pyrimidin-4(3*H*)-one;

3-(((1*R*,5*S*)-3-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-8-hydroxy-3-azabicyclo[3.2.1]octan-8-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*)-5-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-2-phenylpyrimidin-4(3*H*)-one;

3-((4-Hydroxy-1-(3-phenylpropanoyl)piperidin-4-yl)methyl)-2-methyl-6-phenylpyrimidin-4(3*H*)-one;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(isobutylamino)pyrimidin-4(3*H*)-one;

(*R*)-1-((1-(3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-4-phenyl-5-(piperidine-1-carbonyl)pyridin-2(1*H*)-one;

(*R*)-2-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-phenylpyridazin-3(2*H*)-one;

(*R*)-4-(2-Cyanophenyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

(*R*)-3-((1-(3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-((1-(2-(Cyclohexylmethyl)butanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

rac-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(*cis*-2-phenylcyclopropanecarbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

6-(2-Fluorophenyl)-3-((4-hydroxy-1-(1-methylcyclohexanecarbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

3-((*S*)-1-(1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)propyl)-6-phenylpyrimidin-4(3*H*)-one;

3-((*R*)-1-(1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)propyl)-6-phenylpyrimidin-4(3*H*)-one;

(*R*,*S*)-3-((1-(3-Cyclohexyl-2-hydroxypropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carbaldehyde;

(*R*)-5-((Dimethylamino)methyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

3-((*R*)-1-(4-Hydroxy-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)ethyl)-6-phenylpyrimidin-4(3*H*)-one;

3-((*S*)-1-(4-Hydroxy-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)ethyl)-6-phenylpyrimidin-4(3*H*)-one;

(*R*)-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(4,4,4-trifluoro-3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-3-((1-(3-Cyclohexyl-2-fluoropropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

3-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

3-(((*R*)-6-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-9-hydroxy-6-azaspiro[3.5]nonan-9-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-(((*S*)-6-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-9-hydroxy-6-azaspiro[3.5]nonan-9-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-5-(3-(Aminomethyl)phenyl)-1-((1-(3-cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-4-(2-fluorophenyl)pyridin-2(1*H*)-one;

3-(((*S*)-4-Hydroxy-3,3-dimethyl-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

3-(((*R*)-4-Hydroxy-3,3-dimethyl-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

(*R*)-6-(4-Fluorophenoxy)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(2-oxopyrrolidin-1-yl)-4-phenylpyridin-2(1*H*)-one;

6-(2-Fluorophenyl)-3-((4-hydroxy-1-(1-methyl-4-methylenecyclohexanecarbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-3-((1-(3-Cyclobutyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R,S*)-3-((1-(3-Cycloheptyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-((1-(3-Cyclobutyl-2,2-dimethylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

6-(2-Fluorophenyl)-3-(((1*R*,5*S*)-8-hydroxy-3-((*R*)-3-phenylbutanoyl)-3-azabicyclo[3.2.1]octan-8-yl)methyl)pyrimidin-4(3*H*)-one;

3-(((*R*)-4-Hydroxy-2,2-dimethyl-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

3-(((*S*)-4-Hydroxy-2,2-dimethyl-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(4-hydroxypiperidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(pyrrolidine-1-carbonyl)pyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(1,4-dioxa-8-azaspiro[4.5]decane-8-carbonyl)pyridin-2(1*H*)-one;

(*R*)-*N*-Cyclohexyl-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(*cis*-2-phenylcyclopropane-1-carbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-3-((1-(3-Cyclohexyl-1H-pyrazole-4-carbonyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(3-phenylpropanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-1-(1-isobutyl cyclopropane-1-carbonyl)-3,3-dimethylpiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R,S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(3-methyl-3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*S*)-1-((1-(4,4-Difluoro-3-phenylbutanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((4-Hydroxy-1-(1-(thiophen-2-yl)cyclopropane-1-carbonyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-3-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-(2-(hydroxymethyl)phenyl)pyrimidin-4(3*H*)-one;

(*R*)-*N*,*N*-Diethyl-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

3-((1-(3-Cyclohexylbutanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(morpholine-4-carbonyl)-4-phenylpyridin-2(1*H*)-one;

(*R*,*S*)-3-((1-(3-Cyclohexylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-1-((1-(3-Cyclobutylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*,*S*)-1-((1-(2-Ethylhexanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R,S*)-6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(1-methylcyclohexane-1-carbonyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

6-(2-Fluorophenyl)-3-((1-(3-(4-fluorophenyl)propanoyl)-4-hydroxypiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

(*R*,*S*)-3-((1-(3-Cyclopropylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

1-((1-(2,2-Dimethylbutanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-*N*-(2-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-1,6-dihydropyrimidin-4-yl)phenyl)acetamide;

(*R*)-5-(4-(Aminomethyl)phenyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-1-((1-(3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(piperidine-1-carbonyl)pyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-4-(2-methoxyphenyl)-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

(*R*)-4-(2-Fluorophenyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

(*R*)-1'-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4'-phenyl-[2,3'-bipyridin]-6'(1'*H*)-one;

1-((1-(3-Cyclohexylpropanoyl)-4-hydroxypiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-*tert*-Butyl 4-(1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carbonyl)piperazine-1-carboxylate;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-(*p*-tolyl)-1,6-dihydropyridine-3-carboxamide;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-methoxy-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4,5-diphenylpyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-[3,3'-bipyridin]-6(1*H*)-one;

(*R*)-5-(3-(Aminomethyl)phenyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-(*m*-tolyl)-1,6-dihydropyridine-3-carboxamide;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-4-phenyl-5-(pyrimidin-5-yl)pyridin-2(1*H*)-one;

(*R*)-*N*-(Cyclopropylmethyl)-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-*N*-Benzyl-1-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

(*R*)-2-(1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridin-3-yl)benzonitrile;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-methyl-6-oxo-*N*,4-diphenyl-1,6-dihydropyridine-3-carboxamide;

3-(1-(1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxypiperidin-4-yl)ethyl)-6-phenylpyrimidin-4(3*H*)-one;

(R)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(1-methyl-1H-pyrazol-4-yl)-4-phenylpyridin-2(1H)-one;

(*R*)-3-((1-(2-(Cyclohexylmethyl)pent-4-enoyl)-4-hydroxypiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-methyl-4-phenylpyridin-2(1*H*)-one;

(*R*)-6-(1,5-Dimethyl-1*H*-pyrazol-4-yl)-3-((4-hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

3-(((1*R*,5*S*)-3-(3-Cyclohexylpropanoyl)-8-hydroxy-3-azabicyclo[3.2.1]octan-8-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carbonitrile;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-*N*-(2-hydroxyethyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((4-Hydroxy-1-((*R*)-3-phenylbutanoyl)piperidin-4-yl)methyl)-5-((*S*)-2-methylpyrrolidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-1-(3-phenylbutanoyl)piperidin-4-yl)methyl)-5-(4-(hydroxymethyl)piperidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

3-((1-(2-(Cyclohexylmethyl)butanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

3-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenyl-5-(pyrrolidine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

3-((1-(2-(Cyclohexyloxy)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((1-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((1-((*R*)-3-Cyclopropyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-[4,5'-bipyrimidin]-6(1*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(1-methyl-1*H*-pyrazol-5-yl)pyrimidin-4(3*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(1*H*-pyrazol-4-yl)pyrimidin-4(3*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(1*H*-pyrazol-5-yl)pyrimidin-4(3*H*)-one;

3-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(thiophen-3-yl)pyrimidin-4(3*H*)-one;

1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(oxazol-2-yl)-4-phenylpyridin-2(1*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-(hydroxymethyl)phenyl)pyrimidin-4(3*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(3-(hydroxymethyl)phenyl)pyrimidin-4(3*H*)-one;

3-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(4-(hydroxymethyl)phenyl)pyrimidin-4(3*H*)-one;

6-(4-(Aminomethyl)phenyl)-3-((1-((*R*)-3-cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

6-(2-(Aminomethyl)phenyl)-3-((1-((*R*)-3-cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(2,4,4-trimethylpentanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(4,4,4-trifluoro-2-methylbutanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

4-Chloro-1-((7-((*R*)-3-cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(dimethylamino)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((1-((*S*)-3-(Benzyloxy)-2-(cyclohexylmethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

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

1-((7-((*R*)-3-Cyclopropyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

6-(2-Fluorophenyl)-3-((4-hydroxy-3,3-dimethyl-1-(2-methyl-3-(1*H*-pyrazol-1-yl)propanoyl)piperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-(hydroxymethyl)phenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*S*)-3-Cyclohexyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*S*)-3-Cyclohexyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1'-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4'-(2-fluorophenyl)-[2,3'-bipyridin]-6'(1'*H*)-one;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-(thiophen-3-yl)-1,6-dihydropyridine-3-carboxamide;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(3-(hydroxymethyl)phenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((7-(3-Cyclohexyl-2-hydroxypropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((10-Hydroxy-7-(2-methyl-3-(piperidin-1-yl)propanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

6-(3-(Aminomethyl)phenyl)-3-((1-((*R*)-3-cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)pyrimidin-4(3*H*)-one;

1-(((*S*)-1-((*S*)-3-Cyclohexyl-2-(methoxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

4-(2-(Aminomethyl)phenyl)-1-((7-((*R*)-3-cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(4-(hydroxymethyl)phenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((10-Hydroxy-7-(2-methyl-3-morpholinopropanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*S*)-2-(Cyclohexylmethyl)-4-hydroxybutanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*S*)-2-(Cyclohexylmethyl)-4-hydroxybutanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*S*)-3-Cyclobutyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*S*)-3-Cyclobutyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(morpholine-4-carbonyl)-4-phenylpyridin-2(1*H*)-one;

5-(4-Acetylpiperazine-1-carbonyl)-1-((1-((*R*)-3-cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenylpyridin-2(1*H*)-one;

1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(4-methylpiperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

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

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

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

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

1-((7-(Cyclopropanecarbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

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

1-((7-(1-(2,2-Difluoroethyl)cyclopropane-1-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(Bicyclo[2.2.1]heptane-1-carbonyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-((*S*)-4,4-Difluoro-3-phenylbutanoyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-((*R*)-4,4-Difluoro-3-phenylbutanoyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(3-Ethoxypropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

1-((7-(3-(4-Fluorophenyl)propanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

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

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

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

1-((7-(3-Cyclohexyl-1*H*-pyrazole-4-carbonyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

1-((7-(Bicyclo[1.1.1]pentane-1-carbonyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((10-Hydroxy-7-(5-phenyloxazole-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(5-Cyclopropyloxazole-4-carbonyl)-10-hydroxy-7-azaspiro [4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(2-(Cyclohexyloxy)acetyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((10-Hydroxy-7-(spiro[2.2]pentane-1-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

1-((7-(2,4-Dimethylpentanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(1-Benzyl-1*H*-pyrrole-2-carbonyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(2-(Cyclohexyloxy)propanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

3-((1-((*S*)-3-Cyclobutyl-2-(hydroxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-(2-fluorophenyl)pyrimidin-4(3*H*)-one;

1-((7-(2-Cyclobutoxyacetyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

1-((10-Hydroxy-7-(2-hydroxy-3-phenylpropanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-4-Hydroxy-3,3-dimethyl-1-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)piperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

(*S*)-1-((4-Hydroxy-3,3-dimethyl-1-(4,4,4-trifluoro-2-(2,2,2-trifluoroethyl)butanoyl)piperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-((*S*)-2-(hydroxymethyl)piperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

1-(((*R*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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(1*H*)-one;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-((*R*)-3-methylpiperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

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

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

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

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

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-cyclopropyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

4-(2-Fluorophenyl)-1-(((*S*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

4-(2-Fluorophenyl)-1-(((*S*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*S*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(4-hydroxypiperidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

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

1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-((2-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-5-hydroxy-9-oxa-2-azaspiro[5.5]undecan-5-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*S*)-1-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-((2-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((2-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-5-hydroxy-2-azaspiro[5.5]undecan-5-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

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

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

1-((1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxylic acid;

1-((7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-methoxy-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-((7-(4,4-Difluoro-2-methylbutanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((7-(4,4-Difluoro-2,2-dimethylbutanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((10-Hydroxy-7-(4-(trifluoromethyl)thiazole-2-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-((10-Hydroxy-7-(2-(trifluoromethyl)thiazole-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

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

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

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

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

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

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

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

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*-isopropyl-*N*-methyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-phenyl-5-(pyrrolidine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*R*)-1-((*S*)-3-Cyclohexyl-2-(methoxymethyl)propanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-4-Hydroxy-3,3-dimethyl-1-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)piperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

(*R*)-1-((4-Hydroxy-3,3-dimethyl-1-(4,4,4-trifluoro-2-(2,2,2-trifluoroethyl)butanoyl)piperidin-4-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-((*S*)-2-(hydroxymethyl)piperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-((*R*)-3-methylpiperazine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

1-(((*R*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

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

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

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

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

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-cyclopropyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*R*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

4-(2-Fluorophenyl)-1-(((*R*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

4-(2-Fluorophenyl)-1-(((*R*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*R*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

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

1-(((*R*)-1-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-5-(4-hydroxypiperidine-1-carbonyl)-4-phenylpyridin-2(1*H*)-one;

1-(((*R*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-7-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

1-(((*R*)-7-((*R*)-3-Cyclohexyl-2-methylpropanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-4-cyclopropyl-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

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

1-(((*R*)-1-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-*N*,*N*-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide;

1-(((*R*)-1-((*R*)-3-Cyclobutyl-2-methylpropanoyl)-4-hydroxy-3,3-dimethylpiperidin-4-yl)methyl)-4-(2-fluorophenyl)-5-(piperazine-1-carbonyl)pyridin-2(1*H*)-one;

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

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

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

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

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

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

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

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

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

3-((10-Hydroxy-7-((3*R*,4*R*)-3-phenylpiperidine-4-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

3-(((*S*)-10-Hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

6-(2-Fluorophenyl)-3-(((*S*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one;

6-(3-Fluorophenyl)-3-(((*S*)-10-hydroxy-7-((*R*)-4,4,4-trifluoro-2-methylbutanoyl)-7-azaspiro[4.5]decan-10-yl)methyl)pyrimidin-4(3*H*)-one;

3-(((*S*)-7-((*R*)-4,4-Difluoro-2-methylpentanoyl)-10-hydroxy-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

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

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

3-(((*S*)-10-Hydroxy-7-((2*R*,3*R*)-2-phenylpyrrolidine-3-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one;

3-(((*S*)-10-Hydroxy-7-((2*S*,3*S*)-2-phenylpyrrolidine-3-carbonyl)-7-azaspiro[4.5]decan-10-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one.

33. A compound, or pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative thereof, for use according to any one of claims 1-6, wherein the compound 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(1*H*)-one.

34. 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(1*H*)-one for use in therapy.

35. 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(1*H*)-one for use in a method of treating muscular atrophy.

36. 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(1*H*)-one for use in a method of treating obesity.

37. 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(1*H*)-one for use in a method of treating insulin resistance.

38. 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(1*H*)-one for use in a method of treating type II diabetes.

39. 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(1*H*)-one for use in a method of treating cachexia or sarcopenia.

40. A pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in any one of claims 1-32, for use in therapy.

41. A pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in any one of claims 1-32, for use in treating muscular atrophy.

42. A pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in any one of claims 1-32, for use in treating obesity.

43. A pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in any one of claims 1-32, for use in treating insulin resistance.

44. A pharmaceutical composition comprising a compound, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in any one of claims 1-32, for use in treating type II diabetes.

45. A pharmaceutical composition for use according to any of claims 40-44, further comprising a pharmaceutically acceptable diluent, excipient or carrier.

46. 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 as defined in any one of claims 1-32, or an effective amount of a pharmaceutical composition as defined in any one of claims 40-45.

47. 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 any one of claims 1-32, or an effective amount of a pharmaceutical composition as defined in any one of claims 40-45.

48. 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 any one of claims 1-32, or an effective amount of a pharmaceutical composition as defined in any one of claims 40-45.

49. 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 any one of claims 1-32, or an effective amount of a pharmaceutical composition as defined in any one of claims 40-45.

50. 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, pharmaceutically acceptable salt, tautomer, stereoisomer or *N*-oxide derivative as defined in any one of claims 1-32, or an effective amount of a pharmaceutical composition as defined in any one of claims 40-45.

51. A USP19 inhibitor for use in treating obesity.

52. A USP19 inhibitor for use in treating muscular atrophy.

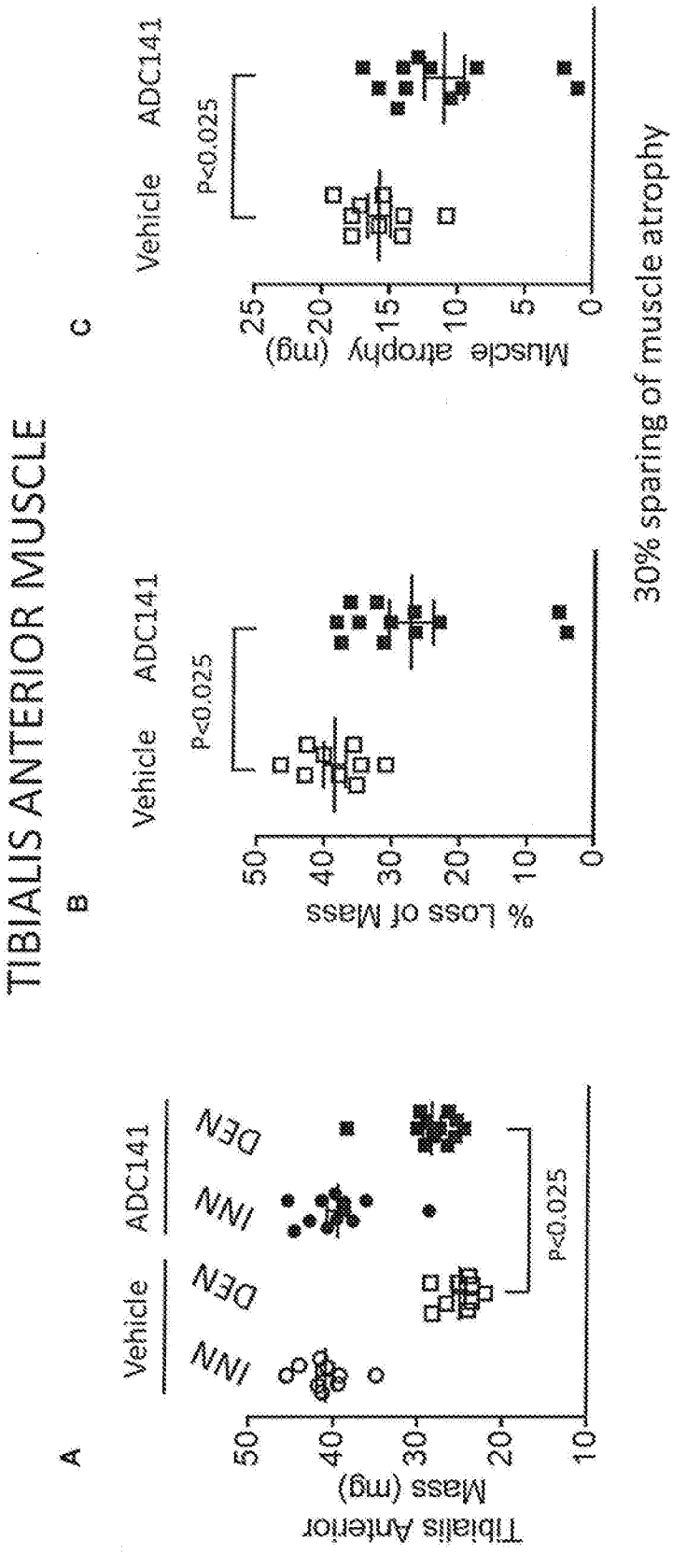
53. A USP19 inhibitor for use in treating type II diabetes.

54. A USP19 inhibitor for use in treating insulin resistance.

55. A USP19 inhibitor for use in treating cancer.

56. A method of treating cancer, obesity, insulin resistance, type II diabetes and/or muscular atrophy comprising administering to a subject in need thereof an effective amount of a USP19 inhibitor.

Figure 1


TIBIALIS ANTERIOR MUSCLE
A
Vehicle
ADC141
INN
DEN
INN
DEN
P<0.025
Tibialis Anterior Mass (mg)
50
40
30
20
10
B
Vehicle
ADC141
P<0.025
% Loss of Mass
50
40
30
20
10
0
C
Vehicle
ADC141
P<0.025
Muscle atrophy (mg)
25
20
15
10
5
0
30% sparing of muscle atrophy

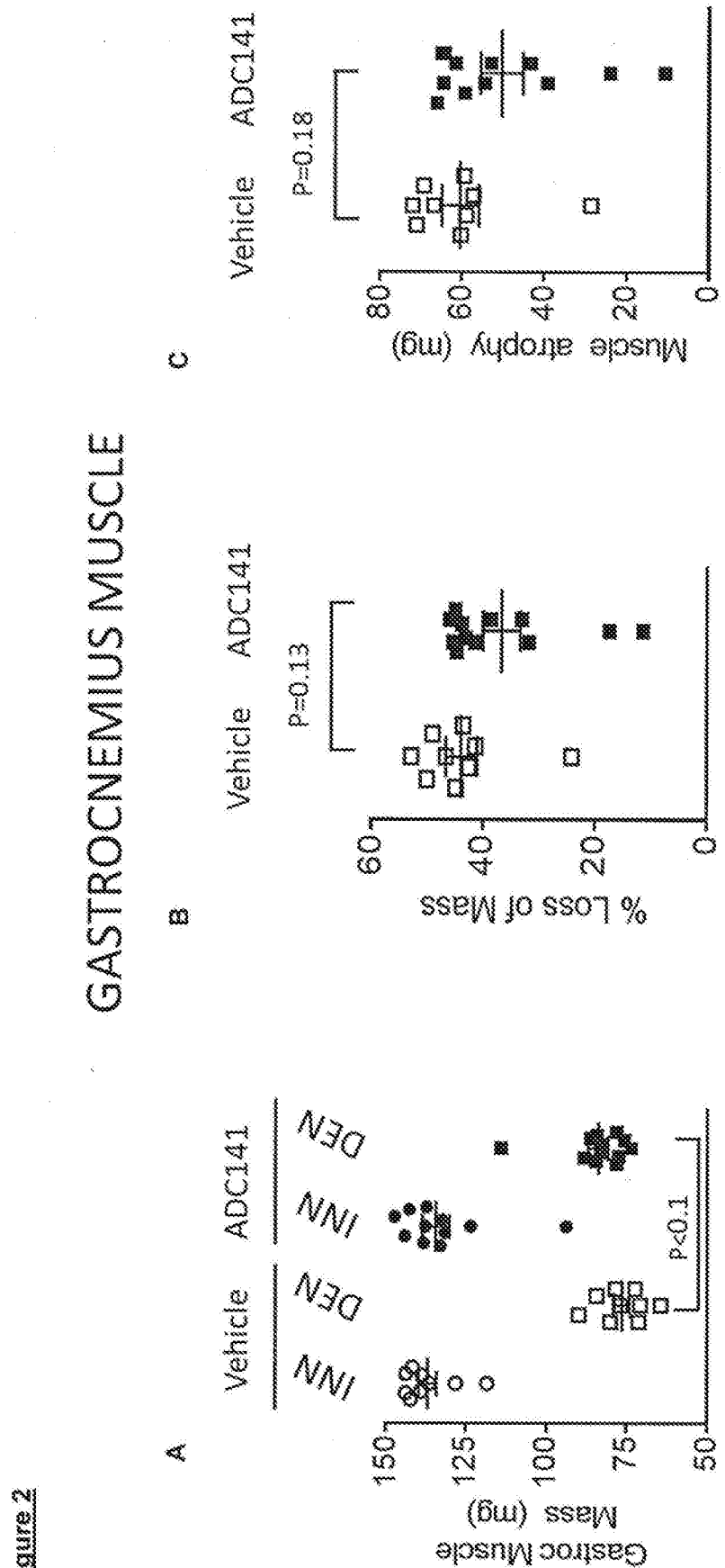
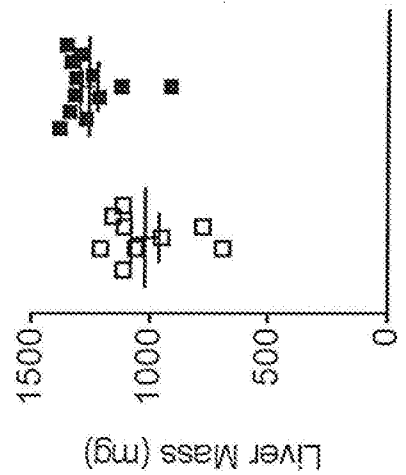

GASTROCNEMIUS MUSCLE
A
Vehicle
ADC141
INN
DEN
INN
DEN
P<0.1
Gastroc Muscle Mass (mg)
150
125
100
75
50
B
Vehicle
ADC141
P=0.13
% Loss of Mass
60
40
20
0
C
Vehicle
ADC141
P=0.18
Muscle atrophy (mg)
80
60
40
20
0

Figure 2

Figure 3


B
Vehicle
ADC141
P<0.005
Liver Mass (mg)
1500
1000
500
0

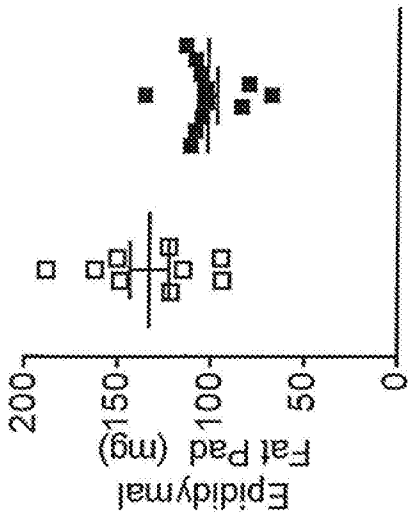
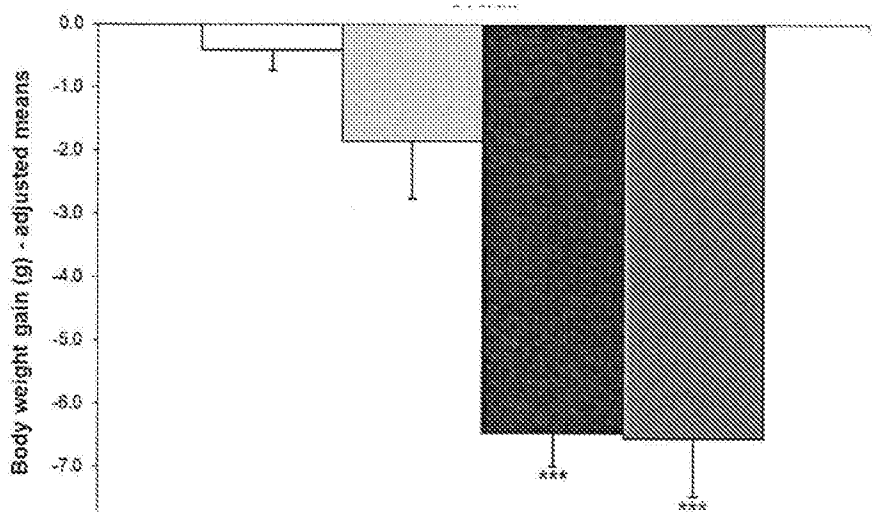

A
Vehicle
ADC141
P<0.025
Epididymal
Fat Pad (mg)
200
150
100
50
0

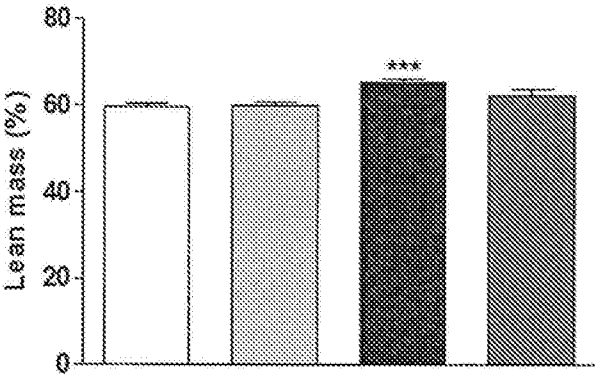
Figure 3 (cont)

C

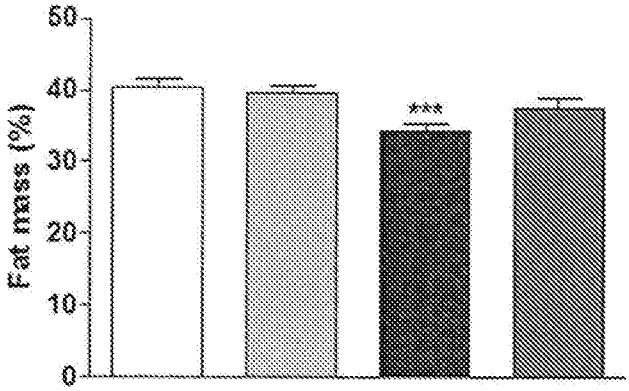


5

D



E



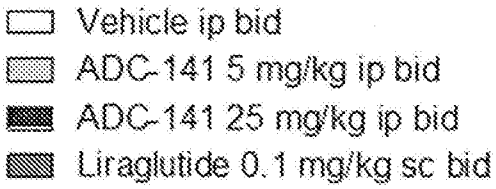


Figure 4

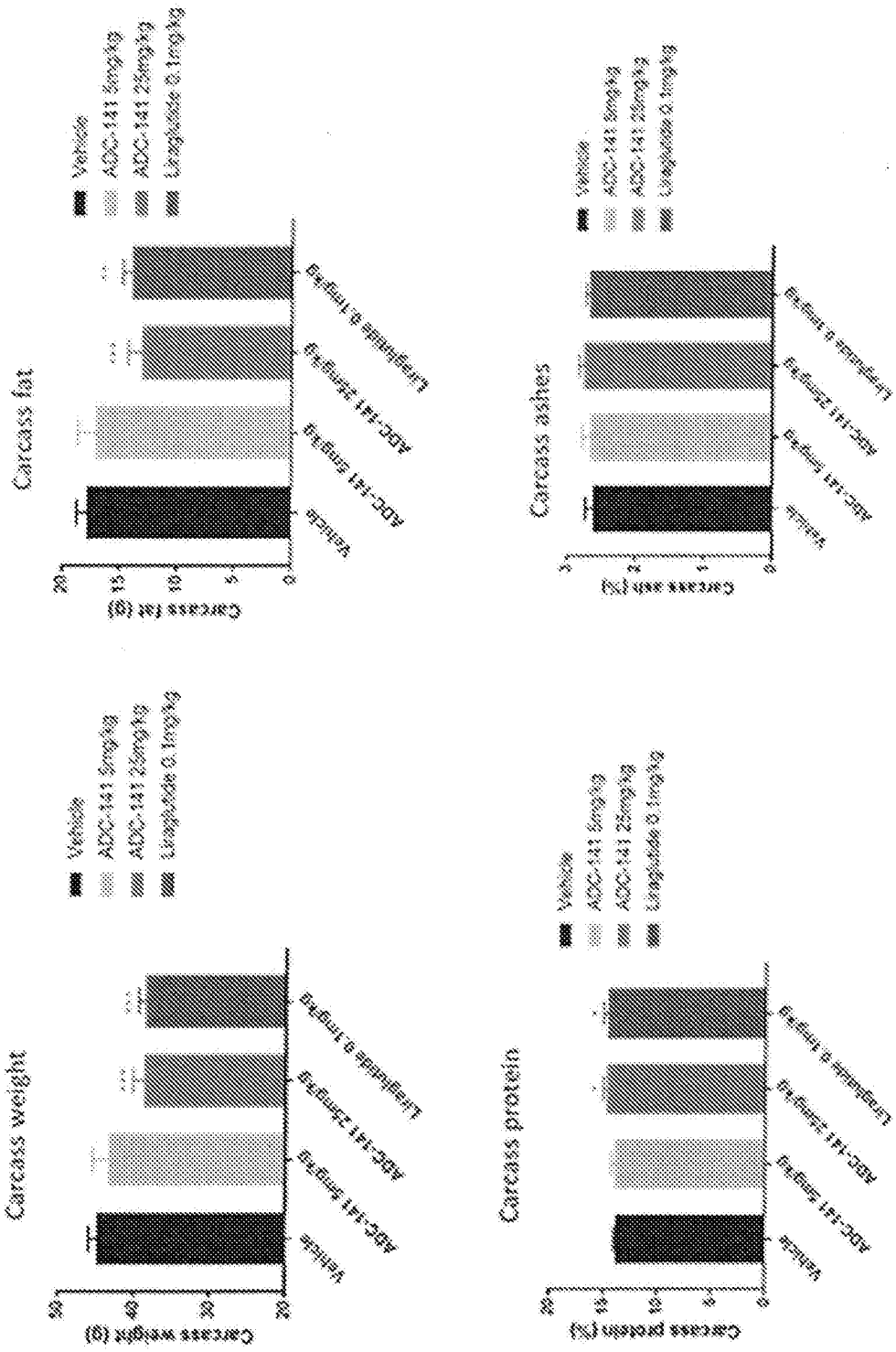

Carcass fat
Carcass weight
Carcass ashes
Carcass protein
Vehicle
ADC-141 5mg/kg
ADC-141 25mg/kg
Liraglutide 0.1mg/kg
Carcass fat (g)
Carcass weight (g)
Carcass ash (%)
Carcass protein (%)

Figure 5

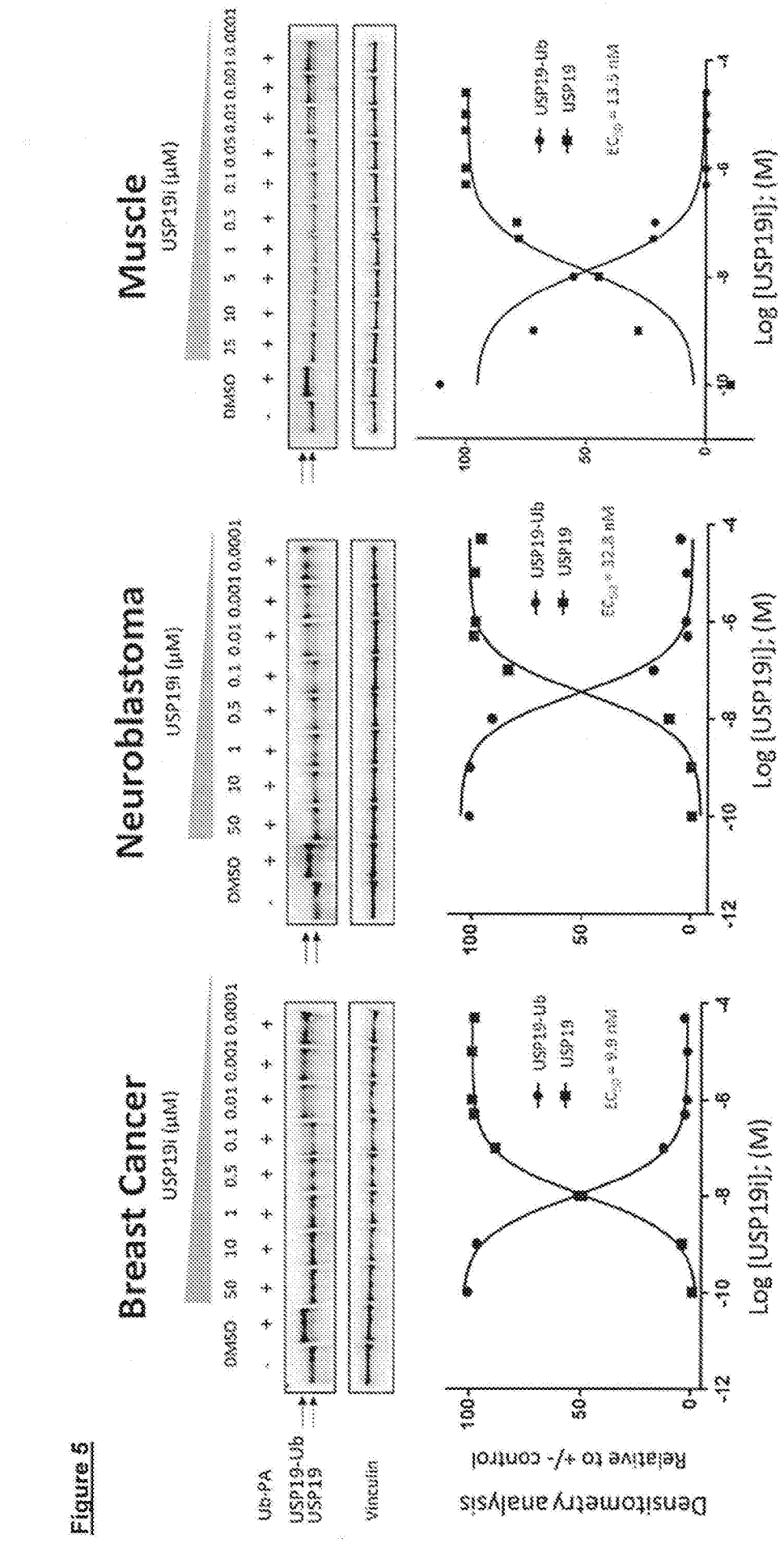
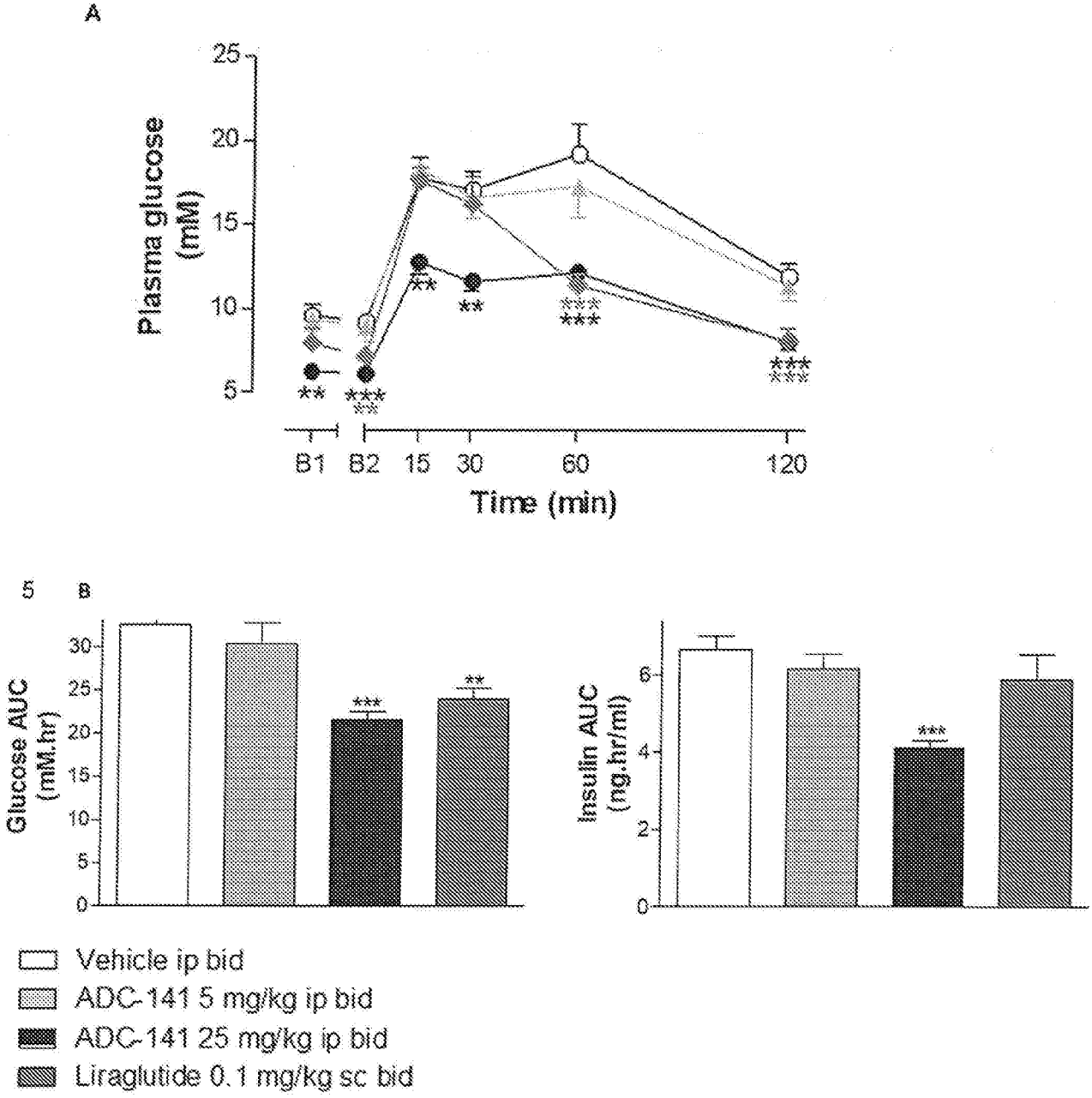

Breast Cancer
Neuroblastoma
Muscle
USP19i (μM)
DMSO 50 10 1 0.5 0.1 0.01 0.001 0.0001
Ub-PA
USP19-Ub
USP19
Vinculin
Densitometry analysis
Relative to +/- control
Log [USP19i]; (M)
USP19-Ub
USP19
EC50 = 9.8 nM
EC50 = 32.8 nM
EC50 = 13.5 nM

Figure 6


A
Plasma glucose (mM)
25
20
15
10
5
B1
B2
15
30
60
120
Time (min)
B
Glucose AUC (mM.hr)
30
25
20
15
10
5
0
Insulin AUC (ng.hr/ml)
6
4
2
0
Vehicle ip bid
ADC-141 5 mg/kg ip bid
ADC-141 25 mg/kg ip bid
Liraglutide 0.1 mg/kg sc bid

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/053456

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4545 A61K31/496 A61K31/513 A61K31/5377 A61P3/04
A61P5/48 A61P21/00 A61P35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/020242 A1 (ALMAC DISCOVERY LTD [GB]) 1 February 2018 (2018-02-01) cited in the application page 251 - page 252; claim 1	1-56
X,P	WO 2019/150119 A1 (ALMAC DISCOVERY LTD [GB]) 8 August 2019 (2019-08-08) cited in the application claims 1,40-50	51-56

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 February 2020	21/02/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bonzano, Camilla

3

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COYNE ERIN S ET AL: "The deubiquitinating enzyme USP19 modulates adipogenesis and potentiates high-fat-diet-induced obesity and glucose intolerance in mice", DIABETOLOGIA, SPRINGER, BERLIN, DE, vol. 62, no. 1, 1 November 2018 (2018-11-01), pages 136-146, XP036914595, ISSN: 0012-186X, DOI: 10.1007/S00125-018-4754-4 [retrieved on 2018-11-01] abstract -----	51,53-56
X	COLIN R. O'DOWD ET AL: "Identification and Structure-Guided Development of Pyrimidinone Based USP7 Inhibitors", ACS MEDICINAL CHEMISTRY LETTERS, vol. 9, no. 3, 21 February 2018 (2018-02-21), pages 238-243, XP055565198, US ISSN: 1948-5875, DOI: 10.1021/acsmedchemlett.7b00512 abstract tables 3,4 -----	1,7-34, 40,45
X	CN 104 174 021 A (HUASHAN HOSPITAL FUDAN UNIV) 3 December 2014 (2014-12-03) abstract -----	51,53-56

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2019/053456

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		JP 2019523266 A	22-08-2019
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		SG 11201900545T A	27-02-2019
		US 2019233394 A1	01-08-2019
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CN 104174021 A	03-12-2014	NONE	