

SPIROLACTAM DERIVATIVES AND USES OF SAME

FIELD OF THE INVENTION

The present invention provides spirolactam derivatives, as well as pharmaceutical compositions and methods of treatment using same.

5 BACKGROUND OF THE INVENTION

This invention concerns spirolactam derivatives, which act as allosteric modulators of the metabotropic glutamate receptor 5 (mGlu5 receptors or mGluR5), as well as pharmaceutical compositions and methods of treatment utilizing these compounds.

10 Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. One means of modulating glutamate neurotransmission is through metabotropic glutamate receptors (mGluRs); another means being ionotropic receptors. Presently, eight mGluRs have been cloned and classified into three groups based on sequence homology, preferred signal transduction pathway and pharmacology. Group I of mGluRs includes mGluR1 and mGluR5, while Group II comprises mGluR2 and mGluR3 and Group III comprises mGlu4,
15 6, 7 and 8 receptors.

mGlu receptors have an essential role in normal brain functions, as well as in neurological, psychiatric, and neuromuscular disorders. mGlu5 receptors are located primarily postsynaptically and highly expressed in the limbic brain regions. mGlu5 receptors also are expressed in the thalamus, spinal cord, and vagal nerve systems, as well as peripherally in the
20 skin on nerve endings and C fibers.

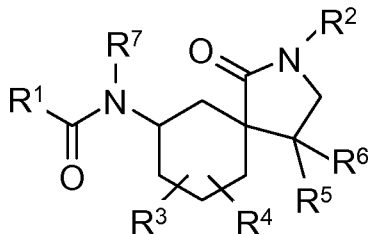
Ligands to the mGlu5 receptors have been shown to have promise for peripheral and central nervous system disorders. See e.g., G. Jaeschke *et al.*, "mGlu5 receptor antagonists and their therapeutic potential," *Expert Opin. Ther. Patents*, **2008**, 18, 2: 123-142. Yet some proffer that glutamate analogs targeting the orthosteric binding site may be limited by low brain
25 penetration and insufficient selectivity with respect to the different mGluRs subtypes. Synthetic agonists may lead to continuous stimulation of the receptor since they are often designed to be metabolically stable. This continuous stimulation is not necessarily desirable, due to potential receptor desensitization issues. Also, with respect to receptor occupancy,

synthetic antagonists may lead to prolonged blockade of receptor function, which may not be compatible with the kinetics of the pathology of a central nervous system disorder.

However, a more selective and controlled “fine-tuning” action on the mGlu5 receptor is feasible through allosteric modulation. *See e.g.*, P. Bach *et al.*, “Metabotropic glutamate receptor 5 modulators and their potential therapeutic applications,” *Expert Opin. Ther. Patents*, **2007**, 17, 4: 371-381. Allosteric modulation refers to binding by a modulator ligand to a site on a receptor that is different from the orthosteric primary substrate or ligand binding site. This ligand binding process results in conformational changes, which may profoundly influence the function of the protein (*e.g.*, G protein-coupled receptors such as mGluRs, including mGluR5). Novel mGluR5 ligands that allosterically modulate the mGlu5 receptor may improve the therapeutic window of traditional central nervous system agents and/or the treatment of central nervous system disorders. The present invention is directed these, and other important, ends.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula (I):



(I)

wherein:

R^1 and R^2 are each independently aryl, heteroaryl, alkyl, cycloalkyl, ketocycloalkyl, or heterocyclyl, which is optionally mono-, di-, or tri-substituted independently with alkyl, cycloalkyl, alkoxy, hydroxy, halogen, cyano, trifluoroalkyl, amino, acyl, aryl, heteroaryl, heterocyclyl, $-C(O)NHR^{30}$, $-C(O)N(R^{30})R^{31}$, $-NHC(O)R^{30}$, $-N(R^{30})C(O)R^{31}$, $-NHR^{30}$, $-N(R^{30})R^{31}$, or $-OR^{30}$; wherein:

R³⁰ and R³¹ are each independently C₁-C₆alkyl or C₁-C₆cycloalkyl that is optionally substituted with acyl, halogen, -CN, -NH₂, -NH(C₁-C₃alkyl), -N(C₁-C₃alkyl)₂, C₁-C₃alkylheterocyclyl, C₁-C₃alkylcarbamate, -C(O)NH(C₁-C₃alkyl), -C(O)N(C₁-C₃alkyl)₂, -NHC(O)-C₁-C₃alkyl, -N(C₁-C₃alkyl)-C(O)-C₁-C₃alkyl, OH, or -O-C₁-C₆alkyl; and

each aryl, heteroaryl, heterocyclyl substituent is optionally substituted with C₁-₃alkyl, C₃-₅cycloalkyl, C₁-₃alkoxy, hydroxy, halogen, cyano, trifluoroalkyl, or amino;

R³, R⁴, R⁵ and R⁶ are each independently H, C₁-₃alkyl, C₃-₅cycloalkyl, halogen, or hydroxy;

R⁷ is H; or

R¹ and R⁷ taken together with the -C(O)N- to which they are attached form a mono- or bicyclic 4- to 12-membered heterocycloalkyl or heteroaryl, which optionally contains 1-3 additional heteroatoms; or

a pharmaceutically acceptable salt thereof.

The present invention also provides a pharmaceutical composition comprising at least one compound of formula (I) or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.

The present invention also provides a method of treating a disease or disorder, the method comprises administering a therapeutically effective amount of at least one compound of the present invention or a pharmaceutically acceptable salt thereof to a mammal in need thereof, wherein the disease or disorder is a central nervous system disease or disorder. In some embodiments of the method, a symptom of the disease or disorder is treated.

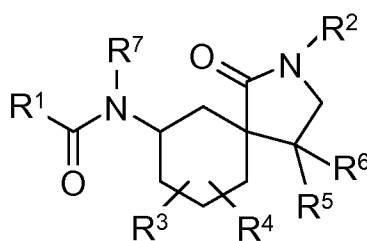
FIGURES

Figure 1: Effect of a compound of formula (I) in a mouse model for affective diseases and disorders in accordance with an embodiment of the invention.

Figure 2: Effect of a compound of formula (I) in a rat model for affective diseases and disorders in accordance with an embodiment of the invention.

Figure 4: Effect of a compound of formula (I) in a rat model for affective diseases and disorders in accordance with an embodiment of the invention.

In one aspect, the present invention provides spiro lactam derivatives. The spiro lactam derivatives are compounds of formula (I):



(I)

R¹ and R² are each independently aryl, heteroaryl, alkyl, cycloalkyl, ketocycloalkyl, or heterocyclyl, which is optionally mono-, di-, or tri-substituted independently with alkyl, cycloalkyl, alkoxy, hydroxy, halogen, cyano, trifluoroalkyl, amino, acyl, aryl, heteroaryl, heterocyclyl, -C(O)NHR³⁰, -C(O)N(R³⁰)R³¹, -NHC(O)R³⁰, -N(R³⁰)C(O)R³¹, -NHR³⁰, -N(R³⁰)R³¹, or -OR³⁰; wherein:

R³⁰ and R³¹ are each independently C₁-C₆alkyl or C₁-C₆cycloalkyl that is optionally substituted with acyl, halogen, -CN, -NH₂, -NH(C₁-C₃alkyl), -N(C₁-C₃alkyl)₂, C₁-C₃alkylheterocyclyl, C₁-C₃alkylcarbamate, -C(O)NH(C₁-C₃alkyl), -C(O)N(C₁-C₃alkyl)₂, -NHC(O)-C₁-C₃alkyl, -N(C₁-C₃alkyl)-C(O)-C₁-C₃alkyl, OH, or -O-C₁-C₆alkyl; and

each aryl, heteroaryl, heterocyclyl substituent is optionally substituted with C₁₋₃alkyl, C₃₋₅cycloalkyl, C₁₋₃alkoxy, hydroxy, halogen, cyano, trifluoroalkyl, or amino;

R³, R⁴, R⁵ and R⁶ are each independently H, C₁₋₃alkyl, C₃₋₅cycloalkyl, halogen, or hydroxy;

R⁷ is H; or

R¹ and R⁷ taken together with the -C(O)N- to which they are attached form a mono- or bicyclic 4- to 12-membered heterocycloalkyl or heteroaryl, which optionally contains 1-3 additional heteroatoms; or

a pharmaceutically acceptable salt thereof.

The term "alkyl", employed alone or as part of a group, is defined herein, unless otherwise stated, as either a straight-chain or branched saturated hydrocarbon of 1 to 8 carbon atoms. In some embodiments, the alkyl moiety contains 8, 7, 6, 5, 4, 3, 2 or 1 carbon atoms. Where the term "alkyl" appears herein without a carbon atom range it means a range of C₁-C₈. Where the term "alkyl" appears herein with a carbon range, it means an alkyl of any number within in the carbon range identified, such as a C₁-C₃alkyl means either methyl, ethyl or propyl. Examples of saturated hydrocarbon alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, *isopropyl*, *n*-butyl, *tert*-butyl, *iso*-butyl, *sec*-butyl, *n*-pentyl, *n*-hexyl, and the like. Alkyl also refers to alkyl moieties where the alkyl group is substituted by hydroxy, cyano, alkoxy, alkylamino, dialkylamino, alkylamide, dialkylamide, and the like, including without limitation, -OC₁-C₄alkyl-OH, -OC₁-C₄alkyl-OCH₃, -OC₁-C₄alkyl-NHCH₃, -OC₁-C₄alkyl-N(CH₃)₂, -OC₁-C₄alkyl-CONHCH₃, -OC₁-C₄alkyl-CON(CH₃)₂, -OC₁-C₄alkyl-NHCOCH₃, and -OC₁-C₄alkyl-N(CH₃)COCH₃.

The term "alkoxy", employed alone or in combination with other terms, is defined herein, unless otherwise stated, as -O-alkyl, where "alkyl" is as previously defined herein. Examples of alkoxy moieties include, but are not limited to, chemical groups such as methoxy, ethoxy, *iso*-propoxy, *sec*-butoxy, *tert*-butoxy, and homologs, isomers, and the like. Alkoxy also refers to -O-alkyl moieties where the alkyl group is substituted by hydroxy, cyano, alkoxy, alkylamino, dialkylamino, alkylamide, dialkylamide, and the like, including without limitation, -OC₁-C₄alkyl-OH, -OC₁-C₄alkyl-OCH₃, -OC₁-C₄alkyl-NHCH₃, -OC₁-C₄alkyl-N(CH₃)₂, -OC₁-C₄alkyl-CONHCH₃, -OC₁-C₄alkyl-CON(CH₃)₂, -OC₁-C₄alkyl-NHCOCH₃, and -OC₁-C₄alkyl-N(CH₃)COCH₃.

The term “hydroxyalkyl”, employed alone or in combination with other terms, is defined herein, unless otherwise stated, as –alkyl-OH, where “alkyl” is as previously defined herein. Nonlimiting examples include methyl-OH, ethyl-OH, *n*-propyl-OH, and the like.

As used herein, the term “cycloalkyl”, employed alone or in combination with other terms, is defined herein, unless otherwise stated, as a cyclized alkyl group having from 3 to 8 ring carbon atoms, where “alkyl” is as defined herein. Examples of cycloalkyl moieties include, but are not limited to, chemical groups such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

As used herein, the term “ketocycloalkyl”, employed alone or in combination with other terms, is defined herein, unless otherwise stated, as a cycloalkyl having a keto radical attached thereto, where “cycloalkyl” is as defined herein. Examples include cyclopentanone or cyclohexanone.

The terms “halo” or “halogen”, employed alone or in combination with other terms, is defined herein, unless otherwise stated, as fluoro, chloro, bromo, or iodo.

The term “aryl”, employed alone or in combination with other terms, is defined herein, unless otherwise stated, as an aromatic hydrocarbon of up to 14 carbon atoms, which can be a single ring (monocyclic) or multiple rings (*e.g.*, bicyclic, tricyclic, polycyclic) fused together or linked covalently. Any suitable ring position of the aryl moiety can be covalently linked to the defined chemical structure. Examples of aryl moieties include, but are not limited to, chemical groups such as phenyl, benzyl, 1-naphthyl, 2-naphthyl, and the like. An aryl group can be unsubstituted or substituted as described herein.

The term “heteroaryl” employed alone or in combination with other terms, is defined herein, unless otherwise stated, as a monocyclic or polycyclic (fused together or linked covalently) aromatic hydrocarbon ring comprising one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. A heteroaryl group comprises up to 14 carbon atoms and 1 to 6 heteroatoms. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, 2-quinoliny,

2-quinazolinyl, 3-phenyl-2-quinolinyl and the like. A heteroaryl group can be unsubstituted or substituted as described herein.

The term “heterocyclyl” employed alone or in combination with other terms, is defined herein, unless otherwise stated, as a univalent group formed by removing a hydrogen atom from any ring atom of a heterocycle.

The term “acyl” employed alone or in combination with other terms, is defined herein, unless otherwise stated, as groups of formula -C(O)-alkyl, where alkyl is a previously described herein; *i.e.*, an alkylcarbonyl, such as formyl, acetyl and the like.

The term “aminoalkyl” employed alone or in combination with other terms, is defined herein, unless otherwise stated, as alkyl-amino, where the term “alkyl” is as previously defined herein and the term “amino” is -NH₂, -NH-, or -N<. Non-limiting examples include -CH₃NH-, CH₃CH₂NH-, (C₁-C₃alkyl)NH-, (C₁-C₃alkyl)₂N-, and the like.

The term “alkylamino” employed alone or in combination with other terms, is defined herein, unless otherwise stated, as amino-alkyl, where the term “alkyl” is as previously defined herein and the term “amino” is -NH₂, -NH-, or -N<. Non-limiting examples include -NHCH₃, -NHCH₂CH₃, -NH(C₁-C₃alkyl), -N(C₁-C₃alkyl)₂, and the like.

In some embodiments, R¹ and R² are both aryl. In some embodiments, R¹ and R² are both heteroaryl. In some embodiments, R¹ is aryl and R² is heteroaryl. In some embodiments, R¹ is heteroaryl and R² is aryl. In some embodiments, either R¹ or R² is heteroaryl. In some embodiments, either R¹ or R² is aryl.

In some embodiments, either R¹ or R² is alkyl. In some embodiments, either R¹ or R² is cycloalkyl. In some embodiments, either R¹ or R² is ketocycloalkyl. In some embodiments, either R¹ or R² is heterocyclyl.

In some embodiments, at least one aryl is phenyl. In some embodiments, at least one heteroaryl is pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiazolyl, pyrazolyl, indazolyl, thiophenyl, furanyl, or benzofuranyl. In some embodiments, both aryls are phenyl. In some embodiments, both heteroaryls are selected from a group consisting of pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiazolyl, pyrazolyl, indazolyl, indazolylimidazolyl, thiophenyl, furanyl, and benzofuranyl. In some embodiments, at least one heteroaryl is

pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, thiazolyl, pyrazolyl, indazolyl, thiophenyl, furanyl, benzofuranyl, benzo[c]isoxazolyl, benzoxazolyl, benzothiazolyl, dihydrothieno[3,4-b][1,4]dioxinyl, furanyl, imidazo[1,2-a]pyridinyl, indazolyl, indolinyl, indolyl, isoquinolinyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolo[3,2-c]pyridinyl, quinolinyl, quinoxalinyl, thiazolyl, or thiophenyl.

In some embodiments, R^1 is aryl or heteroaryl and R^2 is cycloalkyl, ketocycloalkyl or heterocyclyl. In some embodiments, R^2 is aryl or heteroaryl and R^1 is cycloalkyl, ketocycloalkyl or heterocyclyl.

In some embodiments, either R^1 or R^2 is cycloalkyl. In some embodiments, at least one cycloalkyl is cyclobutyl, cyclohexyl, cycloheptyl, cyclopentyl, or cyclopropyl. In some embodiments, the cycloalkyl is further substituted beyond the tri-substitution previously defined, *i.e.*, the cycloalkyl is substituted more than three times as previously described; for example, the cycloalkyl is tetra-substituted with fluorine.

In some embodiments, the heteroaryl is pyridinyl, and the pyridinyl is mono-, di-, or tri-substituted as previously defined. In some such embodiments, the mono-, di-, or tri-substitutions are independently aryl, heteroaryl, and heterocyclyl. In some such embodiments, the aryl, heteroaryl and heterocyclyl substituent is further substituted, such as, *e.g.*, with halogen or C_{1-3} alkyl.

In some embodiments, at least one aryl or heteroaryl is substituted as previously described.

In some some embodiments, wherein the mono-, di-, or tri-substituents are independently selected from the group consisting of methyl, methoxy, dimethylamino-ethoxy, amino, methylamino, dimethylamino, cyano, chloro, cyano, dimethylamino, dimethylamino-ethoxy, methyl, methylamino, methoxy, fluoro, $-C(O)NHCH_3$, phenyl, furanyl, pyrrolidinyl, thiophenyl and trifluoromethyl. In some embodiments, the 1, 2, or 3 substituents are independently selected from the group consisting of methyl, methoxy, dimethylamino-ethoxy, amino, methylamino, dimethylamino, cyano, chloro, fluoro, phenyl, furanyl and thiophenyl.

In some embodiments, the phenyl, furanyl or thiophenyl substituent of at least one aryl or heteroaryl is substituted with at least one alkyl, alkoxy, hydroxyalkyl, halogen, cyano, or trifluoroalkyl. In some such embodiments, the phenyl is substituted with fluorine.

In some embodiments, R¹ and R² each are independently selected from a group consisting of the aryl, heteroaryl, alkyl, cycloalkyl, ketocycloalkyl and heterocyclyl groups of the compounds of Table 1 and 2, below.

In some embodiments, R³, R⁴, R⁵ and R⁶ are each independently H, C₁₋₃alkyl, C₃₋₅cycloalkyl, halogen, or hydroxy. In some embodiments, R³, R⁴, R⁵ and R⁶ are each independently methyl or fluorine.

In some embodiments, R⁷ is hydrogen. In some embodiments, R⁷ along with R¹ are taken together with the -C(O)N< to which they are attached form a mono- or bicyclic 4- to 12-membered heterocycloalkyl or heteroaryl, which optionally contains 1-3 additional heteroatoms.

In some embodiments, the compound of formula (I) is a compound disclosed in the Experimental Section below. In some embodiments, the compound is one from Table 1 or 2, below.

Another aspect of the present invention is a composition that comprises a pharmaceutically effective amount of a compound according to the present invention, and a pharmaceutically acceptable carrier or excipient.

A composition of the present invention may be adapted to any mode of administration, such as orally (including sublingually), *via* implants, parentally (including intravenous, intraperitoneal, intraarticularly and subcutaneous injections), rectally, intranasally, topically, ocularly (*via* eye drops), vaginally, and transdermally.

A compound of the present invention can be used either as a free base or in the form of a salt derived from pharmaceutically acceptable acids or bases. The salt includes without limitation the following: salts with inorganic acids, *e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid, and organic acids *e.g.*, acetic acid, oxalic acid, citric acid, tartaric acid, succinic acid, maleic acid, benzoic acid, benzene sulfonic acid, fumaric acid, malic acid, methane sulfonic acid, pamoic acid, and para-toluene sulfonic acid. Other

salts include salts with alkali metals or alkaline earth metals, *e.g.*, sodium, potassium, calcium and magnesium, or with organic bases, including quaternary ammonium salts. Further non-limiting examples of pharmaceutically acceptable inorganic and organic acid addition salts include those listed in [S.M. Berge *et al.*, *J. Pharm. Sci.* **1977**, 66, 1: 2, and G.S. Paulekuhn, *et al.*, *J. Med. Chem.* **2007**, 50, 26: 6665-6672].

A compound of the present invention can also be used in the form of an ester, carbamate and other conventional prodrug form, which generally will be a functional derivative of the compound that is readily converted to the active moiety *in vivo*. Also included are metabolites of a compound of the present invention defined as active species produced upon introduction of the compound into a biological system.

When a compound of the present invention is employed as described above, it may be combined with one or more pharmaceutically acceptable excipients or carriers, *e.g.*, solvents, diluents and the like. Such pharmaceutical preparations may be administered orally in such forms as tablets, capsules (including, *e.g.*, time release and sustained release formulations), pills, lozenges, aerosols, dispersible powders, granules, solutions, suspensions (containing, *e.g.*, a suspending agent, at, *e.g.*, from about 0.05 to about 5% of suspending agent), syrups (containing, *e.g.*, sugar or a sugar substitute such as aspartame, at, *e.g.*, about 10 to about 50% sugar or sugar substitute), elixirs and the like, or parenterally in the form of sterile injectable solutions, suspensions or emulsions containing, *e.g.*, from about 0.05 to about 5% suspending agent in an isotonic medium. Such preparations may contain, *e.g.*, from about 25 to about 90% of the active ingredient in combination with the carrier, more customarily from about 5% and about 60% by weight. The effective dosage of an active ingredient (*e.g.*, a compound or salt of the present invention and a prodrug or metabolite thereof) employed may vary depending on the particular compound, salt, prodrug or metabolite used, the mode of administration, age, weight, sex and medical condition of the patient, and the severity of the disease, disorder, condition, and/or system being treated. The selection of the appropriate administration and dosage form for an individual mammal will be apparent to those skilled in the art. Such determinations are routine to a physician, veterinarian or clinician of ordinary skill in the art (*see e.g.*, *Harrison's Principles of Internal Medicine*, Anthony Fauci *et al.* (eds.) 14th ed. New York: McGraw Hill (1998)). Further, the dosage regimen may be

adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the needs of the therapeutic situation.

5 Solid carriers, *e.g.*, starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, liquid carriers, *e.g.*, sterile water, polyethylene glycols, glycerol, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, may be employed as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included. Non-limiting examples of adjuvants include flavoring
10 agents, coloring agents, preserving agents, and antioxidants, such as vitamin E, ascorbic acid, BHT and BHA.

An active compound also may be administered parenterally or intraperitoneally. Solutions or suspensions of the active compound as a free base, neutral compound or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as
15 hydroxypropylcellulose. Dispersions also can be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. These preparations may contain a preservative to prevent the growth of microorganisms under ordinary conditions of storage and use.

The pharmaceutical forms suitable for injectable or infusing use include sterile aqueous solutions, suspensions or dispersions, and sterile powders for the extemporaneous preparation
20 of sterile injectable or infusing solutions, suspension or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy injectability and infusing exists. It must be stable under conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, and polyol (*e.g.*, glycerol, propylene glycol,
25 and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

Furthermore, active compounds of the present invention can be administered intranasally or transdermally using vehicles suitable for intranasal or transdermal delivery known to those ordinarily skilled in the art. Transdermal administration includes all administrations across the surface of the body and the inner linings of bodily passages including epithelial and

mucosal tissues, using carrier systems such as lotions, creams, foams, pastes, patches, suspensions, solutions, and suppositories (rectal and vaginal). Creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient also may be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature. When using a transdermal delivery system, the dosage administration will be continuous rather than a single or divided daily dose.

A compound of the present invention can also be administered in the form of a liposome delivery system where the liposomal lipid bilayer is formed from a variety of phospholipids. A compound of the present invention also may be delivered by the use of a carrier such as monoclonal antibodies to which the compound is coupled. Other carriers to which a compound of the present invention also may be coupled are a soluble polymer or a biodegradable polymer useful in achieving controlled release of an active ingredient.

It is understood by those practicing the art that some of the compounds of the present invention may contain one or more asymmetric centers, and thus may give rise to enantiomers and diastereomers. The present invention includes all stereoisomers including individual diastereomers and resolved, enantiomerically pure stereoisomers, as well as racemates, and all other variations of stereoisomers, and mixtures and pharmaceutically acceptable salts thereof, which possess the indicated activity. Optical isomers may be obtained in pure form by procedures known to those skilled in the art, and include, but are not limited to, chiral chromatographic separations, diastereomeric salt formation, kinetic resolution, and asymmetric synthesis. It is also understood that this invention encompasses all possible regioisomers, endo-exo isomers, and mixtures thereof that possess the indicated activity. Such isomers can be obtained in pure form by procedures known to those skilled in the art, and include, but are not limited to, column chromatography, thin-layer chromatography, and high-performance liquid chromatography. It is understood by those practicing the art that some of the compounds of the present invention may be chiral due to

hindered rotation, and give rise to atropisomers, which can be resolved and obtained in pure form by procedures known to those skilled in the art. It is further understood by those practicing the art that some of the compounds of the present invention include structural isomers, including tautomers.

5 Included also in this invention are polymorphs and hydrates of the compounds of the present invention, as well as isotopically labeled analogs thereof (e.g., ^2H , ^3H , ^{13}C , ^{15}N and the like).

Another aspect of the present invention is a method for using the compounds of the invention. The invention is to be understood as embracing all simultaneous, sequential or separate use of any combination of the compounds of the invention with any pharmaceutical
10 composition useful in the methods and uses described herein.

In some embodiments, the method includes administering an effective amount of a compound of formula (I), or salt thereof. In some embodiments, the method includes administering a therapeutically effective amount of a compound described herein, or salt thereof.

15 As used herein, the phrase “effective amount” when applied to a compound of the invention, is intended to denote an amount sufficient to cause an intended biological effect. The phrase “therapeutically effective amount” when applied to a compound of the invention is intended to denote an amount of the compound that is sufficient to ameliorate, palliate, stabilize, reverse, slow or delay the progression of a disorder or disease state, or of a symptom of the
20 disorder or disease. In some embodiments, the method or use of the present invention provides for administration of combinations of compounds. In such instances, the “effective amount” is the amount of the combination sufficient to cause the intended biological effect.

In some embodiments, the method includes administering an effective amount of a combination of two or more of the compounds described herein, or salts thereof. It is
25 specifically intended that the phrases “combination of two or more of the compounds described herein, or salts thereof,” or “at least one compound as described herein, or a pharmaceutically acceptable salt thereof,” or similar language describing specific compounds, includes the administration of such compounds in any proportion and combination of salt, neutral or free base forms; *i.e.*, includes the administration of such

compounds each in the base form, each in the neutral form or each in the salt form, or one or more in the base form and one or more in the neutral form, or one or more in the base form and one or more in the salt form, or one or more in the neutral form and one or more in the salt form, in any proportion of the neutral and/or basic compounds and/or salts.

5 The term "treatment" or "treating" as used herein means ameliorating or reversing the progress of a disease or disorder, or ameliorating or reversing one or more symptoms or side effects of such disease or disorder. For example, "treatment" or "treating" can refer to slowing, interrupting, controlling, lessening, stopping, or regulating the progression or continuation of a disease or disorder. "Treatment" or "treating", as used herein, also means
10 to, inhibit or block, as in retard, arrest, restrain, impede or obstruct, the progress of a system, condition or state of a disease or disorder. For purposes of this invention, "treatment" or "treating" further means an approach for obtaining beneficial or desired clinical results, where "beneficial or desired clinical results" include, without limitation, alleviation of a symptom, diminishment of (or reducing) the extent of a disorder or disease, stabilized (i.e.,
15 not worsening) disease or disorder state, delay or slowing of a disease or disorder state, amelioration or palliation of a disease or disorder state, and remission of a disease or disorder, whether partial or total, detectable or undetectable.

The term "prevent" or "preventing" as used herein means to keep from happening or existing. The term "administering" as used herein refers to either directly administering a compound of
20 the present invention, or administering a prodrug, derivative, or analog of same, that will form an effective amount of the compound within a mammal.

The present invention also provides a method of treating a disease or disorder, the method comprises administering a therapeutically effective amount of at least one compound of the present invention or a pharmaceutically acceptable salt thereof to a mammal in need thereof,
25 wherein the disease or disorder is a central nervous system disease or disorder.

The present invention also provides a use of compound of the present invention, including a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of a central nervous system disease or disorder. The present invention further provides a compound of the present invention for use in treating a disease or disorder.

A compound of the present invention can allosterically modulate the mGlu5 receptor. An allosteric modulator that enhances or potentiates the affinity of an orthosteric ligand for the mGluR5 receptor and/or enhances or potentiates an orthosteric agonist's efficacy is an allosteric enhancer (or potentiator) or positive allosteric modulator (PAM). *See e.g.*, May, L.T. *Annu. Rev. Pharmacol. Toxicol.* **2007**, 47, 1-51. An allosteric modulator that reduces or diminishes the affinity of an orthosteric ligand for the mGluR5 receptor and/or reduces or diminishes an orthosteric agonist's efficacy is an allosteric antagonist (or inhibitor) or negative allosteric modulator (NAM). *Id.* A silent allosteric modulator (SAM) binds to an allosteric site of the receptor but has no measurable intrinsic efficacy. A SAM may indirectly demonstrate efficacy by preventing an allosterically binding compound from displaying its own positive (PAM) or negative (NAM) efficacy.

In some embodiments, the mammal of the method of the invention is a human.

In some embodiments of the method or use of the invention, the central nervous system disease or disorder is a cognitive, neurodegenerative, psychiatric or neurological disease or disorder. In some such embodiments, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is selected from a group consisting of a mood disorder, an anxiety, a schizophrenia (including schizoaffective disorders), Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's chorea, amyotrophic lateral sclerosis, Creutzfeld-Jakob disease, a trauma-induced neurodegeneration, AIDS-induced encephalopathy, another infection-related encephalopathy (*i.e.*, a non-AIDS-induced encephalopathy), Fragile X syndrome, an autism spectrum disorder, and a combination thereof.

As used herein, the phrase "mood disorder" refers to any of several psychological disorders characterized by abnormalities of emotional state, such as, without limitation, bipolar disorders, depressive disorders, cyclothymic disorders, dysthymic disorders, mood disorders due to a general medical condition, mood disorders not otherwise specified and substance-induced mood disorders; and as characterized by the *Diagnostic and Statistical Manual of*

Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association: Arlington, VA, 1994).

As used herein, the phrase “autism spectrum disorder” (ASD) refers to a disorder that causes severe and pervasive impairment in thinking, feeling, language, and the ability to relate to others, which is often first diagnosed in early childhood and range from a severe form, called autistic disorder (“classic” autism), through pervasive development disorder not otherwise specified (PDD-NOS), to a much milder form, Asperger syndrome. The phrase, as used herein, also includes Rett syndrome and childhood disintegrative disorder, and as used herein, is synonymous with the phrase, “pervasive developmental disorders” (PDDs).

In some such embodiments, the mood disorder is a depression (*i.e.*, a depressive disorder). In some such embodiments, the depression is selected from the group consisting of atypical depression, bipolar depression, unipolar depression, major depression, endogenous depression (*i.e.*, acute depression with no obvious cause), involuntal depression (*i.e.*, depression that occurs in mid-life or the elderly), reactive depression (*i.e.*, depression caused by an obvious traumatic life episode), postpartum depression, primary depression (*i.e.*, depression that has no obvious physical or psychological cause such as a medical illness or disorder), psychotic depression, and secondary depression (*i.e.*, depression that seems to be caused by some other underlying condition such another medical illness or disorder).

In some such embodiments, the anxiety disease or disorder is selected from a group comprising generalized anxiety disorder, panic anxiety, obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, an adjustment disorder, a hypochondriacal disorder, separation anxiety disorder, agoraphobia, a specific phobia, anxiety disorder due to general medical condition, substance-induced anxiety disorder, alcohol withdrawal-induced anxiety, and a combination thereof.

In some embodiments, the central nervous system disease or disorder of the method or use comprising a compound of the invention is a seizure disease or disorder. In some embodiments, the seizure disease or disorder is selected from the group consisting of a convulsion, epilepsy, status epilepticus, and a combination thereof.

In some embodiments, the central nervous system disease or disorder of the method or use comprising a compound of the invention is a pain disease or disorder selected from the group consisting of inflammatory pain, neuropathic pain and migraine pain. In some embodiments, the neuropathic pain or migraine pain disease or disorder is selected from the group consisting of allodynia, hyperalgesic pain, phantom pain, neuropathic pain related to diabetic neuropathy, neuropathic pain related to migraine, and a combination thereof.

In some embodiments, the central nervous system disease or disorder of the method or use comprising a compound of the invention is a neuronal hyperexcitation state disease or disorder. In some embodiments, the neuronal hyperexcitation state disease or disorder is a neuronal hyperexcitation state in medicament withdrawal, a neuronal hyperexcitation state in intoxication, or a combination thereof.

In some embodiments of the method or use comprising a compound of the invention, at least one symptom of the cognitive neurodegenerative, psychiatric or neurological disease or disorder is treated.

In some embodiments, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is a depression. In some such embodiments, the at least one symptom of the depression is depressed feeling, depressed mood, loss of interest or pleasure in some or all activities, changes in appetite, changes in weight, changes in sleep patterns, lack of energy, fatigue, low self esteem, diminished capacity for thinking, concentration, or decisiveness, feelings of hopelessness or worthlessness, psychomotor agitation or retardation, self-reproach, inappropriate guilt, frequent thoughts of death or suicide, plans or attempts to commit suicide, or a combination thereof.

In some embodiments, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is an anxiety. In some such embodiments, the at least one symptom of anxiety is apprehension, fear, trembling, muscle aches, insomnia, abdominal upsets, dizziness, irritability, persistent, recurring thoughts, compulsions, heart palpitations, chest pain, chest discomfort, sweating, tingling sensations, feeling of choking, fear of losing control, flashbacks, nightmares, intrusive thoughts, intrusive recollections, avoidance behaviors, emotional numbing, an inability to sleep, anxious feelings, overactive startle response,

hypervigilance, outbursts of anger, faintness, blushing, profuse sweating, or a combination thereof.

In some embodiments, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is schizophrenia. In some such embodiments, the at least one symptom of schizophrenia is a positive symptom selected from the group consisting of hallucination, delusion, paranoia, and a combination thereof. In some such embodiments, the symptom of schizophrenia is a negative symptom selected from the group consisting of social withdrawal, flat affect, anhedonia, decreased motivation, and a combination thereof. In some such embodiments, the symptom of schizophrenia is a cognitive symptom selected from the group consisting of severe deficit in attention, severe deficit in object naming, severe deficit in working memory, severe deficit in long-term memory storage, severe deficit in executive functioning, a slowing of information processing, a slowing of neural activity, long term depression, and a combination thereof.

In some embodiments of the method or use comprising a compound of the invention, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is Parkinson's disease. In some such embodiments, the at least one symptom of Parkinson's disease is levodopa-induced dyskinesia, poor balance, Parkinsonian gait, bradykinesia, rigidity, tremor, change in speech, loss of facial expression, micrographia, difficulty swallowing, drooling, pain, dementia, confusion, a sleep disturbance, constipation, a skin problem, depression, fear, anxiety, difficulty with memory, slowed thinking, sexual dysfunction, an urinary problem, fatigue, aching, loss of energy, or a combination thereof.

In some embodiments, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is Alzheimer's disease. In some such embodiments, the at least one symptom of Alzheimer's disease is impairment in memory, impairment in attention, impairment in judgment, impairment in decision-making, impairment in orientation to physical surroundings, language impairment, impairment in speed-dependent activities, impairment in abstract reasoning, impairment in visuospatial abilities, impairment in executive functioning, impairment in behavioral disturbances, disinterest and passivity, apathy, inappropriate dressing, poor self care, agitation, violent outburst, aggression, depression, anxiety,

hallucination, delusion, change in personality, change in mood, dementia, or a combination thereof.

In some embodiments, the cognitive, neurodegenerative, psychiatric or neurological disease or disorder is multiple sclerosis. In some such embodiments, the at least one symptom of multiple sclerosis is optic neuritis blurred vision, eye pain, loss of color vision, blindness, diplopia double vision, nystagmus jerky eye movements, ocular dysmetria, constant under- or overshooting eye movements, internuclear ophthalmoplegia, nystagmus, diplopia, movement and sound phosphenes, diplopia, afferent pupillary defect, motor paresis, monoparesis, paraparesis, hemiparesis, quadraparesis plegia, paraplegia, hemiplegia, tetraplegia, quadraplegia, spasticity, dysarthria, muscle atrophy, spasms, cramps, hypotonia, clonus, myoclonus, myokymia, restless leg syndrome, footdrop dysfunctional reflexes (MRSs, Babinski's, Hoffman's, Chaddock's), paraesthesia, anaesthesia, neuralgia, neuropathic pain, neurogenic pain, l'hermitte's, proprioceptive dysfunction, trigeminal neuralgia, ataxia, intention tremor, dysmetria, vestibular ataxia, vertigo, speech ataxia, dystonia, dysdiadochokinesia, frequent micturation, bladder spasticity, flaccid bladder, detrusor-sphincter dyssynergia, erectile dysfunction, anorgasmy, retrograde ejaculation, frigidity, constipation, fecal urgency, depression, cognitive dysfunction, dementia, mood swings, emotional lability, euphoria, bipolar syndrome, anxiety, aphasia, dysphasia, fatigue, uhthoffs symptom, gastroesophageal reflux, a sleeping disorder, or a combination thereof.

The present invention further provides a method of treating gastroesophageal reflux, the method comprises administering a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt thereof to a mammal in need thereof. The present invention further provides a use of a compound of the invention in the preparation of a medicament for the treatment of gastroesophageal reflux. The present invention further provides a compound of the invention for use in treating gastroesophageal reflux.

The present invention further provides a method of treating alcohol dependence, the method comprises administering a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt thereof to a mammal in need thereof. The present invention further provides a use of a compound of the invention in the preparation of

a medicament for the treatment of alcohol dependence. The present invention further provides a compound of the invention for use in treating alcohol dependence.

In some embodiments, the compound of the present invention is used in the preparation of a medicament for treatment of a central nervous system disease or disorder. In some
5 embodiments, the central nervous disease or disorder is as previously disclosed herein.

Another aspect of the present invention is a process for producing the compounds of the present invention.

PREPARATION OF THE COMPOUNDS OF THE PRESENT INVENTION

The compounds of the present invention may be prepared, without limitation, according to
10 one of the general methods outlined below. For example, Schemes 1-22 that follow are intended as an illustration of some embodiments of the invention and no limitation of the present invention is implied because of them.

The following defines acronyms as used herein unless specified otherwise in a particular instance.

15 BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene, CAS No. 98327-87-8

Boc = *tert*-butyloxycarbonyl

BOP = Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate,
CAS No. 56602-33-6

CAN = Ceric ammonium nitrate, CAS No. 16774-21-3

20 DAST = (Diethylamino)sulfur trifluoride, CAS No. 38078-09-0

DCM = Dichloromethane or Methylene chloride, CAS No. 75-09-2

DIBAL or DIBAL-H = Diisobutylaluminium hydride, CAS No. 1191-15-7

DIEA = *N,N*-diisopropylethylamine, CAS No. 7087-68-5

DMA = *N,N*-dimethylacetamide, CAS No. 127-19-5

25 DMAP = 4-dimethylaminopyridine, CAS No. 1122-58-3

DMC = 2-Chloro-1,3-dimethylimidazolium chloride, CAS No.37091-73-9

DMF = *N,N*-dimethylformamide, CAS No. 68-12-2

DMPU = 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, CAS No. 7226-23-5

DMSO = Dimethyl sulfoxide, CAS No. 67-68-5

DPPA = Diphenylphosphoryl azide, CAS No. 26386-88-9

5 EDCI = *N*-Ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride, CAS No. 93128-40-6

HATU = 2-(1*H*-7-Azabenzotriazol-1-yl)--1,1,3,3-tetramethyl uronium hexafluorophosphate Methanaminium, CAS No. 148893-10-1

10 HBTU = 2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-Tetramethyluronium hexafluorophosphate, CAS No. 94790-37-1

HOBt = 1-Hydroxybenzotriazole, CAS No. 2592-95-2

LDA = Lithium diisopropylamide solution, CAS No. 4111-54-0

L-Selectride= Lithium tri-*sec*-butyl(hydrido)borate, CAS No. 38721-51-7

NMP = *N*-Methyl-Pyrrolidone, CAS No. 872-50-4

15 PDC = Pyridinium dichromate, CAS No. 20039-37-6

PMB = 4-Methoxybenzyl

PTSA = *p*-Toluenesulfonic acid, CAS No. 6192-52-5

PyBOP = Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate, CAS No. 128625-52-5

20 rt = room temperature

RT = LC-MS retention time

TBAF = Tetrabutylammonium fluoride solution, CAS No. 429-41-4

TBSCl = *tert*-Butyldimethylsilyl chloride, CAS No. 18162-48-6

TBSOTf = *tert*-Butyldimethylsilyl trifluoromethanesulfonate, CAS No. 69739-34-0

25 TBS = *tert*-Butyldimethylsilyl

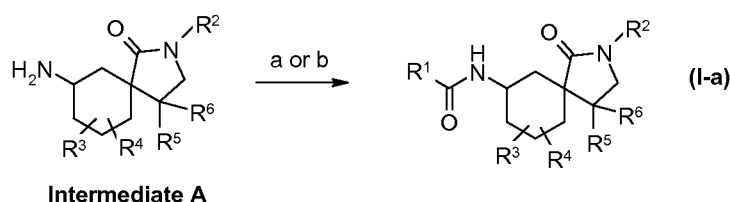
TEA = Triethyl amine, CAS No.121-44-8

TFA = Trifluoroacetic acid, CAS No. 76-05-1

THF = Tetrahydrofuran, CAS No. 109-99-9

A compound of formula **(I-a)** can be prepared *via* the processes outlined in **Scheme 1** by using customary amidation procedures from intermediate **A** and $R^1\text{COCl}$ or $R^1\text{CO}_2\text{H}$ (*see e.g.*, steps a and b of **Scheme 1**), where R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as previously defined.

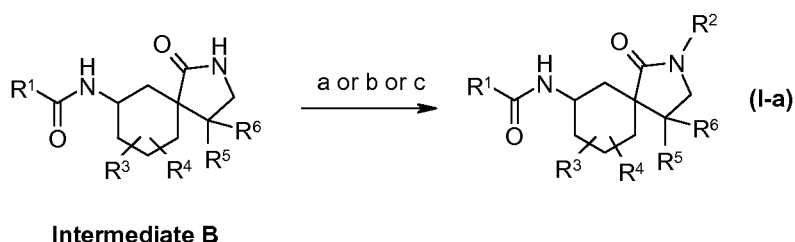
Scheme 1



a) $R^1\text{COCl}$, DIEA or TEA, DCM; **b)** $R^1\text{CO}_2\text{H}$, PyBOP (or BOP or DMC or EDCI or HBTU, etc.), DIEA or TEA, DCM (or THF or DMF or CH_3CN , etc.); or $R^1\text{CO}_2\text{H}$, HATU, DMAP, THF.

A compound of formula **(I-a)** can also be made *via* the process outlined in **Scheme 2**. *N*-arylation of intermediate **B** with $R^2\text{X}$ (R^2 is aryl or heteroaryl, X is halogen such as iodo, bromo, chloro and fluoro) by using copper-assisting cross coupling (*see e.g.*, step a in **Scheme 2**), or by palladium-catalyzed cross coupling (*see e.g.*, step b of **Scheme 2**), or *N*-alkylation of intermediate **B** with $R^2\text{X}$ (R^2 is alkyl) in the presence of base (*see e.g.*, step c of **Scheme 2**) affords a compound of formula of **(I-a)**, where R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined herein.

Scheme 2

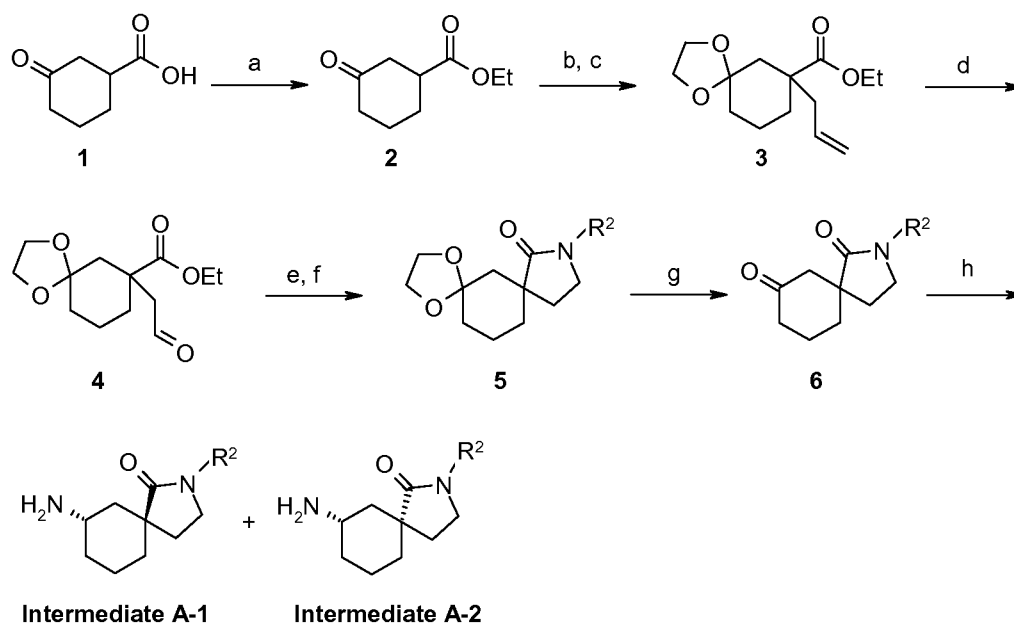


a) CuI , $R^2\text{X}$, $\text{NHMeCH}_2\text{CH}_2\text{NHMe}$, K_2CO_3 , dioxane, microwave, 160 °C; **b)** $R^2\text{X}$, tris(dibenzylideneacetone)dipalladium(0) chloroform adduct, BINAP, Cs_2CO_3 , toluene, 80 °C; **c)** $R^2\text{X}$, NaH, THF, 0 °C to rt.

Intermediates **A-1** and **A-2** can be prepared *via* the processes outlined in **Scheme 3**.

Esterification of commercially available 3-oxo-cyclohexanecarboxylic acid (compound **1**) by using customary procedures (*see e.g.*, step a of **Scheme 3**), gives compound **2**. Protection of the carbonyl group of compound **2** by using customary procedures (*see e.g.*, step b of **Scheme 3**), followed by alkylation with allyl bromide in the presence of base (*see e.g.*, step c of **Scheme 3**) yields compound **3**. Oxidation of compound **3**, such as ozonolysis in DCM affords aldehyde **4**. Reductive amination of aldehyde **4** with amine R^2NH_2 by using customary procedures (*see e.g.*, step e of **Scheme 3**), followed by cyclization in the presence of base (*see e.g.*, step f of **Scheme 3**), gives compound **5**. In some cases (especially when R^2 is alkyl), lactam **5** can be formed directly from aldehyde **4** under reductive amination conditions without further treatment by base (step f). Hydrolysis of compound **5** by customary procedures (*see e.g.*, step g of **Scheme 3**) affords ketone **6**, which can be readily converted to intermediates **A-1** and **A-2** by reductive amination with ammonium acetate (*see e.g.*, step h in **Scheme 3**). The *trans* isomer **A-1** and *cis* isomer **A-2**, where R^2 is as defined herein, can be separated by silica gel chromatography or reverse-phase HPLC.

Scheme 3

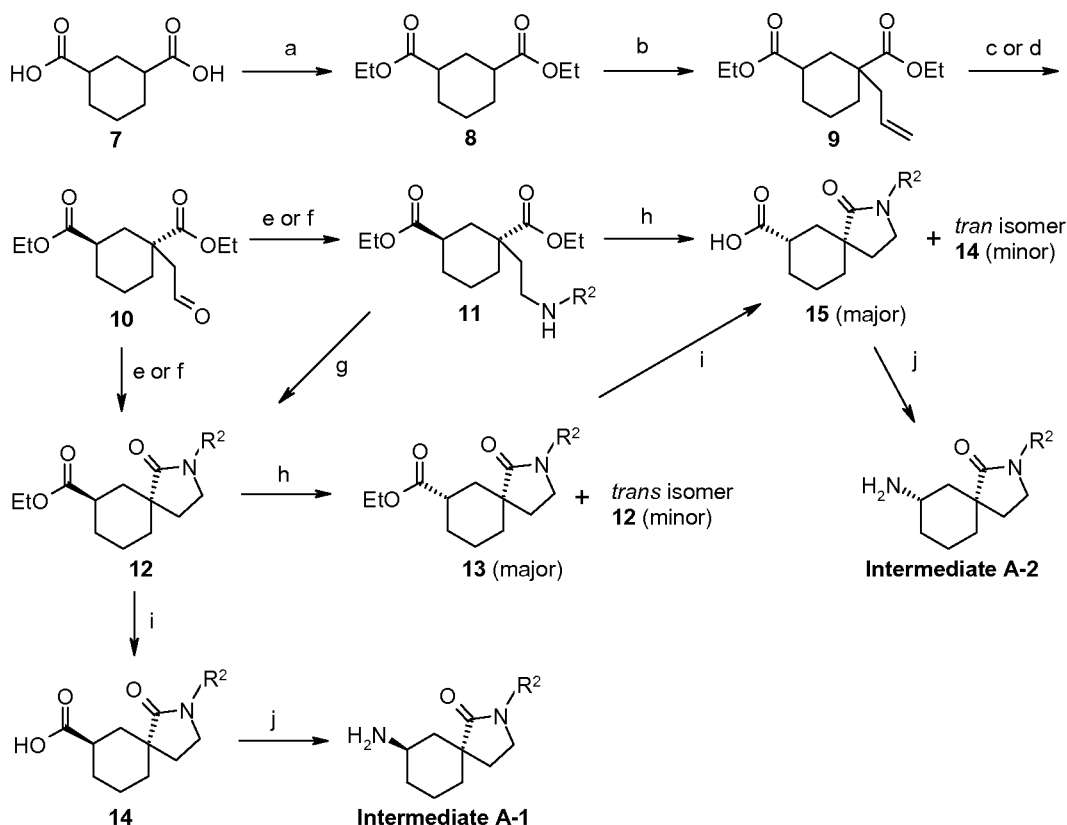


a) EtOH, PTSA, toluene, heat; **b)** (CH₂OH)₂, PTSA, toluene, heat; **c)** LDA, THF, -78 °C, allyl bromide; **d)** O₃, CH₂Cl₂, Me₂S; **e)** R²NH₂, NaBH(OAc)₃, HOAc, THF; **f)** i-PrMgCl, THF, 0 °C; **g)** 2N HCl/THF, **h)** NH₄OAc, NaBH₃CN, MeOH.

Intermediates **A-1** and **A-2** can also be prepared *via* the processes outlined in **Scheme 4**. Esterification of commercially available cyclohexane-1,3-dicarboxylic acid (compound **7**) by customary procedures (*see e.g.*, step **a** in **Scheme 4**) gives bis-ethyl ester **8**. Alkylation of compound **8** with allyl bromide (*see e.g.*, step **b** in **Scheme 4**) affords compound **9**. Oxidation of compound **9**, such as ozonolysis (*see e.g.*, step **c** of **Scheme 4**) or a two-step oxidation (*see e.g.*, step **d** of **Scheme 4**: compound **9** is oxidized to diol first, then further oxidized to aldehyde), gives *trans* aldehyde **10** as a major product. Reductive amination of aldehyde **10** with amine R²NH₂ by using customary procedures (*see e.g.*, steps **e** and **f** of **Scheme 4**), yields compound **11**, which upon cyclization by treatment with base, such as i-PrMgCl in THF at 0 °C, gives lactam **12**. In some cases, especially when R² is alkyl, compound **10** can be directly converted to lactam **12** under reductive amination conditions. The *trans* lactam **12** can be epimerized to *cis* lactam **13** under basic conditions (*see e.g.*, step **h** of **Scheme 4**). Saponification of compounds **12** and **13** using customary procedures *see e.g.*, step **i** of **Scheme 4**) gives carboxylic acids **14** and **15**, respectively. In some cases, depending on R² and reaction time, compound **11** can be converted to compound **15** under basic conditions,

such as NaH, EtOH, 0 °C to reflux. Curtius rearrangement of compound **14** and **15** followed by acid hydrolysis by using customary procedures (*see e.g.*, step j of **Scheme 4**) affords intermediate **A-1** and intermediate **A-2**, where R² is as defined herein, respectively.

Scheme 4



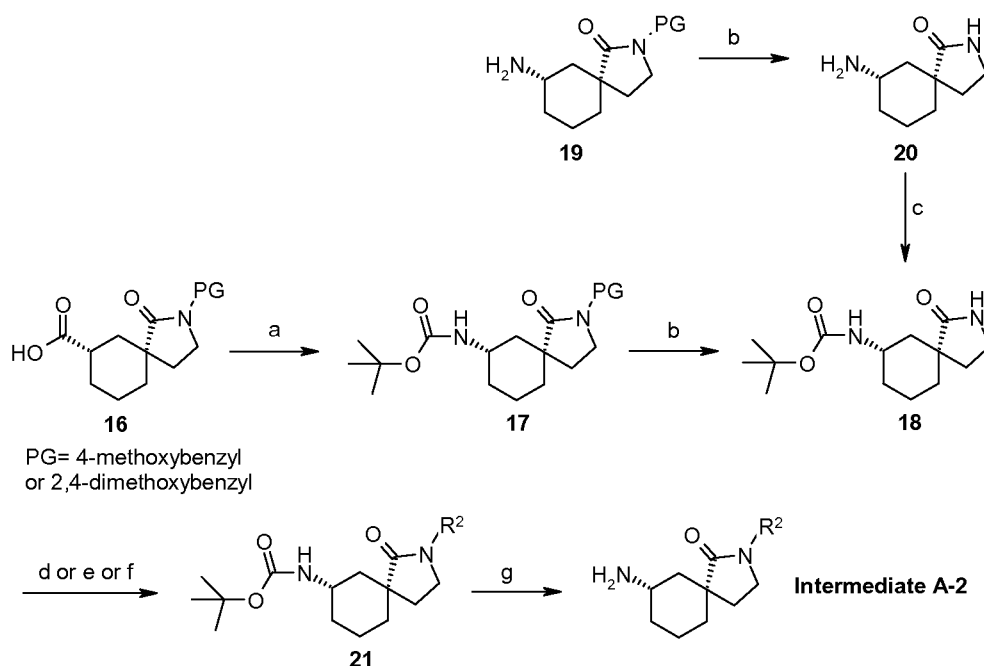
a) EtOH, H₂SO₄, reflux; **b)** i-Pr₂NH, BuLi, DMPU, THF, allyl bromide, -78 °C to rt; **c)** O₃, DCM, Me₂S; **d)** 1) K₃Fe(CN)₆, K₂OsO₄·2H₂O, K₂CO₃, quinuclidine, *t*-BuOH, H₂O; 2) NaIO₄, NaHCO₃, THF, *t*-BuOH; **e)** R²NH₂, NaBH(OAc)₃, HOAc, THF; **f)** 1) R²NH₂, AcOH, ClCH₂CH₂Cl; 2) NaBH(OAc)₃; **g)** i-PrMgCl, THF, 0 °C; **h)** NaH, EtOH, 0 °C to reflux; **i)** LiOH, THF; **j)** 1) DPPA, TEA, toluene, rt to 90 °C; 2) 6M HCl/H₂O, then basified with Na₂CO₃.

Intermediate **A-2** can also be prepared *via* the processes outlined in **Scheme 5**.

Compound **16** can be made in the same manner as compound **15** in **Scheme 4**. Curtius reaction of compound **16** by using customary procedures (*see e.g.*, step a of **Scheme 5**) gives compound **17**. Removal of protecting group 4-methoxybenzyl or 2,4-dimethoxybenzyl in compound **17** by using customary procedures (*see e.g.*, step b of **Scheme 5**) yields compound **18**. Compound **18** can also be made from compound **19** (intermediate **A-2**, R² = 4-methoxybenzyl or 2,4-dimethoxybenzyl), which can be prepared *via* the processes outlined

in **Scheme 4**). Removal of the protecting group 4-methoxybenzyl or 2,4-dimethoxybenzyl in compound **19** by using customary procedures (*see e.g.*, step b of **Scheme 5**) gives compound **20**. Boc protection of compound **20** by using customary procedures (*see e.g.*, step c of **Scheme 5**) affords compound **18**. *N*-arylation of compound **18** with R^2X (R^2 is aryl or heteroaryl and X is as previously defined) by using copper-assisting cross coupling (*see e.g.*, step d of **Scheme 5**), or by palladium-catalyzed cross coupling (*see e.g.*, step e of **Scheme 5**), or *N*-alkylation of compound **18** with R^2X (R^2 is alkyl and X is as previously defined) in the presence of base (*see e.g.*, step f of **Scheme 5**), yields compound **21**. Removal of Boc group by using customary conditions (*see e.g.*, step g of **Scheme 5**) affords intermediate **A-2**, where R^2 is as defined herein.

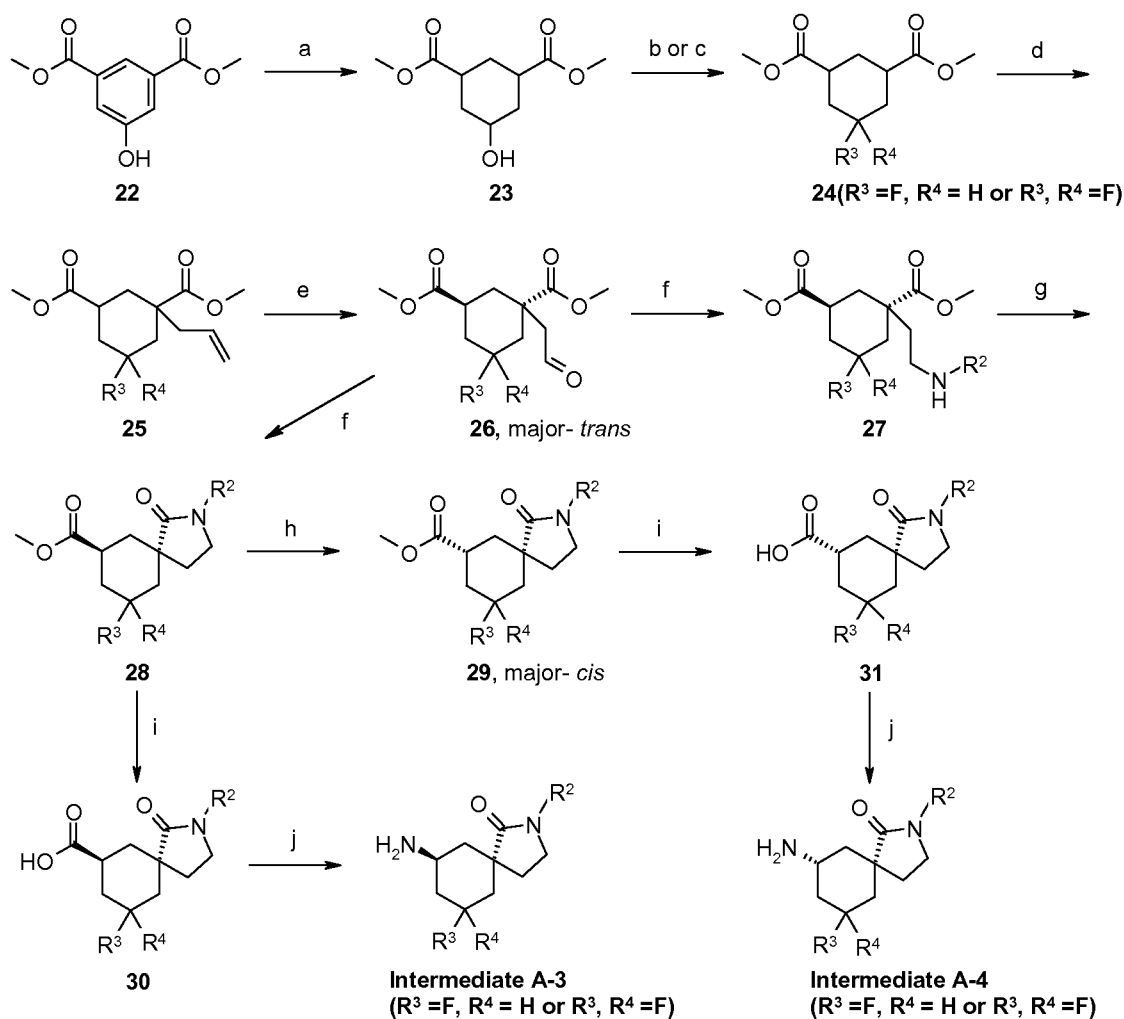
Scheme 5



Intermediates **A-3** and **A-4** can be made *via* the processes outlined in **Scheme 6**. Reduction of commercially available 5-hydroxy-isophthalic acid dimethyl ester (compound **22**) by using the procedures described by Gensler, W. J. *et al.* (*J. Org. Chem.*, **1973**, 38, 1726; *see* step a of **Scheme 6**) gives compound **23**. Fluorination of **23** by using customary procedures affords

mono-fluorinated compound **24** ($R^3 = F$, $R^4 = H$, *see e.g.*, step b of **Scheme 6**). Oxidation of alcohol **23** to its corresponding ketone, followed by fluorination by using customary conditions affords di-fluorinated compound **24** (R^3 , $R^4 = F$, *see e.g.*, step c of **Scheme 6**). Alkylation of compound **24** with allyl bromide (*see e.g.*, step d of **Scheme 6**) gives compound **25**. Oxidation of compound **25**, such as ozonolysis (*see e.g.*, step e of **Scheme 6**), gives *trans* aldehyde **26** as a major product. Reductive amination of aldehyde **26** with R^2NH_2 by using customary procedures (*see e.g.*, step f of **Scheme 6**) yields compound **27**, which upon cyclization by treatment with base, such as *i*-PrMgCl in THF at 0 °C, gives lactam **28**. In some cases (especially when R^2 is alkyl), compound **26** can be directly converted to lactam **28** under reductive amination conditions. The *trans* lactam **28** can be epimerized to *cis* lactam **29** under basic conditions (*see e.g.*, step h of **Scheme 6**). Saponification of compounds **28** and **29** by using customary procedures (*see e.g.*, step i of **Scheme 6**) gives corresponding carboxylic acids **30** and **31**, respectively. In some cases, depending on R^2 and reaction time, compound **28** can be converted to compound **31** under basic conditions, such as NaH, EtOH, 0 °C to reflux. Curtius rearrangement of compounds **30** and **31**, followed by acid hydrolysis (*see e.g.*, step j in **Scheme 6**), affords intermediates **A-3** and **A-4**, where R^2 - R^4 are as defined herein, respectively.

Scheme 6

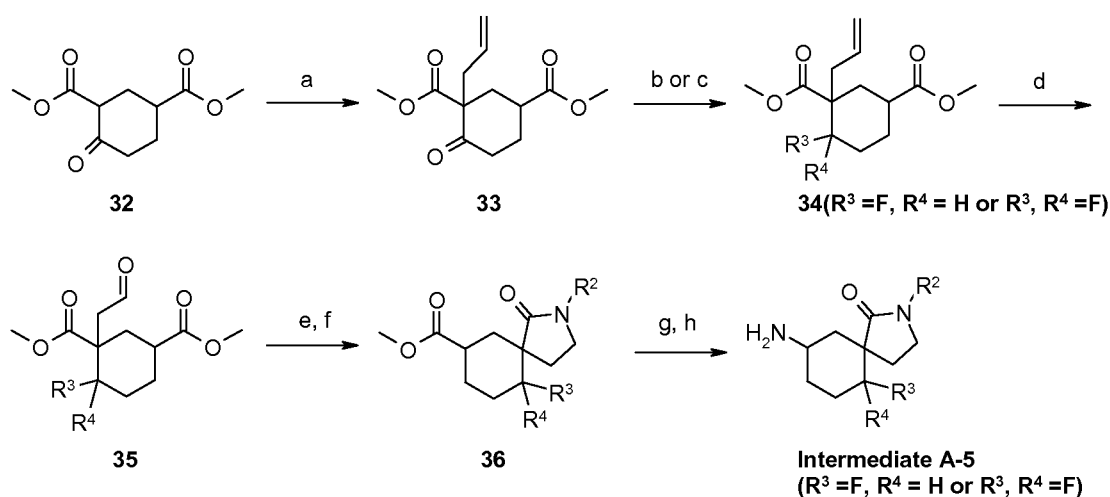


a) H_2 , MeOH, Rh on alumina; **b)** DAST, DCM; **c)** 1) $\text{Py} \cdot \text{SO}_3$, DMSO; 2) DAST, DCM; **d)** $i\text{-Pr}_2\text{NH}$, BuLi, DMPU, THF, allyl bromide, -78°C to rt; **e)** O_3 , DCM, Me_2S ; **f)** R^2NH_2 , $\text{NaBH}(\text{OAc})_3$, THF; **g)** $i\text{-PrMgCl}$, THF, 0°C ; **h)** NaH, EtOH, 0°C to reflux; **i)** LiOH, THF; **j)** 1) DPPA, TEA, toluene, rt to 90°C ; 2) 6M $\text{HCl}/\text{H}_2\text{O}$, then basicified with Na_2CO_3 .

Intermediate **A-5** may be prepared *via* the processes outlined in **Scheme 7**. Alkylation of commercially available 4-oxo-cyclohexane-1,3-dicarboxylic acid dimethyl ester (compound **32**) with allyl bromide in the presence of base (such as under the conditions shown in step a of **Scheme 7**) could give compound **33**. Reduction of **33**, followed by fluorination by using customary procedures, such as those in step b of **Scheme 7**, could yield mono-fluorinated compound **34** ($\text{R}^3 = \text{F}, \text{R}^4 = \text{H}$). Fluorination of compound **33** by using customary procedures, such as those in step c of **Scheme 7** could yield di-fluorinated compound **34** (R^3 ,

$R^4 = F$). Oxidation of compound **34**, such as ozonolysis (*see e.g.*, step d of **Scheme 7**), could give aldehyde **35**. Reductive amination with R^2NH_2 , followed by cyclization under conditions such as those shown in steps e and f of **Scheme 7** could afford compound **36**. In some cases (especially when R^2 is alkyl), compound **35** could be directly converted to lactam **36** under reductive amination conditions without step f. Saponification of **36**, followed by Curtius rearrangement and acid hydrolysis using customary procedures, such as those in steps g and h of **Scheme 7**, could give intermediate **A-5**, where R^2 - R^4 are as defined herein.

Scheme 7

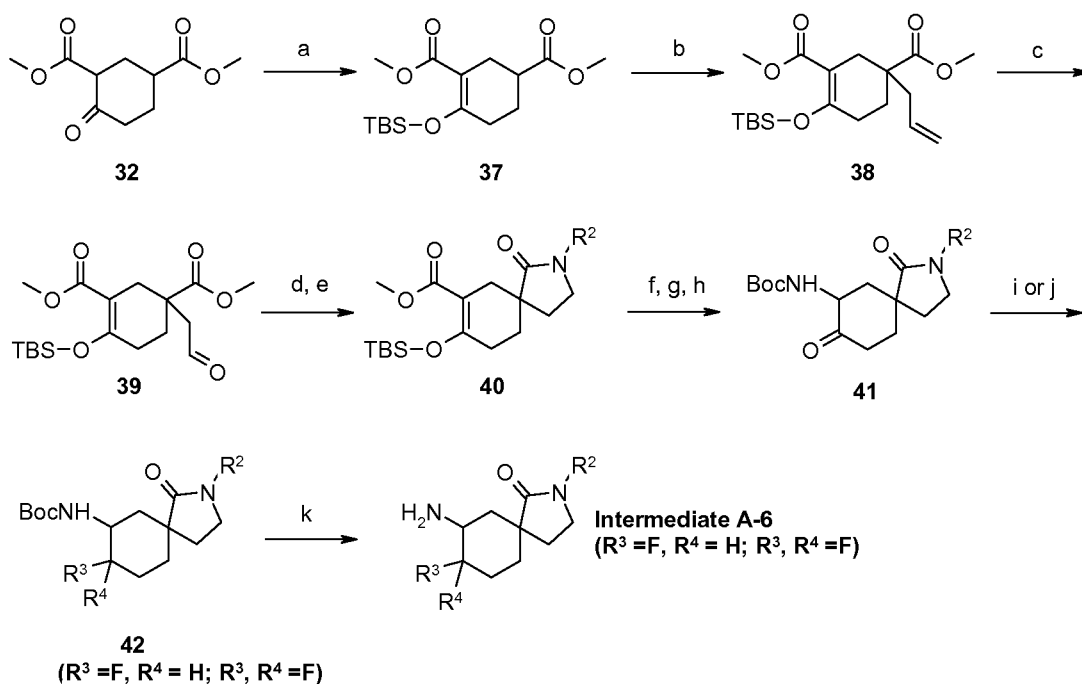


a) NaH, allyl bromide, THF; **b) 1)** NaBH₄, THF; **2)** DAST, DCM; **c)** DAST, DCM; **d)** O₃, DCM, Me₂S; **e)** R²NH₂, NaBH(OAc)₃, THF; **f)** i-PrMgCl, THF, 0 °C; **g)** LiOH, THF; **h) 1)** DPPA, TEA, toluene, rt to 90 °C; **2)** 6M HCl/H₂O, then basicified with Na₂CO₃.

Intermediate **A-6** may be prepared *via* the processes outlined in **Scheme 8**. Reaction of compound **32** with TBSOTf by using customary procedures, such as those in step a of **Scheme 8**, could give compound **37**. Alkylation of **37** with allyl bromide in the presence of base (*see e.g.*, step b of **Scheme 8**) could yield compound **38**. Oxidation of compound **38**, such as ozonolysis (*see e.g.*, step c in **Scheme 8**), could give aldehyde **39**. Reductive amination of **39** with R^2NH_2 , followed by cyclization (*see e.g.*, steps d and e in **Scheme 8**), could afford lactam **40**. In some cases (especially when R^2 is alkyl), compound **39** could be directly converted to lactam **40** under reductive amination conditions without step e. Saponification of **40**, followed by Curtius rearrangement and then de-protection of TBS using customary procedures (*see e.g.*, steps f, g and h of **Scheme 8**), could give compound

41. Reduction of **41** followed by fluorination (*see e.g.*, step i of **Scheme 8**) could yield mono-fluorinated compound **42** ($R^3 = F$, $R^4 = H$). Fluorination of compound **41** by using customary procedures (*see e.g.*, step j of **Scheme 8**) could yield di-fluorinated compound **42** ($R^3, R^4 = F$). Removal of Boc group using customary procedures (*see e.g.*, step k of **Scheme 8**) could afford intermediate **A-6**, where R^2 - R^4 are as defined herein.

Scheme 8

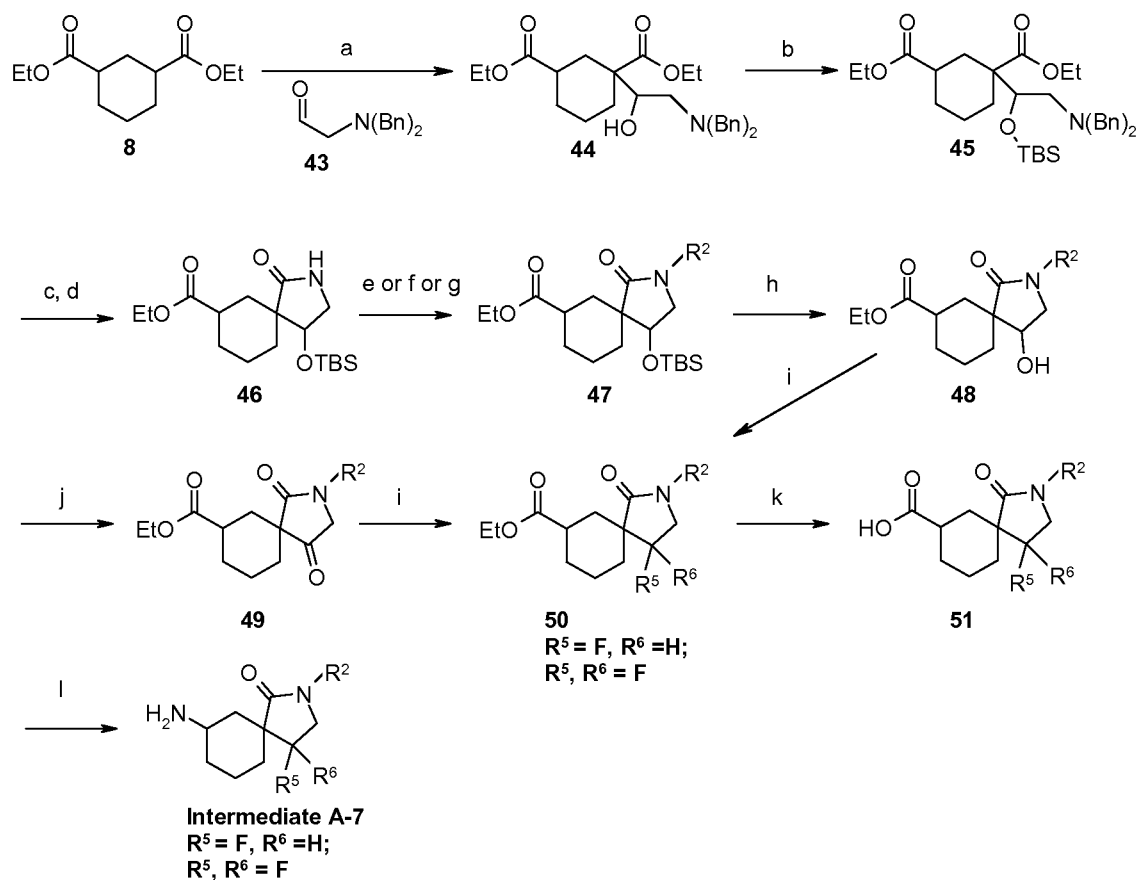


a) TEA, TBSOTf, DCM; **b)** NaH, allyl bromide, THF; **c)** O_3 , DCM, Me_2S ; **d)** R^2NH_2 , $NaBH(OAc)_3$, THF; **e)** NaH, MeOH; **f)** LiOH, THF; **g)** 1) DPPA, TEA, toluene, rt to 90 °C; 2) t -BuOH; **h)** TBAF, THF; **i)** 1) $NaBH_4$, THF; 2) DAST, DCM; **j)** DAST, DCM; **k)** 4M HCl/dioxane, DCM.

Intermediate **A-7** may be prepared *via* the processes outlined in **Scheme 9**. Reaction of compound **8** with commercially available dibenzylamino-acetaldehyde (compound **43**) in the presence of base, such as LDA at -78 °C in THF, could give compound **44**. Protecting the hydroxyl group of compound **44** with TBS using customary procedures (*see e.g.*, step b of **Scheme 9**) could yield compound **45**. Removal of dibenzyl groups followed by cyclization (*see e.g.*, steps c and d of **Scheme 9**) could afford lactam **46**. *N*-arylation of compound **46** with R^2X (R^2 is aryl or heteroaryl and X is as previously defined) using copper-assisting cross coupling (*see e.g.*, step e of **Scheme 9**), or palladium-catalyzed cross coupling (*see e.g.*, step f of **Scheme 9**), or *N*-alkylation of compound **47** with R^2X (R^2 is alkyl and X is as

previously defined) in the presence of base (*see e.g.*, step g of **Scheme 9**) could give compound **47**. Removal of the TBS group of compound **47** using customary procedures (*see e.g.*, step h in **Scheme 9**) could afford alcohol **48**, which could be readily oxidized to ketone **49** using customary procedures, such as step j of **Scheme 9**. Fluorination of compound **48** using customary procedures (*see e.g.*, step i of **Scheme 9**) could yield mono-fluorinated compound **50** ($R^5 = F$, $R^6 = H$). Fluorination of ketone **49** using customary procedures, such as DAST in DCM, could yield di-fluorinated compound **50** ($R^5, R^6 = F$). Saponification of compound **50** (*see e.g.*, step k of **Scheme 9**) gives carboxylic acid **51**, which upon Curtius rearrangement followed by acid hydrolysis using customary procedures (*see e.g.*, step k of **Scheme 9**), could be converted to intermediate **A-7**, where R^2 , R^5 and R^6 are as defined herein.

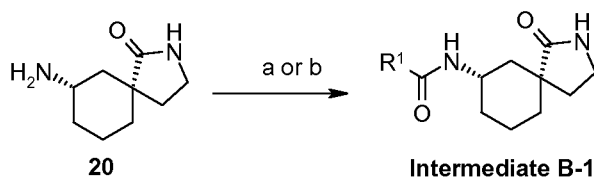
Scheme 9



a) LDA, THF, -78 °C; b) 1H-imidazole, TBSCl, DMF; c) H₂, Pd-C, EtOAc/EtOH, 50 psi; d) K₂CO₃, CH₃CN; e) CuI, R²X, NHMeCH₂CH₂NHMe, K₂CO₃, dioxane, microwave, 160 °C; f) R²X, tris(dibenzylideneacetone)dipalladium(0) chloroform adduct, BINAP, Cs₂CO₃, toluene, 80 °C; g) R²X, NaH, THF, 0 °C to rt; h) TBAF, THF; i) DAST, DCM; j) PySO₃, DMSO; k) LiOH, THF; l) 1) DPPA, TEA, toluene, rt to 90 °C; 2) 6M HCl/H₂O, then basified with Na₂CO₃.

Intermediate **B-1** can be made *via* the processes outlined in **Scheme 10**. Amidation of compound **20** with R¹CO₂H or R¹COCl using customary amidation procedures (*see e.g.*, step a or b of **Scheme 10**) affords intermediate **B-1**, where R¹ is as defined herein.

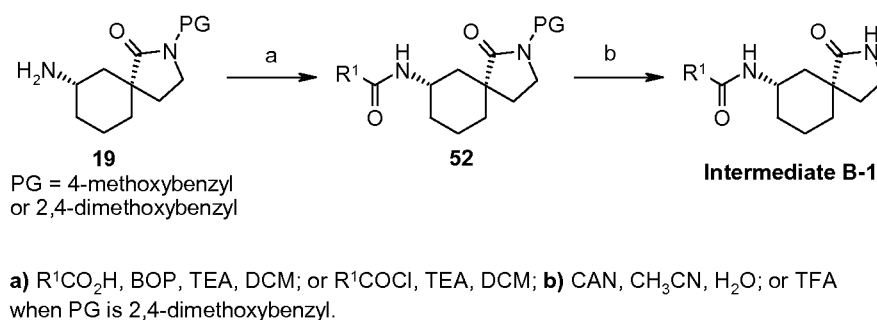
Scheme 10



a) R¹CO₂H, TEA, BOP, DCM; b) R¹COCl, TEA, DCM.

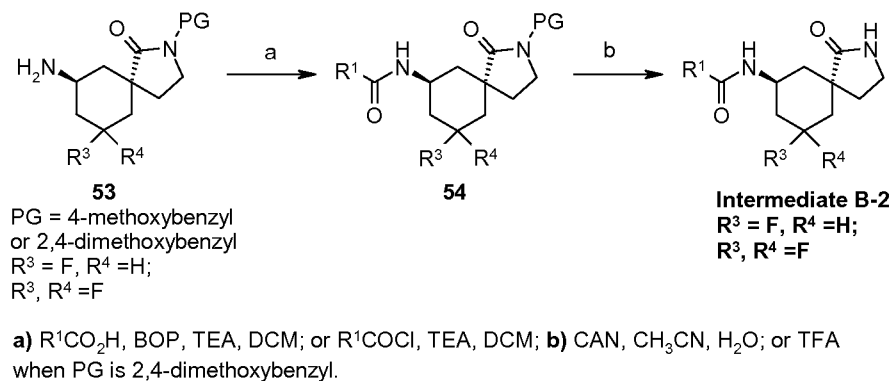
Intermediate **B-1** can also be made *via* the processes outlined in **Scheme 11**. Amidation of compound **19** with R^1CO_2H or R^1COCl using customary procedures (*see e.g.*, step a of **Scheme 11**) yields compound **52**. Removal of the protecting group 4-methoxybenzyl or 2,4-dimethoxybenzyl of compound **52** using customary procedures (*see e.g.*, step b of **Scheme 11**) affords intermediate **B-1**, where R^1 is as defined herein.

Scheme 11



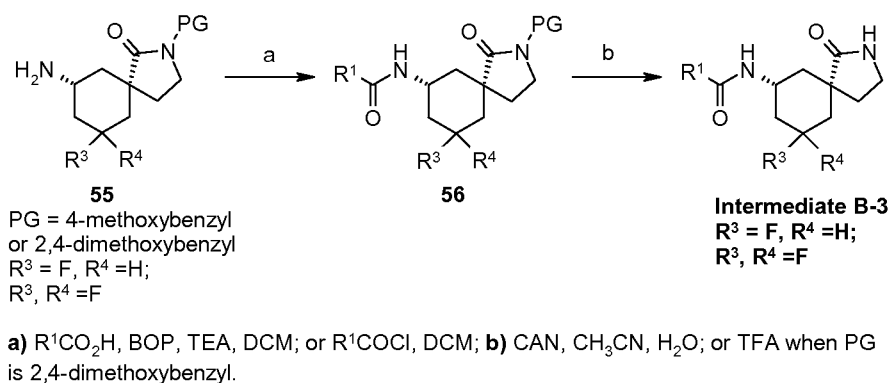
In a similar manner to intermediate **B-1**, intermediate **B-2** can be prepared from compound **53** (intermediate **A-3** where R^2 is 4-methoxybenzyl or 2,4-dimethoxybenzyl) *via* the processes outlined in **Scheme 12**, where R^1 , R^3 and R^4 are as defined herein.

Scheme 12



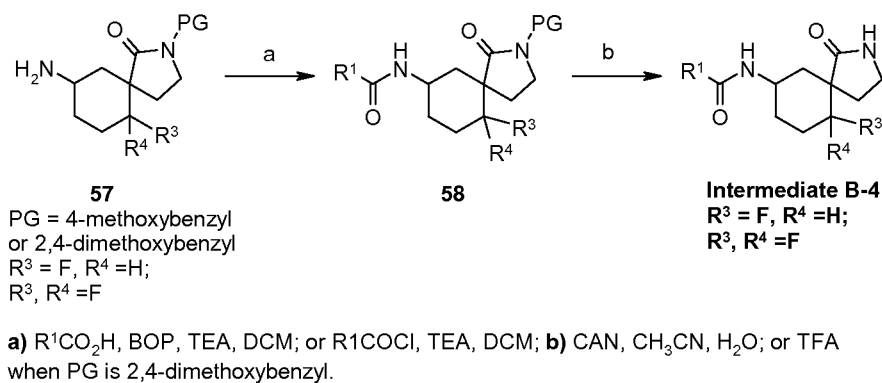
In a similar manner to intermediate **B-1**, intermediate **B-3** can be prepared from compound **55** (intermediate **A-4** where R^2 is 4-methoxybenzyl or 2,4-dimethoxybenzyl) *via* the processes outlined in **Scheme 13**, where R^1 , R^3 and R^4 are as defined herein.

Scheme 13



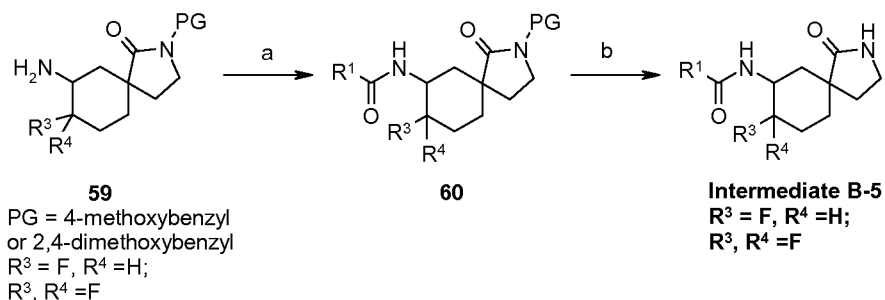
In a similar manner to intermediate **B-1**, intermediate **B-4** can be prepared from compound **57** (intermediate **A-5** where R^2 is 4-methoxybenzyl or 2,4-dimethoxybenzyl) *via* the processes outlined in **Scheme 14**, where R^1 , R^3 and R^4 are as defined herein.

Scheme 14



In a similar manner to intermediate **B-1**, intermediate **B-5** can be prepared from compound **59** (intermediate **A-6** where R^2 is 4-methoxybenzyl or 2,4-dimethoxybenzyl) *via* the processes outlined in **Scheme 15**, where R^1 , R^3 and R^4 are as defined herein.

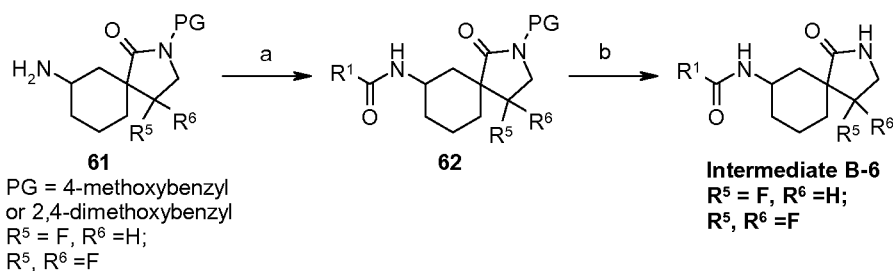
Scheme 15



a) R¹CO₂H, BOP, TEA, DCM; or R¹COCl, TEA, DCM; b) CAN, CH₃CN, H₂O; or TFA when PG is 2,4-dimethoxybenzyl.

In a similar manner to intermediate **B-1**, intermediate **B-6** can be prepared from compound **61** (intermediate **A-7** where R² is 4-methoxybenzyl or 2,4-dimethoxybenzyl) *via* the processes outlined in **Scheme 16**, where R¹, R⁵ and R⁶ are as defined herein.

Scheme 16

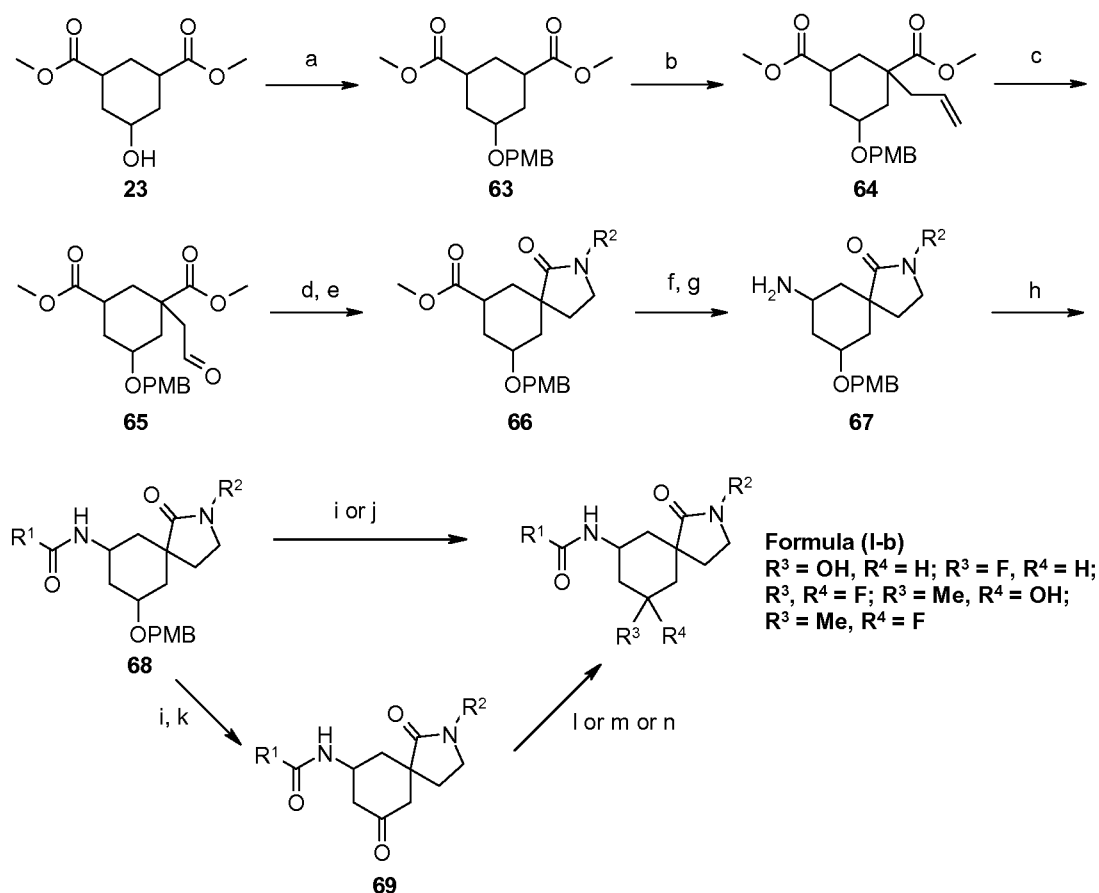


a) R¹CO₂H, BOP, TEA, DCM; or R¹COCl, TEA, DCM; b) CAN, CH₃CN, H₂O; or TFA when PG is 2,4-dimethoxybenzyl.

A compound of formula **(I-b)** may be prepared *via* the processes outlines in **Scheme 17**. Protecting the hydroxyl group of compound **23** with PMB using customary procedures (*see e.g.*, step a of **Scheme 17**) could give compound **63**. Alkylation of compound **63** with allyl bromide in the presence of base (*see e.g.*, step b of **Scheme 17**) could yield compound **64**. Oxidation of compound **64**, such as oxonolysis (*see* step c in **Scheme 17**), could afford aldehyde **65**. Reductive amination of aldehyde **65** with R²NH₂ using customary procedures (*see e.g.*, step d of **Scheme 17**), followed by cyclization under basic conditions (*see e.g.*, step e of **Scheme 17**), could give lactam **66**. In some cases (*e.g.*, when R² is alkyl), lactam **66** could be formed under reductive amination conditions. Saponification, followed by Curtius rearrangement and acid hydrolysis using customary conditions (*see e.g.*, steps f and g of **Scheme 17**) could afford amine **67**, which could be converted to amide **68** by reacting with R¹CO₂H or R¹COCl under customary conditions, such as step h of **Scheme 17**. Removal of

the PMB group of compound **68** using customary procedures (*see e.g.*, step i of **Scheme 17**) could give an alcohol, such as a compound of formula **(I-b)** where R^3 is OH and R^4 is H. Fluorination of this alcohol using customary procedures, such as DAST in DCM, could yield a compound of formula **(I-b)** where R^3 is F and R^4 is H. Oxidation of this alcohol using customary procedures (*see e.g.*, step k of **Scheme 17**) could give ketone **69**. Fluorination of **69** under customary conditions, such as DAST in DCM, could afford a compound of formula **(I-b)** where R^3 and R^4 are F. Grignard Reaction of **69** with MeMgBr using customary procedures (*see e.g.*, step m of **Scheme 17**) could afford a tertiary alcohol, such as a compound of formula **(I-b)** where R^3 is Me and R^4 is OH. Fluorination of this alcohol using customary conditions, such as DAST in DCM, could afford a compound of formula **(I-b)** where R^3 is Me and R^4 is F. In each instance of the compound of formula **(I-b)**, R^1 and R^2 are as defined herein.

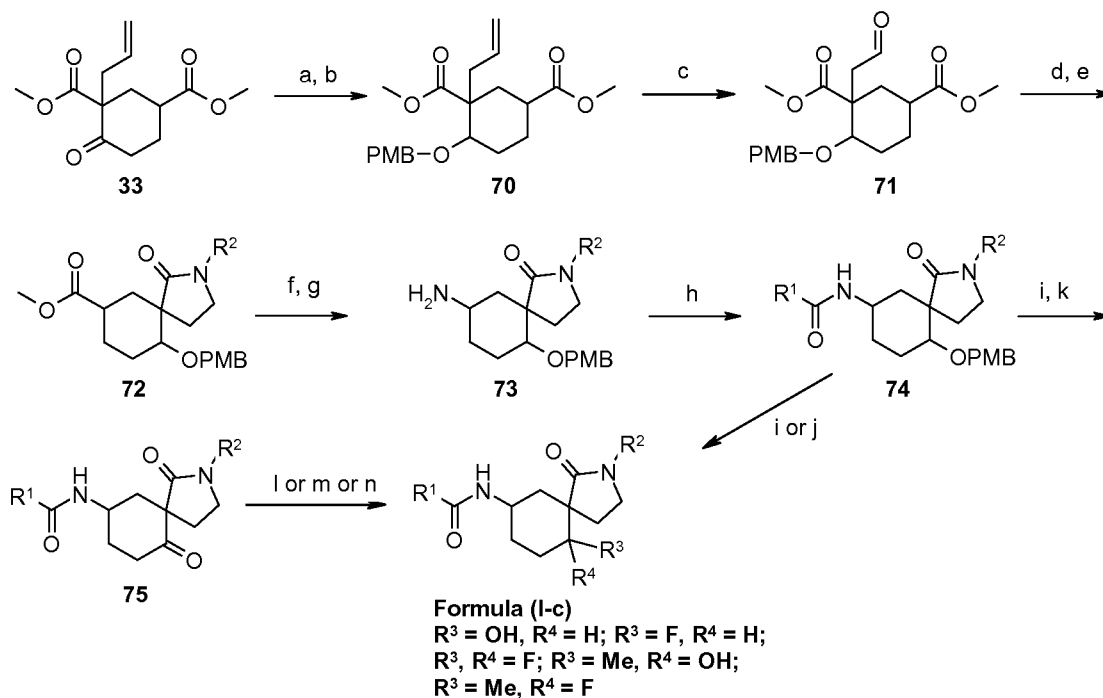
Scheme 17



a) 4-methoxybenzyl-2,2,2-trichloroacetimidate, $BF_3 \cdot Et_2O$, THF, 0 °C; **b)** $i\text{-Pr}_2\text{NH}$, BuLi, DMPU, THF, allyl bromide, -78 °C to rt; **c)** O_3 , DCM, Me_2S ; **d)** R^2NH_2 , $NaBH(OAc)_3$, THF; **e)** R_2X , NaH, THF, 0 °C to rt; $i\text{-PrMgCl}$, THF, 0 °C; **f)** LiOH, THF; **g)** **1)** DPPA, TEA, toluene, rt to 90 °C; **2)** 6M HCl/ H_2O , then basified with Na_2CO_3 ; **h)** R^1CO_2H , BOP, TEA, DCM; or R^1COCl , TEA, DCM; **i)** H_2 , Pd/C, EtOH/EtOAc; **j)** **1)** H_2 , Pd/C, EtOH/EtOAc; **2)** DAST, DCM; **k)** $PySO_3$, DMSO; **l)** DAST, DCM; **m)** MeMgBr, THF, 0 °C; **n)** **1)** MeMgBr, THF, 0 °C; **2)** DAST, DCM.

In a similar manner to a compound of formula (I-b), a compound of formula (I-c) could be prepared *via* the processes outlined in Scheme 18 from compound 33. In the compound of formula (I-c), $R^1 - R^4$ are as defined herein.

Scheme 18

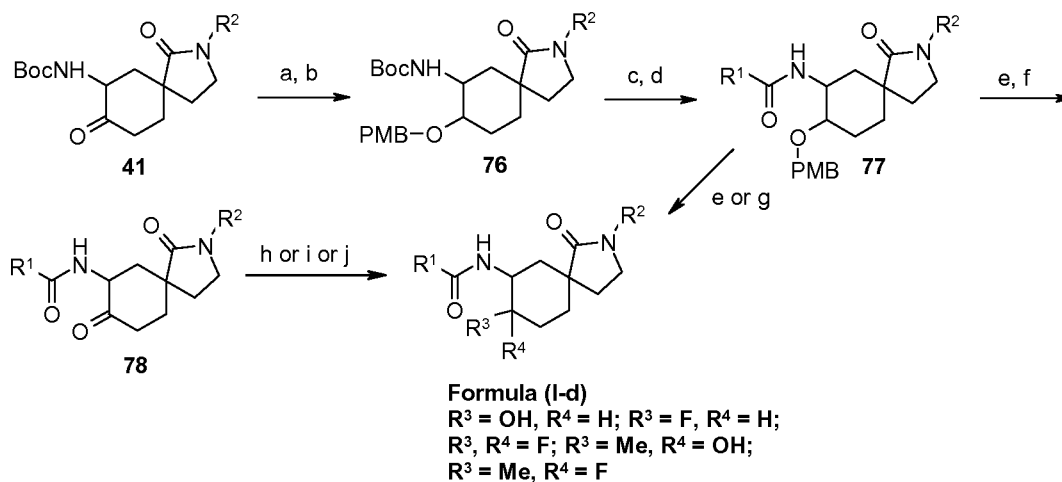


a) NaBH_4 , THF; **b)** 4-methoxybenzyl-2,2,2-trichloroacetimidate, $\text{BF}_3 \cdot \text{Et}_2\text{O}$; THF, 0 °C; **c)** O_3 , DCM, Me_2S ; **d)** R^2NH_2 , $\text{NaBH}(\text{OAc})_3$, THF; **e)** $i\text{-PrMgCl}$, THF, 0 °C; **f)** LiOH , THF; **g)** **1)** DPPA, TEA, toluene, rt to 90 °C; **2)** 6M $\text{HCl}/\text{H}_2\text{O}$, then basified with Na_2CO_3 ; **h)** $\text{R}^1\text{CO}_2\text{H}$, BOP, TEA, DCM; or R^1COCl , TEA, DCM; **i)** H_2 , Pd/C, EtOH/EtOAc; **j)** **1)** H_2 , Pd/C, EtOH/EtOAc; **2)** DAST, DCM; **k)** PySO_3 , DMSO; **l)** DAST, DCM; **m)** MeMgBr , THF, 0 °C; **n)** **1)** MeMgBr , THF, 0 °C; **2)** DAST, DCM.

A compound of formula (I-d) may be prepared *via* the processes outlined in Scheme 19. Reduction of the carbonyl group of compound 41, followed by adding the protecting group PMB using customary procedures (*see e.g.*, steps a and b of Scheme 19), could give compound 76. Removal of the Boc group followed by amidation under customary conditions (*see e.g.*, steps c and d of Scheme 19) could afford compound 77. Removal of PMB using customary procedures (*see e.g.*, step e of Scheme 19) could give an alcohol, such as a compound of formula (I-d) where R^3 is OH and R^4 is H. Fluorination of this alcohol using customary conditions, such as DAST in DCM, could afford a compound of formula (I-d) where R^3 is F and R^4 is H. Oxidation of this compound using customary conditions (*see e.g.*, step f of Scheme 19) could yield ketone 78. Fluorination of this ketone under customary conditions (*see e.g.*, step h of Scheme 19) could afford a compound of formula (I-d) where both R^3 and R^4 are F. Grignard reaction of compound 78 with MeMgBr under customary conditions (*see e.g.*, step i of Scheme 19) could afford a tertiary alcohol, such as a compound

of formula **(I-d)** where R^3 is Me and R^4 is OH. Fluorination of this tertiary alcohol using customary procedures, such as DAST in DCM, could give a compound of formula **(I-d)** where R^3 is Me and R^4 is F. In each instance of the compound of formula **(I-d)**, R^1 and R^2 are as defined herein.

5 **Scheme 19**

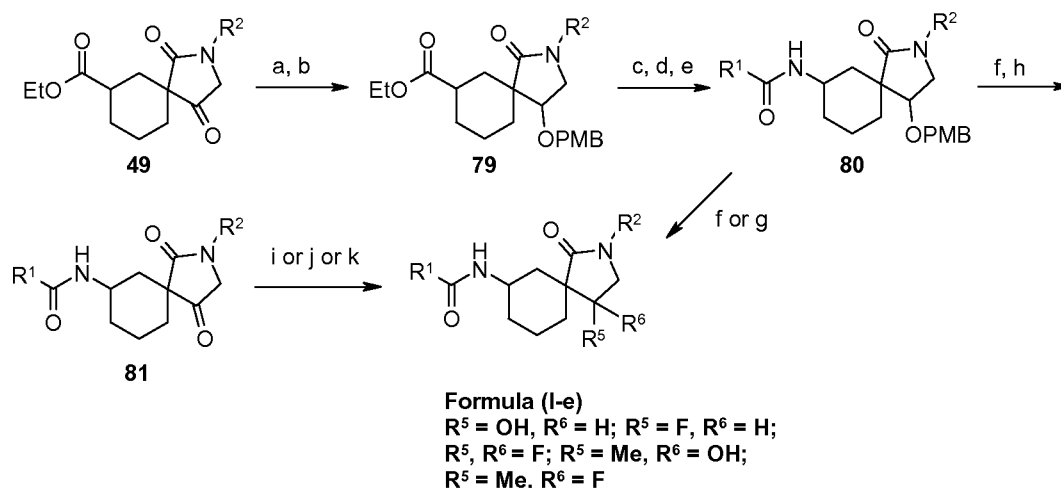


a) $NaBH_4$, THF; **b)** 4-methoxybenzyl-2,2,2-trichloroacetimidate, $BF_3 \cdot Et_2O$, THF, 0 °C; **c)** 4M HCl/dioxane, DCM; **d)** R^1CO_2H , BOP, TEA, DCM; or R^1COCl , TEA, DCM; **e)** H_2 , Pd/C, EtOH/EtOAc; **f)** $PySO_3$, DMSO; **g)** **1)** H_2 , Pd/C, EtOH/EtOAc; **2)** DAST, DCM; **h)** DAST, DCM; **i)** MeMgBr, THF, 0 °C; **j)** **1)** MeMgBr, THF, 0 °C; **2)** DAST, DCM.

A compound of formula **(I-e)** may be prepared *via* the processes outlined in **Scheme 20**. Reduction of the carbonyl group in compound **49**, followed by adding the protecting group PMB using customary procedures (*see e.g.*, steps a and b of **Scheme 20**), could give compound **79**. Saponification of compound **79**, followed by Curtius rearrangement and then amidation under customary conditions (*see e.g.*, steps c, d and e of **Scheme 20**), could afford compound **80**. Removal of PMB using customary procedures (*see e.g.*, step f of **Scheme 20**) could give an alcohol, such as a compound of formula **(I-e)** where R^5 is OH and R^6 is H. Fluorination of this alcohol using customary conditions, such as DAST in DCM, could afford a compound of formula **(I-e)** where R^5 is F and R^6 is H. Oxidation of this compound using customary conditions (*see e.g.*, step h of **Scheme 20**) could yield ketone **81**. Fluorination of this ketone under customary conditions (*see e.g.*, step i of **Scheme 20**) could afford a compound of formula **(I-e)** where both R^5 and R^6 are F. Grignard reaction of compound **81** with MeMgBr under customary conditions (*see e.g.*, step j of **Scheme 20**) could afford a

tertiary alcohol, such as a compound of formula **(I-e)** where R^5 is Me and R^6 is OH. Fluorination of this tertiary alcohol using customary procedures, such as DAST in DCM, could give a compound of formula **(I-e)** where R^5 is Me and R^6 is F. In each instance of the compound of formula **(I-e)**, R^1 and R^2 are as defined herein.

5 Scheme 20

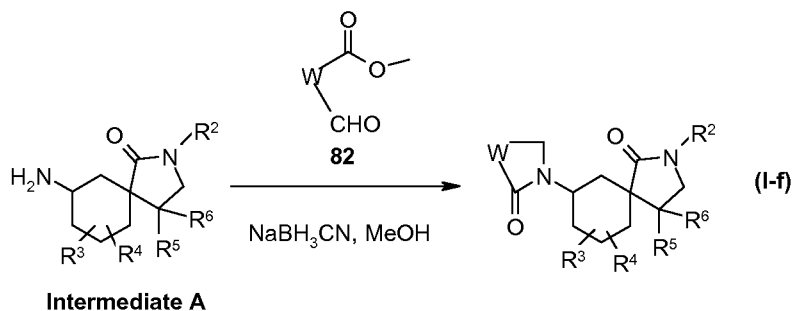


a) NaBH_4 , THF; b) 4-methoxybenzyl-2,2,2-trichloroacetimidate, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, 0 °C; c) LiOH , THF; d) 1) DPPA, TEA, toluene, rt to 90 °C; 2) 6M $\text{HCl}/\text{H}_2\text{O}$, then basicified with Na_2CO_3 ; e) $\text{R}^1\text{CO}_2\text{H}$, BOP, TEA, DCM; or R^1COCl , TEA, DCM; f) H_2 , Pd/C, EtOH, EtOAc; g) 1) H_2 , Pd/C, EtOH/EtOAc; 2) DAST, DCM; h) PySO_3 , DMSO; i) DAST, DCM; j) MeMgBr , THF, 0 °C; k) 1) MeMgBr , THF, 0 °C; 2) DAST, DCM.

A compound of formula **(I-f)** can be made *via* the processes outlined in **Scheme 21**. Reaction of intermediate **A** with compound **82** (W is an aryl or heteraryl, and $-\text{CO}_2\text{Me}$ and $-\text{CHO}$ are on the two adjacent carbons of W) under reductive amination conditions, such as NaBH_3CN in MeOH, could give a compound of formula **(I-f)**, where R^2 - R^6 are as defined herein.

10

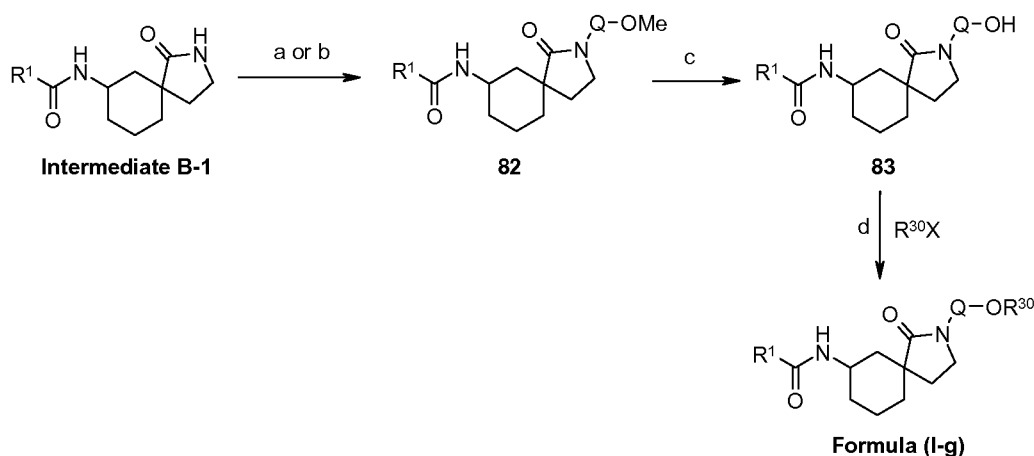
Scheme 21



A compound of formula **(I-g)** may be made *via* the processes outlined in **Scheme 22**.

N-arylation of intermediate **B-1** with X-Q-OMe (Q is an aryl or heteroaryl, X is as previously defined) using copper-assisting cross coupling (*see* step a in **Scheme 22**) or palladium-catalyzed cross coupling (*see* step b in **Scheme 22**) could give compound **82**. De-methylation using customary conditions, such as BBr₃ in DCM, could yield compound **83**. *O*-Alkylation of compound **83** with R³⁰X in the presence of base, such as Cs₂CO₃ in DMF, at elevated temperature could afford a compound of formula (**I-g**), where R¹, R³⁰ and Q are as defined herein.

Scheme 22

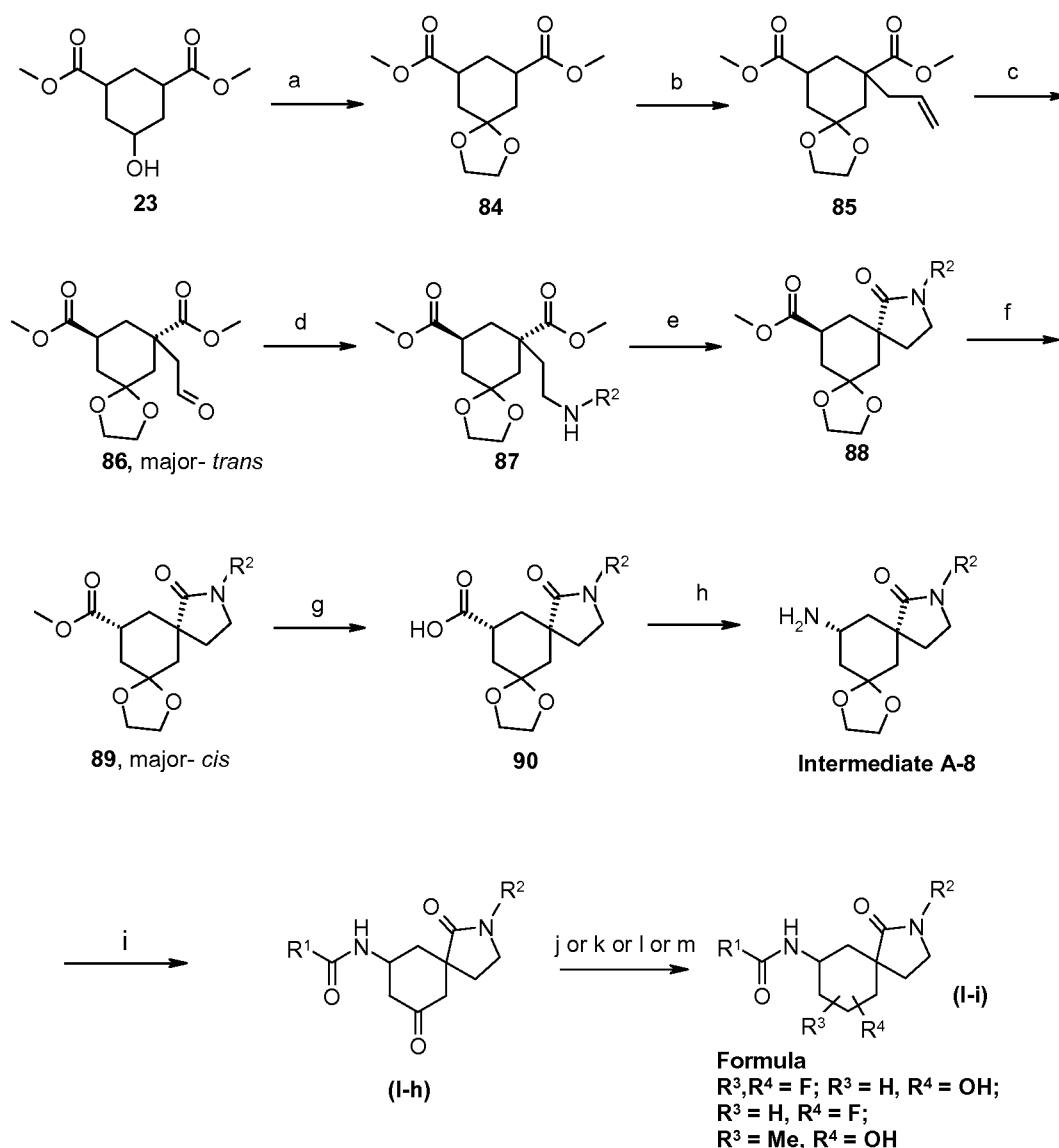


a) Cul, X-Q-OMe, NHMeCH₂CH₂NHMe, K₂CO₃, dioxane, microwave, 160 °C; **b)** X-Q-OMe, tris-(dibenzylideneacetone)dipalladium(0) chloroform adduct, BINAP, Cs₂CO₃, toluene, 80 °C; **c)** BBr₃, DCM; **d)** R³⁰X, Cs₂CO₃, DMF, heat.

A compound of formula (**I-i**) may be prepared *via* the processes outlines in **Scheme 23**. Oxidation of alcohol **23** to its corresponding ketone, followed by protecting the ketone by using customary conditions affords compound **84** (*see e.g.*, step a of **Scheme 23**). Alkylation of compound **84** with allyl bromide in the presence of base (*see e.g.*, step b of **Scheme 23**) could yield compound **85**. Oxidation of compound **85**, such as oxonolysis (*see* step c in **Scheme 23**), could afford aldehyde **86**. Reductive amination of aldehyde **86** with R²NH₂ using customary procedures (*see e.g.*, step d of **Scheme 23**), followed by cyclization under basic conditions (*see e.g.*, step e of **Scheme 23**), could give lactam **88**. In some cases (especially when R² is alkyl), lactam **88** could be formed under reductive amination conditions. The *trans* lactam **88** can be epimerized to *cis* lactam **89** under basic conditions (*see e.g.*, step f of **Scheme 23**). Saponification, followed by Curtius rearrangement and

hydrogenation using customary conditions (*see e.g.*, steps g and h of **Scheme 23**) could afford amine **intermediate A-8**, which could be converted to amide **I-h** by reacting with R^1CO_2H or R^1COCl , followed by removing the protecting group of ketone under customary conditions, such as step i of **Scheme 23**. Fluorination of amide **I-h** under customary conditions, such as DAST in DCM, could afford a compound of formula (**I-i**) where R^3 and R^4 are F. The reduction of the ketone of amide **I-h** using customary procedures (*see e.g.*, step k of **Scheme 23**) could give an alcohol, such as a compound of formula (**I-i**) where R^3 is OH and R^4 is H. Fluorination of this alcohol using customary procedures, such as DAST in DCM, could yield a compound of formula (**I-i**) where R^3 is F and R^4 is H. Grignard Reaction of amide **I-h** with MeMgBr using customary procedures (*see e.g.*, step l of **Scheme 23**) could afford a tertiary alcohol, such as a compound of formula (**I-i**) where R^3 is Me and R^4 is OH. In each instance of the compound of formula (**I-h** and **I-i**), R^1 and R^2 are as defined herein.

Scheme 23

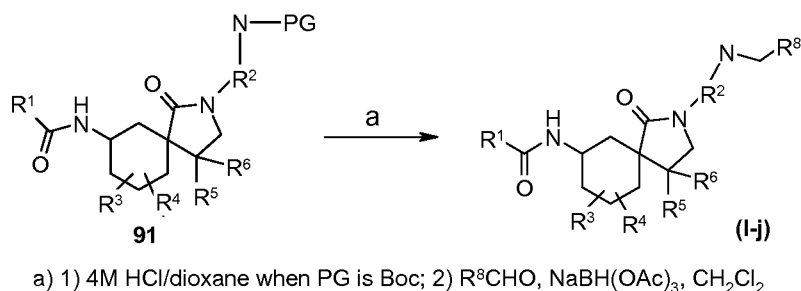


a) 1) $Py.SO_3$, DMSO; **2)** $HOCH_2CH_2OH$, pTSA, toluene, reflux; **b)** $i-Pr_2NH$, BuLi, DMPU, THF, allyl bromide, $-78^\circ C$ to rt; **c)** O_3 , DCM, Me_2S ; **d)** R^2NH_2 , $NaBH(OAc)_3$, THF; **e)** $i-PrMgCl$, THF, $0^\circ C$; **f)** NaH, EtOH, $0^\circ C$ to reflux or NaH, THF, rt; **g)** LiOH, THF; **h)** **1)** DPPA, TEA, toluene, rt to $90^\circ C$; **2)** BnOH; **3)** Pd/C, H_2 , MeOH; **i)** **1)** R^1COCl , TEA, DCM or R^1CO_2H , PyBOP, TEA, DCM; **2)** THF, HCl, H_2O ; **j)** DAST, DCM; **k)** $NaBH_4$ or Red-Al, THF; **l)** **1)** $NaBH_4$ or Red-Al, THF; **2)** DAST; **m)** $RMgBr$, THF

A compound of formula (I-j) can be made *via* the processes outlined in Scheme 24. Removal of the protecting group Boc of compound 91 using customary procedures (*see e.g.*, steps a in Scheme 24), followed by the reductive amination with aldehyde RCHO (R^8 : alkyl, cyclic

alkyl, or H), and NaBH(OAc)₃ in CH₂Cl₂, could give a compound of formula (I-j), where R¹-R⁶ are as defined herein.

Scheme 24



5 EXPERIMENTAL SECTION

1. General Methods

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions. All operations were carried out at room temperature (about 18 °C to about 25 °C) under nitrogen atmosphere. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure or in a high performance solvent evaporation system HT-4X (Genevac Inc., Valley Cottage, NY, USA). Microwave oven used was a Biotage Initiator™ synthesizer (Charlottesville, VA, USA). The course of the reaction was followed by thin layer chromatography (TLC) or liquid chromatography-mass spectrometry (LC-MS), and reaction times are given for illustration only. Silica gel chromatography was carried out on a CombiFlash® system (Teledyne Isco, Inc., Lincoln, NE, USA) with pre-packed silica gel cartridge or performed on Merck silica gel 60 (230-400 mesh). The structure and purity of all final products was assured by at least one of the following analytical methods: nuclear magnetic resonance (NMR) and LC-MS. NMR spectra was recorded on a Bruker Avance™ 300 spectrometer (Bruker BioSpin Corp., Billerica, MA, USA) or a Varian UNITY INOVA® 400 (Varian, Inc., Palo Alto, CA, USA) using the indicated solvent. Chemical shift (δ) is given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard. Coupling constants (*J*) are expressed in hertz (Hz), and conventional abbreviations used for signal shape are: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad; etc. Unless stated otherwise, mass spectra were obtained using electrospray ionization (ESMS) via either a Micromass® Platform II system or

a Quattro microTM system (both from Waters Corp., Milford, MA, USA) and (M+H)⁺ is reported.

General LC-MS methods:

Method A: Mobile phase: A) water/acetonitrile (99/1) and 0.2% ammonium formate; B) acetonitrile. Gradient: 20-85% B from 0 to 1.7 min, 85% B from 1.7 to 1.84 min, 85-100% B from 1.84 to 1.85 min, 100% B from 1.85-1.99 min, 100-20% B from 1.99 to 2 min. Flow rate: 5.0 mL/min. Column: Inertsil® ODS-3, 50 x 4.6 mm, 3 µm particle size.

Method B: Mobile phase: A) water/acetonitrile (99/1) and 0.2% ammonium formate; B) acetonitrile. Gradient: 30-90% B from 0 to 1.7 min, 90% B from 1.7 to 1.84 min, 90-100% B from 1.84 to 1.85 min, 100% B from 1.85-1.99 min, 100-20% B from 1.99 to 2 min. Flow rate: 5.0 mL/min. Column: Inertsil® C8, 50 x 4.6 mm, 3 µm particle size.

Method C: Mobile phase: A) water/acetonitrile (99/1) and 0.2% ammonium formate; B) acetonitrile. Gradient: 10-85% B from 0 to 1.7 min, 85% B from 1.7 to 1.84 min, 85-100% B from 1.84 to 1.85 min, 100% B from 1.85-1.99 min, 100-20% B from 1.99 to 2 min. Flow rate: 5.0 mL/min. Column: Inertsil® C8, 50 x 4.6 mm, 3 µm particle size.

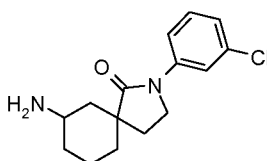
Method D: Mobile phase: A) water/acetonitrile (99/1) and 0.2% acetic acid; B) acetonitrile. Gradient: 0-30% B from 0 to 1.3 minutes, 30-85% B from 1.3 to 1.7 min, 85%B from 1.7-1.84 min, 85-100% B from 1.84 to 1.85 min, 100%B from 1.85 to 1.99 min, and 100-20% B from 1.99 to 2.00 min. Flow rate: 5.0 mL/min. Column: Inertsil® ODS-3, 50 x 4.6 mm, 3 µm particle size.

Method E: Mobile phase: A) water/acetonitrile (99/1) and 0.2% ammonium formate; B) acetonitrile. Gradient: 0-30% B from 0 to 1.3 minutes, 30-85% B from 1.3 to 1.7 min, 85%B from 1.7-1.84 min, 85-100% B from 1.84 to 1.85 min, 100%B from 1.85 to 1.99 min, and 100-20% B from 1.99 to 2.00 min. Flow rate: 5.0 mL/min. Column: Inertsil® ODS-3, 50 x 4.6 mm, 3 µm particle size.

2. Preparation of Intermediates of the Invention

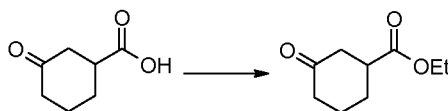
Unless specified otherwise, all starting materials and reagents were obtained from commercial suppliers, such as Sigma-Aldrich (St. Louis, MO, USA) and its subsidiaries, and used without further purification.

Intermediate 1: 7-Amino-2-(3-chloro-phenyl)-2-aza-spiro[4.5]decan-1-one



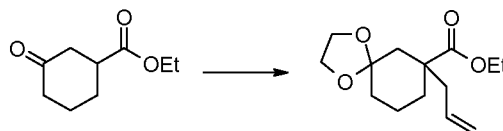
Intermediate 1 was prepared *via* the process of **Scheme 3**, *supra*, as follows:

Step 1: 3-Oxo-cyclohexanecarboxylic acid ethyl ester



To a round bottom flask was added 3-oxo-1-cyclohexanecarboxylic acid (3.85 g, 27.1 mmol), ethanol (7.91 mL), p-toluenesulfonic acid (0.097 g, 0.56 mmol) and toluene (65.9 mL). The mixture was refluxed with Dean-star trap overnight. The reaction mixture was cooled down and concentrated under reduced pressure to afford 4.61 g (100%) of the title compound, 3-oxo-cyclohexanecarboxylic acid ethyl ester, as a yellow oil, which was used in the next step without further purification.

Step 2: 7-Allyl-1, 4-dioxaspiro[4.5]decane-7-carboxylic acid ethyl ester

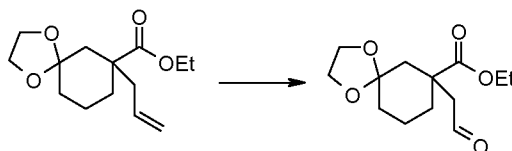


The residue obtained in step 1 was dissolved in toluene (100.0 mL). 1,2-ethanediol (3.02 mL, 54.2 mmol) was added. The mixture was refluxed with Dean-star trap overnight. The mixture was cooled down, diluted with ethyl acetate (60 mL), and washed sequentially with saturated NaHCO₃ (20 mL x 2), water and brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was dried under high vacuum

overnight to afford 4.50 g (78 %) of protected ketone, 1,4-dioxo-spiro[4.5]dicane-7-carboxylic acid ethyl ester, as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 4.11(q, J = 7.1 Hz, 2H), 3.90-3.97 (m, 4H), 2.58 (tt, J = 15.7, 3.8 Hz, 1H), 1.88-1.99 (m, 2H), 1.75-1.83 (m, 1H), 1.68-1.73 (m, 1H), 1.64 (t, J = 2.6 Hz, 1H), 1.47-1.59 (m, 2H), 1.31-1.45 (m, 1H), 1.24 (t, J = 7.2 Hz, 3 H).

Then, to a round bottom flask was added *N,N*-diisopropylamine (3.97 mL, 28.4 mmol) and THF (22.1 mL). The mixture was cooled at -20°C . 1.6 M of *n*-butyllithium in hexane (15.8 mL) was added. The crude mixture was stirred at 0°C for 30 min and then cooled down at -20°C , and 1,4-dioxo-spiro[4.5]dicane-7-carboxylic acid ethyl ester (4.50 g, 21.0 mmol) from step 1 was added dropwise. The mixture was stirred at 0°C for 30 min, and then cooled at -20°C , and allyl bromide (2.00 mL, 23.1 mmol) was added. The mixture was warmed up to rt slowly and stirred at rt for 30 min. The reaction mixture was quenched with ice, diluted with ethyl acetate (60 mL), and washed sequentially with 1N aqueous HCl (5 mL), water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford 4.30 g (81%) of the title compound, 7-allyl-1, 4-dioxo-spiro[4.5]decane-7-carboxylic acid ethyl ester, as a yellow oil. It was used in the next step without further purification. ^1H NMR (400 MHz, CDCl_3): δ 5.64-5.74 (m, 1H), 4.97-5.05 (m, 2H), 4.05-4.17 (m, 2H), 3.82-3.99 (m, 4H), 2.34-2.41 (m, 1H), 2.27 (dt, J = 13.6, 2.1 Hz, 1H), 2.08-2.16 (m, 2H), 1.76-1.88 (m, 1H), 1.60-1.72 (m, 2H), 1.46-1.54 (m, 1H), 1.42 (d, J = 13.6 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.08-1.16 (m, 1H).

Step 3: 7-(2-Oxo-ethyl)-1,4-dioxo-spiro[4.5]decane-7-carboxylic acid ethyl ester



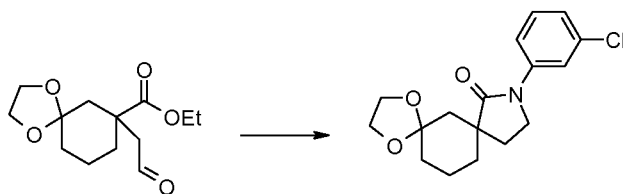
The title compound was prepared *via* two oxidation methods.

Method 1: Oxidation with OsO_4 and NaIO_4 : 7-allyl-1,4-dioxo-spiro[4.5]dicane-7-carboxylic acid ethyl ester from step 2 (2.00 g, 7.86 mmol) was dissolved in THF (30.0 mL) and water (12.0 mL). Osmium tetroxide (0.50 g, 1.97 mmol) was added, followed by the addition of sodium periodate (4.00 g, 18.7 mmol). The crude mixture was stirred at rt for 4

hrs and quenched with saturated aqueous sodium thiosulfate (100 mL). The mixture was stirred at rt for 30 min and diluted with ethyl acetate (150 mL). The organic layer was washed with water and brine, dried over Na₂SO₄ and concentrated under reduced pressure to afford 1.0 g (50%) of the title compound, 7-(2-oxo-ethyl)-1,4-dioxaspiro[4.5]decane-7-carboxylic acid ethyl ester, as a yellow oil. It was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 9.71 (dd, *J* = 2.0, 1.5 Hz, 1H), 4.08-4.23 (m, 2H), 3.83-3.96 (m, 4H), 2.95 (dd, *J* = 17.0, 1.6 Hz, 1H), 2.68 (dd, *J* = 17.1, 1.6 Hz, 1H), 2.17 (d, *J* = 13.8 Hz, 1H), 1.43-2.00 (m, 7H), 1.26 (t, *J* = 7.0 Hz, 3H).

Method 2: Ozonolysis: 7-Allyl-1,4-dioxaspiro[4.5]decane-7-carboxylic acid ethyl ester from step 2 (4.1 g, 16 mmol) was dissolved in CH₂Cl₂ (100 mL). The solution was cooled at -78 °C. Ozone generated with LG-7 (CD laboratory, ozone generator) was bubbled through the solution for 1.5 hrs until the solution turned light blue. Then oxygen was bubbled through until the solution turned to colorless. Dimethyl sulfide (11 mL, 150 mmol) was added at -78 °C. The mixture was warmed up slowly to rt and stirred overnight. The crude mixture was quenched with water (30 mL), and the aqueous layer was extracted with CH₂Cl₂ (50 mL x2). The combined organic layer was washed with water and brine, dried over Na₂SO₄, and concentrated under reduced pressure to afford 3.20 g (77%) of the title compound, 7-(2-oxo-ethyl)-1,4-dioxaspiro[4.5]decane-7-carboxylic acid ethyl ester, as a yellow oil. It was used in the next step without further purification.

Step 4: 9-(3-Chloro-phenyl)-1,4-dioxaspiro[4.1.4.3]tetradecan-8-one

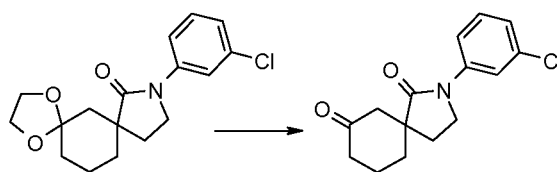


The residue obtained in step 3 (3.20 g, 12.5 mmol) was dissolved in THF (20.0 mL), *m*-chloroaniline (1.58 mL, 15.0 mmol) and 1 drop of acetic acid were added. The crude mixture was stirred at rt for 30 min. Then sodium triacetoxyborohydride (3.97 g, 18.7 mmol) was added. The mixture was stirred at rt for 24 hrs, then quenched with ice, and diluted with ethyl acetate (100 mL). The organic layer was washed sequentially with 1N aqueous NaOH (10

mL), water and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The resulting residue was purified with silica gel chromatography (eluted with CH₂Cl₂ first, then MeOH/CH₂Cl₂: 1/9) to afford 7-[2-(3-chloro-phenylamino)-ethyl]-1,4-dioxaspiro[4.5]decane-7-carboxylic acid ethyl ester (2.42 g, 53%), as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 7.04 (t, *J* = 8.1 Hz, 1H), 6.62-6.65 (m, 1H), 6.51 (t, *J* = 1.9 Hz, 1H), 6.38-6.42 (m, 1H), 4.09-4.17 (m, 2H), 3.96-4.02 (m, 1H), 3.83-3.94 (m, 3H), 3.71 (bs, 1H), 3.10-3.18 (m, 1H), 2.97-3.04 (m, 1H), 2.30 (dt, *J* = 13.6, 1.9 Hz, 1H), 2.14-2.22 (m, 1H), 1.99-2.07 (m, 1H), 1.81-1.92 (m, 1H), 1.52-1.75 (m, 4H), 1.49 (d, *J* = 13.6 Hz, 1H), 1.17-1.28 (m, 4H). ESI-MS *m/z*: 368 (M+H)⁺.

This oil (2.42g, 6.58 mmol) was dissolved in anhydrous THF (37.0 mL). The solution was cooled at 0 °C, 2M of isopropylmagnesium chloride in THF (0.632 mL) was added dropwise. The mixture was stirred at 0 °C for 1 hr, then quenched with ice and diluted with ethyl acetate (80 mL). The organic layer was washed with water and brine, dried over Na₂SO₄, and concentrated under reduce pressure to afford 2.10 g (99%) of the title compound, 9-(3-chloro-phenyl)-1,4-dioxo-9-aza-dispiro[4.1.4.3]tetradecan-8-one, as a white solid, which was used in the next step without further purification. ESI-MS *m/z*: 322 (M+H)⁺.

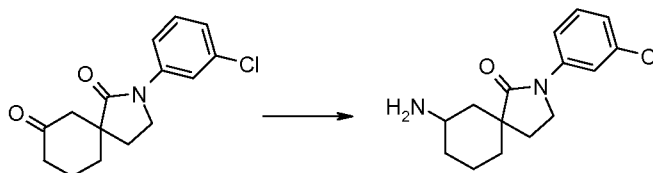
Step 5: 2-(3-Chloro-phenyl)-2-aza-spiro[4.5]decane-1,7-dione



To a round bottom flask was added 9-(3-chloro-phenyl)-1,4-dioxo-9-aza-dispiro[4.1.4.3]tetradecan-8-one from step 4 (0.45 g, 0.84 mmol), THF (10.2 mL), and 2N aqueous HCl (7.0 mL). After stirring at rt overnight, the reaction mixture was diluted with ethyl acetate (60 mL). The organic layer was washed with water and brine, dried over Na₂SO₄, and concentrated under reduced pressure to afford 0.38 g (97%) of the title compound, 2-(3-chloro-phenyl)-2-aza-spiro[4.5]decane-1,7-dione, as a white solid, which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 7.74 (t, *J* = 2.0 Hz, 1H), 7.52 (ddd, *J* = 8.3, 2.2, 1.0 Hz, 1H), 7.29 (t, *J* = 8.1 Hz, 1H), 7.13 (ddd, *J* = 8.1, 2.0, 1.0 Hz, 1H), 3.72-3.81 (m, 2H), 2.73 (dd, *J* = 13.9, 1.0 Hz, 1H), 2.35-2.50 (m, 2H), 2.29

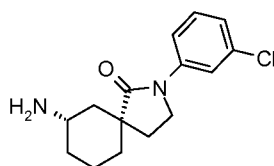
(dt, $J = 13.9, 1.7$ Hz, 1H), 2.12-2.22 (m, 2H), 2.02-2.07 (m, 2H), 1.71-1.89 (m, 2H). ESI-MS m/z : 278 ($M+H$)⁺.

Step 6: 7-Amino-2-methyl-2-aza-spiro[4.5]decan-1-one



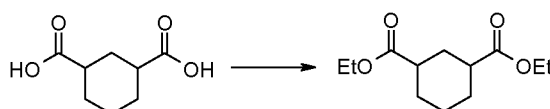
5 To a round bottom flask was added 2-(3-chloro-phenyl)-2-aza-spiro[4.5]decan-1,7-dione of step 5 (0.38 g, 1.35 mmol), methanol (4.92 mL), and ammonium acetate (1.25 g, 16.2 mmol). The mixture was stirred at rt for 1 hr. Sodium cyanoborohydride (0.085 g, 1.35 mmol) was then added. After stirring at rt for 2 hrs, the reaction mixture was quenched with ice and diluted with ethyl acetate (60 mL). The organic layer was washed with brine, dried over
10 Na_2SO_4 , and concentrated under reduced pressure to afford 0.35 g (94%) of the title compound, 7-amino-2-methyl-2-aza-spiro[4.5]decan-1-one, as a white solid. The title compound is a mixture of two diastereomers (*trans/cis*: 5/2; under LC-MS method C, the first peak with RT of 0.80 min was assigned as *cis*, and the second peak with RT of 0.83 min was assigned as *trans*). ESI-MS m/z : 279 ($M+H$)⁺. It was used without further purification.

15 **Intermediate 2: *cis*-7-Amino-2-(3-chloro-phenyl)-2-aza-spiro[4.5]decan-1-one**



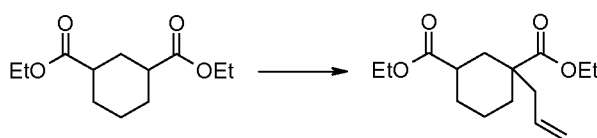
Intermediate 2 was made *via* the process of **Scheme 4**, *supra*, as follows:

Step 1: Cyclohexane-1,3-dicarboxylic acid diethyl ester

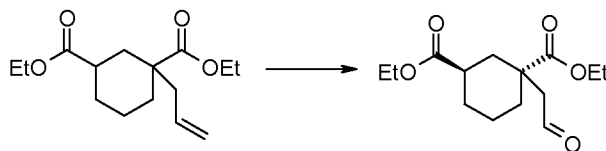


1,3-cyclohexanecarboxylic acid (60.0 g, 348.4 mmol, mixture of *cis* and *trans*) was dissolved in ethanol (600 mL). Concentrated sulfuric acid (10 mL) was added dropwise at rt. The mixture was refluxed for 5 hours and then cooled down to rt. The solvent was removed under reduced pressure, and the resulting residue was diluted with ethyl acetate (1500 mL). The organic layer was washed with cold saturated aqueous NaHCO₃ (400 mL) and brine (2 × 200 mL), dried over Na₂SO₄, and concentrated under reduced pressure to afford 77.4 g (97%) of the title compound, cyclohexane-1,3-dicarboxylic acid diethyl ester, as a colorless oil, which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 4.01 - 4.22 (m, 4 H), 2.67 (m, 1 H), 2.31 (t, *J* = 11.71 Hz, 1 H), 1.30 - 2.25 (m, 8 H), 1.20 - 1.31 (m, 6 H).

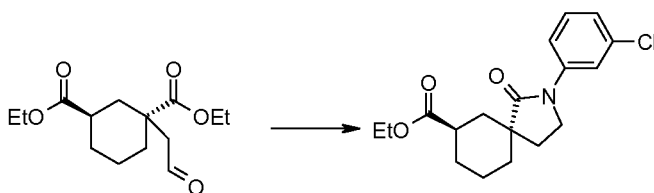
Step 2: 1-Allyl-cyclohexane-1,3-dicarboxylic acid diethyl ester



N,N-Diisopropylamine (31.8 mL, 227 mmol) was dissolved in anhydrous THF (260 mL), and then cooled to -78 °C. BuLi in THF (1.6 M, 141.9 mL, 227 mmol) was added. The mixture was stirred at 0 °C for 30 min, then cooled down to -78 °C. DMPU (97.7 mL, 810 mL) was added dropwise, followed by the addition of cyclohexane-1,3-dicarboxylic acid diethyl ester from step 1 (37.0 g, 162 mmol) in THF (60 mL). The mixture was stirred at -78 °C for 1 hr, allyl bromide (15.4 mL, 178 mmol) was then added. The mixture was warmed up slowly to rt. After stirring at rt overnight, the reaction mixture was quenched with ice-cold aqueous 1N HCl, and diluted with ethyl acetate (300 mL). The organic layer was washed with brine (2 × 200 mL), dried over Na₂SO₄, and concentrated under reduced pressure to give 43.5 g (quantitative yield) of the title compound, 1-allyl-cyclohexane-1,3-dicarboxylic acid diethyl ester, as an orange oil. ¹H NMR (400 MHz, CDCl₃): δ 5.66-5.77 (m, 1H), 5.00-5.06 (m, 2H), 4.08-4.19 (m, 4H), 2.50 - 1.31 (m, 11H), 1.30 (m, 6H).

Step 3: *trans*-1-(2-Oxo-ethyl)-cyclohexane-1,3-dicarboxylic acid diethyl ester

1-Allyl-cyclohexane-1,3-dicarboxylic acid diethyl ester of step 2 (38.0 g, 140 mmol) was dissolved in CH₂Cl₂ (500 mL) and MeOH (50 mL), and then cooled to -78 °C. Ozone was bubbled through the solution for 6 h, then nitrogen was bubbled through for 20 min. Dimethylsulfide (104 mL, 1.4 mol) was added at -78 °C dropwise. The mixture was warmed up to rt and stirred at rt overnight. The reaction mixture was concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (hexanes/EtOAc, 85:15 to 80:20) to give 12.4 g (32%) of the title compound, *trans*-1-(2-oxo-ethyl)-cyclohexane-1,3-dicarboxylic acid diethyl ester, as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 9.78 (dd, *J* = 2.40 and 1.60 Hz, 1H), 4.20 (q, *J* = 7.20 Hz, 2H), 4.10 (q, *J* = 7.20 Hz, 2H), 2.70 – 2.48 (m, 4H), 2.20 (m, 1H), 2.00 (m, 1H), 1.75 (m, 1H), 1.60 – 1.22 (m, 10H). ESI-MS *m/z*: 271 (M+H)⁺.

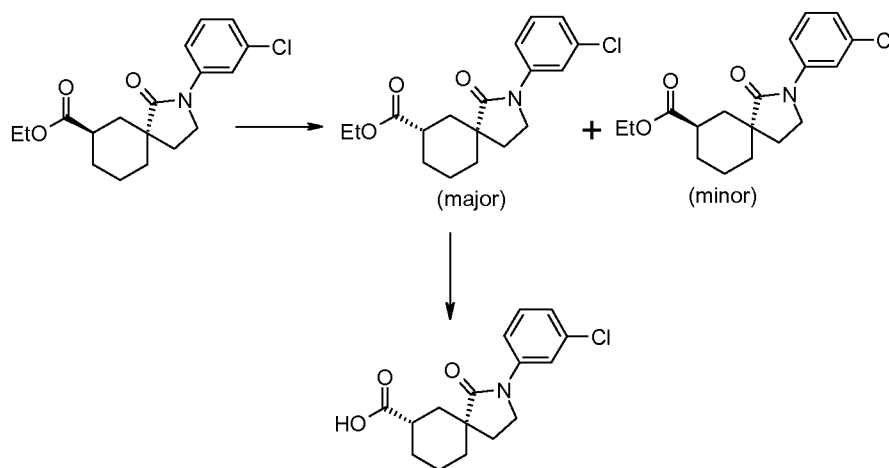
Step 4: *trans*-2-(3-Chloro-phenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid ethyl ester

To a round bottom flask was added *trans*-1-(2-oxo-ethyl)-cyclohexane-1,3-dicarboxylic acid diethyl ester from step 3 (9.63 g, 35.6 mmol), 1,2-dichloroethane (109 mL), *m*-chloroaniline (4.15 mL, 39.2 mmol) and acetic acid (0.05 mL). The reaction mixture was stirred at rt for 30 min. Sodium triacetoxyborohydride (9.00 g, 42.5 mmol) was added. After stirring at rt for 1 week, the reaction was quenched with ice, and diluted with ethyl acetate. The organic layer was washed with water and brine, dried over Na₂SO₄, and concentrated under reduced

pressure. The resulting residue was purified by silica gel chromatography to afford *trans*-1-[2-(3-chloro-phenylamino)-ethyl]-cyclohexane-1,3-dicarboxylic acid diethyl ester (3.20 g, 23%). ¹H NMR (300 MHz, CDCl₃): δ 7.05 (t, *J* = 8.0 Hz, 1H), 6.64 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 6.51 (t, *J* = 2.1 Hz, 1H), 6.40 (ddd, *J* = 8.2, 2.3, 0.9 Hz, 1H), 4.08-4.19 (m, 4H), 3.74 (bs, 1H), 3.07-3.15 (m, 2H), 2.42-2.51 (m, 2H), 2.20-2.28 (m, 1H), 1.70-2.01 (m, 4H), 1.13-1.35 (m, 10 H). ESI-MS *m/z*: 383 (M+H)⁺.

This intermediate was dissolved in THF (68.0 mL), and cooled at 0 °C. Isopropylmagnesium chloride (2M in THF, 6.28 mL) was added dropwise. After stirring at 0 °C for 1 hr, the reaction was quenched with ice-cold 1N aqueous HCl and diluted with ethyl acetate (60.0 mL). The organic layer was washed with water and brine, dried over Na₂SO₄, and concentrated under reduced pressure to afford 2.80 g (100%) of the title compound, *trans*-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid ethyl ester, which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 7.74 (t, *J* = 2.0 Hz, 1H), 7.51 (ddd, *J* = 8.3, 2.1, 1.0 Hz, 1H), 7.28 (t, *J* = 8.2 Hz, 1H), 7.11 (ddd, *J* = 7.9, 2.0, 0.9 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.70-3.79 (m, 2H), 3.16-3.24 (m, 1H), 2.13-2.19 (m, 1H), 1.65-2.04 (m, 6H), 1.58-1.64 (m, 1H), 1.33-1.49 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H). ESI-MS *m/z*: 336 (M+H)⁺.

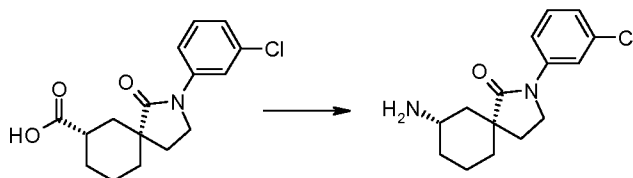
Step 5: : *cis*-2-(3-Chloro-phenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid



Anhydrous ethanol (150 mL) was cooled at 0 °C, and sodium hydride (0.68 g, 16.7 mmol) was added. After the mixture turned clear, *trans*-2-(3-chloro-phenyl)-1-oxo-2-aza-

spiro[4.5]decane-7-carboxylic acid ethyl ester from step 4 (2.80 g, 8.34 mmol) in anhydrous ethanol (10.0 mL) was added. The mixture was refluxed for 3 hrs. Then it was cooled down to rt and concentrated under reduced pressure. Two peaks with same m/z (336) were observed on LC-MS (method B): The new peak with RT of 1.22 min was assigned as *cis* diastereomer, while the peak with RT of 1.33 min was the starting material, *trans* diastereomer. The residue was diluted with ethyl acetate (200 mL) and its pH was adjusted to 2 with 2N aqueous HCl. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to afford the desired *cis* ester as a white solid, which was then dissolved in THF (30.0 mL) and water (30.0 mL). Lithium hydroxide monohydrate (3.50 g, 83.4 mmol) was added. The mixture was stirred at rt overnight, and diluted with ethyl acetate (200 mL). The pH of mixture was adjusted to 2 with 2 N aqueous HCl. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to afford 1.04 g (41%) of the title compound, *cis*-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid, as a white solid, which was used in the next step without further purification. ESI-MS m/z: 308 (M+H)⁺. ESI-MS m/z: 306 (M-H)⁺.

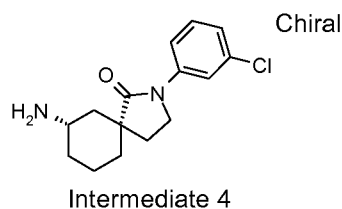
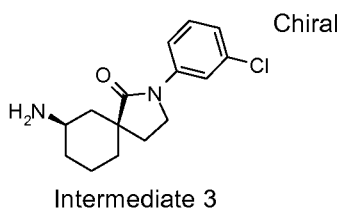
Step 6: *cis*-7-Amino-2-methyl-2-aza-spiro[4.5]decan-1-one



cis-2-(3-Chloro-phenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid from step 6 (1.04 g, 3.41 mmol) was dissolved in toluene (17.9 mL), triethylamine (0.571 mL, 4.09 mmol) was added, followed by the addition of diphenylphosphonic azide (0.809 mL, 3.75 mmol). The mixture was stirred at rt for 1 h, and then heated at 90 °C for 2 hrs. The reaction mixture was cooled down to rt and poured into ice-cold aqueous 6N HCl (5.69 mL). After stirring at rt for 1 hr, the aqueous layer was separated. Aqueous HCl (1 M, 10.0 mL) was added into the organic layer, the mixture was stirred for 10 min, and the aqueous layer was separated. The combined aqueous layer was basified with solid Na₂CO₃ to pH 9, and extracted with CH₂Cl₂ (50 mL x2). The combined organic layer was dried over Na₂SO₄ and concentrated under

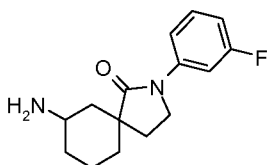
reduced pressure. The residue was purified with RP-HPLC (Gradient: acetonitrile in water, 15-95% in 3.9 minutes with a cycle time of 5 min. Flow rate: 77 mL/min. Mobile phase additive: 10 mM of ammonium hydroxide. Column: Xbridge Prep C18 OBD (Waters Corp., Milford, MA, USA), 19 x 50 mm, 5 μ m particle size) to afford 0.420 g (44%) of the title compound, *cis*-7-amino-2-methyl-1-aza-spiro[4.5]decan-1-one, as a white solid. LC/MS (method C): RT: 0.79 min; ESI-MS m/z : 279 ($M+H$)⁺.

Intermediates 3 and 4: (5*R*,7*R*)-7-Amino-2-(3-chloro-phenyl)-2-aza-spiro[4.5]decan-1-one and (5*S*,7*S*)-7-Amino-2-(3-chloro-phenyl)-2-aza-spiro[4.5]decan-1-one



The racemic intermediate 2 (*cis* diastereomer) (420 mg) were resolved by HPLC (column: Chiralpak[®] OD (Diacel Chemical Industries, Inc., Osaka, Japan), 250x20 mm; mobile phase: 20% isopropanol, 80% hexane; flow rate: 14 mL/min; UV at 254 nm) to afford two enantiomers. The first peak (RT: 15.1 min) from the chiral HPLC was assigned as (5*R*, 7*R*)-7-amino-2-(3-chloro-phenyl)-2-aza-spiro[4.5]decan-1-one (140 mg), and the second peak (RT: 20.7 min) from the chiral HPLC was assigned (5*S*, 7*S*)-7-Amino-2-(3-chloro-phenyl)-2-aza-spiro[4.5]decan-1-one (120 mg).

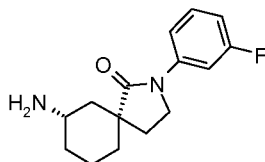
Intermediate 5: 7-Amino-2-(3-fluoro-phenyl)-2-aza-spiro[4.5]decan-1-one



Using the same experimental procedures described for intermediate 1, intermediate 5 was made from 12.5 mmol of 7-(2-Oxo-ethyl)-1,4-dioxaspiro[4.5]decan-7-carboxylic acid ethyl ester and 15.0 mmol of 3-fluoroaniline; 1.30 g of crude title compound was obtained. The title compound is a mixture of *cis* and *trans* diastereoisomers (LC-MS (method C): RT 0.70

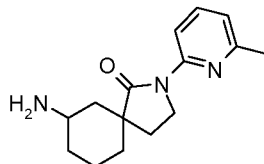
min (*cis*) and 0.73 min (*trans*); *cis/trans*: 1/2; purity (*cis* + *trans*) (UV₂₅₄): 94%). ESI-MS *m/z*: 263 (M+H)⁺. It was used without further purification.

Intermediate 6: *cis*-7-Amino-2-(3-fluoro-phenyl)-2-aza-spiro[4.5]decan-1-one



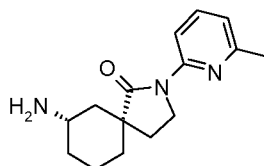
Using the same experimental procedures described in the synthesis of intermediate 2, intermediate 6 was made from 49.9 mmol of *trans*-1-(2-oxo-ethyl-cyclohexane-1,3-dicarboxylic acid diethyl ester and 59.9 mmol of *m*-fluoroaniline. As only a portion of an intermediate was used for the synthesis of the title compound, the amount and the yield obtained of the title compound are not provided. LC-MS (method C): RT: 0.70 min (*cis*); purity (UV₂₅₄): 95%. ESI-MS *m/z*: 263 (M+H)⁺. It was used without further purification.

Intermediate 7: 7-Amino-2-(6-methyl-pyridin-2-yl)-2-aza-spiro[4.5]decan-1-one



Using the same experimental procedures described in intermediate 1, intermediate 7 was made from 3.55 mmol of 7-(2-oxo-ethyl)-1,4-dioxo-spiro[4.5]decan-7-carboxylic acid ethyl ester and 3.91 mmol of 2-amino-6-methylpyridine. LC-MS (method D): RT: 0.84 min (*cis* and *trans* in one peak). ESI-MS *m/z*: 260 (M+H)⁺. It was used without further purification.

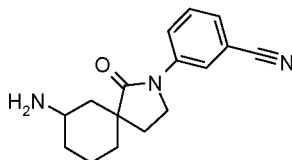
Intermediate 8: *cis*-7-Amino-2-(6-methyl-pyridin-2-yl)-2-aza-spiro[4.5]decan-1-one



Using the same experimental procedures described in intermediate 2, intermediate 8 was made from 3.55 mmol of *trans*-1-(2-oxo-ethyl-cyclohexane-1,3-dicarboxylic acid diethyl

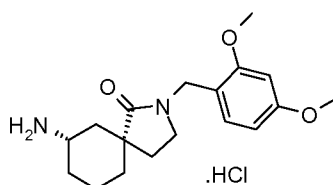
ester and 3.91 mmol of 2-amino-6-methylpyridine LC-MS (method D): RT: 0.66 min; ESI-MS m/z : 260 ($M+H$)⁺. It was used without further purification.

Intermediate 9: *cis*-7-Amino-2-(3-cyano-phenyl)-2-aza-spiro[4.5]decan-1-one



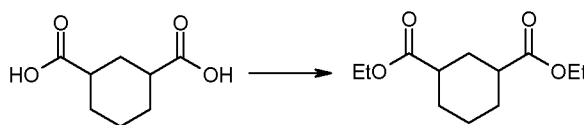
Using the same experimental procedures described in intermediate 1, intermediate 9 was made from 1.66 mmol of 7-(2-oxo-ethyl)-1,4-dioxo-spiro[4.5]decan-7-carboxylic acid ethyl ester and 1.99 mmol of 3-amino-benzonitrile, LC-MS (method A): two peaks were observed with RT of 0.40 min (*cis*) and 0.44 min (*trans*) respectively. ESI-MS m/z : 270 ($M+H$)⁺. It was used without further purification.

Intermediate 10: *cis*-7-Amino-2-(2,4-dimethoxy-benzyl)-2-aza-spiro[4.5]decan-1-one hydrochloric acid salt



Intermediate 10 was made *via* the process of **Scheme 4**, *supra*, as follows:

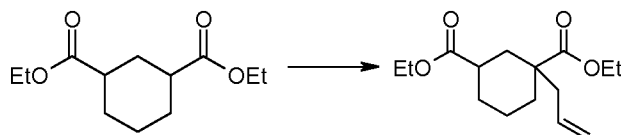
Step1: Cyclohexane-1,3-dicarboxylic acid diethyl ester



To a solution of 1,3-cyclohexanecarboxylic acid (340 g, 2.0 mol, mixture of *cis/trans* isomers) in ethanol (3.5 L), sulfuric acid (conc., 53 mL) was added dropwise at room temperature and the mixture was refluxed for 6.5 h. After cooling down, the solvent was removed, and the residue was diluted with ethyl acetate (1 L) and treated with cold aqueous NaOH until pH 9. The organic layer was washed with water, brine, dried with Na₂SO₄ and

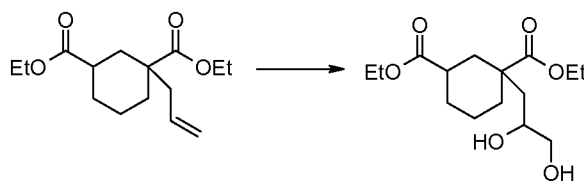
concentrated under vacuum to afford the title product (466 g, quant.) as a colorless oil, which was used in the next step without further purification.

Step 2: 1-Allyl-cyclohexane-1,3-dicarboxylic acid diethyl ester



To a cooled solution (-78 °C) of *N,N*-diisopropylamine (272 mL, 1.94 mol) in anhydrous THF (1.4 L) was added *n*-BuLi (1.6 M in hexane, 1.21 L, 1.94 mol) over the period of one hour and 20 minutes. The mixture was stirred at 0 °C for one hour and again cooled down to -78 °C. DMPU (834 mL, 6.92 mol) was added dropwise, followed by the addition of the solution of cyclohexane-1,3-dicarboxylic acid diethyl ester from step 1 (316 g, 1.38 mol) in THF (400 mL). The mixture was stirred at -78 °C for 2.5 hours, and then allyl bromide (132 mL, 1.52 mol) was added. The mixture was warmed up to rt slowly and stirred at rt overnight. The mixture was quenched with ice-cold aqueous HCl (1 N, 1 L), diluted with ethyl acetate (30 mL) and extracted. The organic layer was washed with water (4 x 1.5 L), brine, dried over Na₂SO₄ and concentrated under reduced pressure to afford 371 g of the title compound as a thick oil, which was used in the next step without further purification.

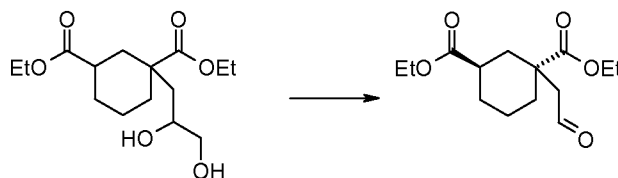
Step 3: 1-(2,3-dihydroxy-propyl)-cyclohexane-1,3-dicarboxylic acid diethyl ester



To a solution of 1-allyl-cyclohexane-1,3-dicarboxylic acid diethyl ester from step 2 (250 g, 0.93 mol) in *t*-butanol (2.3 L) and water (2.3 L) was added potassium ferricyanade (920 g, 2.79 mol), potassium carbonate (386 g, 2.79 mol), potassium osmate dihydrate (4.75 g, 13 mmol) and quinuclidine (0.073 g, 7.0 mmol). The resulting dark colored solution was stirred at rt overnight and then quenched with portion-wise addition of sodium sulfite (1.05 kg, 8.37 mol). After dilution with ethyl acetate, it was extracted, washed with water and brine, dried

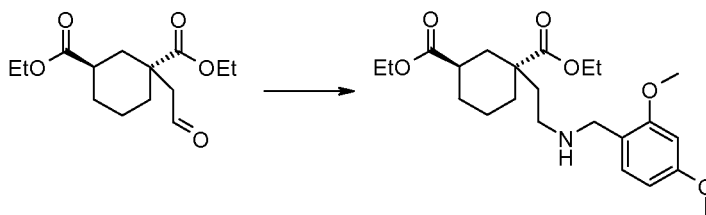
over Na₂SO₄, and concentrated under reduced pressure. The resulting residue (224 g) was used in the next step without delay and without further purification.

Step 4: *trans*-1-(2-oxo-ethyl)-cyclohexane-1,3-dicarboxylic acid diethyl ester



To a solution of 1-(2,3-dihydroxy-propyl)-cyclohexane-1,3-dicarboxylic acid diethyl ester from step 3 (224 g, 0.74 mol) in THF (0.74 L), *t*-butanol (1.48 L) and water (1.48 L) was added sodium bicarbonate (560 g, 6.66 mol), followed by the portion-wise addition of sodium periodate (475 g, 2.22 mol). The resulting white slurry was stirred at rt for two hours. The white solid was filtered off and washed with ethyl acetate. The organic layer of the filtrate was washed with a saturated aqueous solution of sodium sulfite, water and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (20% ethyl acetate in hexane) to afford 87 g (35%, combined yield of steps 1 and 2) of the title compound as a thick oil.

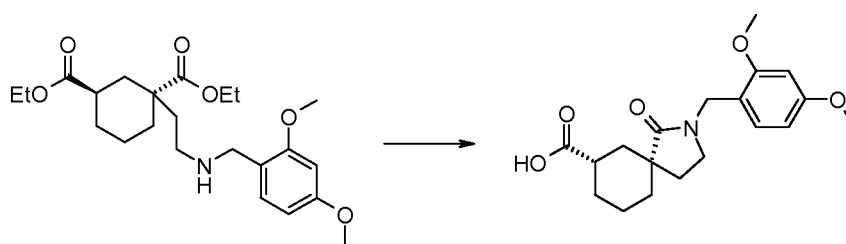
Step 5: *trans*-1-[2-(3,5-dimethoxy-benzylamino)-ethyl]-cyclohexane-1,3-dicarboxylic acid diethyl ester



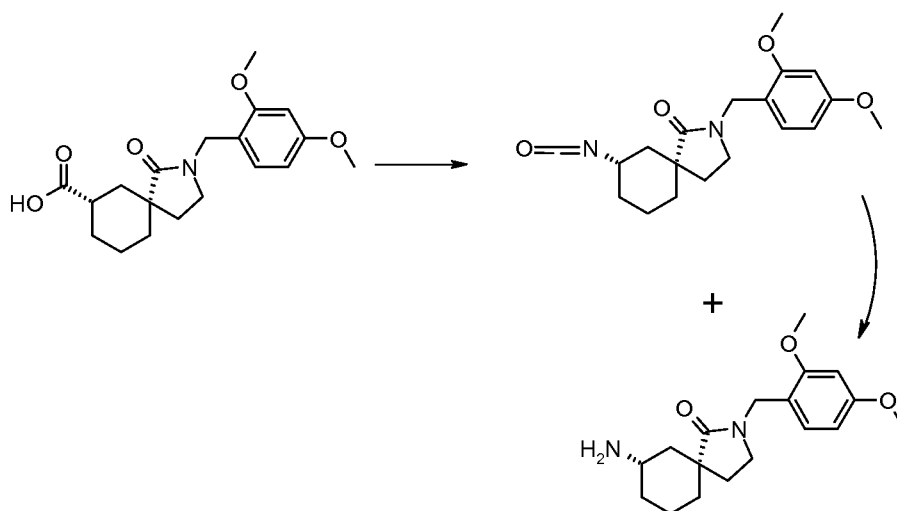
To a solution of *trans*-1-(2-oxo-ethyl)-cyclohexane-1,3-dicarboxylic acid diethyl ester from step 4 (89.0 g, 329 mmol) and 2,4-dimethoxybenzylamine (59.4 mL, 395 mmol) in 1,2-dichloroethane (659 mL) was added acetic acid (3.80 mL, 65.9 mmol). The mixture was stirred at room temperature for 1.5 hours. Then sodium triacetoxyborohydride (102.8 g, 461 mmol) was added portion-wise and stirred again at rt for 2.5 hours. The mixture was quenched with crushed ice, diluted with dichloromethane and extracted. The organic layer was washed with water and brine, dried over Na₂SO₄, and concentrated under reduced

pressure. The resulting residue was purified by silica gel chromatography (Solvent: 10% methanol in ethyl acetate) to afford 58.2 g (42%) of the title compound, 1-[2-(3,5-dimethoxy-benzylamino)-ethyl]-cyclohexane-1,3-dicarboxylic acid diethyl ester, as a yellow gum. ¹H NMR (400 MHz, CDCl₃): δ 7.07 - 7.21 (m, 1 H), 6.34 - 6.60 (m, 3 H), 4.11 (q, J = 7.0 Hz, 4 H), 3.68 - 3.91 (m, 8 H), 2.50 - 2.79 (m, 2 H), 2.27 - 2.50 (m, 2 H), 2.15 (d, J = 12.9 Hz, 1 H), 1.97 (s, 2 H), 1.55 - 1.95 (m, 4 H), 1.00-1.45 (m, 8 H).

Step 6: *cis*-2-(2,4-dimethoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decan-7-carboxylic acid



To a cooled (0 °C) ethanol (0.7 L) was added sodium hydride (60% in mineral oil, 16.2 g, 406 mmol) portion-wise. The mixture was stirred at rt for 30 min to get clear solution. Then a solution of 1-[2-(3,5-dimethoxy-benzylamino)-ethyl]-cyclohexane-1,3-dicarboxylic acid diethyl ester from step 5 (57.0 g, 135 mmol) in ethanol (0.7 L) was added slowly and the mixture was refluxed for 16 hours. The resulting mixture was concentrated under reduced pressure at rt and then diluted with ethyl acetate, washed with 1N HCl solution. The organic layer was washed with water and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (solvent: 10% methanol in dichloromethane) to yield 20.0 g (43%) of the title compound, *cis*-2-(2,4-dimethoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decan-7-carboxylic acid. ¹H NMR (400 MHz, CDCl₃) δ 6.98 - 7.13 (m, 1 H), 6.29 - 6.56 (m, 2 H), 4.21 - 4.56 (m, 2 H), 3.79 (d, J = 5.1 Hz, 6 H), 2.82 - 3.33 (m, 2 H), 1.28 - 2.51 (m, 11 H).

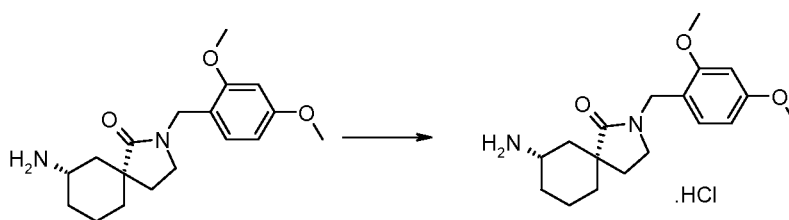
Step 7: *cis*-7-amino-2-(2,4-dimethoxy-benzyl)-2-aza-spiro[4.5]decan-1-one

To a solution of *cis*-2-(2,4-dimethoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decan-7-carboxylic acid from step 6 (20.0 g, 57.6 mmol) in toluene (290 mL) was added triethyl amine (9.63 mL, 69.1 mmol), followed by the addition of diphenyl phosphoril azide (13.7 mL, 63.3 mmol). The mixture was stirred at room temperature for 1.5 hours and then heated at 90 °C for three hours. The reaction mixture was cooled down to 0 °C, treated with slow addition of HCl (6N, 50 mL), and stirred at rt for 1 hour. The resulting mixture was diluted with water and two layers were separated. The aqueous layer was cooled down to 0 °C, neutralized with 40% aqueous KOH solution to pH ~7, then basicified with saturated NaHCO₃ and extracted with ethyl acetate, washed with brine, dried with Na₂SO₄ and concentrated to get 4.3 g of crude *cis*-7-amino-2-(2,4-dimethoxy-benzyl)-2-aza-spiro[4.5]decan-1-one. The organic layer was washed with water, brine, dried with Na₂SO₄ and concentrated. NMR of the resulting residue (35 g) showed that it was *cis*-2-(2,4-dimethoxy-benzyl)-7-isocyanato-2-aza-spiro[4.5]decan-1-one (contaminated with DPPA), which was not hydrolyzed. ¹H NMR (400 MHz, CDCl₃) δ 1.02 - 1.97 (m, 10 H), 2.65 - 3.14 (m, 3 H), 3.68 - 3.82 (m, 6 H), 4.20 (d, 1 H), 4.39 - 4.52 (m, 1 H), 6.17 - 6.54 (m, 2 H), 6.83 - 7.09 (m, 1 H).

To a solution of *cis*-2-(2,4-dimethoxy-benzyl)-7-isocyanato-2-aza-spiro[4.5]decan-1-one (34.8 g, contaminated with DPPA) in THF (313 mL) was added HCl solution (6N, 103 mL) and stirred at rt for 14 hours. After cooling down to 0 °C it was basicified with KOH (40%, until pH ~9) and extracted with EtOAc, washed with water, brine, dried with Na₂SO₄ and

concentrated. Combined with the residue obtained previously from the aqueous layer, it was purified by chromatography using 10% methanol in dichloromethane to get 11.2 g (61%) of the title compound, as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 0.94 - 2.10 (m, 10 H), 2.67 (t, $J=11.33$ Hz, 1 H), 2.94 - 3.25 (m, 2 H), 3.71 - 3.84 (m, 6 H), 4.42 (s, 2 H), 6.26 - 6.59 (m, 2 H), 7.08 (d, $J=8.21$ Hz, 1 H)

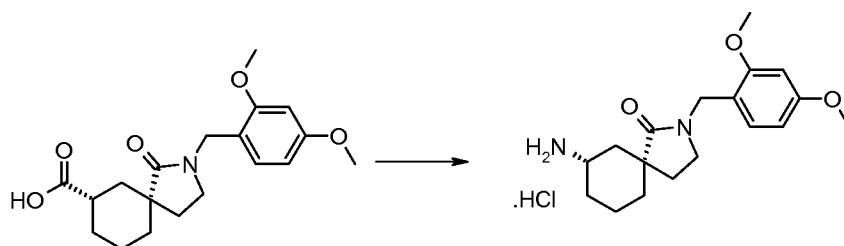
Step 8: *cis*-7-Amino-2-(2,4-dimethoxy-benzyl)-2-aza-spiro[4.5]decan-1-one Hydrochloric acid salt



To a solution of free base *cis*-7-amino-2-(2,4-dimethoxy-benzyl)-2-aza-spiro[4.5]decan-1-one from step 8 (11.16 g, 35.04 mmol) in dichloromethane (100 mL) at 0 °C was added HCl solution (4 M in dioxane, 25 mL) and stirred at 0 °C for 30 minutes. The resulting white slurry was concentrated under reduced pressure at ~ 25-30 °C. The white solid was dried under reduced pressure for 18 hours at room temperature to afford 12.73 g (quantitative yield) of the title compound, *cis*-7-amino-2-(2,4-dimethoxy-benzyl)-2-aza-spiro[4.5]decan-1-one hydrochloric acid salt. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.09 - 2.21 (m, 10 H), 2.83 - 3.33 (m, 3 H), 3.75 (d, $J=5.46$ Hz, 6 H), 4.27 (s, 2 H), 6.48 (dd, $J=8.39, 2.15$ Hz, 1 H), 6.56 (d, $J=2.34$ Hz, 1 H), 6.97 (d, $J=8.20$ Hz, 1 H). MS: m/z 319.13 ($\text{M}+\text{H}$) $^+$. Elemental analysis: calculated for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_3 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$ C, 59.41; H, 7.76; N, 7.70. Found: C, 59.41; H, 7.84; N, 17.81.

Step 7b: *cis*-7-amino-2-(2,4-dimethoxy-benzyl)-2-aza-spiro[4.5]decan-1-one hydrochloric acid salt

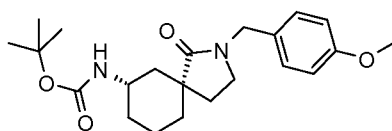
Alternatively Step 7 can be carried out as described next, which eliminates Step 8.



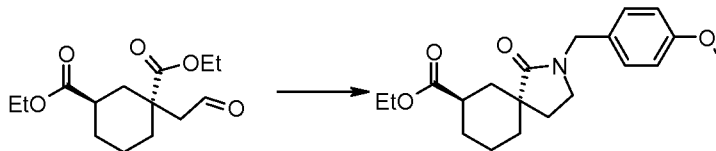
To a solution of *cis*-2-(2,4-dimethoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decan-7-carboxylic acid from step 6 (20.0 g, 57.6 mmol) in toluene (300 mL) was added triethyl amine (9.63 mL, 69.1 mmol), followed by the addition of diphenyl phosphoryl azide (12.4 mL, 57.6 mmol). The mixture was stirred at room temperature for 2 hours and then heated at 90 °C for 3.5 hours. The reaction mixture was cooled down rt, and poured into ice-cold aqueous 6N HCl (120 mL). The mixture was stirred at rt overnight. The solid formed was filtered, washed with toluene (50 mL x 2), and dried under oven to afford 16.6 g (81%) of the title compound *cis*-7-amino-2-(2,4-dimethoxy-benzyl)-2-aza-spiro[4.5]decan-1-one hydrochloric acid salt.

¹H NMR (400 MHz, DMSO-*d*₆): δ 6.97 (d, *J* = 8.20 Hz, 1 H), 6.56 (d, *J* = 2.34 Hz, 1 H), 6.48 (dd, *J* = 8.39, 2.15 Hz, 1 H), 4.27 (s, 2 H), 3.75 (d, *J* = 5.46 Hz, 6 H), 2.83 - 3.33 (m, 3 H), 1.09 - 2.21 (m, 10 H). ESI-MS *m/z*: 319.13 (M+H)⁺. Elemental analysis: calculated for C₁₈H₂₆N₂O₃·HCl·0.5H₂O C, 59.41; H, 7.76; N, 7.70. Found: C, 59.41; H, 7.84; N, 17.81.. The aqueous layer of the filtrate was cooled down to 0 °C, neutralized with solid K₂CO₃ to pH 7, extracted with CH₂Cl₂. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to afford 1.4 g of free base *cis*-7-amino-2-(2,4-dimethoxy-benzyl)-2-aza-spiro[4.5]decan-1-one. ¹H NMR (400 MHz, CDCl₃) δ 7.08 (d, *J* = 8.2 Hz, 1 H), 6.26 - 6.59 (m, 2 H), 4.42 (s, 2 H), 3.71 - 3.84 (m, 6 H), 2.94 - 3.25 (m, 2 H), 2.67 (t, *J* = 11.3 Hz, 1 H), 0.94 - 2.10 (m, 10 H). ESI-MS *m/z*: 319.13 (M+H)⁺.

Intermediate 11: [*cis*-2-(4-Methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-carbamic acid *tert*-butyl ester

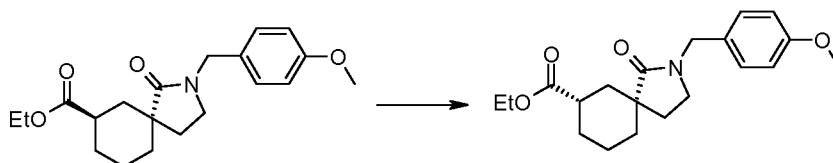


Step 1: *trans*-2-(4-Methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid ethyl ester



To a solution of *trans*-1-(2-oxo-ethyl)-cyclohexane-1,3-dicarboxylic acid diethyl ester from step 4 for intermediate 10 (4.36 g, 16.1 mmol) and 4-methoxybenzylamine (2.32 g, 16.9 mmol) in THF (100 mL) was added sodium triacetoxyborohydride (5.13 g, 24.2 mmol). The mixture was stirred at rt overnight and then quenched with cold saturated aqueous NaHCO₃. The aqueous layer was extracted with DCM (3x50 mL). The combined organic layers were concentrated under reduced pressure. The residue was dissolved in DCM, washed sequentially with 1N HCl (2x50 mL), saturated aqueous NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure to give 5.10 g (91.6%) of the title compound, *trans*-2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid ethyl ester. ¹H NMR (400 MHz, CDCl₃): δ 7.14 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.40 (d, *J* = 14.5 Hz, 1H), 4.31 (d, *J* = 14.5 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.24(tt, *J* = 3.9, 10.9 Hz, 1H), 3.07-3.15 (m, 2H), 1.31-2.08 (m, 10H), 1.25 (t, *J* = 7.1 Hz, 2H). ESI-MS *m/z*: 346 (M+H)⁺. It was used in the next step without further purification.

Step 2: *cis*-2-(4-Methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid ethyl ester

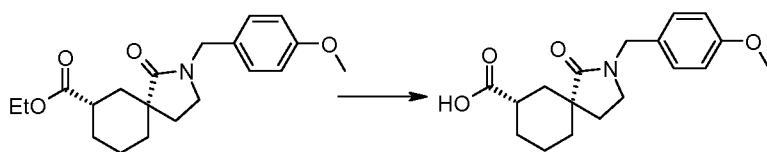


To a solution of *trans*-2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid ethyl ester from step 2 (5.10 g, 14.74 mmol) in anhydrous ethanol (80 mL) at 0 °C was added NaH (60% in mineral oil; 0.968 g) portion-wise. The reaction mixture was stirred at 65 °C overnight, then cooled to rt, and concentrated under reduced pressure. The residue was dissolved in water (20 mL) and the aqueous layer was extracted with DCM (3x30 mL). The

combined organic layers were washed with saturated aqueous NaHCO_3 and brine, filtered, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (0 to 50% ethyl acetate in hexanes) to give 2.56 g (46%) of the title compound, *cis*-2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid ethyl ester. ^1H NMR (400 MHz, CDCl_3): δ 7.14 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 4.39 (s, 2H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.79 (s, 3H), 3.07-3.20 (m, 2H), 2.32 (tt, $J = 3.4, 12.6$ Hz, 1H), 1.62-2.01 (m, 7H), 1.29-1.52 (m, 3H), 1.24 (t, $J = 7.1$ Hz, 2H). ESI-MS m/z : 346 ($\text{M}+\text{H}$) $^+$.

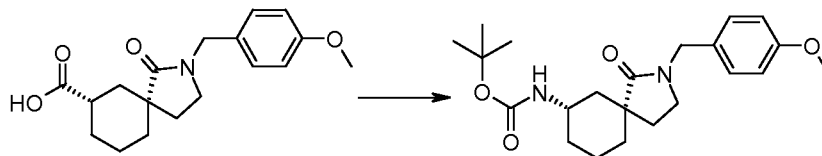
The aqueous layer was acidified to $\sim\text{pH}2$ with 1N HCl, extracted with DCM (3x30 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated to give 0.79 g (15%) of 2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid as a mixture of two diastereomers.

Step 3: *cis*-2-(4-Methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid



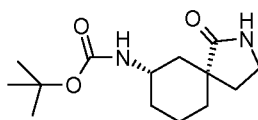
To a solution of *cis*-2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid ethyl ester from step 2 (1.76 g, 5.10 mmol) in THF (45 mL) was added 1.0 M of LiOH in water (15 mL) at rt. The reaction mixture was stirred at rt overnight and THF was evaporated under reduced pressure. The remaining aqueous layer was washed with ethyl ether (20 mL), acidified to pH2 with 1N HCl. The resulting precipitates were filtered, washed with water (3x), and dried under reduced pressure to give 1.4 g (87%) of the title compound, *cis*-2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid, as a white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.14 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 4.39 (s, 2H), 3.80 (s, 3H), 3.08-3.23 (m, 2H), 2.36 (tt, $J = 3.4, 12.4$ Hz, 1H), 1.63-2.06 (m, 7H), 1.29-1.55 (m, 3H). ESI-MS m/z : 318 ($\text{M}+\text{H}$) $^+$.

Step 4: [*cis*-2-(4-Methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-carbamic acid *tert*-butyl ester



cis-2-(4-Methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid from step 3 (0.510 g, 1.61 mmol) was dissolved in toluene (20.0 mL). Triethylamine (0.246 mL, 1.77 mmol) was added, followed by the addition of diphenylphosphonic azide (0.381 mL, 1.77 mmol). The reaction mixture was stirred at rt for 1 hr and then heated at 90 °C for 2 hours. The mixture was cooled to rt, *tert*-butyl alcohol (6.15 mL, 64.3 mmol) was added, and the mixture was then heated at 90 °C for 24 hrs. The reaction mixture was cooled down to rt and concentrated under reduced pressure. The resulting residue was diluted with ethyl acetate (100 mL), washed with saturated aqueous NaHCO₃, water and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate: 30/70) to afford 0.50 g (80%) of the title compound, *cis*-2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-carbamic acid *tert*-butyl ester. ¹H NMR (400 MHz, CDCl₃): δ 7.13 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.71 (bs, 1H), 4.38 (m, 2H), 3.79 (s, 3H), 3.55 (bs, 1H), 3.07-3.18 (m, 2H), 1.35-1.98 (m, 18H), 1.13-1.22 (m, 1H). ESI-MS *m/z*: 389 (M+H)⁺.

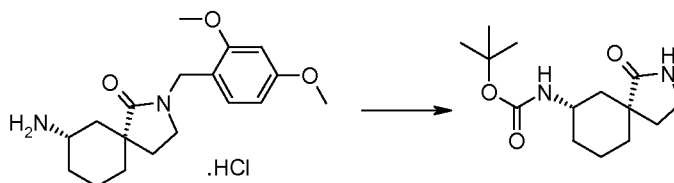
Intermediate 12: (*cis*-1-Oxo-2-aza-spiro[4.5]dec-7-yl)-carbamic acid *tert*-butyl ester



To a round bottom flask was added [*cis*-2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-carbamic acid *tert*-butyl ester (intermediate 11) (0.500 g, 1.29 mmol,) and acetonitrile (25 mL). Ceric ammonium nitrate (2.12 g, 3.86 mmol) in water (10.0 mL) was added. The crude mixture was stirred at rt for one day and then diluted with CH₂Cl₂ (100 mL). The organic layer was washed with water and brine, dried with Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH₂Cl₂/MeOH: 9/1) to

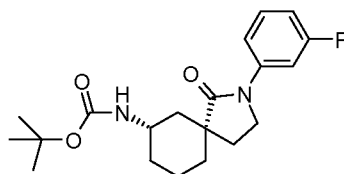
afford 0.252 g (73%) of the title compound, *cis*-1-oxo-2-aza-spiro[4.5]dec-7-yl)-carbamic acid *tert*-butyl ester. ^1H NMR (400 MHz, CDCl_3): δ 6.31 (bs, 1H), 4.66 (d, $J = 7.0$ Hz, 1H), 3.48-3.60 (bs, 1H), 3.27-3.38 (m, 2H), 1.92-2.16 (m, 3H), 1.74-1.84 (m, 2H), 1.43-1.60 (m, 12H), 1.08-1.30 (m, 12H). ESI-MS m/z : 269 ($\text{M}+\text{H}$) $^+$.

5 Intermediate 12 was also made as follows:



To a round bottom flask was added *cis*-7-amino-2-(2,4-dimethoxybenzyl)-2-aza-spiro[4.5]decan-1-one HCl salt from step 8 for intermediate 10 (3.00 g, 8.46 mmol, intermediate 10) and trifluoroacetic acid (10.0 mL). The mixture was refluxed for 1.5 hrs, and then cooled down to rt and concentrated under reduced pressure. The resulting residue was diluted with CH_2Cl_2 (10 mL) and concentrated under reduced pressure. This procedure was repeated twice to remove excess trifluoroacetic acid. The resulting residue was dissolved in THF (20.0 mL), di-*tert*-butyldicarbonate (2.03 g, 9.30 mmol) and triethylamine (3.53 mL, 25.4 mmol) were added. After stirring at rt overnight, the reaction mixture was filtered through Celite[®], and the filtrate was concentrated under reduced pressure to afford the title compound. LC-MS (method C): RT: 0.94 min. ESI-MS m/z : 269 ($\text{M}+\text{H}$) $^+$. It was used without further purification.

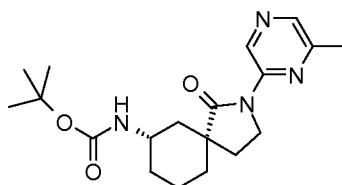
Intermediate 13: *cis*-2-(3-Fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-carbamic acid *tert*-butyl ester



A mixture of (*cis*-1-oxo-2-aza-spiro[4.5]dec-7-yl)-carbamic acid *tert*-butyl ester (0.036 g, 0.13 mmol, intermediate 12), 3-fluoriodobenzene (0.030 g, 0.13 mmol), copper(I) iodide (0.013 g, 0.067 mmol), potassium carbonate (0.037 g, 0.27 mmol) and *N,N'*dimethyl-ethane-

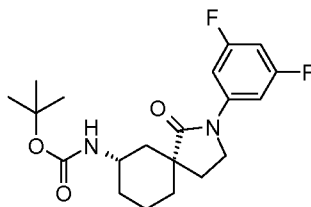
1,2-diamine (0.012 g, 0.13 mmol) in 1,4-dioxane (2.0 mL, 26 mmol) was heated *via* microwave (Biotage) at 160 °C for 2 hours. The mixture was cooled to rt and passed through a layer of Celite®. The filtrate was concentrated under reduced pressure. The residue was purified with preparative TLC (hexane/ethyl acetate: 1/1) to afford 0.030 g (62%) of the title compound, *cis*-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-carbamic acid *tert*-butyl ester. ¹H NMR (400 MHz, CDCl₃): δ 7.57 (dt, *J* = 11.4, 2.3 Hz, 1H), 7.27-7.37 (m, 2H), 6.81-6.87 (m, 1H), 4.60 (bs, 1H), 3.71-3.82 (m, 2H), 3.58 (bs, 1H), 1.95-2.22 (m, 3H), 1.80-1.90 (m, 2H), 1.60-1.70 (m, 1H), 1.47-1.57 (m, 3H), 1.44 (s, 9H), 1.12-1.23 (m, 1H). ESI-MS *m/z*: 363 (M+H)⁺.

Intermediate 14: *cis*-[2-(6-Methyl-pyrazin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-carbamic acid *tert*-butyl ester



Using the same experimental procedures described for intermediate 13, intermediate 14 was made at 0.28 mmol reaction scale from intermediate 12 and 2-chloro-6-methylpyrazine, and 0.040 g (40%) of the title compound was obtained. ¹H NMR (400 MHz, CDCl₃): δ 9.51 (s, 1H), 8.18 (s, 1H), 4.57 (d, *J* = 7.9 Hz, 1H), 3.90-4.05 (m, 2H), 3.59 (s, 1H), 2.49 (s, 3H), 1.96-2.22 (m, 3H), 1.81-1.93 (m, 2H), 1.47-1.69 (m, 4H), 1.44 (s, 9H), 1.17 (qd, *J* = 12.4, 4.1 Hz, 1H). ESI-MS *m/z*: 361 (M+H)⁺.

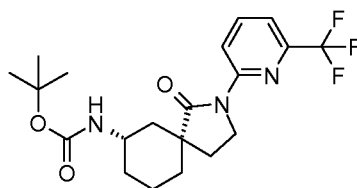
Intermediate 15: *cis*-[2-(3,5-Difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-carbamic acid *tert*-butyl ester



Using the same experimental procedures described for intermediate 13, intermediate 15 was made at 0.47 mmol reaction scale from intermediate 12 and 1-bromo-3,5-difluorobenzene,

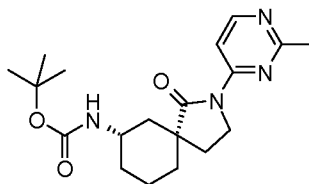
and 0.030 g (17 %) of product was obtained. ^1H NMR (400 MHz, CDCl_3) δ 7.29 (dd, J = 9.8, 2.2 Hz, 2H), 6.59 (tt, J = 8.9, 2.2 Hz, 1H), 4.54 (d, J = 8.1 Hz, 1H), 3.68-3.79 (m, 2H), 3.58 (bs, 1H), 1.96-2.24 (m, 3H), 1.80-1.90 (m, 2H), 1.40-1.68 (m, 13H), 1.17 (qd, J = 12.4, 4.0 Hz, 1H). ESI-MS m/z : 381 ($\text{M}+\text{H}$) $^+$.

5 **Intermediate 16: *cis*-[1-Oxo-2-(6-trifluoromethyl-pyridin-2-yl)-2-aza-spiro[4.5]dec-7-yl]-carbamic acid *tert*-butyl ester**



Using the same experimental procedures described for intermediate 13, intermediate 16 was made at 0.34 mmol reaction scale from intermediate 12 and 2-bromo-6-(trifluoromethyl)pyridine. LC-MS (Method C): RT: 1.66 min; ESI-MS m/z : 414 ($\text{M}+\text{H}$) $^+$. It was used without further purification.

10 **Intermediate 17: *cis*-2-(2-Methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl] carbamic acid *tert*-butyl ester**

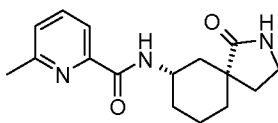


15 Intermediate 17 was prepared *via* the process of **Scheme 2**, *supra*, as follows:

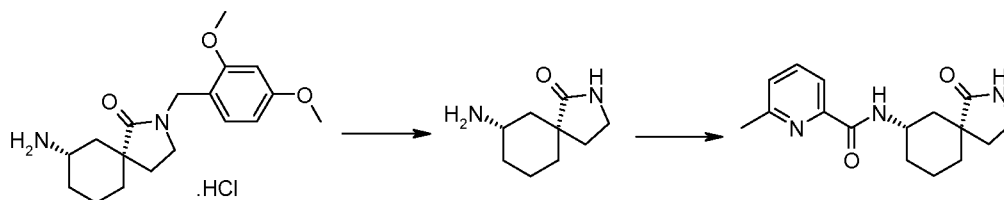
A mixture of 4-chloro-2-methylpyrimidine (0.192 g, 1.49 mmol), (*cis*-1-oxo-2-aza-spiro[4.5]dec-7-yl)-carbamic acid *tert*-butyl ester (0.40 g, 1.49 mmol, intermediate 12), tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (0.154 g, 0.149 mmol), dicesium carbonate (0.680 g, 2.09 mmol) and racemic BINAP (0.278 g, 0.447 mmol) in toluene (5.0 mL) was heated at 80 °C for 4 hours. The reaction mixture was cooled to rt. The catalyst was filtered off and the filtrate was concentrated under reduce pressure. The residue was purified by silica gel chromatography (0-30% ethyl acetate in hexane) to give 0.318 g (59%) of the title compound, *cis*-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-

yl] carbamic acid *tert*-butyl ester, as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.49 (d, J = 5.8 Hz, 2H), 8.17 (d, J = 5.8 Hz, 1H), 4.52 (bs, 1H), 3.92-4.13 (m, 2H), 3.58 (bs, 1H), 2.64 (s, 3H), 1.97-2.17 (m, 3H), 1.80-1.92 (m, 2H), 1.47-1.63 (m, 4H), 1.44 (s, 9H), 1.11-1.22 (m, 1H). ESI-MS m/z : 361 ($\text{M}+\text{H}$) $^+$.

5 **Intermediate 18: *cis*-6-Methyl-pyridine-2-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide**



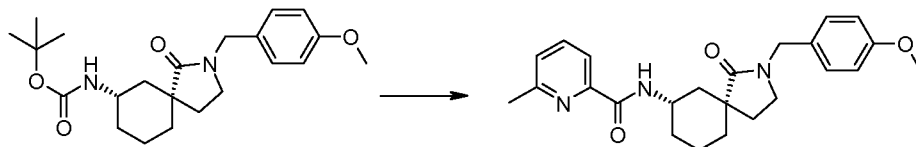
Route 1: Intermediate 18 was prepared *via* the process of **Scheme 10**, *supra*, as follows:



10 To a round bottom flask was added *cis*-7-amino-2-(2,4-dimethoxy-benzyl)-2-aza-spiro[4.5]decan-1-one HCl salt from step 8 for intermediate 10 (2.00 g, 5.64 mmol, intermediate 10) and trifluoroacetic acid (8.0 mL). The mixture was refluxed for 1.5 hrs, then cooled down to rt and concentrated under reduced pressure. The resulting residue was diluted with CH_2Cl_2 (10 mL) and concentrated under reduced pressure. This procedure was repeated
15 twice to remove excess trifluoroacetic acid. The resulting residue was dissolved in CH_2Cl_2 (40.0 mL), 6-methylpicolinic acid (0.773 g, 5.64 mmol), and BOP (2.49 g, 5.64 mmol), and triethylamine (3.93 mL, 28.2 mmol) in CH_2Cl_2 (5.0 mL) were added. The reaction mixture was stirred at rt for 4 hours and then concentrated under reduced pressure. The residue was purified by silica gel chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$: 80/20) to afford 1.23 g (76%) of the
20 title compound, *cis*-6-methyl-pyridine-2-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide, as a white solid. ESI-MS m/z : 288 ($\text{M}+\text{H}$) $^+$.

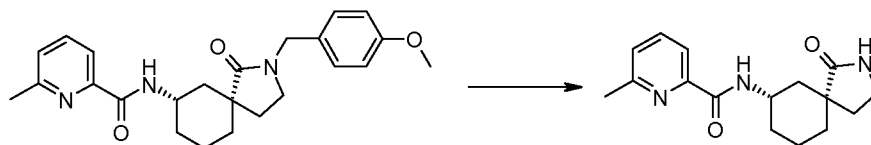
Route 2: Intermediate 18 was also made *via* the process of **Scheme 11**, *supra*, as follows:

Step 1: *cis*-6-Methyl-pyridine-2-carboxylic acid [2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide



[*cis*-2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-carbamic acid *tert*-butyl ester (0.50 g, 1.29 mmol, intermediate 11) was dissolved in CH₂Cl₂ (10.0 mL), and 4 M HCl/dioxane (3.2 mL) was added. The mixture was stirred at rt for 2 hrs and concentrated. The residue was dissolved in CH₂Cl₂ (20.0 mL), 6-methylpicolinic acid (0.176 g, 1.29 mmol), and BOP (0.569 g, 1.29 mmol), and triethylamine (0.538 mL, 3.86 mmol) in CH₂Cl₂ (5.0 mL) were added. The reaction mixture was stirred at rt for 4 hours and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate: 3/7) to afford 0.48 g (91%) of the title compound, *cis*-6-methyl-pyridine-2-carboxylic acid [2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide. ¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J* = 8.6 Hz, 1H), 7.94 (d, *J* = 7.1 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.10-7.12 (m, 2H), 6.80-6.84 (m, 2H), 4.33-4.41 (m, 2H), 3.98-4.08 (m, 1H), 3.77 (s, 3H), 3.10-3.19 (m, 2H), 2.55 (s, 3H), 1.91-2.09 (m, 3H), 1.80-1.86 (m, 1H), 1.75-1.79 (m, 2H), 1.63-1.71 (m, 1H), 1.29-1.58 (m, 3H). ESI-MS *m/z*: 408 (M+H)⁺.

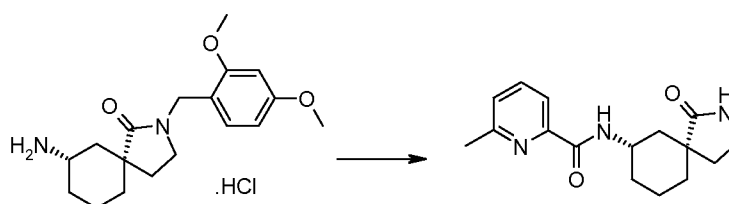
Step 2: *cis*-6-Methyl-pyridine-2-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide



To a round bottom flask was added *cis*-6-methyl-pyridine-2-carboxylic acid [2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide from step 1 (0.480 g, 1.18 mmol), acetonitrile (18.3 mL), and ceric ammonium nitrate (1.94 g, 3.53 mmol) in water (7.2 mL). The reaction mixture was stirred at rt for one day and then diluted with CH₂Cl₂ (100 mL). The organic layer was washed with water and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CH₂Cl₂/MeOH: 4/1) to afford 0.210 g (61%) of title compound, *cis*-6-methyl-pyridine-2-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide.

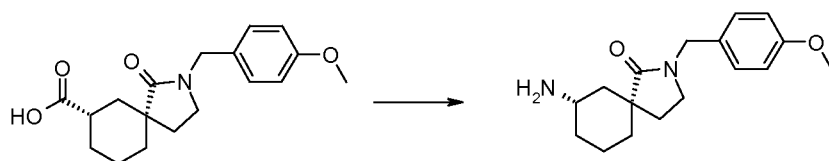
aza-spiro[4.5]dec-7-yl)-amide, as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, J = 8.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 6.23 (s, 1H), 4.00-4.10 (m, 1H), 3.30-3.39 (m, 2H), 2.56 (s, 3H), 2.15-2.23 (m, 1H), 2.07-2.14 (m, 2H), 1.81-1.87 (m, 2H), 1.70 (t, J = 12.4 Hz, 1H), 1.48-1.64 (m, 3H), 1.30-1.38 (m, 1H). ESI-MS m/z : 288 ($\text{M}+\text{H}$) $^+$.

Route 3: Intermediate 18 was also made from *cis*-7-amino-2-(2, 4-dimethoxy-benzyl)-2-aza-spiro[4.5]decan-1-one (intermediate 10).

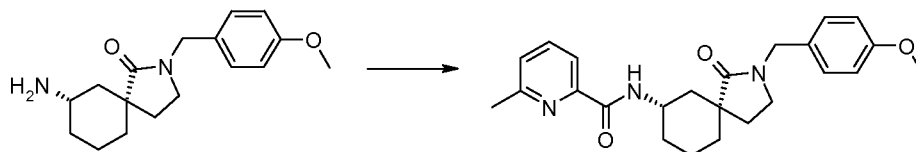


To a solution of 7-amino-2-(2,4-dimethoxy-benzyl)-2-aza-spiro[4.5]decan-1-one HCl salt from step 8 for intermediate 10 (0.20 g, 0.63 mmol) in CH_2Cl_2 (9.37 mL) was added 6-methyl-pyridine-2-carboxylic acid (0.095 g, 0.691 mmol) and PyBOP (0.360 g, 0.691 mmol), followed by triethylamine (0.306 mL, 2.20 mmol). The reaction mixture was stirred at rt overnight and then transferred to a 125-mL separatory funnel with CH_2Cl_2 (30 mL). The organic layer was washed with saturated NH_4Cl , saturated NaHCO_3 and brine, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 to 50% ethyl acetate in methylene chloride) to give *cis*-6-methyl-pyridine-2-carboxylic acid [2-(2,4-dimethoxy-benzyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide, which was then heated in TFA (0.537 mL) to reflux for 1 hr. The reaction mixture was cooled to rt and concentrated. The residue was dissolved in CH_2Cl_2 , washed with saturated NaHCO_3 and brine, dried over MgSO_4 , and concentrated under reduced pressure to give 0.15 g (83%) of the title compound, *cis*-6-methyl-pyridine-2-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide, which was used in the next step without further purification. ESI-MS m/z : 288 ($\text{M}+\text{H}$) $^+$.

Route 4: Intermediate 18 was also made *via* the process of **Scheme 11**, *supra*, as follows:

Step 1: *cis*-7-Amino-2-(4-methoxy-benzyl)-2-aza-spiro[4.5]decan-1-one

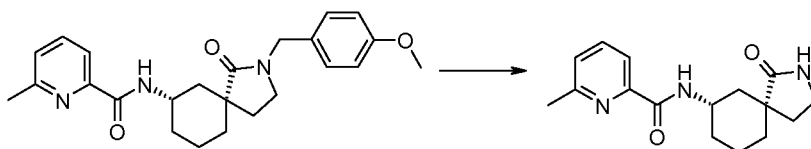
cis-2-(4-Methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decan-7-carboxylic acid from step 3 for intermediate 11 (1.52 g, 4.79 mmol) was dissolved in toluene (22.0 mL). Triethylamine (0.801 mL, 5.75 mmol) was added, followed by the addition of diphenylphosphonic azide (1.14 mL, 5.27 mmol). The reaction mixture was stirred at rt for 1 hr and then heated at 90 °C for 2 hrs. The mixture was cooled to rt and was added slowly to ice-cold 6.0 M of HCl in water (8.0 mL). The resulting biphasic mixture was stirred vigorously at rt for 1 hr. The aqueous layer was separated, diluted with water (50 mL), and basified with solid Na₂CO₃ to pH 10. The mixture was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 1.38 g of the title compound, *cis*-7-amino-2-(4-methoxy-benzyl)-2-aza-spiro[4.5]decan-1-one, which was used for the next step without further purification. ¹H NMR (300 MHz, CDCl₃) δ 7.1 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.44 (d, *J* = 14.5 Hz, 1H), 4.23 (d, *J* = 14.5 Hz, 1H), 3.00-3.14 (m, 2H), 2.83-2.98 (br, 1H), 1.25-1.94 (m, 10 H). ESI-MS *m/z*: 289 (M+H)⁺.

Step 2: *cis*-6-Methyl-pyridine-2-carboxylic acid [2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide

To a solution of *cis*-7-amino-2-(2, 4-dimethoxy-benzyl)-2-aza-spiro[4.5]decan-1-one from step 1 (675 mg, 2.34 mmol) in CH₂Cl₂ (34.9 mL) was added 6-methylpyridine-2-carboxylic acid (353 mg, 2.57 mmol) and PyBOP (1.34 g, 2.57 mmol), followed by triethylamine (1.14 mL, 8.19 mmol). The reaction mixture was stirred at rt overnight and then transferred to a 125-mL separatory funnel with CH₂Cl₂ (30 mL). The organic layer was washed with saturated aqueous NH₄Cl, saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄, filtered,

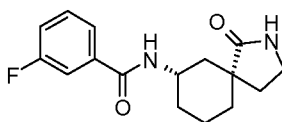
and concentrated under reduced pressure. The residue was purified by CombiFlash[®] system (12 g silica gel cartridge; gradient: 0 to 50% ethyl acetate in hexanes over 10 min, then 50% ethyl acetate in hexanes for 20 min) to give 0.62 g (65%) of the title compound, *cis*-6-methyl-pyridine-2-carboxylic acid [2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide. ¹H NMR (400 MHz, CDCl₃): δ 8.10 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 4.39 (s, 2H), 3.99-4.11 (m, 1H), 3.79 (s, 3H), 3.10-3.22 (m, 2H), 2.57 (s, 3H), 1.64-2.14 (m, 7H), 1.30-1.56 (m, 3H). ESI-MS *m/z*: 408 (M+H)⁺.

Step 3: *cis*-6-Methyl-pyridine-2-carboxylic acid ((5*S*,7*S*)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide



Using the same experimental procedures described in the synthesis of intermediate 18 in route 2 (step 2), intermediate 18 also was made at 1.52 mmol reaction scale from *cis*-6-methyl-pyridine-2-carboxylic acid [2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide from route 4 (step 2), and 0.37 g (55 %) of the title compound was obtained by CombiFlash[®] system (4 g silica gel cartridge; gradient: 0 to 10% MeOH with 2N NH₃ in DCM over 8 min, then 10% MeOH with 2N NH₃ in DCM for 8 min). ESI-MS *m/z*: 288 (M+H)⁺.

Intermediate 19: *cis*-3-Fluoro-*N*-((5*S*,7*S*)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-benzamide

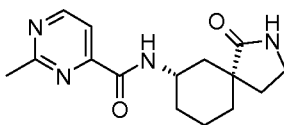


Using the same experimental procedures described in route 1 for intermediate 18, intermediate 19 was made at 1.19 mmol reaction scale from intermediate 10 and 3-fluorobenzoic acid and purified by silica gel chromatography (CH₂Cl₂/MeOH: 10/1) to afford 0.145 g (42 %) of the title compound. LC-MS (method C): RT: 0.86 min; ESI-MS *m/z*: 291 (M+H)⁺.

Using the same experimental procedures described in route 2 for intermediate 18, intermediate 19 was also made from 0.643 mmol of [*cis*-2-(4-methoxy-benzyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-carbamic acid *tert*-butyl ester and 0.643 mmol of 3-fluorobenzoic acid. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (bs, 1H), 7.59-7.68 (m, 2H), 7.35-7.42 (m, 1H), 7.13-7.19 (m, 1H), 6.22 (bs, 1H), 4.29-4.38 (m, 1H), 3.35-3.45 (m, 2H), 2.09-2.18 (m, 1H), 1.97-2.04 (m, 1H), 1.39-1.93 (m, 8H). ESI-MS m/z: 291 (M+H)⁺.

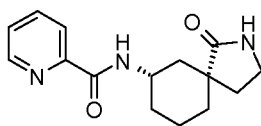
Using the same experimental procedures described in route 3 for intermediate 18, intermediate 19 was also made from 2.82 mmol of intermediate 10 and 2.82 mmol of 3-fluorobenzoic acid. LC-MS (method C): RT: 0.86 min; ESI-MS m/z: 291 (M+H)⁺. It was used without further purification.

Intermediate 20: *cis*-2-Methyl-pyrimidine-4-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide



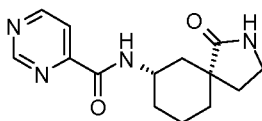
Using the same experimental procedures described in route 1 for intermediate 18, intermediate 20 was made at 2.82 mmol reaction scale from intermediate 10 and 2-methyl-pyrimidine-4-carboxylic acid, and purified by RP-HPLC purification system (Gradient: acetonitrile in water, 12-95% in 3.5 minutes with a cycle time of 5 min. A shallow gradient between 18-42% of acetonitrile was used between 0.6-3.1 min to separate close-eluting impurities. Flow rate: 100 mL/min. Mobile phase additive: 39 mM of ammonium acetate. Column: Inertsil[®] C18, 30 x 50 mm, 5 μm particle size (GL Sciences, Tokyo, Japan)) to afford 0.330 g (41 %) of the title compound. LC-MS (method C): RT: 0.63 min; ESI-MS m/z: 289 (M+H).

Intermediate 21: *cis*-Pyridine-2-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide



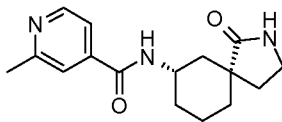
Using the same experimental procedures described in route 1 for intermediate 18, intermediate 21 was made at 2.82 mmol reaction scale from intermediate 10 and picolinic acid, and purified by chromatography (CH₂Cl₂/MeOH: 4/1) to afford 0.420 g (54 %) of the title compound. LC-MS (method C): retention time RT: 0.72 min; ESI-MS m/z: 274 (M+H)⁺.

Intermediate 22: *cis*-Pyrimidine-4-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide



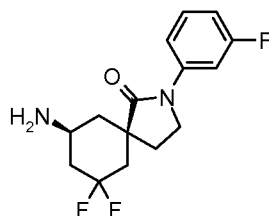
Using the same experimental procedures described in route 1 for intermediate 18, intermediate 22 was made at 0.71 mmol reaction scale from intermediate 10 and pyrimidine-4-carboxylic acid, and purified by chromatography (CH₂Cl₂/MeOH: 4/1) to afford 0.045 g (23 %) of the title compound. LC-MS (method D): RT: 1.15 min; ESI-MS m/z: 275 (M+H)⁺.

Intermediate 23: *cis*-2-Methyl-N-(1-oxo-2-aza-spiro[4.5]dec-7-yl)-isonicotinamide



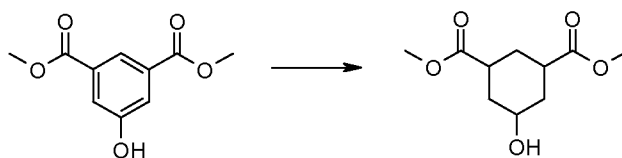
Using the same experimental procedures described in route 1 for intermediate 18, intermediate 23 was made at 2.82 mmol reaction scale from intermediate 10 and 2-methylisonicotinic acid, and purified on a RP-HPLC/MS purification system (Gradient: acetonitrile in water, 12-95% in 3.0 minutes with a cycle time of 5 min. A shallow gradient between 13-30% of acetonitrile was used between 0.5-2.0 min to separate close-eluting impurities. Flow rate: 100 mL/min. Mobile phase additive: 39 mM of ammonium acetate. Column: Inertsil[®] C18, 30 x 50 mm, 5 um particle size (GL Sciences)) to afford 0.300 g (37 %) of the title compound was obtained. LC-MS (method C): RT: 0.66 min; ESI-MS m/z: 288 (M+H)⁺.

Intermediate 24: *cis*-9-Amino-7,7-difluoro-2-(3-fluoro-phenyl)-2-aza-spiro[4.5]decan-1-one



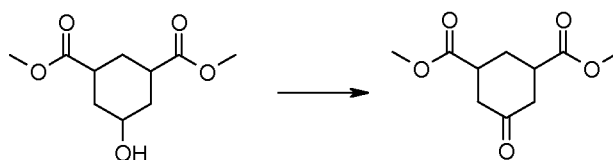
Intermediate 24 was prepared *via* the process of **Scheme 6**, *supra*, as follows:

Step 1: 5-Hydroxy-cyclohexane-1,3-dicarboxylic acid dimethyl ester



To a solution of dimethyl-5-hydroxyisophthalate (3.50 g, 16.6 mmol) in methanol (60.0 mL) was added 5% rhodium on alumina (0.80 g) at 0 °C, followed by acetic acid (0.60 mL, 10.6 mmol). The reaction mixture was shaken under hydrogen (55 psi) at room temperature overnight and then filtered through Celite[®] and concentrated under reduced pressure. The residue was purified by CombiFlash[®] system (12 g silica gel cartridge; gradient: 0 to 50% ethyl acetate in DCM over 30 min) to give 3.00 g (83%) of the title compound, 5-hydroxy-cyclohexane-1,3-dicarboxylic acid dimethyl ester. ¹H NMR (400 MHz, CDCl₃): δ 3.56-3.78 (m, 7H), 2.15-2.51 (m, 5H), 1.25-1.66 (m, 3 H).

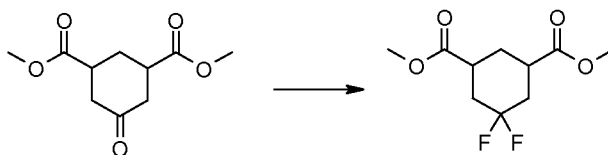
Step 2: 5-Oxo-cyclohexane-1,3-dicarboxylic acid dimethyl ester



To a mixture of 5-hydroxy-cyclohexane-1,3-dicarboxylic acid dimethyl ester from step 1 (3.00 g, 13.9 mmol) and triethylamine (5.80 mL, 41.6 mmol) in dimethyl sulfoxide (6.00 mL, 84.5 mmol) and DCM (0.60 mL, 9.36 mmol) was added portion-wise sulfur trioxide-pyridine complex (5.08 g, 31.9 mmol) at 10 °C. The reaction mixture was stirred at room temperature

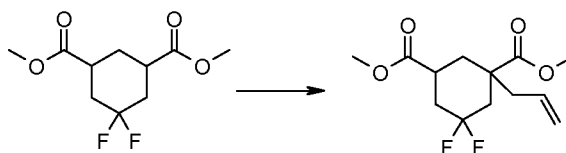
for 2 hrs and then quenched with water (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2 x 40 mL) and concentrated under reduced pressure. The residue was purified by CombiFlash[®] system (gradient: 0 to 50% ethyl acetate in DCM over 30 min) to give 2.2 g (74%) the title compound, 5-oxo-cyclohexane-1,3-dicarboxylic acid dimethyl ester. ¹H NMR (400 MHz, CDCl₃): δ 3.72 (s, 6H), 2.61-2.75 (m, 2H), 2.31-2.47 (m, 3H), 1.83 (ddt, J = 2.9, 13.5, 34.4 Hz, 2H), 1.53 (q, J = 13.2 Hz, 1H).

Step 3: 5,5-Difluoro-cyclohexane-1,3-dicarboxylic acid dimethyl ester



To a solution of diethylaminosulfur trifluoride (3.45 mL, 26.1 mmol) in DCM (30.0 mL) at 0 °C was added a solution of 5-oxo-cyclohexane-1,3-dicarboxylic acid dimethyl ester (2.80 g, 13.1 mmol) in DCM (26.0 mL), followed by addition of ethanol (0.15 mL, 2.61 mmol). The reaction mixture was stirred at room temperature overnight and then quenched carefully with cold saturated aqueous NaHCO₃. The aqueous layer was extracted with DCM (x3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by CombiFlash[®] system (12 g silica gel cartridge; gradient: 0 to 30% ethyl acetate in DCM over 19 min, then 30% ethyl acetate in DCM for 5 min) to give 2.5 g (81%) of the title compound, 5,5-difluoro-cyclohexane-1,3-dicarboxylic acid dimethyl ester. ¹H NMR (400 MHz, CDCl₃): δ 3.73 (s, 6H), 2.70-2.80 (m, 2H), 2.60-2.68 (m, 2H), 2.44-2.55 (m, 3H), 1.92 (q, J = 13.5 Hz, 1H).

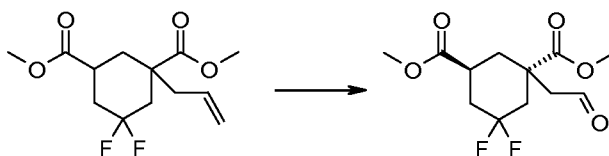
Step 4: 1-Allyl-5,5-difluoro-cyclohexane-1,3-dicarboxylic acid dimethyl ester



Using the same experimental procedures described in step 2 for intermediate 2, starting from 5,5-difluoro-cyclohexane-1,3-dicarboxylic acid dimethyl ester (10.6 mmol), 2.5 g (86%) of

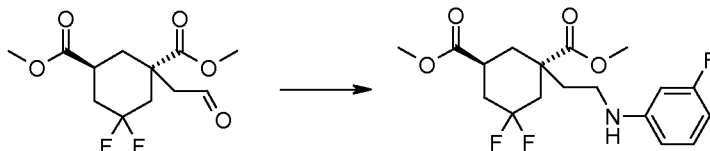
the title compound was obtained. ^1H NMR (400 MHz, CDCl_3): δ 5.57-5.73 (m, 1H), 5.02-5.17 (m, 2H), 3.64-3.77 (m, 6H), 1.58-3.05 (m, 9H).

Step 5: *trans*-5,5-Difluoro-1-(2-oxo-ethyl)-cyclohexane-1,3-dicarboxylic acid dimethyl ester



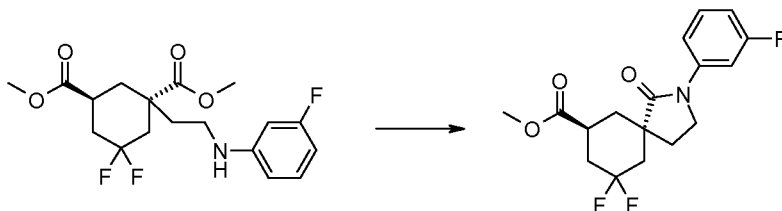
Using the same experimental procedures described in step 3 for intermediate 2, starting from 1-allyl-5,5-difluoro-cyclohexane-1,3-dicarboxylic acid dimethyl ester (7.24 mmol), 1.3 g (65%) of the title compound was obtained. ^1H NMR (400 MHz, CDCl_3): δ 9.68 (dd, $J = 1.2$, 2.1 Hz, 1H), 3.69-3.77 (m, 6H), 2.95-3.25 (m, 1H), 2.84 (dd, $J = 0.9$, 16.9 Hz, 1H), 2.63-2.75 (m, 2H), 2.56 (dd, $J = 2.1$, 16.9 Hz, 1H), 2.34-2.45 (m, 1H), 1.72-1.90 (m, 2H), 1.37 (t, $J = 13$ Hz, 1H).

Step 6: *trans*-5,5-Difluoro-1-[2-(3-fluoro-phenylamino)-ethyl]-cyclohexane-1,3-dicarboxylic acid dimethyl ester



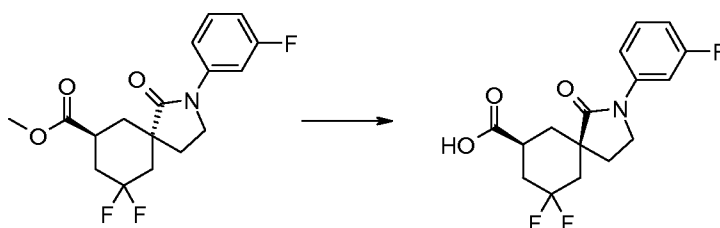
Using the same experimental procedures described in step 4 for intermediate 2, starting from *trans*-5,5-difluoro-1-(2-oxo-ethyl)-cyclohexane-1,3-dicarboxylic acid dimethyl ester (4.67 mmol), 1.32 g (75%) of the title compound was obtained. ^1H NMR (400 MHz, CDCl_3): δ 7.04-7.13 (m, 1H), 6.18-6.48 (m, 3H), 3.65-3.79 (m, 6H), 2.96-3.27 (m, 3H), 2.62-2.82 (m, 2H), 2.32-2.45 (m, 2H), 2.06-2.15 (m, 1H), 1.57-2.93 (m, 3H), 1.20-1.33 (m, 1H). ESI-MS m/z : 374 ($\text{M}+\text{H}$) $^+$.

Step 7: *trans*-9,9-Difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid methyl ester



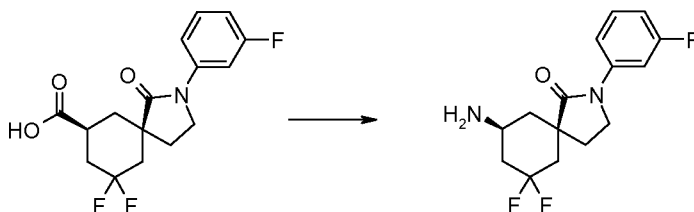
Using the same experimental procedures described in step 4 of intermediate 2, starting from *trans*-5,5-difluoro-1-[2-(3-fluoro-phenylamino)-ethyl]-cyclohexane-1,3-dicarboxylic acid dimethyl ester (3.51 mmol), 0.55 g of the title compound was obtained. LC-MS (Method A): retention time RT: 1.29 min; ESI-MS m/z : 342 ($M+H$)⁺. It was used without further purification.

Step 8: *cis*-9,9-Difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid



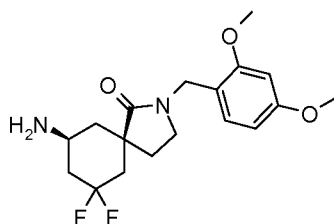
Using the same experimental procedures described in step 5 for intermediate 2, starting from 5,5-difluoro-1-[2-(3-fluoro-phenylamino)-ethyl]-cyclohexane-1,3-dicarboxylic acid dimethyl ester (1.02 mmol), 0.27 g (80%) of the title compound was obtained. During the epimerization, all ester was hydrolyzed to a desired acid. LC-MS (Method A): RT: 0.70 min; purity (UV₂₅₄): 91%; ESI-MS m/z : 328 ($M+H$)⁺. It was used without further purification.

Step 9: *cis*-9-Amino-7,7-difluoro-2-(3-fluoro-phenyl)-2-aza-spiro[4.5]decan-1-one



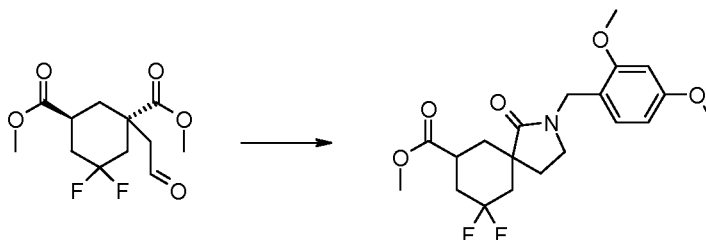
Using the same experimental procedures described in step 7 for intermediate 2, starting from 5,5-difluoro-1-[2-(3-fluoro-phenylamino)-ethyl]-cyclohexane-1,3-dicarboxylic acid dimethyl ester (0.37 mmol), a small amount of crude title compound was obtained and used without measuring the amount obtained and without further purification. ESI-MS m/z : 299 ($M+H$)⁺.

Intermediate 25: *cis*-9-Amino-2-(2,4-dimethoxy-benzyl)-7,7-difluoro-2-aza-spiro[4.5]decan-1-one



Intermediate 25 was made *via* the process of **Scheme 6**, *supra*, as follows:

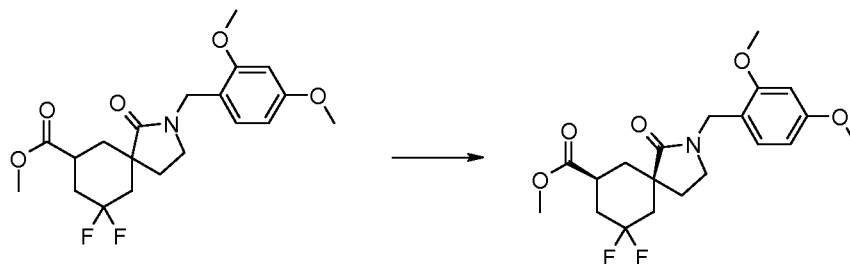
Step 1: *trans*-2-(2,4-Dimethoxy-benzyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid methyl ester



To a solution of *trans*-5,5-difluoro-1-(2-oxo-ethyl)-cyclohexane-1,3-dicarboxylic acid dimethyl ester (4.00 g, 14.4 mmol) and 2,4-dimethoxybenzylamine (2.40 g, 14.4 mmol) in THF (50.0 mL) was added sodium triacetoxyborohydride (4.56 g, 21.5 mmol) was added portion-wise and stirred at rt overnight. The mixture was quenched with cold saturated NaHCO₃. The aqueous layer was extracted with EtOAc (3x30mL). The combined organic layers were washed with saturated NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (Solvent: 50% ethyl acetate in hexanes) to afford 1.8 g (32%) of the title compound, *trans*-2-(2,4-Dimethoxy-benzyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid methyl ester. ¹H NMR (400 MHz, CDCl₃): δ 7.12-7.07 (m, 1H), 6.47-6.40

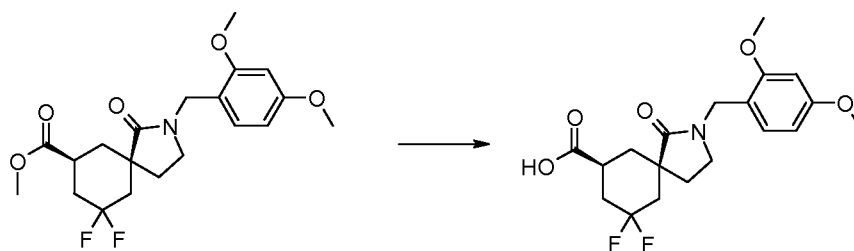
(m, 2H), 4.52 (d, $J = 14.3$ Hz, 1 H), 4.32 (d, $J = 14.3$ Hz, 1 H), 3.80 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 3.48-3.38 (m, 1H), 3.12 (dd, $J = 7.5, 5.9$ Hz, 2H), 2.41-1.67 (m, 8H). ESI-MS m/z : 398 (M+H)⁺.

Step 2: *cis*-2-(2,4-Dimethoxy-benzyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid methyl ester



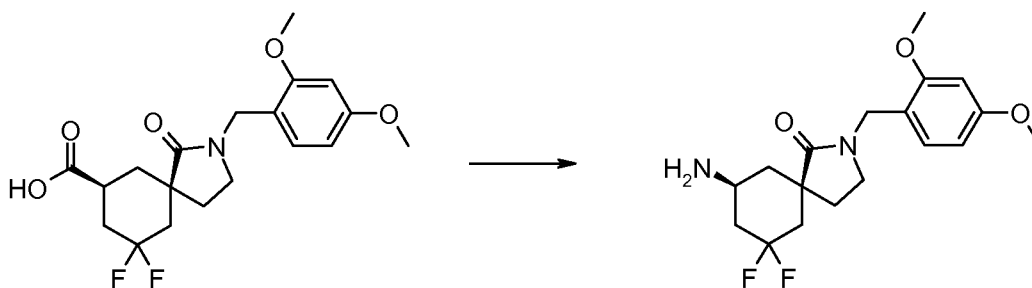
To a solution of *trans*-2-(2,4-Dimethoxy-benzyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid methyl ester (1.80 g, 4.53 mmol) in MeOH (20.0 mL) was added NaH (200 mg, 5.00 mmol, 60% in mineral oil) at 0 °C. The reaction mixture was stirred at room temperature overnight and quenched with ice. The aqueous layer was extracted with DCM (3x30mL). The combined organic layers were washed with brine and concentrated. The resulting residue was purified by silica gel chromatography (Solvent: 30% ethyl acetate in hexanes) to afford 1.25 g (69%) of the title compound, *cis*-2-(2,4-Dimethoxy-benzyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid methyl ester. ¹H NMR (400 MHz, CDCl₃): δ 7.08 (d, $J = 8.9$ Hz, 1 H), 6.46-6.42 (m, 2H), 4.48 (d, $J = 14.4$ Hz, 1 H), 4.37 (d, $J = 14.3$ Hz, 1 H), 3.80 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 3.19-3.11 (m, 2H), 2.78-1.74 (m, 9H). ESI-MS m/z : 398 (M+H)⁺.

Step 3: *cis*-2-(2,4-Dimethoxy-benzyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid



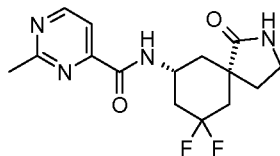
The solution of *cis*-2-(2,4-Dimethoxy-benzyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]decan-7-carboxylic acid methyl ester (1.25 g, 3.14 mmol) and LiOH (0.239 g, 10.0 mmol) in water (10 mL) and THF (30 mL) was stirred at room temperature overnight and concentrated. The aqueous layer was acidified with 1N HCl up to pH2 and extracted with DCM (3x30 mL).
 5 The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to yield 1.42 g of the title compound, *cis*-2-(2,4-dimethoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decan-7-carboxylic acid, which was used for the next step without further purification. ESI-MS m/z: 384 (M+H)⁺.

Step 4: *cis*-9-Amino-2-(2,4-dimethoxy-benzyl)-7,7-difluoro-2-aza-spiro[4.5]decan-1-one



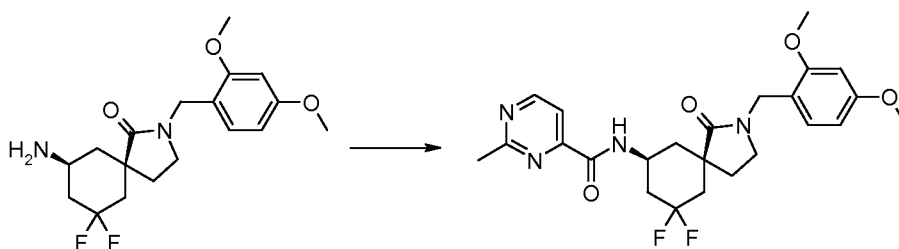
To a solution of *cis*-2-(2,4-dimethoxy-benzyl)-1-oxo-2-aza-spiro[4.5]decan-7-carboxylic acid (0.700 g, 1.82 mmol) in toluene (15 mL) was added triethylamine (0.34 mL, 2.5 mmol), followed by the addition of diphenyl phosphoryl azide (0.47 mL, 2.2 mmol). The mixture was stirred at room temperature for 1 hour and then heated at 90 °C for 2 hours. The reaction mixture was cooled down to room temperature, then was added slowly to ice-cold HCl (6N, 10 mL). The resulting mixture was stirred vigorously at room temperature for 2 hours. Two layers were separated. The aqueous layer was basified with solid NaCO₃ to pH ~10 and extracted with DCM (3x30 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated to give 0.4 g of the title compound, *cis*-9-amino-2-(2,4-dimethoxy-benzyl)-7,7-difluoro-2-aza-spiro[4.5]decan-1-one, which was used for the next step without further purification. ESI-MS m/z: 355 (M+H)⁺.

Intermediate 26: *cis*-2-Methyl-pyrimidine-4-carboxylic acid (9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide



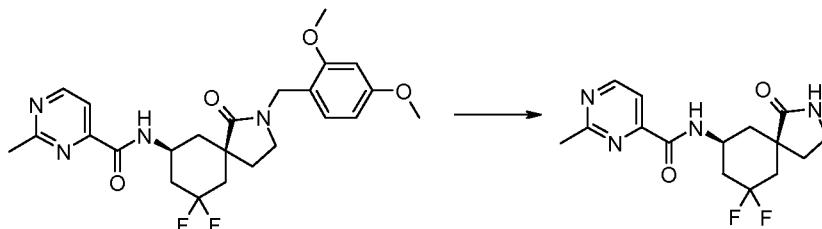
Intermediate 26 was prepared *via* the process of **Scheme 13**, *supra*, as follows:

Step 1: *cis*-2-Methyl-pyrimidine-4-carboxylic acid [2-(2,4-dimethoxy-benzyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide



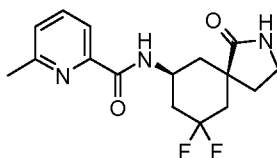
To a solution of 2-methylpyridine-4-carboxylic acid (171 mg, 1.24 mmol) in CH₂Cl₂ (15 mL) was added EDCI (263 mg, 1.69 mmol) and HOBt (152 mg, 1.13 mmol) at 0 °C, followed by the addition of *cis*-9-amino-2-(2,4-dimethoxy-benzyl)-7,7-difluoro-2-aza-spiro[4.5]decan-1-one (400 mg, 1.13 mmol). The reaction mixture was stirred at rt overnight and then diluted with CH₂Cl₂ (30 mL). The organic layer was washed with saturated aqueous NaHCO₃ and brine and concentrated under reduced pressure. The residue was purified by CombiFlash[®] system (12 g silica gel cartridge; gradient: 0 to 2% MeOH (2N NH₃) in CH₂Cl₂ over 10 min) to give 0.4 g (70%) of the title compound, *cis*- 2-Methyl-pyrimidine-4-carboxylic acid [2-(2,4-dimethoxy-benzyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide. ¹H NMR (400 MHz, CDCl₃): δ 8.89 (d, *J* = 5.0 Hz, 1 H), 8.00 (d, *J* = 8.6 Hz, 1 H), 7.90 (d, *J* = 5.1 Hz, 1 H), 7.10 (d, *J* = 8.7 Hz, 1 H), 6.48-6.43 (m, 2H), 4.45 (s, 2H), 4.44-4.34 (m, 1H), 3.82 (s, 3H), 2.81 (s, 3H), 3.25-3.20 (m, 2H), 2.80 (s, 3H), 2.66-2.53 (m, 1H), 2.37-1.72 (m, 7H). ESI-MS *m/z*: 475 (M+H)⁺.

Step 2: *cis*-2-Methyl-pyrimidine-4-carboxylic acid (9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide



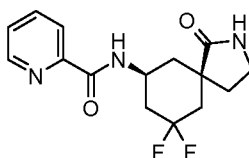
Using the same experimental procedures described in the synthesis of intermediate 18 in route 2 (step 2), intermediate 18 also was made at 0.8 mmol reaction scale from *cis*-2-Methyl-pyrimidine-4-carboxylic acid [2-(2,4-dimethoxy-benzyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide, and 0.3 g of the title compound was obtained, which was used for the next step without further purification. ESI-MS m/z : 325 ($M+H$)⁺.

Intermediate 27: *cis*-6-Methyl-pyridine-2-carboxylic acid (9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide



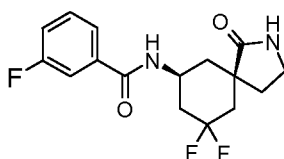
Using the same experimental procedures described in the synthesis of intermediate 26, intermediate 27 was also made from 0.635 mmol of *cis*-9-amino-2-(2,4-dimethoxy-benzyl)-7,7-difluoro-2-aza-spiro[4.5]decan-1-one and 0.698 mmol of 2-methylpicolinic acid. ¹H NMR (400 MHz, CDCl₃) δ 8.09 (d, J = 8.4 Hz, 1 H), 7.98 (d, J = 7.6 Hz, 1 H), 7.73 (t, J = 7.7 Hz, 1 H), 7.29 (d, J = 7.8 Hz, 1 H), 5.55 (s, 1H), 4.52-4.36 (m, 1H), 3.44-3.33 (m, 2H), 2.66-2.58 (m, 1H), 2.57 (s, 3H), 2.34-1.64 (m, 7H). ESI-MS m/z : 324 ($M+H$)⁺.

Intermediate 28: *cis*- Pyridine-2-carboxylic acid (9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide



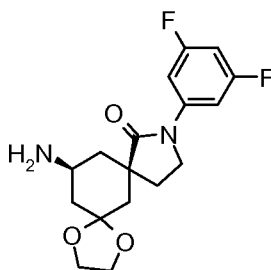
Using the same experimental procedures described in the synthesis of intermediate 26, intermediate 19 was also made from 0.254 mmol of *cis*-9-amino-2-(2,4-dimethoxybenzyl)-7,7-difluoro-2-aza-spiro[4.5]decan-1-one and 0.305 mmol of pyridine-2-carbonyl chloride. ESI-MS m/z : 310 ($M+H$)⁺. It was used without further purification.

5 **Intermediate 29: *cis*- N-(9,9-Difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl)-3-fluoro-benzamide**



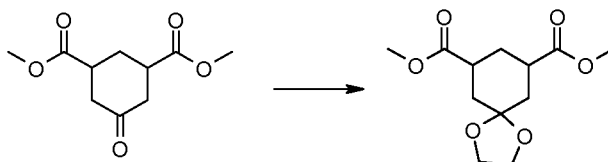
Using the same experimental procedures described in the synthesis of intermediate 26, intermediate 29 was also made from 1.29 mmol of *cis*-9-amino-2-(2,4-dimethoxybenzyl)-7,7-difluoro-2-aza-spiro[4.5]decan-1-one and 1.6 mmol of 3-fluorobenzoyl chloride. ESI-MS m/z : 327 ($M+H$)⁺. It was used without further purification.

10 **Intermediate 30: *cis*-13-Amino-9-(3,5-difluoro-phenyl)-1,4-dioxo-9-aza-dispiro[4.1.4.3]tetradecan-8-one**



15 Intermediate 30 was prepared *via* the process of **Scheme 23**, *supra*, as follows:

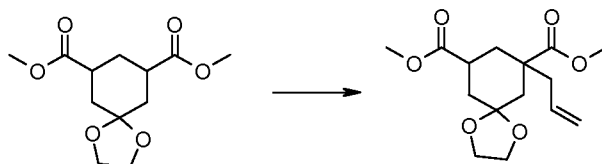
Step 1: 1,4-Dioxo-spiro[4.5]decane-7,9-dicarboxylic acid dimethyl ester



A solution of 5-oxocyclohexane-1,3-dicarboxylic acid dimethyl ester (22.8 g, 106.4 mmol), ethylene glycol (13.3 g, 215 mmol) and *p*-toluenesulfonic acid monohydrate (0.22 g, 1.3

mmol) in toluene (230 mL), in a flask fitted with Dean-Stark trap was heated under reflux for 5 h. The reaction was cooled to room temperature, water was added and the mixture was extracted with ethyl acetate. Organic layer was separated, washed with NaHCO₃ solution and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give an oil, which was triturated with hexane and left in the fridge overnight. The precipitated solid was filtered and dried under vacuum to provide 17.1 (63%) g of the title compound, 1,4-Dioxaspiro[4.5]decane-7,9-dicarboxylic acid dimethyl ester as a white solid. ¹HNMR (400 MHz, CDCl₃), δ : 3.95 (m, 4H), 3.7 (s, 6H), 2.72-2.62 (m, 3H), 2.32-2.22 (m, 1H), 2.02-1.96 (m, 2H), 1.6-1.4 (m, 3H).

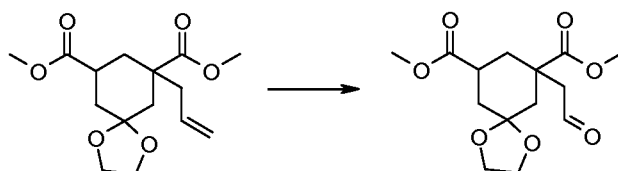
Step 2: 7-Allyl-1,4-dioxaspiro[4.5]decane-7,9-dicarboxylic acid dimethyl ester



A 1.6 M hexane solution of *n*-BuLi (101 mL, 161 mmol) was added to the stirred anhydrous THF (300 mL) at -78 °C, followed by diisopropylamine (16.2 g, 161 mmol). The reaction mixture was stirred at -78 °C for 15 min and at 0 °C for 1 h. The mixture was re-cooled to -78 °C, 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPO) (48 g, 372 mmol) was added slowly, and the resultant white suspension was stirred for 30 min. A solution of 1,4-dioxaspiro [4.5]decane-7,9-dicarboxylic acid dimethyl ester (32 g, 124 mmol) in THF (100 mL) was added, the light yellowish solution was stirred for 30 min, then allyl bromide (16.6 g, 137 mmol) was added, the reaction mixture was allowed to warm to room temperature and left stirring at room temperature overnight. The reaction was quenched with saturated aqueous NH₄Cl solution and extracted with ethyl acetate; the organic extracts were combined and washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give 40 g of crude product as viscous oil. Purification by flash column chromatography on silica gel (hexane – chloroform – ethyl acetate 8:1:1) gave 23.8 g (65%) of the title compound, 1-allyl-5,5-difluoro-cyclohexane-1,3-dicarboxylic acid dimethyl ester as colorless oil. ¹H NMR (400 MHz, CDCl₃), δ : 5.7-5.6 (m, 1H), 5.10-5.00 (m, 2H), 4.0-3.8

(m, 4H), 3.68 (s, 6H), 3.08-2.98 (m, 1H), 2.5-2.3 (m, 2H), 2.15-2.08 (m, 1H), 1.98-1.92 (m, 1H), 1.65-1.58 (m, 1H), 1.45-1.38 (m, 1H), 1.28-1.18 (m, 1H). ES MS: 299.2 (M+1)⁺.

Step 3: *trans*- 7-(2-Oxo-ethyl)-1,4-dioxa-spiro[4.5]decane-7,9-dicarboxylic acid dimethyl ester

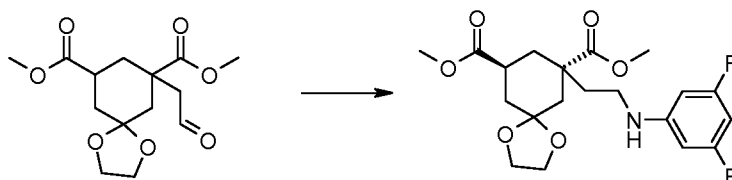


5

Using the same experimental procedures described in step 3 for intermediate 2, starting from 1-allyl-5,5-difluoro-cyclohexane-1,3-dicarboxylic acid dimethyl ester (5.00 g, 16.8 mmol), 5.5 g of the title compound was obtained, which was used for the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 9.78-9.69 (m, 1H), 4.04-3.68 (m, 10 H), 3.26-3.15 (m, 1H), 2.78-1.31 (m, 8H).

10

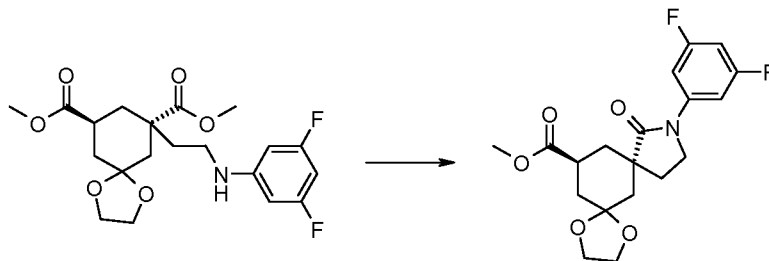
Step 4: *trans*- 7-[2-(3,5-Difluoro-phenylamino)-ethyl]-1,4-dioxa-spiro[4.5]decane-7,9-dicarboxylic acid dimethyl ester



Using the same experimental procedures described in step 4 for intermediate 2, starting from *trans*-5,5-difluoro-1-(2-oxo-ethyl)-cyclohexane-1,3-dicarboxylic acid dimethyl ester (1.80 g, 5.99 mmol) and 3,5-difluoroaniline (0.772 g, 5.98 mmol), 0.835 g (75%) of the title compound was obtained. ¹H NMR (400 MHz, CDCl₃): δ 6.23 (br, 3H), 4.04-3.74 (m, 6H), 3.72 (s, 3H), 3.70 (s, 3H), 3.29-2.97 (m, 3H), 2.62-1.18 (m, 6H). ESI-MS m/z: 414 (M+H)⁺.

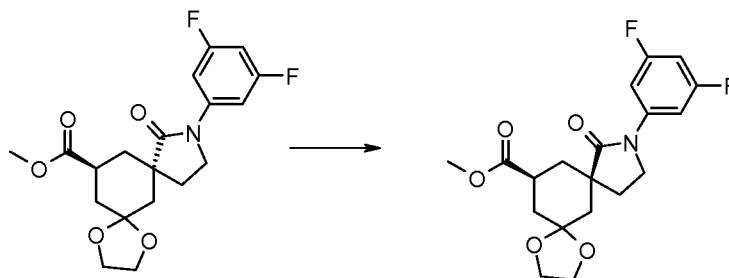
15

Step 5: *trans*-9-(3,5-Difluoro-phenyl)-8-oxo-1,4-dioxo-9-aza-dispiro[4.1.4.3]tetradecane-13-carboxylic acid methyl ester



Using the same experimental procedures described in step 4 of intermediate 2, starting from *trans*-5,5-difluoro-1-[2-(3-fluoro-phenylamino)-ethyl]-cyclohexane-1,3-dicarboxylic acid dimethyl ester (0.835 g, 2.02 mmol), 0.7 g (99%) of the title compound was obtained. ¹H NMR (400 MHz, CDCl₃): δ 7.38-7.30 (m, 2H), 6.64-6.57 (m, 1H), 3.98-3.91 (m, 4H), 3.81-3.67 (m, 5H), 3.32-3.23 (m, 1H), 2.41-1.63 (m, 8H). ESI-MS *m/z*: 382 (M+H)⁺.

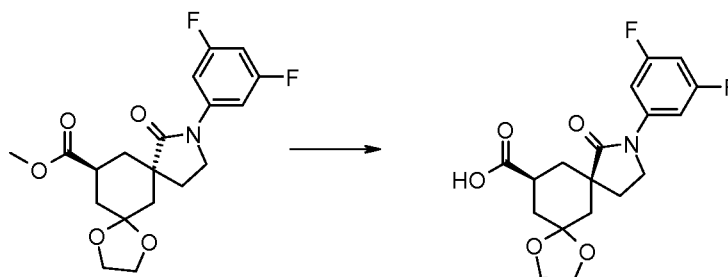
Step 6: *cis*-9-(3,5-Difluoro-phenyl)-8-oxo-1,4-dioxo-9-aza-dispiro[4.1.4.3]tetradecane-13-carboxylic acid methyl ester



To a solution of *trans*-9-(3,5-Difluoro-phenyl)-8-oxo-1,4-dioxo-9-aza-dispiro[4.1.4.3]tetradecane-13-carboxylic acid methyl ester (0.68 g, 1.78 mmol) in THF (10 mL) was added NaH (60% in mineral oil, 93 mg, 2.3 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight, cooled to 0 °C, and quenched with ice. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layer was washed with brine and concentrated. Purification by flash column chromatography on silica gel (gradient: 0 to 50% EtOAc in hexanes) gave 0.553 g (81%) of the title compound was obtained. ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.27 (m, 2H), 6.63-6.56 (m, 1H), 3.99-3.69

(m, 4H), 3.74-3.70 (m, 2H), 3.69 (s, 3H), 2.82-2.72 (m, 1H), 2.44-2.35 (m, 1H), 2.16-1.60 (m, 7H). ESI-MS m/z : 382 (M+H)⁺.

Step 7: *cis*-9-(3,5-Difluoro-phenyl)-8-oxo-1,4-dioxo-9-aza-dispiro[4.1.4.3]tetradecane-13-carboxylic acid

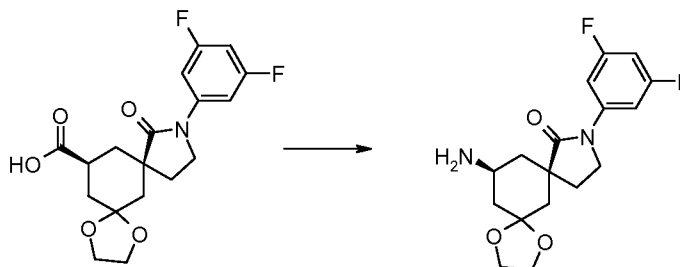


5

Using the same experimental procedures described in step 5 for intermediate 2, starting from *cis*-9-(3,5-Difluoro-phenyl)-8-oxo-1,4-dioxo-9-aza-dispiro[4.1.4.3]tetradecane-13-carboxylic acid methyl ester (0.553 g, 1.45 mmol), 0.447 g (84%) of the title compound was obtained. It was used without further purification. ESI-MS m/z : 368 (M+H)⁺.

10

Step 8: *cis*-13-Amino-9-(3,5-difluoro-phenyl)-1,4-dioxo-9-aza-dispiro[4.1.4.3]tetradecan-8-one



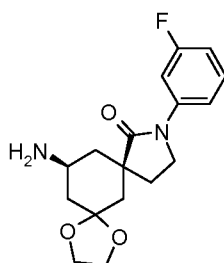
15

To a solution of *cis*-9-(3,5-Difluoro-phenyl)-8-oxo-1,4-dioxo-9-aza-dispiro[4.1.4.3]tetradecane-13-carboxylic acid (0.447 g, 1.22 mmol) in toluene (15 mL) was added triethylamine (0.24 mL, 1.58 mmol), followed by the addition of diphenyl phosphoryl azide (0.31 mL, 1.46 mmol). The mixture was stirred at room temperature for 1 hour and then heated at 90 °C for 2 hours. The reaction mixture was cooled down to room temperature, then benzyl alcohol (0.263 g, 2.43 mmol) was added. The resulting mixture was heated at 90 °C overnight. The solvent was concentrated and the residue was purified by flash column chromatography on silica gel (0 to 70% EtOAc in hexanes) to give 0.4 g of Cbz-protected

20

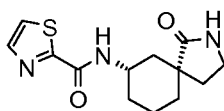
intermediate, which was dissolved in MeOH (80 mL) and passed through H-cube[®] (Pd/C 10%, 10 bar, 25 °C, flow rate 0.5 mL/min). The resulting mixture was concentrated to give 0.3 g (70% over 2 steps) of the title compound. It was used for the next step without further purification. ¹H NMR (400 MHz, CDCl₃): δ 7.33-7.28 (m, 2H), 6.65-6.58 (m, 1H), 4.04-3.91 (m, 4H), 3.78-3.69 (m, 2H), 3.40-3.29 (m, 1H), 2.45-1.37 (m, 8H). ESI-MS m/z: 339 (M+H)⁺.

Intermediate 31: *cis*-13-Amino-9-(3-fluoro-phenyl)-1,4-dioxo-9-aza-dispiro[4.1.4.3]tetradecan-8-one



Using the same experimental procedures described in the synthesis of intermediate 30, intermediate 31 was also made from 9.30 mmol of *cis*-9-(3-fluoro-phenyl)-8-oxo-1,4-dioxo-9-aza-dispiro[4.1.4.3] tetradecane-13-carboxylic acid. ESI-MS m/z: 321 (M+H)⁺.

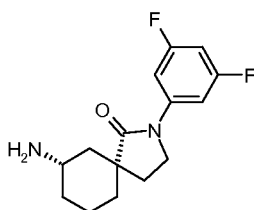
Intermediate 32: *cis*-Thiazole-2-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide



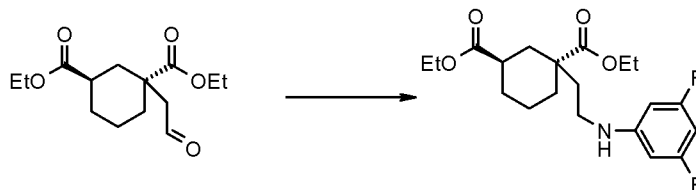
Into a vial was added intermediate **10** (90 mg, 0.2 mmol), triethylamine (76 mg, 0.75 mmol) and methylene chloride (5.0 mL). The mixture was cooled in ice bath. Thiazole-2-carbonyl chloride (56 mg, 0.38 mmol) was then added. After stirring at rt for 2 hrs, the mixture was then washed with saturated sodium bicarbonate, dried over Na₂SO₄, and concentrated under reduced pressure to afford thiazole-2-carboxylic acid [2-(2,4-dimethoxy-benzyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide (60 mg, 60%). ¹H NMR (300 MHz, CDCl₃): δ 7.86 (d, *J* = 3.1 Hz, 1H), 7.69-7.79 (m, 1H), 7.54 (d, *J* = 3.1 Hz, 1H), 7.04-7.10 (m, 1H), 6.38-6.46 (m, 2H), 4.35-4.50 (m, 2H), 4.00-4.18 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.12-3.20 (m, 2H), 1.24-2.05 (m, 10H). ESI-MS m/z: 429 (M+H)⁺. The residue obtained above was treated with

TFA (1.0 mL), and heated at 60°C for 3 hrs. The mixture was then partitioned into dichloromethane and saturated sodium bicarbonate, and the organic layer was dried over sodium sulfate and concentrated *in vacuo* to give the title compound *cis*-Thiazole-2-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide. ESI-MS *m/z*: 280 (M+H)⁺ (Method A, RT: 0.57). It was used in next step without further purification.

**Intermediate 33: *cis*-7-Amino-2-(3,5-difluoro-phenyl)-2-aza-spiro[4.5]decan-1-one
Hydrochloric acid salt**

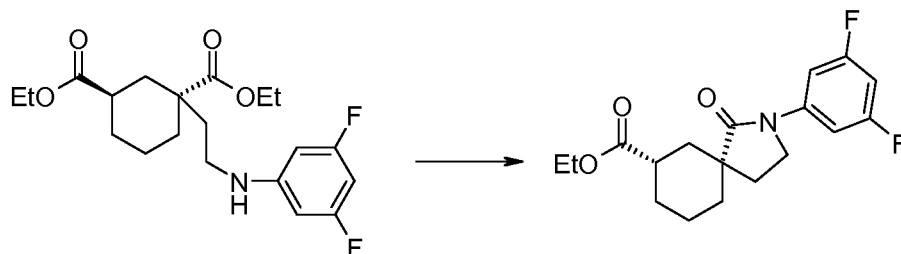


Step 1: *trans*-1-[2-(3,5-Difluorophenylamino)-ethyl]-cyclohexane-1,3-dicarboxylic acid diethyl ester



To a solution of *trans*-1-(2-oxo-ethyl)-cyclohexane-1,3-dicarboxylic acid diethyl ester (86.4 g, 320 mmol) in 1,2-dichloroethane (640 mL) was added acetic acid (3.66 mL, 64.0 mmol) followed by the slow addition of a solution of 3,5-difluoroaniline (57.8 g, 448 mmol) in 1,2-dichloroethane (320 mL). The mixture was stirred at room temperature for 1.5 h, then cooled to 0 °C, sodium triacetoxyborohydride (94.8 g, 447 mmol) was added portionwise, and stirring continued at room temperature for 14 h. The mixture was cooled to 0 °C and quenched with crushed ice and extracted with dichloromethane. The organic layer was separated, washed with water, brine, dried with Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (hexane/EtOAc: 4/1) to give 110.8 g (90%) of the title compound as transparent oil. ¹H NMR (400 MHz, CDCl₃) δ 5.85 - 6.23 (m, 4 H), 4.01 - 4.24 (m, 4 H), 3.81 (t, *J* = 5.7 Hz, 2 H), 2.97 - 3.21 (m, 2 H), 2.36 - 2.56 (m, 2 H), 2.24 (d, *J* = 11.7 Hz, 1 H), 1.62 - 2.03 (m, 4 H), 1.02 - 1.42 (m, 8 H).

Step 2: *cis*-2-(3,5-Difluorophenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid ethyl ester



To a cooled (0 °C) solution of *trans*-1-[2-(3,5-Difluorophenylamino)-ethyl]-cyclohexane-1,3-dicarboxylic acid diethyl ester (110.8 g, 289 mmol) in ethanol (725 mL), sodium hydride (60% in mineral oil, 34.7 g, 867 mmol) was added portionwise, and the reaction mixture was stirred at room temperature for 4 h, then refluxed for 15 h. The resulting mixture was concentrated under vacuum at room temperature, diluted with ethyl acetate, cooled to 0 °C and treated with a 6 N HCl solution until pH ~4. The organic layer was washed with water, brine, dried with Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc: 3/1) to give 32.7 g (33.5%) of the title compound as a yellow gum. ¹H NMR (400 MHz, CDCl₃) δ 7.23 - 7.38 (m, 2 H), 6.59 (tt, *J* = 8.7, 2.2 Hz, 1 H), 4.12 (q, *J* = 7.0 Hz, 2 H), 3.66 - 3.80 (m, 2 H), 2.27 - 2.50 (m, 0 H), 1.95 - 2.14 (m, 4 H), 1.77 - 1.94 (m, 3 H), 1.62 - 1.76 (m, 1 H), 1.34 - 1.53 (m, 2 H), 1.25 (t, *J* = 7.0 Hz, 3 H).

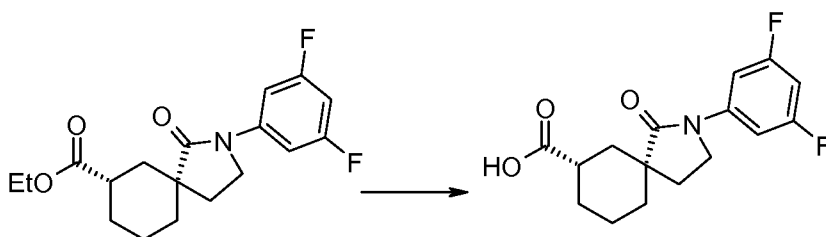
Together with *cis*-2-(3,5-difluorophenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid ethyl ester, *trans*-2-(3,5-difluorophenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid ethyl ester (12.5 g, 13%), *cis*-2-(3,5-difluorophenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid (11.0 g, 12%) and *trans*-2-(3,5-difluorophenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid (7.97 g, 9%) were isolated, all yellow gums as well.

trans-2-(3,5-Difluorophenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid ethyl ester: ¹H NMR (400 MHz, CDCl₃) δ 7.23 - 7.33 (m, 2 H), 6.52 - 6.64 (m, 1 H), 4.12 (q, *J* = 7.0 Hz, 2 H), 3.65 - 3.76 (m, 2 H), 3.10 - 3.26 (m, 1 H), 2.10 - 2.19 (m, 1 H), 1.84 - 2.08 (m, 5 H), 1.52 - 1.75 (m, 2 H), 1.28-1.50 (m, 2 H), 1.22 (t, *J* = 7.0 Hz, 3 H).

cis-2-(3,5-Difluorophenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid: ^1H NMR (400 MHz, CDCl_3) δ 7.22 - 7.36 (m, 2 H), 6.52 - 6.67 (m, 1 H), 3.66 - 3.81 (m, 2 H), 2.34 - 2.52 (m, 1 H), 2.00 - 2.18 (m, 3 H), 1.78 - 1.99 (m, 3 H), 1.32 - 1.76 (m, 4 H).

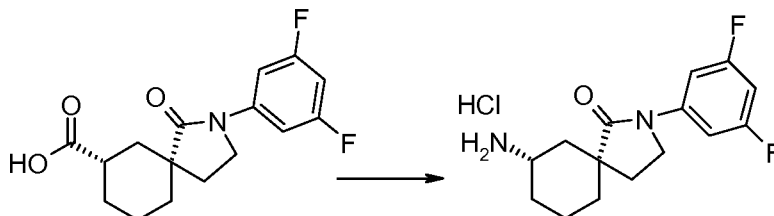
trans-2-(3,5-Difluorophenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid: ^1H NMR (400 MHz, CDCl_3) δ 7.20 - 7.37 (m, 2 H), 6.58 (tt, $J = 8.8, 2.34$ Hz, 1 H), 3.60 - 3.81 (m, 2 H), 3.13 - 3.37 (m, 1 H), 2.19 (dd, $J = 13.5, 4.10$ Hz, 1 H), 1.84 - 2.12 (m, 5 H), 1.16 - 1.78 (m, 4 H).

Step 3: *cis*-2-(3,5-Difluorophenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid.



To a solution of *cis*-2-(3,5-Difluorophenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid ethyl ester (31.7 g, 94.0 mmol) in THF (376 mL) and water (376 mL) was added solid anhydrous lithium hydroxide (22.5 g, 9.40 mmol). The resulting slurry was stirred at room temperature for 15 h, then cooled to 0 °C, treated with 4 N HCl until pH ~ 5 (slow addition), and extracted with ethyl acetate. The organic layer was separated, washed with water, brine, dried with Na_2SO_4 and concentrated under vacuum to give 27.8 g of the title compound as sticky gum, which was used in the next step without further purification. ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ 7.22 - 7.36 (m, 2 H), 6.52 - 6.67 (m, 1 H), 3.66 - 3.81 (m, 2 H), 2.34 - 2.52 (m, 1 H), 2.00 - 2.18 (m, 3 H), 1.78 - 1.99 (m, 3 H), 1.32 - 1.76 (m, 4 H).

Step 4: *cis*-7-Amino-2-(3,5-difluorophenyl)-2-aza-spiro[4.5]decan-1-one HCl salt (Ref.: 09-057-7).

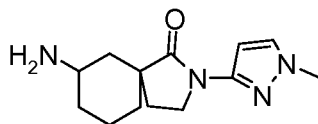


To a suspension of *cis*-2-(3,5-Difluorophenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid (5.53 g, 17.9 mmol) in toluene (90 mL) at room temperature, triethylamine (2.98 mL,

21.4 mmol) was added, followed by diphenylphosphoryl azide (3.86 mL, 17.9 mmol), and the mixture was stirred at room temperature for 2 h. After that the reaction mixture was heated at 90 °C for 3.5 h, then cooled to 0 °C, treated with 6 N HCl (10 mL, slow addition !), and stirring continued at room temperature for 14 h. The resulting white precipitate was filtered, washed with toluene and dried under vacuum to give 5.05 g (89%) of the title compound as a white solid.

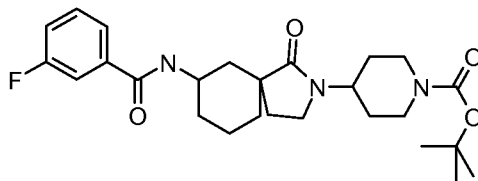
¹H NMR (400 MHz, DMSO-*d*₆) δ 7.42 - 7.54 (m, 2 H), 7.00 (tt, *J* = 9.2, 2.30 Hz, 1 H), 3.73 - 3.81 (m, 2 H), 3.04 - 3.17 (m, 1 H), 1.87 - 2.20 (m, 3 H), 1.83 (d, *J* = 11.7 Hz, 1 H), 1.68 - 1.78 (m, 1 H), 1.63 (t, *J* = 12.5 Hz, 1 H), 1.39 - 1.57 (m, 2 H), 1.22 - 1.38 (m, 2 H), MS: *m/z* 281.19 (M+H)⁺. HPLC: 96.45%. Analysis: calculated for C₁₅H₁₈N₂O.HCl .0.65 H₂O: C, 54.85; H, 6.23; N, 8.53. Found: C, 54.84; H, 6.06; N, 8.79.

Intermediate 34: 7-Amino-2-(1-methyl-1H-pyrazol-3-yl)-2-aza-spiro[4.5]decan-1-one

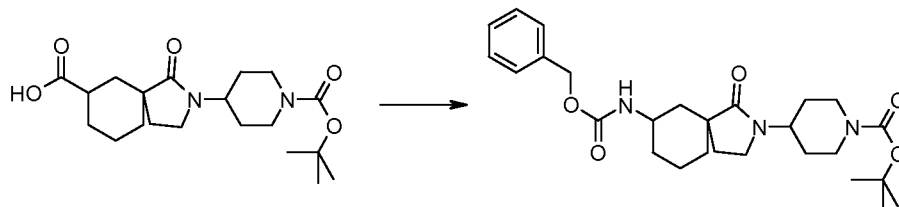


Using the similar experimental procedures described in intermediate 33, intermediate 34 hydrochloric acid salt was made from 3.7 mmol of *trans*-1-(2-oxo-ethyl-cyclohexane-1,3-dicarboxylic acid diethyl ester and 3.7 mmol of 1-methyl-1H-pyrazol-3-amine. The intermediate 34 hydrochloric acid salt was basified with sodium hydroxide to afford the title compound which is a mixture of two diastereomers (*cis/trans*: 7/2; under LC-MS method E, the first peak with RT of 1.06 min was assigned as *cis*, and the second peak with RT of 1.10 min was assigned as *trans*). ESI-MS *m/z*: 249 (M+H)⁺. It was used without further purification.

Intermediate 35: 4-[7-(3-Fluoro-benzoylamino)-1-oxo-2-aza-spiro[4.5]dec-2-yl]-piperidine-1-carboxylic acid tert-butyl ester



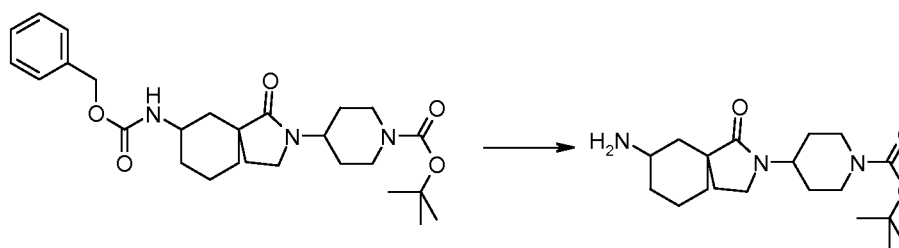
Step 1: 4-(7-Benzyloxycarbonylamino-1-oxo-2-aza-spiro[4.5]dec-2-yl)-piperidine-1-carboxylic acid tert-butyl ester



Using the same experimental procedures described in the synthesis of intermediate 10, 2-(1-tert-Butoxycarbonyl-piperidin-4-yl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid (mixture of *cis* and *trans* diastereomers) was made from 7.40 mmol of 1-(2-oxo-ethyl)-cyclohexane-1,3-dicarboxylic acid diethyl ester and 7.40 mmol of 4-amino-1-Boc-piperidine.

2-(1-tert-Butoxycarbonyl-piperidin-4-yl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid (1.24 g, 3.25 mmol) was dissolved in toluene (20.0 mL), triethylamine (0.54 mL, 3.90 mmol) was added, followed by the addition of diphenylphosphonic azide (0.70 mL, 3.25 mmol). The mixture was stirred at rt for 1.5 hrs, and then heated at 90 °C for 2 hrs. Benzyl alcohol (2.0 mL, 19.5 mmol) was added, and the mixture was heated at 90 °C overnight. The mixture was cooled down, concentrated under reduce pressure to afford 0.85 g (54%) of the title compound which is a mixture of two diastereomers (*cis/trans*: 1/1; under LC-MS method C, the first peak with RT of 1.56 min was assigned as *cis*, and the second peak with RT of 1.59 min was assigned as *trans*). ESI-MS *m/z*: 486 (*M*+H)⁺.

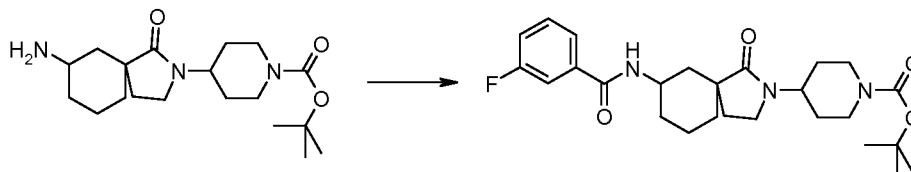
Step 2: 4-(7-Amino-1-oxo-2-aza-spiro[4.5]dec-2-yl)-piperidine-1-carboxylic acid tert-butyl ester



4-(7-Benzyloxycarbonylamino-1-oxo-2-aza-spiro[4.5]dec-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (0.75 g, 1.54 mmol) in methanol (50.0 mL) was shaken under hydrogenated at

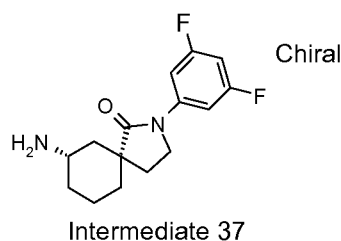
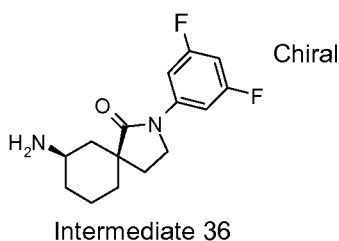
50 psi and rt for 2.5 hrs. The catalyst was filtered off, and the filtrate was concentrated to afford 0.42 g (77%) of the title compound. LC-MS (method C): RT: 0.94 min; ESI-MS m/z : 352 ($M+H$)⁺. It was used in the next step without further purification.

Step 3: 4-[7-(3-Fluoro-benzoylamino)-1-oxo-2-aza-spiro[4.5]dec-2-yl]-piperidine-1-carboxylic acid tert-butyl ester



4-(7-Amino-1-oxo-2-aza-spiro[4.5]dec-2-yl)-piperidine-1-carboxylic acid tert-butyl ester (0.20g, 0.57 mmol), 3-fluorobenzoic acid (0.080 g, 0.56 mmol), BOP (0.252 g, 0.57 mmol), and triethylamine (0.115g, 1.14 mmol) in methylene chloride (5.0 mL) was stirred at rt overnight. The mixture was concentrated, and the resulting residue was purified with chromatography (ethyl acetate) to afford the title compound which is a mixture of two diastereomers (*cis/trans*: 3/2; under LC-MS method C, the first peak with RT of 1.47 min was assigned as *cis*, and the second peak with RT of 1.50 min was assigned as *trans*). ¹H NMR (400 MHz, CDCl₃) δ 8.5 (s, 0.6 H), 7.60-7.68 (m, 1H), 7.36-7.50 (m, 2H), 7.14-7.20 (m, 1H), 5.92 (d, J = 6.8 Hz, 0.4 H), 4.55-4.65 (m, 0.4 H), 4.04-4.38 (m, 3.6H), 3.20-3.30 (m, 2H), 2.71-2.86 (m, 2H), 1.28-2.25 (m, 23H). ESI-MS m/z : 474 ($M+H$)⁺.

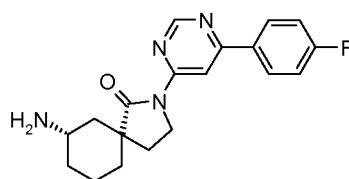
Intermediates 36 and 37: (5*R*,7*R*)-7-Amino-2-(3, 5-difluoro-phenyl)-2-aza-spiro[4.5]decan-1-one and (5*S*,7*S*)-7-Amino-2-(3, 5-difluoro-phenyl)-2-aza-spiro[4.5]decan-1-one



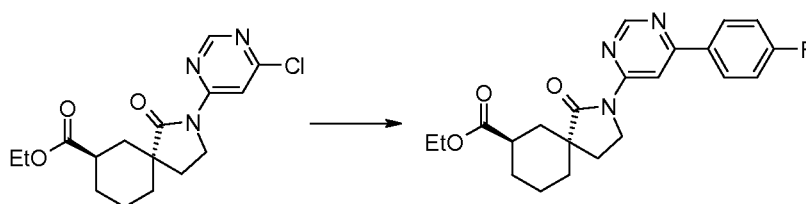
The racemic intermediate 33 (*cis* diastereomer) (650 mg) were resolved by HPLC (column: Chiralpak[®] IC (Chiral Technologies, Inc.), 150x30 mm, 5 μ M particle size; mobile phase:

30% isopropanol, 70% CO₂; flow rate: 100 g/min; UV at 254 nm) to afford two enantiomers. The first peak (RT: 3.18 min) from the chiral HPLC was assigned as (5*S*, 7*S*)-7-amino-2-(3,5-difluoro-phenyl)-2-aza-spiro[4.5]decan-1-one (270 mg), and the second peak (RT: 6.92 min) from the chiral HPLC was assigned (5*R*, 7*R*)-7-Amino-2-(3,5-difluoro-phenyl)-2-aza-spiro[4.5]decan-1-one (250 mg).

Intermediate 38: *cis*-7-Amino-2-(6-(4-fluorophenyl)pyrimidin-4-yl)-2-azaspiro[4.5]decan-1-one



Steps 1-4: *trans*-ethyl 2-(6-(4-fluorophenyl)pyrimidin-4-yl)-1-oxo-2-azaspiro[4.5]decane-7-carboxylate



Using analogous procedures as described in the synthesis of intermediate 2 (steps 1 to 4), *trans*-ethyl 2-(6-chloropyrimidin-4-yl)-1-oxo-2-azaspiro[4.5]decane-7-carboxylate was made from 219 mmol of 1,3-cyclohexanecarboxylic acid.

Step 5: *trans*-ethyl 2-(6-(4-fluorophenyl)pyrimidin-4-yl)-1-oxo-2-azaspiro[4.5]decane-7-carboxylate

To a de-oxygenated solution of *trans*-ethyl 2-(6-chloropyrimidin-4-yl)-1-oxo-2-azaspiro[4.5]decane-7-carboxylate (6.75 g, 20.03 mmol), 4-fluorobenzeneboronic acid (3.35 g, 24.04 mmol) and cesium carbonate (13 g, 40.06 mmol) in 1,4-dioxane (180 mL) was added Pd₂(dba)₃ (1.1 g, 1.2 mmol) and P(^tBu)₃ (1M in THF, 2.4 mL, 2.4 mmol) under argon atmosphere. The reaction mass mixture heated at reflux for 4 h. The reaction mixture was filtered through a bed of Celite[®] and the filtrate was concentrated. The crude residue was purified by combiflash column chromatography to afford 7.2 g (90.5%) of *trans*-ethyl 2-(6-

(4-fluorophenyl)pyrimidin-4-yl)-1-oxo-2-azaspiro[4.5]decan-7-carboxylate. ESI-MS m/z : 398 (M+H)⁺.

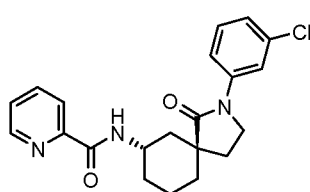
Steps 6-7: ***cis*-7-Amino-2-(6-(4-fluorophenyl)pyrimidin-4-yl)-2-azaspiro[4.5]decan-1-one**

Using analogous procedures as described in the synthesis of intermediate 2 (steps 5 and 6), intermediate 38 was made from 5.03 mmol of *trans*-ethyl 2-(6-(4-fluorophenyl)pyrimidin-4-yl)-1-oxo-2-azaspiro[4.5]decan-7-carboxylate. ESI-MS m/z : 341 (M+H)⁺.

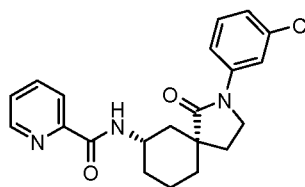
3. Preparation of Compounds of the Invention

Unless specified otherwise, all starting materials and reagents were obtained from commercial suppliers, such as Sigma-Aldrich Corp. (St. Louis, MO, USA) and its subsidiaries, and used without further purification. Unless indicated as the absolute stereochemistry, the stereochemistry of compounds of the invention has been assigned arbitrarily when indicated, such as for di-fluoro-cyclohexane-spirolactam compounds of formula (I).

Example 1 and Example 2: *trans*-Pyridine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide and *cis*-pyridine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide, respectively



Example 1



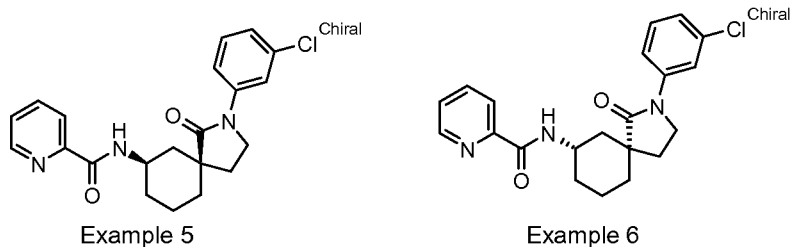
Example 2

Example 1 and Example 2 were prepared from intermediate 1 *via* the process of **Scheme 1**, *supra*, as follows:

7-Amino-2-(3-chloro-phenyl)-2-aza-spiro[4.5]decan-1-one (0.140 g, 0.502 mmol, intermediate 1) was dissolved in CH₂Cl₂ (2.0 mL), picolinic acid (0.068 g, 0.552 mmol), and BOP (0.244 g, 0.552 mmol), and triethylamine (0.31 mL, 2.21 mmol) in CH₂Cl₂ (1.0 mL) were added. The reaction mixture was stirred at rt overnight and then concentrated under reduced pressure. The resulting residue was purified by preparative TLC (hexane/ethyl acetate:1/2) to afford two diastereomers. The less polar one was assigned as *trans*, Example 1

(0.097 g, 51%), and the polar one was assigned as *cis*, Example 2 (0.043 g, 22%). *Trans* diastereomer (Example 1): ^1H NMR (400 MHz, CDCl_3): δ 8.54 (ddd, $J = 4.8, 1.7, 1.1$ Hz, 1H), 8.20 (dt, $J = 7.6, 1.1$ Hz, 1H), 8.02 (d, $J = 7.6$ Hz, 1H), 7.84 (td, $J = 7.8, 1.7$ Hz, 1H), 7.72 (t, $J = 2.0, 1.0$ Hz, 1H), 7.55 (ddd, $J = 8.3, 2.1, 1.0$ Hz, 1H), 7.42 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H), 7.27 (t, $J = 8.0$ Hz, 1H), 7.10 (ddd, $J = 7.9, 2.1, 1.0$ Hz, 1H), 4.63-4.71 (m, 1H), 3.67-3.80 (m, 2H), 2.32 (dd, $J = 13.3, 4.3$ Hz, 1H), 2.01-2.14 (m, 3H), 1.86-1.92 (m, 1H), 1.70-1.77 (m, 2H), 1.63 (dd, $J = 13.4, 8.6$ Hz, 1H), 1.45-1.58 (m, 2H). ESI-MS m/z : 384 ($\text{M}+\text{H}$) $^+$. *Cis* diastereomer (Example 2): ^1H NMR (400 MHz, CDCl_3): δ 8.55 (ddd, $J = 4.8, 1.7, 1.0$ Hz, 1H), 8.19 (dt, $J = 7.8, 1.1$ Hz, 1H), 8.05 (d, $J = 8.7$ Hz, 1H), 7.84 (td, $J = 7.5, 1.5$ Hz, 1H), 7.73 (t, $J = 2.0, 1.0$ Hz, 1H), 7.55 (ddd, $J = 7.7, 2.2, 1.0$ Hz, 1H), 7.42 (ddd, $J = 7.5, 4.7, 1.2$ Hz, 1H), 7.28 (t, $J = 8.1$ Hz, 1H), 7.11 (ddd, $J = 8.1, 2.0, 1.0$ Hz, 1H), 4.07-4.18 (m, 1H), 3.74-3.84 (m, 2H), 2.23-2.30 (m, 1H), 2.09-2.19 (m, 2H), 1.88-1.98 (m, 2H), 1.69-1.79 (m, 2H), 1.65-1.65 (m, 2H), 1.34-1.44 (m, 1H). ESI-MS m/z : 384 ($\text{M}+\text{H}$) $^+$.

Example 5 and Example 6: Pyridine-2-carboxylic acid [(5*R*,7*R*)-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide and pyridine-2-carboxylic acid [(5*S*,7*S*)-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide



The racemic Example 2 (30 mg) were resolved by HPLC (column: Chiralpak[®] AD (Diacel), 250x20 mm; mobile phase: 20% isopropanol, 79.9% hexane, 0.1% diethylamine; flow rate: 14 mL/min; UV at 254 nm) to afford two enantiomers. The first peak from chiral HPLC was assigned as Example 5, pyridine-2-carboxylic acid [(5*R*, 7*R*)-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]-dec-7-yl]amide (8 mg), and the second peak from chiral HPLC was assigned as Example 6, pyridine-2-carboxylic acid [(5*S*, 7*S*)-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]-dec-7-yl]amide (7 mg).

Example 5: ^1H NMR (400 MHz, CDCl_3): δ 8.55 (ddd, $J = 4.8, 1.7, 1.0$ Hz, 1H), 8.19 (dt, $J = 7.8, 1.1$ Hz, 1H), 8.05 (d, $J = 8.7$ Hz, 1H), 7.84 (td, $J = 7.5, 1.5$ Hz, 1H), 7.73 (t, $J = 2.0, 1.0$ Hz, 1H), 7.55 (ddd, $J = 7.7, 2.2, 1.0$ Hz, 1H), 7.42 (ddd, $J = 7.5, 4.7, 1.2$ Hz, 1H), 7.28 (t, $J = 8.1$ Hz, 1H), 7.11 (ddd, $J = 8.1, 2.0, 1.0$ Hz, 1H), 4.07-4.18 (m, 1H), 3.74-3.84 (m, 2H), 2.23-2.30 (m, 1H), 2.09-2.19 (m, 2H), 1.88-1.98 (m, 2H), 1.69-1.79 (m, 2H), 1.65-1.65(m, 2H), 1.34-1.44 (m, 1H). ESI-MS m/z : 384 ($\text{M}+\text{H}$) $^+$.

Example 6: ^1H NMR (400 MHz, CDCl_3): δ 8.55 (ddd, $J = 4.8, 1.7, 1.0$ Hz, 1H), 8.19 (dt, $J = 7.8, 1.1$ Hz, 1H), 8.05 (d, $J = 8.7$ Hz, 1H), 7.84 (td, $J = 7.5, 1.5$ Hz, 1H), 7.73 (t, $J = 2.0, 1.0$ Hz, 1H), 7.55 (ddd, $J = 7.7, 2.2, 1.0$ Hz, 1H), 7.42 (ddd, $J = 7.5, 4.7, 1.2$ Hz, 1H), 7.28 (t, $J = 8.1$ Hz, 1H), 7.11 (ddd, $J = 8.1, 2.0, 1.0$ Hz, 1H), 4.07-4.18 (m, 1H), 3.74-3.84 (m, 2H), 2.23-2.30 (m, 1H), 2.09-2.19 (m, 2H), 1.88-1.98 (m, 2H), 1.69-1.79 (m, 2H), 1.65-1.65(m, 2H), 1.34-1.44 (m, 1H). ESI-MS m/z : 384 ($\text{M}+\text{H}$) $^+$.

In an analogous manner to Examples 1 and 2, Examples 3-4 and 12-14 in Table 1 (below) were made from commercially available 6-methyl-pyridine-2-carboxylic acid, 6-methyl-pyrazine-2-carboxylic acid, pyrazine-2-carboxylic acid, and 1-methyl-1H-pyrazole-3-carboxylic acid at 0.14 to 0.22 mmol reaction scales.

In a similar manner to Examples 1 and 2, Examples 17-22 in Table 1 were made at 0.22 mmol reaction scales from intermediate 5 and commercially available 6-methyl-pyridine-2-carboxylic acid, picolinic acid, and 6-methyl-pyrazine-2-carboxylic acid

In a similar manner to Examples 1 and 2, Example 19 in Table 1 also was made at a 7.62 mmol reaction scale from commercially available picolinic acid and intermediate 6.

In a similar manner to Example 1 and 2, Examples 7-8 and 23-24 in Table 1 were made at 0.11-0.22 mmol reaction scales from intermediate 7 and commercially available picolinic acid, 3-chlorobenzoic acid, 6-methyl-pyridine-2-carboxylic acid, and 3-fluorobenzoic acid, respectively.

In a similar manner to Example 1 and 2, Example 27 in Table 1 was made at a 1.24 mmol reaction scale from commercially available 3-fluorobenzoic acid and intermediate 8.

Example 27: ^1H NMR (300 MHz, CDCl_3) δ 8.16 (d, $J=8.3$ Hz, 1H), 7.77 (br, 1H), 7.66-7.55 (m, 3H), 7.41 (dt, $J=5.7, 8.3$ Hz, 1H), 7.23-7.14 (m, 1H), 6.91 (d, $J=7.4$ Hz, 1H), 4.39-4.24 (m, 1H), 4.18-3.97 (m, 2H), 2.48 (s, 3H), 2.18-1.47 (m, 10H). ESI-MS m/z : 382 ($\text{M}+\text{H}$) $^+$.

In a similar manner to Example 1 and 2, Examples 9-11 and 15-16 in Table 1 were made at a 0.19 mmol reaction scale from intermediate 9 and commercially available picolinic acid, 6-methyl-pyridine-2-carboxylic acid, 6-methyl-pyrazine-2-carboxylic acid, 3-fluorobenzoic acid, and 3-chloro-orobenzoic acid, respectively.

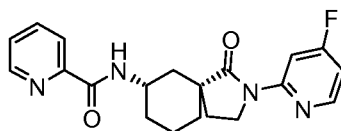
Example 15: ^1H NMR (400 MHz, CDCl_3): δ 8.02-8.04 (m, 1H), 7.89-7.93 (m, 1H), 7.28-7.60 (m, 5H), 7.16-7.22 (m, 1H), 4.23-4.34 (m, 1H), 3.78-3.89 (m, 2H), 1.75-2.27 (m, 7H), 1.50-1.70 (m, 3H). ESI-MS m/z : 392 ($\text{M}+\text{H}$) $^+$.

In a similar manner to Examples 1 and 2, Example 158 in Table 1 was made at 0.2 mmol reaction scale from intermediate 34 and commercially available 3-fluorobenzoic acid.

Example 158: ^1H NMR (400 MHz, CDCl_3): δ 8.20 (bs, 0.8H), 7.60-7.69 (m, 1.6 H), 7.44-7.51 (m, 0.4H), 7.35-7.42 (m, 1H), 7.25-7.29 (m, 1H), 7.13-7.20 (m, 1H), 6.80-6.83 (m, 1H), 5.99 (d, $J = 7.0$ Hz, 0.2 H), 4.65-4.75 (m, 0.2H), 4.30-4.40 (m, 0.8H), 3.80-3.95 (m, 5H), 1.35-2.34 (m, 10H). ESI-MS m/z : 371 ($\text{M}+\text{H}$) $^+$.

In a similar manner to Examples 1 and 2, Example 86-88 in Table 1 was made at 0.81 mmol reaction scale from intermediate 38 and commercially available 6-methyl-pyrazine-2-carboxylic acid, 6-methyl-pyridine-2-carboxylic acid and 3-fluorobenzoic acid.

Example 30: *cis*-Pyridine-2-carboxylic acid [2-(4-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide



Example 30 was prepared from intermediate 21 *via* the process of **Scheme 2**, *supra*, as follows:

cis-Pyridine-2-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide (60.0 mg, 0.22 mmol, intermediate 21), 2-chloro-4-fluoropyridine (28.8 mg, 0.219 mmol), potassium carbonate

(60.6 mg, 0.438 mmol), copper(I) iodide (41.7 mg, 0.219 mmol), and (1*R*,2*R*)-*N,N'*-dimethyl-cyclohexane-1,2-diamine (31.2 mg, 0.219 mmol) in 1,4-dioxane (3.00 mL) were placed in a sealed-tube. The reaction mixture was heated at 80 °C overnight. The crude mixture was cooled to rt and diluted with DCM (50 mL). The organic layer was washed with ammonia water/water (1:1, 2x15 mL) and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by CombiFlash[®] system (4 g silica gel cartridge; gradient: 0 to 40% ethyl acetate in DCM) to afford 24 mg (30%) of the title compound, *cis*-Pyridine-2-carboxylic acid [2-(4-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide. ¹H NMR (400 MHz, CDCl₃) δ 8.55 (ddd, *J* = 1.0, 1.7, 4.8 Hz, 1H), 8.30 (dd, *J* = 8.8, 5.7 Hz, 1H), 8.25 (dd, *J* = 11.6, 2.3 Hz, 1H), 8.18 (dt, *J* = 7.8, 1.0 Hz, 1H), 8.06 (br d, *J* = 8.2 Hz, 1H), 7.84 (td, *J* = 6.0, 2.3 Hz, 1H), 6.79 (ddd, *J* = 7.8, 5.7, 2.3 Hz, 1H), 3.97-4.20 (m, 3H), 2.09-2.27 (m, 3H), 1.56-2.01 (m, 6H), 1.33-1.46 (m, 1H). ESI-MS *m/z*: 369 (M+H)⁺.

In an analogous manner to Example 30, Examples 31-32, 34, and 63-64 in Table 1 (below) were made at 0.21-0.49 mmol reaction scales from intermediate 18 and commercially available heteroaryl halides; 2-chloro-5-fluoropyridine, 2-chloro-4-fluoropyridine, 2-chloro-4-methylpyrimidine, 5-bromo-2-methylpyridine, and 3-bromo-5-fluoropyridine, respectively.

Example 31: ¹H NMR (400 MHz, CDCl₃) δ 8.47 (dd, *J* = 9.2, 4.1 Hz, 1H), 8.24-8.31 (m, 1H), 8.22 (d, *J* = 3.0 Hz, 1H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.77 (t, *J* = 7.7 Hz, 1H), 7.45 (ddd, *J* = 9.2, 7.7, 3.0 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 3.96-4.21 (m, 3H), 2.62 (s, 3H), 2.10-2.28 (m, 3H), 1.58-2.02 (m, 6H), 1.36-1.51 (m, 1H). ESI-MS *m/z*: 383 (M+H)⁺.

Example 32: ¹H NMR (400 MHz, CDCl₃) δ 8.24 (dd, *J* = 8.8, 5.7 Hz, 1H), 8.19 (dd, *J* = 2.3, 11.7 Hz, 1H), 8.12 (br d, *J* = 7.4 Hz, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 6.73 (ddd, *J* = 7.8, 5.7, 2.3 Hz, 1H), 3.90-4.12 (m, 3H), 2.52 (s, 3H), 2.02-2.20 (m, 3H), 1.46-1.94 (m, 6H), 1.27-1.41 (m, 1H). ESI-MS *m/z*: 383 (M+H)⁺.

Example 34: ¹H NMR (400 MHz, CDCl₃) δ 8.37 (d, *J* = 5.0 Hz, 1H), 8.06 (br d, *J* = 7.0 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 6.73 (d, *J* = 5.0 Hz, 1H), 3.76-4.01 (m, 3H), 2.54 (s, 3H), 2.35 (s, 3H), 1.92-2.08 (m, 3H), 1.37-1.84 (m, 6H), 1.19-1.31 (m, 1H). ESI-MS *m/z*: 380 (M+H)⁺.

Example 63: ^1H NMR (400 MHz, CDCl_3) δ 8.60 (d, $J = 2.6$ Hz, 1H), 8.14 (dd, $J = 2.6$, 8.5 Hz, 1H), 8.11 (br d, $J = 8.6$ Hz, 1H), 7.97 (d, $J = 7.6$ Hz, 1H), 7.71 (t, $J = 7.7$ Hz, 1H), 7.26 (d, $J = 7.2$ Hz, 1H), 7.17 (d, $J = 8.6$ Hz, 1H), 4.06-4.18 (m, 1H), 3.77-3.88 (m, 2H), 2.57 (s, 3H), 2.54 (s, 3H), 2.09-2.34 (m, 3H), 1.59-1.99 (m, 6H), 1.33-1.47 (m, 1H). ESI-MS m/z : 379 (M+H) $^+$.

Example 64: ^1H NMR (400 MHz, CDCl_3) δ 8.51 (br, 1H), 8.22-8.29 (m, 2H), 8.12 (br d, $J = 8.4$ Hz, 1H), 7.97 (d, $J = 7.6$ Hz, 1H), 7.71 (t, $J = 7.7$ Hz, 1H), 7.27 (d, $J = 7.4$ Hz, 1H), 4.06-4.19 (m, 1H), 3.78-3.91 (m, 2H), 2.57 (s, 3H), 2.10-2.37 (m, 3H), 1.88-1.98 (m, 2H), 1.53-1.84 (m, 4H), 1.34-1.48 (m, 1H). ESI-MS m/z : 383 (M+H) $^+$.

In a similar manner to Example 30, Examples 35-37 in Table 1 (below) were made at a 0.55 mmol reaction scale from intermediate 19 and commercially available heteroaryl halides; 2-chloro-5-fluoropyridine, 2-chloro-4-fluoropyridine, and 2-chloro-4-methylpyrimidine, respectively.

Example 35: ^1H NMR (400 MHz, CDCl_3) δ 8.45 (dd, $J = 4.1$, 9.2 Hz, 1H), 8.24 (d, $J = 3.0$ Hz, 1H), 7.57-7.64 (m, 2H), 7.40-7.51 (m, 2H), 7.18-7.25 (m, 1H), 4.28-4.40 (m, 1H), 3.98-4.16 (m, 2H), 2.04-2.22 (m, 2H), 1.81-1.98 (m, 5H), 1.53-1.67 (m, 3H). ESI-MS m/z : 386 (M+H) $^+$.

Example 36: ^1H NMR (400 MHz, CDCl_3) δ 8.25 (dd, $J = 5.7$, 8.8 Hz, 1H), 8.18 (dd, $J = 11.6$, 2.3 Hz, 1H), 7.47-7.56 (m, 2H), 7.35 (td, $J = 8.1$, 5.6 Hz, 1H), 7.09-7.16 (m, 1H), 6.76 (ddd, $J = 7.8$, 5.7, 2.3 Hz, 1H), 4.18-4.29 (m, 1H), 3.91-4.11 (m, 2H), 1.96-2.13 (m, 2H), 1.71-1.89 (m, 5H), 1.44-1.59 (m, 3H). ESI-MS m/z : 386 (M+H) $^+$.

Example 37: ^1H NMR (400 MHz, CDCl_3) δ 8.57 (d, $J = 5.0$ Hz, 1H), 7.57-7.65 (m, 2H), 7.42 (td, $J = 8.1$, 5.6 Hz, 1H), 7.16-7.23 (m, 1H), 6.95 (d, $J = 5.0$ Hz, 1H), 4.27-4.38 (m, 1H), 3.99-4.18 (m, 2H), 2.55 (s, 3H), 2.04-2.22 (m, 2H), 1.87-1.95 (m, 5H), 1.54-1.68 (m, 3H). ESI-MS m/z : 383 (M+H) $^+$.

In a similar manner to Example 30, Example 57 in Table 1 (below) was made at a 0.22 mmol reaction scale from intermediate 20 and commercially available 2-chloro-5-fluoro-pyridine.

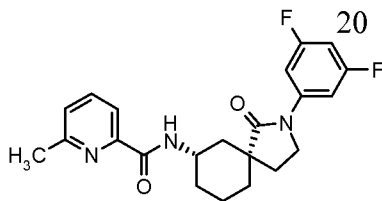
Example 57: ^1H NMR (400 MHz, CDCl_3) δ 8.85 (d, $J = 5.0$ Hz, 1H), 8.44 (dd, $J = 9.2, 4.1$ Hz, 1H), 8.20 (d, $J = 3.0$ Hz, 1H), 8.08 (br d, $J = 8.6$ Hz, 1H), 7.89 (d, $J = 4.9$ Hz, 1H), 7.44 (ddd, $J = 9.2, 7.6, 3.0$ Hz, 1H), 3.95-4.19 (m, 3H), 2.78 (s, 3H), 2.08-2.24 (m, 3H), 1.58-1.98 (m, 6H), 1.35-1.47 (m, 1H). ESI-MS m/z : 384 ($\text{M}+\text{H}$) $^+$.

5 In a similar manner to Example 30, Examples 29, 33 and 74 in Table 1 (below) were made at 0.22-0.44 mmol reaction scales from intermediate 21 and commercially available heteroaryl halides: 2-chloro-4-methylpyrimidine, 2-chloro-5-fluoropyridine, and 3-bromo-5-fluoropyridine, respectively.

10 Example 33: ^1H NMR (400 MHz, CDCl_3) δ 8.55-8.60 (m, 1H), 8.47 (dd, $J = 9.4, 4.0$ Hz, 1H), 8.19-8.24 (m, 2H), 8.11 (br d, $J = 8.1$ Hz, 1H), 7.89 (td, $J = 7.7, 1.7$ Hz, 1H), 7.42-7.49 (m, 2H), 3.98-4.21 (m, 3H), 2.11-2.29 (m, 3H), 1.59-2.02 (m, 6H), 1.36-1.48 (m, 1H). ESI-MS m/z : 369 ($\text{M}+\text{H}$) $^+$.

15 Example 74: ^1H NMR (400 MHz, CDCl_3) δ 8.56-8.60 (m, 1H), 8.54 (br, 1H), 8.26-8.33 (m, 2H), 8.17-8.22 (m, 1H), 8.07 (br d, $J = 8.8$ Hz, 1H), 7.87 (td, $J = 7.7, 1.7$ Hz, 1H), 7.45 (ddd, $J = 7.6, 4.8, 1.2$ Hz, 1H), 4.09-4.21 (m, 1H), 3.81-3.95 (m, 2H), 2.20-2.40 (m, 2H), 2.11-2.18 (m, 1H), 1.90-2.03 (m, 2H), 1.56-1.83 (m, 4H), 1.37-1.49 (m, 1H). ESI-MS m/z : 369 ($\text{M}+\text{H}$) $^+$.

Example of 42: *cis*-6-Methyl-pyridine-2-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide



Example 42 was prepared from intermediate 18 *via* the process of **Scheme 2**, *supra*, as follows:

25 *cis*-6-Methyl-pyridine-2-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide (0.450 g, 1.56 mmol, intermediate 18), (1-bromo-3,5-difluoro-benzene (0.363 g, 1.88 mmol), potassium carbonate (0.649 g, 4.70 mmol) and *N,N'*-dimethyl-ethane-1,2-diamine (0.138 g, 1.56 mmol) in 1,4-dioxane (15.0 mL) were heated in a microwave synthesizer (Biotage) at

160 °C for 2 hours. The reaction mixture was cooled to rt and filtered through a layer of Celite[®]. The filtrate was concentrated under reduced pressure and the resulting residue was purified on a reversed phase liquid chromatography/mass spectrometry (RP-HPLC/MS) purification system (Gradient: acetonitrile in water, 28-95% in 3.6 minutes with a cycle time of 5 min. A shallow gradient between 40-70% of acetonitrile was used between 0.75-3.4 min to separate close-eluting impurities. Flow rate: 100 mL/min. Mobile phase additive: 39 mM of ammonium acetate. Column: Inertsil[®] C18, 30 x 50 mm, 5 um particle size (GL Sciences)) to afford 0.120 g (20%) of the title compound, *cis*-6-methyl-pyridine-2-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 8.12 (d, *J* = 8.1 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.29-7.32 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 1 H), 6.59 (tt, *J* = 8.8, 2.2 Hz, 1H), 4.06-4.16 (m, 1H), 3.71-3.81 (m, 2H), 2.57 (s, 3H), 2.23-2.30 (m, 1H), 2.10-2.19 (m, 2H), 1.88-1.96 (m, 2H), 1.78 (t, *J* = 12.4 Hz, 1H), 1.68-1.76 (m, 1H), 1.54-1.65 (m, 2H), 1.35-1.45 (m, 1H). ESI-MS *m/z*: 400 (M+H)⁺.

The racemic Example 42 (220 mg, accumulated by repeating the above reaction one more time) were resolved by HPLC (column: Chiralpak[®] AD, 250x20 mm; mobile phase: 25% isopropanol, 75% hexane; flow rate: 14 mL/min; UV at 254 nm) to afford two enantiomers. The first peak from the chiral HPLC was assigned as Example 67, 6-methyl-pyridine-2-carboxylic acid [(5*R*, 7*R*)-2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]-dec-7-yl]amide (106 mg), and the second peak from the chiral HPLC was assigned as Example 81, 6-methyl-pyridine-2-carboxylic acid [(5*S*, 7*S*)-2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]-dec-7-yl]amide (93 mg).

Example 67: ¹H NMR (400 MHz, CDCl₃): δ 8.12 (d, *J* = 8.1 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.29-7.32 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 1 H), 6.59 (tt, *J* = 8.8, 2.2 Hz, 1H), 4.06-4.16 (m, 1H), 3.71-3.81 (m, 2H), 2.57 (s, 3H), 2.23-2.30 (m, 1H), 2.10-2.19 (m, 2H), 1.88-1.96 (m, 2H), 1.78 (t, *J* = 12.4 Hz, 1H), 1.68-1.76 (m, 1H), 1.54-1.65 (m, 2H), 1.35-1.45 (m, 1H). ESI-MS *m/z*: 400 (M+H)⁺.

Example 81: ¹H NMR (400 MHz, CDCl₃): δ 8.12 (d, *J* = 8.1 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 7.8 Hz, 1H), 7.29-7.32 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 1 H), 6.59 (tt, *J* = 8.8, 2.2 Hz, 1H), 4.06-4.16 (m, 1H), 3.71-3.81 (m, 2H), 2.57 (s, 3H), 2.23-2.30 (m, 1H), 2.10-

2.19 (m, 2H), 1.88-1.96 (m, 2H), 1.78 (t, $J=12.4$ Hz, 1H), 1.68-1.76 (m, 1H), 1.54-1.65 (m, 2H), 1.35-1.45 (m, 1H). ESI-MS m/z : 400 (M+H)⁺.

In an analogous manner to Example 42, Examples 43-52 and 71-72 in Table 1 (below) were made at 0.07-1.56 mmol reaction scales from intermediate 18 and commercially available 6-bromo-pyridine-2-carbonitrile, 1-fluoro-4-iodo-benzene, 2-bromo-pyridine, bromobenzene, 1-iodo-3-methylbenzene, 2-bromo-4-methylpyridine, 2-bromo-5-methylpyridine, 2-bromo-3-methylpyridine, 1-fluoro-2-iodobenzene, 4-bromo-2-methylpyridine, 3-bromo-5-methylpyridine, and 1-bromo-3-methoxybenzene, respectively.

Example 43: ¹H NMR (400 MHz, CDCl₃) δ 8.70 (dd, $J=0.8, 8.7$ Hz, 1H), 8.10 (d, $J=8.5$ Hz, 1H), 8.00-7.96 (m, 1H), 7.79 (dd, $J=7.4, 8.7$ Hz, 1H), 7.71 (t, $J=7.7$ Hz, 1H), 7.43 (dd, $J=0.8, 7.4$ Hz, 1H), 7.29-7.25 (m, 1H), 4.18-3.97 (m, 3H), 2.57 (s, 3H), 2.28-1.34 (m, 10H). ESI-MS m/z : 390 (M+H)⁺.

Example 44: ¹H NMR (400 MHz, CDCl₃): δ 8.11 (d, $J = 8.6$ Hz, 1H), 7.97 (d, $J = 8.5$ Hz, 1H), 7.71 (t, $J = 7.6$ Hz, 1H), 7.57-7.63 (m, 2H), 7.26 (d, $J = 7.6$ Hz, 1H), 7.02-7.08 (m, 2H), 4.06-4.17 (m, 1H), 3.74-3.83 (m, 2H), 2.57 (s, 3H), 2.22-2.30 (m, 1H), 2.10-2.19 (m, 2H), 1.86-1.97 (m, 2H), 1.54-1.83 (m, 4H), 1.34-1.45 (m, 1H). ESI-MS m/z : 382 (M+H)⁺.

Example 45: ¹H NMR (400 MHz, CDCl₃) δ 8.41 (d, $J=8.5$ Hz, 1H), 8.38-8.35 (m, 1H), 8.13 (d, $J=8.5$ Hz, 1H), 7.98 (d, $J=7.7$ Hz, 1H), 7.74-7.66 (m, 2H), 7.26 (d, $J=7.4$ Hz, 1H), 7.06-7.01 (m, 2H), 4.18-3.97 (m, 3H), 2.57 (s, 3H), 2.28-1.34 (m, 10H). ESI-MS m/z : 365 (M+H)⁺.

Example 46: ¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, $J= 8.4$ Hz, 1H), 7.97 (d, $J=7.6$ Hz, 1H), 7.71 (t, $J=7.7$ Hz, 1H), 7.67-7.62 (m, 2H), 7.39-7.34 (m, 1H), 7.26 (d, $J=7.5$ Hz, 1H), 7.17-7.11 (m, 1H), 4.18-4.06 (m, 1H), 3.87-3.76 (m, 2H), 2.57 (s, 3H), 2.30-1.33 (m, 10H). ESI-MS m/z : 364 (M+H)⁺.

Example 47: ¹H NMR (400 MHz, CDCl₃) δ 8.13 (d, $J=8.5$ Hz, 1H), 7.97 (d, $J=7.6$ Hz, 1H), 7.71 (d, $J=7.7$ Hz, 1H), 7.51 (br, 1H), 7.39 (d, $J=8.2$ Hz, 1H), 7.28-7.22 (m, 2H), 6.96 (d, $J=7.5$ Hz, 1H), 4.18-4.06 (m, 1H), 3.86-3.74 (m, 2H), 2.57 (s, 3H), 2.36 (s, 3H), 2.28-1.34 (m, 10H). ESI-MS m/z : 378 (M+H)⁺.

Example 48: ^1H NMR (400 MHz, CDCl_3) δ 8.25 (s, 1H), 8.21 (d, $J=5.1$ Hz, 1H), 8.14 (d, $J=6.6$ Hz, 1H), 7.98 (d, $J=7.6$ Hz, 1H), 7.71 (t, $J=7.7$ Hz, 1H), 7.26 (d, $J=7.3$ Hz, 1H), 6.89-6.85 (m, 1H), 4.19-3.97 (m, 3H), 2.57 (s, 3H), 2.36 (s, 3H), 2.24-1.33 (m, 10H). ESI-MS m/z : 379 ($\text{M}+\text{H}$) $^+$.

5 In a similar manner to Examples 67 and 81, Examples 25, 28, 73, 80, 82, 95, 147, 148, 152, and 156 in Table 1 (below) were separated from their corresponding racemates: Example 19, 27, 31, 44, 76, 78, 65, 58, 84, and 41 by chiral HPLC, respectively.

10 Example 25: ^1H NMR (400 MHz, CDCl_3): δ 8.54-8.56 (m, 1H), 8.16-8.19 (m, 1H), 8.04 (d, $J = 8.3$ Hz, 1H), 7.84 (td, $J = 7.9, 1.7$ Hz, 1H), 7.58 (dt, $J = 11.3, 2.0$ Hz, 1H), 7.40-7.44 (m, 1H), 7.28-7.37 (m, 2H), 6.81-6.87 (m, 1H), 4.07-4.18 (m, 1H), 3.74-3.85 (m, 2H), 2.23-2.30 (m, 1H), 2.08-2.19 (m, 2H), 1.87-1.98 (m, 2H), 1.55-1.80 (m, 4H), 1.34-1.44 (m, 1H). ESI-MS m/z : 368 ($\text{M}+\text{H}$) $^+$.

15 Example 28: ^1H NMR (300 MHz, CDCl_3) δ 8.16 (d, $J=8.3$ Hz, 1H), 7.77 (br, 1H), 7.66-7.55 (m, 3H), 7.41 (dt, $J=5.7, 8.3$ Hz, 1H), 7.23-7.14 (m, 1H), 6.91 (d, $J=7.4$ Hz, 1H), 4.39-4.24 (m, 1H), 4.18-3.97 (m, 2H), 2.48 (s, 3H), 2.18-1.47 (m, 10H). ESI-MS m/z : 382 ($\text{M}+\text{H}$) $^+$.

Example 73: ^1H NMR (400 MHz, CDCl_3) δ 8.47 (dd, $J = 4.0, 9.3$ Hz, 1H), 8.22 (d, $J = 3.0$ Hz, 1H), 8.16 (br d, $J = 8.5$ Hz, 1H), 8.01 (d, $J = 7.7$ Hz, 1H), 7.74 (t, $J = 7.7$ Hz, 1H), 7.45 (ddd, $J = 9.2, 7.7, 3.0$ Hz, 1H), 7.29 (d, $J = 6.8$ Hz, 1H), 3.97-4.21 (m, 3H), 2.60 (s, 3H), 2.11-2.28 (m, 3H), 1.56-2.01 (m, 6H), 1.35-1.48 (m, 1H). ESI-MS m/z : 383 ($\text{M}+\text{H}$) $^+$.

20 Example 80: ^1H NMR (400 MHz, CDCl_3): δ 8.11 (d, $J = 8.6$ Hz, 1H), 7.97 (d, $J = 8.5$ Hz, 1H), 7.71 (t, $J = 7.6$ Hz, 1H), 7.57-7.63 (m, 2H), 7.26 (d, $J = 7.6$ Hz, 1H), 7.02-7.08 (m, 2H), 4.06-4.17 (m, 1H), 3.74-3.83 (m, 2H), 2.57 (s, 3H), 2.22-2.30 (m, 1H), 2.10-2.19 (m, 2H), 1.86-1.97 (m, 2H), 1.54-1.83 (m, 4H), 1.34-1.45 (m, 1H). ESI-MS m/z : 382 ($\text{M}+\text{H}$) $^+$.

25 Example 82: ^1H NMR (400 MHz, CDCl_3): δ 8.85 (d, $J = 5.0$ Hz, 1H), 8.12 (d, $J = 8.3$ Hz, 1H), 7.89 (d, $J = 4.3$ Hz, 1H), 7.28-7.34 (m, 2H), 6.59 (tt, $J = 8.8, 2.3$ Hz, 1H), 4.07-4.17 (m, 1H), 3.73-3.82 (m, 2H), 2.78 (s, 3H), 2.06-2.28 (m, 3H), 1.89-1.96 (m, 2H), 1.55-1.85 (m, 4H), 1.37-1.48 (m, 1H). ESI-MS m/z : 401 ($\text{M}+\text{H}$) $^+$.

Example 95: ^1H NMR (400 MHz, CDCl_3): δ 8.56 (d, $J = 5.0$ Hz, 1H), 8.20 (bs, 1H), 7.60 (bs, 1H), 7.54-7.59 (m, 1H), 7.49-7.52 (m, 1H), 7.30-7.34 (m, 2H), 6.84-6.90 (m, 1H), 4.28-4.38 (m, 1H), 3.76-3.90 (m, 2H), 2.59 (s, 3H), 2.14-2.23 (m, 1H), 1.82-2.12 (m, 6H), 1.48-1.64 (m, 3H). ESI-MS m/z : 382 ($\text{M}+\text{H}$) $^+$.

5 Example 147: ^1H NMR (400 MHz, CDCl_3): δ 8.51 (d, $J = 6.0$ Hz, 1H), 8.17 (d, $J = 5.8$ Hz, 1H), 7.80-7.86 (m, 2H), 7.06-7.15 (m, 3H), 4.23-4.33 (m, 1H), 3.94-4.16 (m, 2H), 2.65 (s, 3H), 2.04-2.20 (m, 2H), 1.75-1.96 (m, 5H), 1.49-1.65 (m, 3H). ESI-MS m/z : 383 ($\text{M}+\text{H}$) $^+$.

10 Example 148: ^1H NMR (400 MHz, CDCl_3): δ 8.49 (d, $J = 6.5$ Hz, 1H), 8.16 (d, $J = 5.8$ Hz, 1H), 7.82 (t, $J = 2.0$ Hz, 1H), 7.67-7.71 (m, 1H), 7.43-7.47 (m, 1H), 7.28-7.39 (m, 2H), 4.21-4.32 (m, 1H), 3.94-4.15 (m, 2H), 2.64 (s, 3H), 2.04-2.19 (m, 2H), 1.76-1.98 (m, 5H), 1.47-1.66 (m, 3H). ESI-MS m/z : 399 ($\text{M}+\text{H}$) $^+$.

15 Example 152: ^1H NMR (400 MHz, CDCl_3) δ 8.49 (d, $J = 5.9$ Hz, 1H), 8.16-8.19 (m, 1H), 7.60-7.63 (m, 1H), 7.55-7.59 (m, 1H), 7.29-7.35 (m, 2H), 6.75 (s, 1H), 4.19-4.29 (m, 1H), 4.07-4.15 (m, 1H), 3.98-4.02 (m, 1H), 2.65 (s, 3H), 2.40 (s, 3H), 2.04-2.22 (m, 2H), 1.85-2.04 (m, 3H), 1.71-1.81 (m, 2H), 1.39-1.65 (m, 3H). ESI-MS m/z : 379 ($\text{M}+\text{H}$) $^+$.

Example 156: ^1H NMR (400 MHz, CDCl_3) δ 8.65 (d, $J = 8.5$ Hz, 1H), 8.10 (d, $J = 8.5$ Hz, 1H), 7.98 (d, $J = 7.6$ Hz, 1H), 7.84 (t, $J = 7.8$ Hz, 1H), 7.71 (t, $J = 7.7$ Hz, 1H), 7.40 (d, $J = 7.4$ Hz, 1H), 7.26 (d, $J = 7.5$ Hz, 1H), 4.18-4.02 (m, 3H), 2.57 (s, 3H), 2.28-1.33 (m, 10H). ESI-MS m/z : 433 ($\text{M}+\text{H}$) $^+$.

20 In a similar manner to Example 42, Examples 26, 53, 130, 132-136, 138-139, and 142 in Table 1 (below) were made at 0.03-1.0 mmol reaction scales from intermediate 19 and commercially available heteroaryl halides: 2-bromo-pyridine, 6-bromo-pyridine-2-carbonitrile, 1-iodo-3-methoxy-benzene, (3-iodo-phenyl)-dimethyl-amine, 1-iodo-4-methoxy-benzene, 4-[3-(3-bromo-phenyl)-propyl]-morpholine, 1-bromo-3-fluoro-5-methoxy-benzene, 2-(3-iodo-phenoxy)-1-pyrrolidin-1-yl-ethanone, (4-iodo-phenyl)-dimethyl-amine, 2-bromo-thiazole, and 3-fluoro-5-iodo-benzonitrile, respectively.

25 Example 130: ^1H NMR (400 MHz, CDCl_3): δ 8.05-7.83 (m, br, 1H), 7.66-7.58 (m, 2H), 7.46 (t, $J = 2.3$ Hz, 1H), 7.42-7.35 (m, 1H), 7.27-7.23 (m, 1H), 7.20-7.13 (m, 1H), 7.10-7.05 (m,

1H), 6.74-6.70 (m, 1H), 4.39-4.28 (m, 1H), 3.91-3.74 (m, 5H), 2.22-1.46 (m, 10H), ESI-MS m/z: 397 (M+H)⁺.

Example 132: ¹H NMR (400 MHz, CDCl₃): δ 8.32 (s, br, 1H), 7.71-7.60 (m, 2H), 7.40-7.32 (m, 2H), 7.24-7.11 (m, 2H), 6.73-6.67 (m, 1H), 6.58-6.53 (m, 1H), 4.41-4.30 (m, 1H),
5 3.93-3.73 (m, 2H), 2.96 (s, 6H), 2.19-2.45 (m, 10H). ESI-MS m/z: 401 (M+H)⁺.

Example 133: ¹H NMR (400 MHz, CDCl₃): δ 8.08-7.86 (m, 1H), 7.65-7.57 (m, 2H), 7.53-7.48 (m, 2H), 7.41-7.35 (m, 1H), 7.19-7.13 (m, 1H), 6.92-6.88 (m, 2H), 4.40-4.27 (m, 1H), 3.87-3.70 (m, 5H), 2.21-1.46 (m, 10H). ESI-MS m/z: 397 (M+H)⁺.

Example 134: ¹H NMR (300 MHz, CDCl₃): δ 7.96-7.75 (m, 1H), 7.68-7.55 (m, 3H), 7.46-7.27 (m, 3H), 7.24-7.11 (m, 1H), 7.00 (m, 1H), 4.44-4.26 (m, 1H), 3.97-3.65 (m, 6H), 2.77-1.47 (m, 20H). ESI-MS m/z: 494 (M+H)⁺.

Example 135: ¹H NMR (300 MHz, CDCl₃): δ 7.82-7.55 (m, 3H), 7.45-7.34 (m, 1H), 7.22-7.13 (m, 2H), 7.04-6.95 (m, 1H), 6.49-6.39 (m, 1H), 4.39-4.24 (m, 1H), 3.87-3.71 (m, 5H), 2.24-1.46 (m, 10H). ESI-MS m/z: 415 (M+H)⁺.

Example 136: ¹H NMR (400 MHz, CDCl₃): δ 7.93-7.71 (m, br, 1H), 7.66-7.56 (m, 2H), 7.43-7.35 (m, 2H), 7.28-7.26 (m, 1H), 7.22-7.13 (m, 2H), 6.79-6.75 (m, 1H), 4.63 (s, 2H), 4.36-4.25 (m, br, 1H), 3.90-3.74 (m, 2H), 3.51 (t, J = 6.8 Hz, 4H), 2.22-1.48 (m, 14H). ESI-MS m/z: 494 (M+H)⁺.

Example 138: ¹H NMR (400 MHz, CDCl₃): δ 8.50-8.07 (m, br, 1H), 7.69-7.60 (m, 2H), 7.48-7.34 (m, 3H), 7.21-7.13 (m, 1H), 6.74 (d, J = 8.7 Hz, 2H), 4.43-4.29 (m, 1H), 3.91-3.67 (m, 2H), 2.95 (m, 6H), 2.22-1.46 (m, 10H). ESI-MS m/z: 410 (M+H)⁺.

Example 139: ¹H NMR (400 MHz, CDCl₃): δ 7.65-7.56 (m, 2H), 7.50 (d, J = 3.5 Hz, 1H), 7.45-7.38 (m, 2H), 7.22-7.16 (m, 1H), 7.05- (d, J = 3.5 Hz, 1H), 4.39-4.29 (m, 1H), 4.24-4.05 (m, 2H), 2.32-2.12 (m, 2H), 1.98-1.55 (m, 8H). ESI-MS m/z: 374 (M+H)⁺.

Example 142: ¹H NMR (400 MHz, CDCl₃): δ 7.89-7.84 (m, 1H), 7.75 (s, br, 1H), 7.59-7.52 (m, 2H), 7.46-7.38 (m, 1H), 7.23-7.07 (m, 3H), 4.32-4.20 (m, 1H), 3.85-3.77 (m, 2H), 2.30-1.45 (m, 10H). ESI-MS m/z: 410 (M+H)⁺.

In a similar manner to Example 42, Examples 59-61, 76 and 141 in Table 1 (below) were made at 0.03-4.16 mmol reaction scales from intermediate 20 and commercially 2-chloro-6-methylpyrazine, 3-iodo-benzonitrile, 2-bromo-6-trifluoromethyl-pyridine, 1,3-difluoro-5-iodo-benzene, and 1-bromo-3-fluoro-5-methoxy-benzene, respectively.

5 Example 141: ^1H NMR (400 MHz, CDCl_3): δ 8.88 (s, br, 1H), 8.20-8.06 (m, 1H), 7.91 (s, br, 1H), 7.15 (s, br, 1H), 7.09-7.04 (m, 1H), 6.46-6.41 (m, 1H), 4.19-4.07 (m, 1H), 3.85-3.75 (m, 5H), 2.81 (s, 3H), 2.30-1.36 (m, 10H). ESI-MS m/z : 413 ($\text{M}+\text{H}$) $^+$.

In a similar manner to Example 42, Example 75 in Table 1 (below) was made at a 0.11 mmol reaction scale from intermediate 21 and commercially available 4-iodo-1,2-difluoro-benzene.

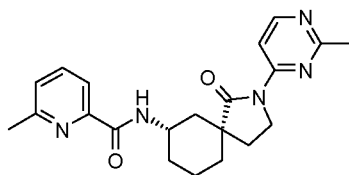
10 In a similar manner to Example 42, Example 79 in Table 1 (below) was made at a 0.13 mmol reaction scale from intermediate 22 and commercially available 1-bromo-3,5-difluoro-benzene.

In a similar manner to Example 42, Example 78 in Table 1 (below) was made at a 1.04 mmol reaction scale from intermediate 23 and commercially available 1-iodo-3-fluoro-benzene.

15 In a similar manner to Example 42, Example 137 in Table 1 (below) was made at a 0.1 mmol reaction scale from intermediate 32 and commercially available 1-iodo-3-fluoro-benzene.

Example 137: ^1H NMR (400 MHz, CDCl_3): δ 7.86 (d, $J = 3.1$ Hz, 1H), 7.60-7.57 (m, 1H), 7.56 (d, $J = 3.1$ Hz, 1H), 7.44 (d, br, $J = 8$ Hz, 1H), 7.38-7.28 (m, 2H), 6.87-6.81 (m, 1H), 4.18-4.04 (m, 1H), 3.85-3.75 (m, 2H), 2.27-1.35 (m, 10H). ESI-MS m/z : 374.0 ($\text{M}+\text{H}$) $^+$.

20 **Example 62: *cis*-6-methyl-pyridine-2-carboxylic acid [2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide**



Example 62 was prepared from intermediate 18 *via* the process of **Scheme 2**, *supra*, as follows:

4-Chloro-2-methylpyrimidine (0.019 g, 0.148 mmol), *cis*-6-methyl-pyridine-2-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide (0.047 g, 0.162 mmol, intermediate 18), dicesium carbonate (0.067 g, 0.206 mmol), tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (0.031 g, 0.030 mmol), and racemic BINAP (0.055 g, 0.089 mmol) in toluene (1.0 mL) were heated at 80 °C for 6 hours. The crude mixture was cooled down to rt, and the catalyst was filtered off. The filtrate was concentrated under reduced pressure, and the resulting residue was purified on a RP-HPLC/MS purification system (Gradient: acetonitrile in water, 24-95% in 3.6 minutes with a cycle time of 5 min. A shallow gradient between 40-68% of acetonitrile was used between 0.75-3.4 min to separate close-eluting impurities. Flow rate: 100 mL/min. Mobile phase additive: 48 mM of ammonium formate. Column: Inertsil® C8, 30 x 50 mm, 5 um particle size (GL Sciences)) to afford 0.032 g (57%) of the title compound, *cis*-6-methyl-pyridine-2-carboxylic acid [2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 8.47 (d, *J* = 5.8 Hz, 1H), 8.17 (d, *J* = 5.8 Hz, 1H), 8.09 (d, *J* = 8.9 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 3.94-4.16 (m, 3H), 2.63 (s, 3H), 2.55 (s, 3H), 2.09-2.24 (m, 3H), 1.86-1.97 (m, 2H), 1.77 (t, *J* = 12.4 Hz, 1H), 1.57-1.69 (m, 3H), 1.33-1.42 (m, 1H). ESI-MS *m/z*: 380 (M+H)⁺.

In a similar manner to Example 62, Example 65 and 66, 150 and 151 in Table 1 (below) were made at 2.81 mmol reaction scale from intermediate 19 and commercially available 4-chloro-2-methyl-pyrimidine and 4-bromo-2-methylpyridine, 4-chloro-2-trifluoromethyl-pyrimidine, and 4-chloro-2,6-dimethyl-pyrimidine, respectively.

Example 65: ¹H NMR (400 MHz, CDCl₃): δ 8.51 (d, *J* = 6.0 Hz, 1H), 8.17 (d, *J* = 5.8 Hz, 1H), 7.80-7.86 (m, 2H), 7.06-7.15 (m, 3H), 4.23-4.33 (m, 1H), 3.94-4.16 (m, 2H), 2.65 (s, 3H), 2.04-2.20 (m, 2H), 1.75-1.96 (m, 5H), 1.49-1.65 (m, 3H). ESI-MS *m/z*: 383 (M+H)⁺.

Example 66: ¹H NMR (400 MHz, CDCl₃): δ 8.42 (s, 1H), 7.51-7.60 (m, 3H), 7.36-7.43 (m, 2H), 7.29 (bs, 1H), 7.15-7.21 (m, 1H), 4.22-4.31 (m, 1H), 3.78-3.83 (m, 2H), 2.54 (s, 3H), 2.06-2.25 (m, 2H), 1.75-1.96 (m, 5H), 1.46-1.63 (m, 3H). ESI-MS *m/z*: 382 (M+H)⁺.

Example 151: ¹H NMR (400 MHz, CDCl₃) δ 8.73 (d, *J* = 6.1 Hz, 1H), 8.54 (d, *J* = 5.8 Hz, 1H), 7.50-7.57 (m, 2H), 7.37-7.44 (m, 1H), 7.16-7.22 (m, 1H), 6.96 (s, 1H), 4.14-4.29 (m,

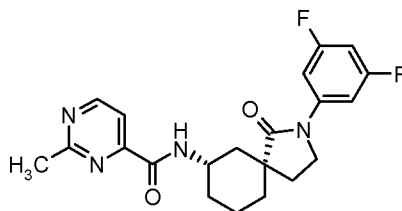
2H), 3.99-4.07 (m, 1H), 2.10-2.25 (m, 2H), 1.74-2.01 (m, 5H), 1.44-1.67 (m, 3H). ESI-MS m/z: 437 (M+H)⁺.

Example 152: ¹H NMR (400 MHz, CDCl₃) δ 8.01 (s, 1H), 7.51-7.59 (m, 2H), 7.32-7.40 (m, 2H), 7.12-7.19 (m, 1H), 4.19-4.29 (m, 1H), 4.04-4.11 (m, 1H), 3.96-3.99 (m, 1H), 2.58 (s, 3H), 2.43 (s, 3H), 2.01-2.16 (m, 2H), 1.73-1.93 (m, 5H), 1.45-1.62 (m, 3H). ESI-MS m/z: 397 (M+H)⁺.

In a similar manner to Example 62, Example 140 in Table 1 (below) was made at 0.1 mmol reaction scale from intermediate 32 and commercially available 4-chloro-2-methylpyrimidine.

Example 140: ¹H NMR (400 MHz, CDCl₃): δ 8.50 (s, br, 1H), 8.19 (d, *J* = 5.8 Hz, 1H), 7.86 (d, *J* = 3.0 Hz, 1H), 7.57 (d, *J* = 3.0 Hz, 1H), 7.43-7.35 (m, 1H), 3.94-4.18 (m, 3H), 2.64 (s, 3H), 1.35-2.23 (m, 10H). ESI-MS m/z: 372 (M+H)⁺.

Example 76: *cis* 2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl) -1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide



Example 76 was also prepared from intermediate 33 via the process of Scheme 1, *supra*, as follows:

In a round-bottom flask was charged with *cis*-7-amino-2-(3,5-difluoro-phenyl)-2-aza-spiro[4.5]decan-1-one. HCl (10.8 g, 34.1 mmol), 2-methylpyrimidine-4-carboxylic acid (4.71 g, 34.1 mmol), and BOP (15.1 g, 34.1 mmol). Methylene chloride (218 mL) was added, and the mixture was cooled at 0 °C. Triethylamine (14.2 mL, 102 mmol) was added dropwise. The mixture was warmed up to rt and stirred at rt overnight. The mixture was diluted with methylene chloride (100 mL) and water (50 mL). The aqueous layer was extracted with CH₂Cl₂ (100 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue obtained was crystallized from ethyl

acetate to afford 8.8 g (77%) of the title compound *cis* 2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl) -1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide. : ^1H NMR (400 MHz, CDCl_3): δ 8.85 (d, $J = 5.0$ Hz, 1H), 8.10 (d, $J = 8.1$ Hz, 1H), 7.89 (d, $J = 5.4$ Hz, 1H), 7.28-7.35 (m, 2H), 6.60 (tt, $J = 8.8, 2.5$ Hz, 1H), 4.07-4.18 (m, 1H), 3.74-3.80 (m, 2H), 2.79 (s, 3H), 2.07-2.28 (m, 3H), 1.89-1.97 (m, 2H), 1.55-1.85 (m, 4H), 1.37-1.48 (m, 1H). ESI-MS m/z : 401 ($\text{M}+\text{H}$) $^+$.

In a similar manner to Example 76, Example 143-146 in Table 1 (below) were made at 0.05-0.07 mmol reaction scales from intermediate 33 and commercially available thiazole-2-carbonyl chloride, 2-methyl-thiazole-4-carboxylic acid, pentanoyl, and butyryl chloride, respectively.

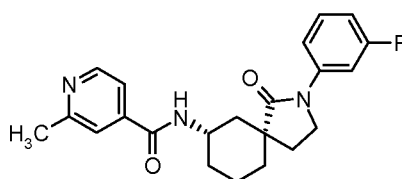
Example 143: ^1H NMR (400 MHz, CDCl_3): δ 7.86 (d, $J = 3.1$ Hz, 1H), 7.56 (d, $J = 3.1$ Hz, 1H), 7.39 (d, br $J = 8.0$ Hz, 1H), 7.28-7.32 (m, 2H), 6.62-6.55 (m, 1H), 4.06-4.17 (m, 1H), 3.72-3.81 (m, 2H), 1.35-2.28 (m, 10H). ESI-MS m/z : 392 ($\text{M}+\text{H}$) $^+$.

Example 144: ^1H NMR (400 MHz, CDCl_3): δ 7.91 (s, 1H), 7.27-7.37 (m, 3H), 6.54-6.61 (m, 1H), 4.03-4.15 (m, 1H), 3.70-3.80 (m, 2H), 2.70 (s, 3H), 1.30-2.29 (m, 10H). ESI-MS m/z : 406 ($\text{M}+\text{H}$) $^+$.

Example 145: ^1H NMR (400 MHz, CDCl_3): δ 7.27-7.31 (m, 2H), 6.56-6.63 (m, 1H), 5.83 (m, 1H), 3.93-4.05 (m, 1H), 3.70-3.79 (m, 2H), 1.22-2.23 (m, 16H), 0.91 (m, 3H). ESI-MS m/z : 365 ($\text{M}+\text{H}$) $^+$.

Example 146: ^1H NMR (400 MHz, CDCl_3): δ 7.26-7.30 (m, 2H), 6.56-6.62 (m, 1H), 5.97 (s, 1H), 3.95-4.06 (m, 1H), 3.71-3.80 (m, 2H), 1.21-2.25 (m, 14H), 0.93 (t, $J = 7.4$ Hz, 3H). ESI-MS m/z : 351 ($\text{M}+\text{H}$) $^+$.

Example 78: *cis*-N-[2-(3-Fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-2-methyl-isonicotinamide



Example 78 was also prepared from intermediate 13 as follows:

[2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-carbamic acid *tert*-butyl ester (0.010 g, 0.028 mmol, intermediate 13) was dissolved in methylene chloride (1.0 mL), 4M of hydrogen chloride in 1,4-dioxane (0.7 mL) was added. The mixture was stirred at rt overnight and then concentrated under reduced pressure. The resulting residue was dissolved in methylene chloride (1.0 mL). Triethylamine (0.015 mL, 0.11 mmol) was added, followed by the addition of 2-methylisonicotinic acid (0.005 g, 0.033 mmol) and BOP (0.015 g, 0.033 mmol). The mixture was stirred at rt for 4 hours and concentrated under reduced pressure. The residue was purified on a RP –HPLC/MS purification system (Gradient: acetonitrile in water, 24-95% in 3.6 minutes with a cycle time of 5 min. A shallow gradient between 28-56% of acetonitrile was used between 0.75-3.3 min to separate close-eluting impurities. Flow rate: 100 mL/min. Mobile phase additive: 48 mM of ammonium formate. Column: Inertsil® C18, 30 x 50 mm, 5 um particle size (GL Sciences)) to afford 0.008 g (80%) of the title compound, *cis-N*-[2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-2-methyl-isonicotinamide as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 8.56 (d, *J* = 5.0 Hz, 1H), 8.20 (bs, 1H), 7.60 (bs, 1H), 7.54-7.59 (m, 1H), 7.49-7.52 (m, 1H), 7.30-7.34 (m, 2H), 6.84-6.90 (m, 1H), 4.28-4.38 (m, 1H), 3.76-3.90 (m, 2H), 2.59 (s, 3H), 2.14-2.23 (m, 1H), 1.82-2.12 (m, 6H), 1.48-1.64 (m, 3H). ESI-MS *m/z*: 382 (M+H)⁺.

In an analogous manner to Example 78, Examples 68-70, 77 and 93-94 in Table 1 were made at 0.03-0.16 mmol reaction scales from intermediate 13 and commercially available 5-fluoropyridine-2-carboxylic acid, 2-methyl-pyrimidine-4-carboxylic acid, pyrimidine-4-carboxylic acid, isonicotinic acid, 2-methylisonicotinic acid, 6-hydroxymethyl-pyridine-2-carboxylic acid, and 6-trifluoromethyl-pyridine-2-carboxylic acid, respectively.

Example 68: ¹H NMR (400 MHz, CDCl₃): δ 8.38 (d, *J* = 3.0 Hz, 1H), 8.19-8.23 (m, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.50-7.60 (m, 2H), 7.28-7.38 (m, 2H), 6.81-6.87 (m, 1H), 4.05-4.16 (m, 1H), 3.75-3.85 (m, 2H), 2.06-2.29 (m, 3H), 1.87-1.97 (m, 2H), 1.33-1.80 (m, 5H). ESI-MS *m/z*: 386 (M+H)⁺.

Example 69: ¹H NMR (400 MHz, CDCl₃): δ 8.85 (d, *J* = 3.8 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 5.0 Hz, 1H), 7.56-7.61 (m, 1H), 7.28-7.37 (m, 2H), 6.82-6.88 (m, 1H), 4.07-

4.18 (m, 1H), 3.77-3.83 (m, 2H), 2.78 (s, 3H), 2.05-2.27 (m, 3H), 1.37-1.96 (m, 7H). ESI-MS m/z: 383 (M+H)⁺.

In a similar manner to Example 78, Examples 38-40 in Table 1 were made at a 0.06 mmol reaction scale from intermediate 14 and commercially available carboxylic acids: 3-fluorobenzoic acid, picolinic acid and 6-methyl-pyridine-2-carboxylic acid, respectively.

Example 38: ¹H NMR (400 MHz, CDCl₃) δ 9.53 (s, 1H), 8.22 (s, 1H), 7.63-7.56 (m, 2H), 7.46-7.39 (m, 1H), 7.23-7.16 (m, 1H), 4.38-4.27 (m, 1H), 4.16-3.93 (m, 2H), 2.50 (s, 3H), 2.23-1.52 (m, 10H). ESI-MS m/z: 383 (M+H)⁺.

In a similar manner to Example 78, Examples 54-56 in Table 1 were made at a 0.03 mmol reaction scale from intermediate 15 and commercially available carboxylic acids: picolinic acid, 6-methyl-pyrazine-2-carboxylic acid and pyrazine-2-carboxylic acid, respectively.

Example 54: ¹H NMR (400 MHz, CDCl₃) δ 8.54-8.57 (m, 1H), 8.15-8.19 (m, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.82-7.87 (m, 1H), 7.40-7.45 (m, 1H), 7.27-7.34 (m, 2H), 6.55-6.62 (m, 1H), 4.07-4.18 (m, 1H), 3.71-3.82 (m, 2H), 2.23-2.31 (m, 1H), 2.07-2.20 (m, 2H), 1.87-1.98 (m, 2H), 1.34-1.80 (m, 5H). ESI-MS m/z: 386 (M+H)⁺.

Example 55: ¹H NMR (400 MHz, CDCl₃) δ 9.18 (s, 1H), 8.61 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.27-7.34 (m, 1H), 6.56-6.63 (m, 1H), 4.09-4.20 (m, 1H), 3.73-3.81 (m, 2H), 2.61 (s, 3H), 2.07-2.29 (m, 3H), 1.89-1.96 (m, 2H), 1.35-1.83 (m, 5H). ESI-MS m/z: 401 (M+H)⁺.

In a similar manner to Example 78, Example 41 in Table 1 was made at 0.05 mmol reaction scale from intermediate 16 and commercially available 6-methyl-pyridine-2-carboxylic acid.

Example 41: ¹H NMR (400 MHz, CDCl₃) δ 8.65 (d, *J*=8.5 Hz, 1H), 8.10 (d, *J*=8.5 Hz, 1H), 7.98 (d, *J*=7.6 Hz, 1H), 7.84 (t, *J*=7.8 Hz, 1H), 7.71 (t, *J*=7.7 Hz, 1H), 7.40 (d, *J*=7.4 Hz, 1H), 7.26 (d, *J*=7.5 Hz, 1H), 4.18-4.02 (m, 3H), 2.57 (s, 3H), 2.28-1.33 (m, 10H). ESI-MS m/z: 433 (M+H)⁺.

In a similar manner to Example 78, Examples 58, 84-85, 89-92, 96 and 149 in Table 1 were made at 0.04-0.08 mmol reaction scales from intermediate 17 and commercially available carboxylic acids: 3-chlorobenzoic acid, 3-methyl-benzoic acid, 3,5-difluorobenzoic acid, 4-fluorobenzoic acid, 3,4-difluorobenzoic acid, 2-fluorobenzoic acid, 2-methyl-isonicotinic

acid, 6-trifluoromethyl-pyridine-2-carboxylic acid and 5-fluoro-pyridine-2-carboxylic acid, respectively.

Example 58: ^1H NMR (400 MHz, CDCl_3): δ 8.49 (d, $J = 6.5$ Hz, 1H), 8.16 (d, $J = 5.8$ Hz, 1H), 7.82 (t, $J = 2.0$ Hz, 1H), 7.67-7.71 (m, 1H), 7.43-7.47 (m, 1H), 7.28-7.39 (m, 2H), 4.21-4.32 (m, 1H), 3.94-4.15 (m, 2H), 2.64 (s, 3H), 2.04-2.19 (m, 2H), 1.76-1.98 (m, 5H), 1.47-1.66 (m, 3H). ESI-MS m/z : 399 ($\text{M}+\text{H}$) $^+$.

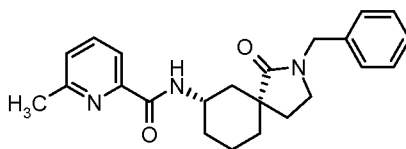
Example 84: ^1H NMR (400 MHz, CDCl_3) δ 8.49 (d, $J = 5.9$ Hz, 1H), 8.16-8.19 (m, 1H), 7.60-7.63 (m, 1H), 7.55-7.59 (m, 1H), 7.29-7.35 (m, 2H), 6.75 (s, 1H), 4.19-4.29 (m, 1H), 4.07-4.15 (m, 1H), 3.98-4.02 (m, 1H), 2.65 (s, 3H), 2.40 (s, 3H), 2.04-2.22 (m, 2H), 1.85-2.04 (m, 3H), 1.71-1.81 (m, 2H), 1.39-1.65 (m, 3H). ESI-MS m/z : 379 ($\text{M}+\text{H}$) $^+$.

Example 85: ^1H NMR (400 MHz, CDCl_3) δ 8.53 (d, $J = 5.8$ Hz, 1H), 8.18 (d, $J = 6.1$ Hz, 1H), 7.62 (s, 1H), 7.35-7.40 (m, 2H), 6.91-6.98 (m, 1H), 4.31 (m, 1H), 4.09-4.18 (m, 1H), 3.94-4.03 (m, 1H), 2.65 (s, 3H), 2.02-2.18 (m, 2H), 1.50-1.93 (m, 8H). ESI-MS m/z : 401 ($\text{M}+\text{H}$) $^+$.

Example 89: ^1H NMR (400 MHz, CDCl_3) δ 8.52 (d, $J = 6.0$ Hz, 1H), 8.17 (d, $J = 6.0$ Hz, 1H), 7.80-7.86 (m, 2H), 7.09-7.15 (m, 3H), 4.22-4.32 (m, 1H), 4.09-4.16 (m, 1H), 3.94-4.02 (m, 1H), 2.65 (s, 3H), 2.05-2.20 (m, 2H), 1.44-2.00 (m, 8H). ESI-MS m/z : 383 ($\text{M}+\text{H}$) $^+$.

Example 149: ^1H NMR (400 MHz, CDCl_3): δ 8.48 (d, $J = 5.9$ Hz, 1H), 8.37 (d, $J = 2.8$ Hz, 1H), 8.16-8.22 (m, 2H), 7.86 (d, $J = 8.6$ Hz, 1H), 7.50-7.55 (m, 1H), 4.04-4.15 (m, 2H), 3.94-4.02 (m, 1H), 2.63 (s, 3H), 2.07-2.24 (m, 3H), 1.86-1.97 (m, 2H), 1.56-1.78 (m, 4H), 1.34-1.42 (m, 1H). ESI-MS m/z : 384 ($\text{M}+\text{H}$) $^+$.

Example 83: *cis*-6-methyl-pyridine-2-carboxylic acid (2-benzyl-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide



Example 83 was prepared from intermediate 18 *via* the process of **Scheme 2**, *supra*, as follows:

To a solution of *cis*-6-Methyl-pyridine-2-carboxylic acid (1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide (0.100 g, 0.348 mmol, intermediate 18) in anhydrous THF (5.0 mL) at 0 °C was added sodium hydride (0.015 g, 0.383 mmol). The reaction mixture was stirred at 0 °C for 30 mins, benzyl bromide (0.041 mL, 0.348 mmol) was then added dropwise. The mixture was stirred at rt overnight, then quenched with water and diluted with ethyl acetate (100 mL). The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (hexane/ethyl acetate: 100/0 to 0/100) to afford 0.115 g (88%) of the title compound, *cis*-6-methyl-pyridine-2-carboxylic acid (2-benzyl-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide, as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 8.11 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.18-7.33 (m, 6H), 4.45 (m, 2H), 4.01-4.11 (m, 1H), 3.14-3.22 (m, 2H), 2.57 (s, 3H), 1.95-2.12 (m, 4H), 1.70-1.89 (m, 3H), 1.67-1.76 (m, 1H), 1.52-1.60 (m, 1H), 1.45-1.50 (m, 1H), 1.32-1.42 (m, 1H). ESI-MS *m/z*: 378 (M+H)⁺.

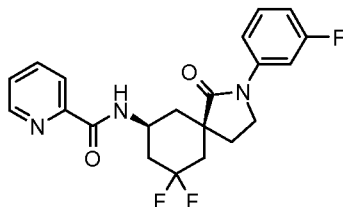
In a similar manner to Example 83, Examples 153-155 in Table 1 was made at 0.11 mmol reaction scale from intermediate 18 and commercially available iodomethane, iodoethane, and 1-iodopropane, respectively.

Example 153: ¹H NMR (400 MHz, CDCl₃): δ 8.08 (d, *J* = 8.6 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 3.99-4.12 (m, 1H), 3.28-3.33 (m, 2H), 2.84 (s, 3H), 2.55 (s, 3H), 1.95-2.14 (m, 3H), 1.26-1.87 (m, 7H). ESI-MS *m/z*: 302 (M+H)⁺.

Example 154: ¹H NMR (400 MHz, CDCl₃): δ 8.08 (d, *J* = 8.6 Hz, 1H), 7.95 (d, *J* = 7.3 Hz, 1H), 7.69 (t, *J* = 8.7 Hz, 1H), 7.24 (d, *J* = 8.9 Hz, 1H), 4.00-4.11 (m, 1H), 3.25-3.37 (m, 4H), 2.55 (s, 3H), 2.04-2.13 (m, 2H), 1.94-2.02 (m, 1H), 1.26-1.87 (m, 7H), 1.09 (t, *J* = 7.3 Hz, 3H). ESI-MS *m/z*: 316 (M+H)⁺.

Example 155: ¹H NMR (400 MHz, CDCl₃): δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 1H), 4.00-4.11 (m, 1H), 3.20-3.33 (m, 4H), 2.55 (s, 3H), 2.04-2.12 (m, 2H), 1.95-2.02 (m, 1H), 1.25-1.87 (m, 9H), 0.87 (t, *J* = 7.4 Hz, 3H). ESI-MS *m/z*: 330 (M+H)⁺.

Example 97: *cis*-Pyridine-2-carboxylic acid [9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide



Example 97 was prepared from intermediate 24 *via* the process of **Scheme 1**, *supra*, as follows:

To a solution of crude *cis*-7-amino-2-(4-methoxy-benzyl)-2-aza-spiro[4.5]decan-1-one, which was prepared from 5,5-difluoro-1-[2-(3-fluoro-phenylamino)-ethyl]-cyclohexane-1,3-dicarboxylic acid dimethyl ester (0.37 mmol), and triethylamine (0.141 mL, 1.01 mmol) in DCM (3.37 mL) was added pyridine-2-carbonyl chloride•HCl (57.3 mg, 0.322 mmol) at 0 °C. The reaction mixture was stirred at rt overnight, and then diluted with DCM (50 mL), washed with saturated aqueous NaHCO₃ and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified on a reversed phase liquid chromatography/mass spectrometry (RP-HPLC/MS) purification system (Gradient: acetonitrile in water, 27-95% in 3.6 minutes with a cycle time of 5 min. A shallow gradient between 38-68% of acetonitrile was used between 0.75-3.3 minutes. Flow rate: 100 mL/min. Mobile phase additive: 48 mM of ammonium formate. Column: Inertsil® C8, 30 x 50 mm, 5 um particle size (GL Sciences)) to give 27 mg of the title compound, pyridine-2-carboxylic acid [9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide. ¹H NMR (400 MHz, CDCl₃): δ 8.57 (d, *J* = 4.8 Hz, 1H), 8.27 (br d, *J* = 7.9 Hz, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 7.94 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.49-7.60 (m, 2H), 7.31-7.38 (m, 2H), 6.85-6.91 (m, 1H), 4.40-4.56 (m, 1H), 3.77-3.91 (m, 2H), 2.55-2.69 (m, 1H), 2.24-2.44 (m, 3H), 2.07-2.16 (m, 2H), 1.93 (ddt, *J* = 3.4, 12.8, 34.1 Hz, 1H), 1.73 (t, *J* = 12.7 Hz, 1H). ESI-MS *m/z*: 404 (M+H)⁺.

Examples 98, 99, 101 and Example 102:

Pyridine-2-carboxylic acid [(5R,7S)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide; Pyridine-2-carboxylic acid [(5S,7R)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide; Pyridine-2-carboxylic acid [(5S,7S)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide; and Pyridine-2-carboxylic acid [(5R,7R)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide, respectively

Examples 101 and 102 were made *via* the process of **Scheme 1** from pyridine-2-carbonyl chloride and intermediate A-3 (R^2 is 3-fluorophenyl) which may be made from *trans*-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]decane-7-carboxylic acid methyl ester (step 7 of intermediate 24) *via* steps i and j in **Scheme 6**, *supra*.

A mixture of Example 97 and *trans*-diastereomers, Examples 101-102, was resolved by HPLC (column: Chiralpak[®] AD, 250x20 mm (Diacel); mobile phase: 15% isopropanol in hexane; flow rate: 14 mL/min; UV at 254 nm) to give two enantiomers of each diastereomer.

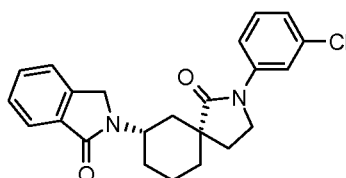
The first peak from chiral HPLC was arbitrarily assigned as Example 99, pyridine-2-carboxylic acid [(5S,7R)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide, the second peak from chiral HPLC was arbitrarily assigned as Example 101, pyridine-2-carboxylic acid [(5S,7S)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide, the third peak from chiral HPLC was arbitrarily assigned as Example 98, pyridine-2-carboxylic acid [(5R,7S)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide, and the fourth peak from chiral HPLC was arbitrarily assigned as Example 102, pyridine-2-carboxylic acid [(5R,7R)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide.

Example 98: ¹H NMR (400 MHz, CDCl₃): δ 8.57 (d, J = 4.8 Hz, 1H), 8.27 (br d, J = 7.9 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 7.94 (dt, J = 7.7, 1.6 Hz, 1H), 7.49-7.60 (m, 2H), 7.31-7.38 (m, 2H), 6.85-6.91 (m, 1H), 4.40-4.56 (m, 1H), 3.77-3.91 (m, 2H), 2.55-2.69 (m, 1H), 2.24-2.44 (m, 3H), 2.07-2.16 (m, 2H), 1.93 (ddt, J = 3.4, 12.8, 34.1 Hz, 1H), 1.73 (t, J = 12.7 Hz, 1H). ESI-MS m/z : 404 (M+H)⁺.

Example 99: ¹H NMR (400 MHz, CDCl₃): δ 8.57 (d, J = 4.8 Hz, 1H), 8.27 (br d, J = 7.9 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 7.94 (dt, J = 7.7, 1.6 Hz, 1H), 7.49-7.60 (m, 2H), 7.31-7.38 (m, 2H), 6.85-6.91 (m, 1H), 4.40-4.56 (m, 1H), 3.77-3.91 (m, 2H), 2.55-2.69 (m, 1H), 2.24-

2.44 (m, 3H), 2.07-2.16 (m, 2H), 1.93 (ddt, $J = 3.4, 12.8, 34.1$ Hz, 1H), 1.73 (t, $J = 12.7$ Hz, 1H). ESI-MS m/z : 404 ($M+H$)⁺.

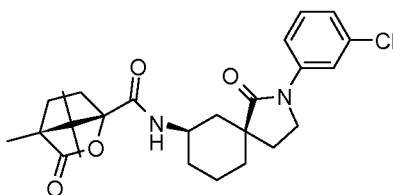
Example 100: *cis*-2-[2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-2,3-dihydro-isoindol-1-one



Example 100 was prepared from intermediate 1 via the process of **Scheme 21**, *supra*, as follows:

A mixture of 7-Amino-2-(3-chloro-phenyl)2-aza-spiro[4.5]decan-1-one (0.080 g, 0.287 mmol, intermediate 1), methyl 2-formylbenzoate (0.047 g, 0.287 mmol), sodium triacetoxyborohydride (0.061 g, 0.287 mmol) and one drop of acetic acid in 1,2-dichloroethane (2.0 mL) was stirred at rt overnight. The reaction mixture was quenched with ice and diluted with ethyl acetate (20.0 mL). The organic layer was washed with water and brine, dried with Na₂SO₄, and concentrated under reduced pressure. The residue was purified by preparative TLC (ethyl acetate) to afford 0.013 g (12%) of the title compound, *cis*-2-[2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-2,3-dihydro-isoindol-1-one as well as 0.032 g (28%) of the *trans* diastereomer. The less polar spot on the TLC plate was assigned as *trans*, and the polar spot was assigned as *cis*, Example 100. ¹H NMR (400 MHz, CDCl₃): δ 7.82-7.85 (m, 1H), 7.74 (t, $J = 2.2$ Hz, 1H), 7.44-7.56 (m, 4H), 7.28 (t, $J = 8.2$ Hz, 1H), 7.12 (ddd, $J = 8.1, 2.1, 1.1$ Hz), 4.41-4.49 (m, 1H), 4.38 (s, 2H), 3.75-3.84 (m, 2H), 2.18-2.34 (m, 2H), 1.91-2.04 (m, 3H), 1.55-1.75 (m, 5H). ESI-MS m/z : 395 ($M+H$)⁺.

(1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid [(5*R*,7*R*)-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide



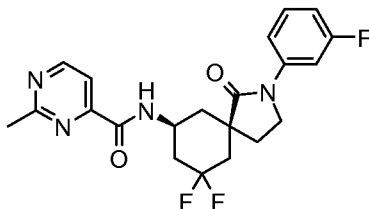
To determine the absolute stereochemistry of the compounds of the invention, (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid [(5*R*,7*R*)-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide was made from intermediate 3 *via* the process of **Scheme 1**, *supra*, as follows:

5 (5*R*, 7*R*)-7-amino-2-(3-chloro-phenyl)-2-aza-apiro[4.5]decan-1-one (0.130 g, 0.467 mmol, intermediate 3) was dissolved in methylene chloride (10.0 mL). Triethylamine (0.0708 g, 0.699 mmol) was added, followed by the addition of (1*S*)-(-)-camphanic acid chloride (0.101 g, 0.466 mmol). The mixture was stirred at rt for 1 hr and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate) to afford 0.20
10 g (93%) of the title compound as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.72 (t, *J* = 2.0 Hz, 1H), 7.57 (ddd, *J* = 8.3, 2.4, 1.0 Hz, 1H), 7.29 (t, *J* = 8.1 Hz, 1H), 7.12 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 6.46 (d, *J* = 8.1 Hz, 1H), 3.90-4.00 (m, 1H), 3.73-3.84 (m, 2H), 2.48-2.56 (m, 1H), 2.08-2.15 (m, 2H), 1.86-1.98 (m, 5H), 1.63-1.72 (m, 2H), 1.50-1.61 (m, 4H), 1.27-1.35 (m, 1H), 1.11 (s, 3H), 1.08 (s, 3H), 0.87 (s, 3H). ESI-MS *m/z*: 459 (M+H)⁺.

15 A single crystal of (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid [(5*R*,7*R*)-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide was grown in methanol and its absolute structure was determined and confirmed by X-ray.

In a similar manner to (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid [(5*R*,7*R*)-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide,
20 (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid [(5*R*,7*R*)-2-(3, 5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide was made at 0.54 mmol reaction scale from intermediate 36 and (1*S*)-(-)-camphanic acid. A single crystal of (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid [(5*R*,7*R*)-2-(3, 5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide was grown in methanol and its absolute
25 structure was determined and confirmed by X-ray.

Example 129: *cis*-2-Methyl-pyrimidine-4-carboxylic acid [9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide



Example 129 was prepared from intermediate 26 *via* the process of **Scheme 2**, *supra*, as follows:

cis-2-Methyl-pyrimidine-4-carboxylic acid (9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide (300 mg, 0.6 mmol), 3-fluoroiodobenzene (287 mg, 1.29 mmol), potassium carbonate (179 mg, 1.29 mmol), copper(I) iodide (190 mg, 0.647 mmol), and (1*R*,2*R*)-*N,N'*-dimethyl-cyclohexane-1,2-diamine (92 mg, 0.65 mmol) in 1,4-dioxane (10 mL) were placed in a sealed-tube. The reaction mixture was heated at 100 °C overnight. The crude mixture was cooled to rt and diluted with DCM (50 mL). The organic layer was washed with ammonia water/water (1:1, 2x20 mL) and brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by CombiFlash[®] system (25 g silica gel cartridge; gradient: 0 to 50% ethyl acetate in DCM) to afford 135 mg (35%) of the title compound, *cis*-2-Methyl-pyrimidine-4-carboxylic acid [9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide. ¹H NMR (400 MHz, CDCl₃) δ 8.81 (d, *J* = 5.0, 1H), 7.94 (d, *J* = 8.2, 1H), 7.83 (d, *J* = 5.0, 1H), 7.52-7.46 (m, 1H), 7.29-7.24 (m, 2H), 6.84-6.78 (m, 1H), 4.46-4.32 (m, 1H), 3.83-3.71 (m, 2H), 2.62-2.50 (m, 1H), 2.35-1.74 (m, 6H), 1.69 (t, *J* = 12.8, 1H). ESI-MS *m/z*: 404 (M+H)⁺.

Mixture of two enantiomers of Example 129 was resolved by HPLC (column: Chiralpak[®] AD, 250x20 mm (Diacel); mobile phase: 15% isopropanol in hexane; flow rate: 14 mL/min; UV at 254 nm) to give two enantiomers. The first peak from chiral HPLC was arbitrarily assigned as Example 103, 2-methyl-pyrimidine-4-carboxylic acid [(5*S*,7*R*)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide, and the second peak from chiral HPLC was arbitrarily assigned as Example 104, 2-methyl-pyrimidine-4-carboxylic acid [(5*R*,7*S*)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide.

In an analogous manner to Example 129, Example 105 in Table 1 (below) was made at 0.216 mmol reaction scale from intermediate 26 and commercially available 3,5-difluoriodobenzene.

In an analogous manner to Example 129, Examples 106 and 110-112 Table 1 (below) were made at 0.097-0.233 mmol reaction scales from intermediate 28 and commercially available 4-fluoriodobenzene, 3,5-difluoriodobenzene, 2-chloro-5-fluoropyridine, 4-chloro-2-methylpyrimidine, respectively.

In an analogous manner to Example 129, Examples 107-109 in Table 1 (below) were made at 0.093-0.233 mmol reaction scales from intermediate 27 and commercially 3-fluoriodobenzene, 4-chloro-2-methylpyrimidine, 2-chloro-5-fluoropyridine, respectively.

In an analogous manner to Example 129, Example 128 in Table 1 (below) was made at 0.214 mmol reaction scale from intermediate 29 and commercially available 4-chloro-2-methylpyrimidine.

In a similar manner to Examples 103 and 104, Examples 110, 109, and 128 in Table 1 (below) were separated into their corresponding enantiomers: Example 113 (1st peak) and 114 (2nd peak), 120 (1st peak) and 121 (2nd peak), and 127 (1st peak) by chiral HPLC, respectively.

Example 103: ¹H NMR (400 MHz, CDCl₃) δ 8.81 (d, J = 5.0, 1H), 7.94 (d, J = 8.2, 1H), 7.83 (d, J = 5.0, 1H), 7.52-7.46 (m, 1H), 7.29-7.24 (m, 2H), 6.84-6.78 (m, 1H), 4.46-4.32 (m, 1H), 3.83-3.71 (m, 2H), 2.62-2.50 (m, 1H), 2.35-1.74 (m, 6H), 1.69 (t, J = 12.8, 1H). ESI-MS m/z : 404 (M+H)⁺.

Example 104: ¹H NMR (400 MHz, CDCl₃) δ 8.81 (d, J = 5.0, 1H), 7.94 (d, J = 8.2, 1H), 7.83 (d, J = 5.0, 1H), 7.52-7.46 (m, 1H), 7.29-7.24 (m, 2H), 6.84-6.78 (m, 1H), 4.46-4.32 (m, 1H), 3.83-3.71 (m, 2H), 2.62-2.50 (m, 1H), 2.35-1.74 (m, 6H), 1.69 (t, J = 12.8, 1H). ESI-MS m/z : 404 (M+H)⁺.

Example 105: ^1H NMR (400 MHz, CDCl_3) δ 8.82 (d, $J = 5.0$, 1H), 8.57 (d, $J = 5.0$, 1H), 7.84 (d, $J = 5.0$, 1H), 7.23-7.15 (m, 2H), 6.59-6.51 (m, 1H), 4.77-4.70 (m, 1H), 3.71-3.57 (m, 2H), 2.74 (s, 3H), 2.40-1.97 (m, 8H). ESI-MS m/z : 437 ($\text{M}+\text{H}$) $^+$.

Example 106: ^1H NMR (400 MHz, CDCl_3) δ 8.58-8.55 (m, 1H), 8.22-8.18 (m, 1H), 8.10 (d, $J = 8.4$ Hz, 1H), 7.89 (dt, $J = 7.7$, 1.7 Hz, 1H), 7.63-7.57 (m, 2H), 7.51-7.46 (m, 1H), 7.13-7.06 (m, 2H), 4.57-4.43 (m, 1H), 3.92-3.75 (m, 2H), 2.70-1.81 (m, 7H), 1.73 (t, $J = 12.8$, 1H). ESI-MS m/z : 404 ($\text{M}+\text{H}$) $^+$.

Example 107: ^1H NMR (400 MHz, CDCl_3) δ 8.14 (d, $J = 8.4$ Hz, 1H), 8.00 (d, $J = 7.6$ Hz, 1H), 7.75 (t, $J = 7.7$ Hz, 1H), 7.61-7.56 (m, 1H), 7.37-7.33 (m, 2H), 7.31 (d, $J = 7.6$ Hz, 1H), 6.92-6.86 (m, 1H), 4.55-4.43 (m, 1H), 3.93-3.78 (m, 2H), 2.70-2.60 (m, 1H), 2.58 (s, 3H), 2.45-1.84 (m, 6H), 1.75 (t, $J = 12.7$ Hz, 1H). ESI-MS m/z : 418 ($\text{M}+\text{H}$) $^+$.

Example 108: ^1H NMR (400 MHz, CDCl_3) δ 8.51 (d, $J = 5.8$ Hz, 1H), 8.14 (d, $J = 5.9$ Hz, 1H), 8.11 (d, $J = 8.6$ Hz, 1H), 7.73 (t, $J = 7.7$ Hz, 1H), 7.29 (d, $J = 7.7$ Hz, 1H), 4.54-4.42 (m, 1H), 4.19-3.95 (m, 2H), 2.65 (s, 3H), 2.63-2.59 (m, 1H), 2.56 (s, 3H), 2.40-1.82 (m, 6H), 1.72 (t, $J = 12.7$ Hz, 1H). ESI-MS m/z : 416 ($\text{M}+\text{H}$) $^+$.

Example 109: ^1H NMR (400 MHz, CDCl_3) δ 8.41 (dd, $J = 9.4$, 4.0 Hz, 1H), 8.23 (d, $J = 3.0$ Hz, 1H), 8.13 (d, $J = 8.6$ Hz, 1H), 8.00 (d, $J = 7.7$ Hz, 1H), 7.75 (t, $J = 7.7$ Hz, 1H), 7.50-7.44 (m, 1H), 7.31 (d, $J = 7.5$ Hz, 1H), 4.56-4.45 (m, 1H), 4.18-3.98 (m, 2H), 2.71-2.61 (m, 1H), 2.58 (s, 3H), 2.43-1.83 (m, 6H), 1.76 (t, $J = 12.8$ Hz, 1H). ESI-MS m/z : 419 ($\text{M}+\text{H}$) $^+$.

Example 110: ^1H NMR (400 MHz, CDCl_3) δ 8.56 (d, $J = 3.9$ Hz, 1H), 8.19 (d, $J = 7.6$ Hz, 1H), 8.08 (d, $J = 7.2$ Hz, 1H), 7.89 (t, $J = 7.7$ Hz, 1H), 7.50-7.45 (m, 1H), 7.33-7.28 (m, 2H), 6.64 (tt, $J = 8.8$, 2.2 Hz, 1H), 4.56-4.43 (m, 1H), 3.89-3.76 (m, 2H), 2.69-2.58 (m, 1H), 2.46-1.82 (m, 6H), 1.71 (t, $J = 12.7$ Hz, 1H). ESI-MS m/z : 422 ($\text{M}+\text{H}$) $^+$.

Example 111: ^1H NMR (400 MHz, CDCl_3) δ 8.53 (d, $J = 4.6$ Hz, 1H), 8.41 (dd, $J = 9.2$, 4.0 Hz, 1H), 8.23 (d, $J = 3.0$ Hz, 1H), 8.20 (d, $J = 7.9$ Hz, 1H), 8.07 (d, $J = 8.4$ Hz, 1H), 7.88 (dt, $J = 7.8$, 1.6 Hz, 1H), 7.50-7.44 (m, 2H), 4.56-4.45 (m, 1H), 4.17-3.98 (m, 2H), 2.71-2.60 (m, 1H), 2.42-1.81 (m, 6H), 1.74 (t, $J = 12.7$ Hz, 1H). ESI-MS m/z : 405 ($\text{M}+\text{H}$) $^+$.

Example 112: ^1H NMR (400 MHz, CDCl_3) δ 8.58-8.51 (m, 2H), 8.22-8.16 (m, 2H), 8.08 (d, $J = 8.3$ Hz, 1H), 7.92-7.86 (m, 1H), 7.50-7.45 (m, 1H), 4.56-4.43 (m, 1H), 4.22-3.97 (m, 2H), 2.69 (s, 3H), 2.67-2.60 (m, 1H), 2.43-1.82 (m, 6H), 1.71 (t, $J = 12.6$ Hz, 1H). ESI-MS m/z : 402 ($\text{M}+\text{H}$) $^+$.

5 Example 113: ^1H NMR (400 MHz, CDCl_3) δ 8.56 (d, $J = 3.9$ Hz, 1H), 8.19 (d, $J = 7.6$ Hz, 1H), 8.08 (d, $J = 7.2$ Hz, 1H), 7.89 (t, $J = 7.7$ Hz, 1H), 7.50-7.45 (m, 1H), 7.33-7.28 (m, 2H), 6.64 (tt, $J = 8.8, 2.2$ Hz, 1H), 4.56-4.43 (m, 1H), 3.89-3.76 (m, 2H), 2.69-2.58 (m, 1H), 2.46-1.82 (m, 6H), 1.71 (t, $J = 12.7$ Hz, 1H). ESI-MS m/z : 422 ($\text{M}+\text{H}$) $^+$.

10 Example 114: ^1H NMR (400 MHz, CDCl_3) δ 8.56 (d, $J = 3.9$ Hz, 1H), 8.19 (d, $J = 7.6$ Hz, 1H), 8.08 (d, $J = 7.2$ Hz, 1H), 7.89 (t, $J = 7.7$ Hz, 1H), 7.50-7.45 (m, 1H), 7.33-7.28 (m, 2H), 6.64 (tt, $J = 8.8, 2.2$ Hz, 1H), 4.56-4.43 (m, 1H), 3.89-3.76 (m, 2H), 2.69-2.58 (m, 1H), 2.46-1.82 (m, 6H), 1.71 (t, $J = 12.7$ Hz, 1H). ESI-MS m/z : 422 ($\text{M}+\text{H}$) $^+$.

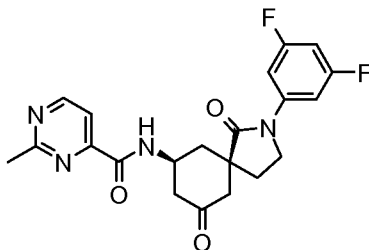
15 Example 120: ^1H NMR (400 MHz, CDCl_3) δ 8.53 (d, $J = 5.9$ Hz, 1H), 8.15 (d, $J = 5.8$ Hz, 1H), 7.54-7.39 (m, 3H), 7.26-7.20 (m, 1H), 6.26 (d, $J = 7.9$ Hz, 1H), 4.58-4.47 (m, 1H), 4.19-4.01 (m, 2H), 2.67 (s, 3H), 2.65-2.56 (m, 1H), 2.40-2.07 (m, 5H), 1.96-1.78 (m, 1H), 1.67 9t, $J = 12.3$, 1H). ESI-MS m/z : 419 ($\text{M}+\text{H}$) $^+$.

20 Example 121: ^1H NMR (400 MHz, CDCl_3) δ 8.53 (d, $J = 5.9$ Hz, 1H), 8.15 (d, $J = 5.8$ Hz, 1H), 7.54-7.39 (m, 3H), 7.26-7.20 (m, 1H), 6.26 (d, $J = 7.9$ Hz, 1H), 4.58-4.47 (m, 1H), 4.19-4.01 (m, 2H), 2.67 (s, 3H), 2.65-2.56 (m, 1H), 2.40-2.07 (m, 5H), 1.96-1.78 (m, 1H), 1.67 9t, $J = 12.3$, 1H). ESI-MS m/z : 419 ($\text{M}+\text{H}$) $^+$.

Example 127: ^1H NMR (400 MHz, CDCl_3) δ 8.41 (dd, $J = 9.4, 4.0$ Hz, 1H), 8.23 (d, $J = 3.0$ Hz, 1H), 8.13 (d, $J = 8.6$ Hz, 1H), 8.00 (d, $J = 7.7$ Hz, 1H), 7.75 (t, $J = 7.7$ Hz, 1H), 7.50-7.44 (m, 1H), 7.31 (d, $J = 7.5$ Hz, 1H), 4.56-4.45 (m, 1H), 4.18-3.98 (m, 2H), 2.71-2.61 (m, 1H), 2.58 (s, 3H), 2.43-1.83 (m, 6H), 1.76 (t, $J = 12.8$ Hz, 1H). ESI-MS m/z : 419 ($\text{M}+\text{H}$) $^+$.

25 Example 128: ^1H NMR (400 MHz, CDCl_3) δ 8.53 (d, $J = 5.9$ Hz, 1H), 8.15 (d, $J = 5.8$ Hz, 1H), 7.54-7.39 (m, 3H), 7.26-7.20 (m, 1H), 6.26 (d, $J = 7.9$ Hz, 1H), 4.58-4.47 (m, 1H), 4.19-4.01 (m, 2H), 2.67 (s, 3H), 2.65-2.56 (m, 1H), 2.40-2.07 (m, 5H), 1.96-1.78 (m, 1H), 1.67 9t, $J = 12.3$, 1H). ESI-MS m/z : 419 ($\text{M}+\text{H}$) $^+$.

Example 115: *cis*-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-1,9-dioxo-2-aza-spiro[4.5]dec-7-yl]-amide



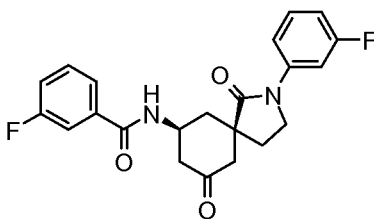
Example 115 was prepared from intermediate 30 *via* the process of **Scheme 23**, *supra*, as follows:

To a solution of *cis*-13-amino-9-(3,5-difluoro-phenyl)-1,4-dioxo-9-aza-dispiro[4.1.4.3]tetradecan-8-one (300 mg, 0.887 mmol) and 2-methylpyrimidine-4-carboxylic acid (128 mg, 1.05 mmol) in DCM (6 mL) was added PYBOP (508 mg, 0.975 mmol) and triethylamine (0.27 mL, 1.95 mmol). The reaction mixture was stirred at room temperature overnight and concentrated. The residue was chromatographed on silica gel (0 to 70% EtOAc in hexanes) to give an intermediate (300 mg), which was dissolved in THF (5 mL), followed by the addition of 3.0 M HCl in water (5 mL). The reaction mixture was stirred at room temperature overnight and concentrated. The residue was suspended in DCM (20 mL) and quenched with saturated aqueous NaHCO₃. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers were concentrated. The residue was chromatographed on silica gel (0 to 80% EtOAc in hexanes) to give 190 mg (49% over 2 steps) of the title compound, *cis*-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-1,9-dioxo-2-aza-spiro[4.5]dec-7-yl]-amide. ¹H NMR (400 MHz, CDCl₃) δ 8.90 (d, *J* = 5.0 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 5.0 Hz, 1H), 7.33-7.29 (m, 2H), 6.65 (tt, *J* = 8.7, 2.2 Hz, 1H), 4.62-4.50 (m, 1H), 3.88-3.80 (m, 2H), 2.96-2.76 (m, 5H), 2.59 (dd, *J* = 13.6, 11.4 Hz, 1H), 2.44-2.09 (m, 5H). ESI-MS *m/z*: 415 (M+H)⁺.

In an analogous manner to Example 115, Example 124 in Table 1 (below) was made at 1.15 mmol reaction scale from intermediate 31 and commercially available 6-methylpicolinic acid.

Example 124: ^1H NMR (400 MHz, CDCl_3) δ 8.32 (d, $J = 8.6$ Hz, 1H), 8.00 (d, $J = 7.7$ Hz, 1H), 7.75 (t, $J = 7.7$ Hz, 1H), 7.62-7.57 (m, 1H), 7.37-7.30 (m, 3H), 6.93-6.87 (m, 1H), 4.61-4.49 (m, 1H), 3.92-3.81 (m, 2H), 2.96-2.90 (m, 1H), 2.81 (d, $J = 14.1$ Hz, 1H), 2.61 (s, 3H), 2.56 (d, $J = 12.9$ Hz, 1H), 2.43-2.07 (m, 5H). ESI-MS m/z : 396 ($\text{M}+\text{H}$) $^+$.

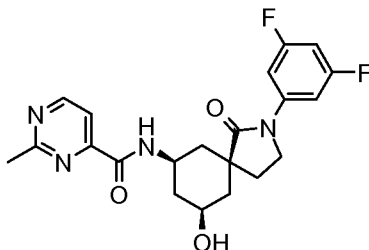
5 **Example 123: *cis*-3-Fluoro-N-[2-(3-fluoro-phenyl)-1,9-dioxo-2-aza-spiro[4.5]dec-7-yl]-benzamide**



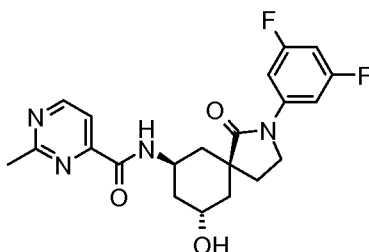
Example 123 was prepared from intermediate 31 *via* the process of **Scheme 23**, *supra*, as follows:

10 To a solution of *cis*-13-amino-9-(3-fluoro-phenyl)-1,4-dioxo-9-aza-dispiro[4.1.4.3]tetradecan-8-one (370 mg, 1.15 mmol) and triethylamine (0.40 mL, 2.9 mmol) in DCM (10 mL) was added 3-fluorobenzoyl chloride (220 mg, 1.38 mmol) at -78°C . The reaction mixture was stirred at room temperature overnight and diluted with DCM (50 mL). The organic layer was washed with saturated NaHCO_3 and brine, dried over MgSO_4 ,
15 filtered, and concentrated. The residue was chromatographed on silica gel (gradient: 0 to 70% EtOAc in hexanes) to give an intermediate (300 mg), which was dissolved in THF (5 mL), followed by the addition of 3.0 M HCl in water (5 mL). The reaction mixture was stirred at room temperature overnight and concentrated. The residue was suspended in DCM (20 mL) and quenched with saturated aqueous NaHCO_3 . The aqueous layer was extracted
20 with DCM (2 x 20 mL). The combined organic layers were concentrated. The residue was chromatographed on silica gel (0 to 80% EtOAc in hexanes) to give 162 mg (21% over 2 steps) of the title compound, *cis*-3-Fluoro-N-[2-(3-fluoro-phenyl)-1,9-dioxo-2-aza-spiro[4.5]dec-7-yl]-benzamide. ^1H NMR (400 MHz, CDCl_3) δ 7.61-7.51 (m, 3H), 7.45 (d, $J = 8.4$ Hz, 1H), 7.43-7.33 (m, 3H), 7.24-7.18 (m, 1H), 6.95-6.89 (m, 1H), 4.85-4.74 (m, 1H),
25 3.95-3.83 (m, 2H), 2.86 (dd, $J = 14.6, 5.6$ Hz, 1H), 2.80 (d, $J = 14.3$ Hz, 1H), 2.60 (dd, $J = 14.6, 7.6$ Hz, 1H), 2.46 (d, $J = 14.3$ Hz, 1H), 2.33-2.11 (m, 4H). ESI-MS m/z : 399 ($\text{M}+\text{H}$) $^+$.

Example 116: *cis*- 2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluorophenyl)-9-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide



Example 117: *trans*- 2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluorophenyl)-9-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide



Route 1: Examples 116 and 117 were prepared from Example 115 *via* the process of **Scheme 23**, *supra*, as follows:

The reaction mixture of *cis*-2-methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-1,9-dioxo-2-aza-spiro[4.5]dec-7-yl]-amide (40 mg, 0.0965 mmol) and sodium borohydride (7.3 mg, 0.193 mmol) in THF (3 mL) was stirred at room temperature for 4 hours. The reaction mixture was quenched with water and extracted with DCM (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated. The residue was purified by HPLC to afford two diastereomers. The first peak from the HPLC (purified on a reversed phase liquid chromatography/mass spectrometry (RP-HPLC/MS) purification system. Gradient: acetonitrile in water, 18-95% in 3.6minutes with a cycle time of 5 min. A shallow gradient between 23-46% of acetonitrile was used between 0.6-3.0 min to separate close-eluting impurities. Flow rate: 100 mL/min. Mobile phase additive: 48 mM of ammonium formate. Column: Inertsil C8, 30 x 50 mm, 5 um particle size) was assigned as Example 116, *cis*- 2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluorophenyl)-9-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide (4 mg), and the second peak from the HPLC was

assigned as Example 117, *trans*- 2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluorophenyl)-9-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide (6 mg).

Example 116: ^1H NMR (400 MHz, CDCl_3) δ 8.89 (d, $J = 5.0$ Hz, 1H), 8.08 (d, $J = 8.6$ Hz, 1H), 7.90 (d, $J = 5.0$ Hz, 1H), 7.33-7.29 (m, 2H), 6.67-6.60 (m, 1H), 4.30-4.17 (m, 1H), 4.01-4.17 (m, 1H), 3.90-3.74 (m, 2H), 2.80 (s, 3H), 2.51-2.42 (m, 1H), 2.29-2.11 (m, 2H), 2.01-1.44 (m, 5H). ESI-MS m/z : 417 ($\text{M}+\text{H}$) $^+$.

Example 117: ^1H NMR (400 MHz, CDCl_3) δ 8.88 (d, $J = 5.0$ Hz, 1H), 8.53 (d, $J = 2.2$ Hz, 1H), 7.90 (d, $J = 4.9$ Hz, 1H), 7.39-7.30 (m, 2H), 6.67-6.58 (m, 1H), 4.72-4.59 (m, 1H), 4.57-4.44 (m, 1H), 3.88-3.74 (m, 2H), 2.82 (s, 3H), 2.53-2.35 (m, 2H), 2.16-1.72 (m, 6H). ESI-MS m/z : 417 ($\text{M}+\text{H}$) $^+$.

Route 2: Example 117 was also made, as follows:

To a solution of *cis*-2-methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-1,9-dioxo-2-aza-spiro[4.5]dec-7-yl]-amide (20 mg, 0.048 mmol) THF (3 mL) was added 1.0 M of L-Selectride in THF (0.1 mL, 0.1 mmol) at -78°C . The reaction mixture was stirred at -78°C for 1h and quenched with ice. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried over MgSO_4 , filtered, and concentrated. The residue was purified by HPLC to give 5 mg (25%) of the title compound.

In an analogous manner (route 2) to Example 117, Example 125 in Table 1 (below) was made at 0.176 mmol reaction scale from Example 123.

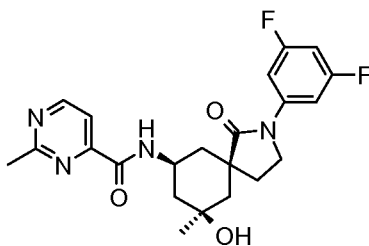
Example 125: ^1H NMR (400 MHz, CDCl_3) δ 8.64 (br s, 1H), 7.62-7.46 (m, 3H), 7.39-7.25 (m, 3H), 7.15-7.08 (m, 1H), 6.87-6.80 (m, 1H), 4.69-4.61 (m, 1H), 4.30-4.21 (m, 1H), 3.89-3.70 (m, 2H), 2.26-2.01 (m, 4H), 1.81 (dq, $J=14.4, 4.6$ Hz, 2H), 1.64 (dq, $J=9.7, 4.0$ Hz, 1H), 1.45 (dq, $J=13.4, 9.4$ Hz, 1H). ESI-MS m/z : 401 ($\text{M}+\text{H}$) $^+$.

In an analogous manner (route 2) to Example 117, Example 126 in Table 1 (below) was made at 0.114 mmol reaction scale from Example 124.

Example 126: ^1H NMR (400 MHz, CDCl_3) δ 8.40 (d, $J=8.3$ Hz, 1H), 8.00 (d, $J=7.5$ Hz, 1H), 7.73 (t, $J=7.7$ Hz, 1H), 7.67-7.61 (m, 1H), 7.39-7.29 (m, 2H), 6.90-6.84 (m, 1H), 4.72-

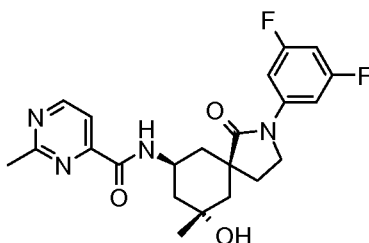
4.60 (m, 1H), 4.53-4.48 (m, 1H), 3.88-3.77 (m, 2H), 2.60 (s, 3H), 2.53-2.40 (m, 2H), 2.21-2.00 (m, 3H), 1.83-1.73 (m, 3H). ESI-MS m/z : 398 (M+H)⁺.

Example 119: *cis*- 2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9-hydroxy-9-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide



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Example 118: *trans*- 2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9-hydroxy-9-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide



Examples 119 and 118 were prepared from Example 115 *via* the process of **Scheme 23**, *supra*, as follows:

10

To a solution of *cis*-2-methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-1,9-dioxo-2-aza-spiro[4.5]dec-7-yl]-amide (30 mg, 0.0724 mmol) in THF (3 mL) was added 3.0M of methylmagnesium bromide in ether (0.05 mL) at -78°C. The reaction mixture was stirred at -78°C for 1 h and quenched with water. The aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated. The residue was purified by RP-HPLC/MS purification system (gradient: acetonitrile in water, 24-95% in 3.6 minutes with a cycle time of 5 min. A shallow gradient between 26-56% of acetonitrile was used between 0.75-3.4 min to separate close-eluting impurities. Flow rate: 100 mL/min. Mobile phase additive: 48 mM of ammonium formate. Column: Inertsil® C8, 30 x 50 mm, 5 μm particle size) to afford two diastereomers. The first peak from the HPLC was assigned as Example 119, *cis*-2-methyl-pyrimidine-4-carboxylic

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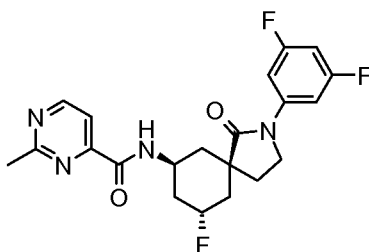
20

acid [2-(3,5-difluoro-phenyl)-9-hydroxy-9-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide (2 mg), and the second peak from the HPLC was assigned as Example 118, *trans*-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9-hydroxy-9-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide (3 mg).

Example 118: ^1H NMR (400 MHz, CDCl_3) δ 8.88 (d, $J = 4.6$ Hz, 1H), 7.95 (d, $J = 8.8$ Hz, 1H), 7.91 (d, $J = 4.8$ Hz, 1H), 7.35-7.29 (m, 2H), 6.65-6.58 (m, 1H), 4.64-4.52 (m, 1H), 3.84-3.71 (m, 2H), 2.78 (s, 3H), 2.60-2.41 (m, 2H), 2.18-2.00 (m, 2H), 1.92 (d, $J = 14.2$, 1H), 1.74-1.54 (m, 3H), 1.38 (s, 3H). ESI-MS m/z : 431 ($\text{M}+\text{H}$) $^+$.

Example 119: ^1H NMR (400 MHz, CDCl_3) δ 8.88 (d, $J = 4.6$ Hz, 1H), 7.95 (d, $J = 8.8$ Hz, 1H), 7.91 (d, $J = 4.8$ Hz, 1H), 7.35-7.29 (m, 2H), 6.65-6.58 (m, 1H), 4.64-4.52 (m, 1H), 3.84-3.71 (m, 2H), 2.78 (s, 3H), 2.60-2.41 (m, 2H), 2.18-2.00 (m, 2H), 1.92 (d, $J = 14.2$, 1H), 1.74-1.54 (m, 3H), 1.38 (s, 3H). ESI-MS m/z : 431 ($\text{M}+\text{H}$) $^+$.

Example 122: *trans*-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9-fluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide

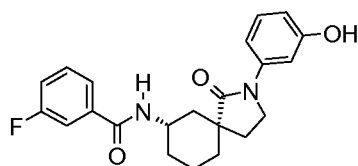


Example 122 was prepared from Example 117 via the process of **Scheme 23**, *supra*, as follows:

To a solution of *trans*-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluorophenyl)-9-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide (crude, <0.121 mmol) in DCM (5 mL) was added DAST (20.3 μL , 0.154 mmol) at 0 $^\circ\text{C}$. The reaction mixture was stirred at room temperature overnight and quenched with saturated aqueous NaHCO_3 . The aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was chromatographed on silica gel (0 to 70% EtOAc in hexanes) to give 2 mg of the title compound, *trans*-2-methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9-fluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide. ^1H

NMR (400 MHz, CDCl₃) δ 8.79 (d, J = 5.0 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.82 (t, J = 5.0 Hz, 1H), 7.26-7.21 (m, 1H), 6.54 (tt, J = 8.8, 2.2 Hz, 1H), 5.22-5.05 (m, 1H), 4.55-4.43 (m, 1H), 3.79-3.66 (m, 2H), 2.71 (s, 3H), 2.45-2.25 (m, 3H), 2.09-1.92 (m, 3H), 1.74-1.54 (m, 2H). ESI-MS m/z : 419 (M+H)⁺.

5 **Example 131: *cis*-3-Fluoro-*N*-[2-(3-hydroxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide**



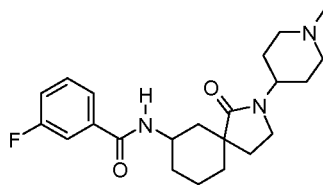
Example 131 was made from Example 130 *via* the process of **Scheme 22** (step c), *supra*, as follows:

10 Into a vial containing *cis* 3-fluoro-*N*-[2-(3-methoxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide (150 mg, 0.38 mmol) was added 20 mL of dichloromethane. The solution was cooled at -70 °C. 2 mL of 2 M boron tribromide in dichloromethane was added, and the mixture was slowly warmed up to rt and stirred at rt for 40 hrs.

15 The reaction was quenched with cold water and the organic layer was separated. The precipitate was extracted with DCM and ethyl acetate. The organic extracts were combined, dried over sodium sulfate and purified on a reversed phase liquid chromatography/mass spectrometry (RP-HPLC/MS) purification system (Gradient: acetonitrile in water, 25-95% in 3.6 minutes with a cycle time of 5 min. A shallow gradient between 27-56% of acetonitrile was used between 0.75-3.4 min to separate close-eluting impurities. Flow rate: 100 mL/min.

20 Mobile phase additive: 48 mM of ammonium acetate. Column: Inertsil® C18, 30 x 50 mm, 5 μ m particle size (GL Sciences)) to afford 50 mg (26%) of the title compound. ¹H NMR (400 MHz, CDCl₃): δ 7.60–7.52 (m, 3H), 7.43–7.36 (m, 1H), 7.26–7.14 (m, 2H), 6.99–6.95 (m, 1H), 6.70–6.66 (m, 1H), 6.58 (s, br, 1H), 4.31–4.20 (m, 1H), 3.84–3.75 (m, 2H), 2.24–1.44 (m, 10H). ESI-MS m/z : 383.0 (M+H)⁺.

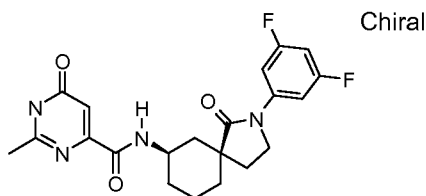
Example 157: 3-Fluoro-*N*-[2-(1-methyl-piperidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide



Example 157 was made from intermediate 35 *via* the process of **Scheme 24**, *supra*, as follows:

4-[7-(3-Fluoro-benzoylamino)-1-oxo-2-aza-spiro[4.5]dec-2-yl]-piperidine-1-carboxylic acid tert-butyl ester (0.135 g, 0.285 mmol) was dissolved in CH₂Cl₂ (2.0 mL). 4 M of Hydrogen chloride in 1,4-dioxane (1.0 mL) was added, the mixture was stirred at rt overnight. The mixture was concentrated under reduced pressure to afford a mixture of two diastereomers (*cis/trans*: 3/2; under LC-MS method C, the first peak with RT of 0.77 min was assigned as *cis*, and the second peak with RT of 0.81 min was assigned as *trans*). ESI-MS *m/z*: 374 (M+H)⁺. It was used in the next step without further purification. 3-Fluoro-*N*-(1-oxo-2-piperidin-4-yl-2-aza-spiro[4.5]dec-7-yl)-benzamide (0.050 g, 0.13 mmol) was dissolved in CH₂Cl₂ (2.3 mL), formaldehyde (0.011 g, 0.13 mmol, 37% aqueous solution) was added, followed by the addition of sodium triacetoxyborohydride (0.043 g, 0.20 mmol). The mixture was stirred at rt overnight, and then quenched with ice. The mixture was diluted with CH₂Cl₂ (20 mL). The organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The resulting residue was purified on RP-HPLC/MS (Gradient: acetonitrile in water, 5-95% in 2.5 minutes with a cycle time of 5 min. A shallow gradient between 5-20% of acetonitrile was used between 0.5-2.0 min. Flow rate: 77 mL/min. Mobile phase additive: 84 mM of ammonium formate. Column: SunFire C18, 19 x 50 mm, 5 μm particle size) to afford 0.011 g (21%) of the title compound 3-fluoro-*N*-[2-(1-methyl-piperidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide. ¹H NMR (400 MHz, CDCl₃) δ 8.5 (s, 0.6 H), 7.60-7.69 (m, 1H), 7.36-7.50 (m, 2H), 7.14-7.20 (m, 1H), 5.92 (d, *J* = 6.8 Hz, 0.4 H), 4.55-4.65 (m, 0.4 H), 4.27-4.37 (m, 0.6 H), 3.91-4.01 (m, 1H), 3.21-3.34 (m, 2H), 2.85-2.95 (m, 2H), 2.29 (s, 1.8 H), 2.28 (s, 1.2H), 1.30-2.24 (m, 16H). ESI-MS *m/z*: 388 (M+H)⁺.

Example 159: 2-Methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid [(5R,7R)-2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]amide



Example 159 was made from intermediate 36 *via* the process of **Scheme 1**, *supra*, as follows:

5 To a solution of intermediate 36 (5R, 7R)-7-amino-2-(3,5-difluoro-phenyl)-2-aza-spiro[4.5]decan-1-one (80 mg, 0.28 mmol), triethylamine (0.16 mL, 1.14 mmol) in DMF (2.0 mL) was added 6-hydroxy-2-methyl-pyrimidine-4-carboxylic acid (49 mg, 0.32 mmol), HOBt (51 mg, 0.38 mmol) and EDCI (73 mg, 0.38 mmol). The mixture was stirred at rt overnight. The solvent was removed with Genevac, and the resulting residue was purified with spectrometry (RP-HPLC/MS) purification system (Gradient: acetonitrile in water, 25-95% in 3.9 minutes with a cycle time of 5 min. Flow rate: 100 mL/min. Mobile phase additive: 48 mM of ammonium formate. Column: Inertsil C18, 30 x 50 mm, 5 um particle size) to afford 26 mg (22%) of the title compound 2-methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid [(5R,7R)-2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]amide. ¹H NMR (400 MHz, CDCl₃) δ 13.0 (bs, 1 H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.25-7.32 (m, 2H), 7.14 (s, 1H), 6.56-6.63 (m, 1H), 4.02-4.12 (m, 1 H), 3.73-3.80 (m, 2H), 2.52 (s, 3H), 2.04-2.26 (m, 3H), 1.86-1.95 (m, 2H), 1.34-1.80 (m, 5H). ESI-MS *m/z*: 417 (M+H)⁺.

Table 1: Spirolactam derivatives

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
1		<i>trans</i> -Pyridine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.46 Calcd. Mass: 383 <i>m/z</i> (M+H): 384
2		<i>cis</i> -Pyridine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.39 Calcd. Mass: 383 <i>m/z</i> (M+H): 384

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
3		<i>trans</i> -6-Methyl-pyridine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: C RT: 1.54 Calcd. Mass: 397 m/z (M+H): 398
4		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.47 Calcd. Mass: 397 m/z (M+H): 398
5		Pyridine-2-carboxylic acid [(5 <i>R</i> ,7 <i>R</i>)-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: C RT: 1.38 Calcd. Mass: 383 m/z (M+H): 384
6		Pyridine-2-carboxylic acid [(5 <i>S</i> ,7 <i>S</i>)-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: C RT: 1.38 Calcd. Mass: 383 m/z (M+H): 384
7		<i>cis</i> -Pyridine-2-carboxylic acid [2-(6-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: C RT: 1.26 Calcd. Mass: 364 m/z (M+H): 365
8		3-Chloro- <i>N</i> -[2-(6-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.49 Calcd. Mass: 397 m/z (M+H): 398
9		<i>cis</i> -Pyridine-2-carboxylic acid [2-(3-cyano-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.20 Calcd. Mass: 374 m/z (M+H): 375

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
10		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(3-cyano-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: C RT: 1.30 Calcd. Mass: 388 m/z (M+H): 389
11		<i>cis</i> -6-Methyl-pyrazine-2-carboxylic acid [2-(3-cyano-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: C RT: 1.15 Calcd. Mass: 389 m/z (M+H): 390
12		<i>cis</i> -6-Methyl-pyrazine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: C RT: 1.33 Calcd. Mass: 398 m/z (M+H): 399
13		<i>cis</i> -Pyrazine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.23 Calcd. Mass: 384 m/z (M+H): 385
14		<i>cis</i> -1-Methyl-1H-pyrazole-3-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.21 Calcd. Mass: 386 m/z (M+H): 387
15		<i>cis</i> -N-[2-(3-Cyano-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide	Method: C RT: 1.30 Calcd. Mass: 391 m/z (M+H): 392
16		<i>cis</i> -N-[2-(3-Cyano-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-chloro-benzamide	Method: C RT: 1.40 Calcd. Mass: 407 m/z (M+H): 408
17		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: B RT: 1.00 Calcd. Mass: 381 m/z (M+H): 382

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
18		<i>trans</i> -6-Methyl-pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: B RT: 1.10 Calcd. Mass: 381 m/z (M+H): 382
19		<i>cis</i> -Pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5] dec-7-yl]-amide	Method: B RT: 0.82 Calcd. Mass: 367 m/z (M+H): 368
20		<i>trans</i> -Pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: B RT: 0.95 Calcd. Mass: 367 m/z (M+H): 368
21		<i>cis</i> -6-Methyl-pyrazine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: B RT: 0.84 Calcd. Mass: 382 m/z (M+H): 383
22		<i>trans</i> -6-Methyl-pyrazine-2-carboxylic acid[2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: B RT: 0.89 Calcd. Mass: 382 m/z (M+H): 383
23		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(6-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.38 Calcd. Mass: 378 m/z (M+H): 379
24		<i>trans</i> -3-Fluoro- <i>N</i> -[2-(6-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5] dec-7-yl]-benzamide	Method: C RT: 1.43 Calcd. Mass: 381 m/z (M+H): 382
25		Pyridine-2-carboxylic acid [(5 <i>R</i> ,7 <i>R</i>)-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: C RT: 1.30 Calcd. Mass: 367 m/z (M+H): 368

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
26		3-Fluoro-N-(1-oxo-2-pyridin-2-yl-2-aza-spiro[4.5]dec-7-yl)-benzamide	Method: C RT: 1.26 Calcd. Mass: 367 m/z (M+H): 368
27		<i>cis</i> -3-Fluoro-N-[2-(6-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.39 Calcd. Mass: 381 m/z (M+H): 382
28		3-Fluoro-N-[(5R,7R)-2-(6-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.38 Calcd. Mass: 381 m/z (M+H): 382
29		<i>cis</i> -Pyridine-2-carboxylic acid [2-(4-methyl-pyrimidin-2-yl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: A RT: 0.75 Calcd. Mass: 365 m/z (M+H): 366
30		<i>cis</i> -Pyridine-2-carboxylic acid [2-(4-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: A RT: 1.16 Calcd. Mass: 368 m/z (M+H): 369
31		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 1.28 Calcd. Mass: 382 m/z (M+H): 383
32		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(4-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 1.30 Calcd. Mass: 382 m/z (M+H): 383
33		<i>cis</i> -Pyridine-2-carboxylic acid [2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: A RT: 1.15 Calcd. Mass: 368 m/z (M+H): 369
34		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(4-methyl-pyrimidin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 0.88 Calcd. Mass: 379 m/z (M+H): 380

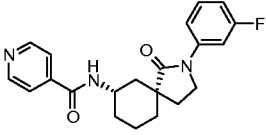
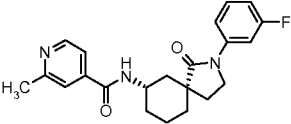
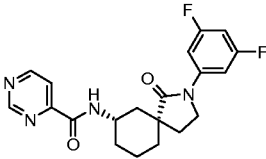
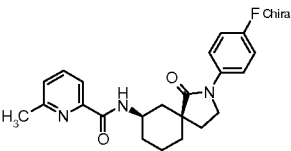
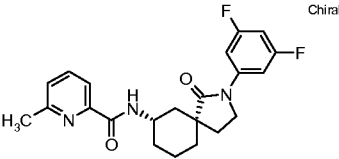
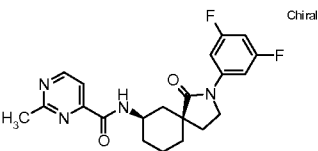
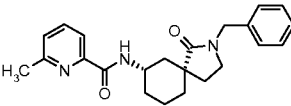
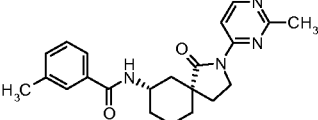
Example No	STRUCTURE	CHEMICAL NAME	LC-MS
35		<i>cis</i> -3-Fluoro- <i>N</i> -[2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: A RT: 1.28 Calcd. Mass: 385 m/z (M+H): 386
36		<i>cis</i> -3-Fluoro- <i>N</i> -[2-(4-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: A RT: 1.28 Calcd. Mass: 385 m/z (M+H): 386
37		<i>cis</i> -3-Fluoro- <i>N</i> -[2-(4-methyl-pyrimidin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: A RT: 0.92 Calcd. Mass: 382 m/z (M+H): 383
38		<i>cis</i> -3-Fluoro- <i>N</i> -[2-(6-methyl-pyrazin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.25 Calcd. Mass: 382 m/z (M+H): 383
39		<i>cis</i> -Pyridine-2-carboxylic acid [2-(6-methyl-pyrazin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.10 Calcd. Mass: 365 m/z (M+H): 366
40		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(6-methyl-pyrazin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.25 Calcd. Mass: 379 m/z (M+H): 380
41		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [1-oxo-2-(6-trifluoromethyl-pyridin-2-yl)-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.59 Calcd. Mass: 432 m/z (M+H): 433
42		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.48 Calcd. Mass: 399 m/z (M+H): 400

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
43		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(6-cyano-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.38 Calcd. Mass: 389 m/z (M+H): 390
44		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(4-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.36 Calcd. Mass: 381 m/z (M+H): 382
45		6-Methyl-pyridine-2-carboxylic acid (1-oxo-2-pyridin-2-yl-2-aza-spiro[4.5]dec-7-yl)-amide	Method: C RT: 1.26 Calcd. Mass: 364 m/z (M+H): 365
46		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid (1-oxo-2-phenyl-2-aza-spiro[4.5]dec-7-yl)-amide	Method: C RT: 1.32 Calcd. Mass: 363 m/z (M+H): 364
47		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid (1-oxo-2-m-tolyl-2-aza-spiro[4.5]dec-7-yl)-amide	Method: C RT: 1.41 Calcd. Mass: 377 m/z (M+H): 378
48		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(4-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.33 Calcd. Mass: 378 m/z (M+H): 379
49		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(5-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.33 Calcd. Mass: 378 m/z (M+H): 379
50		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(3-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.10 Calcd. Mass: 378 m/z (M+H): 379

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
51		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(2-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.27 Calcd. Mass: 381 m/z (M+H): 382
52		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(2-methyl-pyridin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.15 Calcd. Mass: 378 m/z (M+H): 379
53		<i>cis</i> -N-[2-(6-Cyano-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide	Method: C RT: 1.34 Calcd. Mass: 392 m/z (M+H): 393
54		<i>cis</i> -Pyridine-2-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro [4.5] dec-7-yl]-amide	Method: C RT: 1.39 Calcd. Mass: 385 m/z (M+H): 386
55		<i>cis</i> -6-Methyl-pyrazine-2-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: C RT: 1.34 Calcd. Mass: 400 m/z (M+H): 401
56		<i>cis</i> -Pyrazine-2-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro [4.5] dec-7-yl]-amide	Method: C RT: 1.26 Calcd. Mass: 386 m/z (M+H): 387
57		<i>cis</i> -2-Methyl-pyrimidine-4-carboxylic acid [2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: A RT: 1.04 Calcd. Mass: 383 m/z (M+H): 384
58		<i>cis</i> -3-Chloro-N-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.32 Calcd. Mass: 398 m/z (M+H): 399
59		<i>cis</i> -2-Methyl-pyrimidine-4-carboxylic acid [2-(6-methyl-pyrazin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.04 Calcd. Mass: 380 m/z (M+H): 381

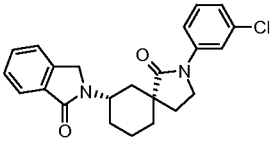
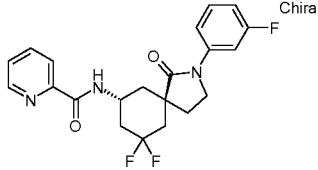
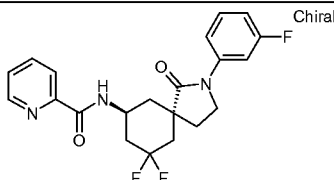
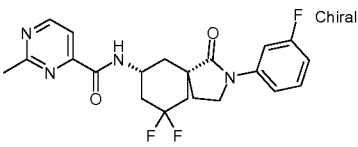
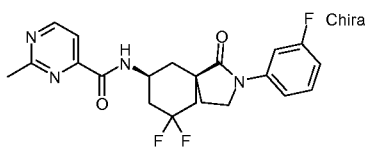
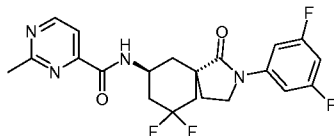
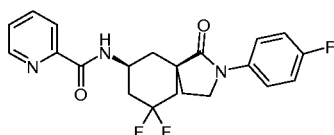
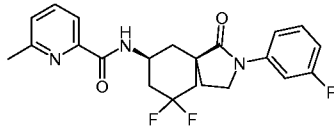
Example No	STRUCTURE	CHEMICAL NAME	LC-MS
60		<i>cis</i> -2-Methyl-pyrimidine-4-carboxylic acid [2-(3-cyano-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: C RT: 1.13 Calcd. Mass: 389 m/z (M+H): 390
61		<i>cis</i> -2-Methyl-pyrimidine-4-carboxylic acid [1-oxo-2-(6-trifluoromethyl-pyridin-2-yl)-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.43 Calcd. Mass: 433 m/z (M+H): 434
62		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.21 Calcd. Mass: 379 m/z (M+H): 380
63		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(6-methyl-pyridin-3-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 0.90 Calcd. Mass: 378 m/z (M+H): 379
64		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(5-fluoro-pyridin-3-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 1.04 Calcd. Mass: 382 m/z (M+H): 383
65		<i>cis</i> -3-Fluoro-N-[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.21 Calcd. Mass: 382 m/z (M+H): 383
66		<i>cis</i> -3-Fluoro-N-[2-(2-methyl-pyridin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.15 Calcd. Mass: 381 m/z (M+H): 382
67		6-Methyl-pyridine-2-carboxylic acid [(5 <i>R</i> ,7 <i>R</i>)-2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.42 Calcd. Mass: 399 m/z (M+H): 400

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
68		<i>cis</i> -5-Fluoro-pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: C RT: 1.36 Calcd. Mass: 385 m/z (M+H): 386
69		<i>cis</i> -2-Methyl-pyrimidine-4-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5] dec-7-yl]-amide	Method: C RT: 1.23 Calcd. Mass: 382 m/z (M+H): 383
70		<i>cis</i> -Pyrimidine-4-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: C RT: 1.16 Calcd. Mass: 368 m/z (M+H): 369
71		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(5-methyl-pyridin-3-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.14 Calcd. Mass: 378 m/z (M+H): 379
72		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(3-methoxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.34 Calcd. Mass: 393 m/z (M+H): 394
73		6-Methyl-pyridine-2-carboxylic acid [(5 <i>R</i> ,7 <i>R</i>)-2-(5-fluoropyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 1.28 Calcd. Mass: 382 m/z (M+H): 383
74		<i>cis</i> -Pyridine-2-carboxylic acid [2-(5-fluoro-pyridin-3-yl)-1-oxo-2-aza-spiro[4.5] dec-7-yl]-amide	Method: A RT: 0.94 Calcd. Mass: 368 m/z (M+H): 369
75		<i>cis</i> -Pyridine-2-carboxylic acid [2-(3,4-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5] dec-7-yl]-amide	Method: C RT: 1.33 Calcd. Mass: 385 m/z (M+H): 386
76		<i>cis</i> -2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide	Method: C RT: 1.31 Calcd. Mass: 400 m/z (M+H): 401

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
77		<i>cis</i> -N-[2-(3-Fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-isonicotinamide	Method: C RT: 1.13 Calcd. Mass: 367 m/z (M+H): 368
78		<i>cis</i> -N-[2-(3-Fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-2-methyl isonicotinamide	Method: C RT: 1.19 Calcd. Mass: 381 m/z (M+H): 382
79		<i>cis</i> -Pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-azaspiro[4.5]dec-7-yl]-amide	Method: C RT: 1.24 Calcd. Mass: 386 m/z (M+H): 387
80		6-Methyl-pyridine-2-carboxylic acid [(5 <i>R</i> ,7 <i>R</i>)-2-(4-fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.34 Calcd. Mass: 381 m/z (M+H): 382
81		6-Methyl-pyridine-2-carboxylic acid [(5 <i>S</i> ,7 <i>S</i>)-2-(3,5-difluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.46 Calcd. Mass: 399 m/z (M+H): 400
82		2-Methyl-pyrimidine-4-carboxylic acid [(5 <i>R</i> ,7 <i>R</i>)-2-(3,5-difluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.30 Calcd. Mass: 400 m/z (M+H): 401
83		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid (2-benzyl-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide	Method: C RT: 1.29 Calcd. Mass: 377 m/z (M+H): 378
84		<i>cis</i> -3-Methyl-N-[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.24 Calcd. Mass: 378 m/z (M+H): 379

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
85		<i>cis</i> -3,5-Difluoro- <i>N</i> -[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.29 Calcd. Mass: 400 m/z (M+H): 401
86		<i>cis</i> -6-Methyl-pyrazine-2-carboxylic acid {2-[6-(4-fluoro-phenyl)-pyrimidin-4-yl]-1-oxo-2-aza-spiro[4.5]dec-7-yl}-amide	Method: A RT: 1.31 Calcd. Mass: 460 m/z (M+H): 461
87		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid {2-[6-(4-fluoro-phenyl)-pyrimidin-4-yl]-1-oxo-2-aza-spiro[4.5]dec-7-yl}-amide	Method: A RT: 1.54 Calcd. Mass: 459 m/z (M+H): 460
88		<i>cis</i> -3-Fluoro- <i>N</i> -{2-[6-(4-fluoro-phenyl)-pyrimidin-4-yl]-1-oxo-2-aza-spiro[4.5]dec-7-yl}-benzamide	Method: A RT: 1.52 Calcd. Mass: 462 m/z (M+H): 463
89		<i>cis</i> -4-Fluoro- <i>N</i> -[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.20 Calcd. Mass: 382 m/z (M+H): 383
90		<i>cis</i> -3,4-Difluoro- <i>N</i> -[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.25 Calcd. Mass: 400 m/z (M+H): 401
91		<i>cis</i> -2-Fluoro- <i>N</i> -[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.18 Calcd. Mass: 382 m/z (M+H): 383
92		<i>cis</i> -2-Methyl- <i>N</i> -[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-isonicotinamide	Method: C RT: 0.99 Calcd. Mass: 379 m/z (M+H): 380
93		<i>cis</i> -6-Hydroxymethyl-pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-	Method: C RT: 1.14 Calcd. Mass: 397 m/z (M+H): 398

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
		amide	
94		<i>cis</i> -6-Trifluoromethylpyridine-2-carboxylic acid [2-(3-fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.51 Calcd. Mass: 435 m/z (M+H): 436
95		<i>N</i> -[(5 <i>R</i> ,7 <i>R</i>)-2-(3-Fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-2-methylisonicotinamide	Method: C RT: 1.19 Calcd. Mass: 381 m/z (M+H): 382
96		<i>cis</i> -6-Trifluoromethylpyridine-2-carboxylic acid [2-(2-methylpyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.35 Calcd. Mass: 433 m/z (M+H): 434
97		Pyridine-2-carboxylic acid [9,9-difluoro-2-(3-fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 1.27 Calcd. Mass: 403 m/z (M+H): 404
98		Pyridine-2-carboxylic acid [(5 <i>R</i> ,7 <i>S</i>)-9,9-difluoro-2-(3-fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide (the third peak from chiral HPLC, arbitrarily assignment)	Method: C RT: 1.34 Calcd. Mass: 403 m/z (M+H): 404
99		Pyridine-2-carboxylic acid [(5 <i>S</i> ,7 <i>R</i>)-9,9-difluoro-2-(3-fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide (the first peak from chiral HPLC, arbitrarily assignment)	Method: C RT: 1.35 Calcd. Mass: 403 m/z (M+H): 404

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
100		<i>cis</i> -2-[2-(3-Chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-2,3-dihydro-isoindol-1-one (relatively polar spot on TLC, arbitrarily assignment)	Method: C RT: 1.41 Calcd. Mass: 394 m/z (M+H): 395
101		Pyridine-2-carboxylic acid [(5R,7R)-9,9-difluoro-2-(3-fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.37 Calcd. Mass: 403 m/z (M+H): 404
102		Pyridine-2-carboxylic acid [(5S,7S)-9,9-difluoro-2-(3-fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.33 Calcd. Mass: 403 m/z (M+H): 404
103		2-Methyl-pyrimidine-4-carboxylic acid [(5S,7R)-9,9-difluoro-2-(3-fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.28 Calcd. Mass: 418 m/z (M+H): 419
104		2-Methyl-pyrimidine-4-carboxylic acid [(5R,7S)-9,9-difluoro-2-(3-fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.28 Calcd. Mass: 418 m/z (M+H): 419
105		<i>trans</i> -2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluorophenyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.35 Calcd. Mass: 436 m/z (M+H): 437
106		<i>cis</i> -Pyridine-2-carboxylic acid [9,9-difluoro-2-(4-fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.3 Calcd. Mass: 403 m/z (M+H): 404
107		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [9,9-difluoro-2-(3-fluorophenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.45 Calcd. Mass: 437 m/z (M+H): 438

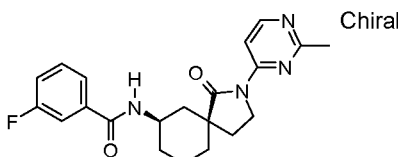
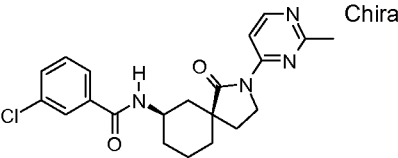
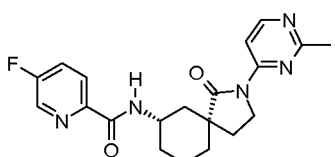
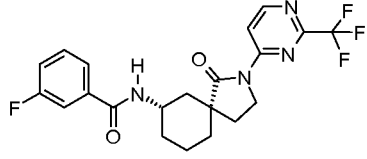
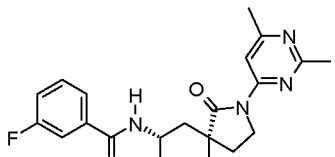
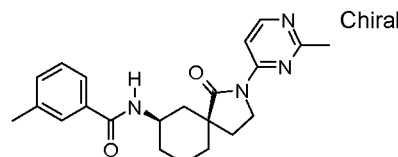
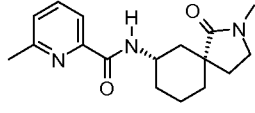
Example No	STRUCTURE	CHEMICAL NAME	LC-MS
108		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [9,9-difluoro-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.28 Calcd. Mass: 415 m/z (M+H): 416
109		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [9,9-difluoro-2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.4 Calcd. Mass: 418 m/z (M+H): 419
110		<i>cis</i> -Pyridine-2-carboxylic acid [2-(3,5-difluoro-phenyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.43 Calcd. Mass: 421 m/z (M+H): 422
111		<i>cis</i> -Pyridine-2-carboxylic acid [9,9-difluoro-2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.3 Calcd. Mass: 404 m/z (M+H): 405
112		<i>cis</i> -Pyridine-2-carboxylic acid [9,9-difluoro-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.18 Calcd. Mass: 401 m/z (M+H): 402
113		Pyridine-2-carboxylic acid [(5 <i>S</i> ,7 <i>R</i>)-2-(3,5-difluoro-phenyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 1.48 Calcd. Mass: 421 m/z (M+H): 422
114		Pyridine-2-carboxylic acid [(5 <i>R</i> ,7 <i>S</i>)-2-(3,5-difluoro-phenyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 1.47 Calcd. Mass: 421 m/z (M+H): 422
115		<i>cis</i> -2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-1,9-dioxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 1.11 Calcd. Mass: 414 m/z (M+H): 415

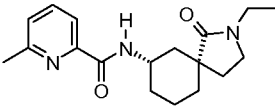
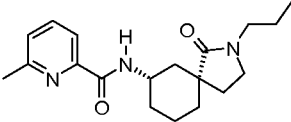
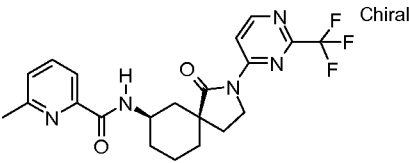
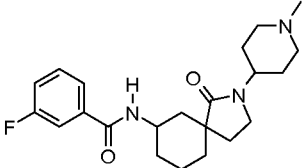
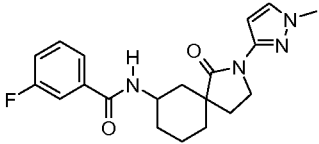
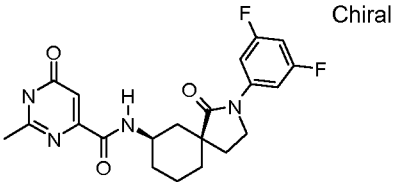
Example No	STRUCTURE	CHEMICAL NAME	LC-MS
116		cis-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 0.96 Calcd. Mass: 416 m/z (M+H): 417
117		trans-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 1.04 Calcd. Mass: 416 m/z (M+H): 417
118		2-Methyl-pyrimidine-4-carboxylic acid [(5R,7S,9S)-2-(3,5-difluoro-phenyl)-9-hydroxy-9-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 1.15 Calcd. Mass: 430 m/z (M+H): 431
119		2-Methyl-pyrimidine-4-carboxylic acid [(5R,7S,9R)-2-(3,5-difluoro-phenyl)-9-hydroxy-9-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 1.02 Calcd. Mass: 430 m/z (M+H): 431
120		N-[(5S,7R)-9,9-Difluoro-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide	Method: C RT: 1.38 Calcd. Mass: 418 m/z (M+H): 419
121		N-[(5R,7S)-9,9-Difluoro-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide	Method: C RT: 1.38 Calcd. Mass: 418 m/z (M+H): 419
122		trans-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9-fluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.38 Calcd. Mass: 418 m/z (M+H): 419
123		cis-3-Fluoro-N-[2-(3-fluoro-phenyl)-1,9-dioxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.33 Calcd. Mass: 398 m/z (M+H): 399

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
124		<i>cis</i> -6-Methyl-pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1,9-dioxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.43 Calcd. Mass: 395 m/z (M+H): 396
125		<i>trans</i> -3-Fluoro- <i>N</i> -[2-(3-fluoro-phenyl)-9-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: A RT: 1.18 Calcd. Mass: 400 m/z (M+H): 401
126		<i>trans</i> -6-Methyl-pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-9-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.27 Calcd. Mass: 397 m/z (M+H): 398
127		6-Methyl-pyridine-2-carboxylic acid [(5 <i>S</i> ,7 <i>R</i>)-9,9-difluoro-2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide	Method: A RT: 1.43 Calcd. Mass: 418 m/z (M+H): 419
128		<i>cis</i> - <i>N</i> -[9,9-Difluoro-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide	Method: C RT: 1.39 Calcd. Mass: 418 m/z (M+H): 419
129		<i>cis</i> -2-Methyl-pyrimidine-4-carboxylic acid [9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-azaspiro[4.5]dec-7-yl]-amide	Method: A RT: 1.21 Calcd. Mass: 418 m/z (M+H): 419
130		<i>cis</i> -3-Fluoro- <i>N</i> -[-2-(3-methoxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: A RT: 1.29 Calcd. Mass: 396 m/z (M+H): 397
131		<i>Cis</i> -3-Fluoro- <i>N</i> -[2-(3-hydroxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: A RT: 1.02 Calcd. Mass: 382 m/z (M+H): 383

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
132		<i>Cis-N-[(5S,7S)-2-(3-Dimethylamino-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide</i>	Method: A RT: 1.37 Calcd. Mass: 400 m/z (M+H): 401
133		<i>cis-3-Fluoro-N-[(2-(4-methoxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-benzamide.</i>	Method: A RT: 1.24 Calcd. Mass: 396 m/z (M+H): 397
134		<i>cis-3-Fluoro-N-{2-[3-(3-morpholin-4-yl-propyl)-phenyl]-1-oxo-2-aza-spiro[4.5]dec-7-yl}-benzamide</i>	Method: A RT: 1.09 Calcd. Mass: 493 m/z (M+H): 494
135		<i>cis-3-Fluoro-N-[2-(3-fluoro-5-methoxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide</i>	Method: A RT: 1.36 Calcd. Mass: 414 m/z (M+H): 415
136		<i>cis-3-Fluoro-N-{1-oxo-2-[3-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-2-aza-spiro[4.5]dec-7-yl}-benzamide</i>	Method: A RT: 1.25 Calcd. Mass: 493 m/z (M+H): 494
137		<i>cis-Thiazole-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide</i>	Method: A RT: 1.33 Calcd. Mass: 373 m/z (M+H): 374
138		<i>cis-N-[2-(4-Dimethylamino-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide</i>	Method: A RT: 1.42 Calcd. Mass: 409 m/z (M+H): 410
139		<i>cis-3-Fluoro-N-(1-oxo-2-thiazol-2-yl-2-aza-spiro[4.5]dec-7-yl)-benzamide</i>	Method: A RT: 1.21 Calcd. Mass: 373 m/z (M+H): 374

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
140		<i>cis</i> -Thiazole-2-carboxylic acid [(2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide	Method: A RT: 1.05 Calcd. Mass: 371 m/z (M+H): 372
141		<i>cis</i> -2-Methyl-pyrimidine-4-carboxylic acid [2-(3-fluoro-5-methoxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide	Method: A RT: 1.30 Calcd. Mass: 412 m/z (M+H): 413
142		<i>cis</i> -N-[2-(3-Cyano-5-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-3-fluoro-benzamide	Method: A RT: 1.44 Calcd. Mass: 409 m/z (M+H): 410
143		<i>cis</i> -Thiazole-2-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide	Method: A RT: 1.43 Calcd. Mass: 391 m/z (M+H): 392
144		<i>cis</i> -2-Methyl-thiazole-4-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide	Method: A RT: 1.43 Calcd. Mass: 405 m/z (M+H): 406
145		<i>cis</i> -Pentanoic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide	Method: A RT: 1.43 Calcd. Mass: 364 m/z (M+H): 365
146		<i>cis</i> -N-[2-(3,5-Difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-butyramide	Method: A RT: 1.30 Calcd. Mass: 350 m/z (M+H): 351

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
147	 Chiral	3-Fluoro- <i>N</i> -[(5 <i>R</i> ,7 <i>R</i>)-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.21 Calcd. Mass: 382 m/z (M+H): 383
148	 Chiral	3-Chloro- <i>N</i> -[(5 <i>R</i> ,7 <i>R</i>)-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.32 Calcd. Mass: 398 m/z (M+H): 399
149		<i>cis</i> 5-Fluoro-pyridine-2-carboxylic acid [(2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide	Method: C RT: 1.28 Calcd. Mass: 383 m/z (M+H): 384
150		<i>cis</i> -3-Fluoro- <i>N</i> -[1-oxo-2-(2-trifluoromethyl-pyrimidin-4-yl)-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.48 Calcd. Mass: 436 m/z (M+H): 437
151		<i>cis</i> - <i>N</i> -[2-(2,6-Dimethyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide	Method: C RT: 1.34 Calcd. Mass: 396 m/z (M+H): 397
152	 Chiral	3-Methyl- <i>N</i> -[(5 <i>R</i> ,7 <i>R</i>)-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.24 Calcd. Mass: 378 m/z (M+H): 379
153		<i>cis</i> -3-Fluoro- <i>N</i> -(2-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl)-benzamide	Method: C RT: 1.03 Calcd. Mass: 301 m/z (M+H): 302

Example No	STRUCTURE	CHEMICAL NAME	LC-MS
154		<i>cis</i> -3-Fluoro- <i>N</i> -(2-ethyl-1-oxo-2-aza-spiro[4.5]dec-7-yl)-benzamide	Method: C RT: 1.11 Calcd. Mass: 315 m/z (M+H): 316
155		<i>cis</i> -3-Fluoro- <i>N</i> -(2-propyl-1-oxo-2-aza-spiro[4.5]dec-7-yl)-benzamide	Method: C RT: 1.20 Calcd. Mass: 329 m/z (M+H): 330
156		6-Methyl-pyridine-2-carboxylic acid[(5 <i>R</i> ,7 <i>R</i>)-1-oxo-2-(2-trifluoromethyl-pyrimidin-4-yl)-2-aza-spiro[4.5]dec-7-yl]-amide	Method: C RT: 1.54 Calcd. Mass: 432 m/z (M+H): 433
157		3-Fluoro- <i>N</i> -[2-(1-methyl-piperidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 0.84, 0.87 Calcd. Mass: 388 m/z (M+H): 388
158		3-Fluoro- <i>N</i> -[2-(1-methyl-1H-pyrazol-3-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide	Method: C RT: 1.14 Calcd. Mass: 370 m/z (M+H): 371
159		2-Methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid [(5 <i>R</i> ,7 <i>R</i>)-2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]amide	Method: C RT: 1.15 Calcd. Mass: 416 m/z (M+H): 417

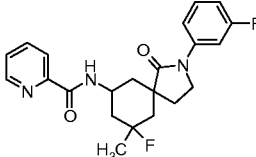
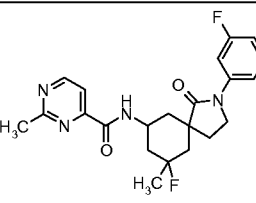
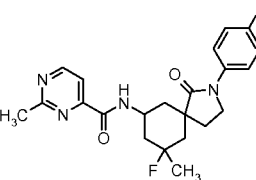
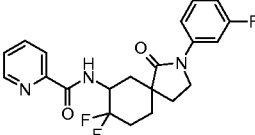
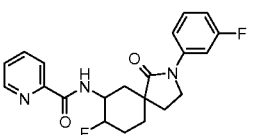
Examples 160-162 may be made *via* the processes outlined in **Scheme 23** herein from compound **23**, which can be made from reduction of commercially available 5-hydroxy-isophthalic acid (compound **22**) *via* the process of step a outlined in **Scheme 6**, *supra*.

Examples 163-177 may be made *via* the processes outlined in **Scheme 19** herein from compound **41** ($R^2 = 3\text{-fluorophenyl}$ or $3,5\text{-difluorophenyl}$ or 4-fluorophenyl), which may be

made *via* the processes outlined in **Scheme 8** herein from commercially available 4-oxo-cyclohexane-1,3-dicarboxylic acid dimethyl ester (compound **32**).

Examples 178-201 may be made *via* the processes outlined in **Scheme 20** herein from compound **49** (R^2 = 3-fluorophenyl or 3,5-difluorophenyl or 4-fluorophenyl), which can be made *via* the processes outlined in **Scheme 9** herein from compound **8**, which can be readily made by esterification of commercially available cyclohexane-1,3-dicarboxylic acid (compound **7**) *via* the process of step a outlined in **Scheme 4**, *supra*.

Table 2: Hypothetic compounds

Example No	STRUCTURE	CHEMICAL NAME
160		Pyridine-2-carboxylic acid [9-fluoro-2-(3-fluoro-phenyl)-9-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
161		2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9-fluoro-9-methyl-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide
162		2-Methyl-pyrimidine-4-carboxylic acid [9-fluoro-2-(4-fluoro-phenyl)-9-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
163		Pyridine-2-carboxylic acid [8,8-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
164		Pyridine-2-carboxylic acid [8-fluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide

Example No	STRUCTURE	CHEMICAL NAME
165		Pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-8-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
166		Pyridine-2-carboxylic acid [8-fluoro-2-(3-fluoro-phenyl)-8-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
167		Pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-8-hydroxy-8-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
168		2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-8,8-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
169		2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-8-fluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
170		2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-8-fluoro-8-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
171		2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-8-hydroxy-8-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
172		2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-8-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide

Example No	STRUCTURE	CHEMICAL NAME
173		2-Methyl-pyrimidine-4-carboxylic acid [8,8-difluoro-2-(4-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5] dec-7-yl]-amide
174		2-Methyl-pyrimidine-4-carboxylic acid [8-fluoro-2-(4-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
175		2-Methyl-pyrimidine-4-carboxylic acid [8-fluoro-2-(4-fluoro-phenyl)-8-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
176		2-Methyl-pyrimidine-4-carboxylic acid [2-(4-fluoro-phenyl)-8-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
177		2-Methyl-pyrimidine-4-carboxylic acid [2-(4-fluoro-phenyl)-8-hydroxy-8-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
178		Pyridine-2-carboxylic acid [4,4-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
179		Pyridine-2-carboxylic acid [4-fluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
180		Pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-4-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide

Example No	STRUCTURE	CHEMICAL NAME
181		Pyridine-2-carboxylic acid [4-fluoro-2-(3-fluoro-phenyl)-4-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
182		Pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-4-hydroxy-4-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
183		2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-4,4-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
184		2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-4-fluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
185		2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-4-fluoro-4-methyl-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide
186		2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-4-hydroxy-4-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
187		2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-4-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
188		2-Methyl-pyrimidine-4-carboxylic acid [4,4-difluoro-2-(4-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide

Example No	STRUCTURE	CHEMICAL NAME
189		2-Methyl-pyrimidine-4-carboxylic acid [4-fluoro-2-(4-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
190		2-Methyl-pyrimidine-4-carboxylic acid [4-fluoro-2-(4-fluoro-phenyl)-4-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
200		2-Methyl-pyrimidine-4-carboxylic acid [2-(4-fluoro-phenyl)-4-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide
201		2-Methyl-pyrimidine-4-carboxylic acid [2-(4-fluoro-phenyl)-4-hydroxy-4-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide

4. Pharmacological Evaluation of Compounds of the Invention

Compounds of the present invention have been tested *in vitro* and *in vivo*, and can be tested *in vitro* and *in vivo*, in the assays as described below.

***In vitro* Assays**

5 Radioligand binding assays

Binding assays were performed as described in [J. A. O'Brien *et al. Mol Pharmacol.*, **2003**, 64, 731-740] with slight modifications. Briefly, after thawing, the membrane homogenates were resuspended in 50 mM Tris-HCl, 0.9% NaCl binding buffer at pH 7.4 to a final assay concentration of 40 µg protein/well for [³H] 2-methyl-6-phenylethynyl-pyridine ([³H] MPEP) (American Radiolabeled Chemicals, Inc., St. Louis, MO) filtration binding. Incubations included 5 nM [³H] MPEP, membranes and either buffer or varying concentrations of compound. Samples were incubated for 60 min at room temperature with shaking. Non-

specific binding was defined with 10 μ M MPEP. After incubation, samples were filtered over a GF/C filter (presoaked in 0.25% polyethyleneimine (PEI)) and then washed 4 times using a Tomtec® Harvester 96® Mach III cell harvester (Tomtec, Hamden, CT) with 0.5 mL ice-cold 50 mM Tris-HCl (pH 7.4).

IC₅₀ values were derived from the inhibition curve and K_i values were calculated according to the Cheng and Prusoff equation of $K_i = IC_{50} / (1 + [L]/K_d)$ described in [Y. Cheng and W.H. Prusoff *Biochem. Pharmacol.* **1973**, 22, 3099-3108] where [L] is the concentration of radioligand and K_d is its dissociation constant at the receptor, derived from the saturation isotherm. The K_i value for Examples 2, 4, 5, 23, and 25 were 250 nM, 74, 95, 190, 130, respectively.

Calcium mobilization assay to test for negative or positive allosteric activity

The cDNA for rat metabotropic glutamate receptor 5 (rmGluR5) and the cDNA for human metabotropic glutamate receptor 5 (hmGluR5) were generous gifts from S. Nakanishi (Kyoto University, Kyoto, Japan). The rmGluR5 or hmGluR5 was stably expressed in a HEK 293 cell line and grown in Dulbecco's Modified Eagle Medium (DMEM) (Invitrogen, Carlsbad, CA) with supplements (10% bovine calf serum, 4 mM glutamine, 100 units/mL penicillin, 100 μ g/mL streptomycin and 0.75mM G1418) at 37 °C, 5% CO₂. Twenty-four hours prior to assay, cells were seeded into 384-well black wall microtiter plates coated with poly-D-lysine. Just prior to assay, media was aspirated and cells dye-loaded (25 μ L/well) with 3 μ M Fluo-4/ 0.01% pluronic acid in assay buffer (Hank's Balanced Saline Solution (HBSS)): 150 mM NaCl, 5 mM KCl, 1 mM CaCl₂, 1 mM MgCl₂, plus 20 mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES), pH 7.4, 0.1% bovine serum albumin (BSA) and 2.5 mM probenidol for 1 hour in 5% CO₂ at 37 °C. After excess dye was discarded, cells were washed in assay buffer and layered with a final volume equal to 30 μ L/well. Basal fluorescence is monitored in a fluorometric imaging plate reader (FLIPR) (Molecular Devices, Sunnyvale, CA) with an excitation wavelength of 488 nm and an emission range of 500 to 560 nm. Laser excitation energy was adjusted so that basal fluorescence readings were approximately 10,000 relative fluorescent units. Cells were stimulated with an EC₂₀ or an EC₈₀ concentration of glutamate in the presence of a compound to be tested, both diluted in assay buffer, and relative fluorescent units were

measured at defined intervals (exposure = 0.6 sec) over a 3 min period at room temperature. Basal readings derived from negative controls were subtracted from all samples. Maximum change in fluorescence was calculated for each well. Concentration-response curves derived from the maximum change in fluorescence were analyzed by nonlinear regression (Hill equation). A negative modulator can be identified from these concentration-response curves if a compound produces a concentration dependent inhibition of the EC₈₀ glutamate response. Exemplified compounds Examples 1-57 were tested in the above assay for negative allosteric modulation using rmGluR5: FLIPR maximum inhibition ranged 81% to 99% while FLIPR IC₅₀ ranged from 2.2 nM to 5100 nM. Examples also were tested in the above assay using hmGluR5: for Examples 58-96, FLIPR maximum inhibition ranged from 73% to 95%, while FLIPR IC₅₀ ranged from 3.3 nM to 500 nM; and for Examples 97-99, FLIPR maximum inhibition ranged from 88% to 93%, while FLIPR IC₅₀ ranged from 4.3 nM to 440 nM. For examples 100-160, FLIPR maximum inhibition ranged from 47% to 93%, while FLIPR IC₅₀ ranged from 4.3 nM to 440 nM.

A positive modulator (PAM) can be identified from these concentration-response curves if a compound produces a concentration dependent increase in the EC₂₀ glutamate response.

A silent allosteric modulator (SAM) can be identified based on results from both the radioligand assay and the calcium mobilization assay. If a compound actively binds to an allosteric site of the receptor based on the radioligand assay, but has no measurable intrinsic efficacy in the calcium mobilization assay, the compound is a SAM.

***In vivo* Assays**

Example 5 exhibited statistically significant *in vivo* anxiolytic effect at 30 mpk (sc) in a mouse marble burying (mMB) assay similar to that described in [K. Njung'e, K. and S.L. Handley, *Pharmacology, Biochemistry and Behavior*, **1991**, 38, 63–67]. See Figure 1.

More specifically for the mMB testing, adult, male CD1 mice (Charles River Laboratories (Kingston, NY)), weighing 25 to 30 g, were used. All animals were group-housed in a standard colony room with a 12:12 light/dark cycle (lights on at 6:00 am) for at least one week prior to testing. Food and water were provided *ad libitum*. Animals were weighed, tail marked, and randomly assigned to treatment groups before testing.

For each test, sixty minutes after the injection of vehicle or test compound, or 30 min after injection of the positive control, buspirone, mice were individually placed into test cages containing 1.5 in of Aspen bedding (PWI brand) and two rows of 10 marbles (20 marbles per test cage total). Filter tops were used to cover each test cage. Thirty minutes later, mice were removed from test cages and returned to their home cages. The number of fully visible marbles (less than 2/3 covered with bedding) were counted and subtracted from 20 to arrive at the number of marbles buried. Twelve mice were tested per group.

Testing included multiple tests with each test performed to evaluate buspirone hydrochloride (BUS; Sigma Aldrich) (positive control) and/or a compound of formula (I). Each compound was dissolved immediately prior to testing in 20% beta-cyclodextrin (compound of formula (I)) or distilled water (BUS) and administered at one or more doses (such as 3, 10, and/or 30 mg/kg) via subcutaneous (SC) or intraperitoneal (IP) injection at the indicated pretreatment times (*i.e.*, 30, 60, or 120 min pretreatment). Doses were measured in mg drug (salt form) per kg body weight. Data was analyzed using one-way ANOVA with post-hoc Dunnett's test.

Anxiolytic effect in vivo can also be tested via a modified Geller-Seifter conflict test described in [N.A. Moore *et al. Behavioural Pharmacology*. **1994**, 5, 196-202]. For example, more specifically, rodent operant chambers (ENV-007CT, Med Associates Inc. (Georgia, VT)) and sound-attenuating chambers (ENV-018MD, Med Associates Inc.) are used and each chamber is equipped with a house light, cue lights, grid floor to deliver foot shocks via a programmable shocker, (ENV-414, Med Associates, Inc.) and food hopper. Two levers are located on either side of the food hopper. Rats are trained to only respond on the left lever. Food reinforcement is used (*e.g.*, Dustless Precision Pellets, 45 mg, BioServ, (Frenchtown, NJ)). MED-PCIV software (Med Associates) is used to run experimental sessions and collect data.

Prior to beginning the Conflict procedure, animals are initially trained to lever press on fixed ratio schedules (FR 1, 2, 5, and 10). Once animals obtain 25 rewards on a FR 10 schedule for 2 consecutive days, animals begin training on a three component Conflict schedule. The three components are as follows: (1) an unpunished, variable interval 30 s (VI30) schedule of food reinforcement to reinforce lever pressing on a variable time schedule that averages 30 s; this

period had a duration of 9 minutes and is signaled by illumination of the rear house light only; (2) immediately following is a 3 minute time out period (TO) that is signaled by total darkness; responding is recorded but is neither rewarded nor punished; (3) a punished, fixed ratio 10 (FR10) schedule of reinforcement that simultaneously presents food and foot shock (0.3 mA, 500 ms) on every tenth lever press during a 3 minute period; this component is signaled by illumination of the rear house light and cue lights above each lever. These three components are repeated twice in the same order during the daily 30 minute session.

Testing begins when stable rates of responding are observed for 5 days (no significant trends up or down). Animals are tested using a Latin-squares design, on, *e.g.*, Wednesdays and Fridays. Animals serve as their own controls and received all treatments. To maintain baseline performance, animals are also trained the remaining three weekdays.

Testing is performed using 12 adult, male Sprague-Dawley rats, weighing 426-567 g (Charles River Laboratories (Kingston, NY)). Animals are pair-housed in colony rooms maintained at controlled temperature (68-72°F) and a 12-h light/dark cycle (lights on 06:00). Animals are given free access to water, while food is limited to 15 g of Bacon Lover's Treats (BioServ) after training/testing Monday through Thursday. Friday through Sunday, animals have free access to Lab Diet 5012 Rat Diet (PMI Nutrition International, LLC, Brentwood, MO) until cages are changed and food removed on Sunday.

Testing includes multiple tests where each test is performed to evaluate either a reference compound or a compound of formula (I). Reference anxiolytics can include chlordiazepoxide, diazepam and buspirone, which are dissolved in saline or water and administered via sc, ip, and/or p.o. Test compounds are dissolved in 20% beta-cyclodextrin, and the pH is adjusted to 7 with NaHCO₃. For each test, the compound to be evaluated is tested at one or more doses (such as 10, 20, 30 and/or 50 mg/kg) via p.o. administration 60 minutes before the test using an injection volume of 2 mL/kg in comparison with a vehicle control group. Doses are measured in mg drug (salt form) per kg body weight. Data is analyzed using Repeated Measures ANOVA with post-hoc Dunnett's test.

The "Vogel Conflict Test" as described by Vogel *et al.* [*Psychopharmacologia*, **1971**, 21, 1-7] was used to detect anxiolytic activity of a compound of formula (I) because anxiolytics

increase punished drinking. In the test, rats were deprived of water for approximately 48 hours and were then placed individually into a transparent Plexiglas[®] enclosure (15 x 32 x 34 cm) with a floor consisting of stainless steel bars (0.4 cm) spaced 1 cm apart. The back wall of the enclosure was made of opaque Plexiglas[®] thereby concealing the observer from the experimental animal. In the center of the opposite wall, 5 cm above the floor, a metal water spout protruded into the cage and was connected to one pole of a shock generator (Apelex: Type 011346). The other pole of the shock generator was connected to the metal grid floor.

The rat was left to explore until it found the water spout. Then, every time it drank, it received a slight electric shock (1.7 mA, 1 s) 2 seconds after it started lapping. The number of punished drinks was counted during a 3 minute test. The test was performed blind with 10 rats per group. Testing included multiple tests using reference compounds and a compound of formula (I) that were prepared and administered as described below in the LES test. Male Rj: Wistar (Hans) rats as described therein were used after acclimatization conditions were achieved. Data was analyzed by comparing treated groups with appropriate controls using unpaired Student's t tests.

Example 82 showed significant activity in the Vogel Conflict Test at 10 mpk (p.o.); and Example 25 showed significant activity at 30 mpk (p.o.). See Figures 2 and 3, respectively. Example 147 showed significant activity in the Vogel Conflict Test at 3, 10 and 30 mpk (p.o.); see Figure 4.

Compounds of formula (I) can be evaluated *in vivo* for antidepressive effects. An assessment of depression-like actions is measured using a forced swim test similar to that described in [J.F. Cryan, *et al. Neuroscience and Biobehavioral Reviews* **2005**, 29, 547–569.] Animals used for testing are adult, male NIH Swiss Webster mice (Harlan Laboratories (Frederick, MD)), weighing 22 to 24 g, which are acclimatized and housed as previously described with the mice used in the mMB tests.

For the mouse Forced Swim Test (mFST), mice are individually placed into clear Pyrex[®] cylinders (11 cm diameter, 16.5 cm height) containing 11 cm deep tap water (23-25 °C) sixty min after the injection of vehicle or test compound, or 30 min after injection of the positive control, imipramine hydrochloride (IMI; Sigma Aldrich, St. Louis, MO). Imipramine is

prepared with isotonic saline and test compound is prepared as described previously with mMB tests. Doses used can be as described previously with mMB tests. The percentage of time spent floating, swimming, and struggling (“climbing”) is measured during a 6 min session. Swim sessions are video monitored and can be analyzed in real-time using the Biobserve Automated FST apparatus and software (Biobserve GmbH, Bonn, Germany). Group size can range from twelve to thirteen mice. Doses are measured in mg drug (salt form) per kg body weight. Data is analyzed using one-way ANOVA with post-hoc Dunnett’s test.

An *in vivo* effect of a compound of the present invention may also be evaluated by using the following, non-limiting, examples of *in vivo* behavioral animal models. The following behavioral models are not intended as the only models useful for determining the efficacy of a compound of the present invention to treat the corresponding disorder or disease.

Compounds of the invention also can be evaluated *in vivo* for anxiolytic effects using a light-enhanced startle (LES) reflex method as that described in [Walker and Davis. *Biol. Psychiatry*, **1997**, 42, 461-471]. The startle response is a coordinated contraction of skeletal muscle groups in response to a high intensity unexpected stimulus. Most sensory modalities can be used, but sound is most frequently employed because it is easily controlled. Thus, when a short burst of sufficient intensity occurs (*e.g.*, 115 dB) an involuntary startle response occurs. High light levels increase the startle response in nocturnal species such as the rat and this effect does not require any pre-conditioning. Anxiolytics – an agent that relieves anxiety - decrease light-enhanced startle.

For the LES test, an apparatus consisting of a commercially available soundproofed startle chamber (*e.g.*, SR-LAB™ Startle Response System, San Diego Instruments, San Diego, CA) can be used. All experimental events and data recording can be controlled by computer program (*e.g.*, SR-LAB™ control unit). Rats are placed within the startle chamber in a small Perspex® cylinder, slightly larger than the rat, which is attached to a base plate containing a strain gauge. Vertical movement of the rat such as occurs during a startle response results in deformation of the base plate, which generates a current in the strain gauge that is proportional to the size of the movement, *i.e.*, the size of the startle response. A loudspeaker

is placed directly above the rat to provide background sound and stimuli. A light source (2500 - 3500 Lux) is located in each startle chamber.

The LES test consists of two 20-minute sessions (first with lights off and then with lights on) of which the first 5 minutes are for habituation, during which background noise of 70 dB intensity is provided within the chamber. At the end of each habituation period, 10 stimulations of 110 dB are presented to habituate the animals. Thereafter, three trial types are presented in pseudo random order, 8 times each. Trials are separated by 15-25 seconds. The trial types are 100, 105 or 110 dB startle during which a 40 ms burst of white noise at 100, 105 or 110 dB is presented, resulting in a startle response. A period of 5 minutes without light or noise separates the two sessions. An appropriate rat species that can be used includes male Rj: Wistar (Hans) rats (180-280 g weight at start of the testing with a maximum weight range per test of 50 g) (Elevage Janvier, Le Genest-Saint-Isle, France). The rats should be allowed to acclimatize to laboratory conditions at least 5 days before testing with free access to food and water. Acclimatization conditions should be comparable to those described in the scientific literature and/or known to those skilled in the art.

The output from the startle platform is recorded for 40 ms starting from the onset of the startle stimulus. Three variables are recorded for each trial: the average response over the whole recording period, the peak response and the time to peak response. The startle intensity is calculated for each rat by averaging the 8 trials of each type under dark or light conditions and calculating the percentage increase in startle amplitude (average and peak values) caused by light (LES). The time to peak response is a measure of reaction time.

The test is performed un-blinded using, e.g., 12 rats per group. Testing includes multiple tests where each test is performed to evaluate a reference compound (e.g., chlordiazepoxide), comparative compound (e.g., pregabalin) and/or a compound of the present invention. For example, in test 1, a known anxiolytic, such as chlordiazepoxide and pregabalin, is used, followed by test 2 using the mGluR5 antagonist 2-methyl-6-(phenylethynyl)-pyridine (MPEP), and then test 3 is performed using a compound of the present invention. Alternatively, each test can be performed concurrently, or in some combination of sequentially and concurrently. For each test, the compound to be evaluated is tested at one or more doses (such as 1, 3, 10, 30 and/or 100 mg/kg) via p.o. administration 60 minutes before

the test in comparison with a vehicle control group. Prior to testing, test compounds can be tested for solubility by cold stirring of the highest intended dose for 10 min in distilled water. If soluble, distilled water can serve as the vehicle. If insoluble, the test compounds can be suspended in 0.2% hydroxypropylmethylcellulose (HPMC) in distilled water. Doses can be prepared as weight to volume (W/V) stock solutions and then serially diluted (V/V) for compounds in solution or separately weighted (W/V) for compounds in suspension.

For each test, data is analyzed by comparing treated groups with the vehicle control using unpaired Student's t tests. LES in each group will be analyzed by comparing within each treated group the intensity of startle reaction under dark and light conditions using paired Student's t tests.

Antidepressive effect can be evaluated using the Flinders Sensitive Line (FSL) rat in the FST and social interaction test as described in [D.H. Overstreet and G. Griebel *Pharmacol Biochem Behav.*, **2005**, 82, 1: 223-227]. More specifically, compounds of the invention are tested at multiple doses (*e.g.*, 10 mg/kg, 30 mg/kg, etc.) by preparing in 20% HP-beta-cyclodextrin and against vehicle control. In addition to an FSL vehicle control group, Flinders Resistant Line rats' vehicle control group is tested. Test compounds are administered daily by IP injection (2 mg/kg injection volume) for 14 days. Animals are tested in the social interaction and forced swim tests on Day 15, 22-24 hours after the injection on Day 14, as described in Overstreet and Griebel **2005**. Six to eight animals per group are tested.

Anxiolytic and antidepressive effect can also be evaluated using a paradigm for decreased HPA axis feedback (David *et al.*, 2007, SFN meeting in San Diego). This model based on the chronic delivery of corticosterone in the drinking water, causes anxiety- and depression-like behaviors in mice. The model consists of a sustained administration of a high dose (35µg/mL), but not a low dose (7µg/mL), of corticosterone for four or seven weeks. Such a treatment induced anxiety- and depression-like behaviour in C57Bl6/NTac mouse strain as indicated by a decreased time spent and number of entries into center of the arena during the 30 minutes open field test (OF), whereas total ambulation was unaltered. Also, the latency to feed was increased in corticosterone-treated mice submitted to the novelty suppressed feeding (NSF) paradigm. As the corticosterone treatment did not alter food-intake in the

home cage (familiar environment), changes in feeding latency were not due to changes in appetite or an underlying metabolic abnormality. Importantly, the adrenocorticotrophic hormone (ACTH) and corticosterone (CORT) response to an acute stressor (6 min forced swim test (FST)), measured as plasma-concentrations, was blunted in C57BL/6NTac mice.

5 These results were confirmed in CD1 strain mice. Three weeks treatment with the antidepressant imipramine (40 mg/kg/day ip) and fluoxetine (18 mg/kg/day ip) reversed the anxiety- and depression-like effects caused by a seven weeks corticosterone treatment in the OF, NSF and FST.

10 In such test, 240 adult male mice of C57Bl/6Ntac strain (Taconic Farms (Denmark)), 8-10 weeks old, which are allowed to acclimate to the facility for at least 1 week prior to testing (e.g., 5 per cage under a 12 h (06:00-18:00) light-dark cycle at 22 °C) with food and water freely available.

15 A compound of the invention (30 or 60 mg/kg, per day in chow), fluoxetine (18 mg/kg per day in drinking water) or vehicle (0.45% β -cyclodextrin $\tilde{e}$, β CD in drinking water) are administered to mice treated via drinking water with either vehicle or corticosterone (35 μ g/mL). After 7 weeks of treatment as indicated below, mice are tested in the following behavioral tests: OF, NSF, FST and sucrose splash grooming test. Treatment is started with either β CD or corticosterone (35 μ g/mL) given via the drinking water for 3 weeks (n=200 mice per group). Thereafter, administration with β CD or corticosterone will continue, and
20 mice are divided into 8 groups of 30 mice as indicated below for 4 additional weeks.

Week 1-8**Week 3-7**vehicle (β CD)

vehicle

vehicle (β CD)

fluoxetine, 18 mg/kg

vehicle (β CD)

test compound, 30 mg/kg

25 vehicle (β CD)

test compound, 60 mg/kg

35 μ g/mL/day corticosterone

vehicle

35 μ g/mL/day corticosterone

fluoxetine, 18mg/kg

35 μ g/mL/day corticosterone

test compound, 30 mg/kg

35µg/mL/day corticosterone test compound, 60 mg/kg

Mice are tested in the behavioral paradigms in this order: OF, NSF, sucrose splash test and then the mouse FST (15 animals/group).

The Open-field test

5 Motor activity is quantified in Plexiglas® open field boxes 43 x 43 cm² (MED associates, Georgia, VT) over a 10 min session. Two sets of 16 pulse-modulated infrared photo beams are placed on opposite walls 2.5 cm apart to record x-y ambulatory movements. A 40-W white bulb placed in the middle of the room provided around 200-lx illumination at floor level. Activity chambers are computer interfaced for data sampling at 100 ms resolution. The
10 computer defined grid lines that divided each open field into center and surrounds regions, with each of four lines being 11 cm from each wall. Dependant measures are total time spent in the center, the numbers of entries into the center and distance traveled in the center divided by total distance traveled. Overall motor activity is quantified as the total distance traveled (cm).

15 *The Novelty-Suppressed Feeding*

The novelty suppressed feeding (NSF) is a conflict test that elicits competing motivations: the drive to eat and the fear of venturing into the center of brightly lit arena. Latency to begin eating is used as an index of anxiety-like behavior because classical anxiolytic drugs decrease it. The NSF is carried out during a 5-min period as previously described (Santarelli
20 et al., 2003). Briefly, the testing apparatus consisted of a plastic box 50x50x20 cm. The floor is covered with approximately 2 cm of wooden bedding. Twenty-four hours prior to behavioral testing, all food is removed from the home cage. At the time of testing, a single pellet of food (regular chow) is placed on a white paper platform positioned in the center of the box. An animal is placed in a corner of the maze and a stopwatch is immediately started.
25 The measure of interest (chewing) is scored when the mouse is sitting on its haunches and biting with the use of forepaws. Immediately after this test, mice are transferred to their home cage and the amount of food consumed in 5 min is measured (home cage food consumption). Mice are tested during the light period. Because antidepressants are known to have various effects on appetite, the feeding drive is assessed by returning animals in their home cage

(familiar environment) immediately after the test. Then, the amount of food consumed over a 5 min-period is measured.

Splash test

The grooming latency is assessed at the end of the corticosterone regimen (end of seventh week) in the presence or absence of 3-weeks of fluoxetine treatment. This test consists in squirting 200 µl of a 10% sucrose solution on the mouse's snout. The grooming frequency is then recorded

The mouse Forced Swim Test

A modified forced swim test procedure as described in [Dulawa *et al. Neuropsychopharmacol.*, **2004**, 29, 1321–1330; Holick *et al. Neuropsychopharmacol.*, **2008**, 33, 2: 406–417] is used. Mice are placed individually into glass cylinders (height: 25 cm, diameter: 10cm) containing 18 cm water that is maintained at 23–25 °C and videotaping will be for 6 min via a tripod-mounted camera positioned directly on the side of the cylinder. An increase of swimming and climbing has been linked to an activation of serotonergic and noradrenergic system in rats [see, e.g., Cryan and Lucki *Pharmacol. & Exp. Therap.*, **2000**, 295, 3: 1120–1126] and in mice [see, e.g., Dulawa *et al.* (**2004**); Holick *et al.*, (**2008**)], respectively. Therefore, the predominant behavior (swimming, immobility or climbing) is scored here during the last 4 min of the 6 min testing period.

Anxiolytic-like properties also can be evaluated using these additional tests: (1) social interaction described in [S.E. File and P. Seth *European Journal of Pharmacology*, **2003**, 463, 35–53], and (2) elevated plus-maze described in [S.M. Korte and S.F. De Boer *European Journal of Pharmacology*, **2003**, 463, 163–175].

Parkinson's disease (PD) can be assessed by measuring the neurotoxicity of MPTP in rats as described in [E. H. Lee *et al. Chin. J. Physiol.*, **1992**, 35, 4: 317–36]. Also experimentally induced striatal DA depletion in animals is a valid model of Parkinsonism, as described in [W. Schultz *Prog. Neurobiol.*, **1982**, 18, 2–3: 121–66]. The capacity of certain substances to damage catecholaminergic neurons has been used extensively to produce DA deficiency in animals, as described in [L. E. Annett *et al. Exp. Neurol.*, **1994**, 125, 2: 228–46]. PD can also be assessed by measuring the neurotoxicity induced by 6-hydroxydopamine (6-OHDA) as

described in [N. Breyse *et al. J. Neurosci.*, **2002**, 22, 13: 5669-5678; D. Rylander *et al. J. Pharmacol. Exp. Ther.*, **2009**, 330, 1: 227-235; and L. Chen *et al.*, "Chronic, systemic treatment with a metabotropic glutamate receptor 5 antagonist in 6-hydroxydopamine partially lesioned rats reverses abnormal firing of dopaminergic neurons," *Brain Res.*, **2009**, 1286, 192-200].

Fragile X Syndrome can be assessed using the *fmr1^{tm1Cgr}* mouse model as described in [Q.J. Yan *et al. Neuropharmacol.*, 2005, 49, 1053-1066] as well as the *Fmr1* knockout mice with a selective reduction in mGluR5 expression as described in [G. Dölen *et al. Neuron*, **2007**, 56, 955-962].

Preclinically, animals also can be evaluated for blockade/attenuation of symptoms associated with schizophrenia. Positive symptoms in animal models of schizophrenia can be evaluated by measuring changes in the overall level of activity of dopamine (DA) activity with concomitant parallel changes in locomotor activity as described in [R. Depoortere *et al. Neuropsychopharmacology*, **2003**, 28, 11: 1889-902], D-amphetamine (AMPH) and phencyclidine (PCP) via induction of model psychosis or locomotor hyperactivity as described in [W. J. Freed *et al. Neuropharmacology*, **1984**, 23, 2A: 175-81; F. Sams-Dodd *Neuropsychopharmacology*, **1998** 19, 1: 18-25]. For example, Depoortere *et al.*, **2003**, have described tests for evaluating locomotor activity, catalepsy, climbing and stereotypy, which relate to positive symptomology and side effect profile, by characterizing compounds with typical and atypical antipsychotic efficacy. Attenuation in apomorphine-induced climbing, stereotypy and catalepsy (AIC) can be evaluated as described in [Y. K. Fung *et al. Pharmacol. Biochem. Behav.*, **1986**, 24, 1: 139-41 and Y. K. Fung *et al. Steroids*, **1987**, 49, 4-5: 287-94]. Additionally, negative symptoms of schizophrenia can be evaluated by measuring social interaction under the influence of NMDA antagonists such as PCP, as described in F. Sams-Dodd, **1998**, *supra*.

Cognitive symptoms of memory, including those from Alzheimer's disease, can be evaluated by such models as the Fear Conditioning Paradigm described in [T. J. Gould *et al. Behav. Pharmacol.*, **2002**, 13, 4: 287-94, and A. O. Hamm *et al. Brain*, **2003**, 126, Pt 2: 267-75] and the Radial Arm Test described in [J. P. Aggleton *et al. Behav. Brain Res.*, **1996**, 19, 2: 133-46], while spatial reference memory and learning can be evaluated in the Morris watermaze

test as described in [Morris. *Learn. Motiv.*, **1981**, 12, 239-260; B. Bontempi *et al.* *Eur. J. Neurosci.* **1996**, 8, 11: 2348-60]. More specifically, in the Morris watermaze test, a circular water tank (150 cm diameter and 45 cm height) is filled with about 30 cm water and maintained at 26–28 °C with an escape platform (15 cm diameter) 18 cm from the perimeter and always in the same position 1.5 cm beneath the surface of the water. The water is made opaque by addition of a non-toxic coloring agent (e.g., milk powder) rendering the platform invisible. Animals are given a single training session over a single day. The training session consists of 4 consecutive trials in the watermaze, each separated by 60 seconds. For each trial, the animal is placed in the watermaze at one of two starting points equidistant from the escape platform and allowed to find the escape platform. The animal is left on the escape platform for 60 seconds before starting a new trial. If the animal does not find the platform within 120 seconds, the animal is removed from the water and placed on the platform for 60 seconds. During the 4 trials, the animals start the watermaze twice from each starting point in a randomly determined order per animal. Appropriate animals for testing with acclimatization conditions are, for example, the male Rj: Wistar (Hans) rats as previously described for the LES test.

The trials are video-recorded and the behavior of animals is analyzed using a video-tracking system (SMART, Panlab, S.L., Cornellà (Barcelona), Spain). The principal measure taken in each trial is the distance traveled to find the platform. Secondary measures taken are the swim speed and escape latency. The test is performed blind using, for example, 12 rats per test group. Testing includes multiple tests using reference compounds and compounds of the present invention that are prepared and administered as previously described LES test. For each test, data is analyzed by comparing treated groups with vehicle controls using one-way ANOVA followed by Dunnett's t tests. To increase comparability with the aforementioned Vogel conflict test, in all tests, rats are subjected to water-deprivation for approximately 24 h before the test (Day 1); however, testing is performed in non-water-deprived rats (Day 2).

Additionally, with respect to cognition, memory and hippocampal hypo-functioning can be assessed by measuring the restoration of synaptic plasticity in ovariectomized (OVX) female rats as described in [M. Day and M. Good *Neurobiol. Learn. Mem.*, **2005**, 83, 1: 13-21]. Further, changes in attention function because of schizophrenia can be examined by the Five

(5) Choice Serial Reaction Time Test (5CSRT) described in [J. L. Muir *et al. Psychopharmacology (Berl)*, **1995**, 118, 1: 82-92 and Robbins *et al. Ann. N. Y. Acad. Sci.*, **1998**, 846, 222-37].

Human patients can be evaluated for cognitive diseases or disorders by any of the tests within the skill of those in the art.

Analgesic activity can be evaluated by neuropathic pain model (the “Chung model”) as described in [Kim and Chung, *Pain*, **1992**, 50, 355-363]. Tight ligation of spinal nerves in rats is associated with hyperalgesia, allodynia and spontaneous pain, and therefore constitutes a model for peripheral neuropathic pain in humans. Antihyperalgesics reduce these chronic signs of pain hypersensitivity. Thus, in the Chung model, rats are anesthetized (sodium pentobarbital 50 mg/kg i.p.) and an incision at the L4-S2 level is performed to expose the left L5 nerve after cleaning the flank with chlorhexidine in spray. A cotton thread (standard, non-surgery quality), disinfected with pure alcohol, is placed around the L5 nerve and a simple ligature is tied tightly around the L5 nerve. The wound is then sutured and sprayed with CothiVet[®] (hydrocotyle tincture spray) (Neogen[®] Corp., Lexington, KY). The rats receive a s.c. injection of Clamoxyl (0.67 mL/kg) and are allowed to recover. At least 2 weeks after the surgery, when the chronic pain state is fully installed, rats are submitted consecutively to tactile and thermal stimulation of both hindpaws.

For tactile stimulation, the animal is placed under an inverted acrylic plastic box (18 x 11.5 x 13 cm) on a grid floor. The tip of an electronic Von Frey probe (Model 1610, BIOSEB, Vitrolles Cedex, France) is then applied with increasing force first to the non-lesioned and then the lesioned hindpaw and the force required to induce paw-withdrawal is automatically recorded. This procedure is carried out 3 times and the mean force per paw is calculated.

For heat stimulation, the apparatus (No. 7371, Ugo Basile, Comerio VA, Italy) consists of individual acrylic plastic boxes (17 x 11 x 13 cm) placed upon an elevated glass floor. A rat is placed in the box and left free to habituate for 10 minutes. A mobile infrared radiant source (96 ± 10 mW/cm²) is then focused first under the non-lesioned and then the lesioned hindpaw and the paw-withdrawal latency is automatically recorded. In order to prevent tissue damage, the heat source is automatically turned off after 45 seconds.

Prior to receiving compound treatment all animals are submitted to tactile stimulation of the hindpaws and assigned to treatment groups matched on the basis of the pain response of the lesioned hindpaw. The test is performed blind using, for example, 10 water-deprived rats per group. Appropriate animals for testing are, for example, the male Rj: Wistar (Hans) rats as previously described for the LES test. Testing includes multiple tests using reference compounds and compounds of the present invention. In addition to the pregabalin and MPEP as previously described for the LES test, duloxetine can be used as a reference compound since it is an antihyperalgesic with respect to neuropathic pain associated with diabetes and fibromyalgia. Compounds are prepared and administered as previously described LES test. Testing can be performed using the same batch of operated rats repeatedly, with a minimum wash-out of 1 week between treatments. Also, to increase comparability with the aforementioned Vogel conflict test, in all tests, rats are subjected to water-deprivation for approximately 48 hours before each test. For each Chung model test, data will be analyzed by comparing treated groups with appropriate controls using unpaired Student's t tests.

Additionally, analgesic/anti-inflammatory activity can be evaluated *in vivo* using the Formalin Paw Test in the mouse such as that described by [Wheeler-Aceto et al, *Psychopharmacology*, **1991**, *104*, 35-44). For the test, mice are given an intraplantar injection of 5% formalin (25 μ l) into the posterior left paw. This treatment induces paw licking in control animals. The time spent licking is counted for 5 minutes, beginning immediately after injection of formalin (early phase) and for 15 minutes starting 15 minutes after injection of formalin (late phase).

The test is performed blind using, e.g., 10 mice per group. Appropriate animals for testing are, for example, male Rj: NMRI mice (Elevage Janvier), weighing 20 - 30 g (max. range per experiment = 5 g) at the beginning of testing. Animals are acclimatized as described for the animals used in the LES test. Testing includes multiple tests using reference compounds (e.g., morphine), comparative compounds (e.g., gabapentin and duloxetine), and compounds of the present invention. Compounds of the invention can be evaluated at multiple doses as previously described in the LES test, and administered s.c. 60 minutes before formalin in comparison with a vehicle control group, while morphine (64 mg/kg p.o.), gabapentin (300

mg/kg p.o.) and duloxetine (10 mg/kg p.o.) are administered p.o. 60 minutes before formalin. Data is analyzed by comparing treated groups with vehicle control groups using unpaired Mann-Whitney U tests.

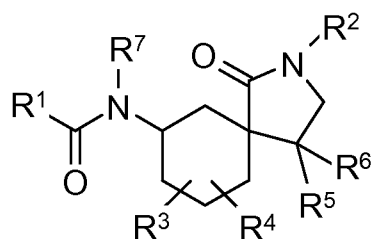
Multiple sclerosis can be evaluated by the experimental autoimmune encephalomyelitis (EAE) model described in [H. Y. Liu *et al. J. Neurosci. Res.*, **2002**, 70, 2: 238-48].

Those skilled in the art will recognize that various changes and/or modifications may be made to aspects or embodiments of this invention and that such changes and/or modifications may be made without departing from the spirit of this invention. Therefore, it is intended that the appended claims cover all such equivalent variations as will fall within the spirit and scope of this invention.

Each reference cited in the present application, including literature references, books, patents and patent applications, is incorporated herein by reference in its entirety.

What is claimed is:

- 1) A compound of formula (I):

**(I)**

wherein:

R^1 and R^2 are each independently aryl, heteroaryl, alkyl, cycloalkyl, ketocycloalkyl, or heterocyclyl, which is optionally mono-, di-, or tri-substituted independently with alkyl, cycloalkyl, alkoxy, hydroxy, halogen, cyano, trifluoroalkyl, amino, acyl, aryl, heteroaryl, heterocyclyl, $-C(O)NHR^{30}$, $-C(O)N(R^{30})R^{31}$, $-NHC(O)R^{30}$, $-N(R^{30})C(O)R^{31}$, $-NHR^{30}$, $-N(R^{30})R^{31}$, or $-OR^{30}$; wherein:

R^{30} and R^{31} are each independently C_1 - C_6 alkyl or C_1 - C_6 cycloalkyl that is optionally substituted with acyl, halogen, $-CN$, $-NH_2$, $-NH(C_1-C_3alkyl)$, $-N(C_1-C_3alkyl)_2$, C_1 - C_3alkyl heterocyclyl, C_1 - C_3alkyl carbamate, $-C(O)NH(C_1-C_3alkyl)$, $-C(O)N(C_1-C_3alkyl)_2$, $-NHC(O)-C_1-C_3alkyl$, $-N(C_1-C_3alkyl)-C(O)-C_1-C_3alkyl$, OH , or $-O-C_1-C_6alkyl$; and

each aryl, heteroaryl, heterocyclyl substituent is optionally substituted with C_1 - $3alkyl$, C_3 - $5cycloalkyl$, C_1 - $3alkoxy$, hydroxy, halogen, cyano, trifluoroalkyl, or amino;

R^3 , R^4 , R^5 and R^6 are each independently H , C_1 - $3alkyl$, C_3 - $5cycloalkyl$, halogen, or hydroxy;

R^7 is H ; or

R¹ and R⁷ taken together with the -C(O)N- to which they are attached form a mono- or bicyclic 4- to 12-membered heterocycloalkyl or heteroaryl, which optionally contains 1-3 additional heteroatoms; or

a pharmaceutically acceptable salt thereof.

- 2) The compound of claim 1, wherein R¹ and R² are both aryl.
- 3) The compound of claim 1, wherein R¹ and R² are both heteroaryl.
- 4) The compound of claim 1, wherein R¹ is aryl and R² is heteroaryl.
- 5) The compound of claim 1, wherein R¹ is heteroaryl and R² is aryl.
- 6) The compound of claim 1, wherein either R¹ or R² is heteroaryl
- 7) The compound of claim 1, wherein either R¹ or R² is aryl.
- 8) The compound of claim 1, wherein at least one aryl is phenyl.
- 9) The compound of claim 1, wherein R¹ is aryl or heteroaryl and R² is cycloalkyl, ketocycloalkyl or heterocyclyl.
- 10) The compound of claim 1, wherein the mono-, di-, or tri-substituents are independently selected from the group consisting of methyl, methoxy, dimethylamino-ethoxy, amino, methylamino, dimethylamino, cyano, chloro, cyano, dimethylamino, dimethylamino-ethoxy, methyl, methylamino, methoxy, fluoro, -C(O)NHCH₃, phenyl, furanyl, pyrrolidinyl, thiophenyl and trifluoromethyl.
- 11) The compound of claim 10, wherein the phenyl, is optionally substituted with fluorine.
- 12) The compound of claim 1, wherein the compound is:

trans-Pyridine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-Pyridine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

trans-6-Methyl-pyridine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [(5R,7R)-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [(5S,7S)-2-(3-chloro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

cis-Pyridine-2-carboxylic acid [2-(6-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

3-Chloro-*N*-[2-(6-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-Pyridine-2-carboxylic acid [2-(3-cyano-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(3-cyano-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

cis-6-Methyl-pyrazine-2-carboxylic acid [2-(3-cyano-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

cis-6-Methyl-pyrazine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

cis-Pyrazine-2-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-1-Methyl-1*H*-pyrazole-3-carboxylic acid [2-(3-chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-*N*-[2-(3-Cyano-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide;

cis-*N*-[2-(3-Cyano-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-chloro-benzamide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

trans-6-Methyl-pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

cis-Pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5] dec-7-yl]-amide;

trans-Pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyrazine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

trans-6-Methyl-pyrazine-2-carboxylic acid[2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(6-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

trans-3-Fluoro-*N*-[2-(6-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5] dec-7-yl]-benzamide;

Pyridine-2-carboxylic acid [(5*R*,7*R*)-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

3-Fluoro-*N*-(1-oxo-2-pyridin-2-yl-2-aza-spiro[4.5]dec-7-yl)-benzamide;

cis-3-Fluoro-*N*-[2-(6-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

3-Fluoro-*N*-[(5*R*,7*R*)-2-(6-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5] dec-7-yl]-benzamide;

cis-Pyridine-2-carboxylic acid [2-(4-methyl-pyrimidin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-Pyridine-2-carboxylic acid [2-(4-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(4-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-Pyridine-2-carboxylic acid [2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(4-methyl-pyrimidin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-3-Fluoro-*N*-[2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-3-Fluoro-*N*-[2-(4-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-3-Fluoro-*N*-[2-(4-methyl-pyrimidin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-3-Fluoro-*N*-[2-(6-methyl-pyrazin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-Pyridine-2-carboxylic acid [2-(6-methyl-pyrazin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(6-methyl-pyrazin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [1-oxo-2-(6-trifluoromethyl-pyridin-2-yl)-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(6-cyano-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(4-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

6-Methyl-pyridine-2-carboxylic acid (1-oxo-2-pyridin-2-yl-2-aza-spiro[4.5]dec-7-yl)-amide;

cis-6-Methyl-pyridine-2-carboxylic acid (1-oxo-2-phenyl-2-aza-spiro[4.5]dec-7-yl)-amide;

cis-6-Methyl-pyridine-2-carboxylic acid (1-oxo-2-m-tolyl-2-aza-spiro[4.5]dec-7-yl)-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(4-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(5-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(3-methyl-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(2-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(2-methyl-pyridin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-*N*-[2-(6-Cyano-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide;

cis-Pyridine-2-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

cis-6-Methyl-pyrazine-2-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

cis-Pyrazine-2-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

cis-2-Methyl-pyrimidine-4-carboxylic acid [2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-3-Chloro-*N*-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-2-Methyl-pyrimidine-4-carboxylic acid [2-(6-methyl-pyrazin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-2-Methyl-pyrimidine-4-carboxylic acid [2-(3-cyano-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-2-Methyl-pyrimidine-4-carboxylic acid [1-oxo-2-(6-trifluoromethyl-pyridin-2-yl)-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(6-methyl-pyridin-3-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(5-fluoro-pyridin-3-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-3-Fluoro-*N*-[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-3-Fluoro-*N*-[2-(2-methyl-pyridin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

6-Methyl-pyridine-2-carboxylic acid [(5*R*,7*R*)-2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-5-Fluoro-pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-2-Methyl-pyrimidine-4-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-Pyrimidine-4-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(5-methyl-pyridin-3-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(3-methoxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

6-Methyl-pyridine-2-carboxylic acid [(5*R*,7*R*)-2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-Pyridine-2-carboxylic acid [2-(5-fluoro-pyridin-3-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-Pyridine-2-carboxylic acid [2-(3,4-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-*N*-[2-(3-Fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-isonicotinamide;

cis-*N*-[2-(3-Fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-2-methyl isonicotinamide;

cis-Pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-azaspiro[4.5]dec-7-yl]-amide;

6-Methyl-pyridine-2-carboxylic acid [(5*R*,7*R*)-2-(4-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

6-Methyl-pyridine-2-carboxylic acid [(5S,7S)-2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [(5R,7R)-2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid (2-benzyl-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide;

cis-3-Methyl-*N*-[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-benzamide;

cis-3,5-Difluoro-*N*-[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-benzamide;

cis-6-Methyl-pyrazine-2-carboxylic acid {2-[6-(4-fluoro-phenyl)-pyrimidin-4-yl]-1-oxo-2-aza-spiro [4.5]dec-7-yl}-amide;

cis-6-Methyl-pyridine-2-carboxylic acid {2-[6-(4-fluoro-phenyl)-pyrimidin-4-yl]-1-oxo-2-aza-spiro [4.5]dec-7-yl}-amide;

cis-3-Fluoro-*N*-{2-[6-(4-fluoro-phenyl)-pyrimidin-4-yl]-1-oxo-2-aza-spiro[4.5]dec-7-yl}-benzamide;

cis-4-Fluoro-*N*-[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-benzamide;

cis-3,4-Difluoro-*N*-[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-benzamide;

cis-2-Fluoro-*N*-[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-benzamide;

cis-2-Methyl-*N*-[2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-isonicotinamide;

cis-6-Hydroxymethyl-pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Trifluoromethyl-pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

N-[(5R,7R)-2-(3-Fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-2-methyl-isonicotinamide;

cis-6-Trifluoromethyl-pyridine-2-carboxylic acid [2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [(5R,7S)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [(5S,7R)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide; or

cis-2-[2-(3-Chloro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-2,3-dihydro-isoindol-1-one;

Pyridine-2-carboxylic acid [(5*S*,7*S*)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [(5*R*,7*R*)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [(5*S*,7*R*)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [(5*R*,7*S*)-9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

trans-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-Pyridine-2-carboxylic acid [9,9-difluoro-2-(4-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [9,9-difluoro-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-6-Methyl-pyridine-2-carboxylic acid [9,9-difluoro-2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-Pyridine-2-carboxylic acid [2-(3,5-difluoro-phenyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-Pyridine-2-carboxylic acid [9,9-difluoro-2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-Pyridine-2-carboxylic acid [9,9-difluoro-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [(5*S*,7*R*)-2-(3,5-difluoro-phenyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [(5*R*,7*S*)-2-(3,5-difluoro-phenyl)-9,9-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-1,9-dioxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

trans-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [(5*R*,7*S*,9*S*)-2-(3,5-difluoro-phenyl)-9-hydroxy-9-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [(5R,7S,9R)-2-(3,5-difluoro-phenyl)-9-hydroxy-9-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

N-[(5S,7R)-9,9-Difluoro-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide;

N-[(5R,7S)-9,9-Difluoro-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide;

trans-2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9-fluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-3-Fluoro-*N*-[2-(3-fluoro-phenyl)-1,9-dioxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-6-Methyl-pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-1,9-dioxo-2-aza-spiro[4.5]dec-7-yl]-amide;

trans-3-Fluoro-*N*-[2-(3-fluoro-phenyl)-9-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

trans-6-Methyl-pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-9-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

6-Methyl-pyridine-2-carboxylic acid [(5S,7R)-9,9-difluoro-2-(5-fluoro-pyridin-2-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-N-[9,9-Difluoro-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide;

cis-2-Methyl-pyrimidine-4-carboxylic acid [9,9-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-azaspiro[4.5]dec-7-yl]-amide;

cis 3-Fluoro-*N*-[2-(3-methoxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis 3-Fluoro-*N*-[2-(3-hydroxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-N-[(5S,7S)-2-(3-Dimethylamino-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide;

cis-3-Fluoro-*N*-[2-(4-methoxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-3-Fluoro-*N*-{2-[3-(3-morpholin-4-yl-propyl)-phenyl]-1-oxo-2-aza-spiro[4.5]dec-7-yl}-benzamide;

cis-3-Fluoro-*N*-[2-(3-fluoro-5-methoxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-3-Fluoro-*N*-{1-oxo-2-[3-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-2-aza-spiro[4.5]dec-7-yl}-benzamide;

cis-Thiazole-2-carboxylic acid [2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

cis-N-[2-(4-Dimethylamino-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide;

cis-3-Fluoro-*N*-(1-oxo-2-thiazol-2-yl-2-aza-spiro[4.5]dec-7-yl)-benzamide;

cis-Thiazole-2-carboxylic acid [(2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide;

cis-2-Methyl-pyrimidine-4-carboxylic acid [2-(3-fluoro-5-methoxy-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide;

cis-*N*-[2-(3-Cyano-5-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide;

cis-Thiazole-2-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide;

cis-2-Methyl-thiazole-4-carboxylic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide;

cis-Pentanoic acid [2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide;

cis-*N*-[2-(3,5-Difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-butyramide;

3-Fluoro-*N*-[(5*R*,7*R*)-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

3-Chloro-*N*-[(5*R*, 7*R*)-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-5-Fluoro-pyridine-2-carboxylic acid [(2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl)-amide;

cis-3-Fluoro-*N*-[1-oxo-2-(2-trifluoromethyl-pyrimidin-4-yl)-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-*N*-[2-(2,6-Dimethyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-3-fluoro-benzamide;

3-Methyl-*N*-[(5*R*, 7*R*)-2-(2-methyl-pyrimidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

cis-3-Fluoro-*N*-(2-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl)-benzamide;

cis-3-Fluoro-*N*-(2-ethyl-1-oxo-2-aza-spiro[4.5]dec-7-yl)-benzamide;

cis-3-Fluoro-*N*-(2-propyl-1-oxo-2-aza-spiro[4.5]dec-7-yl)-benzamide;

6-Methyl-pyridine-2-carboxylic acid[(5*R*,7*R*)-1-oxo-2-(2-trifluoromethyl-pyrimidin-4-yl)-2-aza-spiro[4.5]dec-7-yl)-amide;

3-Fluoro-*N*-[2-(1-methyl-piperidin-4-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

3-Fluoro-*N*-[2-(1-methyl-1*H*-pyrazol-3-yl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-benzamide;

2-Methyl-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid [(5*R*,7*R*)-2-(3,5-difluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]amide; or

a pharmaceutically acceptable salt thereof.

- 13) The compound of claim 1, wherein the compound is:

Pyridine-2-carboxylic acid [9-fluoro-2-(3-fluoro-phenyl)-9-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-9-fluoro-9-methyl-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [9-fluoro-2-(4-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [8,8-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [8-fluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-8-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [8-fluoro-2-(3-fluoro-phenyl)-8-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-8-hydroxy-8-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-8,8-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-8-fluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-8-fluoro-8-methyl-1-oxo-2-aza-spiro [4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-8-hydroxy-8-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-8-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [8,8-difluoro-2-(4-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [8-fluoro-2-(4-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [8-fluoro-2-(4-fluoro-phenyl)-8-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(4-fluoro-phenyl)-8-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(4-fluoro-phenyl)-8-hydroxy-8-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [4,4-difluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [4-fluoro-2-(3-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-4-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [4-fluoro-2-(3-fluoro-phenyl)-4-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

Pyridine-2-carboxylic acid [2-(3-fluoro-phenyl)-4-hydroxy-4-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-4,4-difluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-4-fluoro-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-4-fluoro-4-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-4-hydroxy-4-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(3,5-difluoro-phenyl)-4-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [4,4-difluoro-2-(4-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [4-fluoro-2-(4-fluoro-phenyl)-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [4-fluoro-2-(4-fluoro-phenyl)-4-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(4-fluoro-phenyl)-4-hydroxy-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide;

2-Methyl-pyrimidine-4-carboxylic acid [2-(4-fluoro-phenyl)-4-hydroxy-4-methyl-1-oxo-2-aza-spiro[4.5]dec-7-yl]-amide; or

a pharmaceutically acceptable salt thereof

- 14) A pharmaceutical composition comprising at least one compound of claim 1 or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier.
- 15) A use of a compound of claim 1 in the preparation of a medicament for the treatment of a cognitive, neurodegenerative, psychiatric or neurological disease or disorder.

- 16) The use of claim 15, wherein the cognitive or neurodegenerative disease or disorder is selected from a group consisting of a mood disorder, an anxiety, a schizophrenia, Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's chorea, amyotrophic lateral sclerosis, Creutzfeld-Jakob disease, a trauma-induced neurodegeneration, AIDS-induced encephalopathy, a non-AIDS-induced encephalopathy, Fragile X syndrome, an autism spectrum disorder, and a combination thereof.
- 17) A use of a compound of claim 1 in the preparation of a medicament for the treatment of a gastroesophageal reflux disease or disorder.
- 18) A use of a compound of claim 1 in the preparation of a medicament for the treatment of alcohol dependence.