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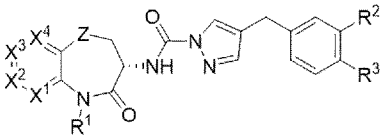
(54) Title: FUSED RING HETEROARYL COMPOUNDS AS RIPK1 INHIBITORS



I

(57) Abstract: The invention provides novel substituted heterocyclic compounds represented by Formula I, or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof, and a composition comprising these compounds. The compounds provided can be used as inhibitors of RIPK1 and the therapeutic methods.

Description

Title of Invention: FUSED RING HETEROARYL COMPOUNDS AS RIPK1 INHIBITORS

Technical Field

[1] This invention relates to a series of substituted heterocyclic compounds which are inhibitors of RIP1 kinase-mediated disease or disorder and use the therapeutics.

Background Art

[2] Receptor-interacting protein-1 (RIPl) kinase is a serine/threonine protein kinase, referred to as RIPK1, RIP1 or RIP. RIPl kinase has a crucial role whether the cell live or die. RIP1 is involved in the apoptosis and non-apoptotic cell death; necroptosis [1]. The intracellular domains of TNF receptor1(TNFR1), FAS and TRAIL receptor 2 (TRAILR2) together include death domain (DD), they were stimulated by ligands tumor necrosis factor alpha (TNFα), Fas ligand (FASL) and TRAIL which recruit RIP1 and binding of their DD to that of RIP1. Stimulation of TNFR1 by TNFα leads to the formation of the complex I which leads to the activation of NF-kB has an important role in modulating the RIP1 of activation and activates an important cell survival program [2]. RIP1 activation can lead to cell death pathway by the formation of a RIP1-TNF receptor associated death domain protein (TRADD)-FAS-associated DD protein (FADD) - caspase 8 complexes (complex IIa), which stimulates caspase activation and leads to RIPK1-dependent apoptosis (RDA). [3-9]. If caspase-8 activity is blocked, the recruited protein receptor-interacting serine/threonine-protein kinase 3 (RIPK3) kinase which drives necroptosis by driving formation of a RIP1-RIP3- mixed lineage kinase domain-like (MLKL) complex (complex IIb), which drives the cell lysis and disruption of cell membrane [10-11].

[3] Necroptosis and RIP1 have been serve a crucial checkpoint during embryonic development. The activation of necroptosis and RIP1 may represent an important pathological mechanism and implicated in many human diseases by mediating cell death and inflammation. Necroptosis may also has been related to disordered of pathogenesis of the central nervous system (CNS) diseases, atherosclerosis, Huntington's disease, colitis, steatohepatitis, acute hepatitis, stroke, myocardial infarction, the intestinal epithelium and skin. Therefore, necroptosis inhibitors are a crucial role for clinical drug development. [12-14]

[4] Necroptosis can be inhibited by inactivating RIP1 kinases or RIP3 kinase. The first and often used inhibitor of necroptosis is RIP1-inhibitor necrostatin-1 (Nec-1). Nec-1 demonstrated efficiency in vitro and in vivo. Nec-1 ameliorated renal and brain ischemia/reperfusion injury, ConA-induced hepatitis, DSS-induced colitis and

decreased the symptoms of Huntington's disease in a murine study [15-19].

[5] Therefore, the synthesis potent selective inhibitors of RIP1 kinase can be treated of diseases, such as inflammation and necroptotic cell death. [20] In recent, RIPl kinase inhibitors differ structurally from necrostatin class of compounds [21-22].

[6] References cited above, each of which is hereby incorporated by reference in its entirety:

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Disclosure of Invention

Technical Problem

[29] The technical problem to be solved by the present invention is to provide novel a compound of formula I.

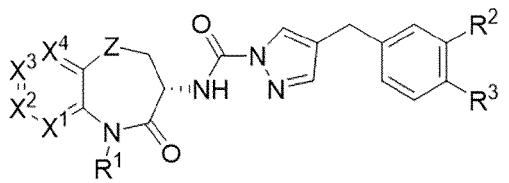
[30] Another technical problem to be solved by the present invention is to provide a novel compound of formula I having inhibitory activity for RIPK1.

[31] Yet another technical problem to be solved by the present invention is to provide a pharmaceutical composition comprising the compounds above, pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof and the salts thereof,

[32] Yet another technical problem to be solved by the present invention is to provide a pharmaceutical composition for preventing and/or treating the diseases associated with RIP1 kinase.

Solution to Problem

[33] In order to solve the problems above, the present invention provides a compound of formula I, or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof:

[34] 

I

[35] wherein

[36] R^1 is H or optionally substituted C1-C6 alkyl;

[37] R^2 and R^3 are each independently H, methyl, CF_3, halogen, or cyano;

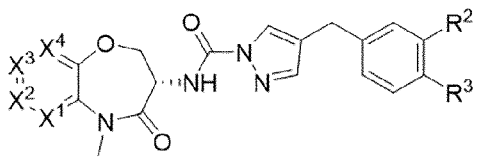
[38] X^1, X^2, X^3, and X^4 are each independently CR^4 or N;

[39] R^4 is H, NH_2, OH, OMe, halogen, cyano, or C1-C6 alkyl;

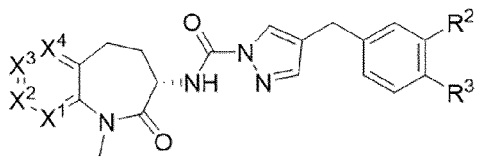
[40] Z is CH_2, NR^1, O, or S;

[41] Compounds of Formula I further include the absolute configuration compounds of Formula IIa and IIb.

[42]



IIa



IIb

[43] or salt thereof,

[44] wherein;

[45] X^1, X^2, X^3, and X^4 are each independently CR^4 or N;

[46] R^4 is H, NH_2, OH, OMe, halogen, cyano, or C1-C6 alkyl;

[47] R^2 and R^3 are each independently H, methyl, CF_3, halogen, or cyano;

[48] Compounds of present invention are inhibitors of the RIP1 kinase and, consequently, are useful for treating inflammatory bowel disease (including Crohn's disease and ulcerative colitis), psoriasis, retinal detachment, retinitis pigmentosa, arthritis (including rheumatoid arthritis, spondyloarthritis, gout, osteoarthritis, and systemic onset juvenile idiopathic arthritis (SoJIA)), transplant rejection, organ transplantation (for donors and recipients), multiple sclerosis, tumor necrosis factor receptor-associated periodic syndrome, multiple organ dysfunction syndrome (MODS), thermal injury/burn, systemic inflammatory response syndrome (SIRS), radiation injury, radiotherapy, chemotherapy, pneumonias, hemorrhagic shock, trauma (including multiple trauma), traumatic brain injury, acute pancreatitis, critical illness (in general), sepsis, septic shock, Stevens-Johnson syndrome, toxic epidermal necrolysis, stroke, heat stroke, stroke-associated pneumonia, Multi-Organ Dysfunction Syndrome (MODS), Acute Respiratory Distress Syndrome (ARDS), intestinal obstruction, liver cirrhosis, surgery, major abdominal operations, abdominal aortic aneurysm repair, large bowel resections, ischemia reperfusion injury (including ischemia reperfusion injury of solid organs, (gut, brain, liver, kidney), and limb ischemia), bowel ischemia (small intestine and large intestine), cardiac surgery requiring cardio-pulmonary bypass, autoimmune hepatitis, autoimmune hepatobiliary diseases, autoimmune ITP, Huntington's disease, Alzheimer's disease, ALS, Parkinson's disease, Lewy body disease, spinal muscular atrophy, allergic disease, asthma, atopic dermatitis, type I diabetes, Wegener's granulomatosis, Behcet's disease, interleukin-1 converting enzyme associated fever syndrome, pancreatic cancer, metastatic adenocarcinoma of the pancreas, pancreatic ductal adenocarcinoma, mesothelioma, melanoma, colorectal cancer, acute myeloid leukemia, metastasis, glioblastoma, breast cancer, gallbladder cancer, clear cell renal carcinoma, non-small cell lung carcinoma, and radiation induced necrosis.

[49] In other aspects, the present invention is directed to a pharmaceutical composition comprising an effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. In some em-

bodiments, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier, adjuvants and/or excipients. In some embodiments, such a composition may contain at least one of preservatives, agents for delaying absorption, fillers, binders, adsorbents, buffers, disintegrating agents, solubilizing agents, and other carriers, adjuvants and/or excipients as inert ingredients. The composition may be formulated with a method well-known in the art.

[50] In some aspects, the present invention is directed to a method of treating a disease in an individual suffering from said disease comprising administering to said individual a therapeutically effective amount of a composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof.

[51] In other aspects, the present invention is directed to a method of treating a disorder in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or pro- drug thereof.

[52] In other aspects, the present invention is directed to a method of treating a disorder in a human, comprising administering to said human a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or pro-drug thereof.

[53] In other aspects, RIP1 kinase-mediated diseases or disorders are described herein and include inflammatory bowel disease (including Crohn's disease and ulcerative colitis), psoriasis, retinal detachment, retinitis pigmentosa, arthritis (including rheumatoid arthritis, spondylarthritis, gout, osteoarthritis, and systemic onset juvenile idiopathic arthritis (SoJIA)), transplant rejection, organ transplantation (for donors and recipients), multiple sclerosis, tumor necrosis factor receptor-associated periodic syndrome, multiple organ dysfunction syndrome (MODS), thermal injury/burn, systemic inflammatory response syndrome (SIRS), radiation injury, radiotherapy, chemotherapy, pneumonias, hemorrhagic shock, trauma (including multiple trauma), traumatic brain injury, acute pancreatitis, critical illness (in general), sepsis, septic shock, Stevens-Johnson syndrome, toxic epidermal necrolysis, stroke, heat stroke, stroke-associated pneumonia, Multi-Organ Dysfunction Syndrome (MODS), Acute Respiratory Distress Syndrome (ARDS), intestinal obstruction, liver cirrhosis, surgery, major abdominal operations, abdominal aortic aneurysm repair, large bowel resections, ischemia reperfusion injury (including ischemia reperfusion injury of solid organs, (gut, brain, liver, kidney), and limb ischemia), bowel ischemia (small intestine and large intestine), cardiac surgery requiring cardio-pulmonary bypass, autoimmune hepatitis, autoimmune hepatobiliary diseases, autoimmune ITP, Huntington's disease, Alzheimer's disease, ALS, Parkinson's disease, Lewy body disease, spinal muscular

atrophy, allergic disease, asthma, atopic dermatitis, type I diabetes, Wegener's granulomatosis, Behcet's disease, and interleukin-1 converting enzyme associated fever syndrome,

[54] In other aspects, the present invention is directed to a method of treating a pancreatic cancer, metastatic adenocarcinoma of the pancreas, pancreatic ductal adenocarcinoma, mesothelioma, melanoma, colorectal cancer, acute myeloid leukemia, metastasis, glioblastoma, breast cancer, gallbladder cancer, clear cell renal carcinoma, non-small cell lung carcinoma, and radiation induced necrosis certain the RIP1 kinase-mediated disease or disorder in a mammal, including a human, comprising administering to said mammal a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable salt, ester, prodrug, solvate, such as hydrate, polymorph or tautomer thereof.

[55] In other aspects, the present invention is directed to a method of treating a disorder or condition which is modulated by the RIP1 kinase in a mammal, including a human, comprising administering to said mammal an amount of the compound of formula I, or a pharmaceutically acceptable salt, ester, prodrug, solvate, such as hydrate, polymorph or tautomer thereof, effective to modulate said cascade. The appropriate dosage for a particular patient can be determined, according to known methods, by those skilled in the art.

[56] In other aspects, the present invention is directed to use of compound of formula I or a pharmaceutically acceptable salt, ester, prodrug, solvate, such as hydrate, polymorph or tautomer thereof in the preparation of a pharmaceutical composition. The pharmaceutical composition can be used for treating a disorder or condition which is modulated by the RIP1 kinase in a mammal, including a human.

[57] In other aspects, the present invention is directed to a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof. In some embodiments, the pharmaceutical composition is in a form suitable for oral administration. In further or additional embodiments, the pharmaceutical composition is in the form of a tablet, capsule, pill, powder, sustained release formulation, solution and suspension. In some embodiments, the pharmaceutical composition is in a form suitable for parenteral injection, such as a sterile solution, suspension or emulsion; for topical administration as an ointment or cream or for rectal administration as a suppository. In further or additional embodiments, the pharmaceutical composition is in unit dosage forms suitable for single administration of precise dosages. In further or additional embodiments, the amount of compound of formula I is in the range of about 0.001 to about 1000 mg/kg body weight/day. In further or additional embodiments, the amount of compound of formula I is in the range of about 0.5 to about 50 mg/kg body weight/day.

[58] In other aspects, the present invention is directed to a process for preparing a compound of formula I or a pharmaceutically acceptable salt, solvate, polymorph, ester, tautomer or prodrug thereof.

Advantageous Effects of Invention

[59] In the present invention, novel compounds are provided to inhibit RIPK1. In this regard, the present invention can be used for preventing and/or treating various RIP1 kinase-mediated diseases or disorders and use the therapeutics.

Best Mode for Carrying out the Invention

[60] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized.

[61] While preferred embodiments of the present invention have been shown and described herein such embodiments are provided by way of example only. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. Those ordinary skilled in the art will appreciate that numerous variations, changes, and substitutions are possible without departing from the invention. It is intended that the following claims define the scope of aspects of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

[62] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, without limitation, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

[63] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. All patents, patent applications, published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety. In the event that there is a plurality of definitions for terms herein, those in this section prevail. Where reference is made to a URL or other such identifier or address, it is understood that such identifiers can change and particular information on the internet can come and go, but equivalent information can be found by searching the internet or other appropriate reference source. Reference thereto evidences the availability and public dissemination of such information.

[64] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any

subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. It should also be noted that use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes", and "included" is not limiting. Likewise, use of the term "comprising" as well as other forms, such as "comprise", "comprises", and "comprised" is not limiting.

[65] Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg "ADVANCED ORGANIC CHEMISTRY 4 TH ED." Vols. A (2000) and B (2001), Plenum Press, New York. Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, IR and UV/Vis spectroscopy and pharmacology, within the skill of the art are employed. Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those known in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Reactions and purification techniques can be performed e.g., using kits of manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed of conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. Throughout the specification, groups and substituents thereof can be chosen by one skilled in the field to provide stable moieties and compounds.

[66] Unless otherwise noted, the use of general chemical terms, such as though not limited to "alkyl," "amine," "aryl," are equivalent to their optionally substituted forms. For example, "alkyl," as used herein, includes optionally substituted alkyl.

[67] The term "optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" means either "alkyl" or "substituted alkyl" as defined below. Further, an optionally substituted group may be un-substituted (e.g., CH_2CH_3), fully substituted (e.g., CF_2CF_3),mono-substituted (e.g., CH_2CH_2F) or substituted at a level anywhere in-between fully substituted and mono- substituted (e.g., CH_2CHF_2, CF_2CH_3,$CFHCHF_2$, etc.). It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns (e.g., substituted alkyl includes op-

tionally substituted cycloalkyl groups, which in turn are defined as including optionally substituted alkyl groups, potentially ad infinitum) that are sterically impractical and/or synthetically non-feasible. Thus, any substituents described should generally be understood as having a maximum molecular weight of about 1,000 daltons, and more typically, up to about 500 daltons (except in those instances where macromolecular substituents are clearly intended, e.g., polypeptides, polysaccharides, polyethylene glycols, DNA, RNA and the like).

[68] As used herein, C_1-Cn, includes C_1-C_2, C_1-C_3, ... C_1-Cn. By way of example only, a group designated as "C_1-C_4" indicates that there are one to four carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms, as well as the ranges C_1-C_2 and C_1-C_3. Thus, by way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl group, i.e., the alkyl group is selected from among methyl, ethyl, propyl, iso-propyl, n-butyl, isobutyl, sec-butyl, and t-butyl. Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range; e.g., "1 to 10 carbon atoms" means that the group may have 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, 6 carbon atoms, 7 carbon atoms, 8 carbon atoms, 9 carbon atoms, or 10 carbon atoms.

[69] The terms "heteroatom" or "hetero" as used herein, alone or in combination, refer to an atom other than carbon and hydrogen. Heteroatoms are independently selected from among oxygen, nitrogen, sulfur, phosphorous, silicon, selenium and tin but are not limited to these atoms. In embodiments in which two or more heteroatoms are present, the two or more heteroatoms can be the same as each another, or some or all of the two or more heteroatoms can each be different from the others.

[70] The term "alkyl" as used herein, alone or in combination, refers to an optionally substituted straight-chain, or optionally substituted branched-chain saturated hydrocarbon monoradical having from one to about ten carbon atoms, more preferably one to six carbon atoms. Examples include, but are not limited to methyl, ethyl, n-propyl, isopropyl, 2-methyl-l-propyl, 2-methyl-2-propyl, 2-methyl-l-butyl, 3 -methyl-l-butyl, 2-methyl-3-butyl, 2,2-dimethyl-l-propyl, 2-methyl-l-pentyl, 3 -methyl-1 -pentyl, 4-methyl-l-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2 -dimethyl-l-butyl, 3,3 -dimethyl-1 -butyl, 2 -ethyl-l-butyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neo-pentyl, tert-amyl and hexyl, and longer alkyl groups, such as heptyl, octyl and the like. Whenever it appears herein, a numerical range such as "C_1-C_6 alkyl" or "C_{1_6} alkyl", means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms or 6 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numeri-cal range is designated.

[71] The term "aliphatic" as used herein, alone or in combination, refers to an optionally substituted, straight- chain or branched-chain, non-cyclic, saturated, partially un-saturated, or fully unsaturated nonaromatic hydrocarbon. Thus, the term collectively includes alkyl, alkenyl and alkynyl groups.

[72] The terms "cycle", "cyclic", "ring" and "membered ring" as used herein, alone or in combination, refer to any covalently closed structure, including alicyclic, heterocyclic, aromatic, heteroaromatic and polycyclic fused or non-fused ring systems as described herein. Rings can be optionally substituted. Rings can form part of a fused ring system. The term "membered" is meant to denote the number of skeletal atoms that constitute the ring. Thus, by way of example only, cyclohexane, pyridine, pyran and pyrimidine are six-membered rings and cyclopentane, pyrrole, tetrahydrofuran and thiophene are five-membered rings.

[73] The term "cycloalkyl" as used herein, alone or in combination, refers to an optionally substituted, saturated, hydrocarbon monoradical ring, containing from three to about fifteen ring carbon atoms or from three to about ten ring carbon atoms, though may include additional, non-ring carbon atoms as substituents (e.g. methylcyclopropyl).

[74] A non-limiting example of "cycloalkyl" includes azinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihy-dropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imida-zolidinyl, 3-azabicyclo[3.1.0]hexyl, 3-azabicyclo [4. 1.0]heptyl, 3H-indolyl and quinolizinyl and the like. The terms also include all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosac-charides.

[75] The term "aromatic" as used herein, refers to a planar, cyclic or polycyclic, ring moiety having a delocal-ized at-electron system containing 4n+2 n electrons, where n is an integer. Aromatic rings can be formed by five, six, seven, eight, nine, or more than nine atoms. Aromatics can be optionally substituted and can be monocyclic or fused- ring polycyclic. The term aromatic encompasses both all carbon containing rings (e.g., phenyl) and those rings containing one or more heteroatoms (e.g., pyridine).

[76] The term "RIP1 kinase inhibitor" as used herein refers to a compound that exhibits an IC_{50}, with respect to RIP1 kinase activity, of no more than about 100 vM or not more than about 50 vM, as measured in the kinase assay described generally herein. "IC_{50}" is that concentration of inhibitor which reduces the activity of an enzyme to half-maximal level. Compounds described herein have been discovered to exhibit inhibition against RIPK1. Compounds of the present invention preferably exhibit an IC_{50} with

respect to RIPK1 of no more than about 10 vM, more preferably, no more than about 5 vM, even more preferably not more than about 1 vM, and most preferably, not more than about 200 nM, as measured in the kinase assay described herein.

[77] The term "selective," "selectively," or "selectivity" as used herein refers to a compound of this invention having a lower IC_{50} value for the enzyme as compared to any other enzymes (e.g., at least 2, 5, 10 or more-fold lower).

[78] The term "subject", "patient" or "individual" as used herein in reference to individuals suffering from a disorder, a condition, and the like, encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non- mammals include, but are not limited to, birds, fish and the like. In one embodiment of the methods and compositions provided herein, the mammal is a human.

[79] The terms "treat," "treating" or "treatment," and other grammatical equivalents as used herein, include alle-viating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition, and are intended to include prophylaxis. The terms further include achieving a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[80] The terms "effective amount", "therapeutically effective amount" or "pharmaceutically effective amount" as used herein, refer to a sufficient amount of at least one agent or compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic

uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in a disease. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

[81] The terms "administer," "administering", "administration," and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein, e.g., as discussed in Goodman and Gilman, The Pharmacological Basis of Therapeutics, current ed.; Pergamon; and Remington's, Pharmaceutical Sciences (current edition), Mack Publishing Co., Easton, Pa. In preferred embodiments, the compounds and compositions described herein are administered orally.

[82] The term "acceptable" as used herein, with respect to a formulation, composition or ingredient, means having no persistent detrimental effect on the general health of the subject being treated.

[83] The term "pharmaceutically acceptable" as used herein, refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compounds described herein, and is relatively nontoxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[84] The term "pharmaceutical composition," as used herein, refers to a biologically active compound, optionally mixed with at least one pharmaceutically acceptable chemical component, such as, though not limited to carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

[85] The term "carrier" as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of a compound into cells or tissues.

[86] The term "agonist," as used herein, refers to a molecule such as a compound, a drug, an enzyme activator or a hormone modulator which enhances the activity of another molecule or the activity of a receptor site.

[87] The term "antagonist," as used herein, refers to a molecule such as a compound, a drug, an enzyme inhibitor, or a hormone modulator, which diminishes, or prevents the action of another molecule or the activity of a receptor site.

[88] The term "modulate," as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to

enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[89] The term "modulator," as used herein, refers to a molecule that interacts with a target either directly or indi-rectly. The interactions include, but are not limited to, the interactions of an agonist and an antagonist.

[90] The term "pharmaceutically acceptable salt" as used herein, refers to salts that retain the biological effectiveness of the free acids and bases of the specified compound and that are not biologically or otherwise undesirable. Compounds described herein may possess acidic or basic groups and therefore may react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. These salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral or organic acid or an inorganic base, such salts including, acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate. metaphosphate, methoxybenzoate, methylben-zoate, monohydrogenphosphate, 1-napthalenesulfonate, 2-napthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate undeconate and xylenesulfonate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts (See examples at Berge et al., J. Pharm. Sci. 1977, 66, 1-19.). Further, those compounds described herein which may comprise a free acid group may react with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Illustrative examples

of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they may contain. Water or oil-soluble or dispersible products may be obtained by such quaternization. See, for example, Berge et al., supra.

[91] The term "solvate" as used herein refers to a combination of a compound of this invention with a solvent molecule formed by solvation. In some situations, the solvate refers to a hydrate, i.e., the solvent molecule is a water molecule, the combination of a compound of this invention and water forms a hydrate.

[92] The term "polymorph" or "polymorphism" as used herein refers to a compound of this invention present in different crystal lattice forms.

[93] The term "ester" as used herein refers to a derivative of a compound of this invention derived from an oxoacid group and a hydroxyl group, either one of which can be present at the compound of this invention.

[94] The term "tautomer" as used herein refers to an isomer readily interconverted from a compound of this invention by e.g., migration of a hydrogen atom or proton.

[95] The term "pharmaceutically acceptable derivative or prodrug" as used herein, refers to any pharmaceutically acceptable salt, ester, salt of an ester or other derivative of a compound of this invention, which, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or a pharmaceutically active metabolite or residue thereof. Par-ticularly favored derivatives or prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a patient (e.g., by allowing orally administered compound to be more readily absorbed into blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system).

[96] Pharmaceutically acceptable prodrugs of the compounds described herein include, but are not limited to, esters, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, phosphate esters, metal salts and sulfonate esters. Various forms of prodrugs are well known in the art. See for example Design of Prodrugs, Bundgaard, A. Ed., Elseview, 1985 and Method in Enzymology, Widder, K. et al., Ed.; Academic, 1985, vol. 42, p. 309-396; Bundgaard, H. "Design and Application of Prodrugs" in A Textbook of Drug Design and Development, Krosgaard-Larsen and H. Bund-gaard, Ed., 1991, Chapter 5, p. 113-191; and Bundgaard, H., Advanced Drug Delivery Review, 1992, 8, 1-38, each of which is incorporated herein

by reference. The prodrugs described herein include, but are not limited to, the following groups and combinations of these groups; amine derived prodrugs: Hydroxy prodrugs include, but are not limited to acyloxyalkyl esters, alkoxycarbonyloxyalkyl esters, alkyl esters, aryl esters and disulfide containing esters.

[97] The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration of a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system.

[98] An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[99] The terms "pharmaceutical combination", "administering an additional therapy", "administering an additional therapeutic agent" and the like, as used herein, refer to a pharmaceutical therapy resulting from mixing or combining more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that at least one of the compounds described herein, and at least one co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that at least one of the compounds described herein, and at least one co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with variable intervening time limits, wherein such administration provides effective levels of the two or more compounds in the body of the patient. These also apply to cocktail therapies, e.g. the administration of three or more active ingredients.

[100] The terms "co-administration", "administered in combination with" and their grammatical equivalents or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different times. In some embodiments the compounds described herein will be co-administered with other agents. These terms encompass administration of two or more agents to an animal so that both agents and/or their metabolites are present in the animal at the same time. They include simultaneous administration in separate compositions, administration at different times in separate compositions, and/or administration in a composition in which both agents are present. Thus, in some embodiments, the compounds of the invention and the other agent (s) are administered in a single composition.

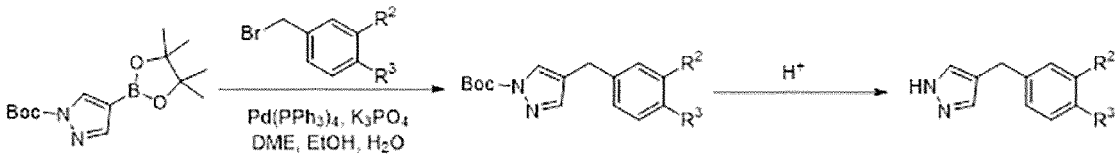
[101] The term "metabolite," as used herein, refers to a derivative of a compound which is formed when the com-pound is metabolized.

[102] The term "active metabolite," as used herein, refers to a biologically active derivative of a compound that is formed when the compound is metabolized.

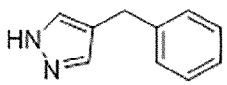
[103] The term "metabolized," as used herein, refers to the sum of the processes (including, but not limited to, hydrolysis reactions and reactions catalyzed by enzymes) by which a particular substance is changed by an organism. Thus, enzymes may produce specific structural alterations to a compound. For example, cytochrome P450 catalyzes a variety of oxidative and reductive reactions while uridine diphosphate glucuronyl transferases catalyze the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulfhydryl groups. Further information on metabolism may be obtained from The Pharmacological Basis of Therapeutics, 9th Edition, McGraw-Hill (1996).

[104] NMR spectra were recorded in $CDCl_3$, DMSO-d_6 or CD_3OD solution in 5-mm o.d. tubes (Norell, Inc. 507-HP) at 30 °C and were collected on Varian VNMRS-400 at 400 MHz for ^1H. The chemical shifts (δ) are relative to tetramethylsilane (TMS = 0.00 ppm) and expressed in ppm. LC/MS was taken on Ion-trap Mass Spectrometer on FINNIGAN Thermo or ISQ EC, Thermo Fisher U3000 RSLC (Column : YMC Hydrosphere (C18, Φ4.6 x 50 mm, 3 μm, 120 Å, 40 °C) operating in ESI(+) ionization mode; flow rate = 1.0 mL/min. Mobile phase = 0.01% heptafluorobutyric acid (HFBA) and 1.0% isopropyl alcohol (IPA) in water or CH_3CN.

[105] General synthetic scheme for pyrazole intermediates

[106] 

[107] Intermediate 1: 4-benzyl-1H-pyrazole

[108] 

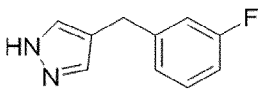
[109] Step A: tert-butyl 4-benzyl-1H-pyrazole-1-carboxylate

[110] To a solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (4.50 g, 15.3 mmol), K_3PO_4 (9.74 g, 45.9 mmol) and (bromomethyl)benzene (2.62 g, 15.3 mmol) in a mixture of DME (30 mL), EtOH (7.5 mL) and H_2O (7.5 mL) was added $Pd(PPh_3)_4$ (2.30 g, 1.99 mmol) at room temperature. The reaction mixture was stirred at 55 °C for 16 hours. After diluted with water, the mixture was extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (pet.Ether:EtOAc = 10:1) to afford tert-butyl 4-benzyl-1H-pyrazole-1-carboxylate (2.20 g, 55%) as a colorless oil. ^1H-NMR (400 MHz, $CDCl_3$): δ 7.98 (1H, s), 7.65 (1H, s), 7.14-7.12 (2H, m), 6.99-6.95 (3H, m), 3.70 (2H, s), 1.50 (9H, s).

[111] Step B: 4-benzyl-1H-pyrazole

[112] To a solution of tert-butyl 4-benzyl-1H-pyrazole-1-carboxylate (2.20 g, 8.52 mmol) in EtOAc (5.0 mL) was added HCl (3.0 M in EtOAc, 8.5 mL, 26 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours. A precipitated solid was collected by filtration, washed with EtOAc, and dried under vacuum to afford 4-benzyl-1H-pyrazole (1.18 g, 71%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d $_6$): δ 13.0 (2H, brs), 7.91 (2H, s), 7.31-7.27 (2H, m), 7.22-7.17 (3H, m), 3.80 (2 H, s).

[113] Intermediate 2: 4-(3-fluorobenzyl)-1H-pyrazole

[114] 

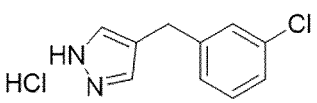
[115] Step A: tert-butyl 4-(3-fluorobenzyl)-1H-pyrazole-1-carboxylate

[116] To a solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (1.50 g, 5.10 mmol), K $_3$PO $_4$ (3.25 g, 15.3 mmol) and 1-(bromomethyl)-3-fluorobenzene (964 mg, 5.10 mmol) in a mixture of DME (20 mL), EtOH (5.0 mL) and H $_2$O (5.0 mL) was added Pd(PPh $_3$) $_4$ (766 mg, 0.663 mmol) at room temperature. The reaction mixture was stirred at 55 °C for 16 hours. After diluted with water, the mixture was extracted with EtOAc twice. The combined organic layers were dried over Na $_2$SO $_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO $_2$ (pet. Ether:EtOAc = 5:1) to afford tert-butyl 4-(3-fluorobenzyl)-1H-pyrazole-1-carboxylate (600 mg, 43%) as a yellow oil. LC-MS: m/z = 177 [M+H-Boc] $^+$.

[117] Step B: 4-(3-fluorobenzyl)-1H-pyrazole

[118] To a solution of tert-butyl 4-(3-fluorobenzyl)-1H-pyrazole-1-carboxylate (600 mg, 2.17 mmol) in EtOAc (2.0 mL) was added HCl (3.0 M in EtOAc, 2.0 mL, 6.00 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours. The mixture was concentrated in vacuo. The residue was purified by prep-HPLC (neutral) to afford 4-(3-fluorobenzyl)-1H-pyrazole (133 mg, 35%) as a white solid. ^{1} H-NMR (400 MHz, DMSO-d $_6$): δ 12.60 (1H, s), 7.45-7.28 (3H, m), 7.06-6.96 (3H, m), 3.80 (2H, s).

[119] Intermediate 3: 4-(3-chlorobenzyl)-1H-pyrazole hydrochloride

[120] 

[121] Step A: tert-butyl 4-(3-chlorobenzyl)-1H-pyrazole-1-carboxylate

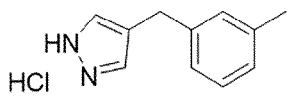
[122] To a solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (1.50 g, 5.10 mmol), K $_3$PO $_4$ (3.25 g, 15.3 mmol) and 1-(bromomethyl)-3-chlorobenzene (1.05

g, 5.10 mmol) in a mixture of DME (20 mL), EtOH (5.0 mL) and H_2O (5.0 mL) was added $Pd(PPh_3)_4$ (766 mg, 0.66 mmol) at room temperature. The reaction mixture was stirred at 55 °C for 16 hours and cooled to room temperature. After diluted with water, the mixture was extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (pet. Ether:EtOAc = 5:1) to afford tert-butyl 4-(3-chlorobenzyl)-1H-pyrazole-1-carboxylate (500 mg, 33%) as a yellow oil. LC-MS: m/z = 193 $[M+H-Boc]^+$.

[123] Step B: 4-(3-chlorobenzyl)-1H-pyrazole hydrochloride

[124] To a solution of tert-butyl 4-(3-chlorobenzyl)-1H-pyrazole-1-carboxylate (500 mg, 1.71 mmol) in EtOAc (3.0 mL) was added HCl (3.0 M in EtOAc, 3.0 mL, 9.0 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours and concentrated in vacuo. The residue was purified by prep-HPLC (neutral) to afford 4-(3-chlorobenzyl)-1H-pyrazole, which was changed to the corresponding HCl salt form by adding several drops of HCl (1 M in water). The mixture was lyophilizaed followed by dried under vacuum to afford 4-(3-chlorobenzyl)-1H-pyrazole hydrochloride (92 mg, 24%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.75 (2H, br), 7.76 (2H, s), 7.33-7.28 (2H, m), 7.26-7.19 (2H, m), 3.84 (2H, s).

[125] Intermediate 4: 4-(3-methylbenzyl)-1H-pyrazole hydrochloride

[126] 

[127] Step A: tert-butyl 4-(3-methylbenzyl)-1H-pyrazole-1-carboxylate

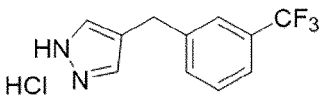
[128] To a solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (1.00 g, 3.40 mmol), K_3PO_4 (2.17 g, 10.2 mmol) and 1-(bromomethyl)-3-methylbenzene (629 mg, 3.40 mmol) in a mixture of DME (20 mL), EtOH (5.0 mL) and H_2O (5.0 mL) was added $Pd(PPh_3)_4$ (511 mg, 0.442 mmol) at room temperature. The reaction mixture was stirred at 55 °C for 16 hours and cooled to room temperature. After diluted with water, the mixture was extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (pet. Ether:EtOAc = 5:1) to afford tert-butyl 4-(3-methylbenzyl)-1H-pyrazole-1-carboxylate (500 mg, 54%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.98 (1H, s), 7.65 (1H, s), 7.14-7.12 (1H, m), 6.99-6.95 (3H, m), 3.70 (2H, s), 2.26 (3H, s), 1.50 (9H, s).

[129] Step B: 4-(3-methylbenzyl)-1H-pyrazole hydrochloride

[130] To a solution of tert-butyl 4-(3-methylbenzyl)-1H-pyrazole-1-carboxylate (500 mg, 1.84 mmol) in EtOAc (2.0 mL) was added HCl (3.0 M in EtOAc, 2.0 mL, 6.0 mmol) at

room temperature. The reaction mixture was stirred at room temperature for 3 hours. A precipitated solid was collected by filtration, washed with EtOAc, and dried under vacuum to afford 4-(3-methylbenzyl)-1H-pyrazole hydrochloride (297 mg, 78%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d $_6$): δ 13.21 (2H, br), 7.91 (2H, s), 7.19-7.15 (1H, m), 7.04-6.99 (3H, m), 3.80 (2H, s), 2.26 (3H, s).

[131] Intermediate 5: 4-(3-(trifluoromethyl)benzyl)-1H-pyrazole hydrochloride

[132] 

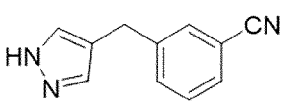
[133] Step A: tert-butyl 4-(3-(trifluoromethyl)benzyl)-1H-pyrazole-1-carboxylate

[134] To a solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (1.50 g, 5.10 mmol), K $_3$PO $_4$ (3.25 g, 15.3 mmol) and 1-(bromomethyl)-3-(trifluoromethyl)benzene (1.22 g, 5.10 mmol) in a mixture of DME (20 mL), EtOH (5.0 mL) and H $_2$O (5.0 mL) was added Pd(PPh $_3$) $_4$ (766 mg, 0.66 mmol) at room temperature. The reaction mixture was stirred at 55 °C for 16 hours and cooled to room temperature. After diluted with water, the mixture was extracted with EtOAc twice. The combined organic layers were dried over Na $_2$SO $_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO $_2$ (pet. Ether:EtOAc = 5:1) to afford tert-butyl 4-(3-(trifluoromethyl)benzyl)-1H-pyrazole-1-carboxylate (800 mg, 48%) as a yellow oil. LC-MS: m/z = 227 [M+H-Boc] $^+$.

[135] Step B: 4-(3-(trifluoromethyl)benzyl)-1H-pyrazole hydrochloride

[136] To a solution of tert-butyl 4-(3-fluorobenzyl)-1H-pyrazole-1-carboxylate (800 mg, 2.45 mmol) in EtOAc (3.0 mL) was added HCl (3.0 M in EtOAc, 3.0 mL, 9.0 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours. After concentration in vacuo, the residue was purified by prep-HPLC (neutral) to afford 4-(3-fluorobenzyl)-1H-pyrazole, which was treated with several drops of HCl (1 M in water) followed by lyophilization and dried under vacuum to afford 4-(3-(trifluoromethyl)benzyl)-1H-pyrazole hydrochloride (72 mg, 11%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d $_6$): δ 8.50 (2H, brs), 7.69-7.68 (2H, s), 7.56-7.53 (4H, m), 3.92 (2H, s).

[137] Intermediate 6: 3-((1H-pyrazol-4-yl)methyl)benzonitrile

[138] 

[139] Step A: tert-butyl 4-(3-cyanobenzyl)-1H-pyrazole-1-carboxylate

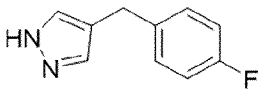
[140] To a solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (2.00 g,

6.80 mmol) in DME (56 mL), EtOH (14 mL) and H_2O (14 mL) was added 4-(bromomethyl)benzonitrile (1.33 g, 6.80 mmol), K_3PO_4 (4.32 g, 20.4 mmol) and $Pd(PPh_3)_4$ (1.01 g, 0.880 mmol) at room temperature. The reaction mixture was stirred at 55 °C for 20 hours. After evaporation of DME and EtOH, the residue was extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4, filtered, concentrated to afford tert-butyl 4-(3-cyanobenzyl)-1H-pyrazole-1-carboxylate (1.80 g, 93%) as a colorless oil. LC-MS: m/z = 184 $(M+H\text{-}Boc)^+$.

[141] Step B: 3-((1H-pyrazol-4-yl)methyl)benzonitrile

[142] To a solution of tert-butyl 4-(3-cyanobenzyl)-1H-pyrazole-1-carboxylate (1.80 g, 6.36 mmol) in DCM (10 mL) was added TFA (5.0 mL, 65 mmol) at room temperature. The reaction mixture was stirred at room temperature for 20 hours. After neutralization with saturated aq. Na_2CO_3 solution, the resulting mixture was extracted with DCM twice. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by prep-HPLC to afford 3-((1H-pyrazol-4-yl)methyl)benzonitrile (101 mg, 9%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6 + D_2O): δ 7.65-7.62 (2H, m), 7.60-7.58 (1H, m), 7.52-7.48 (3H, m), 3.89 (2H, s).

[143] Intermediate 7: 4-(4-fluorobenzyl)-1H-pyrazole

[144] 

[145] Step A: tert-butyl 4-(3-cyanobenzyl)-1H-pyrazole-1-carboxylate

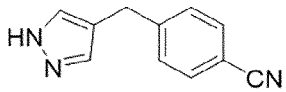
[146] To a solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (860 mg, 2.92 mmol), K_3PO_4 (1.86 g, 8.76 mmol) and 1-(bromomethyl)-4-fluorobenzene (552 mg, 2.92 mmol) in a mixture of DME (12 mL), EtOH (3.0 mL) and H_2O (3.0 mL) was added $Pd(PPh_3)_4$ (438 mg, 0.379 mmol) at room temperature. The reaction mixture was stirred at 55 °C for 16 hours. After evaporation of DME and EtOH, the residue was extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (pet. Ether:EtOAc = 1:5) to afford tert-butyl 4-(4-fluorobenzyl)-1H-pyrazole-1-carboxylate (500 mg, 62%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.81 (1H, s), 7.53 (1H, s), 7.16-7.12 (2H, m), 7.00-6.95 (2H, m), 3.79 (2H, s), 1.63 (9H, s).

[147] Step B: 4-(4-fluorobenzyl)-1H-pyrazole

[148] To a solution of tert-butyl 4-(4-fluorobenzyl)-1H-pyrazole-1-carboxylate (400 mg, 1.45 mmol) in EtOAc (5.0 mL) was added HCl (3.0 M in EtOAc, 1.5 mL, 4.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours.

After concentration in vacuo, the residue was purified by prep-HPLC (neutral) to afford 4-(4-fluorobenzyl)-1H-pyrazole (182 mg, 71%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d $_6$): δ 12.58 (1H, s), 7.41 (2H, s), 7.25-7.21 (2H, m), 7.11-7.05 (2H, m), 3.76 (2H, s).

[149] Intermediate 8: 4-(4-fluorobenzyl)-1H-pyrazole

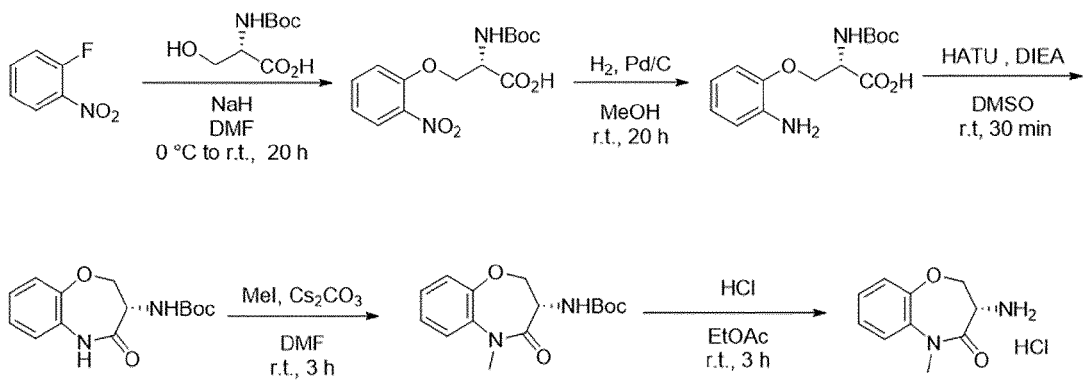
[150] 

[151] Step A: tert-butyl 4-(3-cyanobenzyl)-1H-pyrazole-1-carboxylate

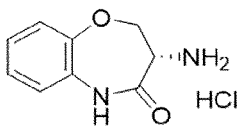
[152] To a solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (2.00 g, 6.80 mmol) in a mixture of DME (56 mL), EtOH (14 mL) and H $_2$O (14 mL) was added 4-(bromomethyl)benzonitrile (1.33 g, 6.80 mmol), K $_3$PO $_4$ (4.32 g, 20.4 mmol) and Pd(PPh $_3$) $_4$ (1.02 g, 0.88 mmol) at room temperature. The reaction mixture was stirred at 55 °C for 20 hours. After evaporation of DME and EtOH, the residue was extracted with EtOAc twice. The combined organic layers were dried over Na $_2$SO $_4$, filtered, and concentrated to afford tert-butyl 4-(4-fluorobenzyl)-1H-pyrazole-1-carboxylate (1.50 g, 78%) as an off-white solid. LC-MS: m/z = 184 (M+H-Boc) $^+$.

[153] Step B: 4-(4-fluorobenzyl)-1H-pyrazole

[154] To a solution of tert-butyl 4-(4-cyanobenzyl)-1H-pyrazole-1-carboxylate (1.50 g, 5.30 mmol) in DCM (10 mL) was added TFA (5.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 20 hours. After neutralization with saturated aq. Na $_2$CO $_3$ solution, the resulting mixture was extracted with DCM twice. The combined organic layers were dried over Na $_2$SO $_4$, filtered, and concentrated in vacuo. The residue was purified by prep-HPLC to afford 4-((1H-pyrazol-4-yl)methyl)benzonitrile (182 mg, 18%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d $_6$ + D $_2$O): δ 7.73 (2H, d, J = 8.4 Hz), 7.45 (2H, br), 7.41 (2H, d, J = 8.4 Hz), 3.87 (2H, s).

[155] 

[156] Intermediate 9: (S)-3-amino-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

[157] 

[158] Step A: (S)-2-((tert-butoxycarbonyl)amino)-3-(2-nitrophenoxy)propanoic acid

[159] To a suspension of NaH (60wt%, 4.90 g, 122 mmol) in dry DMF (150 mL) was slowly added a solution of N-Boc-L-serine (10.0 g, 48.7 mmol) in dry DMF at 0 ℃ under N_2 atmosphere. Once gas evolution had ceased, 1-fluoro-2-nitrobenzene (5.10 mL, 48.7 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 20 hours and quenched with 0.5 M aq. HCl solution. The mixture was extracted with EtOAc three times. The combined organic layers were washed with brine and water, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (pet. Ether:EtOAc = 5:1 to DCM:MeOH = 20:1) to afford (S)-2-((tert-butoxycarbonyl)amino)-3-(2-nitrophenoxy)propanoic acid (10.0 g, 62%) as a brown solid. LC-MS: m/z = 271.0 $[M+H-tBu]^+$

[160] Step B: (S)-3-(2-aminophenoxy)-2-((tert-butoxycarbonyl)amino)propanoic acid

[161] A suspension of (S)-2-((tert-butoxycarbonyl)amino)-3-(2-nitrophenoxy)propanoic acid (9.00 g, 27.6 mmol) and Pd/C (10wt%, 900 mg) in MeOH (50 mL) was stirred at room temperature for 20 hours under hydrogen atmosphere (1 atm). After filtered through a 0.45 um PTFE needle filter (MeOH flushed), the filtrate was concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (pet. Ether:EtOAc = 1:1) to afford (S)-3-(2-aminophenoxy)-2-((tert-butoxycarbonyl)amino)propanoic acid (4.00 g, 48%) as an off-white solid. LC-MS: m/z = 297.1 $[M+H]^+$.

[162] Step C: (S)-tert-butyl (4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl) carbamate

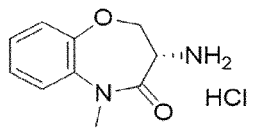
[163] To a solution of (S)-3-(2-aminophenoxy)-2-((tert-butoxycarbonyl)amino)propanoic acid (4.00 g, 13.5 mmol) in DMSO (20 mL) was added DIPEA (5.23 g, 40.5 mmol) followed by HATU (5.13 g, 13.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min. After diluted with H_2O (300 mL), the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (pet. Ether:EtOAc = 5:1) to afford (S)-tert-butyl (4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl) carbamate (2.00 g, 53%) as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.91 (1H, s), 7.14-7.07 (5H, m), 4.33-4.27 (3H, m), 1.35 (9H, s).

[164] Step D: (S)-3-amino-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one

[165] To a solution of (S)-tert-butyl

(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl) carbamate (2.00 g, 7.19 mmol) in EtOAc (5.0 mL) was added HCl (5 M in EtOAc, 10 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 hours and concentrated in vacuo to afford (S)-3-amino-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one (1.30 g, 84%) as a brown solid. ^{1}H-NMR (400 MHz, DMSO-d $_6$): δ 10.50 (1H, s), 8.73 (3H, s), 7.14 (4H, s), 4.68-4.63 (1H, m), 4.45-4.40 (1H, m), 4.30-4.26 (1H, m).

[166] Intermediate 10: (S)-3-amino-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one hydrochloride

[167] 

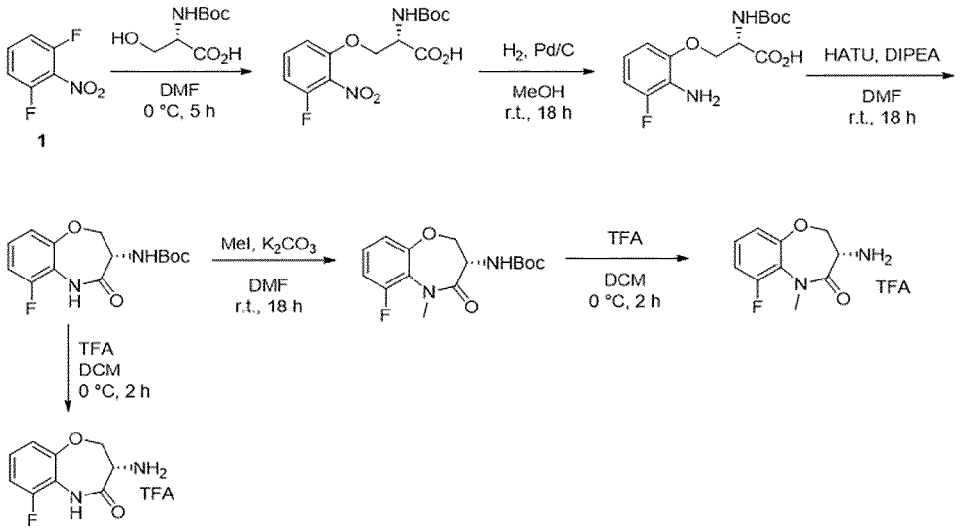
[168] Step A: (S)-tert-butyl (5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl) carbamate

[169] To a solution of (S)-tert-butyl (4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl) carbamate (2.00 g, 7.19 mmol) in DMF (20 mL) was added Cs $_2$CO $_3$ (3.20 g, 9.90 mmol) followed by MeI (1.20 g, 8.50 mmol) dropwise at room temperature under N $_2$ atmosphere. The reaction mixture was stirred at room temperature for 3 hours. After quenched with cold H $_2$O (100 mL), a precipitated solid was collected by filtration, and washed with water. The solid was purified by reversed column on C18 (MeCN:H $_2$O) to afford (S)-tert-butyl (5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl) carbamate (1.20 g, 57%) as a light yellow solid. ^{1}H-NMR (400 MHz, DMSO-d $_6$): δ 7.47-7.45 (1H, m), 7.32-7.13 (4H, m), 4.37-4.27 (3H, m), 3.28 (3H, s), 1.34 (9H, s).

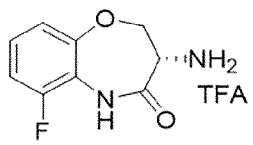
[170] Step B: (S)-3-amino-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one hydrochloride

[171] To a solution of (S)-tert-butyl (5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl) carbamate (1.20 g, 4.10 mmol) in EtOAc (5.0 mL) was added HCl (5 M in EtOAc, 10 mL, 50 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours and concentrated in vacuo to afford (S)-3-amino-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one hydrochloride (820 mg, 87%) as a brown solid. ^{1}H-NMR (400 MHz, MeOH-d $_4$): δ 8.74 (3H, s), 7.53-7.50 (1H, m), 7.36-7.25 (3H, m), 4.67-4.63 (1H, m), 4.48 (1H, t, J = 11.2 Hz), 4.21-4.16 (1H, m), 3.34 (3H, s).

[172]



[173] Intermediate 11: (S)-3-amino-6-fluoro-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one 2,2,2-trifluoroacetate

[174] 

[175] Step A: (S)-2-(tert-butoxycarbonylamino)-3-(3-fluoro-2 nitrophenoxy)propanoic acid

[176] To a suspension of NaH (55wt%, 823 mg, 18.9 mmol) in DMF (10 mL) was slowly added a solution of N-Boc-L-serine (1.55 g, 7.54 mmol) in DMF (5.0 mL) at 0 ℃. The mixture was stirred at 0 ℃ for 1 hour. After addition of a solution of 1,3-difluoro-2-nitrobenzene (1.00 g, 6.29 mmol) in DMF (5.0 mL) at 0 ℃, the reaction mixture was stirred at 0 ℃ for 4 hours. After quenched with 0.5 M aq. HCl at 0 ℃, the mixture was extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 1:1 to 1:3) to afford (S)-2-(tert-butoxycarbonylamino)-3-(3-fluoro-2-nitrophenoxy)propanoic acid (1.20 g, 55%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.38 (1H, brs), 7.40 (1H, q, J = 7.6 Hz), 6.87-6.82 (2H, m), 5.54 (1H, d, J = 7.6 Hz), 4.73 (1H, d, J = 8.4 Hz), 4.58 (1H, dd, J = 9.2, 2.4 Hz), 4.41 (1H, dd, J = 9.0, 2.6 Hz), 1.45 (9H, s).

[177] Step B: (S)-3-(2-amino-3-fluorophenoxy)-2-(tert-butoxycarbonylamino)propanoic acid

[178] A suspension of (S)-2-(tert-butoxycarbonylamino)-3-(3-fluoro-2-nitrophenoxy)propanoic acid (1.60 g, 4.65 mmol) and Pd/C (10 wt%, 495 mg, 0.465 mmol) in MeOH (15 mL) was stirred at room temperature for 18 hours under H_2 atmosphere (1 atm). After filtered through a Celite pad while washing with MeOH, the filtrate was concentrated in vacuo to afford (S)-3-(2-amino-3-fluorophenoxy)-2-(tert-butoxycarbonylamino)propanoic acid (1.46 g,

100%) as a yellow oil. ^{1}H-NMR (400 MHz, DMSO-d $_6$): δ 7.54 (1H, d, J = 8.4 Hz), 6.68-6.61 (2H, m), 6.48-6.42 (1H, m), 4.80 (2H, brs), 4.43-4.41 (1H, m), 4.32-4.28 (1H, m), 3.98 (1H, dd, J = 9.2, 2.8 Hz), 1.36 (9H, s).

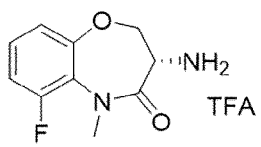
[179] Step C: tert-butyl 6-fluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate

[180] To a solution of (S)-3-(2-amino-3-fluorophenoxy)-2-(tert-butoxycarbonylamino)propanoic acid (1.40 g, 4.45 mmol) in DMF (15 mL) was added DIPEA (2.33 mL, 13.4 mmol) followed by HATU (2.54 g, 6.68 mmol) at 0 ℃. The reaction mixture was stirred at room temperature for 2 hours. After quenched with water, the mixture was extracted with EtOAc. The separated organic layer was washed with brine, dried over Na $_2$SO $_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO $_2$ (Hexanes:EtOAc = 4:1) to afford (S)-tert-butyl 6-fluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (328 mg, 25%) as a white solid. ^{1}H-NMR (400 MHz, CDCl $_3$): δ 7.35 (1H, s), 7.08 (1H, q, J = 8.4 Hz), 6.93-6.87 (2H, m), 5.52 (1H, s), 4.70-4.62 (2H, m), 4.23 (1H, t, J = 10.0 Hz), 1.44 (9H, s).

[181] Step D: (S)-3-amino-6-fluoro-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one TFA

[182] To a solution of tert-butyl 6-fluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (178 mg, 0.601 mmol) in DCM (1.2 mL) was added TFA (0.93 mL, 12 mmol) at 0 ℃. The reaction mixture was stirred at 0 ℃ for 2 hours, and then concentrated in vacuo to afford (S)-3-amino-6-fluoro-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one TFA as a brown oil. ^{1}H-NMR (400 MHz, DMSO-d $_6$): δ 10.5 (1H, s), 8.44 (2H, s), 7.26-7.20 (1H, m), 7.17-7.13 (1H, m), 7.09-7.06 (1H, m), 4.56-4.53 (1H, m), 4.49-4.46 (2H, m).

[183] Intermediate 12: (S)-3-amino-6-fluoro-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one TFA

[184] 

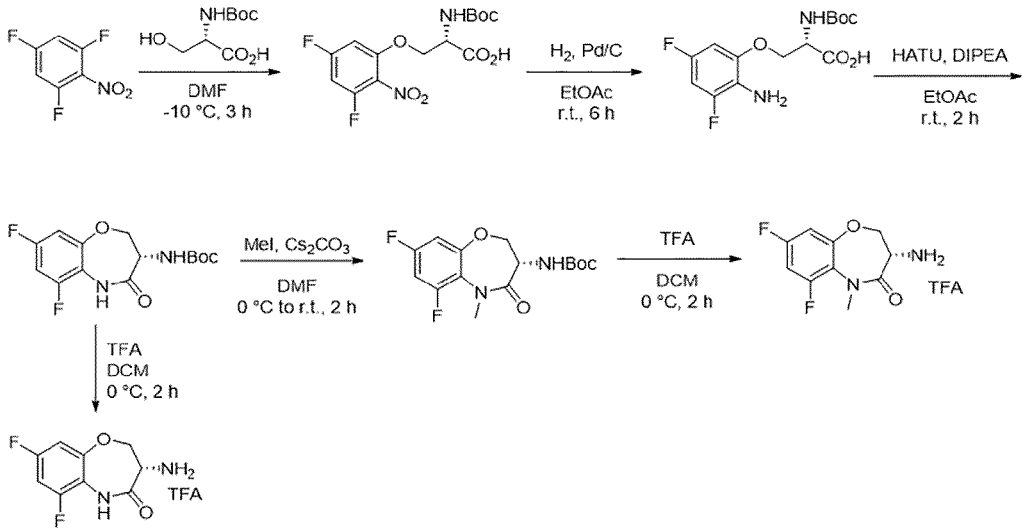
[185] Step A: Preparation of (S)-tert-butyl 6-fluoro-5-methyl-4-oxo-2,3,4,5 tetrahydrobenzo[b][1,4] oxazepin-3-ylcarbamate

[186] To a solution of (S)-tert-butyl 6-fluoro-4-oxo-2,3,4,5-tetrahydrobenxo[b][1,4]oxazepin-3-ylcarbamate (146 mg, 0.493 mmol) in DMF (4.9 mL) was added K $_2$CO $_3$ (82.0 mg, 0.591 mmol) and MeI (0.0370 mL, 0.591 mmol) at room temperature. The reaction mixture was stirred for 18 hours at room temperature. After diluted with water, the mixture was extracted with

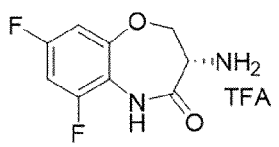
EtOAc. The separated organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 6:1) to afford (S)-tert-butyl 6-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (95 mg, 62%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.21 (1H, q, J = 7.6 Hz), 7.01-6.96 (2H, m), 5.51 (1H, d, J = 6.8 Hz), 4.71-7.64 (1H, m), 4.55 (1H, t, J = 8.6 Hz), 4.15 (1H, t, J = 10.6 Hz), 3.35 (3H, d, J = 2.4 Hz), 1.40 (9H, s).

[187] Step B: (S)-3-amino-6-fluoro-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one TFA

[188] To a solution of (S)-tert-butyl 6-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (63.0 mg, 0.203 mmol) in DCM (2.0 mL) was added TFA (0.31 mL, 4.1 mmol) at 0 ℃. The reaction mixture was stirred at 0 ℃ for 2 hours, and then concentrated in vacuo to afford (S)-3-amino-butyl 6-fluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate TFA (62 mg, 100%) as a brown oil. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.41 (2H, s), 7.40 (1H, q, J = 7.5 Hz), 7.28 (1H, t, J = 9.4 Hz), 7.14 (1H, d, J = 8.4 Hz), 4.49-4.42 (3H, m), 3.25 (3H, d, J = 2.0 Hz).

[189] 

[190] Intermediate 13: 3-amino-6,8-difluoro-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one TFA

[191] 

[192] Step A: (S)-2-(tert-butoxycarbonylamino)-3-(3,5-difluoro-2-nitrophenoxy)propanoic acid

[193] To a suspension of NaH (55wt%, 1.55 g, 35.6 mmol) in DMF (20 mL) was slowly

added a solution of N-Boc-L-serine (3.48 g, 16.9 mmol) in DMF (5.0 mL) at -10 °C. The mixture was stirred at -10 °C for 1 hour. After addition of a solution of 1,3,5-trifluoro-2-nitrobenzene (3.00 g, 16.9 mmol) in DMF (5.0 mL) at -10 °C, the reaction mixture was stirred at -10 °C for 2 hours. After quenched with 0.5 M aq. HCl at -10 °C, the mixture was extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 5:1 to 1:1) to afford (S)-2-(tert-butoxycarbonylamino)-3-(3,5-difluoro-2-nitrophenoxy)propanoic acid (4.60 g, 75%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.64-6.59 (2H, m), 5.49 (1H, d, J = 7.2 Hz), 4.74 (1H, d, J = 7.2 Hz), 4.55 (1H, d, J = 6.8 Hz), 4.40 (1H, dd, J = 9.6, 3.2 Hz), 1.46 (9H, s).

[194] Step B: (S)-3-(2-amino-3,5-difluorophenoxy)-2-(tert-butoxycarbonylamino)propanoic acid

[195] A suspension of (S)-2-(tert-butoxycarbonylamino)-3-(3,5-difluoro-2-nitrophenoxy)propanoic acid (500 mg, 1.38 mmol) and Pd/C (5wt%, 100 mg) in EtOAc (20 mL) was stirred at room temperature for 6 hours under H_2 atmosphere (1 atm). The reaction mixture was filtered through a Celite pad and washed with EtOAc (40 mL) to afford a solution of (S)-3-(2-amino-3,5-difluorophenoxy)-2-(tert-butoxycarbonylamino)propanoic acid (460 mg, 100%) in EtOAc (40 mL), which was used for next step without concentration. LC-MS: m/z = 332.78 $[M+H]^+$.

[196] Step C: tert-butyl 6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate

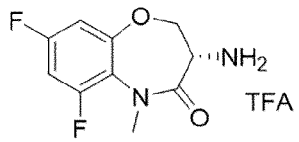
[197] To a solution of (S)-3-(2-amino-3,5-difluorophenoxy)-2-(tert-butoxycarbonylamino)propanoic acid (460 mg, 1.38 mmol) in EtOAc (40 mL) was added DIPEA (723 μL, 4.14 mmol) followed by HATU (787 mg, 2.07 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours. After concentration in vacuo, the residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 4:1 to 3:1) to afford tert-butyl 6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (300 mg, 69%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22 (1Θ, brs), 6.71-6.66 (2H, m), 5.52 (1H, brs), 4.69-4.61 (2H, m), 4.25 (1H, t, J = 9.6 Hz), 1.44 (9H, s).

[198] Step D: 3-amino-6,8-difluoro-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one TFA

[199] To a solution of tert-butyl 6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (60 mg, 0.191 mmol) in DCM (5.0 mL) was added TFA (294 μL, 3.82 mmol) at 0 °C. The mixture was stirred at room temperature for 2 hours and concentrated in vacuo to afford 3-amino-6,8-difluoro-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one TFA (60

mg, 96%) as a yellow oil. LC-MS: m/z = 214.93 $[M+H]^+$.

[200] Intermediate 14:
3-amino-6,8-difluoro-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one TFA

[201] 

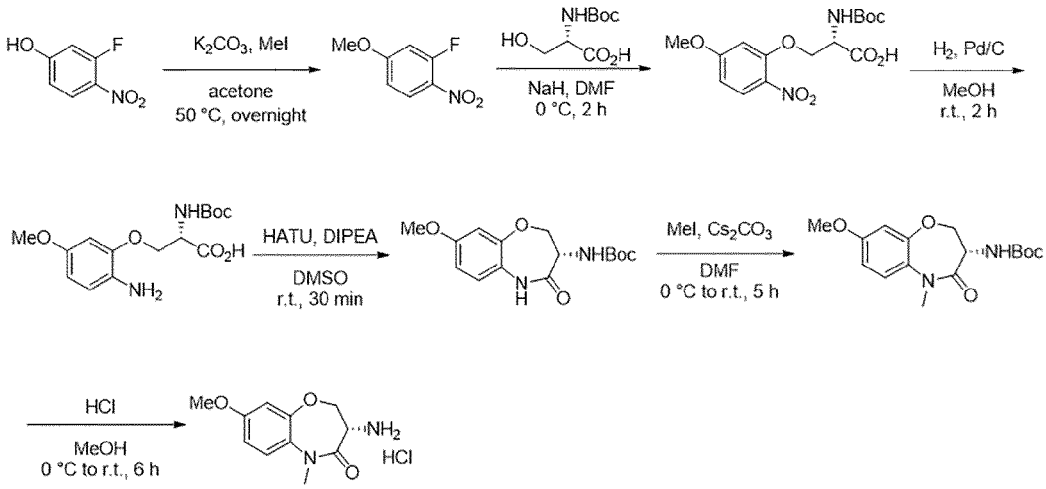
[202] Step A: (S)-tert-butyl
6,8-difluoro-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate

[203] A mixture of tert-butyl
6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (150 mg, 0.477 mmol) and Cs_2CO_3 (187 mg, 0.573 mmol) in DMF (4.0 mL) was stirred at 0 °C for 5 minutes. After addition of a solution of MeI (36.0 μL, 0.573 mmol) in DMF (1.0 mL), the reaction mixture was stirred at 0 °C for 1 hour and then at room temperature for further 1 hour. After quenched with water, the mixture was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 2:1) to afford (S)-tert-butyl
6,8-difluoro-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (120 mg, 77%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.80-6.73 (2H, m), 5.51 (1H, d, J = 6.0 Hz), 4.70-4.64 (1H, m), 4.54 (1H, dd, J = 9.2, 6.8 Hz), 4.17 (1H, t, J = 10.4 Hz), 3.32 (3H, d, J = 2.4 Hz), 1.41 (9H, s).

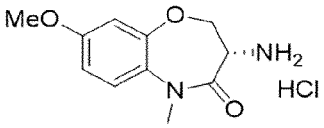
[204] Step B: 3-amino-6,8-difluoro-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one TFA

[205] To a solution of tert-butyl
6,8-difluoro-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (80 mg, 0.244 mmol) in DCM (5.0 mL) was added TFA (375 μL, 4.87 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours and concentrated in vacuo to afford
3-amino-6,8-difluoro-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one TFA (83 mg, 100%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.80-6.73 (2H, m), 5.51 (1H, d, J = 6.0 Hz), 4.70-4.64 (1H, m), 4.54 (1H, dd, J = 9.2, 6.8 Hz), 4.17 (1H, t, J = 10.4 Hz), 3.32 (3H, d, J = 2.4 Hz), 1.41 (9H, s).

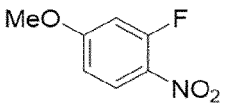
[206]



[207] Intermediate 15: (S)-3-amino-8-methoxy-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one hydrochloride

[208] 

[209] Step A: 2-fluoro-4-methoxy-1-nitrobenzene

[210] 

[211] To a solution of 3-fluoro-4-nitrophenol (1.00 g, 6.37 mmol) in acetone (20 mL) was added K_2CO_3 (4.40 g, 31.8 mmol) followed by MeI (0.796 mL, 12.7 mmol). The reaction mixture was stirred at 50 °C overnight. After dilution with DCM, the mixture was filtered through a Celite pad and washed with DCM. The filtrate was concentrated in vacuo. The residue was dissolved in EtOAc, washed with 1 N aq. NaOH, dried over Na_2SO_4, filtered and concentrated in vacuo to afford 2-fluoro-4-methoxy-1-nitrobenzene (900 mg, 83%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.10 (1H, t, J = 8.8 Hz), 6.79-6.72 (2H, m), 3.91 (3H, s).

[212] Step B: 2. Preparation of (S)-2-(tert-butoxycarbonylamino)-3-(5-methoxy-2-nitrophenoxy) propanoic acid

[213] To a suspension of NaH (55wt%, 213 mg, 4.87 mmol) in dry DMF was slowly added a solution of N-Boc-L-serine (500 mg, 2.44 mmol) in dry DMF (10 mL) at 0 °C. The mixture was stirred at room temperature for 30 minutes and cooled to 0 °C. After addition of a solution of 2-fluoro-4-methoxy-1-nitrobenzene (417 mg, 2.44 mmol) in dry DMF (5.0 mL) at 0 °C, the reaction mixture was stirred at 0 °C for 2 hours. After quenched with 0.5 M aq. HCl, the mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography SiO_2 (Hexanes:EtOAc = 4:1 to 1:1) to afford

(S)-2-(tert-butoxycarbonylamino)-3-(5-methoxy-2-nitrophenoxy)propanoic acid (400 mg, 46%) as a yellow oil. LC-MS: m/z = 257.05 $[M+H]^+$.

[214] Step C: (S)-3-(2-amino-5-methoxyphenoxy)-2-(tert-butoxycarbonylamino)propanoic acid

[215] A suspension of (S)-2-(tert-butoxycarbonylamino)-3-(5-methoxy-2-nitrophenoxy)propanoic acid (400 mg, 1.12 mmol) and Pd/C (5wt%, 50 mg) in MeOH (10 mL) was stirred at room temperature for 2 hours under H_2 atmosphere (1 atm). After filtration through a Celite pad while washing with MeOH, the filtrate was concentrated in vacuo to afford (S)-3-(2-amino-5-methoxyphenoxy)-2-(tert-butoxycarbonylamino)propanoic acid (200 mg, 55%) as a black solid. LC-MS: m/z = 326.92 $[M+H]^+$.

[216] Step D: (S)-tert-butyl 8-methoxy-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate

[217] To solution of (S)-3-(2-amino-5-methoxyphenoxy)-2-(tert-butoxycarbonylamino)propanoic acid (200 mg, 0.613 mmol) in DMSO (3.0 mL) was added DIPEA (321 μL, 1.84 mmol) followed by HATU (233 mg, 0.613 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 minutes. After quenched with ice-water, the mixture was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography SiO_2 (Hexanes:EtOAc = 2:1) to afford (S)-tert-butyl 8-methoxy-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (100 mg, 53%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.43 (1H, brs), 7.07 (1H, d, J = 8.8 Hz), 6.70 (1H, dd, J = 8.8, 2.8 Hz), 5.45 (1H, d, J = 6.8 Hz), 4.73-4.66 (1H, m), 4.61 (1H, t, J = 9.6 Hz), 4.16 (1H, t, J = 10.0 Hz), 3.78 (3H, s), 1.42 (9H, s).

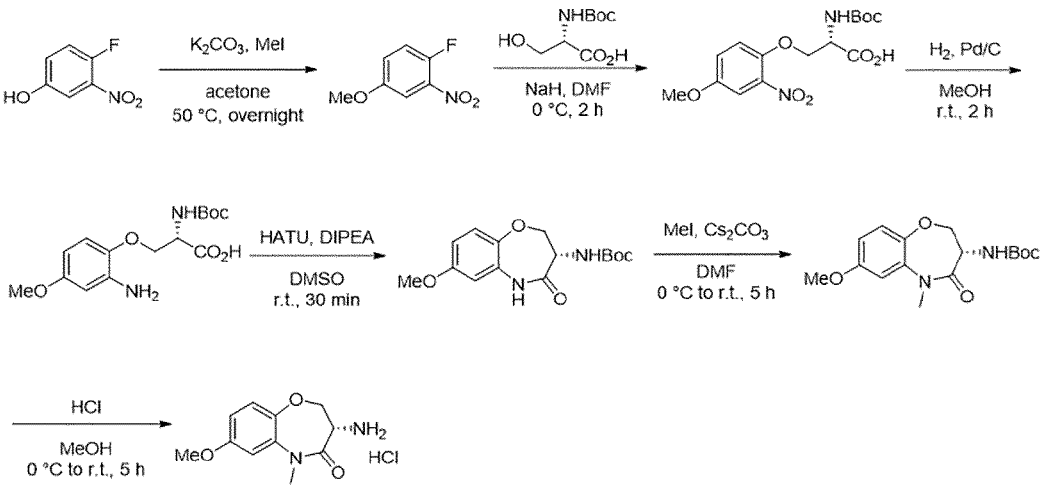
[218] Step E: (S)-tert-butyl 8-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate

[219] To a solution of (S)-tert-butyl 8-methoxy-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (100 mg, 0.324 mmol) in DMF (5.0 mL) was added Cs_2CO_3 (106 mg, 0.324 mmol) followed by a solution of MeI (20.3 μL, 0.324 mmol) in DMF (1.0 mL) at 0 °C. The reaction mixture was stirred for 4 hours at 0 °C and then at room temperature for 1 hour. After quenched with ice-water, the mixture was extracted with EtOAc, dried over Na_2SO_4, filleted, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 3:1) to afford (S)-tert-butyl 8-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (100 mg, 96%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.09 (1H, d, J = 8.4 Hz), 6.74 (1H, d, J = 8.4 Hz), 6.69 (1H, s), 5.50 (1H, d, J = 6.0 Hz), 4.69-4.63 (1H, m),

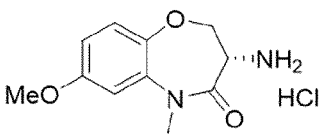
4.57 (1H, t, J = 9.2 Hz), 4.15 (1H, t, J = 10.0 Hz), 3.80 (3H, s), 3.36 (3H, s), 1.40 (9H, s).

[220] Step F: (S)-3-amino-8-methoxy-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one hydrochloride

[221] To a solution of (S)-tert-butyl 8-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (50.0 mg, 0.155 mmol) in MeOH (3.0 mL) was added HCl (2 M in diethyl ether, 1.55 mL, 3.10 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 6 hours and then concentrated in vacuo to afford (S)-3-amino-8-methoxy-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one hydrochloride (40 mg, 100%) as a white solid. LC-MS: m/z = 223.05 $[M+H]^+$.

[222] 

[223] Intermediate 16: (S)-3-amino-7-methoxy-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one hydrochloride

[224] 

[225] Step A: 1-fluoro-4-methoxy-2-nitrobenzene

[226] To a solution of 4-fluoro-3-nitrophenol (1.00 g, 6.37 mmol) in acetone (30 mL) was added K_2CO_3 (4.40 g, 31.8 mmol followed by MeI (0.796 mL, 12.7 mmol) at room temperature. The reaction mixture was stirred at 50 °C overnight. After dilution with DCM, the mixture was filtered through a Celite pad and washed with DCM. The filtrate was concentrated in vacuo. The residue was diluted with EtOAc, washed with 1 N aq. NaOH, dried over Na_2SO_4, filtered and concentrated in vacuo to afford 1-fluoro-4-methoxy-2-nitrobenzene (1.00 g, 92%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.54-7.52 (1H, m) 7.23-7.14 (2H, m), 3.86 (3H, s).

[227] Step B: 2. (S)-2-(tert-butoxycarbonylamino)-3-(4-methoxy-2-nitrophenoxy)propanoic acid

[228] To a suspension of NaH (55wt%, 460 mg, 10.54 mmol) in dry DMF (20 mL) was slowly added a solution of N-Boc-L-serine (1.00 g, 4.87 mmol) in dry DMF (5.0 mL) at 0 ℃. The mixture was stirred at room temperature for 30 minutes and cooled to 0 ℃. After addition of a solution of 1-fluoro-4-methoxy-2-nitrobenzene (900 mg, 5.26 mmol) in dry DMF (5.0 mL) at 0 ℃, the reaction mixture was stirred at 0 ℃ for 2 hours. After quenched with 0.5 M aq. HCl, the mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 4:1 to 1:1) to afford (S)-2-(tert-butoxycarbonylamino)-3-(4-methoxy-2-nitrophenoxy)propanoic acid (900 mg, 48%) as a yellow oil. LC-MS: m/z = 257.01 $[M+H]^+$.

[229] Step C: (S)-3-(2-amino-4-methoxyphenoxy)-2-(tert-butoxycarbonylamino)propanoic acid

[230] A suspension of (S)-2-(tert-butoxycarbonylamino)-3-(4-methoxy-2-nitrophenoxy)propanoic acid (350 mg, 0.982 mmol) and Pd/C (5wt%, 50 mg) in MeOH (10 mL) was stirred at room temperature for 2 hours under H_2 atmosphere (1 atm). After filtration through a Celite pad while washing with MeOH, the filtrate was concentrated in vacuo to afford (S)-3-(2-amino-4-methoxyphenoxy)-2-(tert-butoxycarbonylamino)propanoic acid (200 mg, 62%) as a black solid. LC-MS: m/z = 326.89 $[M+H]^+$.

[231] Step D: (S)-tert-butyl 7-methoxy-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate

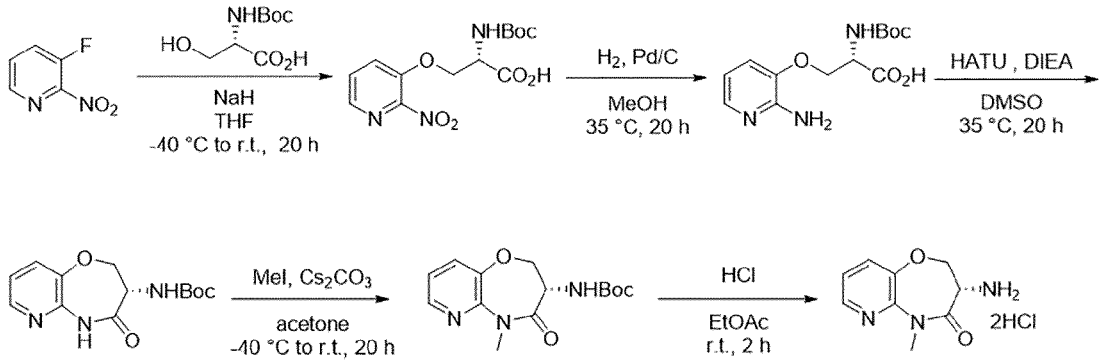
[232] To solution of (S)-3-(2-amino-4-methoxyphenoxy)-2-(tert-butoxycarbonylamino)propanoic acid (320 mg, 0.981 mmol) in DMSO (3.0 mL) was added DIPEA (514 μL, 2.94 mmol) followed by HATU (373 mg, 0.981 mmol) at 0 ℃. The reaction mixture was stirred at room temperature for 30 minutes. After quenched with ice-water, the mixture was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 2:1) to afford (S)-tert-butyl 7-methoxy-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (200 mg, 66%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.17 (1H, brs), 6.90 (1H, d, J = 8.8 Hz), 6.68-6.64 (2H, m), 5.48 (1H, brs), 4.69-4.61 (2H, m), 4.21 (1H, t, J = 9.6 Hz), 3.79 (3H, s), 1.42 (9H, s).

[233] Step E: (S)-tert-butyl 7-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate

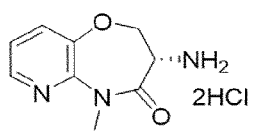
[234] To a solution of (S)-tert-butyl 7-methoxy-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (200 mg, 0.649 mmol) in DMF (5.0 mL) was added Cs_2CO_3 (254 mg, 0.778 mmol) followed by a solution of MeI (48.7 μL, 0.778 mmol) in DMF (1.0 mL) at 0 °C. The reaction mixture was stirred for 4 hours at 0 °C and then at room temperature for further 1 hour. After quenched with ice-water, the mixture was extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 3:1) to afford (S)-tert-butyl 7-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-ylcarbamate (150 mg, 72%) as a colorless oil. LC-MS: m/z = $[M+H]^+$.

[235] Step F: (S)-3-amino-7-methoxy-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one hydrochloride

[236] To a solution of (S)-tert-butyl 7-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo [b][1,4]oxazepin-3-ylcarbamate (40 mg, 0.124 mmol) in MeOH (3.0 mL) was added HCl (2 M in Et_2O, 1.24 mL, 2.48 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 5 hours and concentrated in vacuo to afford (S)-3-amino-7-methoxy-5-methyl-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one hydrochloride (32 mg, 100%) as a white solid. LC-MS: m/z = 223.05 $[M+H]^+$.

[237] 

[238] Intermediate 17: (S)-3-amino-5-methyl-2,3-dihydropyrido[3,2-b][1,4]oxazepin-4(5H)-one dihydrochloride

[239] 

[240] Step A: (S)-2-((tert-butoxycarbonyl)amino)-3-((2-nitropyridin-3-yl)oxy)propanoic acid

[241] To a solution of N-Boc-L-serine (22.8 g, 111 mmol) in dry THF (200 mL) was slowly added NaH (60 wt%, 8.31 g, 207 mmol) in portions at -40 °C. The mixture was stirred at 0 °C for 2 hours and then cooled to -40 °C. After slow addition of a solution

of 3-fluoro-2-nitropyridine (15.0 g, 101 mmol) in dry THF (100 mL) at -40 ℃, the reaction mixture was stirred at room temperature for 20 hours. After quenched with water, the mixture was acidified until pH 6 with 1 M aq. HCl solution and then extracted with EtOAc (300 mL x 3). The combined organic layers were washed with brine and water, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified on SiO_2 (DCM:MeOH = 20:1) to afford (S)-2-((tert-butoxycarbonyl)amino)-3-((2-nitropyridin-3-yl)oxy)propanoic acid (21.1 g, 61%) as a yellow semi-solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.12 (1H, d, J = 4.0 Hz), 7.98 (1H, d, J = 8.0 Hz), 7.76 (1H, dd, J = 8.8, 4.8 Hz), 7.17 (1H, d, J = 7.6 Hz), 4.50-4.48 (1H, m), 4.43-4.39 (2H, m), 1.37 (9H, s)

[242] Step B: (S)-3-((2-aminopyridin-3-yl)oxy)-2-((tert-butoxycarbonyl)amino)propanoic acid

[243] A suspension of (S)-2-((tert-butoxycarbonyl)amino)-3-((2-nitropyridin-3-yl)oxy)propanoic acid (21.1 g, 64.5 mmol) and Pd/C (10 wt%, 2.11 g) in MeOH (100 mL) was stirred at 35 ℃ for 20 hours under hydrogen atmosphere (1 atm). After filtration through a 0.45 um PTFE needle filter washing with DCM/MeOH+AcOH (v/v = 20:1), the filtrate was concentrated in vacuo to afford (S)-3-((2-aminopyridin-3-yl)oxy)-2-((tert-butoxycarbonyl)amino)propanoic acid (19.6 g, >99%) as a grey semi-solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.57 (1H, d, J = 9.2 Hz), 7.49 (1H, d, J = 4.4 Hz), 6.98 (1H, d, J = 7.6 Hz), 6.46 (1H, dd, J = 7.6, 5.2 Hz), 5.89 (2H, br), 4.48-4.45 (1H, m), 4.34 (1H, dd, J = 9.2, 4.4 Hz), 3.98 (1H, dd, J = 9.6, 3.2 Hz), 1.40 (9H, s).

[244] Step C: (S)-tert-butyl (4-oxo-2,3,4,5-tetrahydropyrido[3,2-b][1,4]oxazepin-3-yl)carbamate

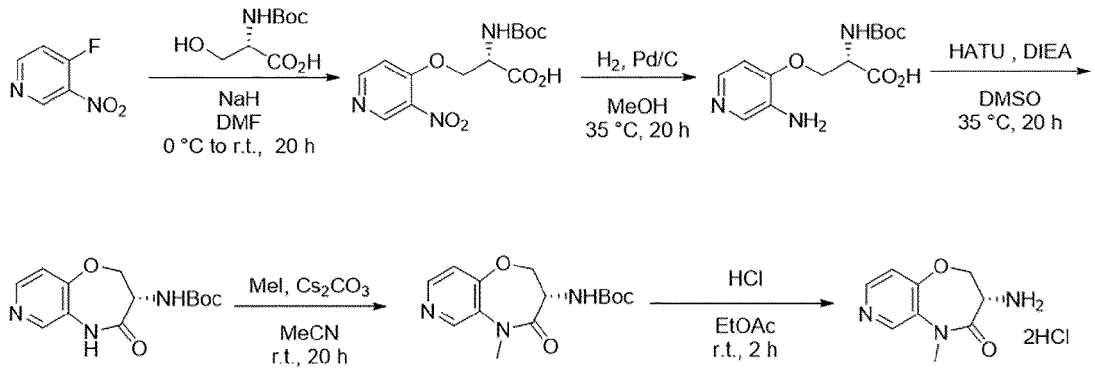
[245] To a solution of (S)-3-((2-aminopyridin-3-yl)oxy)-2-((tert-butoxycarbonyl)amino)propanoic acid (9.00 g, 25.1 mmol) in DMSO (20 mL) was added DIPEA (9.71 g, 75.3 mmol) followed by HATU (9.54 g, 25.1 mmol) at room temperature. The reaction mixture was stirred at 35 ℃ for 20 hours. After dilution with H_2O (100 mL), the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (pet. ether:EtOAc = 5:1) to afford (S)-tert-butyl (4-oxo-2,3,4,5-tetrahydropyrido[3,2-b][1,4]oxazepin-3-yl)carbamate (1.80 g, 25%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.37 (1H, s), 8.14 (1H, d, J = 4.4 Hz), 7.54 (1H, d, J = 7.6 Hz), 7.17-7.14 (2H, m), 4.39-4.29 (3H, m), 1.37 (9H, s).

[246] Step D: (S)-tert-butyl (5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-b][1,4]oxazepin-3-yl)carbamate

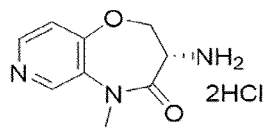
[247] To a solution of (S)-tert-butyl (4-oxo-2,3,4,5-tetrahydropyrido[3,2-b][1,4]oxazepin-3-yl)carbamate (1.80 g, 6.45 mmol) in acetone (100 mL) was added Cs_2CO_3 (2.30 g, 7.09 mmol) followed by a solution of MeI (1.11 g, 7.83 mmol) in acetone (8.0 mL) dropwise at -40 °C. The reaction mixture was stirred at -40 °C for 1 hour and then at room temperature for 20 hours. After quenched with H_2O, the mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (pet. ether:EtOAc = 5:1) to afford (S)-tert-butyl (5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-b][1,4]oxazepin-3-yl)carbamate (705 mg, 37%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.34 (1H, dd, J = 4.8, 1.2 Hz), 7.65 (1H, dd, J = 8.0, 1.6 Hz), 7.31-7.25 (2H, m), 4.42-4.35 (3H, m), 3.32 (3H, s), 1.35 (9H, s).

[248] Step E: (S)-3-amino-5-methyl-2,3-dihydropyrido[3,2-b][1,4]oxazepin-4(5H)-one dihydrochloride

[249] To a solution of (S)-tert-butyl (5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-b][1,4]oxazepin-3-yl)carbamate (700 mg, 2.38 mmol) in EtOAc (5.0 mL) was added HCl (6 M in EtOAc, 10 mL, 60 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 hours and concentrated in vacuo to afford (S)-3-amino-5-methyl-2,3-dihydropyrido[3,2-b][1,4]oxazepin-4(5H)-one dihydrochloride (450 mg, 82%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6 + D_2O): δ 8.39 (1H, d, J = 4.4 Hz), 7.76 (1H, d, J = 8.0 Hz), 7.39-7.37 (1H, m), 4.70 (1H, t, J = 8.0 Hz), 4.55 (1H, t, J = 10.0 Hz), 4.43-4.39 (1H, m), 3.40 (3H, s).

[250] 

[251] Intermediate 18: (S)-3-amino-5-methyl-2,3-dihydropyrido[4,3-b][1,4]oxazepin-4(5H)-one dihydrochloride

[252] 

[253] Step A: (S)-2-((tert-butoxycarbonyl)amino)-3-((3-nitropyridin-4-yl)oxy)propanoic acid

[254] To a suspension of NaH (60 wt%, 15.7 g, 394 mmol) in dry DMF (200 mL) was slowly added a solution of N-Boc-L-serine (32.2 g, 157 mmol) in dry DMF (50 mL) at 0 ℃. The mixture was stirred at 0 ℃ for 1 hour. After slow addition of a solution of 1-fluoro-2-nitrobenzene (25.0 g, 157 mmol) in DMF (50 mL), the reaction mixture was stirred at room temperature for 20 hours. After quenched with water, the mixture was neutralized with 1 M aq. HCl solution and then extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine and water, dried over Na_2SO_4, filtered and concentrated in vacuo to afford (S)-2-((tert-butoxycarbonyl)amino)-3-((3-nitropyridin-4-yl)oxy)propanoic acid (44 g, 76%) as a brown oil. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 13.0 (1H, brs), 8.97 (1H, s), 8.66 (1H, d, J = 6.0 Hz), 7.46 (1H, d, J = 6.0 Hz), 7.19 (1H, d, J = 3.6 Hz), 4.54-4.45 (3H, m), 1.38 (9H, s).

[255] Step B: (S)-3-((3-aminopyridin-4-yl)oxy)-2-((tert-butoxycarbonyl)amino)propanoic acid

[256] A suspension of (S)-2-((tert-butoxycarbonyl)amino)-3-((3-nitropyridin-4-yl)oxy)propanoic acid (40.0 g, 122 mmol) and Pd/C (10wt%, 4.00 g) in MeOH (50 mL) was stirred at 35 ℃ for 20 hours under hydrogen atmosphere (1 atm). After filtration through a 0.45 um PTFE needle filter washing with MeOH, the filtrate was concentrated in vacuo to afford (S)-3-((3-aminopyridin-4-yl)oxy)-2-((tert-butoxycarbonyl)amino)propanoic acid (35.5 g, 98%) as a brown solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.83 (1H, s), 7.69 (1H, d, J = 5.2 Hz), 7.44 (1H, d, J = 8.8 Hz), 6.79 (1H, d, J = 5.2 Hz), 4.47-4.43 (1H, m), 4.39 (1H, dd, J = 9.6, 4.4 Hz), 4.07 (1H, dd, J = 9.6, 3.2 Hz), 1.40 (9H, s).

[257] Step C: (S)-tert-butyl (4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate

[258] To a solution of (S)-3-((3-aminopyridin-4-yl)oxy)-2-((tert-butoxycarbonyl)amino)propanoic acid (35.0 g, 117 mmol) in DMSO (100 mL) was added DIPEA (45.9 g, 353 mmol) followed by HATU (44.7 g, 117 mmol) at room temperature. The reaction mixture was stirred at 35 ℃ for 20 hours. After diluted with H_2O (300 mL), the mixture was extracted with EtOAc (300 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (pet. ether:EtOAc = 1:1) to afford (S)-tert-butyl (4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate (2.50 g, 7%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.25 (1H, s), 8.32 (1H, s), 8.12 (1H, d, J = 5.2 Hz), 7.12 (1H, d, J = 6.8 Hz), 7.03 (1H, d, J = 5.6 Hz), 4.38-4.33 (3H, m),

1.39 (9H, s).

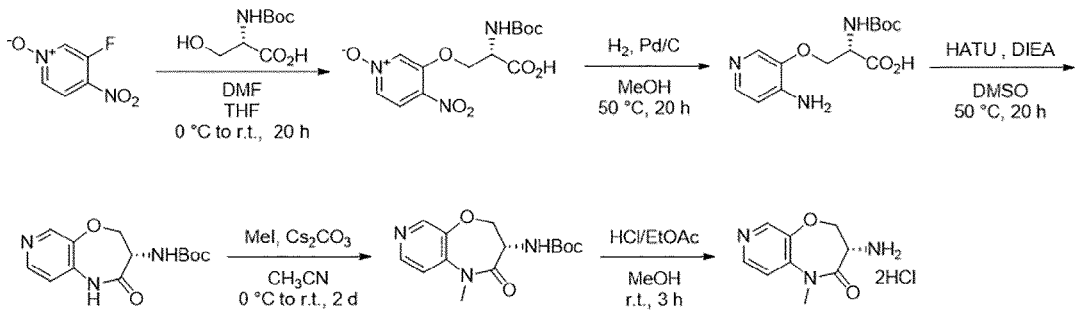
[259] Step D: (S)-tert-butyl (5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate

[260] To a solution of (S)-tert-butyl (4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate (2.00 g, 7.16 mmol) in MeCN (10 mL) was added Cs_2CO_3 (4.66 g, 14.3 mmol) followed by MeI (1.11 g, 7.83 mmol) in MeCN (10 mL) dropwise at room temperature. The reaction mixture was stirred at room temperature for 20 hours. After quenched with water, the mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (pet. ether:EtOAc = 1:1) to afford (S)-tert-butyl (5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate (600 mg, 28%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.71 (1H, s), 8.41 (1H, d, J = 4.4 Hz), 7.21 (1H, d, J = 5.2 Hz), 7.18 (1H, d, J = 5.6 Hz), 4.42-4.38 (3H, m), 3.33 (3H, s), 1.35 (9H, s).

[261] Step E: (S)-3-amino-5-methyl-2,3-dihydropyrido[4,3-b][1,4]oxazepin-4(5H)-one dihydrochloride

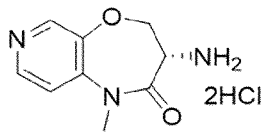
[262] To a solution of (S)-tert-butyl (5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate (600 mg, 2.04 mmol) in EtOAc (5.0 mL) was added HCl (5 M solution in EtOAc, 6.0 mL, 30 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 hours and concentrated in vacuo to afford (S)-3-amino-5-methyl-2,3-dihydropyrido[4,3-b][1,4]oxazepin-4(5H)-one dihydrochloride (300 mg, 64%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d_6 + D_2O): δ 7.98 (1H, d, J = 6.4 Hz), 7.98 (1H,s), 6.95 (1H, d, J = 6.8 Hz), 4.41 (1H, m), 3.87 (1H, d, J = 3.2 Hz), 3.85 (1H, d, J = 3.2 Hz), 3.28 (3H, s).

[263]



[264] Intermediate 19: (S)-3-amino-1-methyl-3,4-dihydropyrido[3,4-b][1,4]oxazepin-2(1H)-one dihydrochloride

[265]



[266] Step A: (S)-3-(2-((tert-butoxycarbonyl)amino)-2-carboxyethoxy)-4-nitropyridine 1-oxide

[267] To a solution of N-Boc-L-serine (34.0 g, 166 mmol) in dry THF (800 mL) was slowly added NaH (60 wt%, 13.3 g, 333 mmol) in portions at 0 ℃. The mixture was stirred at 0 ℃ for 1 hour. After slow addition of a solution of 3-fluoro-4-nitropyridine 1-oxide (24.0 g, 151 mmol) in dry THF (100 mL), the reaction mixture was stirred at room temperature for 20 hours. After quenched with water, the mixture was neutralized with 1 M aq. HCl solution and then extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine and water, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (DCM:MeOH = 20:1) to afford (S)-3-(2-((tert-butoxycarbonyl)amino)-2-carboxyethoxy)-4-nitropyridine 1-oxide (8.20 g, 16%) as a yellow solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.50 (1H, s), 8.02 (2H, s), 7.14 (1H, d, J = 8.0 Hz),4.46-4.38 (3H, m), 1.37 (9H, s).

[268] Step B: (S)-3-((4-aminopyridin-3-yl)oxy)-2-((tert-butoxycarbonyl)amino)propanoic acid

[269] A suspension of (S)-3-(2-((tert-butoxycarbonyl)amino)-2-carboxyethoxy)-4-nitropyridine 1-oxide (8.10 g, 23.6 mmol) and Pd/C (10 wt%, 1.00 g, 0.12 eq.) in MeOH (100 mL) was stirred at 50 ℃ for 20 hours under hydrogen atmosphere (1 atm). After filtration through a Celite pad while washing with MeOH, the filtrate was concentrated in vacuo to afford (S)-3-((4-aminopyridin-3-yl)oxy)-2-((tert-butoxycarbonyl)amino)propanoic acid (7.01 g, 100%) as a brown solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.83-7.73 (1H, m), 6.56-6.52 (1H, m), 6.15-5.95 (1H, m), 3.69-3.58 (2H, m), 3.46-3.41 (1H, m), 1.37 (9H, s).

[270] Step C: (S)-tert-butyl (4-oxo-2,3,4,5-tetrahydropyrido[3,2-b][1,4]oxazepin-3-yl)carbamate

[271] To a solution of (S)-3-((4-aminopyridin-3-yl)oxy)-2-((tert-butoxycarbonyl)amino)propanoic acid (6.00 g, 23.6 mmol) in DMSO (50 mL) was added DIPEA (7.15 g, 70.8 mmol) followed by HATU (8.96 g, 23.6 mmol) at room temperature. The reaction mixture was stirred at 50 ℃ for 20 hours. After dilution with H_2O (100 mL), the mixture was extracted with EtOAc (150 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on

C18 (MeCN/H $_2$O) to afford (S)-tert-butyl (2-oxo-1,2,3,4-tetrahydropyrido[3,4-b][1,4]oxazepin-3-yl)carbamate (510 mg, 9%) as a light yellow solid.

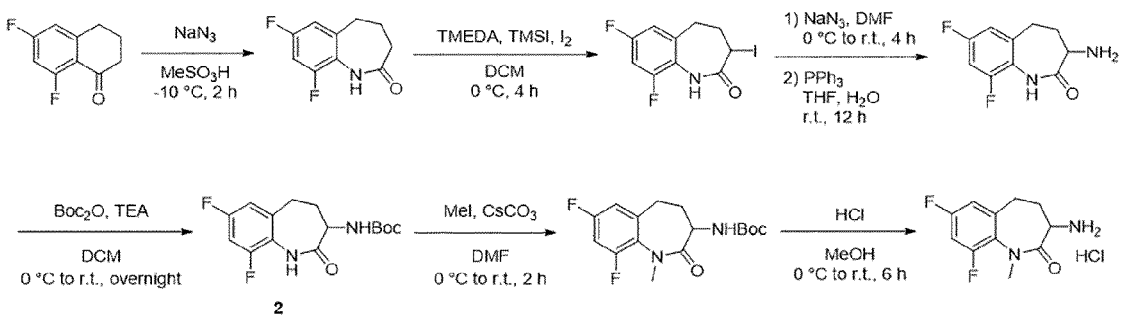
[272] ^{1}H-NMR (400 MHz, DMSO-d $_6$): δ 10.96 (1H, br), 8.35 (1H, br), 8.07 (1H, s), 8.02 (1H, d, J = 5.2 Hz), 6.83 (1H, d, J = 5.2 Hz), 1.51 (3H, s), 1.31 (9H, s).

[273] Step D: (S)-tert-butyl (1-methyl-2-oxo-1,2,3,4-tetrahydropyrido[3,4-b][1,4]oxazepin-3-yl)carbamate

[274] To a solution of (S)-tert-butyl (2-oxo-1,2,3,4-tetrahydropyrido[3,4-b][1,4]oxazepin-3-yl)carbamate (400 mg, 1.43 mmol) in MeCN (5.0 mL) was added Cs $_2$CO $_3$ (232 mg, 0.710 mmol) followed by a solution of MeI (161 mg, 1.41 mmol) in MeCN (2.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 days. After quenched with water, the mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na $_2$SO $_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO $_2$ (pet. ether:EtOAc = 1:1) to afford (S)-tert-butyl (1-methyl-2-oxo-1,2,3,4-tetrahydropyrido[3,4-b][1,4]oxazepin-3-yl)carbamate (110 mg, 26%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d $_6$): δ 8.35 (1H, br), 8.15 (1H, d, J = 5.6 Hz), 8.12 (1H, s), 7.11 (1H, d, J = 5.2 Hz), 3.27 (3H, s), 1.54 (3H, s), 1.28 (9H, s).

[275] Step E: (S)-3-amino-1-methyl-3,4-dihydropyrido[3,4-b][1,4]oxazepin-2(1H)-one dihydrochloride

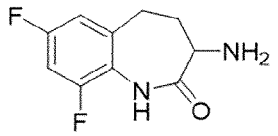
[276] To a solution of (S)-tert-butyl (1-methyl-2-oxo-1,2,3,4-tetrahydropyrido[3,4-b][1,4]oxazepin-3-yl)carbamate (110 mg, 0.370 mmol) in MeOH (5.0 mL) was added HCl (6 M solution in EtOAc, 5.0 mL, 30 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours and concentrated in vacuo to afford (S)-3-amino-1-methyl-3,4-dihydropyrido[3,4-b][1,4]oxazepin-2(1H)-one dihydrochloride (51 mg, 51%) as a brown solid. ^{1}H-NMR (400 MHz, DMSO-d $_6$): δ 8.65 (1H, s), 8.57 (1H, d, J = 6.4 Hz), 7.70 (1H, d, J = 6.0 Hz), 3.41 (3H, s), 1.76 (3H, s).

[277] 

2

[278] Intermediate 20: 3-amino-7,9-difluoro-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one

[279]



[280] Step A: 7,9-difluoro-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one

[281] To a solution of 6,8-difluoro-3,4-dihydronaphthalen-1(2H)-one (800 mg, 4.39 mmol) in methansulfonic acid (6.0 mL, 92 mmol) was added sodium azide (350 mg, 5.38 mmol) at -10 ℃. The reaction mixture was stirred at -10 ℃ for 2 hours. After quenched with ice-water, a precipitated solid was collected by filtration, washed with hexanes, and then dried under vacuum to afford 7,9-difluoro-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one (700 mg, 81%) as a white solid. ^{1}H-NMR (400 MHz, DMSO-d $_6$): δ 9.40 (1H, brs), 7.19 (1H, t, J = 9.6 Hz), 7.60 (1H, d, J = 10.0 Hz), 2.91 (1H, q, J = 6.4 Hz), 2.73 (2H, t, J = 6.8 Hz), 2.14-2.08 (2H, m), 1.87-1.82 (1H, m).

[282] Step B: 7,9-difluoro-3-iodo-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one

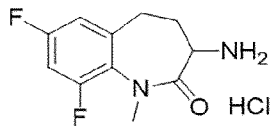
[283] To a solution of 7,9-difluoro-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one (700 mg, 3.55 mmol) in DCM (10 mL) was slowly added TMEDA (1.61 mL, 10.7 mmol) followed by TMSI (1.45 mL, 10.7 mmol) at 0 ℃ under Ar atmosphere. The mixture was stirred at 0 ℃ for 2 hours. After addition of iodine (1.30 g, 5.12 mmol), the reaction mixture was stirred at 0 ℃ for further 2 hours and then quenched with saturated aq. Na $_2$S $_2$O $_3$. The mixture was stirred at room temperature for 1 hour and extracted with EtOAc. The separated organic layer was washed with 1 M aq. HCl and brine, dried over Na $_2$SO $_4$, filtered and concentrated in vacuo to afford 7,9-difluoro-3-iodo-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one (700 mg, 61%). ^{1} H-NMR (400 MHz, DMSO-d $_6$): δ 9.98 (1H, brs), 7.26-7.21 (1H, m), 7.09 (1H, d, J = 8.4 Hz), 4.01 (1H, dd, J = 11.2, 8.0 Hz), 2.80-2.73 (2H, m), 2.43-2.33 (1H, m), 2.14-2.08 (1H, m).

[284] Step C: 3-amino-7,9-difluoro-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one

[285] To a solution of 7,9-difluoro-3-iodo-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one (700 mg, 2.17 mmol) in DMF (5.0 mL) was added sodium azide (211 mg, 3.25 mmol) at 0 ℃. The mixture was stirred at room temperature for 4 hours. After quenched with ice-water, the mixture was stirred at 0 ℃ for 1 hour. A precipitated solid was collected by filtration, washed with cold water to afford azide compound. To a solution of the azide compound in THF (10 mL) and water (1.0 mL) was added PPh $_3$ (568 mg, 2.17 mmol). The reaction mixture was stirred at room temperature for 12 hours. After concentrated in vacuo, the residue was purified by column chromatography on SiO $_2$ (Hexanes:EtOAc = 1:2) to afford 3-amino-7,9-difluoro-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one (350 mg, 76%) as a

white solid. LC-MS: m/z = 213.00 $[M+H]^+$.

[286] Intermediate 21:
3-amino-7,9-difluoro-1-methyl-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one hydrochloride

[287] 

[288] Step A: tert-butyl
7,9-difluoro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-ylcarbamate

[289] A mixture of 3-amino-7,9-difluoro-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one (130 mg, 0.613 mmol) and TEA (171 μL, 1.23 mmol) in DCM (5.0 mL) was stirred at room temperature for 5 minutes and cooled to 0 ℃. After addition of a solution of Boc_2O (156 μL, 0.674 mmol) in DCM (3.0 mL), the reaction mixture was stirred at 0 ℃ for 2 hours and then at room temperature overnight. After quenched with water, the mixture was extracted with EtOAc, washed with 0.5 M aq. HCl and water, dried over Na_2SO_4, filtered, concentrated in vacuo to afford tert-butyl
7,9-difluoro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-ylcarbamate (180 mg, 94%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.21 (1Θ, brs), 6.82-6.78 (2H, m), 5.45 (1H, d, J = 6.8 Hz), 4.32-4.26 (1H, m), 3.00-2.93 (1H, m), 2.75-2.65 (2H, m), 2.04-1.96 (1H, m), 1.41 (9H, s).

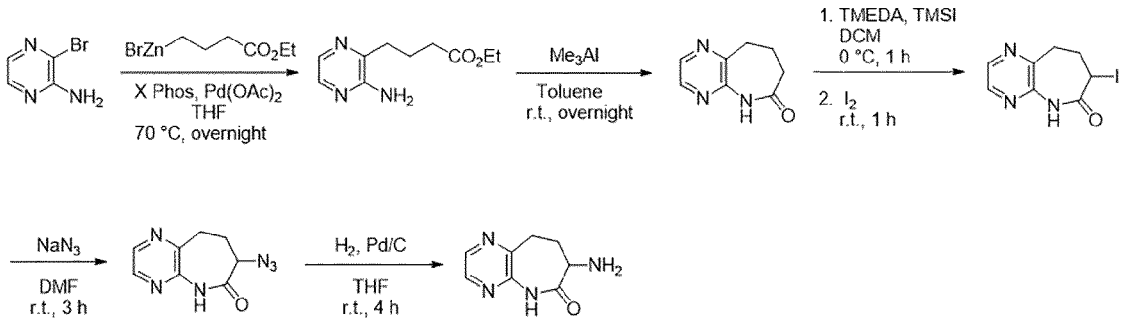
[290] Step B: tert-butyl
7,9-difluoro-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-ylcarbamate

[291] To a solution of tert-butyl
7,9-difluoro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-ylcarbamate (180 mg, 0.576 mmol) in DMF (4.0 mL) was added Cs_2CO_3 (225 mg, 0.692 mmol) at 0 ℃. The mixture was stirred at 0 ℃ for 5 minutes. After addition of a solution of MeI (43.2 μL, 0.692 mmol) in DMF (1.0 mL), the reaction mixture was stirred at 0 ℃ for 1 hour and then at room temperature for further 1 hour. After quenched with water, the mixture was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 2:1) to afford tert-butyl
7,9-difluoro-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-ylcarbamate (150 mg, 80%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.84-6.76 (2Θ, m), 5.51 (1H, d, J = 6.4 Hz), 4.25-4.19 (1H, m), 3.30 (3H, d, J = 2.0 Hz), 2.86-2.77 (1H, m), 2.63-2.51 (2H, m), 1.96-1.88 (1H, m), 1.40 (9H, s).

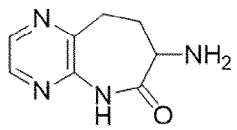
[292] Step C: 3-amino-7,9-difluoro-1-methyl-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one hydrochloride

[293] To a solution of tert-butyl

7,9-difluoro-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-ylcarbamate (60 mg, 0.184 mmol) in MeOH (3.0 mL) was added HCl (2 M in Et_2O, 919 μL, 1.84 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 6 hours and then concentrated in vacuo to afford 3-amino-7,9-difluoro-1-methyl-1,3,4,5-tetrahydro-2H-benzo[b]azepin-2-one hydrochloride (48 mg, 100%). LC-MS: m/z = 227.04 $[M+H]^+$.

[294] 

[295] Intermediate 22: 7-amino-5H,7H,8H,9H-pyrazino[2,3-b]azepin-6-one

[296] 

[297] Step A: Ethyl 4-(3-aminopyrazin-2-yl)butanoate

[298] To a mixture of 3-bromopyrazin-2-amine (1.20 g, 6.89 mmol), X-Phos (657 mg, 1.38 mmol) and $Pd(OAc)_2$ (154 mg, 0.690 mmol) in THF (20 mL) was added a solution of ethyl 4-(bromozincio)butanoate (0.5 M in THF, 80 mL, 40 mmol) at room temperature under N_2 atmosphere. The reaction mixture was stirred at 70 °C overnight and cooled to room temperature. After quenched with 1 N aq. HCl (100 mL), the mixture was extracted with EtOAc twice. The separated aqueous layer was basified with 6 N aq. NaOH until pH 9 and then extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to afford ethyl 4-(3-aminopyrazin-2-yl)butanoate (1.19 g, 89%) as a yellow oil. LC-MS: m/z = 210.10 $[M+H]^+$

[299] Step B: 5H,7H,8H,9H-pyrazino[2,3-b]azepin-6-one

[300] To a solution of ethyl 4-(3-aminopyrazin-2-yl)butanoate (1.04 g, 4.99 mmol) in toluene (45 mL) was added a solution of $AlMe_3$ (2 M in toluene, 15.0 mL, 30.0 mmol). The reaction mixture was stirred at room temperature overnight. After quenched with water, the mixture was extracted with DCM twice. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (DCM:MeOH = 10:1) to give 5H,7H,8H,9H-pyrazino[2,3-b]azepin-6-one (600 mg, 73%) as a yellow solid. LC-MS: m/z = 164.05 $[M+H]^+$

[301] Step C: 7-iodo-5H,7H,8H,9H-pyrazino[2,3-b]azepin-6-one

[302] To a solution of 5H,7H,8H,9H-pyrazino[2,3-b]azepin-6-one (300 mg, 1.84 mmol) in DCM (20 mL) was added TMEDA (2.13 g, 18.3 mmol), followed by TMSI (3.67 g, 18.3 mmol) over 25 min at 0 °C. The mixture was stirred for 1 hour. After addition of I_2 (933 mg, 3.67 mmol), the reaction mixture was stirred at room temperature for further 1 hour and then quenched with saturated aq. sodium thiosulfate. The mixture was extracted with DCM twice. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Pet. ether:EtOAc = 1:1) to give 7-iodo-5H,7H,8H,9H-pyrazino[2,3-b]azepin-6-one (330 mg, 62%) as a yellow solid. LC-MS: m/z = 289.95 $[M+H]^+$

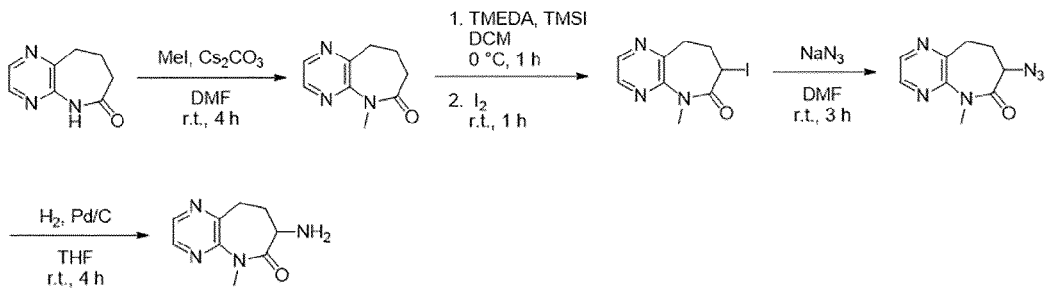
[303] Step D: 7-azido-5H,7H,8H,9H-pyrazino[2,3-b]azepin-6-one

[304] To a solution of 7-iodo-5H,7H,8H,9H-pyrazino[2,3-b]azepin-6-one (300 mg, 1.03 mmol) in DMF (5.0 mL) was added NaN_3 (269 mg, 4.15 mmol). The reaction mixture was stirred at room temperature for 3 hours. After quenched with water, the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to afford 7-azido-5H,7H,8H,9H-pyrazino[2,3-b]azepin-6-one (163 mg, 77%) as a yellow solid. LC-MS: m/z = 205.05 $[M+H]^+$

[305] Step E: 7-amino-5H,7H,8H,9H-pyrazino[2,3-b]azepin-6-one

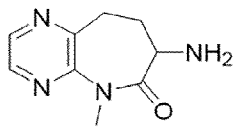
[306] A suspension of 7-azido-5H,7H,8H,9H-pyrazino[2,3-b]azepin-6-one (163 mg, 0.80 mmol) and Pd/C (10%, 16.0 mg) in THF (30 mL) was stirred at room temperature for 4 hours under H_2 atmosphere (1 atm). After filtration through a Celite pad, the filtrate was concentrated in vacuo. The residue was purified by reverse phase column to afford 7-amino-5H,7H,8H,9H-pyrazino[2,3-b]azepin-6-one (60 mg, 42%) as a white solid. ^{1}H-NMR (400 MHz, CD_3OD): δ 8.32 (1H, dd, J = 2.6, 0.7 Hz), 8.29 (1H, d, J = 2.6 Hz), 3.45 (1H, dd, J = 11.8, 7.5 Hz), 3.08 (1H, ddd, J = 14.4, 12.0, 8.1 Hz), 2.99 (1H, ddd, J = 14.2, 7.6, 2.2 Hz), 2.62 (1H, ddt, J = 13.1, 12.1, 7.5 Hz), 2.09 (1H, dddd, J = 13.0, 11.8, 8.1, 2.1 Hz).

[307]



[308] Intermediate 23: 7-amino-5-methyl-7H,8H,9H-pyrazino[2,3-b]azepin-6-one

[309]



[310] Step A: 5-methyl-7H,8H,9H-pyrazino[2,3-b]azepin-6-one

[311] To a solution of 5H,7H,8H,9H-pyrazino[2,3-b]azepin-6-one (See Intermediate 22, 300 mg, 1.84 mmol) in DMF (5.0 mL) was added Cs_2CO_3 (1.19 g, 3.67 mmol) followed by MeI (521 mg, 3.68 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 hours. After quenched with water, the mixture was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give 5-methyl-7H,8H,9H-pyrazino[2,3-b]azepin-6-one (210 mg, 64%) as a yellow solid. LC-MS: m/z = 178.05 $[M+H]^+$

[312] Step B: 7-iodo-5-methyl-7H,8H,9H-pyrazino[2,3-b]azepin-6-one

[313] To a solution of 5-methyl-7H,8H,9H-pyrazino[2,3-b]azepin-6-one (200 mg, 1.13 mmol) in DCM (20 mL) was added TMEDA (1.31 g, 11.3 mmol) followed by TMSI (2.25 g, 11.3 mmol) over 25 min at 0 °C. The mixture was stirred at 0 °C for 1 hour. After addition of I_2 (572 mg, 2.26 mmol), the reaction mixture was stirred at room temperature for further 1 hour and then quenched with saturated aq. sodium thiosulfate. The mixture was extracted with DCM twice. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Pet. ether:EtOAc = 1:1) to give 7-iodo-5-methyl-7H,8H,9H-pyrazino[2,3-b]azepin-6-one (250 mg, 73%) as a yellow solid. LC-MS: m/z = 303.90 $[M+H]^+$

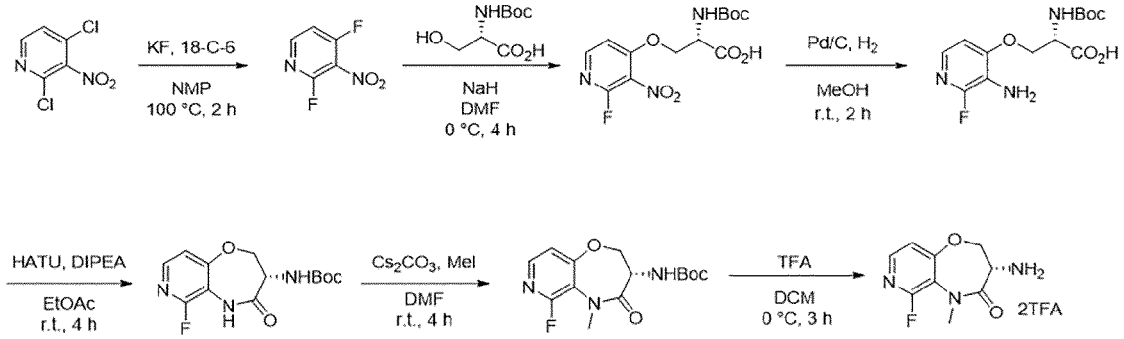
[314] Step C: 7-iodo-5-methyl-7H,8H,9H-pyrazino[2,3-b]azepin-6-one

[315] To a solution of 7-iodo-5-methyl-7H,8H,9H-pyrazino[2,3-b]azepin-6-one (250 mg, 0.82 mmol) in DMF (5.0 mL) was added NaN_3 (214 mg, 3.29 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 hours. After quenched with water, the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to afford 7-azido-5-methyl-7H,8H,9H-pyrazino[2,3-b]azepin-6-one (160 mg, 88%) as a yellow solid. LC-MS: m/z = 219.15 $[M+H]^+$

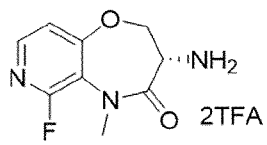
[316] Step D: 7-amino-5-methyl-7H,8H,9H-pyrazino[2,3-b]azepin-6-one

[317] A suspension of 7-azido-5-methyl-7H,8H,9H-pyrazino[2,3-b]azepin-6-one (160 mg, 0.730 mmol) and Pd/C (10%, 16.0 mg) in THF (30 mL) was stirred at room temperature for 4 hours under H_2 atmosphere (1 atm). After filtration through a Celite pad, the filtrate was concentrated in vacuo. The residue was purified by reverse phase column to afford 7-amino-5-methyl-7H,8H,9H-pyrazino[2,3-b]azepin-6-one (70 mg,

50%) as a white oil. ^{1}H-NMR (400 MHz, CD_3OD): δ 8.44 (1H, dd, J = 2.6, 0.7 Hz), 8.34 (1H, d, J = 2.6 Hz,), 3.48 (3H, s), 3.39 (1H, dd, J = 11.9, 7.6 Hz), 3.09-2.87 (2H, m), 2.57 (1H, tt, J = 12.8, 7.6 Hz,), 2.06 (1H, dddd, J = 13.1, 11.9, 8.4, 1.4 Hz).

[318] 

[319] Intermediate 24: (S)-3-amino-6-fluoro-5-methyl-2,3-dihydropyrido[4,3-b][1,4]oxazepin-4(5H)-one 2TFA

[320] 

[321] Stpe A: 2,4-difluoro-3-nitropyridine

[322] A mixture of 2,4-dichloro-3-nitropyridine (5.00 g, 25.9 mmol), KF (spray-dried, 4.52 g, 78.0 mmol) and 18-Crown-6 (1.10 g, 4.15 mmol) in NMP (26 mL) was stirred at 100 °C for 2 hours. The reaction mixture was cooled to room temperature and then partitioned between of water and MTBE. The separated organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 5:1) to afford 2,4-difluoro-3-nitropyridine (2.60 g, 63%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.4 (1H, t, J = 6.4 Hz), 7.24 (1H, t, J = 7 Hz).

[323] Step B: N-(tert-butoxycarbonyl)-O-(2-fluoro-3-nitropyridin-4-yl)-L-serine

[324] To a suspension of NaH (60wt%, 1.35 g, 33.7 mmol) in DMF (24 mL) was slowly added a solution of (tert-butoxycarbonyl)-L-serine (3.45 g, 16.8 mmol) in DMF (12 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour. After addition of a solution of 2,4-difluoro-3-nitropyridine (2.45 g, 15.3 mmol) in DMF (12 mL) at 0 °C, the reaction mixture was stirred at 0 °C for 4 hours. After quenched with 0.5 M aq. HCl at 0 °C, the mixture was extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 1:1 to 1:3) to afford N-(tert-butoxycarbonyl)-O-(2-fluoro-3-nitropyridin-4-yl)-L-serine (1.65 g, 31%) as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.20 (1H, d, J = 5.6 Hz), 6.98 (1H, d, J = 5.6 Hz), 5.56 (1H, d, J = 6.4 Hz), 4.66-4.56 (3H, m), 1.45 (9H, s).

[325] Step C: O-(3-amino-2-fluoropyridin-4-yl)-N-(tert-butoxycarbonyl)-L-serine

[326] A suspension of N-(tert-butoxycarbonyl)-O-(2-fluoro-3-nitropyridin-4-yl)-L-serine (1.50 g, 4.34 mmol) and Pd/C (10 wt%, 0.46 g, 0.43 mmol) in MeOH (21 mL) was stirred at room temperature for 2 hours under H_2 atmosphere (1 atm). After filtration through a Celite pad while washing with MeOH, the filtrate was concentrated in vacuo to afford O-(3-amino-2-fluoropyridin-4-yl)-N-(tert-butoxycarbonyl)-L-serine (1.30 g, 95%) as a brown oil. LC-MS: m/z = 316.13 $[M+H]^+$.

[327] Step D: tert-butyl (S)-(6-fluoro-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate

[328] To a solution of O-(3-amino-2-fluoropyridin-4-yl)-N-(tert-butoxycarbonyl)-L-serine (1.30 g, 4.12 mmol) in EtOAc (41 mL) was added DIPEA (2.20 mL, 12.4 mmol) followed by HATU (2.35 g, 6.18 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 hours. After quenched with water, the mixture was extracted with EtOAc. The separated organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 4:1) to afford tert-butyl (S)-(6-fluoro-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate (200 mg, 16%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.75 (1H, dd, J = 4, 1.6 Hz), 8.39 (1H, dd, J = 8.8, 1.2 Hz), 7.43 (1H, q, J = 8.6 Hz), 4.67-4.58 (1H, m), 4.39 (1H, d, J = 3.6 Hz), 3.78-3.69 (1H, m), 3.25-3.14 (1H, m), 1.46 (9H, s).

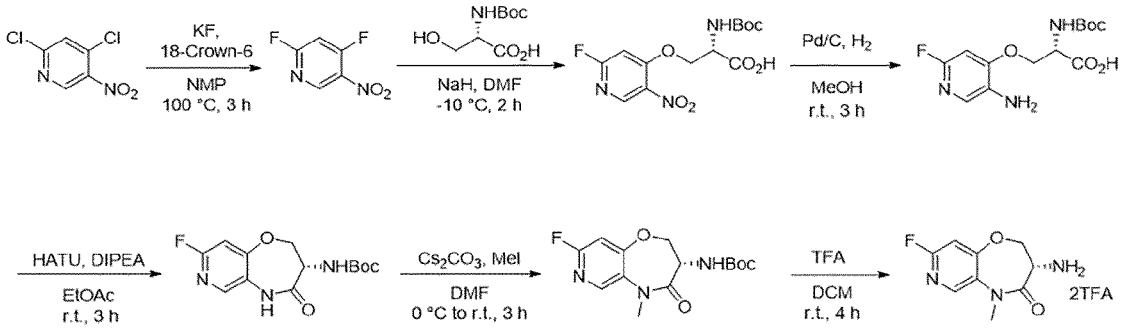
[329] Step E: tert-butyl (S)-(6-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate

[330] To a solution of tert-butyl (S)-(6-fluoro-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate (200 mg, 0.670 mmol) in DMF (6.7 mL) was added Cs_2CO_3 (260 mg, 0.810 mmol) followed by MeI (0.0500 mL, 0.810 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 hours. After dilution with water, the mixture was extracted with EtOAc. The separated organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 6:1) to afford tert-butyl (S)-(6-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate (100 mg, 48%) as a colorless foam. LC-MS: m/z = 312.13 $[M+H]^+$.

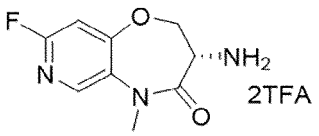
[331] Step F: (S)-3-amino-6-fluoro-5-methyl-2,3-dihydropyrido[4,3-b][1,4]oxazepin-4(5H)-one 2TFA

[332] To a solution of tert-butyl (S)-(6-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carba

mate (80 mg, 0.257 mmol) in DCM (2.5 mL) was added TFA (0.400 mL, 5.14 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 hours, and then concentrated in vacuo to afford (S)-6-fluoro-5-methyl-3-((2,2,2-trifluoroacetyl)-l4-azanyl)-2,3-dihydropyrido[4,3-b][1, 4]oxazepin-4(5H)-one 2TFA (50 mg, 63%) as a brown oil. LC-MS: m/z = 212.08 $[M+H]^+$.

[333] 

[334] Intermediate 25: (S)-8-fluoro-5-methyl-3-((2,2,2-trifluoroacetyl)-l4-azanyl)-2,3-dihydropyrido[4,3-b][1, 4]oxazepin-4(5H)-one 2TFA

[335] 

[336] Step A: 2,4-difluoro-5-nitropyridine

[337] A mixture of 2,4-dichloro-5-nitropyridine (4.00 g, 20.7 mmol), 18-crown-6 (0.880 g, 3.32 mmol), KF (spray-dried, 3.61 g, 62.2 mmol) in NMP (21 mL) was stirred at 100 °C for 3 hours. The reaction mixture was cooled to room temperature, and then partitioned between water and MTBE. The separated organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 9:1) to afford 2,4-difluoro-5-nitropyridine (1.83 g, 55%) as a yellow oil. ^{1}H-NMR(400 MHz, $CDCl_3$) : δ 9.05 (1H, d, J = 7.2 Hz) , 6.94 (1H, dd, J = 7.2, 2.4 Hz)

[338] Step B: N-(tert-butoxycarbonyl)-O-(2-fluoro-5-nitropyridin-4-yl)-L-serine

[339] To a suspension of NaH (60 wt%, 0.960 g, 23.9 mmol) in DMF (64 mL) was slowly added a solution of (tert-butoxycarbonyl)-L-serine (2.10 g, 10.2 mmol) in DMF (25 mL) at -10 °C. The mixture was stirred at for 1 hour at -10 °C. After addition of a solution of 2,4-difluoro-5-nitropyridine (1.82 g, 11.4 mmol) in DMF (25 mL) at -10 °C, the reaction mixture was stirred at for 2 hours at -10 °C. After quenched with 0.5 M aq. HCl at -10 °C, the mixture was extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 5:1 to 1:1) to afford N-

(tert-butoxycarbonyl)-O-(2-fluoro-5-nitropyridin-4-yl)-L-serine (1.34 g, 34%) as a yellow oil. ^{1}H NMR(400 MHz, $CDCl_3$) : δ 8.73 (1H, s) , 6.62 (1H, s), 5.59 (1H, d, J = 7.2 Hz), 4.80 (1H, dt, J = 7.2, 2.8 Hz), 4.68 (1H, dd, J = 9.2 , 2.4 Hz), 4.52 (1H, dd, J = 9.6, 2.8 Hz), 1.45 (9H, s)

[340] Step C: O-(5-amino-2-fluoropyridin-4-yl)-N-(tert-butoxycarbonyl)-L-serine

[341] A suspension of N-(tert-butoxycarbonyl)-O-(2-fluoro-5-nitropyridin-4-yl)-L-serine (1.34 g, 3.87 mmol) and 5% Pd/C (0.28 g, 0.132 mmol) in MeOH (77 mL) was stirred at room temperature for 3 hours under H_2 atmosphere (1 atm). After filtration through a Celite pad while washing with MeOH, the filtrate was concentrated in vacuo to afford O-(5-amino-2-fluoropyridin-4-yl)-N-(tert-butoxycarbonyl)-L-serine (1.22 g, 100%). LC-MS: m/z = 316 $[M+H]^+$.

[342] Step D: tert-butyl (S)-(8-fluoro-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate

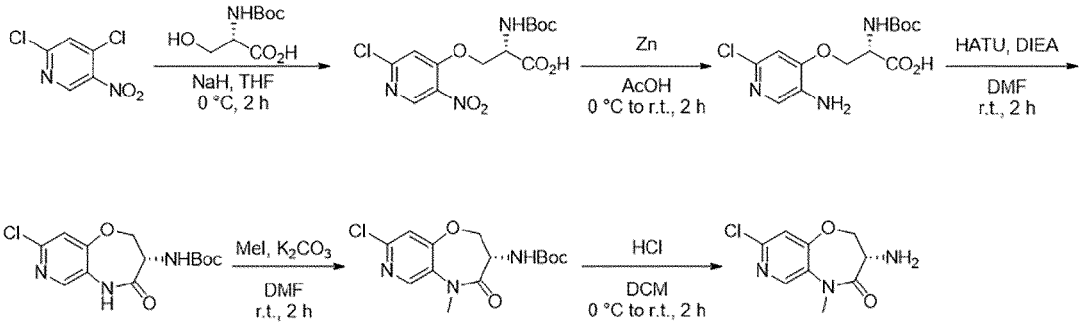
[343] To a solution of O-(5-amino-2-fluoropyridin-4-yl)-N-(tert-butoxycarbonyl)-L-serine (1.22 g, 3.87 mmol) in EtOAc (40 mL) was added DIPEA (1.02 mL, 5.81 mmol) followed by HATU (4.42 g, 11.6 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 hours. After concentration in vacuo, the residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 2:1) to afford tert-butyl (S)-(8-fluoro-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate (370 mg, 32%) as a white solid. ^{1}H NMR(400 MHz, $CDCl_3$): δ 8.55 (1Θ, s), 7.92 (1H, s), 6.59 (1H, d, J = 2 Hz), 5.64 (1H, d, J = 4.4 Hz), 4.65-4.57 (2H, m), 4.31 (1H, td, J = 10, 0.8 Hz), 1.46 (9H, s)

[344] Step E: tert-butyl (S)-(8-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate

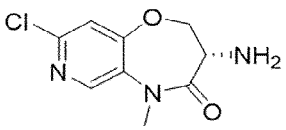
[345] A mixture of tert-butyl (S)-(8-fluoro-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate (0.370 g, 1.24 mmol) and Cs_2CO_3 (0.490 g, 1.50 mmol) in DMF (10 mL) was stirred at 0 °C for 5 minutes. After addition of solution of MeI (0.0940 mL, 1.50 mmol) in DMF (5.0 mL), the reaction mixture was stirred at 0 °C for 1 hour and then at room temperature for further 2 hours. After quenched with water, the mixture was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 2:1) to afford tert-butyl (S)-(8-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate (0.150 g, 40%) as a white solid. ^{1}H NMR(400 MHz, $CDCl_3$) : δ 8.09 (1H, s), 6.69 (1H, d, J = 2 Hz), 5.53 (1H, d, J = 6.4 Hz), 4.70 - 4.57 (2H, m), 4.31 (1H, dd, J = 9.6, 11.6 Hz), 3.44 (3H, s), 1.41 (9H, s)

[346] Step F:
(S)-8-fluoro-5-methyl-3-((2,2,2-trifluoroacetyl)-l4-azanyl)-2,3-dihydropyrido[4,3-b][1,4]oxazepin-4(5H)-one 2TFA

[347] To a solution of tert-butyl (S)-(8-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)carbamate (0.150 g, 0.490 mmol) in DCM (9.8 mL) was added TFA (0.760 mL, 9.83 mmol) at 0 ℃. The reaction mixture was stirred at room temperature for 4 hours and concentrated in vacuo to afford (S)-8-fluoro-5-methyl-3-((2,2,2-trifluoroacetyl)-l4-azanyl)-2,3-dihydropyrido[4,3-b][1,4]oxazepin-4(5H)-one (0.150 g, 99%) as a yellow oil. LC-MS: m/z = 212 $[M+H]^+$.

[348] 

[349] Intermediate 26:
(3S)-3-amino-8-chloro-5-methyl-2H,3H-pyrido[4,3-b][1,4]oxazepin-4-one

[350] 

[351] Step A:
(2S)-2-[(tert-butoxycarbonyl)amino]-3-[(2-chloro-5-nitropyridin-4-yl)oxy]propanoic acid

[352] To a suspension of NaH (60wt%, 3.60 g, 90.0 mmol) in dry THF (100 mL) was slowly added a solution of (tert-butoxycarbonyl)-L-serine (6.38 g, 31.1 mmol) in dry THF (50 mL) at 0 ℃. The mixture was stirred at 0 ℃ for 30 minutes. After addition of a solution of 2,4-dichloro-5-nitropyridine (2.00 g, 10.3 mmol) in dry THF (25 mL) at 0 ℃, the reaction mixture was stirred at 0 ℃ for 2 hours. After quenched with cold 0.5 M aq. HCl solution, the mixture was extracted with EtOAc (200 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford (2S)-2-[(tert-butoxycarbonyl)amino]-3-[(2-chloro-5-nitropyridin-4-yl)oxy]propanoic acid (1.20 g, crude) as a yellow oil. ^{1}HNMR (400 MHz, DMSO-d_6): δ 13.03 (1H, s), 8.88 (1H, s), 7.67 (1H, s), 7.22 (1H, d, J = 8.2 Hz), 4.56 (2H, qd, J = 10.3, 5.3 Hz), 4.48-4.40 (1H, m), 1.38 (9H, s).

[353] Step B: (2S)-3-[(5-amino-2-chloropyridin-4-yl)oxy]-2-[(tert-butoxycarbonyl)amino]

propanoic acid

[354] To solution of (2S)-2-[(tert-butoxycarbonyl)amino]-3-[(2-chloro-5-nitropyridin-4-yl)oxy]propanoic acid (1.20 g, 3.31 mmol) in AcOH (20 mL) was added Zn (1.08 g, 16.5 mmol) at 0 ℃. The reaction mixture was stirred at 0 ℃ for 2 hours. After filtration through a Celite pad, the filtrate was concentrated in vacuo. The residue was purified by reverse phase column to afford (2S)-3-[(5-amino-2-chloropyridin-4-yl)oxy]-2-[(tert-butoxycarbonyl)amino]propanoic acid (550 mg, 50%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d $_6$): δ 7.58 (1H, s), 6.84 (2H, m), 5.04 (2H, s), 4.37-4.08 (3H, m), 1.39 (9H, s).

[355] Step C: tert-butyl N-[(3S)-8-chloro-4-oxo-2H,3H,5H-pyrido[4,3-b][1,4]oxazepin-3-yl] carbamate

[356] To solution of (2S)-3-[(5-amino-2-chloropyridin-4-yl)oxy]-2-[(tert-butoxycarbonyl)amino] propanoic acid (550 mg, 1.65 mmol) in DMF (5.0 mL) was added DIPEA (642 mg, 4.97 mmol) followed by HATU (945 mg, 2.48 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 hours. After quenched with ice-water, the mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 2:1) to afford tert-butyl N-[(3S)-8-chloro-4-oxo-2H,3H,5H-pyrido[4,3-b][1,4]oxazepin-3-yl]carbamate (200 mg, 38%) as a yellow solid. LCMS (ESI) m/z: $[M+H]^+$ = 314.

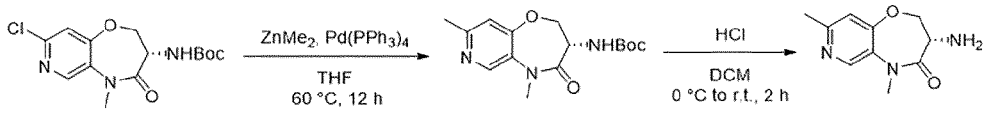
[357] Step D: tert-butyl N-[(3S)-8-chloro-5-methyl-4-oxo-2H,3H-pyrido[4,3-b][1,4]oxazepin-3-yl]carbamate

[358] To a solution of tert-butyl N-[(3S)-8-chloro-4-oxo-2H,3H,5H-pyrido[4,3-b][1,4]oxazepin-3-yl]carbamate (200 mg, 0.637 mmol) in DMF (5.0 mL) was added K_2CO_3 (176 mg, 1.27 mmol) followed by a solution of MeI (112 mg, 0.80 mmol) in DMF (1.0 mL). The reaction mixture was stirred at room temperature for 2 hours. After quenched with ice-water, the mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 3:1) to afford tert-butyl N-[(3S)-8-chloro-5-methyl-4-oxo-2H,3H-pyrido[4,3-b][1,4]oxazepin-3-yl]carbamate (180 mg, 86%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d $_6$): δ 8.56 (1H, s), 7.39 (1H, s), 7.20 (1H, d, J = 7.5 Hz), 4.54-4.40 (3H, m), 3.32 (3H, s), 1.36 (9H, s).

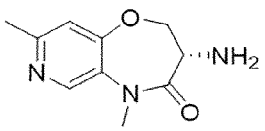
[359] Step E: (3S)-3-amino-8-chloro-5-methyl-2H,3H-pyrido[4,3-b][1,4]oxazepin-4-one

[360] To a solution of tert-butyl N-[(3S)-8-chloro-5-methyl-4-oxo-2H,3H-pyrido[4,3-b][1,4]oxazepin-3-yl]carbamate (180 mg, 0.549 mmol) in CH_2Cl_2 (3.0 mL) was added

HCl (4 M in dioxane, 2.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 hour and then concentrated in vacuo. The residue was purified by prep-HPLC to afford (3S)-3-amino-8-chloro-5-methyl-2H,3H-pyrido[4,3-b][1,4]oxazepin-4-one (60 mg, 48%). LCMS (ESI) m/z: $[M+H]^+$ = 227.95.

[361] 

[362] Intermediate 27:

[363] 

[364] Step A: tert-butyl N-[(3S)-5,8-dimethyl-4-oxo-2H,3H-pyrido[4,3-b][1,4]oxazepin-3-yl]carbamate

[365] To a solution of tert-butyl N-[(3S)-8-chloro-5-methyl-4-oxo-2H,3H-pyrido[4,3-b][1,4]oxazepin-3-yl]carbamate (200 mg, 0.610 mmol) and $Pd(PPh_3)_4$ (141 mg, 0.122 mmol) in THF (2.0 mL) was slowly added $Zn(CH_3)_2$ (1 M in hexane, 2.0 mL, 2.0 mmol) at room temperature. The reaction mixture was stirred at 60 °C for 12 hours. After quenched with 0.5 M aq. AcOH (10 mL) at 0 °C, the mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with water and brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 (Hexanes:EtOAc = 4:1 to 1:1) to afford tert-butyl N-[(3S)-5,8-dimethyl-4-oxo-2H,3H-pyrido[4,3-b][1,4]oxazepin-3-yl]carbamate (130 mg, 69%) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 308.

[366] Step B: (3S)-3-amino-5,8-dimethyl-2H,3H-pyrido[4,3-b][1,4]oxazepin-4-one

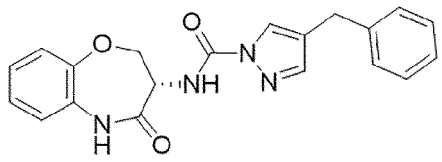
[367] To a solution of tert-butyl N-[(3S)-5,8-dimethyl-4-oxo-2H,3H-pyrido[4,3-b][1,4]oxazepin-3-yl]carbamate (130 mg, 0.423 mmol) in DCM (3.0 mL) was added HCl (4 M in 1,4-dioxane, 2.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 hours and concentrated in vacuo. The residue was purified by prep-HPLC to afford (3S)-3-amino-5,8-dimethyl-2H,3H-pyrido[4,3-b][1,4]oxazepin-4-one (45 mg, 51%) as a white solid. LCMS (ESI) m/z: $[M+H]^+$ = 208.05.

Mode for the Invention

[368] **Example**

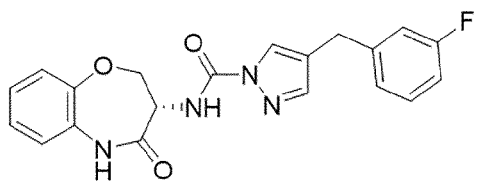
[369] **Example 1:**

(S)-4-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[370] 

[371] To a solution of (S)-3-amino-2,3-dihydrobenzo[b][1,4]oxazepin-4(5H)-one hydrochloride (Intermediate 9,100 mg, 0.466 mmol) and TEA (0.195 mL, 1.40 mmol) in THF (4.7 mL) was added 4-nitrophenyl carbonochloridate (122 mg, 0.606 mmol) at 0 ℃. The mixture was stirred at 0 ℃ for 45 minutes. After addition of 4-benzyl-1H-pyrazole hydrochloride (Intermediate 1, 118 mg, 0.606 mmol) followed by TEA (0.195 mL, 1.40 mmol) at 0 ℃, the reaction mixture stirred at room temperature for 18 hours. After quenched with water, the mixture was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 1:3) to give (S)-4-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (10 mg, 6%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.94 (1H, d, J = 8.0 Hz), 7.90 (1H, s), 7.48 (2H, s), 7.32-7.27 (2H, m), 7.24-7.15 (5H, m), 7.01 (1H, d, J = 8.0 Hz), 4.97-4.91 (1H, m), 4.76 (1H, dd, J = 10.2, 6.6 Hz), 4.35 (1H, t, J = 10.6 Hz), 3.82 (2H, s). LC-MS: m/z = 363.2 $[M+H]^+$.

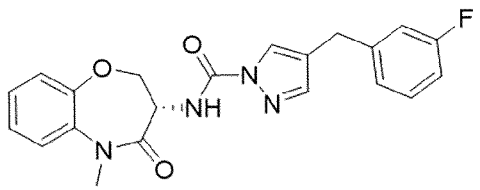
[372] **Example 2:**
(S)-4-(3-fluorobenzyl)-N-(4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[373] 

[374] The title compound was prepared in a similar fashion to Example 1 with Intermediates 2 and 9. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) to give (S)-4-(3-fluorobenzyl)-N-(4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (30%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.96 (1H, d, J = 6.8 Hz), 7.92 (1H, s), 7.53 (1H, s), 7.48 (1H, s), 7.29-7.12 (4H, m), 7.03-6.86 (4H, m), 4.98-4.92 (1H, m), 4.77 (1H, dd, J = 10.4, 6.8 Hz), 4.36 (1H, t, J = 10.4 Hz), 3.82 (2H, s). LC-MS: m/z = 380.2 $[M+H]^+$.

[375] **Example 3:**
(S)-4-(3-fluorobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-1H-pyrazole-1-carboxamide

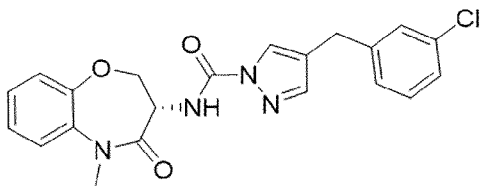
[376]



[377] The title compound was prepared in a similar fashion to Example 1 with Intermediates 2 and 10. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 3:1) to give (S)-4-(3-fluorobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (36%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.00 (1H, d, J = 6.8 Hz), 7.88 (1H, s), 7.47 (1H, s), 7.28-7.19 (5H, m), 6.96-6.85 (2H, m), 4.94-4.87 (1H, m), 4.71 (1H, t, J = 8.6 Hz), 4.31 (1H, t, J = 10.2 Hz), 3.81 (2H, s), 3.44 (3H, s). LC-MS: m/z = 395.2 $[M+H]^+$.

[378] **Example 4:**
(S)-4-(3-chlorobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4] oxazepin-3-yl)-1H-pyrazole-1-carboxamide

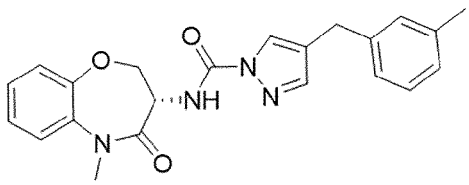
[379]



[380] The title compound was prepared in a similar fashion to Example 1 with Intermediates 3 and 10. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 3:1) to give (S)-4-(3-chlorobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (38%) as a pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.01 (1H, d, J = 6.8 Hz), 7.88 (1H, s), 7.47 (1H, s), 7.24-7.01 (5H, m), 7.16 (1H, s), 7.06 (1H, d, J = 6.8 Hz), 4.94-4.88 (1H, m), 4.72 (1H, t, J = 8.4 Hz), 4.32 (1H, t, J = 10.4 Hz), 3.79 (2H, s), 3.44 (3H, s). LC-MS: m/z = 411.2 $[M+H]^+$.

[381] **Example 5:**
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(3-methylbenzyl)-1H-pyrazole-1-carboxamide

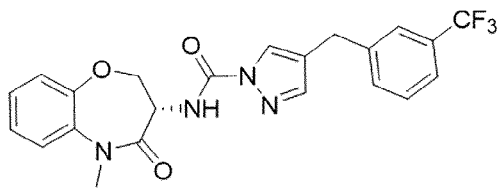
[382]



[383] The title compound was prepared in a similar fashion to Example 1 with Intermediates 4 and 10. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 5:1) to give

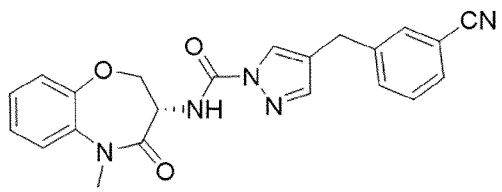
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(3-methylbenzyl)-1H-pyrazole-1-carboxamide (43%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.99 (1H, d, J = 7.2 Hz), 7.86 (1H, s), 7.47 (1H, s), 7.25-7.16 (4H, m), 7.02 (1H, d, J = 7.6 Hz), 6.98-6.96 (2H, m), 4.94-4.87 (1H, m), 4.71 (1H, t, J = 8.6 Hz), 4.31 (1H, t, J = 10.6 Hz), 3.77 (2H, s), 3.44 (3H, s), 2.31 (3H, s). LC-MS: m/z = 391.2 $[M+H]^+$.

[384] **Example 6:**
(S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(3-(trifluoromethyl)benzyl)-1H-pyrazole-1-carboxamide

[385] 

[386] The title compound was prepared in a similar fashion to Example 1 with Intermediates 5 and 10. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 3:1) to give (S)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(3-(trifluoromethyl)benzyl)-1H-pyrazole-1-carboxamide (32%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.01 (1H, d, J = 6.8 Hz), 7.89 (1H, s), 7.49 (1H, d, J = 8.0 Hz), 7.48 (1H, s), 7.43 (1H, s), 7.40 (1H, d, J = 8.0 Hz), 7.36 (1H, d, J = 7.6 Hz), 7.25-7.19 (3H, m), 4.94-4.87 (1H, m), 4.71 (1H, t, J = 8.6 Hz), 4.32 (1H, t, J = 10.4 Hz), 3.88 (2H, s), 3.44 (3H, s). LC-MS: m/z = 445.2 $[M+H]^+$.

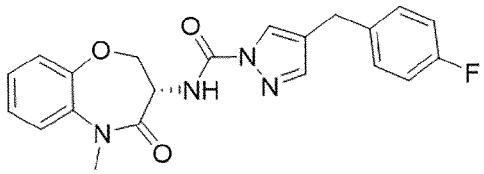
[387] **Example 7:**
(S)-4-(3-cyanobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[388] 

[389] The title compound was prepared in a similar fashion to Example 1 with Intermediates 6 and 10. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) to give (S)-4-(3-cyanobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (41%) as a white foam. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.02 (1H, d, J = 7.2 Hz), 7.89 (1H, s), 7.54-7.50 (1H, m), 7.47 (1H, s), 7.42-7.38 (2H, m), 7.24-7.20 (4H, m), 4.94-4.87 (1H, m), 4.72 (1H, t, J = 8.4 Hz), 4.32 (1H, t, J = 10.4 Hz), 3.86 (2H, s), 3.44 (3H, s). LC-MS: m/z = 402.2 $[M+H]^+$.

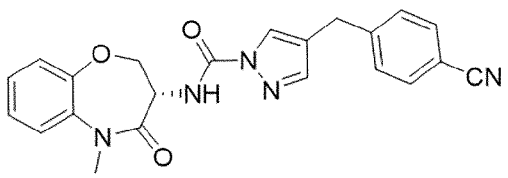
[390] **Example 8:**

(S)-4-(4-fluorobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4] oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[391] 

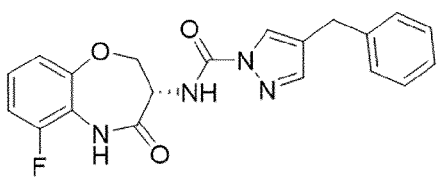
[392] The title compound was prepared in a similar fashion to Example 1 with Intermediates 7 and 10. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 4:1) to give (S)-4-(4-fluorobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (26%) as a white foam. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.99 (1H, d, J = 6.8 Hz), 7.85 (1H, s), 7.45 (1H, s), 7.25-7.19 (3H, m), 7.13 (2H, t, J = 6.8 Hz), 6.98 (2H, t, J = 8.6 Hz), 4.94-4.87 (1H, m), 4.71 (1H, t, J = 8.6 Hz), 4.31 (1H, t, J = 10.4 Hz), 3.78 (2H, s), 3.44 (3H, s). LC-MS: m/z = 395.2 $[M+H]^+$.

[393] **Example 9:**
(S)-4-(4-cyanobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4] oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[394] 

[395] The title compound was prepared in a similar fashion to Example 1 with Intermediates 8 and 10. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) to give (S)-4-(4-cyanobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (73%) as a white foam. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.01 (1H, d, J = 7.2 Hz), 7.89 (1H, s), 7.59 (2H, d, J = 8.4 Hz), 7.46 (1H, s), 7.28 (2H, d, J = 8.8 Hz), 7.26-7.20 (3H, m), 4.93-4.87 (1H, m), 4.71 (1H, t, J = 8.6 Hz), 4.31 (1H, t, J = 10.6 Hz), 3.88 (2H, s), 3.44 (3H, s). LC-MS: m/z = 402.2 $[M+H]^+$.

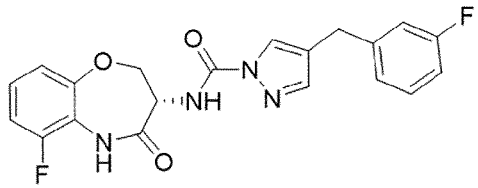
[396] **Example 10:**
(S)-4-benzyl-N-(6-fluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[397] 

[398] The title compound was prepared in a similar fashion to Example 1 with Intermediates 1 and 11. The crude product was purified by column chromatography on NH-

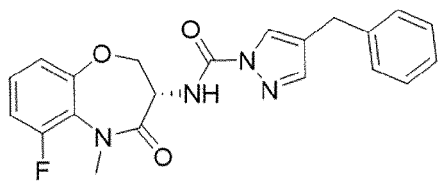
SiO_2 (Hexanes:EtOAc = 2:1) to afford (S)-4-benzyl-N-(6-fluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (3%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.97 (1H, d, J = 6.8 Hz), 7.92 (1H, s), 7.49 (1H, s), 7.46 (1H, s), 7.30 (1H, t, J = 7.4 Hz), 7.24-7.18 (2H, m), 7.12 (1H, q, J = 7.6 Hz), 6.98-6.01 (2H, m), 4.98-4.92 (1H, m), 4.75 (1H, q, J = 5.5 Hz), 4.36 (1H, t, J = 10.2 Hz), 3.83 (2H, s). LC-MS: m/z = 381.2 $[M+H]^+$.

[399] **Example 11:**
(S)-N-(6-fluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1 carboxamide

[400] 

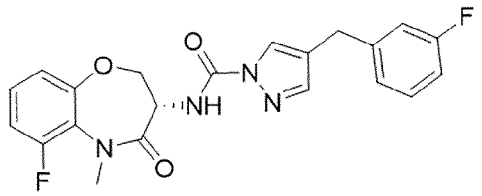
[401] The title compound was prepared in a similar fashion to Example 1 with Intermediates 2 and 11. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) to afford (S)-N-(6-fluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1 carboxamide (3.5%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.98 (1H, d, J = 6.8 Hz), 7.93 (1H, s), 7.49 (1H, s), 7.44 (1H, s), 7.29-7.24 (2H, m), 7.12 (1H, q, J = 7.6 Hz), 6.98-6.87 (4H, m), 4.98-4.93 (1H, m), 4.76 (1H, q, J = 5.3 Hz), 4.37 (1H, t, J = 10.6 Hz), 3.83 (2H, s). LC-MS: m/z = 399.1 $[M+H]^+$.

[402] **Example 12:**
(S)-4-benzyl-N-(6-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[403] 

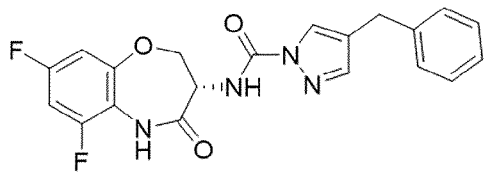
[404] The title compound was prepared in a similar fashion to Example 1 with Intermediates 1 and 12. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) followed by SiO_2 (Hexanes:EtOAc = 6:1) to afford (S)-4-benzyl-N-(6-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (27%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.99 (1H, d, J = 7.2 Hz), 7.87 (1H, s), 7.48 (1H, s), 7.31-7.22 (4H, m), 7.20-7.17 (2H, m), 7.06-7.01 (2H, m), 4.96-4.90 (1H, m), 4.69-4.65 (1H, m), 4.30 (1H, t, J = 10.4 Hz), 3.82 (2H, s), 3.38 (3H, d, J = 1.6 Hz). LC-MS: m/z = 395.2 $[M+H]^+$.

[405] **Example 13:**
(S)-N-(6-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide

[406] 

[407] The title compound was prepared in a similar fashion to Example 1 with Intermediates 2 and 12. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) followed by SiO_2 (Hexanes:EtOAc = 6:1) to afford (S)-N-(6-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide (7.5%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.00 (1H, d, J = 6.8 Hz), 7.88 (1H, s), 7.48 (1H, s), 7.29-7.23 (2H, m), 7.06-7.02 (2H, m), 6.97-6.86 (2H, m), 4.96-4.90 (1H, m), 4.68 (1H, t, J = 8.6 Hz), 4.30 (1H, t, J = 10.6 Hz), 3.82 (2H, s), 3.38 (3H, d, J = 1.6 Hz). LC-MS: m/z = 413.2 $[M+H]^+$.

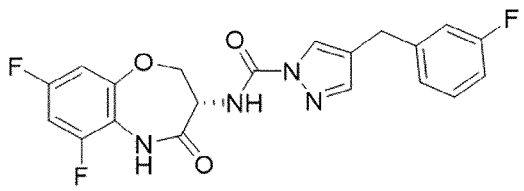
[408] **Example 14:**
(S)-4-benzyl-N-(6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[409] 

[410] The title compound was prepared in a similar fashion to Example 1 with Intermediates 1 and 13. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) to afford (S)-4-benzyl-N-(6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (30%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.96 (1H, d, J = 6.4 Hz), 7.91 (1H, s), 7.49 (1H, s), 7.32-7.18 (6H, m), 6.74-6.69 (2H, m), 4.96-4.91 (1H, m), 4.74 (1H, dd, J = 10.8, 5.2 Hz), 4.38 (1H, t, J = 10.4 Hz), 3.83 (2H, s). LC-MS: m/z = 399.2 $[M+H]^+$.

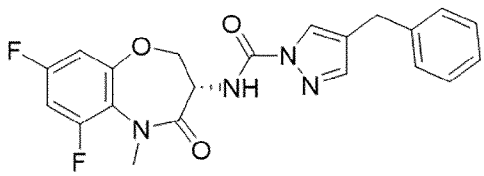
[411] **Example 15:**
(S)-N-(6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide

[412]



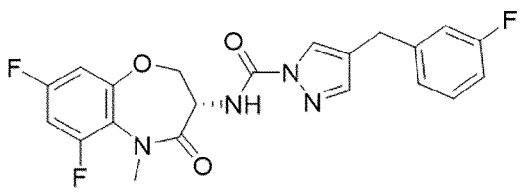
[413] The title compound was prepared in a similar fashion to Example 1 with Intermediates 2 and 13. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 1:1) to afford (S)-N-(6,8-difluoro-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide (33%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.98 (1H, d, J = 6.8 Hz), 7.93 (1H, s), 7.49 (1H, s), 7.45 (1H, brs), 7.29-7.24 (1H, m), 6.98-6.89 (3H, m), 6.75-6.69 (2H, m), 4.94 (1H, dt, J = 10.4, 5.6 Hz), 4.75 (1H, dd, J = 10.8, 5.6 Hz), 4.39 (1H, t, J = 10.4 Hz), 3.82 (2H, s). LC-MS: m/z = 417.2 $[M+H]^+$.

[414] **Example 16:**
(S)-4-benzyl-N-(6,8-difluoro-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[415] 

[416] The title compound was prepared in a similar fashion to Example 1 with Intermediates 1 and 14. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 1:1) to afford (S)-4-benzyl-N-(6,8-difluoro-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (32%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.97 (1H, d, J = 7.2 Hz), 7.87 (1H, s), 7.48 (1H, s), 7.31-7.17 (5H, m), 6.84-6.78 (2H, m), 4.93 (1H, dt, J = 11.6, 7.2 Hz), 4.66 (1H, dd, J = 10.0, 7.6 Hz), 4.31 (1H, t, J = 10.4 Hz), 3.82 (2H, s), 3.35 (3H, d, J = 2.0 Hz). LC-MS: m/z = 413.2 $[M+H]^+$.

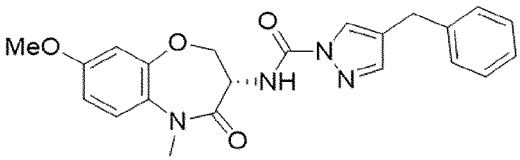
[417] **Example 17:**
(S)-N-(6,8-difluoro-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide

[418] 

[419] The title compound was prepared in a similar fashion to Example 1 with Intermediates 2 and 14. The crude product was purified by column chromatography on NH-

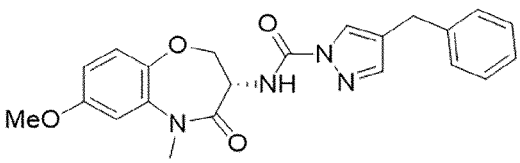
SiO_2 (Hexanes:EtOAc = 2:1) to afford (S)-N-(6,8-difluoro-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide (41%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.98 (1H, d, J = 7.2 Hz), 7.89 (1H, s), 7.48 (1H, s), 7.28-7.23 (1H, m), 6.97-6.78 (5H, m), 4.93 (1H, dt, J = 11.2, 7.2 Hz), 4.67 (1H, dd, J = 9.6, 6.8 Hz), 4.31 (1H, dd, J = 10.8, 9.6 Hz), 3.82 (2H, s), 3.35 (3Θ, d, J = 2.4 Hz). LC-MS: m/z = 431.2 $[M+H]^+$.

[420] **Example 18:**
(S)-4-benzyl-N-(8-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[421] 

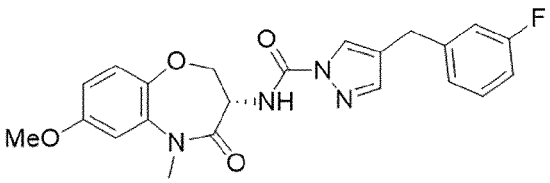
[422] The title compound was prepared in a similar fashion to Example 1 with Intermediates 1 and 15. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) to give (S)-4-benzyl-N-(8-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (29%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.99 (1H, d, J = 7.2 Hz), 7.87 (1H, s), 7.47 (1H, s), 7.31-7.16 (4H, m), 7.12 (1Θ, d, J = 8.4 Hz), 6.80-6.73 (2H, m), 7.01 (1H, d, J = 8.0 Hz), 4.94-4.87 (1H, m), 4.80 (1H, dd, J = 9.6, 7.6 Hz), 4.29 (1H, t, J = 10.4 Hz), 3.83 (3H, s), 3.81 (2H, s), 3.39 (3H, s). LC-MS: m/z = 407.2 $[M+H]^+$.

[423] **Example 19:**
(S)-4-benzyl-N-(7-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[424] 

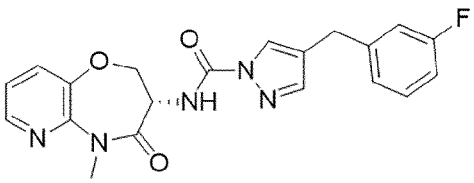
[425] The title compound was prepared in a similar fashion to Example 1 with Intermediates 1 and 16. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) to give (S)-4-benzyl-N-(7-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (32%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.96 (1H, d, J = 8.0 Hz), 7.86 (1H, s), 7.46 (1H, s), 7.30-7.10 (6H, m), 6.77-6.73 (2H, m), 4.93-4.86 (1H, m), 4.65 (1H, dd, J = 9.6, 7.6 Hz), 4.24 (1H, dd, J = 11.6, 10 Hz), 3.82 (3H, s), 3.81 (2H, s), 3.41 (3H, s). LC-MS: m/z = 407.3 $[M+H]^+$.

[426] **Example 20:**
(S)-4-(3-fluorobenzyl)-N-(7-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[427] 

[428] The title compound was prepared in a similar fashion to Example 1 with Intermediates 2 and 16. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) to give (S)-4-(3-fluorobenzyl)-N-(7-methoxy-5-methyl-4-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (35%) as a pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.98 (1H, d, J = 7.2 Hz), 7.88 (1H, s), 7.47 (1H, s), 7.28-7.22 (2H, m), 7.12 (1H, d, J = 8.4 Hz), 6.96-6.85 (2H, m), 6.78-6.74 (2H, m), 4.94-4.87 (1H, m), 4.66 (1H, dd, J = 10, 7.6 Hz), 4.25 (1H, dd, J = 11.2, 9.6 Hz), 3.82 (3H, s), 3.81 (2H, s), 3.42 (3H, s). LC-MS: m/z = 425.1 $[M+H]^+$.

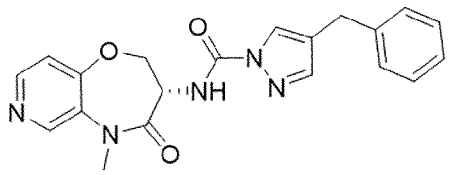
[429] **Example 21:**
(S)-4-(3-fluorobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[430] 

[431] The title compound was prepared in a similar fashion to Example 1 with Intermediates 2 and 17. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 1:2) followed by SiO_2 (Hexanes:EtOAc = 1:1) to give (S)-4-(3-fluorobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (27%) as a pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.31 (1H, d, J = 3.6 Hz), 8.07 (1H, d, J = 6.8 Hz), 7.89 (1H, s), 7.52 (1H, d, J = 7.2 Hz), 7.48 (1H, s), 7.27-7.22 (1H, m), 7.20-7.17 (1H, m), 6.96-6.85 (3H, m), 4.93-4.87 (1H, m), 4.78 (1H, t, J = 8.2 Hz), 4.38 (1H, t, J = 10.4 Hz), 3.81 (2H, s), 3.53 (3H, s). LC-MS: m/z = 396.2 $[M+H]^+$.

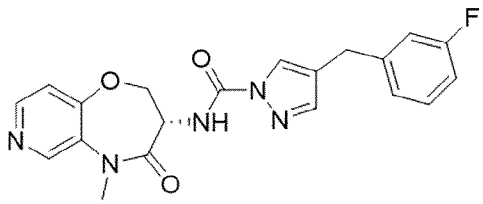
[432] **Example 22:**
(S)-4-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[433]



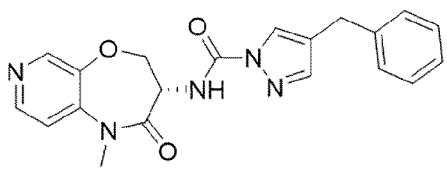
[434] The title compound was prepared in a similar fashion to Example 1 with Intermediates 1 and 18. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 3:1 to EtOAc) to give (S)-4-benzyl-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (40%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.54 (1H, s), 8.44 (1H, d, J = 5.2 Hz), 8.00 (1H, d, J = 6.4 Hz), 7.87 (1H, s), 7.48 (1H, s), 7.32-7.26 (3H, m), 7.24-7.19 (2H, m), 7.12 (1H, d, J = 5.6 Hz), 4.96-4.89 (1H, m), 4.73 (1H, dd, J = 10, 6.4 Hz), 4.44 (1H, t, J = 10.6 Hz), 3.82 (2H, s), 3.50 (3H, s). LC-MS: m/z = 378.1 $[M+H]^+$.

[435] **Example 23:**
(S)-4-(3-fluorobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[436] 

[437] The title compound was prepared in a similar fashion to Example 1 with Intermediates 2 and 18. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 1:2) to give (S)-4-(3-fluorobenzyl)-N-(5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (29%) as a pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.54 (1H, s), 8.44 (1H, d, J = 4.8 Hz), 8.01 (1H, d, J = 7.2 Hz), 7.89 (1H, s), 7.48 (1H, s), 7.29-7.23 (2H, m), 7.12 (1H, d, J = 5.2 Hz), 6.97-6.86 (2H, m), 4.96-4.90 (1H, m), 4.74 (1H, dd, J = 10, 6.4 Hz), 4.45 (1H, t, J = 10.4 Hz), 3.82 (2H, s), 3.50 (3H, s). LC-MS: m/z = 396.2 $[M+H]^+$.

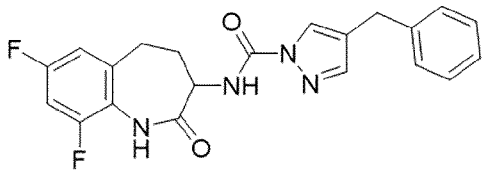
[438] **Example 24:**
(S)-4-benzyl-N-(1-methyl-2-oxo-1,2,3,4-tetrahydropyrido[3,4-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[439] 

[440] The title compound was prepared in a similar fashion to Example 1 with Inter-

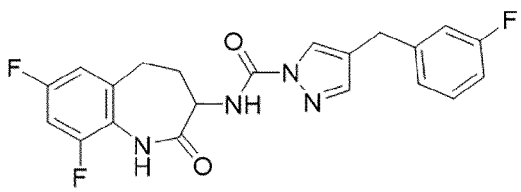
mediates 1 and 19. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 3:1 to EtOAc only) to give (S)-4-benzyl-N-(1-methyl-2-oxo-1,2,3,4-tetrahydropyrido[3,4-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (8%) as a white foam. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.72 (1H, s), 8.19 (1H, d, J = 5.6 Hz), 8.14 (1H, s), 8.05 (1H, s), 7.23 (1H, s), 7.31-7.16 (6H, m), 3.81 (2H, s), 3.31 (3H, s), 1.77 (3H, s). LC-MS: m/z = 378.1 $[M+H]^+$.

[441] **Example 25:**
4-benzyl-N-(7,9-difluoro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-1H-pyrazole-1-carboxamide

[442] 

[443] The title compound was prepared in a similar fashion to Example 1 with Intermediates 1 and 20. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 1:1) to give 4-benzyl-N-(7,9-difluoro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-1H-pyrazole-1-carboxamide (32%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.92 (1H, d, J = 7.6 Hz), 7.90 (1H, s), 7.46 (1H, s), 7.39 (1H, brs), 7.31-7.17 (4H, m), 6.86-6.74 (2H, m), 4.59-4.52 (1H, m), 3.82 (2H, s), 3.07-2.98 (1H, m), 2.87-2.70 (2H, m), 2.20-2.12 (1H, m). LC-MS: m/z = 397.2 $[M+H]^+$.

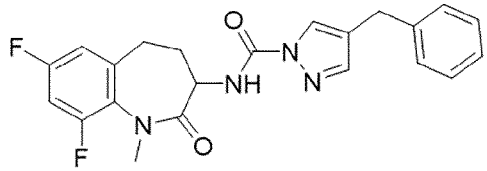
[444] **Example 26:**
(S)-N-(7,9-difluoro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide

[445] 

[446] The title compound was prepared in a similar fashion to Example 1 with Intermediates 2 and 20. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) to give (S)-N-(7,9-difluoro-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide (37%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.94 (1H, d, J = 7.6 Hz), 7.91 (1H, s), 7.46 (1H, s), 7.28-7.23 (2H, m), 6.97-6.82 (4H, m), 4.59-4.53 (1H, m), 3.82 (2H, s), 3.05-2.99 (1H, m), 2.88-2.71 (2H, m), 2.20-2.12 (1H, m). LC-MS: m/z = 415.2 $[M+H]^+$.

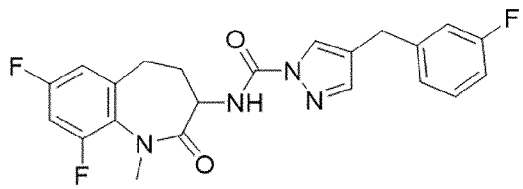
[447] **Example 27:**

4-benzyl-N-(7,9-difluoro-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-1H-pyrazole-1-carboxamide

[448] 

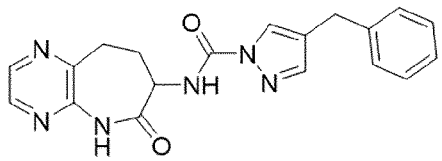
[449] The title compound was prepared in a similar fashion to Example 1 with Intermediates 1 and 21. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) to afford 4-benzyl-N-(7,9-difluoro-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-1H-pyrazole-1-carboxamide (56%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.98 (1H, d, J = 7.6 Hz), 7.88 (1H, s), 7.45 (1H, s), 7.31-7.17 (5H, m), 6.88-6.82 (2H, m), 4.51-4.45 (1H, m), 3.81 (2H, s), 3.34 (3H, d, J = 1.6 Hz), 2.93-2.83 (1H, m), 2.73-2.64 (2H, m), 2.11-2.03 (1H, m). LC-MS: m/z = 411.2 $[M+H]^+$.

[450] **Example 28: N-(7,9-difluoro-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide**

[451] 

[452] The title compound was prepared in a similar fashion to Example 1 with Intermediates 2 and 21. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) to afford N-(7,9-difluoro-1-methyl-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide (51%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.00 (1H, d, J = 7.2 Hz), 7.90 (1H, s), 7.45 (1H, s), 7.27-7.22 (1H, m), 6.96-6.82 (5H, m), 4.51-4.45 (1H, m), 3.81 (2H, s), 3.34 (3H, d, J = 2.0 Hz), 2.94-2.84 (1H, m), 2.74-2.63 (2H, m), 2.11-2.04 (1H, m). LC-MS: m/z = 429.2 $[M+H]^+$.

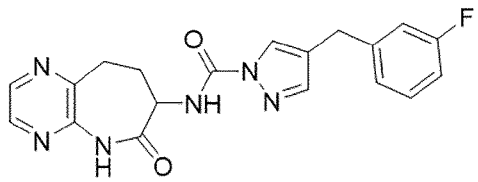
[453] **Example 29: 4-benzyl-N-(6-oxo-6,7,8,9-tetrahydro-5H-pyrazino[2,3-b]azepin-7-yl)-1H-pyrazole-1-carboxamide**

[454] 

[455] The title compound was prepared in a similar fashion to Example 1 with Intermediates 1 and 22. The crude product was purified by column chromatography on NH-

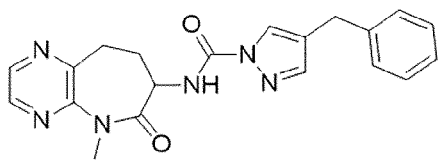
SiO_2 (Hexanes:EtOAc = 1:1 to EtOAc only) to afford 4-benzyl-N-(6-oxo-6,7,8,9-tetrahydro-5H-pyrazino[2,3-b]azepin-7-yl)-1H-pyrazole-1-carboxamide (30%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.37 (1H, d, J = 2.8 Hz), 8.30 (1H, d, J = 2.8 Hz), 7.97-7.91 (3H, m), 7.48 (1H, s), 7.32-7.18 (5H, m), 4.60 (1H, dt, J = 11.6, 7.6 Hz), 3.83 (2H, s), 3.20-3.16 (2H, m), 3.01-2.91 (1H, m), 2.34-2.25 (1H, m). LC-MS: m/z = 363.2 $[M+H]^+$.

[456] **Example 30:**
4-(3-fluorobenzyl)-N-(6-oxo-6,7,8,9-tetrahydro-5H-pyrazino[2,3-b]azepin-7-yl)-1H-pyrazole-1-carboxamide

[457] 

[458] The title compound was prepared in a similar fashion to Example 1 with Intermediates 2 and 22. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 1:1 to EtOAc only) to afford 4-(3-fluorobenzyl)-N-(6-oxo-6,7,8,9-tetrahydro-5H-pyrazino[2,3-b]azepin-7-yl)-1H-pyrazole-1-carboxamide (35%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.38 (1H, d, J = 2.8 Hz), 8.30 (1H, d, J = 2.4 Hz), 7.98-7.92 (3H, m), 7.48 (1H, s), 7.29-7.23 (1H, m), 6.98-6.87 (3H, m), 4.60 (1H, dt, J = 11.6, 7.2 Hz), 3.82 (2H, s), 3.21-3.17 (2H, m), 3.02-2.92 (1H, m), 2.34-2.25 (1H, m). LC-MS: m/z = 381.2 $[M+H]^+$.

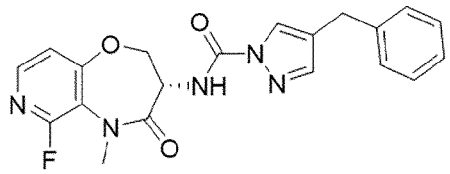
[459] **Example 31:**
4-benzyl-N-(5-methyl-6-oxo-6,7,8,9-tetrahydro-5H-pyrazino[2,3-b]azepin-7-yl)-1H-pyrazole-1-carboxamide

[460] 

[461] The title compound was prepared in a similar fashion to Example 1 with Intermediates 1 and 23. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 4:1 to 2:1) to afford 4-benzyl-N-(5-methyl-6-oxo-6,7,8,9-tetrahydro-5H-pyrazino[2,3-b]azepin-7-yl)-1H-pyrazole-1-carboxamide (25%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.39 (1H, d, J = 2.4 Hz), 8.36 (1H, d, J = 2.4 Hz), 8.00 (1H, d, J = 7.2 Hz), 7.88 (1H, s), 7.47 (1H, s), 7.31-7.17 (5H, m), 4.52 (1H, dt, J = 11.6, 8.0 Hz), 3.82 (2H, s), 3.52 (3H, s), 3.09-2.90 (3H, m), 2.28-2.20 (1H, m). LC-MS: m/z = 377.2 $[M+H]^+$.

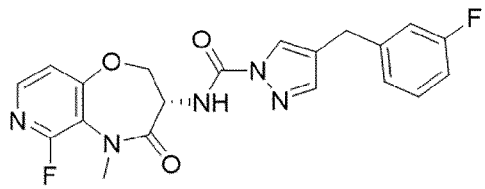
[462] **Example 32:**
(S)-4-benzyl-N-(6-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxaz

epin-3-yl)-1H-pyrazole-1-carboxamide

[463] 

[464] To a solution of (S)-6-fluoro-5-methyl-3-((2,2,2-trifluoroacetyl)-l4-azanyl)-2,3-dihydropyrido[4,3-b][1,4]oxazepin-4(5H)-one (Intermediate 24) (20 mg, 0.065 mmol) in DCE (0.79 mL) was added TEA (16.4 mg, 0.160 mmol) and di(1H-imidazol-1-yl)methanone (10 mg, 0.0650 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 hour. After diluted with water, the mixture was extracted with EtOAc. The separated organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was dissolved in DCE (0.79 mL). After addition of 4-benzyl-1H-pyrazole hydrochloride (Intemediate 1) (15 mg, 0.078 mmol) and TEA (0.210 g, 2.12 mmol) at 0 °C, the reaction mixture is stirred at room temperature for 18 hours. After concentration in vacuo, the residue was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 1:2 to 1:1) to afford (S)-4-benzyl-N-(6-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (31%) as a white foam. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.09 (1H, d, J = 4.8 Hz), 7.98 (1H, d, J = 6.4 Hz), 7.87 (1H, dd, J = 3.2, 0.8 Hz), 7.48 (1H, s), 7.32-7.28 (1H, m), 7.24-7.17 (3H, m), 7.06 (1H, d, J = 5.6 Hz), 4.99-4.88 (1H, m), 4.73 (1H, q, J = 9.6 Hz), 4.49-4.43 (2H, m), 3.82 (3H, s), 3.37 (2H, d, J = 2.8 Hz). LC-MS: m/z = 396.14 $[M+H]^+$.

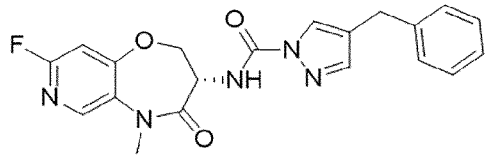
[465] **Example 33: (S)-N-(6-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide**

[466] 

[467] The title compound was prepared in a similar fashion to Example 32 with Intermediates 2 and 24. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 1:2 to 1:1) to give (S)-N-(6-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide (11%) as a white foam. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.01 (1H, dd, J = 5.6, 0.8 Hz), 7.99 (1H, d, J = 8 Hz), 7.89 (1H, d, J = 0.8 Hz), 7.49 (1H, s), 7.06 (1H, d, J = 5.6 Hz), 6.97-6.86 (3H, m), 5.33-5.36 (1H, m),

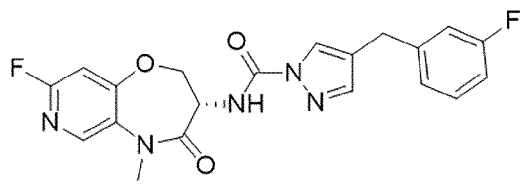
4.99-4.93 (1H, m), 4.74 (1H, q, J = 8 Hz), 4.48-4.43 (1H, m), 3.81 (3H, s), 3.38 (2H, d, J = 2.8 Hz). LC-MS: m/z = 414.13 $[M+H]^+$.

[468] **Example 34:**
(S)-4-benzyl-N-(8-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[469] 

[470] The title compound was prepared in a similar fashion to Example 32 with Intermediates 1 and 25. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1 to 1:1) to afford (S)-4-benzyl-N-(8-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (17%) as a white solid. ^{1}H NMR(400 MHz, $CDCl_3$) : δ 8.13 (1H, s), 7.99 (1H, d, J = 6.8 Hz), 7.88 (1H, s), 7.48 (1H, s), 7.31-7.17 (5H, m), 6.76 (1H, d, J = 2.8 Hz), 4.92 (1H, dt, J = 11.6, 6.8 Hz), 4.72 (1H, dd, J = 10, 6 Hz), 4.47 (1H, dd, J = 11.6, 10 Hz), 3.82 (2H, s), 3.48 (3H, s). LC-MS: m/z = 396 $[M+H]^+$.

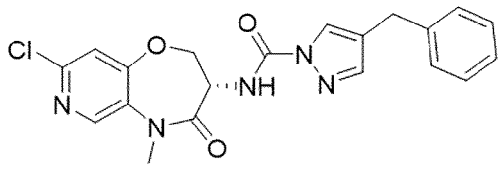
[471] **Example 35:**
(S)-N-(8-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide

[472] 

[473] The title compound was prepared in a similar fashion to Example 32 with Intermediates 2 and 25. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1 to 1:1) to afford (S)-N-(8-fluoro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-4-(3-fluorobenzyl)-1H-pyrazole-1-carboxamide (24%) as a white solid. ^{1}H NMR(400 MHz, $CDCl_3$) : δ 8.13 (1H, s), 8.00 (1H, d, J = 6.8 Hz), 7.89 (1H, s), 7.48 (1H, s), 7.28-7.23 (1H, m), 7.00-6.83 (3H, m), 6.76 (1H, d, J = 2.4 Hz), 4.93 (1H, dt, J = 11.6, 6.4 Hz), 4.73, (1H, dd, J = 10, 6 Hz), 4.44 (1H, dd, J = 11.2, 10 Hz), 3.81 (2H, s), 3.48 (3H, s). LC-MS: m/z = 414 $[M+H]^+$.

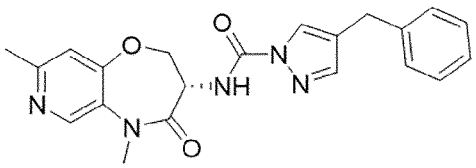
[474] **Example 36:**
(S)-4-benzyl-N-(8-chloro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[475]



[476] The title compound was prepared in a similar fashion to Example 32 with Intermediates 1 and 26. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1 to 1:1) to afford (S)-4-benzyl-N-(8-chloro-5-methyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (22%) as a white solid. LC-MS: m/z = 412 $[M+H]^+$.

[477] **Example 37:**
(S)-4-benzyl-N-(5,8-dimethyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide

[478] 

[479] The title compound was prepared in a similar fashion to Example 32 with Intermediates 1 and 27. The crude product was purified by column chromatography on NH-SiO_2 (Hexanes:EtOAc = 2:1) to afford (S)-4-benzyl-N-(5,8-dimethyl-4-oxo-2,3,4,5-tetrahydropyrido[4,3-b][1,4]oxazepin-3-yl)-1H-pyrazole-1-carboxamide (31%) as a white solid. LC-MS: m/z = 392 $[M+H]^+$.

[480] **Biological Activity**

[481] **Cell culture:**

[482] Human colon carcinoma cell HT-29 (KCLB 30038), BV2 mouse microglial cell (cell was a kind gift from Dr. Nak-Yun Sung, Senior researcher at Korea Prime Pharmacy CO., LTD.) and human microglial cell HMC3 (ATCC® CRL-3304TM). HT-29 cell was grown in Roswell Park Memorial Institute (RPMI) 1640, BV2 cell was grown in Dulbecco's Modified Eagle's Medium (DMEM) and HMC3 cell was grown in Minimum Essential Media Eagle (MEM) supplemented with 10% fetal bovine serum and 1% mixture of penicillin and streptomycin (Gibco). Cells were maintained at 37°C in a humidified 5% CO_2 atmosphere.

[483] **Cell-based necroptosis assay for RIPK1 activity:**

[484] To measure the activity of RIPK1 inhibitor in necroptotic cells, HT-29 cells were treated by control DMSO, human TNFα (Peprotech, Rocky Hill, USA), SM-164 (Biovision, California, USA) and a pan-caspase inhibitor Z-VAD-FMK (Invivogen, San Diego, USA). Cells were pretreated with Z-VAD-FMK 20 μM. After 30 min, human TNFα 10 ng/ml, SM-164 100 nM and RIPK1 Inhibitor (0.0001, 0.001, 0.01,

0.02, 0.05, 0.1, 1, 10 uM) were treated for 24 h. Cell viability was measured by Cell Counting Kit 8 (CCK-8) (Dong-in, Seoul, Korea).

[485] **Immunoblotting:**

[486] Biological activity of the compounds of RIPK1 inhibitor was determined by measuring their ability to inhibitor TNFα induced phospho-RIPK1 (ser 166) levels, phospho-RIPK3 levels, phospho-MLKL levels in HMC3 cells. Cells were pretreated with Z-VAD-FMK 20 μM. After 30 min, human TNFα 20 ng/ml, SM-164 100 nM and RIPK1 inhibitor (0.1, 1, 10 nM) were treated for 7 h under serum free media. Cells were lysed with cold lysis buffer containing 25 mM HEPES pH 7.6, 150 nM NaCl, 1% NP40, 1% sodium deoxycholate, 0.1% SDS, and protease inhibitor mixture (Bimake, Houston, USA) using sonicators. The cells were centrifuged at 15,000 rpm, 4℃ for 5 min. After protein concentration of the lysates (supernatants) was quantified using BCA assay (Thermo Fisher Scientific, Waltham, USA), lysates were mixed with LDS sample buffer and heating at 70 for 10 min. (Invitrogen, California, USA). Extracts were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) followed by electro-transfer to polyvinylidene difluoride (PVDF) membranes and probed with an anti-phospho-RIPK1 antibody, anti-phospho-RIPK3 antibody and anti-phospho-MLKL antibody (Cell Signaling technology, Danvers, USA) and β-actin (Proteintech, Rosement, USA), followed by horseradish peroxidase conjugated anti-rabbit (Cell Signaling technology, Danvers, USA), anti-mouse IgG and revealed with Super Signal West dura kit (Pierce). The membranes are placed in an image analyzer (Imagequant, LAS 500, GE Healthcare), connected to a computer which allows the image generation (software Image reader LAS 500).

[487] **Inflammation cytokine:**

[488] Total RNA was extracted and purified from PureLink ™ RNA mini kit (Thermo Fisher Scientific, Waltham, USA) according to the manufacture's protocol. Reverse transcription reactions were performed with AccuPower CycleScript RT PreMix (dT20) (Bioneer, Daejeon, Korea). Synthesis of cDNA was carried out using SimpliAmp Thermal Cycler (Applied Biosystems, Carlsbad, CA) and RT-PCR conditions were 15 ℃ for 30 sec, 42 ℃ for 4 min, 55 ℃ for 30 sec in 12 cycles, and heat inactivation was performed 95 ℃ for 5 min. For qPCR, SYBR Green PCR Master Mix (Thermo Fisher Scientific, Waltham, USA) was used in QuantStudio 3 (Applied Biosystems, Carlsbad, CA) and the PCR conditions were 95 ℃ for 10 min, 40 cycles of 95 ℃ for 15 s, and 60 ℃ for 30 s. The relative mRNA levels were calculated using cycle threshold (Ct) method. GAPDH was used as the endogenous control. PCR primers used in this study are listed in Table 1.

[489]

[Table 1]

Primer	Species	Sequence	
TNF-a	mouse	Forward	TGTAGCCCACGTCGTAGCAA (SEQ ID NO.1)
		Reverse	AGGTACAACCCATCGGCTGG (SEQ ID NO.2)
IL-1β	mouse	Forward	TGTGCAAGTGTCTGAAGCAGC (SEQ ID NO.3)
		Reverse	TGGAAGCAGCCCTTCATCTT (SEQ ID NO.4)
IL-6	mouse	Forward	CCACTTCACAAGTCGGAGGC (SEQ ID NO.5)
		Reverse	GCCATTGCACAACTCTTTTCTC (SEQ ID NO.6)
GAPDH	mouse	Forward	TCACCACCATGGAGAAGGC (SEQ ID NO.7)
		Reverse	GCTAAGCAGTTGGTGGTGCA (SEQ ID NO.8)

[490]

[Table 2]

Example Number	Necroptosis inhibition (IC50, nM)	HT29 (human colon cancer)Necroptosis inhibition			BV2 (mouse microglia)Pro-inflammation cytokine inhibition		
		p-RIPK1 inhibition (nM)	p-RIPK3 inhibition (nM)	p-MLKL inhibition (nM)	TNF-a (uM)	IL-1β(uM)	IL-6(uM)
1	<100	-	-	-	-	-	-
2	<100	-	-	-	-	-	-
3	<10	>10	>10	>10	>10	>100	>10
4	<10	-	-	-	-	-	-
5	<10	>10	>100	>100	>100	>100	>100
6	<100	-	-	-	-	-	-
7	<10	-	-	-	-	-	-
8	<100	-	-	-	-	-	-
9	<100	-	-	-	-	-	-
10	<100	-	-	-	-	-	-
11	<100	-	-	-	-	-	-
12	<10	>10	>10	>10	>100	>10	>100
13	<10	>10	>10	>10	>100	>10	>100
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16	<10	>10	>10	>10	>100	>10	>10
17	<10	>10	>10	>10	>100	>10	>10
18	<10	<100	<100	<100	>100	>10	>100
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22	<10	-	-	-	-	-	-
23	<10	-	-	-	-	-	-

24	<100	-	-	-	-	-	-
25	<100	-	-	-	-	-	-
26	<10	>10	<100	>10	>10	>10	>10
27	<10	>10	>10	<100	>100	>100	>10
28	<10	>10	>10	>10	>10	>10	>10
29	>100	-	-	-	-	-	-
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31	>100	-	-	-	-	-	-
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33	<100	>10	-	>10	-	-	-
34	<10	>1	-	>10	-	-	-
35	<10	>1	-	>10	-	-	-
36	<10	-	-	-	-	-	-
37	<10	-	-	-	-	-	-

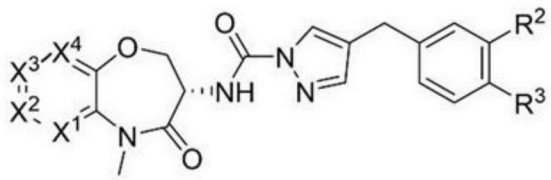
[491]

Industrial Applicability

[492] The present invention can be used to develop a pharmaceutical composition for preventing and/or treating various diseases associated with RIPKl.

[493] Any reference to any prior art in this specification is not, and should not be taken as an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge.

[494] In a first aspect of the invention, there is provided a compound of formula IIa or a pharmaceutically acceptable salt, solvate, or tautomer thereof, and a pharmaceutically acceptable carrier.



IIa

wherein

R^2 and R^3 are each independently H, methyl, CF_3, halogen, or cyano;

X^1 and X^3 are each independently CH or CF, with the proviso that at

least one of X^1 and X^3 is CF;

X^2 and X^4 are each independently CR^4 or N; and

R^4 is H, NH_2, OH, OMe, halogen, cyano, or C1-C6 alkyl.

[495] In a second aspect of the invention, there is provided a pharmaceutical composition comprising the compound of the first aspect or a pharmaceutically acceptable salt, solvate, or tautomer thereof, and a pharmaceutically acceptable carrier.

[496] In a third aspect of the invention, there is provided the use of a compound of the first aspect or a pharmaceutically acceptable salt, solvate, or tautomer thereof in the manufacture of a medicament for the treatment or prophylaxis of an RIPK1 mediated disease or disorder, wherein the disease or disorder is selected from the group consisting of: inflammatory bowel disease including Crohn's disease and ulcerative colitis, psoriasis, retinal detachment, retinitis pigmentosa, arthritis including rheumatoid arthritis, spondyloarthritis, gout, osteoarthritis, and systemic onset juvenile idiopathic arthritis (SoJIA), transplant rejection, organ transplantation for donors and recipients, multiple sclerosis, tumor necrosis factor receptor-associated periodic syndrome, multiple organ dysfunction syndrome (MODS), thermal injury/burn, systemic inflammatory response syndrome (SIRS), radiation injury, radiotherapy, chemotherapy, pneumonias, hemorrhagic shock, trauma including multiple trauma, traumatic brain injury, acute pancreatitis, critical illness, sepsis, septic shock, Stevens-Johnson syndrome, toxic epidermal necrolysis, stroke, heat stroke, stroke-associated pneumonia, Multi-Organ Dysfunction Syndrome (MODS), Acute Respiratory Distress Syndrome (ARDS), intestinal obstruction, liver cirrhosis, surgery, major abdominal operations, abdominal aortic aneurysm repair, large bowel resections, ischemia reperfusion injury including ischemia reperfusion injury of solid organs, limb ischemia, bowel ischemia, cardiac surgery requiring cardio-pulmonary bypass, autoimmune hepatitis, autoimmune hepatobiliary diseases, autoimmune ITP, Huntington's disease, Alzheimer's disease, ALS, Parkinson's disease, Lewy body disease, spinal muscular atrophy, allergic disease, asthma, atopic dermatitis, type I diabetes, Wegener's granulomatosis, Behcet's disease, interleukin-1 converting enzyme associated fever syndrome, pancreatic cancer, metastatic adenocarcinoma of the pancreas, pancreatic ductal adenocarcinoma, mesothelioma, melanoma, colorectal cancer, acute myeloid leukemia, metastasis, glioblastoma, breast cancer, gallbladder cancer, clear cell renal carcinoma, non-small cell lung carcinoma, or radiation induced necrosis.

[497] In a fourth aspect of the invention, there is provided the use of a compound of the first aspect or a pharmaceutically acceptable salt, solvate, or tautomer thereof in the manufacture of a medicament for the treatment or prophylaxis of an RIPK1 kinase mediated disease or disorder, wherein the disease or disorder is selected from the group consisting of: papillary thyroid carcinoma, pancreatic cancer, lung cancer, colon cancer, breast carcinoma, neuroblastoma, cachexia, dermatitis or asthma.

[498] In a fifth aspect of the invention, there is provided the use of a compound of the first aspect or a pharmaceutically acceptable salt, solvate, or tautomer thereof in the manufacture of a medicament for the treatment or prophylaxis of proliferative disorders associated with RIPK1.

[499] In a sixth aspect of the invention, there is provided a method for the treatment or prophylaxis of an RIPK1 mediated disease or disorder the method comprising administering to an individual in need thereof an effective amount of the compound of the first aspect or a pharmaceutically acceptable salt, solvate, or tautomer thereof, wherein the disease or disorder is selected from the group consisting of: inflammatory bowel disease including Crohn's disease and ulcerative colitis, psoriasis, retinal detachment, retinitis pigmentosa, arthritis including rheumatoid arthritis, spondyloarthritis, gout, osteoarthritis, and systemic onset juvenile idiopathic arthritis (SoJIA), transplant rejection, organ transplantation for donors and recipients, multiple sclerosis, tumor necrosis factor receptor-associated periodic syndrome, multiple organ dysfunction syndrome (MODS), thermal injury/burn, systemic inflammatory response syndrome (SIRS), radiation injury, radiotherapy, chemotherapy, pneumonias, hemorrhagic shock, trauma including multiple trauma, traumatic brain injury, acute pancreatitis, critical illness, sepsis, septic shock, Stevens-Johnson syndrome, toxic epidermal necrolysis, stroke, heat stroke, stroke-associated pneumonia, Multi-Organ Dysfunction Syndrome (MODS), Acute Respiratory Distress Syndrome (ARDS), intestinal obstruction, liver cirrhosis, surgery, major abdominal operations, abdominal aortic aneurysm repair, large bowel resections, ischemia reperfusion injury including ischemia reperfusion injury of solid organs, limb ischemia, bowel ischemia, cardiac surgery requiring cardio-pulmonary bypass, autoimmune hepatitis, autoimmune hepatobiliary diseases, autoimmune ITP, Huntington's disease, Alzheimer's disease, ALS, Parkinson's disease, Lewy body disease, spinal muscular atrophy, allergic disease, asthma, atopic dermatitis, type I diabetes, Wegener's granulomatosis, Behcet's disease, interleukin-1 converting enzyme associated fever syndrome, pancreatic cancer, metastatic adenocarcinoma of the pancreas, pancreatic ductal adenocarcinoma, mesothelioma, melanoma,

colorectal cancer, acute myeloid leukemia, metastasis, glioblastoma, breast cancer, gallbladder cancer, clear cell renal carcinoma, non-small cell lung carcinoma, or radiation induced necrosis.

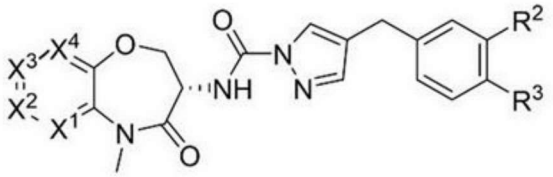
[500] In a seventh aspect of the invention, there is provided a method for the treatment or prophylaxis of an RIPK1 mediated disease or disorder, the method comprising administering to an individual in need thereof an effective amount of a composition comprising a compound of the first aspect or a pharmaceutically acceptable salt, solvate, or tautomer thereof, wherein the disease or disorder is selected from the group consisting of: papillary thyroid carcinoma, pancreatic cancer, lung cancer, colon cancer, breast carcinoma, neuroblastoma, cachexia, dermatitis or asthma.

[501] In an eighth aspect of the invention, there is provided a method for the treatment or prophylaxis of proliferative disorders associated with RIPK1, the method comprising administering to an individual in need thereof an effective amount of a compound of the first aspect or a pharmaceutically acceptable salt, solvate, or tautomer.

Claims

[Claim 1]

A compound of formula IIa or a pharmaceutically acceptable salt, solvate, or tautomer thereof, and a pharmaceutically acceptable carrier.



IIa

wherein

R^2 and R^3 are each independently H, methyl, CF_3, halogen, or cyano;

X^1 and X^3 are each independently CH or CF, with the proviso that at least one of X^1 and X^3 is CF;

X^2 and X^4 are each independently CR^4 or N; and

R^4 is H, NH_2, OH, OMe, halogen, cyano, or C1-C6 alkyl.

[Claim 2]

A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt, solvate, or tautomer thereof, and a pharmaceutically acceptable carrier.

[Claim 3]

Use of a compound of claim 1 or a pharmaceutically acceptable salt, solvate, or tautomer thereof in the manufacture of a medicament for the treatment or prophylaxis of an RIPK1 mediated disease or disorder, wherein the disease or disorder is selected from the group consisting of: inflammatory bowel disease including Crohn's disease and ulcerative colitis, psoriasis, retinal detachment, retinitis pigmentosa, arthritis including rheumatoid arthritis, spondyloarthritis, gout, osteoarthritis, and systemic onset juvenile idiopathic arthritis (SoJIA), transplant rejection, organ transplantation for donors and recipients, multiple sclerosis, tumor necrosis factor receptor-associated periodic syndrome, multiple organ dysfunction syndrome (MODS), thermal injury/burn, systemic inflammatory response syndrome (SIRS), radiation injury, radiotherapy, chemotherapy, pneumonias, hemorrhagic shock, trauma including multiple trauma, traumatic brain injury, acute pancreatitis, critical illness, sepsis, septic shock, Stevens-Johnson syndrome, toxic epidermal necrolysis, stroke, heat stroke, stroke-associated pneumonia, Multi-Organ Dysfunction Syndrome (MODS), Acute Respiratory Distress Syndrome (ARDS), intestinal obstruction, liver cirrhosis, surgery, major abdominal operations, abdominal aortic aneurysm repair, large bowel resections, ischemia reperfusion injury including

ischemia reperfusion injury of solid organs, limb ischemia, bowel ischemia, cardiac surgery requiring cardio-pulmonary bypass, autoimmune hepatitis, autoimmune hepatobiliary diseases, autoimmune ITP, Huntington's disease, Alzheimer's disease, ALS, Parkinson's disease, Lewy body disease, spinal muscular atrophy, allergic disease, asthma, atopic dermatitis, type I diabetes, Wegener's granulomatosis, Behcet's disease, interleukin-1 converting enzyme associated fever syndrome, pancreatic cancer, metastatic adenocarcinoma of the pancreas, pancreatic ductal adenocarcinoma, mesothelioma, melanoma, colorectal cancer, acute myeloid leukemia, metastasis, glioblastoma, breast cancer, gallbladder cancer, clear cell renal carcinoma, non-small cell lung carcinoma, or radiation induced necrosis.

[Claim 4]

Use of a compound of claim 1 or a pharmaceutically acceptable salt, solvate, or tautomer thereof in the manufacture of a medicament for the treatment or prophylaxis of an RIPK1 kinase mediated disease or disorder, wherein the disease or disorder is selected from the group consisting of: papillary thyroid carcinoma, pancreatic cancer, lung cancer, colon cancer, breast carcinoma, neuroblastoma, cachexia, dermatitis or asthma.

[Claim 5]

Use of a compound of claim 1 or a pharmaceutically acceptable salt, solvate, or tautomer thereof in the manufacture of a medicament for the treatment or prophylaxis of proliferative disorders associated with RIPK1.

[Claim 6]

Use of claim 5, wherein the proliferative disorders are selected from the group consisting of cancer, inflammation, neurodegenerative disease and infectious diseases.

[Claim 7]

A method for the treatment or prophylaxis of an RIPK1 mediated disease or disorder the method comprising administering to an individual in need thereof an effective amount of the compound of claim 1 or a pharmaceutically acceptable salt, solvate, or tautomer thereof, wherein the disease or disorder is selected from the group consisting of: inflammatory bowel disease including Crohn's disease and ulcerative colitis, psoriasis, retinal detachment, retinitis pigmentosa, arthritis including rheumatoid arthritis, spondyloarthritis, gout, osteoarthritis, and systemic onset juvenile idiopathic arthritis (SoJIA), transplant rejection, organ transplantation for donors and recipients, multiple sclerosis, tumor necrosis factor receptor-associated periodic syndrome, multiple organ dysfunction syndrome (MODS), thermal injury/burn, systemic inflammatory response syndrome (SIRS), radiation injury, radiotherapy, chemotherapy, pneumonias, hemorrhagic shock, trauma including multiple trauma, traumatic brain injury, acute pancreatitis, critical illness, sepsis, septic shock, Stevens-Johnson syndrome, toxic epidermal necrolysis, stroke, heat stroke, stroke-associated pneumonia, Multi-Organ Dysfunction Syndrome (MODS), Acute Respiratory Distress Syndrome (ARDS), intestinal

obstruction, liver cirrhosis, surgery, major abdominal operations, abdominal aortic aneurysm repair, large bowel resections, ischemia reperfusion injury including ischemia reperfusion injury of solid organs, limb ischemia, bowel ischemia, cardiac surgery requiring cardio-pulmonary bypass, autoimmune hepatitis, autoimmune hepatobiliary diseases, autoimmune ITP, Huntington's disease, Alzheimer's disease, ALS, Parkinson's disease, Lewy body disease, spinal muscular atrophy, allergic disease, asthma, atopic dermatitis, type I diabetes, Wegener's granulomatosis, Behcet's disease, interleukin-1 converting enzyme associated fever syndrome, pancreatic cancer, metastatic adenocarcinoma of the pancreas, pancreatic ductal adenocarcinoma, mesothelioma, melanoma, colorectal cancer, acute myeloid leukemia, metastasis, glioblastoma, breast cancer, gallbladder cancer, clear cell renal carcinoma, non-small cell lung carcinoma, or radiation induced necrosis.

[Claim 8]

A method for the treatment or prophylaxis of an RIPK1 mediated disease or disorder, the method comprising administering to an individual in need thereof an effective amount of a composition comprising a compound of claim 1 or a pharmaceutically acceptable salt, solvate, or tautomer thereof, wherein the disease or disorder is selected from the group consisting of: papillary thyroid carcinoma, pancreatic cancer, lung cancer, colon cancer, breast carcinoma, neuroblastoma, cachexia, dermatitis or asthma.

[Claim 9]

The method of claim 8, wherein the disorder or disease is proliferative disorders.

[Claim 10]

A method for the treatment or prophylaxis of proliferative disorders associated with RIPK1, the method comprising administering to an individual in need thereof an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt, solvate, or tautomer.

[Claim 11]

The method of claim 10, wherein the proliferative disorders are selected from the group consisting of cancer, inflammation, neurodegenerative disease and infectious diseases.

SEQUENCE LISTING

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<120> COMPOSITION AND METHODS OF TARGETING THE PRE-B CELL RECEPTOR FOR THE TREATMENT OF LEUKEMIAS AND LYMPHOMAS

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Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
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Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Ser Asn Gly Arg Ile Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Ser Lys Ala Thr Leu Thr Val Asp Ile Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Gly Leu Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr
100 105 110

Asp Ser Ser
115

<210> 7
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 7

Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Gln Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Ser Asn Gly Arg Asn Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Arg Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Gly Leu Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr
100 105 110

Val Ser Ser
115

<210> 8
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 8

Glu Val Gln Leu Glu Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Asp Ser Ile Thr Ser Asp
20 25 30

Tyr Trp Thr Trp Ile Arg Lys Phe Pro Gly Asn Lys Leu Glu Tyr Met
35 40 45

Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Tyr Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Lys Gln Tyr Tyr Leu
65 70 75 80

Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg Glu Arg Tyr Tyr Tyr Gly Ser Leu Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 9
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 9

Glu Val Gln Leu Glu Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Asp Ser Ile Thr Ser Asp
20 25 30

Tyr Trp Thr Trp Ile Arg Lys Phe Pro Gly Asn Lys Leu Glu Tyr Met
35 40 45

Gly Tyr Ile Ser Tyr Ser Gly Arg Thr Tyr Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Arg Asn Gln Tyr Tyr Leu
65 70 75 80

Gln Leu Ser Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg Glu Arg Tyr Tyr Tyr Gly Ser Leu Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 10
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 10

Glu Val Gln Leu Glu Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Asp Ser Ile Thr Ser Asp
20 25 30

Tyr Trp Thr Trp Ile Arg Lys Phe Pro Gly Asn Ile Leu Glu Tyr Met

35 40 45

Gly Tyr Ile Ser Ser Ser Gly Arg Ile Tyr Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Tyr Tyr Leu
65 70 75 80

Gln Leu Ser Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala
85 90 95

Arg Glu Arg Tyr Tyr Tyr Gly Ser Leu Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Leu Thr Val Ser Ser
115

<210> 11
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 11

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Asn
20 25 30

Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn Pro Ser Asn Gly Arg Ile Asn Tyr Asn Glu Lys Phe
50 55 60

Lys Ser Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Gln Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Gly Leu Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr
100 105 110

Val Ser Ser
115

<210> 12
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 12

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Ile His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu His Trp Ser Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Ser Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
85 90 95

Thr Tyr Val Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Arg

<210> 13
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 13

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser

85 90 95

Thr Tyr Val Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Arg

<210> 14
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 14

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Thr
85 90 95

Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg

<210> 15
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 15

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

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Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Thr
                85                  90                  95

Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg
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<210>  16
<211>  113
<212>  PRT
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<220>
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<400>  16

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1               5                   10                  15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Gly Leu Val His Ser
            20                  25                  30

Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Thr
                85                  90                  95

Thr His Val Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110

Arg
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<210>  17
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<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 17

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
85 90 95

Thr Tyr Leu Pro Leu Thr Phe Gly Ala Gly Thr Arg Leu Glu Leu Lys
100 105 110

Arg

<210> 18
<211> 30
<212> PRT
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<220>
<223> Synthetic peptide

<400> 18

Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
20 25 30

<210> 19
<211> 5
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<220>
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<400> 19

Ser Tyr Trp Met Gln
1 5

<210> 20
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 20

Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
1 5 10

<210> 21
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
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<400> 21

Glu Ile Asn Pro Ser Asn Gly Arg Ile Asn Tyr Asn Glu Lys Phe Lys
1 5 10 15

Ser

<210> 22
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 22

Lys Ala Thr Leu Thr Val Asp Ile Ser Ser Ser Thr Ala Tyr Met Gln
1 5 10 15

Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 23
<211> 6
<212> PRT
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<220>
<223> Synthetic peptide

<400> 23

Ser Gly Leu Leu Asp Tyr
1 5

<210> 24

<211> 11
<212> PRT
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<220>
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<400> 24

Trp Gly Gln Gly Thr Thr Leu Thr Asp Ser Ser
1 5 10

<210> 25
<211> 30
<212> PRT
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<220>
<223> Synthetic peptide

<400> 25

Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Gln Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
20 25 30

<210> 26
<211> 17
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<220>
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<400> 26

Glu Ile Asn Pro Ser Asn Gly Arg Asn Asn Tyr Asn Glu Lys Phe Lys
1 5 10 15

Arg

<210> 27
<211> 32
<212> PRT
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<220>
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<400> 27

Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Ser Thr Ala Tyr Met Gln
1 5 10 15

Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 28
<211> 11

<212> PRT
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<220>
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<400> 28

Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
1 5 10

<210> 29
<211> 30
<212> PRT
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<220>
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<400> 29

Glu Val Gln Leu Glu Glu Ser Gly Pro Ser Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Ser Val Thr Gly Asp Ser Ile Thr
20 25 30

<210> 30
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
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<400> 30

Ser Asp Tyr Trp Thr
1 5

<210> 31
<211> 14
<212> PRT
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<220>
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<400> 31

Trp Ile Arg Lys Phe Pro Gly Asn Lys Leu Glu Tyr Met Gly
1 5 10

<210> 32
<211> 16
<212> PRT
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<220>
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<400> 32

Tyr Ile Ser Tyr Ser Gly Arg Thr Tyr Tyr Asn Pro Ser Leu Lys Ser

1 5 10 15

<210> 33
<211> 32
<212> PRT
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<220>
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<400> 33

Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Lys Gln Tyr Tyr Leu Gln
1 5 10 15

Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg
20 25 30

<210> 34
<211> 10
<212> PRT
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<220>
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<400> 34

Glu Arg Tyr Tyr Tyr Gly Ser Leu Asp Tyr
1 5 10

<210> 35
<211> 32
<212> PRT
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<220>
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<400> 35

Arg Ile Ser Ile Thr Arg Asp Thr Ser Arg Asn Gln Tyr Tyr Leu Gln
1 5 10 15

Leu Ser Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg
20 25 30

<210> 36
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<400> 36

Trp Ile Arg Lys Phe Pro Gly Asn Ile Leu Glu Tyr Met Gly
1 5 10

<210> 37
<211> 16

<212> PRT
<213> Artificial Sequence

<220>
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<400> 37

Tyr Ile Ser Ser Ser Gly Arg Ile Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 38
<211> 32
<212> PRT
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<220>
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<400> 38

Arg Ile Ser Ile Thr Arg Asp Thr Ser Lys Asn Gln Tyr Tyr Leu Gln
1 5 10 15

Leu Ser Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys Ala Arg
20 25 30

<210> 39
<211> 5
<212> PRT
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<220>
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<400> 39

Ser Asn Trp Met Asn
1 5

<210> 40
<211> 32
<212> PRT
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<220>
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<400> 40

Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Ser Thr Ala Tyr Met Gln
1 5 10 15

Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys Ala Arg
20 25 30

<210> 41
<211> 23
<212> PRT
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<220>
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<400> 41

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys
20

<210> 42
<211> 16
<212> PRT
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<220>
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<400> 42

Arg Ser Ser Gln Ser Leu Ile His Ser Asn Gly Asn Thr Tyr Leu His
1 5 10 15

<210> 43
<211> 15
<212> PRT
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<220>
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<400> 43

Trp Ser Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr
1 5 10 15

<210> 44
<211> 7
<212> PRT
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<220>
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<400> 44

Lys Val Ser Asn Arg Phe Ser
1 5

<210> 45
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
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<400> 45

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Lys Ile Ser Ser Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys
20 25 30

<210> 46
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<400> 46

Ser Gln Ser Thr Tyr Val Pro Leu Thr
1 5

<210> 47
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 47

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
1 5 10

<210> 48
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
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<400> 48

Arg Ser Ser Gln Ser Leu Val His Ser Asn Gly Asn Thr Tyr Leu His
1 5 10 15

<210> 49
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
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<400> 49

Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr
1 5 10 15

<210> 50
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<212> PRT
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<220>
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<400> 50

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr

1 5 10 15

Leu Thr Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys
20 25 30

<210> 51
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<220>
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<400> 51

Asp Val Val Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys
20

<210> 52
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<220>
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<400> 52

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys
20 25 30

<210> 53
<211> 9
<212> PRT
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<220>
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<400> 53

Ser Gln Thr Thr His Val Pro Pro Thr
1 5

<210> 54
<211> 11
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<220>
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<400> 54

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
1 5 10

<210> 55
<211> 16
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<220>
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<400> 55

Arg Ser Ser Gln Gly Leu Val His Ser Asn Gly Asn Thr Tyr Leu His
1 5 10 15

<210> 56
<211> 9
<212> PRT
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<220>
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<400> 56

Ser Gln Ser Thr Tyr Leu Pro Leu Thr
1 5

<210> 57
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 57

Phe Gly Ala Gly Thr Arg Leu Glu Leu Lys Arg
1 5 10

<210> 58
<211> 5
<212> PRT
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<220>
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<220>
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<222> (2)..(2)
<223> Xaa is Tyr or Asn

<220>
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<222> (5)..(5)
<223> Xaa is Gln or Asn

<400> 58

Ser Xaa Trp Met Xaa
1 5

<210> 59
<211> 17
<212> PRT
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<220>
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<220>
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<222> (9)..(9)
<223> Xaa is Ile or Asn

<220>
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<222> (17)..(17)
<223> Xaa is Ser or Arg

<400> 59

Glu Ile Asn Pro Ser Asn Gly Arg Xaa Asn Tyr Asn Glu Lys Phe Lys
1 5 10 15

Xaa

<210> 60
<211> 16
<212> PRT
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<220>
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<400> 60

Arg Ser Ser Gln Ser Leu Xaa His Ser Asn Gly Asn Thr Tyr Leu His
1 5 10 15

<210> 61
<211> 9
<212> PRT
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<220>
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<220>
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<222> (6)..(6)
<223> Xaa is Val or Leu

<400> 61

Ser Gln Ser Thr Tyr Xaa Pro Leu Thr
1 5

<210> 62
<211> 16
<212> PRT
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<220>
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<220>
<221> MISC_FEATURE
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<223> Xaa is Tyr or Ser

<220>
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<223> Xaa is Thr or Ile

<400> 62

Tyr Ile Ser Xaa Ser Gly Arg Xaa Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> 63
<211> 16
<212> PRT
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<220>
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<220>
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<222> (5)..(5)
<223> Xaa is Ser or Gly

<400> 63

Arg Ser Ser Gln Xaa Leu Val His Ser Asn Gly Asn Thr Tyr Leu His
1 5 10 15

<210> 64
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tcctgcaagg cttctggcta caccttcacc agctactgga tgcagtgggt gaagcagagg 120

cctggacaag gccttgagtg gattggagag attaatccta gcaacggtcg tattaactac 180

aatgagaagt tcaagagcaa ggccacactt actgtagaca tatcgtccag cacagcctac 240

atgcaactca gcagtctgac atctgaggac tctgcggtct attactgtgc aagatcgggg 300

ctccttgact actggggcca aggcaccact ctcacagact cctca 345

<210> 65
<211> 345

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 65
gaggtccagc tgcaacagtc tggggctgaa ctggtgaagc ctggggcttc agtgcagctg 60

tcctgcaagg cttctggcta caccttcacc agctactgga tgcagtgggt gaaacagagg 120

cctggacaag gccttgagtg gattggagag attaatccta gcaacggtcg caataattac 180

aatgagaagt tcaagagaaa ggccacactt actgttgaca catcctccag cacagcctac 240

atgcaactca gcagcctgac atctgaggac tctgcggtct attactgtgc aagatcgggg 300

ctccttgact actggggcca aggcaccact ctcacagtct cctca 345

<210> 66
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 66
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acctgttctg tcactggcga ctccatcacc agtgattact ggacctggat ccggaaattc 120

ccagggaata aacttgagta catggggtac ataagctaca gtggtagaac ttactacaat 180

ccatctctca aaagtcgaat ctccatcact cgagacacat ccaagaagca gtactacctg 240

cagttgaatt ctgtgacaac tgaggacaca gccacatatt actgtgcaag agagcgttat 300

tactacggta gtcttgacta ctggggccaa ggcaccactc tcacagtctc ctca 354

<210> 67
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 67
gaggtgcagc tggaggagtc aggacctagc ctcgtgaaac cttctcagac tctgtccctc 60

acctgttctg tcactggcga ctccatcacc agtgattact ggacctggat ccggaaattc 120

ccagggaata aacttgagta catggggtac ataagctaca gtggtagaac ttactacaat 180

ccatctctca aaagtcgaat ctccatcact cgagacacat ccaggaacca gtactacctg 240

cagttgagtt ctgtgactac tgaggacaca gccacatatt actgtgcaag agagcgttat 300

tactacggta gtcttgacta ctggggccag ggcaccactc tcacagtctc ctca 354

<210> 68
<211> 354
<212> DNA
<213> Artificial Sequence

<220>
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<400> 68
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ccagggaata tacttgagta catggggtac ataagctcca gtggtaggat ttattacaat 180

ccatctctca aaagtcgaat ctccatcact cgagacacat ccaagaacca gtactacctg 240

cagttgagtt ctgtgactac tgaggacaca gccacatatt actgtgcaag agagcgttat 300

tactacggta gtcttgacta ctggggccaa ggcaccactc tcacagtctc ctca 354

<210> 69
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 69
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tcctgcaagg cttctggcta caccttcacc agcaactgga tgaactgggt gaagcagagg 120

cctggacaag gccttgagtg gattggagag attaatccta gcaacggtcg tattaattac 180

aatgagaagt tcaagagcaa ggccacactt actgtggaca aatcctccag cacagcctac 240

atgcaactca gcagcctgac atctgaggac tctgcggtct attactgtgc aagatcgggg 300

ctccttgact actggggcca aggcaccact ctcacagtct cctca 345

<210> 70
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 70
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atctcttgca gatctagtca gagccttata cacagtaatg gaaacaccta tttacattgg 120

tccctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagcgtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac atatgtcccg 300

ctcacgttcg gtgctgggac caagctggag ctgaaacgg 339

<210> 71
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 71
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atctcttgca gatctagtca gagccttgta cacagtaatg gcaacaccta tttacattgg 120

tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc taaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcacgatc 240

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ctcacgttcg gtgctgggac caagctggag ctgaaacgg 339

<210> 72
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 72
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atctcttgca gatctagtca gagccttgta cacagtaatg gaaacaccta tttacattgg 120

tacctgcaga agccaggcca gtctccaaag ctcctgattt acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaactac acatgttcct 300

cccacgttcg gaggggggac caagctggaa ataaaacgg 339

<210> 73
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 73
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atctcttgca gatctagtca gagccttgta cacagtaatg gaaacaccta tttacattgg 120

tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaactac acatgttcct 300

cccacgttcg gaggggggac caagctggaa ataaaacgg 339

<210> 74
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 74
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atctcttgca gatctagtca gggccttgta cacagtaatg gaaacaccta tttacattgg 120

tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaactac acatgttcct 300

cccacgttcg gaggggggac caagctggaa ataaaacgg 339

<210> 75
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 75
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atctcttgca gatctagtca gagccttgta cacagtaatg gaaacaccta tttacattgg 120

tacctgcaga agccaggcca gtctccaaag ctcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac atatcttccg 300

ctcacgttcg gtgctgggac caggctggag ctgaaacgg 339

<210> 76
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 76

Glu Val Gln Leu Glu Glu Ser Gly Ala Glu Leu Val Arg Ser Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Tyr
20 25 30

Tyr Leu His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Asp Pro Glu Asn Gly Asn Thr Asp Tyr Ala Pro Lys Phe
50 55 60

Gln Gly Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Leu Gln Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Asn Glu Gly Tyr Tyr Asp Tyr Asp Thr Asp Ser Ala Met Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 77
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 77

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asp Gly Ile Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
85 90 95

Thr Arg Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg

<210> 78
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 78

Glu Val Gln Leu Glu Glu Ser Gly Ala Glu Leu Val Arg Ser Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys
20 25 30

<210> 79
<211> 5
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 79

Asp Tyr Tyr Leu His
1 5

<210> 80
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 80

Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile Gly
1 5 10

<210> 81
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 81

Trp Ile Asp Pro Glu Asn Gly Asn Thr Asp Tyr Ala Pro Lys Phe Gln
1 5 10 15

Gly

<210> 82
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 82

Lys Ala Thr Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr Leu Gln
1 5 10 15

Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys Asn Glu
20 25 30

<210> 83
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 83

Gly Tyr Tyr Asp Tyr Asp Thr Asp Ser Ala Met Asp Tyr
1 5 10

<210> 84
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 84

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
1 5 10

<210> 85
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 85

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys
20

<210> 86
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 86

Arg Ser Ser Gln Ser Leu Val His Ser Asp Gly Ile Thr Tyr Leu His
1 5 10 15

<210> 87
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 87

Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Lys Leu Leu Ile Tyr
1 5 10 15

<210> 88
<211> 7
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 88

Lys Val Ser Asn Arg Phe Ser
1 5

<210> 89
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 89

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys
20 25 30

<210> 90
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 90

Ser Gln Ser Thr Arg Val Pro Trp Thr
1 5

<210> 91
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 91

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg
1 5 10

<210> 92
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 92
gaggtgcagc tggaggagtc tggggcagag cttgtgaggt caggggcctc agtcaagttg 60

tcctgcacag cttctggctt caacattaaa gactactatt tgcactgggt gaagcagagg 120

cctgaacagg gcctggagtg gattggatgg attgatcctg agaatggtaa tactgattat 180

gccccgaagt tccagggcaa ggccactatg actgcagaca catcctccaa cacagcctac 240

ctgcagctca gcagcctgac atctgaggac actgccgtct attactgtaa tgaggggtat 300

tatgattacg acacagactc tgctatggac tactggggtc aaggaacctc agtcaccgtc 360

tcctca 366

<210> 93
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 93
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atctcttgca gatctagtca gagccttgta cacagtgatg gaatcaccta tttacattgg 120

tacctacaga agccaggcca gtctccaaaa ctcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggagtt tatttctgct ctcaaagtac acgtgttccg 300

tggacgttcg gtggaggcac caagctggaa atcaaacgg 339

<210> 94
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 94

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Tyr Pro Gly Asn Ser Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Phe Cys
85 90 95

Thr Arg Ala Asp Tyr Asp Gly Thr Pro Phe Asp Tyr Trp Gly Gln Gly

100 105 110

Thr Thr Leu Thr Val Ser Ser
115

<210> 95
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 95

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Arg Met Ser Cys Arg Ala Ser Gly Tyr Ser Phe Asn Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Tyr Pro Gly Ser Ser Asp Thr Ser Tyr Ser Gln Lys Phe
50 55 60

Lys Gly Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Gly Asp Tyr Asp Gly Thr Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser Ser
115

<210> 96
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 96

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Thr
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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Gly Ala Ile Tyr Leu Gly Asn Thr Asp Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Gly Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Ser Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Arg Ala Asp Tyr Asp Gly Thr Pro Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Thr Leu Thr Val Ser Ser
        115


<210>  97
<211>  119
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  97

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1               5                   10                  15


Ser Val Lys Met Ser Cys Arg Pro Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30


Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Asp Leu Glu Trp Ile
        35                  40                  45


Gly Ala Ile Tyr Pro Gly Asn Ser Asp Thr Ser Tyr Asn Gln Lys Phe
    50                  55                  60


Lys Gly Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Arg Ala Asp Tyr Asp Gly Thr Pro Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Thr Leu Thr Val Ser Ser
        115


<210>  98
<211>  119
<212>  PRT
<213>  Artificial Sequence
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<220>
<223> Synthetic peptide

<400> 98

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Arg Met Ser Cys Arg Ala Ser Gly Tyr Ser Phe Asn Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Tyr Pro Gly Ser Ser Asp Thr Ser Tyr Ser Gln Lys Phe
50 55 60

Lys Gly Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Asn Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Gly Asp Tyr Asp Gly Thr Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser Ser
115

<210> 99
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 99

Glu Val Gln Leu Glu Glu Ser Gly Ala Glu Leu Val Arg Ser Gly Ala
1 5 10 15

Ser Val Lys Leu Ser Cys Thr Ala Ser Gly Phe Asn Ile Lys Asp Tyr
20 25 30

Tyr Leu His Trp Val Lys Gln Arg Pro Glu Gln Gly Leu Glu Trp Ile
35 40 45

Gly Trp Ile Asp Pro Glu Asn Gly Ala Thr Asp Tyr Ala Pro Lys Phe
50 55 60

Gln Gly Lys Ala Ser Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr
65 70 75 80

Leu Gln Leu Ser Ser Leu Thr Phe Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

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Asn Glu Gly Tyr Tyr Asp Tyr Asp Ala Asp Ser Ala Met Asp Tyr Trp
            100                 105                 110


Gly Gln Gly Thr Ser Val Thr Val Ser Ser
        115                 120


<210>  100
<211>  119
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  100

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1               5                   10                  15


Ser Val Lys Met Ser Cys Gln Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30


Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45


Gly Ala Ile Tyr Pro Gly Asn Ser Asp Thr Ser Tyr Asn Gln Asn Phe
    50                  55                  60


Lys Gly Lys Ala Glu Leu Thr Ala Val Thr Ser Ala Thr Thr Ala Tyr
65                  70                  75                  80


Met Glu Leu Ser Ser Leu Thr Asp Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95


Thr Arg Ala Asp Tyr Asp Gly Thr Pro Phe Asp Tyr Trp Gly Gln Gly
            100                 105                 110


Thr Thr Leu Thr Val Ser Ser
        115


<210>  101
<211>  119
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Synthetic peptide

<400>  101

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1               5                   10                  15


Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asn Tyr
            20                  25                  30
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Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Val Tyr Pro Gly Asn Ser Asp Thr Ser Tyr Ser Gln Lys Phe
50 55 60

Thr Gly Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Asp Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Ala Asp Tyr Asp Gly Thr Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser Ser
115

<210> 102
<211> 119
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 102

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Tyr Pro Gly Asn Ser Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Arg Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Ala Asp Tyr Asp Gly Thr Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser Ser
115

<210> 103
<211> 119

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 103

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr Ser Tyr
20 25 30

Trp Met His Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Ala Ile Tyr Pro Gly Asn Ser Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Gly Asp Tyr Asp Gly Thr Pro Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Leu Thr Val Ser Ser
115

<210> 104
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 104

Asp Ile Leu Met Thr Gln Ser Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

His Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Glu Thr Tyr Leu Ser Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Glu Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Arg

<210> 105
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 105

Asp Ile Leu Met Thr Gln Ser Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Gly Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu His Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Arg

<210> 106
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 106

Asp Val Val Met Thr Gln Asn Ala Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

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His Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Asp Ser
            20                  25                  30

Asp Gly Glu Thr Tyr Leu Ser Trp Leu Leu Gln Arg Pro Gly Gln Ser
        35                  40                  45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
                85                  90                  95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105                 110

Arg
```

<210> 107
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 107

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Asp Ile Val Met Thr Gln Ser Pro Leu Thr Leu Ser Val Thr Ile Gly
1               5                   10                  15

His Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
            20                  25                  30

Asp Gly Glu Thr Tyr Leu Ser Trp Leu Leu Gln Arg Pro Gly Gln Ser
        35                  40                  45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
                85                  90                  95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105                 110

Arg
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<210> 108
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 108

Asp Ile Val Met Thr Gln Ser Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Gly Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Lys Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu His Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Arg

<210> 109
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 109

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1 5 10 15

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val His Ser
20 25 30

Asp Gly Ile Thr Tyr Leu His Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Lys Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Phe Cys Ser Gln Ser
85 90 95

Ala Arg Val Pro Trp Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg

<210> 110
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 110

Asp Ile Val Met Thr Gln Ser Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

His Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Glu Thr Tyr Leu Ser Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Val Glu Leu Lys
100 105 110

Arg

<210> 111
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 111

Asp Val Leu Met Thr Gln Thr Pro Leu Thr Leu Ser Val Ile Ile Gly

1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Glu Thr Tyr Leu Ser Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Arg

<210> 112
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 112

Asp Ile Val Met Thr Gln Ser Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

His Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Glu Thr Tyr Leu Ser Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Arg

<210> 113
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 113

Asp Val Leu Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Asp Gly Glu Thr Tyr Leu Asn Trp Leu Leu Gln Arg Pro Gly Gln Ser
35 40 45

Pro Lys Arg Leu Ile Tyr Leu Ala Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys Trp Gln Gly
85 90 95

Thr His Phe Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

Arg

<210> 114
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 114

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
20 25 30

<210> 115
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 115

Asn Tyr Trp Met His
1 5

<210> 116
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 116

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Arg Met Ser Cys Arg Ala Ser Gly Tyr Ser Phe Asn
20 25 30

<210> 117
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 117

Ser Tyr Trp Met His
1 5

<210> 118
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 118

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Thr
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr
20 25 30

<210> 119
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 119

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Arg Pro Ser Gly Tyr Thr Phe Thr
20 25 30

<210> 120
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 120

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Gln Ala Ser Gly Tyr Thr Phe Thr
20 25 30

<210> 121
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 121

Glu Val Gln Leu Gln Gln Ser Gly Thr Val Leu Ala Arg Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Ser Phe Thr
20 25 30

<210> 122
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 122

Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile Gly
1 5 10

<210> 123
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 123

Ala Ile Tyr Pro Gly Asn Ser Asp Thr Ser Tyr Asn Gln Lys Phe Lys

1 5 10 15

Gly

<210> 124
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 124

Ala Ile Tyr Pro Gly Ser Ser Asp Thr Ser Tyr Ser Gln Lys Phe Lys
1 5 10 15

Gly

<210> 125
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 125

Ala Ile Tyr Leu Gly Asn Thr Asp Thr Ser Tyr Asn Gln Lys Phe Lys
1 5 10 15

Gly

<210> 126
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 126

Trp Val Lys Gln Arg Pro Gly Gln Asp Leu Glu Trp Ile Gly
1 5 10

<210> 127
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 127

Trp Ile Asp Pro Glu Asn Gly Ala Thr Asp Tyr Ala Pro Lys Phe Gln
1 5 10 15

Gly

<210> 128
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 128

Ala Ile Tyr Pro Gly Asn Ser Asp Thr Ser Tyr Asn Gln Asn Phe Lys
1 5 10 15

Gly

<210> 129
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 129

Ala Val Tyr Pro Gly Asn Ser Asp Thr Ser Tyr Ser Gln Lys Phe Thr
1 5 10 15

Gly

<210> 130
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 130

Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Phe Cys Thr Arg
20 25 30

<210> 131
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 131

Ala Asp Tyr Asp Gly Thr Pro Phe Asp Tyr
1 5 10

<210> 132
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 132

Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Asn Thr Ala Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys Thr Arg
20 25 30

<210> 133
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 133

Gly Asp Tyr Asp Gly Thr Pro Phe Asp Tyr
1 5 10

<210> 134
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 134

Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Ser Ala Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys Thr Arg
20 25 30

<210> 135
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 135

Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys Thr Arg
20 25 30

<210> 136
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 136

Lys Ala Ser Met Thr Ala Asp Thr Ser Ser Asn Thr Ala Tyr Leu Gln
1 5 10 15

Leu Ser Ser Leu Thr Phe Glu Asp Thr Ala Val Tyr Tyr Cys Asn Glu
20 25 30

<210> 137
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 137

Gly Tyr Tyr Asp Tyr Asp Ala Asp Ser Ala Met Asp Tyr
1 5 10

<210> 138
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 138

Lys Ala Glu Leu Thr Ala Val Thr Ser Ala Thr Thr Ala Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Thr Asp Glu Asp Ser Ala Val Tyr Tyr Cys Thr Arg
20 25 30

<210> 139
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 139

Lys Ala Lys Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr Met Asp
1 5 10 15

Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys Thr Arg

20 25 30

<210> 140
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 140

Lys Ala Arg Leu Thr Ala Val Thr Ser Ala Ser Thr Ala Tyr Met Glu
1 5 10 15

Leu Ser Ser Leu Thr Asn Glu Asp Ser Ala Val Tyr Tyr Cys Thr Arg
20 25 30

<210> 141
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 141

Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser
1 5 10

<210> 142
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 142

Asp Ile Leu Met Thr Gln Ser Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

His Pro Ala Ser Ile Ser Cys
20

<210> 143
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 143

Lys Ser Ser Gln Ser Leu Leu Asp Ser Asp Gly Glu Thr Tyr Leu Ser
1 5 10 15

<210> 144
<211> 23

<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 144

Asp Ile Leu Met Thr Gln Ser Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys
20

<210> 145
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 145

Lys Ser Gly Gln Ser Leu Leu Asp Ser Asp Gly Lys Thr Tyr Leu Asn
1 5 10 15

<210> 146
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 146

Asp Val Val Met Thr Gln Asn Ala Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

His Pro Ala Ser Ile Ser Cys
20

<210> 147
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 147

Arg Ser Ser Gln Ser Leu Leu Asp Ser Asp Gly Glu Thr Tyr Leu Ser
1 5 10 15

<210> 148
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 148

Asp Ile Val Met Thr Gln Ser Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

His Pro Ala Ser Ile Ser Cys
20

<210> 149
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 149

Asp Ile Val Met Thr Gln Ser Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys
20

<210> 150
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 150

Asp Val Leu Met Thr Gln Thr Pro Leu Thr Leu Ser Val Ile Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys
20

<210> 151
<211> 23
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 151

Asp Val Leu Met Thr Gln Thr Pro Leu Thr Leu Ser Val Thr Ile Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys
20

<210> 152
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 152

Lys Ser Ser Gln Ser Leu Leu Asp Ser Asp Gly Glu Thr Tyr Leu Asn
1 5 10 15

<210> 153
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 153

Trp Leu Leu Gln Arg Pro Gly Gln Ser Pro Glu Arg Leu Ile Tyr
1 5 10 15

<210> 154
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 154

Leu Val Ser Lys Leu Asp Ser
1 5

<210> 155
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 155

Trp Leu Leu Gln Arg Pro Gly Gln Ser Pro Lys Arg Leu Ile Tyr
1 5 10 15

<210> 156
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 156

Leu Val Ser Lys Leu His Ser
1 5

<210> 157
<211> 7
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 157

Leu Ala Ser Lys Leu Asp Ser
1 5

<210> 158
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 158

Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys
20 25 30

<210> 159
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 159

Trp Gln Gly Thr His Phe Pro Leu Thr
1 5

<210> 160
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 160

Ser Gln Ser Ala Arg Val Pro Trp Thr
1 5

<210> 161
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 161

Gly Val Pro Asp Arg Phe Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Leu Gly Ile Tyr Tyr Cys
20 25 30

<210> 162
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 162

Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg
1 5 10

<210> 163
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<400> 163

Phe Gly Ala Gly Thr Lys Val Glu Leu Lys Arg
1 5 10

<210> 164
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa is Asn or Ser

<400> 164

Xaa Tyr Trp Met His
1 5

<210> 165
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is Ile or Val

<220>

<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa is Pro or Leu

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is Asn or Ser

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is Ser or Thr

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa is Asn or Ser

<220>
<221> MISC_FEATURE
<222> (14)..(14)
<223> Xaa is Lys or Asn

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> Xaa is Lys or Thr

<400> 165

Ala Xaa Tyr Xaa Gly Xaa Xaa Asp Thr Ser Tyr Xaa Gln Xaa Phe Xaa
1 5 10 15

Gly

<210> 166
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa is Arg or Gly

<400> 166

Xaa Asp Tyr Asp Gly Thr Pro Phe Asp Tyr
1 5 10

<210> 167
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<220>

<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa is Lys or Arg

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Ser or Gly

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa is Glu or Lys

<220>
<221> MISC_FEATURE
<222> (16)..(16)
<223> Xaa is Ser or Asn

<400> 167

Xaa Ser Xaa Gln Ser Leu Leu Asp Ser Asp Gly Xaa Thr Tyr Leu Xaa
1 5 10 15

<210> 168
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is Val or Ala

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is Asp or His

<400> 168

Leu Xaa Ser Lys Leu Xaa Ser
1 5

<210> 169
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa is Ala or Asn

<400> 169

Trp Ile Asp Pro Glu Asn Gly Xaa Thr Asp Tyr Ala Pro Lys Phe Gln
1 5 10 15

Gly

<210> 170
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is Ala or Thr

<400> 170

Gly Tyr Tyr Asp Tyr Asp Xaa Asp Ser Ala Met Asp Tyr
1 5 10

<210> 171
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic peptide

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa is Ala or Thr

<400> 171

Ser Gln Thr Xaa His Val Pro Pro Thr
1 5

<210> 172
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 172
gaggttcaac tccagcagtc tgggactgtg ctggcaaggc ctggggcttc cgtgaagatg 60

tcctgcaagg cttctggcta cacctttacc aactactgga tgcactgggt aaaacagagg 120

cctggacagg gtctagaatg gattggtgct atttatcctg gaaatagtga tactagctac 180

aaccagaagt tcaagggcaa ggccaaactg actgcagtca catccgccag cactgcctac 240

atggagctca gcagcctgac aaatgaggac tctgcggtct atttctgtac aagggctgat 300

tacgacggga ccccctttga ctactggggc caaggcacca ctctcacagt ctcctca 357

<210> 173
<211> 357

<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 173
gaggttcagc tccagcagtc tgggactgtg ctggcaaggc ctggggcttc cgtgaggatg 60

tcctgcaggg cttctggcta cagctttaac agctactgga tgcactgggt aaaacagagg 120

cctggacagg gtctagaatg gattggtgct atttatcctg gaagtagtga tactagctac 180

agccagaagt tcaagggcaa ggccaaactg actgcagtca catccgccaa cactgcctac 240

atggagctca gcagcctgac aaatgaggac tctgcggtct attactgtac aaggggtgat 300

tacgacggga ccccctttga ctactggggc caaggcacca ctctcacagt ctcctca 357

<210> 174
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 174
gaggttcaac tccagcagtc tgggactgtg ctggcaaggc ctgggacttc cgtgaagatg 60

tcctgcaagg cttctggcta cacctttacc agctactgga tgcactgggt aaaacagagg 120

cctggacagg gtctagaatg gattggtgcc atttatcttg gaaatactga tactagctac 180

aaccagaagt tcaagggcaa ggccaaactg actgcagtca catccgccag cagtgcctac 240

atggagctca gcagcctgac aaatgaggac tctgcggtct attattgtac aaggggctgat 300

tacgacggga ccccctttga ctactggggc caaggcacca ctctcacagt ctcctca 357

<210> 175
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 175
gaggttcaac tccagcagtc tgggactgtg ctggcaaggc ctggggcttc cgtgaagatg 60

tcctgcaggc cttctggcta cacctttacc agctactgga tgcactgggt aaaacagagg 120

cctggacagg atctagaatg gattggtgct atttatcctg gaaatagtga tactagctac 180

aaccagaagt tcaagggcaa ggccaaactg actgcagtca catccgccag cactgcctac 240

atggagctca gcagcctgac aaatgaggac tctgcggtct attactgtac aagggctgat 300

tacgacggga ccccctttga ctactggggc caaggcacca ctctcacagt ctcctca 357

<210> 176
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 176
gaggttcagc tccagcagtc tgggactgtg ctggcaaggc ctggggcttc cgtgaggatg 60

tcctgcaggg cttctggcta cagctttaac agctactgga tgcactgggt aaaacagagg 120

cctggacagg gtctagaatg gattggtgct atttatcctg gaagtagtga tactagctac 180

agccagaagt tcaagggcaa ggccaaactg actgcagtca catccgccaa cactgcctac 240

atggagctca gcagcctgac aaatgaggac tctgcggtct attactgtac aaggggtgat 300

tacgacggga ccccctttga ctactggggc caaggcacca ctctcacagt ctcctca 357

<210> 177
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 177
gaggtgcagc tggaggagtc tggggcagag cttgtgaggt caggggcctc agtcaagttg 60

tcctgcacag cttctggctt caacattaaa gactactatt tacactgggt gaagcagagg 120

cctgaacagg gcctggagtg gattggatgg attgatcctg agaatggtgc cactgattat 180

gccccgaagt tccagggcaa ggcctctatg actgcagaca catcctccaa cacagcctac 240

ctgcagctca gcagcctgac atttgaggac actgccgtct attattgtaa tgaggggtat 300

tatgattacg acgcggactc tgctatggac tactggggtc aaggaacctc agtcaccgtc 360

tcctca 366

<210> 178
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 178
gaggttcaac tccagcagtc tgggactgtg ctggcaaggc ctggggcttc cgtgaagatg 60

tcctgccagg cttctggcta cacctttacc aactactgga tgcactgggt aaaacagagg 120

cctggacagg gtctagaatg gattggtgct atctatcctg gaaatagtga tactagctat 180

aaccagaatt tcaagggcaa ggccgaactg actgcagtca catccgccac cactgcctac 240

atggaactca gcagcctgac agatgaagac tctgcggtct attactgtac aagggctgat 300

tacgacggga ccccctttga ctactggggc caaggcacca ctctcacagt ctcctca 357

<210> 179
<211> 357
<212> DNA
<213> Artificial Sequence

<220>

<223> Synthetic polynucleotide

<400> 179
gaggttcaac tccagcagtc tgggactgtg ctggcaaggc ctggggcttc cgtgaagatg 60

tcctgcaagg cttctggcta cacctttacc aactactgga tgcactgggt aaaacagagg 120

cctggacagg gtctagaatg gattggtgct gtttatcctg gaaacagtga tactagttac 180

agccagaagt tcacgggcaa ggccaaactg actgcagtca catccgccag cactgcctac 240

atggacctca gcagcctgac aaatgaggac tctgcggtct attactgtac aagggctgat 300

tacgacggga ccccctttga ctactggggc caaggcacta ctctcacagt ctcctca 357

<210> 180
<211> 357
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic polynucleotide

<400> 180
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tcctgcaagg cttctggcta cacctttacc agctactgga tgcactgggt aaaacagagg 120

cctggacagg gtctagaatg gattggtgct atttatcctg gaaatagtga tactagctac 180

aaccagaagt tcaagggcaa ggccagactg actgcagtca catccgccag cactgcctac 240

atggagctca gcagcctgac aaatgaggac tctgcggtct attattgtac aagggctgat 300

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cctggacagg gtctagaatg gattggtgct atttatcctg gaaatagtga tactagctac 180

aaccagaagt tcaagggcaa ggccaaactg actgcagtca catccgccag cactgcctac 240

atggagctca gcagcctgac aaatgaggac tctgcggtct attactgtac aaggggtgat 300

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ctcacgttcg gtgctgggac caagctggag ctgaaacgg 339

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ctcacgttcg gtgctgggac caagctggag ctgaaacgg 339