

Description

Title of Invention: METHODS AND COMPOSITIONS FOR TREATING CARDIO-PULMONARY DISORDERS

[0001] CROSS-REFERENCE TO RELATED APPLICATION

[0002] This application claims priority to PCT Application PCT/CN2023/124511, filed on October 13, 2023, the content of which is incorporated by reference in its entirety for all purposes.

BACKGROUND

[0003] Coronary artery disease, the most common of the cardiovascular diseases, often leads to myocardial infarction or cardiac arrest, and is the leading cause of death in the United States. Thus, there is an urgent need for improved therapies to prevent, treat and/or ameliorate cardiac tissue damage resulting from myocardial infarction, cardiac arrest and other cardiovascular diseases and disorders. Coronary artery bypass grafting (CABG) has become the gold-standard treatment for coronary artery disease. While great progress has been made in surgical technique, which has improved survival rates, patients still suffer cardiac damage resulting from ischemia as the heart is isolated from systemic circulation, and reperfusion as circulation is restored (ischemia-reperfusion injury) . High-risk patients, with comorbidities such as hypertension, obesity and diabetes, are particularly vulnerable to this type of perioperative myocardial injury and infarction (PMI) . Despite the significant need to protect vulnerable patients from post-procedural cardiac damage and to treat cardiac damage resulting from myocardial infarction and other cardiovascular disorders or diseases, there are currently no approved therapies, with numerous compounds demonstrating lack of efficacy in clinical trials.

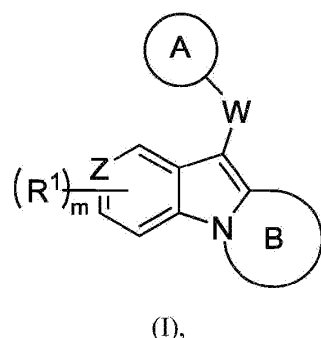
[0004] Additionally, the cardiovascular system has a complex and interwoven relationship the pulmonary system. Individuals with respiratory disorders often exhibit pulmonary vascular abnormalities. These abnormalities may include, but not limited to, fibrosis, pulmonary disease, sarcoidosis, neuromuscular or chest wall disorders, and disorders of ventilatory control. In particular, patients with an interstitial lung disease, such as idiopathic pulmonary fibrosis, have been shown to cause decreased quality of life and increased risk of death. Further, increased cardiac deaths have been observed in patients with systemic manifestations of lung disease. Accordingly, there remains a need to address the interconnected systems through small molecule therapy.

[0005] Hibernating mammals are a treasure trove of transient genetic resistance information whose state can be monitored with body temperature. They are able to completely prevent or reverse pathologies that closely resemble human diseases, including ischemia-reperfusion damage from heart attack. While in deep torpor, model hi-

bernators such as ground squirrels have a heart rate at 1% of normal, and their body temperature drops to 4°C. At least 25 times during winter hibernation, they rapidly rewarm to 37°C in just 2-3 hours; remarkably, heart rate increases 100-fold by the time core body temperature reaches just 7°C (MacCannell et al., 2018). This phenotype mimics an ischemia-reperfusion event similar to a heart attack or stroke, yet they are protected from the associated tissue damage. Studies show that when surgically simulating an ischemia-reperfusion event, winter squirrels are largely protected from damage compared to summer squirrels (reduced plasma levels of troponin I, myocardial apoptosis, and left ventricular contractile dysfunction) (Quinones et al., 2016). Thus, studying hibernating animals can help identify potential therapeutic compounds to protect against and treat cardiac tissue.

SUMMARY

[0006] The present disclosure includes a compound of Formula (I):



[0007] or a pharmaceutically acceptable salt thereof

[0008] wherein

[0009] Ring A is selected from the group consisting of 4-7 membered monocyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur, 7-10 membered bicyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring wherein Ring A may be substituted by one, two, or three R³;

[0010] Ring B is 5-7 membered heterocyclyl ring containing 1-3 ring heteroatoms including the ring nitrogen to which it is attached, where the additional ring heteroatoms may each independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein Ring B may be substituted by one or two R²;

[0011] W is selected from the group consisting of -C(O)-, -C(O)O-, -C(O)N(H)-, -C(O)OCH₂-, -C(O)N(H)CH₂-, and 5-membered heteroaryl ring having 1-3 ring heteroatoms;

[0012] Z is CR¹ or N;

- [0013] R^1 for each occurrence is independently selected from the group consisting of hydrogen, halogen, -OH, C_1 - C_3 alkyl (optionally substituted with one, two or three halogens), C_{3-7} cycloalkyl; and 3-7 membered heterocyclyl ring containing 1-3 nitrogen atoms;
- [0014] R^2 for each occurrence is independently selected from hydrogen, halogen, C_1 - C_3 alkyl (optionally substituted with one, two or three halogens), -C(O) - (C_1 - C_3 alkyl (optionally substituted with one, two or three halogens)), and -C(O) O- (C_1 - C_3 alkyl (optionally substituted with one, two or three halogens));
- [0015] R^3 is independently for each occurrence selected from the group consisting of halogen, C_1 - C_3 alkyl (optionally substituted with one, two or three halogens), C_{3-7} cycloalkyl, 4-6 membered monocyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur (optionally substituted with one, two or three halogens); and
- [0016] m is 1, 2, or 3.
- [0017] In certain aspects, described herein are methods of treating, ameliorating or preventing cardiovascular disease, a cardiovascular disorder, or cardiac injury comprising:
- [0018] administering to a subject in need thereof a therapeutically effective amount of a compound of the present disclosure. In certain embodiments, the cardiac injury is ischemia-reperfusion (I/R) injury. In certain embodiments, the ischemia-reperfusion injury is a result of myocardial infarction or ischemic stroke. In certain embodiments, the subject is at high risk of developing the disease or condition.
- [0019] In some embodiments, a proposed of compound disclosed herein has no known connection to cardiac I-R injury. While further study into the mechanism of action is required for verification, the presently disclosed compounds are potentially a first in class drug for a large number of clinical applications where there is damage to cardiac tissue.
- [0020] In certain embodiments, the cardiovascular disease or cardiovascular disorder, is selected from the group consisting of: arrhythmia, aorta disease, cardiomyopathy, congenital heart disease, coronary artery disease, deep vein thrombosis, heart valve disease, hypertension, Marfan syndrome, pericardial disease, pulmonary embolism, rheumatic heart disease, vascular disease, and drug induced cardiotoxicity. In certain embodiments, the subject is expected to undergo coronary artery bypass grafting (CABG) surgery. In certain embodiments, the subject has undergone CABG surgery.
- [0021] In certain embodiments, following administration of a compound of the present disclosure, the subject has reduced symptoms selected from the group consisting of arrhythmias, microvascular dysfunction, myocardial stunning and myocyte death. In

certain embodiments, wherein cardiomyocytes of the subject exhibit reduced reactive oxygen species production following administration of a compound of the present disclosure compared to cardiomyocytes prior to administration of a compound of the present disclosure or compared to control samples of cardiomyocytes. In certain embodiments, cardiomyocytes from the subject exhibit reduced release of Troponin I following administration of a compound of the present disclosure compared to cardiomyocytes or cardiac tissue prior to administration of a compound of the present disclosure or compared to control samples of cardiomyocytes or cardiac tissue from subjects that have not been administered a compound of the present disclosure. In certain embodiments, cardiomyocytes from the subject exhibit a cellular response selected from the group consisting of: reduced cell death, increased cell survival, decreased cell damage, and reduced oxidative stress, following administration of a compound of the present disclosure compared to cardiomyocytes prior to administration of a compound of the present disclosure or compared to control samples of cardiomyocytes, or cardiac tissue from subjects that have not been administered a compound of the present disclosure. In certain embodiments, administration of a compound of the present disclosure causes increased aortic velocity in the subject as compared to prior to administration of a compound of the present disclosure or subjects that have not been administered a compound of the present disclosure. In certain embodiments, administration of a compound of the present disclosure causes improved cardiac output in the subject as compared to prior to administration of a compound of the present disclosure or subjects that have not been administered a compound of the present disclosure. In certain embodiments, administration of a compound of the present disclosure causes a reduction of indicators of cardiovascular disease selected from the group consisting of: decreased collagen deposition, decreased fibroblast differentiation into myofibroblasts, increased or decreased expression of Smad Binding Elements (SBE), increased cardiac contractile force generation or contractility, increased or enhanced maintenance of calcium handling, decreased hypertrophy (cell size), and decreased expression of cardiac hypertrophic marker genes.

[0022] In certain aspects, described herein is a method of treating a subject that has undergone myocardial infarction or cardiac arrest, and is in need of treatment, comprising administering a sufficient amount of a compound of the present disclosure to the subject after the myocardial infarction or cardiac arrest. In certain embodiments, a compound of the present disclosure causes reduced infarct size in the heart tissue of the subject compared to a subject that was not administered a compound of the present disclosure after myocardial infarction or cardiac arrest. In certain embodiments, the a compound of the present disclosure causes reduced cardiac tissue wall thinning after the myocardial infarction or cardiac arrest. In certain embodiments, the a compound

of the present disclosure causes reduced granulation of cardiac tissue after the myocardial infarction or cardiac arrest. In certain embodiments, the a compound of the present disclosure causes reduced neovascularization in cardiac tissue after the myocardial infarction or cardiac arrest. In certain embodiments, a compound of the present disclosure causes reduced neovascularization in cardiac tissue after the myocardial infarction or cardiac arrest. In certain embodiments, a compound of the present disclosure is administered in more than one dose. In certain embodiments, the effective amount is less than 300 ug/kg. In certain embodiments, the effective amount is 0.3-30 ug/kg. In certain embodiments, a compound of the present disclosure is administered in combination with at least one additional therapeutic agent.

[0023] A method of preventing or minimizing cardiac injury in a subject at risk of myocardial infarction or cardiac arrest, comprising administering to the subject an effective amount of a compound of the present disclosure before the myocardial infarction or cardiac arrest, thereby preventing or ameliorating cardiovascular damage. In certain embodiments, the subject at risk of myocardial infarction or cardiac arrest has a cardiovascular disease or condition selected from the group consisting of: arrhythmia, aorta disease, cardiomyopathy, congenital heart disease, coronary artery disease, deep vein thrombosis, heart valve disease, hypertension, Marfan syndrome, pericardial disease, pulmonary embolism, rheumatic heart disease, and vascular disease. In certain embodiments, a compound of the present disclosure is administered in more than one dose.

[0024] In certain aspects, described herein is a method of reducing cardiac damage in a subject resulting from coronary artery bypass grafting (CABG) surgery, comprising administering to the subject, before, after and/or during the surgery, a therapeutically effective amount of a compound of the present disclosure. In certain aspects, described herein is a method of reducing cardiac damage in a subject resulting cardiopulmonary bypass surgery, comprising administering to the subject, before, after and/or during the surgery, a therapeutically effective amount of a compound of the present disclosure. In certain embodiments, a compound of the present disclosure is administered in more than one dose. In certain embodiments, a compound of the present disclosure is administered prior to surgery, following surgery or both prior to and following surgery.

[0025] In certain aspects, described herein is a method of treating a subject with cardiac tissue damage, and is in need of treatment, comprising administering a sufficient amount of a compound of the present disclosure to the subject, thereby ameliorating the cardiac tissue damage. In certain embodiments, a compound of the present disclosure causes reduced neovascularization in the damaged cardiac tissue. In certain embodiments, a compound of the present disclosure is administered in combination with at least one additional therapeutic agent. In certain embodiments, the additional

therapeutic agent is an agent selected from the group consisting of an agent that: reduces cholesterol, reduces low-density lipoprotein, reduces system blood pressure, and reduces blood glucose levels. In certain embodiments, the method increases overall survival rate of the subjects compared to subjects that have not been administered a compound of the present disclosure.

- [0026] In certain aspects, described herein are pharmaceutical compositions formulated for a route of administration selected from the group consisting of: intravenous administration, intracardiac administration, and administration within a cardioplegic solution, comprising: a compound of the present disclosure and a pharmaceutically acceptable excipient.

DETAILED DESCRIPTION

- [0027] Definitions
- [0028] “Treating” includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.
- [0029] The term “alkoxy” as used herein refers to a straight or branched alkyl group attached at oxygen (alkyl-O-). Exemplary alkoxy groups include, but are not limited to, alkoxy groups of 1-6 or 2-6 carbon atoms, referred to herein as C₁-C₆ alkoxy, and C₂-C₆ alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.
- [0030] The term “alkyl” as used herein refers to a saturated straight or branched hydrocarbon. Exemplary alkyl groups include, but are not limited to, straight or branched hydrocarbons of 1-6, 1-4, or 1-3 carbon atoms, referred to herein as C₁-C₆ alkyl, C₁-C₄ alkyl, and C₁-C₃ alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-butyl, 3-methyl-2-butyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2, 2-dimethyl-1-butyl, 3, 3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.
- [0031] The term “cyano” as used herein refers to the radical -CN.
- [0032] The terms “cycloalkyl” or a “carbocyclic group” as used herein refers to a saturated or partially unsaturated hydrocarbon group of, for example, 3-6, or 4-6 carbons, referred to herein as C₃-C₆ cycloalkyl or C₄-C₆ cycloalkyl, respectively. Exemplary cycloalkyl groups include, but are not limited to, cyclohexyl, cyclopentyl, cyclopentenyl, cyclobutyl or cyclopropyl.
- [0033] The term “cycloalkylalkyl” as used herein refers to a saturated straight or branched hydrocarbon substituted with a saturated or partially unsaturated hydrocarbon group of, for example, 3-6, or 4-6 carbons.
- [0034] The terms “halo” or “halogen” as used herein refer to F, Cl, Br, or I.

- [0035] The terms “heterocyclyl” or “heterocyclic group” are art-recognized and refer to saturated or partially unsaturated, 4-10 membered ring structures, including bridged or fused rings, and whose ring structures include one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Where possible, heterocyclyl rings may be linked to the adjacent radical through carbon or nitrogen. Examples of heterocyclyl groups include, but are not limited to, pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, oxetane, azetidine, tetrahydrofuran or dihydrofuran etc.
- [0036] The terms “hydroxy” and “hydroxyl” as used herein refers to the radical -OH.
- [0037] “Pharmaceutically or pharmacologically acceptable” include molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, and general safety and purity standards as required by FDA Office of Biologics standards.
- [0038] The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.
- [0039] The term “pharmaceutical composition” as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers.
- [0040] “Individual,” “patient,” or “subject” are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. The compounds of the invention can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, e.g., domestic animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, sheep, pigs, horses, and the like) and laboratory animals (e.g., rats, mice, guinea pigs, and the like). The mammal treated in the methods of the invention is desirably a mammal in which treatment of psychiatric disease or disorder is desired. “Modulation” includes antagonism (e.g., inhibition), agonism, partial antagonism and/or partial agonism.
- [0041] In the present specification, the term “therapeutically effective amount” means the amount of the subject compound that will elicit the biological or medical response of a tissue, system or animal, (e.g. mammal or human) that is being sought by the researcher, veterinarian, medical doctor or other clinician. The compounds of the invention are administered in therapeutically effective amounts to treat a disease. Alternatively, a therapeutically effective amount of a compound is the quantity required

to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in a decrease in symptoms of a psychiatric disorder.

[0042] The term "pharmaceutically acceptable salt (s)" as used herein refers to salts of acidic or basic groups that may be present in compounds used in the compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including, but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzene-sulfonate, p-toluenesulfonate and pamoate (i.e., 1, 1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts, particularly calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

[0043] The compounds of the disclosure may contain one or more chiral centers and, therefore, exist as stereoisomers. The term "stereoisomers" when used herein consist of all enantiomers or diastereomers. These compounds may be designated by the symbols "(+)", "(-)", "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[0044] The compounds of the disclosure may contain one or more double bonds and, therefore, exist as geometric isomers resulting from the arrangement of substituents around a carbon-carbon double bond. The symbol --- denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the "Z" or "E" configuration wherein the terms "Z" and "E" are used in accordance with IUPAC standards. Unless otherwise

specified, structures depicting double bonds encompass both the “E” and “Z” isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as “cis” or “trans,” where “cis” represents substituents on the same side of the double bond and “trans” represents substituents on opposite sides of the double bond.

- [0045] Compounds of the disclosure may contain a carbocyclic or heterocyclic ring and therefore, exist as geometric isomers resulting from the arrangement of substituents around the ring. The arrangement of substituents around a carbocyclic or heterocyclic ring are designated as being in the “Z” or “E” configuration wherein the terms “Z” and “E” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting carbocyclic or heterocyclic rings encompass both “Z” and “E” isomers. Substituents around a carbocyclic or heterocyclic rings may also be referred to as “cis” or “trans”, where the term “cis” represents substituents on the same side of the plane of the ring and the term “trans” represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated “cis/trans.”
- [0046] Individual enantiomers and diastereomers of compounds of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well known methods, such as chiral-phase liquid chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations, and may involve the use of chiral auxiliaries. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.
- [0047] The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. In one embodiment, the compound is amorphous. In one embodiment, the compound is a single

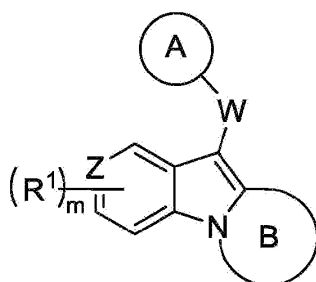
polymorph. In another embodiment, the compound is a mixture of polymorphs. In another embodiment, the compound is in a crystalline form.

[0048] The invention also embraces isotopically labeled compounds of the invention which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. For example, a compound of the invention may have one or more H atom replaced with deuterium.

[0049] Certain isotopically-labeled disclosed compounds (e.g., those labeled with ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^3H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in the examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0050] Compounds

[0051] The present disclosure includes a compound of Formula (I) :



(I),

[0052] or a pharmaceutically acceptable salt thereof

[0053] wherein

[0054] Ring A is selected from the group consisting of 4-7 membered monocyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur, 7-10 membered bicyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of

nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring wherein Ring A may be substituted by one, two, or three R^3 ;

[0055] Ring B is 5-7 membered heterocyclyl ring containing 1-3 ring heteroatoms including the ring nitrogen to which it is attached, where the additional ring heteroatoms may each independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein Ring B may be substituted by one or two R^2 ;

[0056] W is selected from the group consisting of $-C(O)-$, $-C(O)O-$, $-C(O)N(H)-$, $-C(O)OCH_2-$, $-C(O)N(H)CH_2-$, and 5-membered heteroaryl ring having 1-3 ring heteroatoms;

[0057] Z is CR^1 or N;

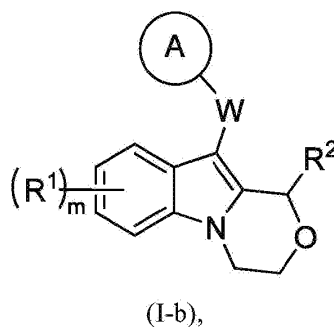
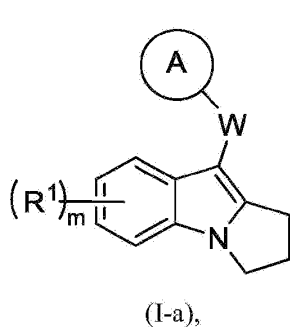
[0058] R^1 for each occurrence is independently selected from the group consisting of hydrogen, halogen, $-OH$, C_1-C_3 alkyl (optionally substituted with one, two or three halogens), C_{3-7} -cycloalkyl; and 3-7 membered heterocyclyl ring containing 1-3 nitrogen atoms;

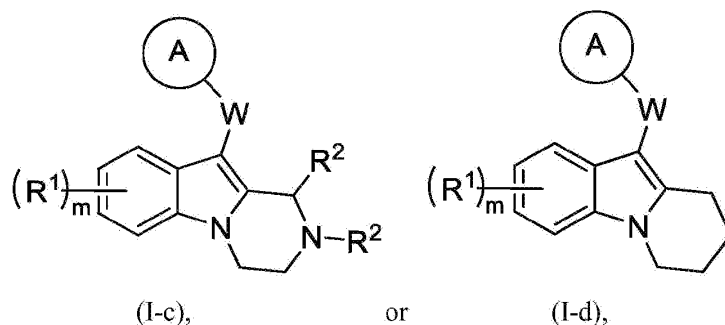
[0059] R^2 for each occurrence is independently selected from hydrogen, halogen, C_1-C_3 alkyl (optionally substituted with one, two or three halogens), $-C(O)-(C_1-C_3 \text{ alkyl (optionally substituted with one, two or three halogens)})$, and $-C(O)O-(C_1-C_3 \text{ alkyl (optionally substituted with one, two or three halogens)})$;

[0060] R^3 is independently for each occurrence selected from the group consisting of halogen, C_1-C_3 alkyl (optionally substituted with one, two or three halogens), C_{3-7} -cycloalkyl, 4-6 membered monocyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur (optionally substituted with one, two or three halogens); and

[0061] m is 1, 2, or 3.

[0062] The present disclosure includes a compound of Formula (I-a), (I-b), (I-c), or (I-d):

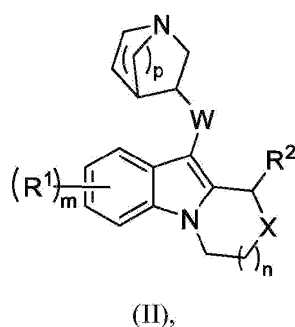




[0063] or a pharmaceutical acceptable salt thereof.

[0064] wherein R^1 , R^2 , A, W, and m are defined herein.

[0065] In some embodiments, the present disclosure includes a compound of Formula (II)



[0066] or a pharmaceutically acceptable salt thereof

[0067] wherein

[0068] X is selected from the group consisting of $-C(R'')_2$ -, $-O$ -, and $-N(H)$ -;

[0069] W is selected from the group consisting of $-C(O)O$ -, $-C(O)N(H)$ -, and a 5-membered heteroaryl ring having 1-3 ring heteroatoms;

[0070] R^1 for each occurrence is independently hydrogen or halogen

[0071] R^2 is hydrogen or C_1 - C_3 alkyl;

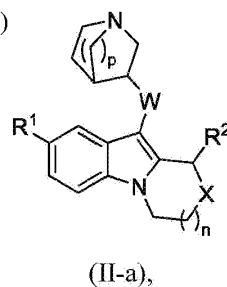
[0072] R'' for each occurrence is independently selected from hydrogen, halogen, and methyl;

[0073] m is 1, 2, or 3;

[0074] n is 0, 1, 2, or 3; and

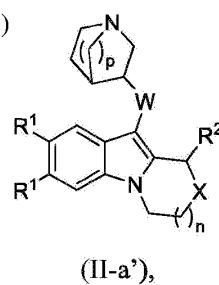
[0075] p is 0, 1, 2, 3.

[0076] In some embodiments, the compound is of Formula (II-a)



[0077] or a pharmaceutically acceptable salt thereof.

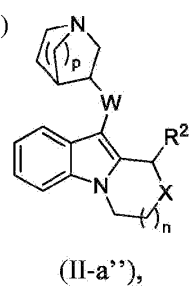
[0078] In some embodiments, the compound is of Formula (II-a')



[0079] or a pharmaceutically acceptable salt thereof,

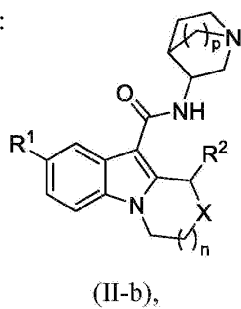
[0080] wherein each R¹ may be the same or different.

[0081] In some embodiments, the compound is of Formula (II-a'')



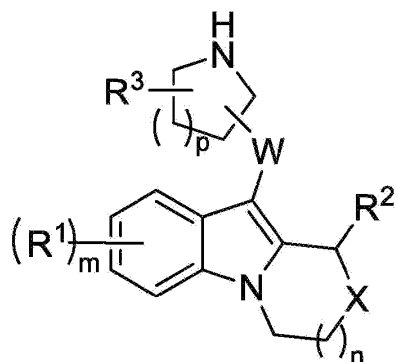
[0082] or a pharmaceutically acceptable salt thereof.

[0083] In some embodiments, the present disclosure includes a compound of Formula (II-b):



[0084] or a pharmaceutically acceptable salt thereof.

[0085] In some embodiments, the present disclosure includes a compound of Formula (III) :



(III),

[0086] or a pharmaceutically acceptable salt thereof

[0087] wherein

[0088] X is selected from the group consisting of $-C(R'')_2$ -, $-O$ -, and $-N(H)$ -;

[0089] W is selected from the group consisting of $-C(O)O$ -, $-C(O)N(H)$ -, and a 5-membered heteroaryl ring having 1-3 ring heteroatoms;

[0090] R^1 for each occurrence is independently hydrogen or halogen

[0091] R^2 is hydrogen or C_1 - C_3 alkyl;

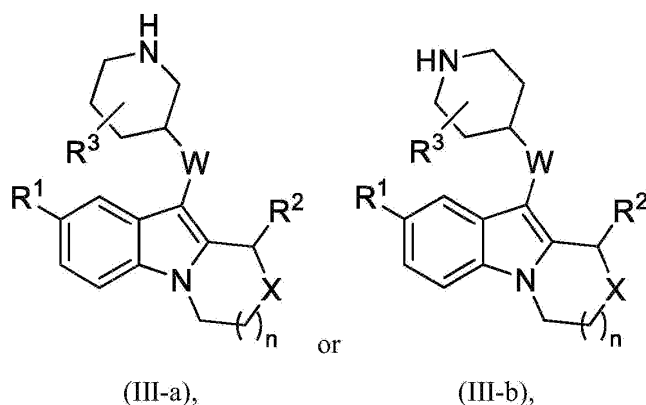
[0092] R^3 is selected from the group consisting of hydrogen, halogen, and C_1 - C_3 alkyl (optionally substituted with one, two or three halogens) ;

[0093] m is 1, 2, or 3;

[0094] n is 0, 1, 2, or 3; and

[0095] p is 0, 1, 2, 3.

[0096] In some embodiments, the present disclosure includes a compound of Formula (III-a) or Formula (III-b)

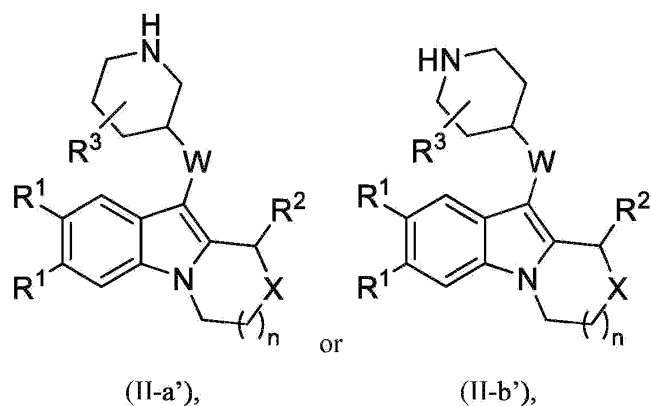


(III-a),

(III-b),

[0097] or a pharmaceutically acceptable salt thereof.

[0098] In some embodiments, the present disclosure includes a compound Formula (III-a') or Formula (III-b')

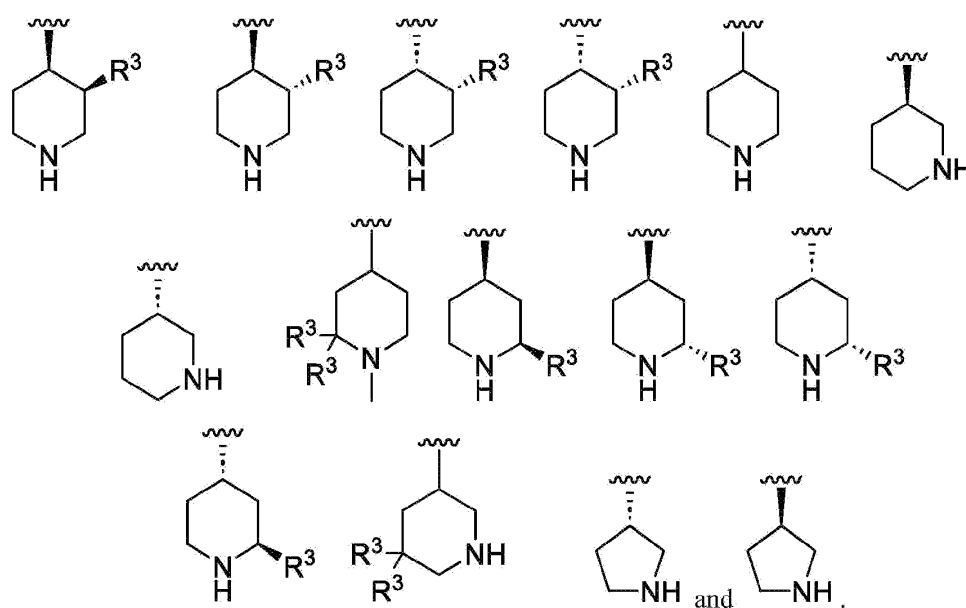


[0099] or a pharmaceutically acceptable salt thereof,

[0100] Ring A

[0101] In some embodiments, Ring A is selected from the group consisting of 4-7 membered monocyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur, 7-10 membered bicyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring wherein Ring A may be substituted by one, two, or three R³.

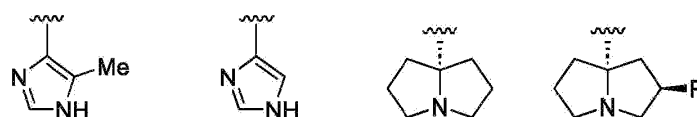
[0102] In some embodiments, Ring A is 4-7 membered monocyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein Ring A may be substituted by one, two, or three R³. In some embodiments, Ring A is selected from the group consisting of azetidiny, pyrrolidinyl, and piperidinyl, wherein Ring A may be substituted by one, two, or three R³. In some embodiments, Ring A is selected from the group consisting of

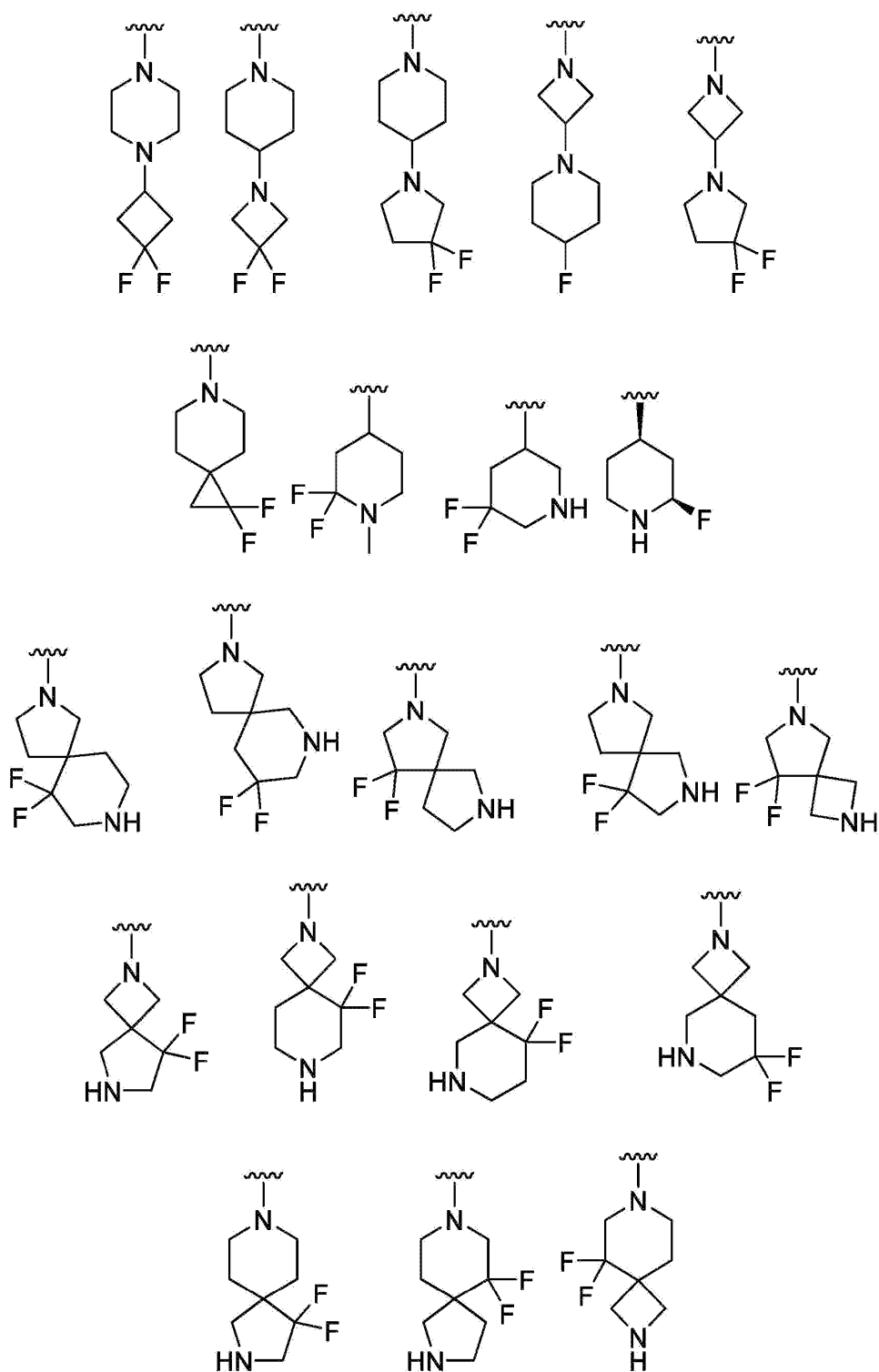


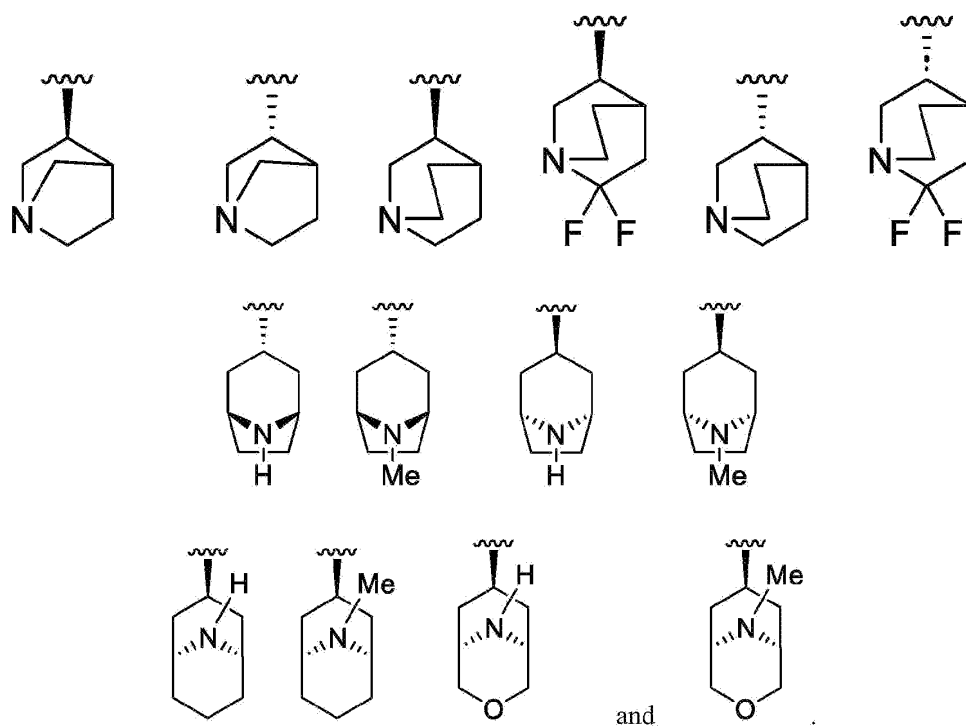
[0103] In some embodiments, Ring A is 7-10 membered bicyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein Ring A may be substituted by one, two, or three R³. In some embodiments, Ring A is selected from the group consisting of bicyclo [2.2.2] heterocyclyl ring, bicyclo [4.4.0] heterocyclyl ring, bicyclo [3.3.1] heterocyclyl, bicyclo [2.2.1] heterocyclyl ring, bicyclo [3.2.1] heterocyclyl ring, quinuclidinyl, and 3-oxa-9-azabicyclo [3.3.1] nonanyl.

[0104] In some embodiments, Ring A is a 5-6 membered heteroaryl ring, wherein Ring A may be substituted by one, two, or three R³.

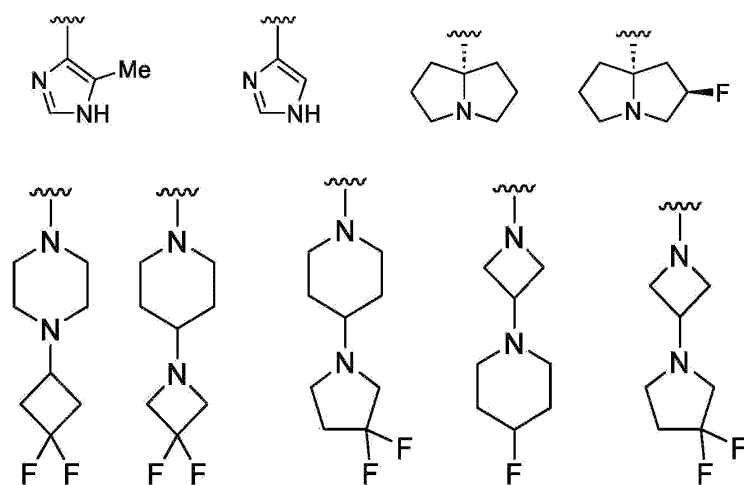
[0105] In some embodiments, wherein Ring A is selected from the group consisting of

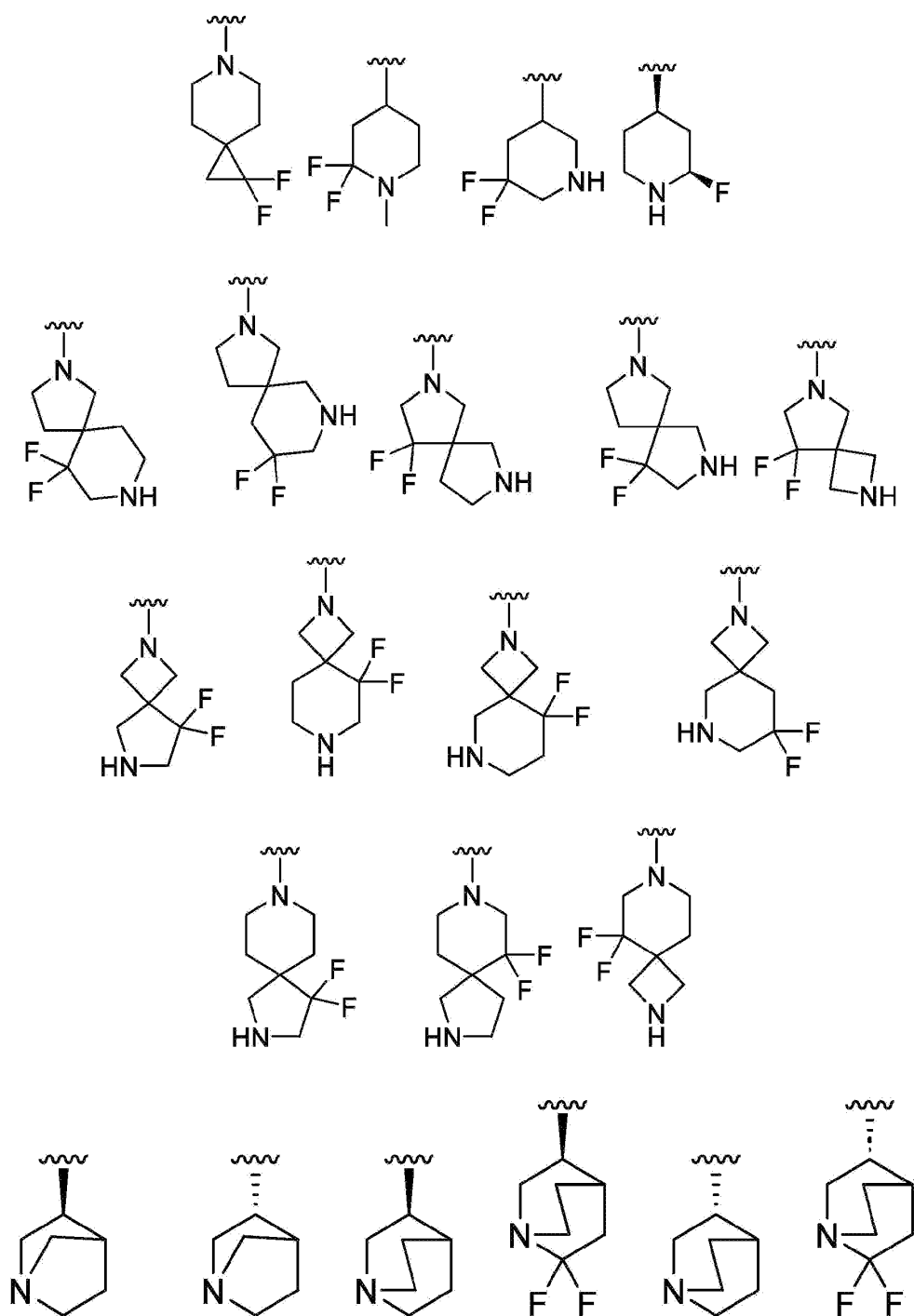


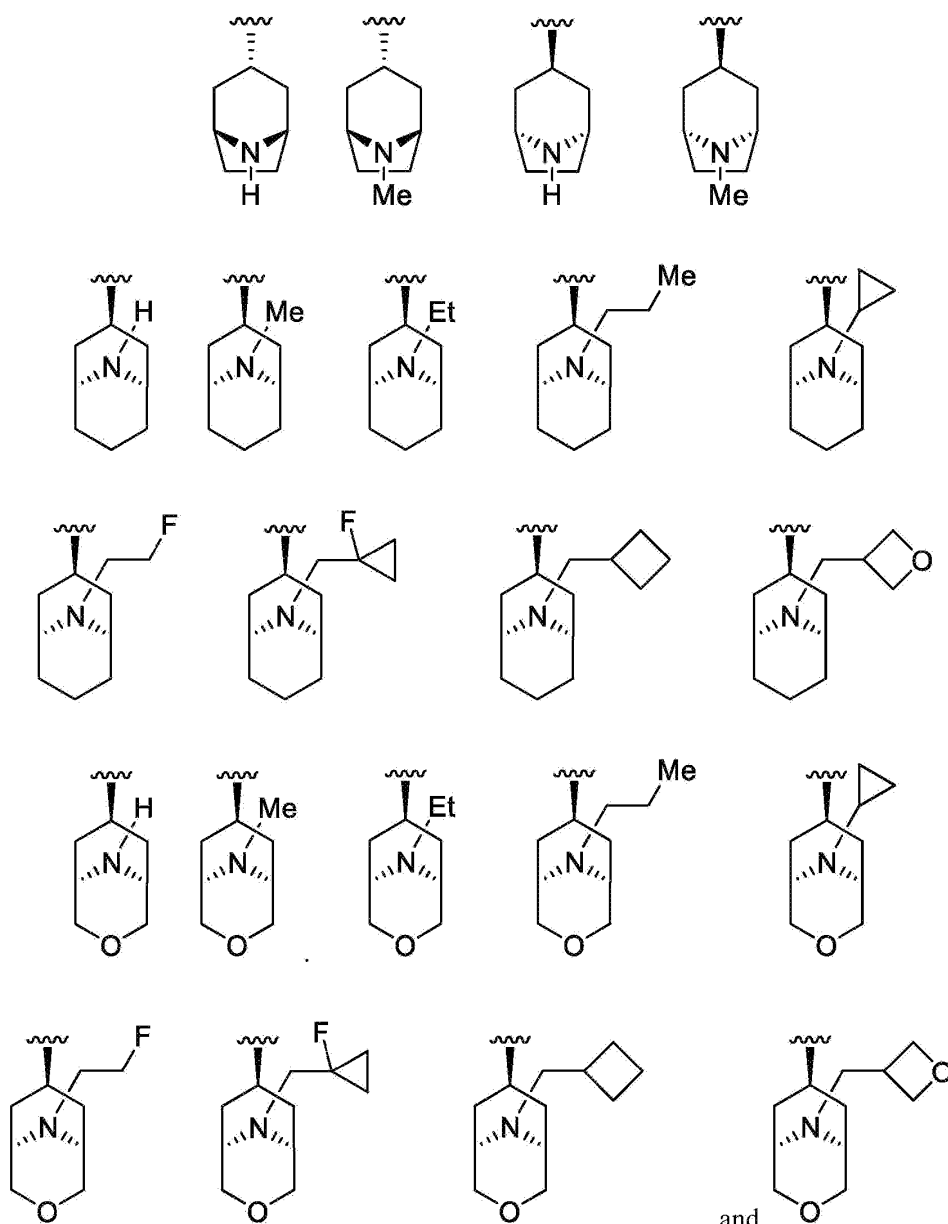




[0106] In some embodiments, wherein Ring A is selected from the group consisting of







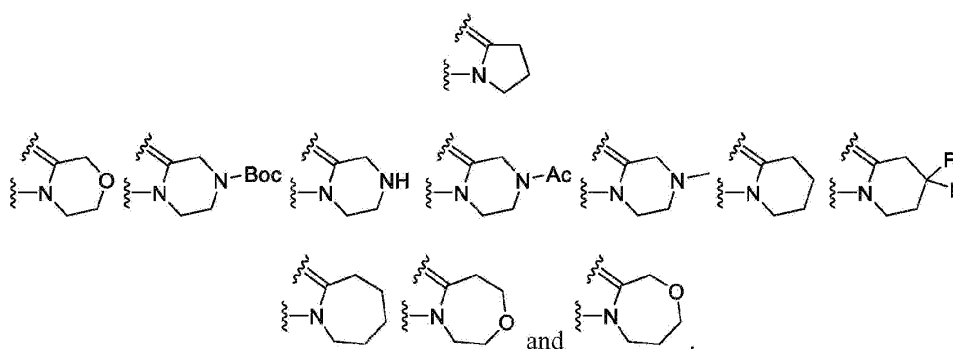
and

[0107] Ring B

[0108] In some embodiments, Ring B is 5-7 membered heterocyclyl ring containing 1-3 ring heteroatoms including the ring nitrogen to which it is attached, where the additional ring heteroatoms may each independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein Ring B may be substituted by one or two R^2 . In some embodiments, Ring B is 5-membered heterocyclyl ring containing 1-3 ring heteroatoms including the ring nitrogen to which it is attached, where the additional ring heteroatoms may each independently selected from the group consisting

of nitrogen, oxygen, and sulfur, wherein Ring B may be substituted by one or two R^2 . In some embodiments, Ring B is 6-membered heterocyclyl ring containing 1-3 ring heteroatoms including the ring nitrogen to which it is attached, where the additional ring heteroatoms may each independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein Ring B may be substituted by one or two R^2 . In some embodiments, Ring B is 7-membered heterocyclyl ring containing 1-3 ring heteroatoms including the ring nitrogen to which it is attached, where the additional ring heteroatoms may each independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein Ring B may be substituted by one or two R^2 .

[0109] In some embodiments Ring B is selected from the group consisting of



[0110] In some embodiments, Ring B is 6-membered heterocyclyl ring containing 1-3 ring heteroatoms including the ring nitrogen to which it is attached, where the additional ring heteroatoms may each independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein Ring B may be substituted by one or two R^2 . In some embodiments, Ring B is 6-membered heterocyclyl ring containing 2 ring heteroatoms including the ring nitrogen to which it is attached, where the additional ring heteroatoms is nitrogen, wherein Ring B may be substituted by one or two R^2 .

[0111] In some embodiments, Ring B is 7-membered heterocyclyl ring containing 1-3 ring heteroatoms including the ring nitrogen to which it is attached, where the additional ring heteroatoms may each independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein Ring B may be substituted by one or two R^2 .

[0112] W

[0113] In some embodiments, W is selected from the group consisting of $-C(O)-$, $-C(O)O-$, $-C(O)N(H)-$, $-C(O)OCH_2-$, $-C(O)N(H)CH_2-$, and 5-membered heteroaryl ring having 1-3 ring heteroatoms. In some embodiments, W is $-C(O)-$. In some embodiments, W is $-C(O)O-$. In some embodiments, W is $-C(O)N(H)-$. In some embodiments, W is $-C(O)OCH_2-$. In some embodiments, W is $-C(O)N(H)CH_2-$. In some embodiments, W is 5-membered heteroaryl ring having 1-3 ring heteroatoms. In some embodiments, W is selected from the group consisting of pyrrolyl, pyrazolyl,

imidazolyl, triazolyl, furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, and thiadiazolyl. In some embodiments, W is oxadiazole.

[0114] R¹

[0115] In some embodiments, R¹ for each occurrence is independently selected from the group consisting of hydrogen, halogen, -OH, C₁-C₃ alkyl (optionally substituted with one, two or three halogens), C₃₋₇cycloalkyl; and 3-7 membered heterocyclyl ring containing 1-3 nitrogen atoms. In some embodiments R¹ is hydrogen or halogen. In some embodiments, R¹ is C₁-C₃ alkyl. In some embodiments, R¹ is methyl. In some embodiments, R¹ is trifluoromethyl. In some embodiments, R¹ is fluoro.

[0116] R²

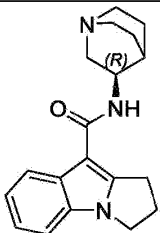
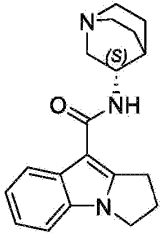
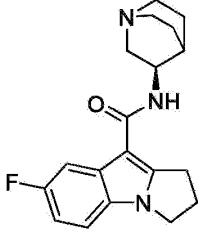
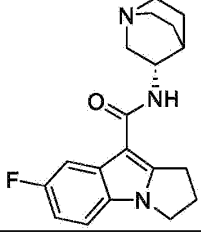
[0117] In some embodiments, R² for each occurrence is independently selected from hydrogen, halogen, C₁-C₃ alkyl (optionally substituted with one, two or three halogens), -C(O)-(C₁-C₃ alkyl (optionally substituted with one, two or three halogens)), and -C(O)O-(C₁-C₃ alkyl (optionally substituted with one, two or three halogens)). In some embodiments, R² is C₁-C₃ alkyl. In some embodiments, R² is methyl. In some embodiments, R² is hydrogen.

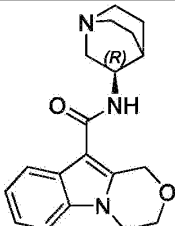
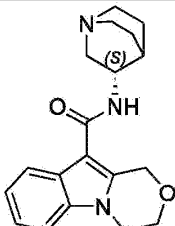
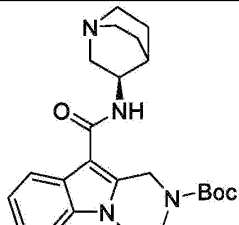
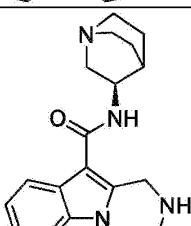
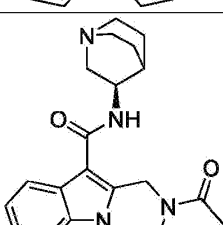
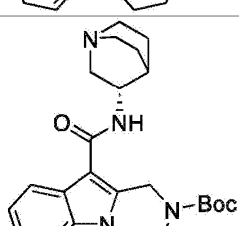
[0118] R³

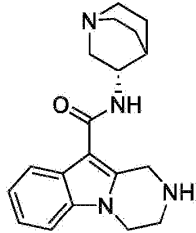
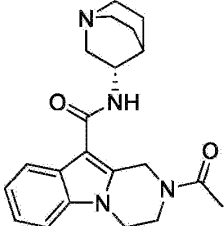
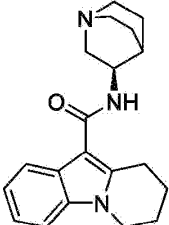
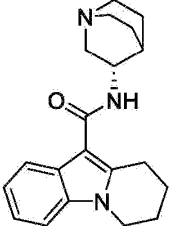
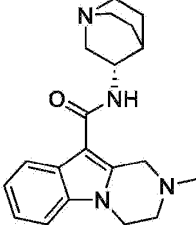
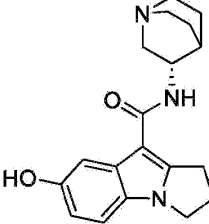
[0119] In some embodiments, R³ is independently for each occurrence selected from the group consisting of halogen, C₁-C₃ alkyl (optionally substituted with one, two or three halogens), C₃₋₇cycloalkyl, 4-6 membered monocyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur (optionally substituted with one, two or three halogens). In some embodiments, R³ is halogen. In some embodiments, R³ is C₁-C₃ alkyl (optionally substituted with one, two or three halogens). In some embodiments, R³ is C₃₋₇cycloalkyl. In some embodiments, R³ is 4-6 membered monocyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur (optionally substituted with one, two or three halogens).

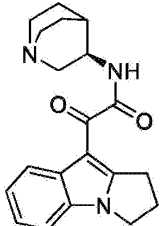
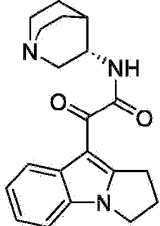
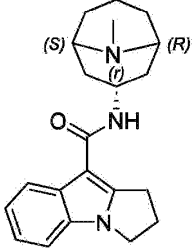
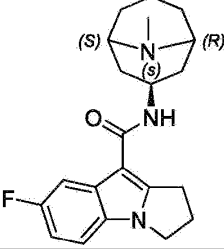
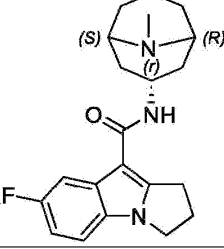
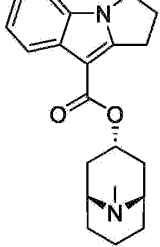
[0120] In some embodiments, the present disclosure includes a compound of Table 1 or a pharmaceutically acceptable salt thereof.

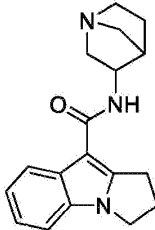
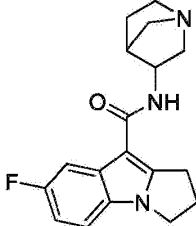
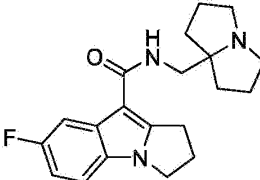
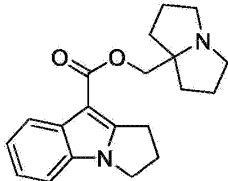
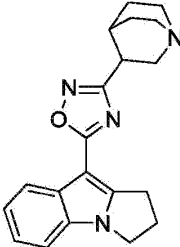
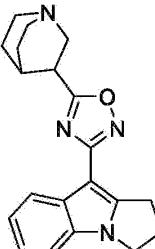
[0121] Table 1

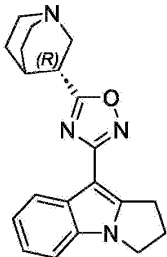
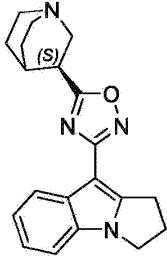
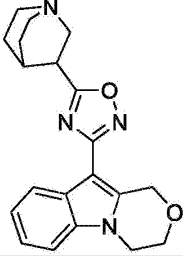
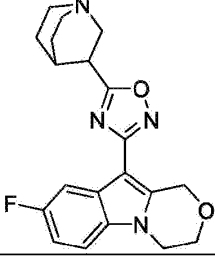
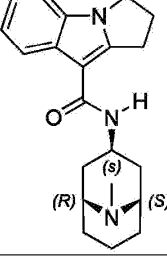
Compound No.	Structure
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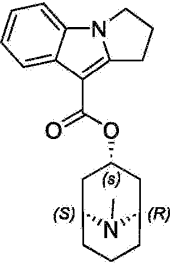
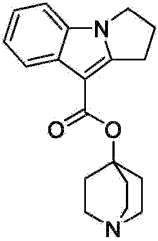
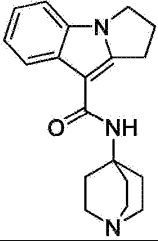
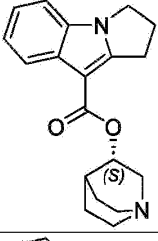
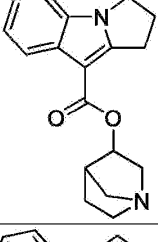
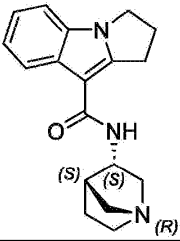
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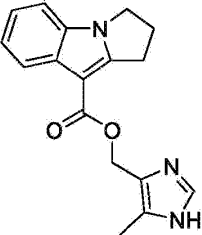
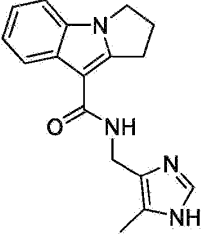
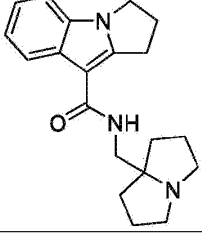
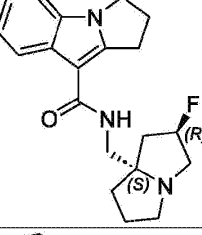
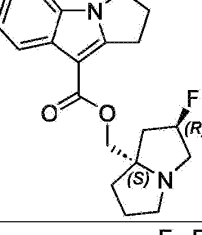
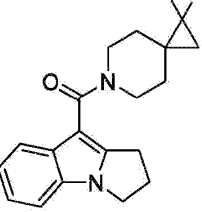
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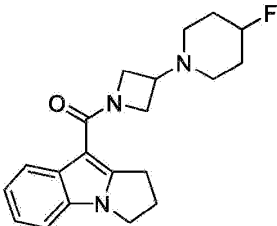
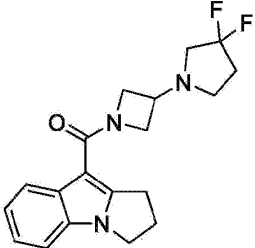
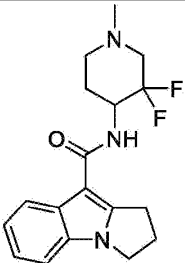
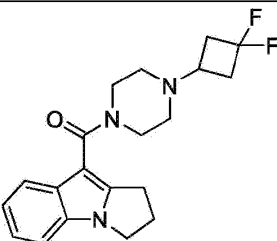
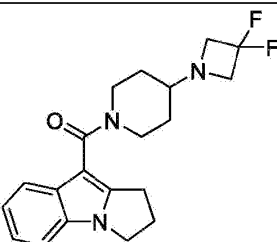
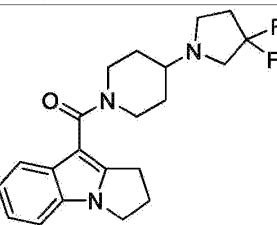
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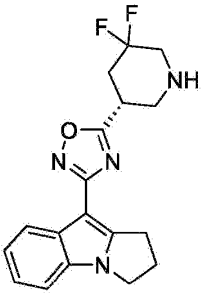
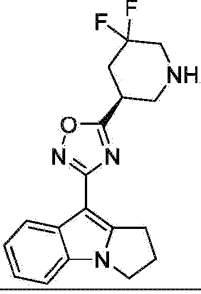
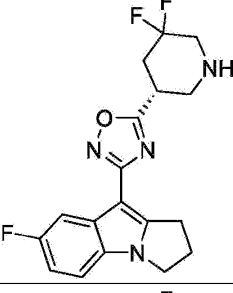
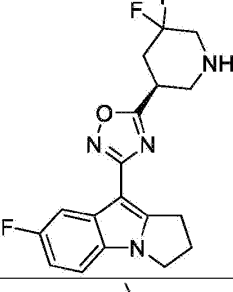
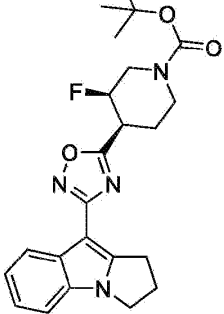
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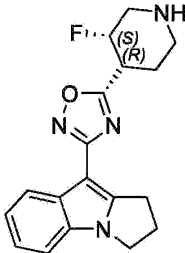
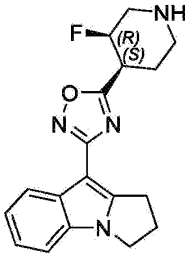
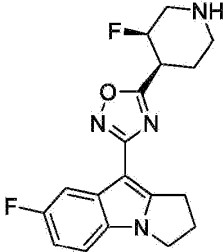
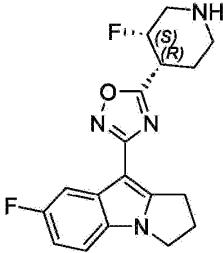
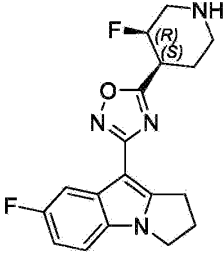
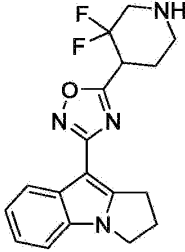
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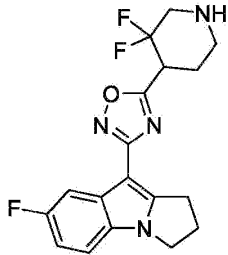
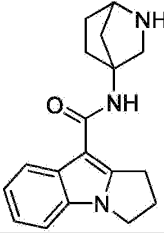
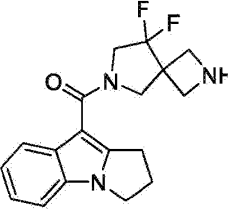
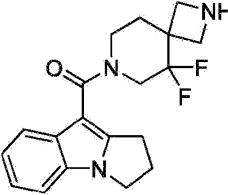
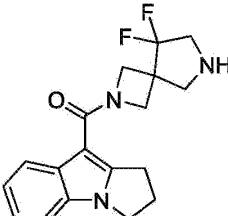
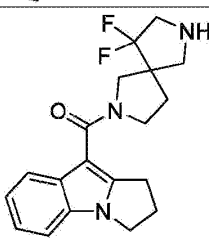
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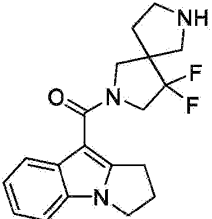
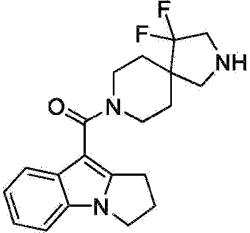
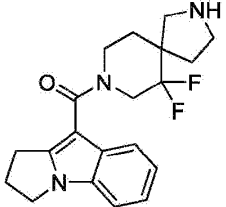
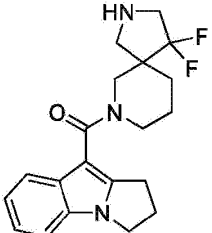
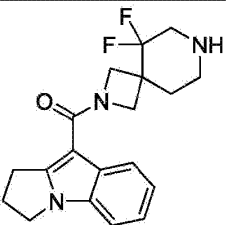
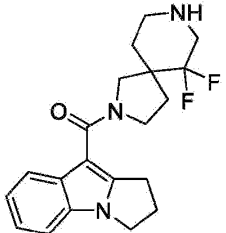
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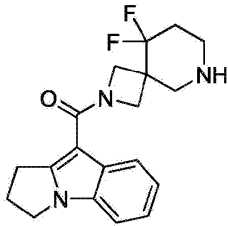
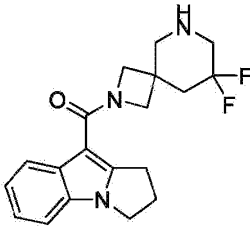
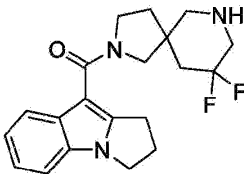
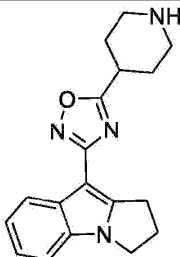
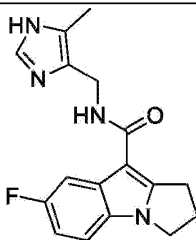
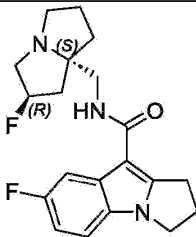
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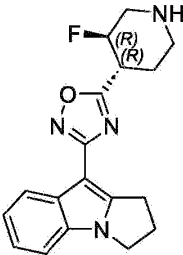
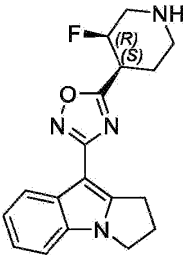
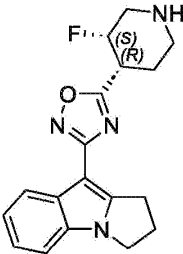
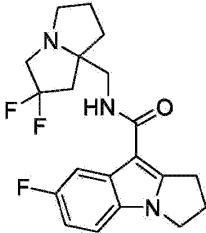
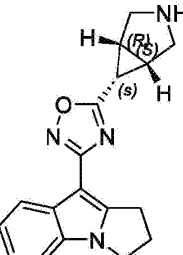
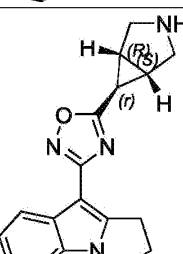
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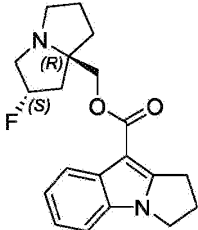
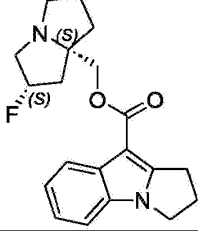
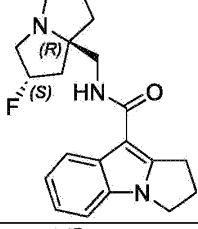
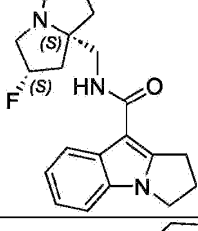
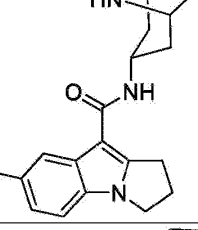
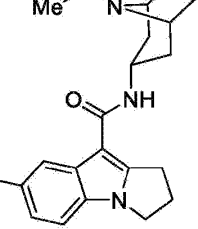
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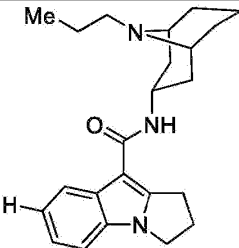
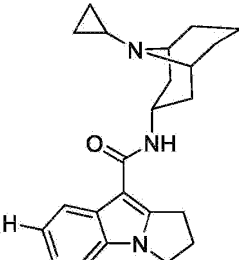
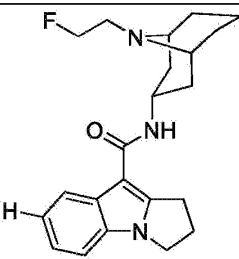
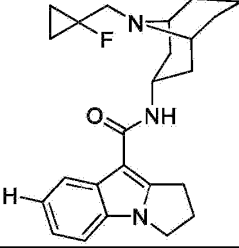
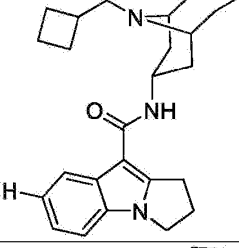
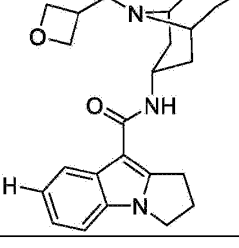
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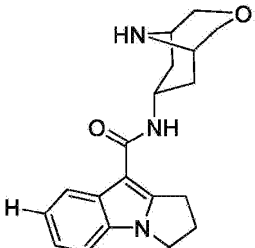
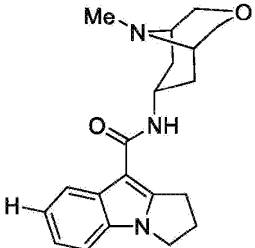
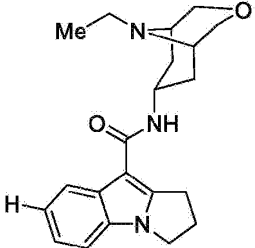
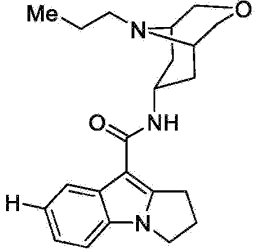
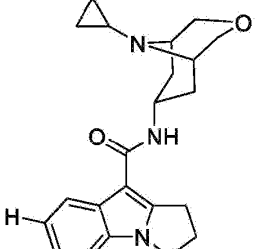
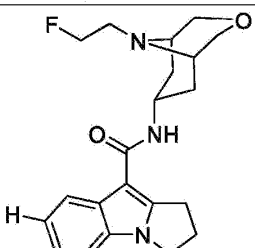
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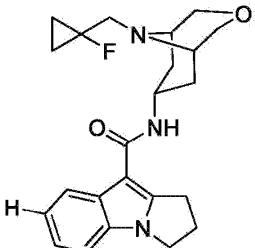
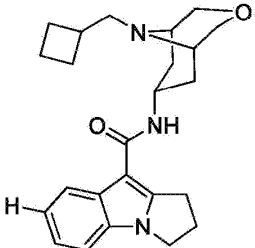
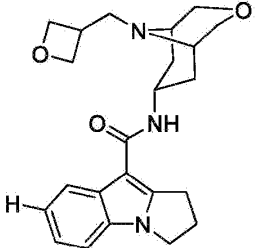
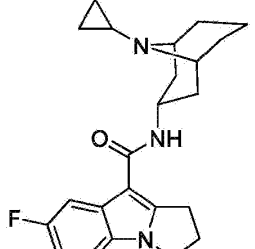
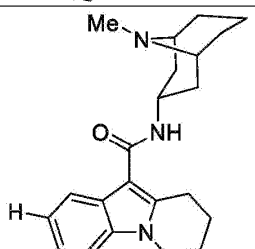
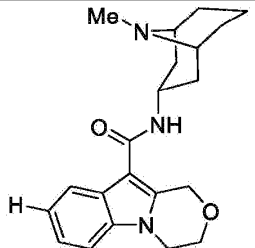
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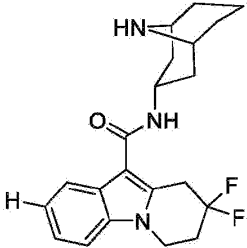
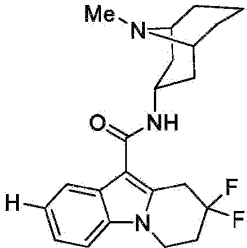
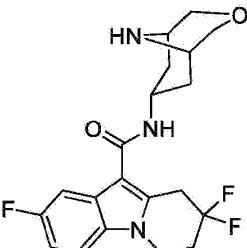
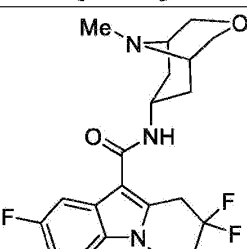
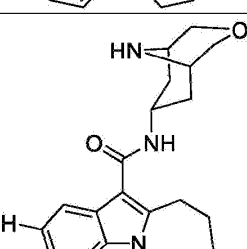
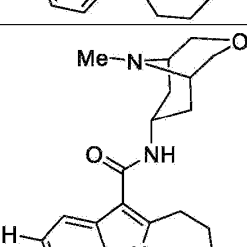
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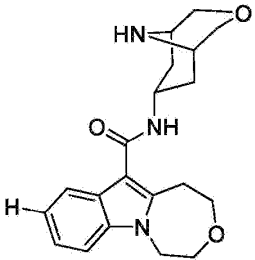
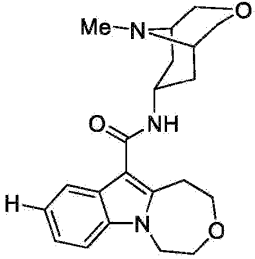
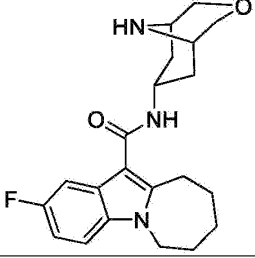
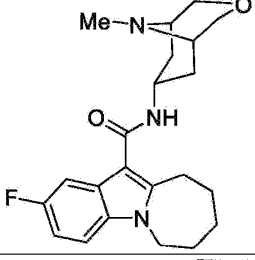
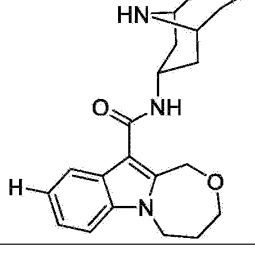
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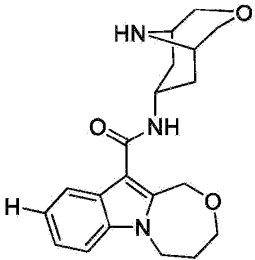
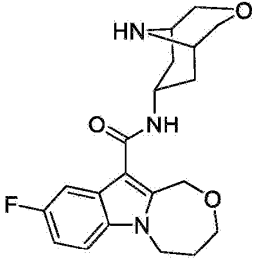
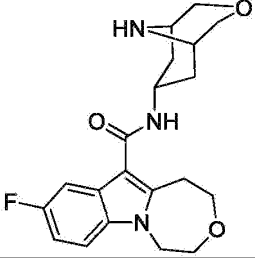
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[0122] Diseases, Disorders and Injuries

[0123] Cardiovascular diseases, cardiovascular disorders, and/or cardiac injury are ameliorated, prevented and/or treated by the methods described herein. In certain embodiments, the cardiovascular disease or cardiovascular disorder is selected from the group consisting of: arrhythmia, aorta disease, cardiomyopathy, congenital heart disease, coronary artery disease, deep vein thrombosis, heart valve disease, hypertension, ischemic stroke, Marfan syndrome, pericardial disease, pulmonary embolism, rheumatic heart disease, vascular disease, and drug induced cardiotoxicity. In certain embodiments, cardiac tissue damage resulting from a cardiovascular surgery or procedure (e.g., coronary artery bypass grafting (CABG) surgery or cardiopulmonary bypass surgery) are ameliorated, prevented and/or treated by the methods described herein.

[0124] In certain embodiments, cardiac injury or cardiac tissue damage resulting from ischemia-reperfusion injury are ameliorated, prevented and/or treated by the methods described herein. In certain embodiments, cardiac injuries or cardiac tissue damage resulting from one or more events including, but not limited to, myocardial infarction, cardiac arrest or ischemic stroke are ameliorated, prevented and/or treated by the methods described herein.

- [0125] In certain embodiments, cardiac injury or cardiac tissue damage resulting from cardiotoxicity or cardiomyopathy are ameliorated, prevented and/or treated by the methods described herein. In certain embodiments, the cardiotoxicity is caused by a chemical or toxin (e.g., chemotherapy such as anthracyclines, adverse effects of heavy metals, abuse of stimulants such as cocaine, alcohol abuse and incorrectly administered bupivacaine) . In certain embodiments, the cardiotoxicity is caused by infection (e.g., viral or bacterial) , by starvation (e.g., anorexia nervosa) , diabetes, high blood pressure, thyroid disease (e.g., hypothyroidism) , Thiamine or Vitamin B deficiency, and genetic defects which cause cardiomyopathy. In certain embodiments, a compound of the present disclosure is administered to a subject when one or more symptoms of cardiotoxicity or cardiomyopathy are present in the subject, including, but not limited to, an enlarged heart muscle, abnormal heart or lung sounds, swelling in hands, unusual weight gain, fatigue, chronic cough, shortness of breath and/or congestive heart failure.
- [0126] In certain embodiments, a disease or disorder ameliorated, prevented and/or treated by the methods described herein is selected from the group consisting of: pulmonary artery hypertension, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis (e.g., idiopathic pulmonary fibrosis, cystic fibrosis) , a coronavirus infection (e.g., SARS-COV2 infection) , acute lung injury, respiratory distress syndrome, respiratory failure, small cell lung cancer, interstitial lung disease, chronic obstructive pulmonary disease, and chronic thromboembolic pulmonary hypertension. In some embodiments, a disease or disorder ameliorated, prevented and/or treated by the methods described herein is chronic thromboembolic pulmonary hypertension.
- [0127] In certain embodiments, a disease or disorder ameliorated, prevented and/or treated by the methods described herein is fibrosis. Fibrosis in the lung is a process that occurs in the interstitium. Pulmonary fibrosis can be localized, segmental, lobar, or affect the entirety of the lung (s) . In some embodiments, a disease is pulmonary fibrosis. In some embodiments, a condition associated with pulmonary fibrosis that is ameliorated, prevented and/or treated by the methods described herein is selected from the group consisting of significant acute insult to the lungs, adult respiratory distress syndrome from a significant pulmonary infection, post COVID fibrosis (especially in patients admitted to ICU and needing intubation/ventilation) , and diffuse alveolar damage from any source.
- [0128] In some embodiments, a condition associated with pulmonary fibrosis that is ameliorated, prevented and/or treated by the methods described herein is a condition as a result of inhaled substances. In some embodiments, an inhaled substance is coal/silica (progressive massive fibrosis) or asbestos (asbestos-related pulmonary fibrosis) . In some embodiments, pulmonary fibrosis is radiation-induced pulmonary fibrosis. In

some embodiments, pulmonary fibrosis is congenital. In some embodiments congenital fibrosis is cystic fibrosis or Hermansky-Pudlak syndrome. In some embodiments, pulmonary fibrosis is an autoimmune condition. In some embodiments, pulmonary fibrosis is a connective tissue disorder. In some embodiments, pulmonary fibrosis is a granulomatous condition. In some embodiments, a granulomatous condition is selected from the group consisting of sarcoidosis, tuberculosis and granulomatosis. In some embodiments, pulmonary fibrosis is airway-centered interstitial fibrosis. In some embodiments, pulmonary fibrosis is chronic. In some embodiments, fibrosis is chronic hypersensitivity pneumonitis or chronic eosinophilic pneumonia. In some embodiments, pulmonary fibrosis is polymyalgia rheumatica. In some embodiments, pulmonary fibrosis is a drug-induced lung disease. In some embodiments, pulmonary fibrosis includes emphysema. In some embodiments, pulmonary fibrosis includes one or more atelectasis-related pulmonary conditions.

[0129] In some embodiments, a disease or disorder ameliorated, prevented and/or treated by the methods described herein is an autoimmune disease with pulmonary involvement. In some embodiments, an autoimmune disease with pulmonary involvement is selected from the group consisting of systemic sclerosis, sjogrens syndrome, sarcoidosis, and amyloidosis.

[0130] In some embodiments, a disease or disorder ameliorated, prevented and/or treated by the methods described herein is a B-Cell related pulmonary lung disorder.

[0131] Methods of Treating, Ameliorating or Preventing Cardiac Injury

[0132] Described herein are methods of ameliorating, preventing and/or treating cardiovascular diseases, cardiovascular disorders, and/or cardiac injuries comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the present disclosure. In certain embodiments, described herein are methods of treating a subject that has undergone myocardial infarction or cardiac arrest, and is in need of treatment, comprising administering a sufficient amount of a compound of the present disclosure to the subject after the myocardial infarction or cardiac arrest. In certain embodiments, described herein are methods of preventing or minimizing cardiac injury in a subject at risk of myocardial infarction or cardiac arrest, comprising administering to the subject an effective amount of a compound of the present disclosure before the myocardial infarction or cardiac arrest, thereby preventing or ameliorating cardiovascular damage. In certain embodiments, described herein are methods of reducing cardiac damage in a subject resulting from coronary artery bypass grafting (CABG) surgery, comprising administering to the subject, before, after and/or during the surgery, a therapeutically effective amount of a compound of the present disclosure. In certain embodiments, a compound of the present disclosure is administered prior to CABG surgery, following CABG surgery or

both prior to and following CABG surgery. In certain embodiments, described herein are methods of reducing cardiac damage in a subject resulting from cardiopulmonary bypass comprising administering to the subject a therapeutically effective amount of a compound of the present disclosure before, after and/or during the surgery.

- [0133] In certain aspects, described herein are methods of preventing cardiac injury in a subject at risk of myocardial infarction or cardiac arrest, comprising: administering to the subject an effective amount of a compound of the present disclosure before the myocardial infarction or cardiac arrest, thereby preventing or ameliorating cardiovascular damage. In certain embodiments, the subject at risk of myocardial infarction or cardiac arrest has a cardiovascular disease or condition selected from the group consisting of: arrhythmia, aorta disease, cardiomyopathy, congenital heart disease, coronary artery disease, deep vein thrombosis, heart valve disease, hypertension, Marfan syndrome, pericardial disease, pulmonary embolism, rheumatic heart disease, and vascular disease. In certain embodiments, the subject has a disorder or disease associated with increased risk of cardiac disease such as, but not limited to, hypertension, elevated cholesterol, obesity, diabetes, substance abuse, and tobacco use. In certain embodiments, the subject has a family history of heart disease and/or has a higher risk of developing a cardiac disease due to factors such as, but not limited to, age, race, gender, diet, substance abuse, physical activity, stress and/or depression.
- [0134] In certain embodiments of the methods described herein, a compound of the present disclosure is administered to the subject by a route selected from the group consisting of: intravenous administration, intracardiac administration, and administration within a cardioplegic solution.
- [0135] Unless stated otherwise, the term “subject” includes any mammalian animal, including but not limited to both humans and non-humans and include, but is not limited to humans, non-human primates, canines, felines, murines, bovines, equines, and porcines.
- [0136] Described herein are methods of ameliorating, preventing and/or treating pulmonary diseases, pulmonary disorders, and/or pulmonary injuries comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the present disclosure.
- [0137] In some embodiments, pulmonary disease or disorder is selected from the group consisting of pulmonary artery hypertension PAH, asthma, chronic obstructive pulmonary disease COPD, pulmonary fibrosis (e.g., idiopathic pulmonary fibrosis IPF, cystic fibrosis), a coronavirus infection (e.g., SARS-COV2 infection), acute lung injury, respiratory distress syndrome, respiratory failure, small cell lung cancer, interstitial lung disease, chronic obstructive pulmonary disease, and chronic thromboembolic pulmonary hypertension.

- [0138] In some embodiments, a pulmonary disease or disorder is an obstructive lung disease or a restrictive lung disease. In some embodiments, a pulmonary disease or disorder is selected from the group consisting of asthma, bronchiolitis obliterans organizing pneumonia (BOOP) , chronic obstructive pulmonary disease (COPD) , emphysema, pulmonary fibrosis, and sarcoidosis. In some embodiments, a pulmonary disease or disorder is selected from the group consisting of acute chest syndrome, acute respiratory distress syndrome, alpha-1 antitrypsin deficiency, asbestosis, aspergillosis, asthma, bronchiectasis, bronchiolitis, bronchiolitis obliterans, bronchitis, bronchopulmonary dysplasia, chronic cough, chronic obstructive pulmonary disease (COPD) , coccidioidomycosis, cryptogenic organizing pneumonia, cystic fibrosis, e-cigarette, or vaping product, use associated lung injury (EVALI) , emphysema, eosinophilic granulomatosis with polyangiitis (EGPA) , common cold, hantavirus pulmonary syndrome (HPS) , histoplasmosis, human metapneumovirus (hMPV) , hypersensitivity pneumonitis, idiopathic pulmonary fibrosis (IPF) , infectious lung diseases, influenza, interstitial lung disease (ILD) , Legionnaires' disease, lung cancer, LAM, MAC lung disease, mesothelioma, NTM lung disease, an occupational lung disease, pertussis, pneumonia, pneumothorax, primary ciliary dyskinesia (PCD) , pulmonary arterial hypertension (PAH) , pulmonary embolism, pulmonary fibrosis, pulmonary hypertension, respiratory syncytial virus, sarcoidosis, silicosis, sleep apnea, coronavirus related disease, and tuberculosis.
- [0139] In some embodiments a pulmonary disorder is bronchitis. In some embodiments, bronchitis is acute bronchitis or chronic bronchitis.
- [0140] In some embodiments, a pulmonary disease or disorder is selected from the group consisting of aspergillosis, asthma, bronchiectasis, bronchitis, chronic cough, chronic obstructive pulmonary disease (COPD) , common cold, croup, cystic fibrosis, hantavirus pulmonary syndrome (HPS) , idiopathic pulmonary fibrosis (IPF) , influenza, lung cancer, LAM, MAC lung disease, pertussis, pleurisy, pneumonia, pulmonary embolism, pulmonary hypertension, respiratory syncytial virus, sarcoidosis, sleep apnea, spirometry, sudden infant death syndrome, tobacco endgame, and tuberculosis.
- [0141] Therapeutic Improvement Resulting From a compound of the present disclosure
Treatment
- [0142] In certain embodiments, following administration of one or more doses of a compound of the present disclosure by the methods described herein, the subject has reduced symptoms cardiac injury including, but not limited to, arrhythmias, microvascular dysfunction, myocardial stunning and myocyte death. In certain embodiments, cardiomyocytes of the subject exhibit reduced reactive oxygen species production following administration of a compound of the present disclosure compared

to cardiomyocytes prior to administration of a compound of the present disclosure or compared to control samples of cardiomyocytes. In certain embodiments, the cardiomyocytes of the subject exhibit reduced release of Troponin I following administration of a compound of the present disclosure compared to cardiomyocytes or cardiac tissue prior to administration of a compound of the present disclosure or compared to control samples of cardiomyocytes or cardiac tissue from subjects that have not been administered a compound of the present disclosure. In certain embodiments, the cardiomyocytes of the subject exhibit a cellular response selected from the group consisting of: reduced cell death, increased cell survival, decreased cell damage, and reduced oxidative stress, following administration of a compound of the present disclosure compared to cardiomyocytes prior to administration of a compound of the present disclosure or compared to control samples of cardiomyocytes, or cardiac tissue from subjects that have not been administered a compound of the present disclosure. Any method known in the art to detect the described cellular responses either in vivo or ex vivo can be used.

- [0143] In certain embodiments, the methods described herein cause increased aortic velocity in the subject as compared to prior to administration of a compound of the present disclosure or subjects that have not been administered a compound of the present disclosure. In certain embodiments, the methods described herein cause improved cardiac output in the subject as compared to prior to administration of a compound of the present disclosure or subjects that have not been administered a compound of the present disclosure. Any method known in the art to detect aspects of cardiac functioning (e.g., aortic velocity or cardiac output) can be used. In certain embodiments, administration of a compound of the present disclosure according to methods described herein causes improvement in cardiac functioning as demonstrated by modifications in parameters such as, but not limited to, fractional shortening, left ventricle ejection fraction (LVEF) , left ventricle end diastolic dimensions (LVEDD) , left ventricle end systolic dimensions (LVESD) , left ventricle end systolic volume (LVESV) , left ventricle end diastolic volume (LVEDV) , and stroke volume.
- [0144] In certain embodiments, the methods described herein cause a reduction of indicators of cardiovascular disease and/or injury selected from the group consisting of: decreased collagen deposition, decreased fibroblast differentiation into myofibroblasts, increased or decreased expression of Smad Binding Elements (SBE) , increased cardiac contractile force generation or contractility, increased or enhanced maintenance of calcium handling, decreased hypertrophy (cell size) , decreased expression of cardiac hypertrophic marker genes, decreased apoptosis, decreased markers of angiogenesis, and decreased troponin I.

- [0145] In certain embodiments, the methods described herein cause reduced cardiac tissue wall thinning (e.g., anterior wall thickening or posterior wall thickening) after myocardial infarction or cardiac arrest. In certain embodiments, the methods described herein cause reduced granulation of cardiac tissue after myocardial infarction or cardiac arrest. In certain embodiments, the methods described herein cause improved organization of the cardiac tissue after myocardial infarction or cardiac arrest. In certain embodiments, a compound of the present disclosure causes reduced neovascularization in cardiac tissue after myocardial infarction or cardiac arrest. In certain embodiments, the methods described herein cause reduced neovascularization in cardiac tissue after myocardial infarction or cardiac arrest.
- [0146] In certain embodiments, the methods described herein result in reduced risk of myocardial infarction or cardiac arrest of the subjects compared to subjects that have not been administered a compound of the present disclosure. In certain embodiments, for subject having undergone at least one prior myocardial infarction or cardiac arrest, the methods described herein result in reduced risk of a subsequent myocardial infarction or cardiac arrest of the subjects compared to subjects that have not been administered a compound of the present disclosure. In certain embodiments, the methods described herein result in increased overall survival of the subjects compared to subjects that have not been administered a compound of the present disclosure.
- [0147] Additional Therapeutic Compounds
- [0148] In certain embodiments, the methods disclosed herein comprise administering a compound of the present disclosure in combination with at least one additional therapeutic agent. In certain embodiments, the additional therapeutic agent is an agent used to lower blood pressure (e.g., an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin II receptor inhibitor, or a vasodilator, such as isosorbide dinitrate) , an agent used to reduce heart rate or modify cardiac output (e.g., a Beta-blocker) , a cholesterol-lowering medication (e.g., a statin) , a calcium channel blocker, a diuretic (e.g., hydrochlorothiazide) , an anti-coagulant, an anti-platelet agent, and/or an agent used to prevent or reduce the occurrence and severity of heart damage caused by drug induced cardiotoxicity (e.g., dexrazoxane hydrochloride) .
- [0149] In certain embodiments, the additional therapeutic agent is administered concurrently with one or more doses of a compound of the present disclosure. In certain embodiments, the additional therapeutic agent is administered prior to one or more doses of a compound of the present disclosure. In certain embodiments, the additional therapeutic agent is administered after one or more doses of a compound of the present disclosure.
- [0150] In certain embodiments, the additional therapeutic agent is one of a small molecule, a nucleic acid or a protein (e.g., an antibody) . In certain embodiments, the nucleic acid

is RNA. In certain embodiments, the RNA is antisense RNA. In certain embodiments the RNA is shRNA. In certain embodiments, the therapeutic compound changes the expression of at least one gene target identified by a method described herein.

- [0151] The term percent “identity,” in the context of two or more nucleic acid or polypeptide sequences, refers to two or more sequences or subsequences that have a specified percentage of nucleotides or amino acid residues that are the same, when compared and aligned for maximum correspondence, as measured using one of the sequence comparison algorithms described below (e.g., BLASTP and BLASTN or other algorithms available to persons of skill) or by visual inspection. Depending on the application, the percent “identity” can exist over a region of the sequence being compared, e.g., over a functional domain, or, alternatively, exist over the full length of the two sequences to be compared.
- [0152] For sequence comparison, typically one sequence acts as a reference sequence to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence (s) relative to the reference sequence, based on the designated program parameters.
- [0153] Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.* 2: 482 (1981) , by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.* 48: 443 (1970) , by the search for similarity method of Pearson & Lipman, *Proc. Nat'l. Acad. Sci. USA* 85: 2444 (1988) , by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.) , or by visual inspection (see generally Ausubel et al., *infra*) .
- [0154] One example of an algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul et al., *J. Mol. Biol.* 215: 403-410 (1990) . Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (www.ncbi.nlm.nih.gov/) .
- [0155] Pharmaceutical compositions
- [0156] The therapeutic compounds described herein can be formulated in pharmaceutical compositions. These compositions can comprise, in addition to one or more of the therapeutic compounds, a pharmaceutically acceptable excipient, carrier, buffer, stabiliser or other materials well known to those skilled in the art. Such materials should be non-toxic and should not interfere with the efficacy of the active ingredient.

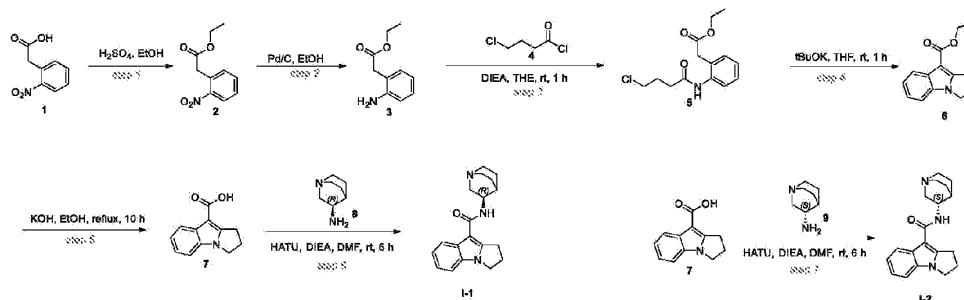
The precise nature of the carrier or other material can depend on the route of administration, e.g. oral, intravenous, cutaneous or subcutaneous, nasal, intramuscular, intraperitoneal, intracardiac routes and administration within a cardioplegic solution.

- [0157] Pharmaceutical compositions for oral administration can be in tablet, capsule, powder or liquid form. A tablet can include a solid carrier such as gelatin or an adjuvant. Liquid pharmaceutical compositions generally include a liquid carrier such as water, petroleum, animal or vegetable oils, mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution or glycols such as ethylene glycol, propylene glycol or polyethylene glycol can be included.
- [0158] For intravenous, cutaneous or subcutaneous injection, or injection at the site of affliction, the active ingredient will be in the form of a parenterally acceptable aqueous solution which is pyrogen-free and has suitable pH, isotonicity and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles such as Sodium Chloride Injection, Ringer's Injection, Lactated Ringer's Injection. Preservatives, stabilizers, buffers, antioxidants and/or other additives can be included, as required.
- [0159] Therapeutic compounds comprising nucleic acids can be formulated by any method known in the art including, but not limited to, formulation with polymeric nanoparticles (e.g., cationic polymers), lipid nanoparticles, and/or other hydrophobic moieties (e.g., cholesterol).
- [0160] A polypeptide, antibody, nucleic acid, small molecule or other pharmaceutically useful compound according to the present disclosure that is to be given to an individual, administration is preferably in a "therapeutically effective amount" that is sufficient to show benefit to the individual. A "prophylactically effective amount" can also be administered, when sufficient to show benefit to the individual. The actual amount administered, and rate and time-course of administration, will depend on the nature and severity of protein aggregation disease being treated. Prescription of treatment, e.g. decisions on dosage etc., is within the responsibility of general practitioners and other medical doctors, and typically takes account of the disorder to be treated, the condition of the individual patient, the site of delivery, the method of administration and other factors known to practitioners. Examples of the techniques and protocols mentioned above can be found in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. (ed), 1980.
- [0161] A composition can be administered alone or in combination with other treatments, either simultaneously or sequentially dependent upon the condition to be treated.
- [0162] EXAMPLES
- [0163] Below are examples of specific embodiments for carrying out the present invention. The examples are offered for illustrative purposes only, and are not intended to limit

the scope of the present invention in any way. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperatures, etc.), but some experimental error and deviation should, of course, be allowed for.

[0164] The practice of the present invention will employ, unless otherwise indicated, conventional methods of protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. See, e.g., T.E. Creighton, *Proteins: Structures and Molecular Properties* (W.H. Freeman and Company, 1993) ; A.L. Lehninger, *Biochemistry* (Worth Publishers, Inc., current addition) ; Sambrook, et al., *Molecular Cloning: A Laboratory Manual* (2nd Edition, 1989) ; *Methods In Enzymology* (S. Colowick and N. Kaplan eds., Academic Press, Inc.) ; Remington's *Pharmaceutical Sciences*, 18th Edition (Easton, Pennsylvania: Mack Publishing Company, 1990) ; Carey and Sundberg *Advanced Organic Chemistry* 3rd Ed. (Plenum Press) Vols A and B (1992) .

[0165] Example 1. Synthesis of I-1 & I-2



[0166] Step 1

[0167] To a solution of 2- (2-nitrophenyl) acetic acid (3.6 g, 0.02 mol) in EtOH (50 ml) stirred at 0°C was added H₂SO₄ (4 mL) and the reaction mixture was stirred at 60 °C for 12 h. The reaction mixture was slowly poured into ice water (200 ml) and extracted with EA (100 mL x 3) . The organic layer was combined, washed with H₂O (100 mL x 3) , and concentrated in vacuo to afford ethyl 2- (2-nitrophenyl) acetate (3.8 g, 91%) as a white solid.

[0168] MS (ESI) : mass calcd. for C₁₀H₁₁NO₄, 209.07, m/z found 232.1 [M+Na] .

[0169] Step 2

[0170] To a solution of ethyl 2- (2-nitrophenyl) acetate (3.8 g, 0.018 mol) in EtOH (50 ml) was added Pd/C (100 mg) and the reaction mixture was stirred at 25 °C for 4 h under H₂ balloon. The mixture was filtered through celite, and the filtrate was concentrated to afford ethyl 2- (2-aminophenyl) acetate (3.1 g, 95%) as a white solid.

[0171] MS (ESI) : mass calcd. for C₁₀H₁₃NO₂, 179.09, m/z found 180.2 [M+H] ⁺.

[0172] Step 3

- [0173] To a solution of ethyl 2- (2-aminophenyl) acetate (2.2 g, 0.012 mol) , TEA (2.49 g, 0.025 mol) in THF (30 ml) was added 4-chlorobutanoyl chloride (2.43 g, 0.017 mol) at 0°C and the reaction mixture was stirred at 25 °C for 4 h. The mixture was quenched with water (100 mL) , extracted with EA (100 mL x 3) . The organic layer was concentrated to afford the crude product which was purified by silica gel column chromatography (PE: EA = 3: 1) to give ethyl 2- (2- (4-chlorobutanamido) phenyl) acetate (3 g, 85%) as a white solid.
- [0174] MS (ESI) : mass calcd. for $C_{14}H_{18}ClNO_3$, 283.10, m/z found 284.4 $[M+H]^+$.
- [0175] Step 4
- [0176] To a solution of ethyl 2- (2- (4-chlorobutanamido) phenyl) acetate (2.84 g, 10 mmol) in THF (40 ml) was added t-BuOK (3.36 g, 30 mmol) in THF (20 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 1 h. The mixture was quenched with water (200 mL) and extracted with EA (200 mL x 3) . The organic layer was concentrated to afford the crude product which was purified by silica gel column chromatography (PE: EA = 3: 1) to give ethyl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate (588 mg, 26%) as a white solid.
- [0177] MS (ESI) : mass calcd. for $C_{14}H_{15}NO_2$, 229.11, m/z found 230.1 $[M+H]^+$.
- [0178] Step 5
- [0179] To a mixture of ethyl 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylate (300 mg, 1.30 mmol) in EtOH (15 mL) and H₂O (5 mL) was added KOH (220.3 mg, 3.93 mmol) . The reaction mixture was stirred at 80°C for 10 h. The reaction mixture was concentrated to remove EtOH and then adjusted to pH = 2 with 1M HCl. The mixture was diluted with water and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (200 mg, crude) as a white solid which was used directly for the next step.
- [0180] MS (ESI) : mass calcd. for $C_{12}H_{11}NO_2$, 201.08, m/z found 202.1 $[M+H]^+$.
- [0181] Step 6
- [0182] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.50 mmol) , (3R) -1-azabicyclo [2.2.2] octan-3-amine (62.7 mg, 0.50 mmol) and DIEA (192.7 mg, 1.49 mmol) in DMF (10 mL) was added HATU (226.8 mg, 0.60 mmol) . After stirring at 20 °C for 6 h, the mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 30 ml/min, wavelength: 214/254 nm) to give N- [(3R) -1-azabicyclo [2.2.2] octan-3-yl]

-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide formate (64.6 mg, 42%) as a white solid.

[0183] MS (ESI) : mass calcd. for $C_{19}H_{23}N_3O$, 309.18, m/z found 310.2 $[M+H]^+$.

[0184] 1H NMR (400 MHz, DMSO- d_6) δ 8.31 (s, 1H) , 7.89-7.87 (m, 1H) , 7.38-7.35 (m, 1H) , 7.23 (d, J = 8.0 Hz, 1H) , 7.15- 7.08 (m, 2H) , 4.13 -4.10 (m, 3H) , 3.39 (t, J = 12.0 Hz, 1H) , 3.28- 3.24 (m, 2H) , 3.13 -3.08 (m, 1H) , 2.97- 2.94 (m, 4H) , 2.62 -2.55 (m, 2H) , 2.08-1.98 (m, 2H) , 1.78- 1.76 (m, 2H) , 1.60 -1.54 (m, 1H) .

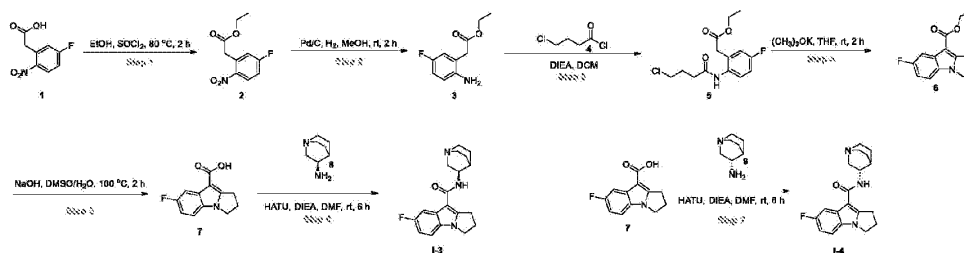
[0185] Step 7

[0186] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.50 mmol) , (3S) -1-azabicyclo [2.2.2] octan-3-amine (62.7 mg, 0.50 mmol) and DIEA (192.7 mg, 1.50 mmol) in DMF (10 mL) was added HATU (226.8 mg, 0.60 mmol) . The reaction mixture was stirred at 20 °C for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude product which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/ WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give N- [(3S) -1-azabicyclo [2.2.2] octan-3-yl] -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide formate (75.6 mg, 49%) as a white solid.

[0187] MS (ESI) : mass calcd. for $C_{19}H_{23}N_3O$, 309.18, m/z found 310.2 $[M+H]^+$.

[0188] 1H NMR (400 MHz, DMSO- d_6) δ 8.26 (s, 0.5H) , 7.89- 7.87 (m, 1H) , 7.38 -7.36 (m, 1H) , 7.23 (d, J = 8.0 Hz, 1H) , 7.15- 7.08 (m, 2H) , 4.17 -4.10 (m, 3H) , 3.39 (t, J = 12.0 Hz, 1H) , 3.26 (t, J = 8.0 Hz, 2H) , 3.15- 3.11 (m, 1H) , 3.03 -2.96 (m, 4H) , 2.63- 2.56 (m, 2H) , 2.12 -2.01 (m, 2H) , 1.81- 1.75 (m, 2H) , 1.64 -1.61 (m, 1H) .

[0189] Example 2. Synthesis of I-3 & I-4:



[0190] Experimental procedure:

[0191] Step 1

[0192] $SOCl_2$ (2.4 g, 20 mmol) was added to (5-fluoro-2-nitrophenyl) acetic acid (2 g, 10 mmol) in EtOH (5 mL) and the reaction mixture was stirred at 80°C for 2 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under

reduced pressure to give a residue which was purified by column chromatography on silica gel eluted with PE/EtOAc (20: 1) to give ethyl 2- (5-fluoro-2-nitrophenyl) acetate (2 g, 83%) as a white solid.

[0193] MS (ESI) : mass calcd. for $C_{10}H_{10}FNO_4$, 227.06, m/z found 228.1 [M+H]⁺.

[0194] Step 2

[0195] Pd/C (80 mg, 0.8 mmol) was added to ethyl 2- (5-fluoro-2-nitrophenyl) acetate (2 g, 8.8 mmol) in MeOH (20 mL) under N₂ and the mixture was stirred at 25 °C for 2 h under H₂. The mixture was filtered through celite and the filtrate was concentrated to afford ethyl 2- (2-amino-5-fluorophenyl) acetate (1.8 g, 93%) as a white solid.

[0196] MS (ESI) : mass calcd. for $C_{10}H_{12}FNO_2$, 197.09, m/z found 198.1 [M+H]⁺.

[0197] Step 3

[0198] 4-chlorobutanoyl chloride (1.4 g, 9.7 mmol) was added to a mixture of ethyl 2- (2-amino-5-fluorophenyl) acetate (1.6 g, 8.1 mmol) and DIEA (3.2 g, 24.3 mmol) in THF (20 mL) . The mixture was stirred at 25 °C for 2 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by column chromatography on silica gel eluted with DCM/MeOH (20: 1) to give ethyl 2- [2- (4-chlorobutanamido) -5-fluorophenyl] acetate (2.4 g, 86%) as a white solid.

[0199] MS (ESI) : mass calcd. for $C_{14}H_{17}ClFNO_3$, 301.09, m/z found 302.1 [M+H]⁺.

[0200] Step 4

[0201] Ethyl 2- [2- (4-chlorobutanamido) -5-fluorophenyl] acetate (200 mg, 0.66 mmol) in THF (2 mL) was added to a mixture of t-BuOK (160 mg, 1.66 mmol) in THF (2 mL) under N₂. After stirring at 25 °C for 2 h, the mixture was diluted with water (20 mL) and extracted with EA (20 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product which was purified by silica gel column chromatography eluted with DCM/MeOH (10: 1) to give ethyl 7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylate (100 mg, 51%) as a white solid.

[0202] MS (ESI) : mass calcd. for $C_{14}H_{14}FNO_2$, 247.1, m/z found 248.1 [M+H]⁺.

[0203] Step 5

[0204] Sodium hydroxide (30 mg, 0.73 mmol) was added to ethyl 7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylate (60 mg, 0.24 mmol) in DMSO (2 mL) and H₂O (0.5 mL) . After stirring at 100°C for 1 h, the mixture was adjusted to pH = 6-7 with 1M HCl (aq.) . The mixture was diluted with water (10 mL) and extracted with EA (5 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and con-

centrated under reduced pressure to give 7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (50 mg, 80%) as a white solid.

[0205] MS (ESI) : mass calcd. for $C_{12}H_{10}FNO_2$, 219.07, m/z found 220.1 [M+H]⁺.

[0206] Step 6

[0207] To a mixture of 7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.46 mmol), (3R)-1-azabicyclo [2.2.2] octan-3-amine (57.6 mg, 0.46 mmol) and DIEA (176.9 mg, 1.37 mmol) in DMF (10 mL) was added HATU (208.2 mg, 0.55 mmol). After stirring at 20 °C for 6 h, the mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile), flow rate : 30 ml/min, wavelength: 214/254 nm) to give N- [(3R)-1-azabicyclo [2.2.2] octan-3-yl] -7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide formate (62.5 mg, 42%) as a white solid.

[0208] MS (ESI) : mass calcd. for $C_{19}H_{22}FN_3O$, 327.17, m/z found 328.1 [M+H]⁺.

[0209] ¹H NMR (400 MHz, DMSO-d₆) δ 8.28 (s, 0.70 H), 7.59 (dd, J = 12.0, 4.0 Hz, 1H), 7.39 (dd, J = 12.0, 4.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.00- 6.95 (m, 1H), 4.13 (t, J = 8.0 Hz, 3H), 3.45 -3.34 (m, 1H), 3.30- 3.25 (m, 2H), 3.12 -3.08 (m, 1H), 2.96- 2.90 (m, 4H), 2.63 -2.54 (m, 2H), 2.07- 1.97 (m, 2H), 1.77 -1.73 (m, 2H), 1.60- 1.54 (m, 1H).

[0210] Step 7

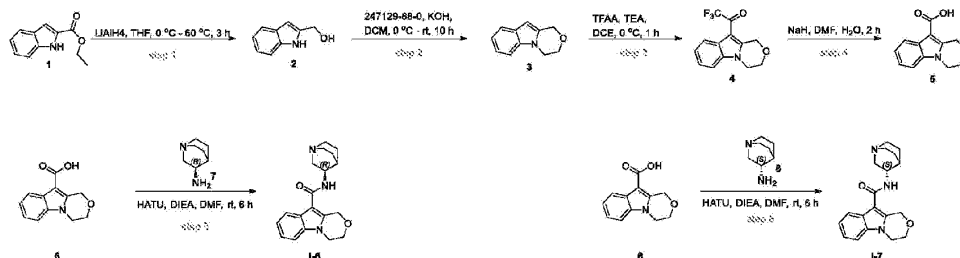
[0211] To a mixture of 7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.46 mmol), (3S)-1-azabicyclo [2.2.2] octan-3-amine (57.6 mg, 0.46 mmol) and DIEA (176.9 mg, 1.37 mmol) in DMF (10 mL) was added HATU (208.2 mg, 0.55 mmol). After stirring at 20 °C for 6 h, the mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile), flow rate : 30 ml/min, wavelength: 214/254 nm) to give N- [(3S)-1-azabicyclo [2.2.2] octan-3-yl] -7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide formate (55.6 mg, 36%) as a white solid.

[0212] MS (ESI) : mass calcd. for $C_{19}H_{22}FN_3O$, 327.17, m/z found 328.1 [M+H]⁺.

[0213] ¹H NMR (400 MHz, DMSO-d₆) δ 8.32 (s, 0.70 H), 7.59 (dd, J = 12.0, 4.0 Hz, 1H), 7.39 (dd, J = 8.0, 4.0 Hz, 1H), 7.25 (d, J = 4.0 Hz, 1H), 7.00- 6.95 (m, 1H), 4.14 -4.11 (m, 3H), 3.44- 3.39 (m, 1H), 3.30 -3.25 (m, 2H), 3.13- 3.11 (m, 1H), 2.99

-2.97 (m, 4H) , 2.62-2.55 (m, 2H) , 2.10- 1.99 (m, 2H) , 1.79 -1.77 (m, 2H) , 1.62- 1.57 (m, 1H) .

[0214] Example 3. Synthesis of I-5 & I-6:



[0215] Experimental procedure:

[0216] Step 1

[0217] To a mixture of ethyl 1H-indole-2-carboxylate (5 g, 26.43 mmol) in THF (60 mL) at 0 °C was added LiAlH₄ (1.5 g, 39.64 mmol) and the reaction mixture was stirred for 3 h at 60 °C. The reaction mixture was quenched with H₂O (3 mL) and 15% NaOH (4.5 mL) . The mixture was filtered, the filtrate was diluted with water (200 mL) and extracted with EA (100 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by Flash Chromatography (PE/EA 100: 1→1: 1) to give 1H-indol-2-yl) methanol (3 g, 77%) as a yellow solid.

[0218] MS (ESI) : mass calcd. for C₉H₉NO, 147.07, m/z found 148.1 [M+H]⁺.

[0219] Step 2

[0220] To a mixture of 1H-indol-2-ylmethanol (1.1 g, 0.0075 mol) in DCM (20 mL) was added KOH (1.05 g, 0.019 mol) at 0 °C and the reaction mixture was stirred at 0 °C for 0.5 h. Ethenyldiphenylsulfonium trifluoromethanesulfonate (3.26 g, 0.0079 mol) was added. The reaction mixture was stirred at 20 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by Flash Chromatography (PE/EA 100: 1→10: 1) to give 1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole (0.57 g, 41%) as a yellow solid.

[0221] MS (ESI) : mass calcd. for C₁₁H₁₁NO, 173.08, m/z found 174.1 [M+H]⁺.

[0222] Step 3

[0223] To a solution of 1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole (570 mg, 3.29 mmol) and TEA (399.6 mg, 3.95 mmol) in DCE (20 mL) was added TFAA (760.3 mg, 3.62 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 1 h. The mixture was diluted with water (100 mL) and extracted with DCM (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by Flash Chromatography (PE/EA 100: 1→2: 1) to

give difluoromethyl 1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carbonyl fluoride (700 mg, 75%) as a yellow solid.

[0224] MS (ESI) : mass calcd. for $C_{13}H_{10}F_3NO_2$, 269.07, m/z found 270.0 $[M+H]^+$.

[0225] Step 4

[0226] To a solution of difluoromethyl 1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carbonyl fluoride (700 mg, 2.59 mmol) in DMF (10 mL) were added NaH (373.0 mg, 15.54 mmol) and H_2O (233.3 mg, 12.95 mmol). The reaction mixture was stirred at 20°C for 2 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL). The aqueous was adjusted to pH = 2 with 1N HCl and extracted with EA (50 mL x 2). The combined organic layer was dried over Na_2SO_4 , concentrated to get the residue. The residue was purified by reverse phase column (phase A: H_2O ; phase B: ACN, 5~100%), fraction with MS signal of desired product was collected and concentrated to give 1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carboxylic acid (400 mg, 68%) as a yellow solid.

[0227] MS (ESI) : mass calcd. for $C_{12}H_{11}NO_3$, 217.07, m/z found 218.1 $[M+H]^+$.

[0228] Step 5

[0229] To a mixture of 1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carboxylic acid (50 mg, 0.23 mmol), (3R) -1-azabicyclo [2.2.2] octan-3-amine (29.1 mg, 0.23 mmol) and DIEA (89.3 mg, 0.69 mmol) in DMF (5 mL) was added HATU (105.0 mg, 0.28 mmol). After stirring at 20°C for 6 h, the mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue which was purified by prep-HPLC (Welch 10u C18 250 x 21.2 mm, Mobile Phase A: water (0.1%FA) B (acetonitrile), flow rate : 25 ml/min, wavelength: 214/254 nm) to give N- [(3R) -1-azabicyclo [2.2.2] octan-3-yl] -1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carboxamide (42.3 mg, 56%) as a white solid.

[0230] MS (ESI) : mass calcd. for $C_{19}H_{23}N_3O_2$, 325.18, m/z found 326.1 $[M+H]^+$.

[0231] 1H NMR (400 MHz, DMSO- d_6) δ 7.81- 7.78 (m, 1H), 7.50 -7.47 (m, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.23- 7.19 (m, 2H), 5.13 (s, 2H), 4.13 (s, 4H), 3.94 -3.92 (m, 1H), 3.11- 2.85 (m, 2H), 2.69 -2.65 (m, 4H), 1.92- 1.80 (m, 2H), 1.61 -1.55 (m, 2H), 1.38- 1.32 (m, 1H).

[0232] Step 6

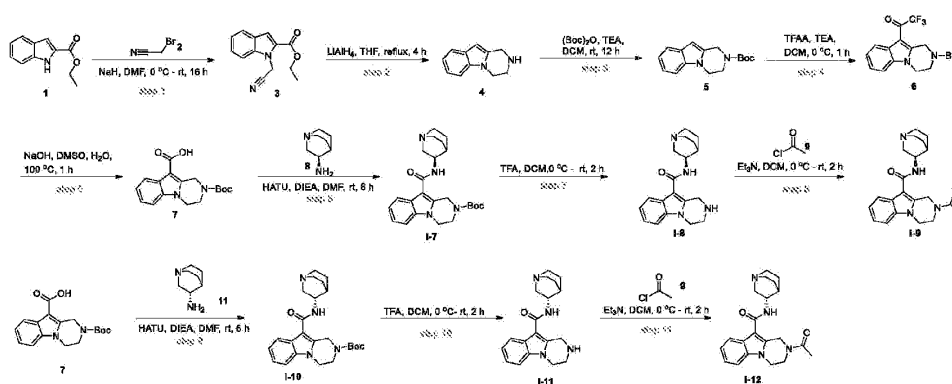
[0233] To a mixture of 1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carboxylic acid (50 mg, 0.23 mmol), (3S) -1-azabicyclo [2.2.2] octan-3-amine (29.1 mg, 0.23 mmol) and DIEA (89.3 mg, 0.69 mmol) in DMF (5 mL) was added HATU (105.0 mg, 0.28 mmol). After stirring at 20°C for 6 h, the mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was dried over anhydrous Na_2SO_4 ,

filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by prep-HPLC (Welch 10u C18 250 x 21.2 mm, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 25 ml/min, wavelength: 214/254 nm) to give N- [(3S) -1-azabicyclo [2.2.2] octan-3-yl] -1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carboxamide (47.5 mg, 63%) as a white solid.

[0234] MS (ESI) : mass calcd. for $C_{19}H_{23}N_3O_2$, 325.18, m/z found 326.1 [M+H]⁺.

[0235] ¹H NMR (400 MHz, DMSO-d₆) δ 7.81- 7.78 (m, 1H) , 7.50 -7.46 (m, 1H) , 7.37 (d, J = 8.0 Hz, 1H) , 7.23- 7.19 (m, 2H) , 5.13 (s, 2H) , 4.13 (s, 4H) , 3.94 -3.92 (m, 1H) , 3.10- 2.84 (m, 2H) , 2.68 -2.61 (m, 4H) , 1.92- 1.81 (m, 2H) , 1.61 -1.52 (m, 2H) , 1.38- 1.32 (m, 1H) .

[0236] Example 4. Synthesis of I-8 to I-12:



[0237] Experimental procedure:

[0238] Step 1

[0239] To a solution of ethyl 1H-indole-2-carboxylate (20.0 g, 0.11 mol) in DMF (100 mL) was added sodium hydride (3.8 g, 0.16 mol) at 0°C. After stirring for 0.5 h, 2-bromoacetonitrile (25.4 g, 0.21 mol) was added and the reaction mixture temperature was stirred at room temperature for 6 h. The mixture was quenched with NH₄Cl aqueous solution and extracted with EA (300 mL x 3) . The organic layer was washed with brine, dried with Na₂SO₄ and concentrated to give a residue which was purified by silica gel column chromatography (EA/PE=1/10) to afford ethyl 1- (cyanomethyl) indole-2-carboxylate (22 g, 91%) as a brown solid.

[0240] MS (ESI) : mass calcd. for $C_{13}H_{12}N_2O_2$, 228.09, m/z found 229.1 [M+H]⁺.

[0241] Step 2

[0242] To a solution of ethyl 1- (cyanomethyl) indole-2-carboxylate (10.0 g, 43.8 mmol) in THF (50 mL) was added LiAlH₄ in THF (109.5 mL, 109.5 mmol) at 0 °C and the mixture was refluxed for 4 h. The mixture was quenched with water and filtered. The filtrate was concentrated to give crude 1H, 2H, 3H, 4H-pyrazino [1, 2-a] indole which was used for the next step without further purification.

- [0243] MS (ESI) : mass calcd. $C_{11}H_{12}N_2$, 172.10, m/z found 173.1 [M+H]⁺.
- [0244] Step 3
- [0245] A mixture of 1H, 2H, 3H, 4H-pyrazino [1, 2-a] indole (5.5 g, 32 mmol), Boc₂O (8.35 g, 38 mmol) and TEA (3.87 g, 38 mmol) in DCM (60 mL) was stirred at room temperature for 12 h. The mixture was diluted with water (200 mL) and extracted with DCM (100 mL x 2). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by flash chromatography (PE/EA=100/1 to 4/1) to give tert-butyl {1H, 3H, 4H-pyrazino [1, 2-a] indol-2-yl} formate (3.2 g, 35%) as a yellow solid.
- [0246] MS (ESI) : mass calcd. for $C_{16}H_{20}N_2O_2$, 272.15, m/z found 273.2 [M+H]⁺.
- [0247] Step 4
- [0248] To a mixture of tert-butyl {1H, 3H, 4H-pyrazino [1, 2-a] indol-2-yl} formate (3.2 g, 12 mmol) and TEA (1.42 g, 14 mmol) in DCE (40 mL) was added TFAA (2.7 g, 12.8 mmol) at 0 °C and the reaction mixture was stirred at this temperature for 1 h. The mixture was diluted with water (200 mL) and extracted with DCM (100 mL x 2). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by Flash Chromatography (PE/EA=100/1 to 2/1) to give tert-butyl (10- { [(difluoromethyl) - $l^{\wedge}$ {2} -fluoranyl] carbonyl} -1H, 3H, 4H-pyrazino [1, 2-a] indol-2-yl) formate (3.5 g, 77%) as a yellow solid.
- [0249] MS (ESI) : mass calcd. for $C_{18}H_{19}F_3N_2O_3$, 368.13, m/z found 369.1 [M+H]⁺.
- [0250] Step 5
- [0251] A mixture of tert-butyl (10- { [(difluoromethyl) - $l^{\wedge}$ {2} -fluoranyl] carbonyl} -1H, 3H, 4H-pyrazino [1, 2-a] indol-2-yl) formate (3.5 g, 9.5 mmol) and NaOH (1.14 g, 28 mmol) in DMSO (20 mL) and H₂O (20 mL) was stirred at 100 °C for 1 h. The mixture was then diluted with water (200 mL) and extracted with EA (100 mL). The aqueous solution was acidified to pH = 2 with HCl (1N) and then extracted with EA (100 mL x 2). The combined organic layer was dried over Na₂SO₄ and concentrated to give 2- (tert-butyl- $l^{\wedge}$ {3} -oxy) -1H, 3H, 4H-pyrazino [1, 2-a] indole-10-carboxylic acid (1.7 g, crude) as a yellow solid which was directly used for the next step.
- [0252] MS (ESI) : mass calcd. for $C_{17}H_{20}N_2O_4$, 316.14, m/z found 339.1 [M+Na]⁺.
- [0253] Step 6
- [0254] To a mixture of 2- (tert-butyl- $l^{\wedge}$ {3} -oxy) -1H, 3H, 4H-pyrazino [1, 2-a] indole-10-carboxylic acid (400 mg, 1.26 mmol), (3R) -1-azabicyclo [2.2.2] octan-3-amine (159 mg, 1.26 mmol) and DIEA (489 mg, 3.78 mmol) in DMF (10 mL) was added HATU (575 mg, 1.51 mmol) and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with water (200 mL) and extracted with EA (100 mL

x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue which was purified by Prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give (10- { [(3R) -1-azabicyclo [2.2.2] octan-3-yl] carbamoyl} -1H, 3H, 4H-pyrazino [1, 2-a] indol-2-yl) tert-butyl formate (250 mg, 45%) as a white solid.

[0255] MS (ESI) : mass calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_4\text{O}_3$, 424.25, m/z found 425.2 [M+H]⁺.

[0256] ¹H NMR (400 MHz, DMSO-d₆) δ 8.25 (s, 1H) , 7.82-7.78 (m, 1H) , 7.58 (d, J = 8.0 Hz, 1H) , 7.50-7.47 (m, 1H) , 7.23-7.18 (m, 2H) , 4.99 (s, 2H) , 4.17-4.14 (m, 2H) , 4.10-4.08 (m, 1H) , 3.88-3.85 (m, 2H) , 3.34-3.28 (m, 1H) , 3.04-3.02 (m, 1H) , 2.86-2.84 (m, 4H) , 2.03-1.97 (m, 2H) , 1.75-1.71 (m, 2H) , 1.51-1.47 (m, 1H) , 1.44 (s, 9H) .

[0257] Step 7

[0258] To a solution of (10- { [(3R) -1-azabicyclo [2.2.2] octan-3-yl] carbamoyl} -1H, 3H, 4H-pyrazino [1, 2-a] indol-2-yl) tert-butyl formate (200 mg, 0.47 mmol) in DCM (12 mL) was added TFA (4 mL) at 0 °C and the mixture was then stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give N- [(3R) -1-azabicyclo [2.2.2] octan-3-yl] -1H, 2H, 3H, 4H-pyrazino [1, 2-a] indole-10-carboxamide formate (150 mg, 94%) as a yellow solid.

[0259] MS (ESI) : mass calcd. for $\text{C}_{19}\text{H}_{24}\text{N}_4\text{O}$, 324.20, m/z found 325.2 [M+H]⁺.

[0260] ¹H NMR (400 MHz, DMSO-d₆) δ 9.29 (s, 1H) , 8.14 (s, 0.2H) , 7.88-7.83 (m, 2H) , 7.56-7.52 (m, 1H) , 7.28-7.23 (m, 2H) , 4.61 (s, 2H) , 4.33-4.20 (m, 3H) , 3.71-3.66 (m, 1H) , 3.61- 3.54 (m, 2H) , 3.39- 3.32 (m, 1H) , 3.26- 3.22 (m, 4H) , 2.26- 2.14 (m, 2H) , 1.94-1.90 (m, 2H) , 1.80-1.75 (m, 1H) .

[0261] Step 8

[0262] To a mixture of N- [(3R) -1-azabicyclo [2.2.2] octan-3-yl] -1H, 2H, 3H, 4H-pyrazino [1, 2-a] indole-10-carboxamide (100 mg, 0.31 mmol) and TEA (94 mg, 0.92 mmol) in DCM (10 mL) was added acetyl chloride (24 mg, 0.31 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give the crude product. The residue was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give

2-acetyl-N- [(3R) -1-azabicyclo [2.2.2] octan-3-yl] -1H, 3H, 4H-pyrazino [1, 2-a] indole-10-carboxamide (22.8 mg, 20%) as a white solid.

[0263] MS (ESI) : mass calcd. for $C_{21}H_{26}N_4O_2$, 366.21, m/z found 367.2 [M+H]⁺.

[0264] ¹H NMR (400 MHz, DMSO-d₆) δ 7.81-7.77 (m, 1H) , 7.51-7.44 (m, 2H) , 7.23-7.18 (m, 2H) , 5.13-5.05 (m, 2H) , 4.24-4.12 (m, 2H) , 3.99-3.97 (m, 3H) , 3.15-3.10 (m, 1H) , 2.88-2.85 (m, 1H) , 2.69-2.66 (m, 4H) , 2.16-2.13 (m, 3H) , 1.93-1.86 (m, 2H) , 1.62-1.58 (m, 2H) , 1.37-1.35 (m, 1H) .

[0265] Step 9

[0266] To a mixture of 2- (tert-butyl- NH {3} -oxy) -1H, 3H, 4H-pyrazino [1, 2-a] indole-10-carboxylic acid (350 mg, 1.10 mmol) , (3S) -1-azabicyclo [2.2.2] octan-3-amine (139.2 mg, 1.10 mmol) and DIEA (428 mg, 3.31 mmol) in DMF (10 mL) was added HATU (503 mg, 1.32 mmol) . After stirring at room temperature for 6 h, the mixture was diluted with water (30 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give (10- { [(3S) -1-azabicyclo [2.2.2] octan-3-yl]carbamoyl} -1H, 3H, 4H-pyrazino [1, 2-a] indol-2-yl) tert-butyl formate (250 mg, 52%) as a white solid.

[0267] MS (ESI) : mass calcd. for $C_{24}H_{32}N_4O_3$, 424.25, m/z found 425.2 [M+H]⁺.

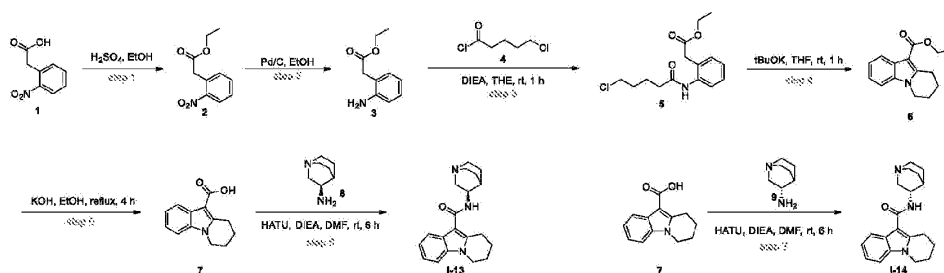
[0268] ¹H NMR (400 MHz, DMSO-d₆) δ 8.28 (s, 1H) , 7.82-7.78 (m, 1H) , 7.58 (d, J = 8.0 Hz, 1H) , 7.50-7.47 (m, 1H) , 7.23-7.18 (m, 2H) , 4.99 (s, 2H) , 4.17-4.14 (m, 2H) , 4.10-4.08 (m, 1H) , 3.88-3.85 (m, 2H) , 3.33-3.27 (m, 1H) , 3.03-3.01 (m, 1H) , 2.87-2.85 (m, 4H) , 2.03-1.96 (m, 2H) , 1.75-1.70 (m, 2H) , 1.50-1.47 (m, 1H) , 1.44 (s, 9H) .

[0269] Step 10

[0270] To a solution of (10- { [(3S) -1-azabicyclo [2.2.2] octan-3-yl] carbamoyl} -1H, 3H, 4H-pyrazino [1, 2-a] indol-2-yl) tert-butyl formate (200 mg, 0.47 mmol) in DCM (12 mL) was added TFA (4 mL) at 0 °C. After stirring at room temperature for 2h, the mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give N- [(3S) -1-azabicyclo [2.2.2] octan-3-yl] -1H, 2H, 3H, 4H-pyrazino [1, 2-a] indole-10-carboxamide (150 mg, 98%) as a yellow solid.

[0271] MS (ESI) : mass calcd. for $C_{19}H_{24}N_4O$, 324.20, m/z found 325.2 [M+H]⁺.

- [0272] ^1H NMR (400 MHz, DMSO- d_6) δ 7.79-7.75 (m, 1H) , 7.45-7.40 (m, 1H) , 7.30 (s, 1H) , 7.18-7.14 (m, 2H) , 4.27 (s, 2H) , 4.00-3.94 (m, 3H) , 3.56-3.54 (m, 1H) , 3.16-3.10 (m, 2H) , 2.91-2.85 (m, 1H) , 2.70-2.65 (m, 4H) , 1.92-1.85 (m, 2H) , 1.62-1.54 (m, 2H) , 1.40-1.34 (m, 1H) .
- [0273] Step 11
- [0274] To a mixture of N- [(3S) -1-azabicyclo [2.2.2] octan-3-yl] -1H, 2H, 3H, 4H-pyrazino [1, 2-a] indole-10-carboxamide (100 mg, 0.31 mmol) and TEA (94 mg, 0.92 mmol) in DCM (10 mL) was added acetyl chloride (24 mg, 0.31 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/ WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give 2-acetyl-N- [(3S) -1-azabicyclo [2.2.2] octan-3-yl] -1H, 3H, 4H-pyrazino [1, 2-a] indole-10-carboxamide formate (60.6 mg, 53%) as a white solid.
- [0275] MS (ESI) : mass calcd. for $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}_2$, 366.21, m/z found 367.2 $[\text{M}+\text{H}]^+$.
- [0276] ^1H NMR (400 MHz, DMSO- d_6) δ 8.26 (s, 1H) , 7.83-7.79 (m, 1H) , 7.60-7.55 (m, 1H) , 7.51-7.48 (m, 1H) , 7.24-7.20 (m, 2H) , 5.13-5.05 (m, 2H) , 4.25-4.22 (m, 1H) , 4.13-4.07 (m, 2H) , 4.00-3.97 (m, 2H) , 3.31-3.25 (m, 1H) , 3.03-2.99 (m, 1H) , 2.85-2.83 (m, 4H) , 2.16-2.13 (m, 3H) , 2.04-1.95 (m, 2H) , 1.70-1.68 (m, 2H) , 1.51-1.48 (m, 1H) .
- [0277] Example 5. Synthesis of I-13 & I-14:



- [0278] Experimental procedure:
- [0279] Step 1
- [0280] To a solution of 2- (2-nitrophenyl) acetic acid (3.6 g, 0.02 mol) in EtOH (50 ml) stirred at 0 °C was added H_2SO_4 (4 mL) and the reaction mixture was stirred at 60 °C for 12 h. The reaction mixture was slowly poured into ice water (200 ml) and extracted with EA (100 mL x 3) . The organic layer was combined, washed with H_2O (100 mL x

3), and concentrated in vacuo to afford ethyl 2- (2-nitrophenyl) acetate (3.8 g, 91%) as a white solid.

[0281] MS (ESI) : mass calcd. for $C_{10}H_{11}NO_4$, 209.07, m/z found 232.1 [M+Na] .

[0282] Step 2

[0283] To a solution of ethyl 2- (2-nitrophenyl) acetate (3.8 g, 0.018 mol) in EtOH (50 ml) was added Pd/C (100 mg) and the reaction mixture was stirred at 25 °C for 4 h under H_2 balloon. The mixture was filtered through celite, and the filtrate was concentrated to afford ethyl 2- (2-aminophenyl) acetate (3.1 g, 95%) as a white solid.

[0284] MS (ESI) : mass calcd. for $C_{10}H_{13}NO_2$, 179.09, m/z found 180.2 [M+H] ⁺.

[0285] Step 3

[0286] To a mixture of ethyl 2- (2-aminophenyl) acetate (2.5 g, 0.014 mol) and DIEA (2.69 g, 0.021 mol) in THF (40 mL) was added 5-chloropentanoyl chloride (2.69 g, 0.021 mol) . After stirring at 20°C for 2 h, the mixture was quenched with water (200 mL) and extracted with EA (200 mL x 3) . The organic layer was concentrated to afford the crude product which was purified by silica gel column chromatography (PE: EA = 3: 1) to give ethyl 2- [2- (5-chloropentanamido) phenyl] acetate (2.5 g, 58%) as a white solid.

[0287] MS (ESI) : mass calcd. for $C_{15}H_{20}ClNO_3$, 297.11, m/z found 298.1 [M+H] ⁺.

[0288] Step 4

[0289] To a mixture of ethyl 2- [2- (5-chloropentanamido) phenyl] acetate (2.5 g, 0.0084 mol) in THF (40 mL) was added t-BuOK (2.36 g, 0.021 mol) . After stirring at 20 °C for 2 h, the mixture was quenched with water (200 mL) and extracted with EA (200 mL x 3) . The organic layer was concentrated to afford a residue which was purified by silica gel column chromatography (PE: EA = 3: 1) to give ethyl 1H, 2H, 3H, 4H-pyrido [1, 2-a] indole-10-carboxylate (500 mg, 24%) as a white solid.

[0290] MS (ESI) : mass calcd. for $C_{15}H_{17}NO_2$, 243.13, m/z found 244.1 [M+H] ⁺.

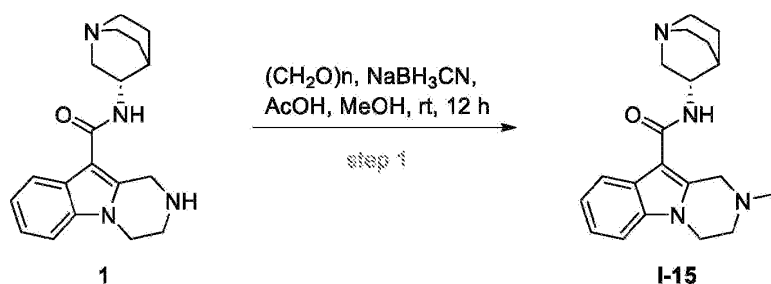
[0291] Step 5

[0292] To a mixture of ethyl 1H, 2H, 3H, 4H-pyrido [1, 2-a] indole-10-carboxylate (500 mg, 2.06 mmol) in EtOH (15 mL) and H_2O (5 mL) was added KOH (345.9 mg, 6.17 mmol) . The reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was concentrated to remove EtOH. The mixture was adjusted to pH = 2 with 1M HCl. The mixture was diluted with water and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give 1H, 2H, 3H, 4H-pyrido [1, 2-a] indole-10-carboxylic acid (400 mg, 89%) as a white solid which was directly used for the next step.

[0293] MS (ESI) : mass calcd. for $C_{13}H_{13}NO_2$, 215.09, m/z found 216.1 [M+H] ⁺.

[0294] Step 6

- [0295] To a mixture of 1H, 2H, 3H, 4H-pyrido [1, 2-a] indole-10-carboxylic acid (50 mg, 0.23 mmol), (3R) -1-azabicyclo [2.2.2] octan-3-amine (29.3 mg, 0.23 mmol) and DIEA (90.1 mg, 0.70 mmol) in DMF (5 mL) was added HATU (106.0 mg, 0.28 mmol). The reaction mixture was stirred at 20 °C for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product which was purified by prep-HPLC (Xbridge prep c18 5um OBD 19*150mm, Mobile Phase A: water (0.1%FA) B (acetonitrile), flow rate: 20 ml/min, wavelength: 214/254 nm) to give N- [(3R) -1-azabicyclo [2.2.2] octan-3-yl] -1H, 2H, 3H, 4H-pyrido [1, 2-a] indole-10-carboxamide formate (28.7 mg, 38%) as a white solid.
- [0296] MS (ESI): mass calcd. for C₂₀H₂₅N₃O, 323.20, m/z found 324.1 [M+H]⁺.
- [0297] ¹H NMR (400 MHz, DMSO-d₆) δ 8.26 (s, 0.7 H), 7.78-7.74 (m, 1H), 7.48 (d, J = 4.0 Hz, 1H), 7.43-7.40 (m, 1H), 7.17-7.12 (m, 2H), 4.14-4.05 (m, 3H), 3.42-3.36 (m, 1H), 3.17 (t, J = 8.0 Hz, 2H), 3.12-3.05 (m, 1H), 2.96-2.88 (m, 4H), 2.09-2.00 (m, 4H), 1.88-1.73 (m, 4H), 1.59-1.53 (m, 1H).
- [0298] Step 7
- [0299] To a mixture of 1H, 2H, 3H, 4H-pyrido [1, 2-a] indole-10-carboxylic acid (50 mg, 0.23 mmol), (3S) -1-azabicyclo [2.2.2] octan-3-amine (29.3 mg, 0.23 mmol) and DIEA (90.1 mg, 0.70 mmol) in DMF (5 mL) was added HATU (106.0 mg, 0.28 mmol). The reaction mixture was stirred at 20 °C for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product which was purified by prep-HPLC (Xbridge prep c18 5um OBD 19*150mm, Mobile Phase A: water (0.1%FA) B (acetonitrile), flow rate: 20 ml/min, wavelength: 214/254 nm) to give N- [(3S) -1-azabicyclo [2.2.2] octan-3-yl] -1H, 2H, 3H, 4H-pyrido [1, 2-a] indole-10-carboxamide formate (35 mg, 46%) as a white solid.
- [0300] MS (ESI): mass calcd. for C₂₀H₂₅N₃O, 323.20, m/z found 324.1 [M+H]⁺.
- [0301] ¹H NMR (400 MHz, DMSO-d₆) δ 8.30 (s, 0.8 H), 7.78-7.74 (m, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.44-7.40 (m, 1H), 7.17-7.12 (m, 2H), 4.14-4.07 (m, 3H), 3.40-3.35 (m, 1H), 3.17 (t, J = 8.0 Hz, 2H), 3.12-3.05 (m, 1H), 2.95-2.88 (m, 4H), 2.08-1.99 (m, 4H), 1.88-1.73 (m, 4H), 1.59-1.53 (m, 1H).
- [0302] ‘
- [0303] Example 6. Synthesis of I-15:



[0304] Experimental procedure:

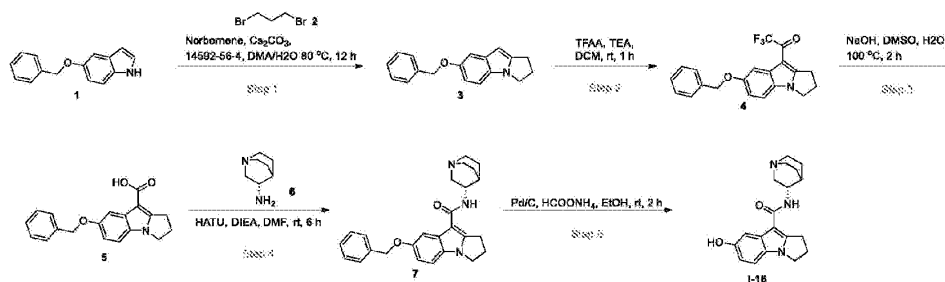
[0305] Step 1

[0306] To a mixture of N-[(3S)-1-azabicyclo[2.2.2]octan-3-yl]-1H,2H,3H,4H-pyrazino[1,2-a]indole-10-carboxamide (80 mg, 0.25 mmol) and paraformaldehyde (153.1 mg, 2.47 mmol) in methanol (5 mL) was added AcOH (14.8 mg, 0.25 mmol). After stirring at 20 °C for 4 h, NaBH₃CN (46.5 mg, 0.7398 mmol) was added and the reaction mixture was stirred at 20 °C for 12 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product which was purified by prep-HPLC (Xbridge prep c18 5um OBD 19*150mm, Mobile Phase A: water (0.1%FA) B (acetonitrile), flow rate: 20 ml/min, wavelength: 214/254 nm) to give N-[(3S)-1-azabicyclo[2.2.2]octan-3-yl]-2-methyl-1H,3H,4H-pyrazino[1,2-a]indole-10-carboxamide (33.5 mg, 40%) as a white solid.

[0307] MS (ESI): mass calcd. for C₂₀H₂₆N₄O, 338.21, m/z found 339.3 [M+H]⁺.

[0308] ¹H NMR (400 MHz, DMSO-d₆) δ 7.77-7.73 (m, 1H), 7.46-7.39 (m, 2H), 7.20-7.16 (m, 2H), 4.11 (t, J = 5.6 Hz, 2H), 3.96-3.92 (m, 3H), 3.14-3.08 (m, 1H), 2.89-2.84 (m, 3H), 2.72-2.64 (m, 4H), 2.43 (s, 3H), 1.91-1.81 (m, 2H), 1.62-1.55 (m, 2H), 1.38-1.32 (m, 1H).

[0309] Example 7. Synthesis of I-16:



[0310] Experimental procedure:

[0311] Step 1

[0312] To a mixture of 5-(benzyloxy)-1H-indole (500 mg, 2.24 mmol), bis(acetonitrile)dichloropalladium (II) (58.1 mg, 0.22 mmol), norbornene (1054.2 mg, 11.20 mmol)

and Cs_2CO_3 (1459.3 mg, 4.48 mmol) in DMA (10 mL) and H_2O (0.1 mL) was added 1, 3-dibromopropane (1130.3 mg, 5.60 mmol). After stirring at 80 °C for 12 h, the mixture was filtered through celite, the filtrate was diluted with water (200 mL) and extracted with EA (100 mL x 2). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give the crude product which was purified by flash chromatography (PE/EA, 100/1 to 10/1) to give 7- (benzyloxy) -1H, 2H, 3H-benzo [b] pyrrolizine (200 mg, 31%) as a yellow solid.

[0313] MS (ESI) : mass calcd. for $\text{C}_{18}\text{H}_{17}\text{NO}$, 263.13, m/z found 264.1 [M+H]⁺.

[0314] Step 2

[0315] To a solution of 7- (benzyloxy) -1H, 2H, 3H-benzo [b] pyrrolizine (200 mg, 0.76 mmol) and TEA (92.2 mg, 0.91 mmol) in DCE (10 mL) was added TFAA (175.5 mg, 0.84 mol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The mixture was diluted with water (200 mL) and extracted with DCM (100 mL x 2). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give the crude product which was purified by flash chromatography (PE/EA, 100/1 to 2/1) to give difluoromethyl 7- (benzyloxy) -1H, 2H, 3H-benzo [b] pyrrolizine-9-carbonyl fluoride (200 mg, 69%) as a yellow solid.

[0316] MS (ESI) : mass calcd. for $\text{C}_{20}\text{H}_{16}\text{F}_3\text{NO}_2$, 359.11, m/z found 360.1 [M+H]⁺.

[0317] Step 3

[0318] A mixture of difluoromethyl 7- (benzyloxy) -1H, 2H, 3H-benzo [b] pyrrolizine-9-carbonyl fluoride (200 mg, 0.56 mmol) and NaOH (44.4 mg, 1.1 mmol) in DMSO (5 mL) and H_2O (5 mL) was stirred at 100°C for 1 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL). The aqueous phase was adjusted to pH = 2 with 1N HCl and extracted with EA (50 mL x 2). The combined organic layer was dried over Na_2SO_4 , concentrated to give 7- (benzyloxy) -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 54%) as a yellow solid.

[0319] MS (ESI) : mass calcd. for $\text{C}_{19}\text{H}_{17}\text{NO}_3$, 307.12, m/z found 308.0 [M+H]⁺.

[0320] Step 4

[0321] To a mixture of 7- (benzyloxy) -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.33 mmol), (3S) -1-azabicyclo [2.2.2] octan-3-amine (41.1 mg, 0.33 mmol) and DIEA (126.2 mg, 0.98 mmol) in DMF (5 mL) was added HATU (148.5 mg, 0.39 mmol). The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give N- [(3S) -1-azabicyclo [2.2.2] octan-3-yl] -7- (benzyloxy) -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (100 mg, 70%) as a yellow solid.

[0322] MS (ESI) : mass calcd. for $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_2$, 415.23, m/z found 416.2 [M+H]⁺.

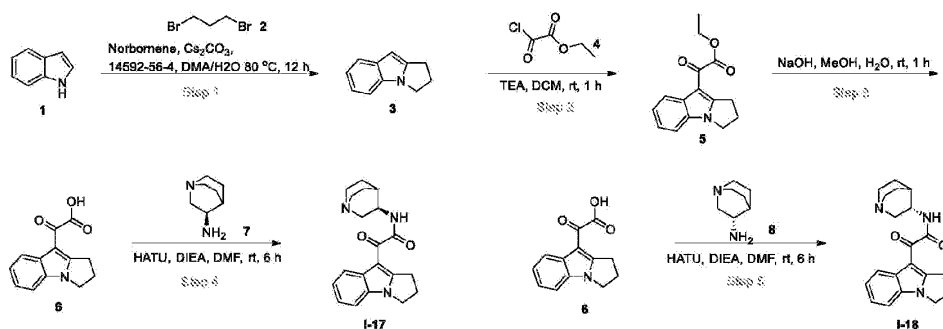
[0323] Step 5

[0324] To a mixture of N- [(3S) -1-azabicyclo [2.2.2] octan-3-yl] -7- (benzyloxy) -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (100 mg, 0.24 mmol) in EtOH (10 mL) were added Pd/C (25.6 mg, 0.24 mmol) and ammonium formate (30.4 mg, 0.48 mmol) under N₂. The reaction mixture was stirred at 20 °C under N₂ for 2 h. The mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give the crude product which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give N- [(3S) -1-azabicyclo [2.2.2] octan-3-yl] -7-hydroxy-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide formate (32.4 mg, 41%) as a grey solid.

[0325] MS (ESI) : mass calcd. for C₁₉H₂₃N₃O₂, 325.18, m/z found 326.1 [M+H]⁺.

[0326] ¹H NMR (400 MHz, DMSO-d₆) δ 8.31 (s, 1H) , 7.27 (d, J = 2.0 Hz, 1H) , 7.14 (d, J = 8.0 Hz, 1H) , 6.99 (d, J = 6.4 Hz, 1H) , 6.60 (dd, J = 8.4, 2.0 Hz, 1H) , 4.05 4.02 (m, 3H) , 3.34-3.26 (m, 1H) , 3.22-3.16 (m, 2H) , 3.05-3.01 (m, 1H) , 2.88-2.80 (m, 4H) , 2.59-2.53 (m, 2H) , 2.02-1.94 (m, 2H) , 1.71-1.69 (m, 2H) , 1.54-1.51 (m, 1H) .

[0327] Example 8. Synthesis of I-17 &I-18:



[0328] Experimental procedure:

[0329] Step 1

[0330] To a mixture of 1H-indole (10 g, 0.085 mol) , bis (acetonitrile) dichloropalladium (II) (2.22 g, 0.0085 mol) , norbornene (40.2 g, 0.43 mol) and Cs₂CO₃ (55.65 g, 0.17 mol) in DMA (200 mL) and H₂O (2 mL) was added 1, 3-dibromopropane (43.1 g, 0.21 mol) . The reaction mixture was stirred at 80 °C for 12 h. The mixture was filtered through celite, the filtrate diluted with water (200 mL) and extracted with EA (100 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product which was purified by flash chromatography (PE/EA, 100/1 to 10/1) to give 1H, 2H, 3H-benzo [b] pyrrolizine (500 mg, 3.4%) as a yellow solid.

[0331] MS (ESI) : mass calcd. for C₁₁H₁₁N, 157.09, m/z found 158.1 [M+H]⁺.

[0332] Step 2

[0333] To a solution of 1H, 2H, 3H-benzo [b] pyrrolizine (500 mg, 3.18 mmol) and TEA (386.2 mg, 3.82 mmol) in DCE (10 mL) was added ethyl 2-chloro-2-oxoacetate (477.7 mg, 3.50 mol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The mixture was diluted with water (100 mL) and extracted with DCM (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give ethyl 2- {1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -2-oxoacetate (180 mg, 18%) as a yellow solid.

[0334] MS (ESI) : mass calcd. for C₁₅H₁₅NO₃, 257.11, m/z found 258.1 [M+H]⁺.

[0335] Step 3

[0336] To a mixture of ethyl 2- {1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -2-oxoacetate (300 mg, 1.30 mmol) in MeOH (9 mL) and H₂O (3 mL) was added NaOH (88.8 mg, 2.22 mmol) . The reaction mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated to remove MeOH and then adjusted to pH= 2 with 1M HCl. The mixture was diluted with water and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl (oxo) acetic acid (90 mg, 50%) as a yellow solid.

[0337] MS (ESI) : mass calcd. for C₁₃H₁₁NO₃, 229.07, m/z found 230.1 [M+H]⁺.

[0338] Step 4

[0339] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl (oxo) acetic acid (45 mg, 0.20 mmol) , (3R) -1-azabicyclo [2.2.2] octan-3-amine (24.8 mg, 0.20 mmol) and DIEA (76.1 mg, 0.59 mmol) in DMF (5 mL) was added HATU (89.6 mg, 0.24 mmol) . The reaction mixture was stirred at 20 °C for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give the crude product which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give N- [(3R) -1-azabicyclo [2.2.2] octan-3-yl] -2- {1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -2-oxoacetamide (25.4 mg, 37%) as a white solid.

[0340] MS (ESI) : mass calcd. for C₂₀H₂₃N₃O₂, 337.18, m/z found 338.1 [M+H]⁺.

[0341] ¹H NMR (400 MHz, DMSO-d₆) δ 8.81 (d, J = 8.0 Hz, 1H) , 8.15-8.13 (m, 1H) , 7.47-7.45 (m, 1H) , 7.26-7.21 (m, 2H) , 4.19 (t, J = 8.0 Hz, 2H) , 3.96-3.94 (m, 1H) , 3.22-3.09 (m, 3H) , 2.87-2.84 (m, 1H) , 2.78-2.66 (m, 4H) , 2.65-2.57 (m, 2H) , 1.91-1.89 (m, 1H) , 1.78-1.75 (m, 1H) , 1.66-1.62 (m, 2H) , 1.40-1.34 (m, 1H) .

[0342] Step 5

[0343] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl (oxo) acetic acid (45 mg, 0.20 mmol) , (3S) -1-azabicyclo [2.2.2] octan-3-amine (24.8 mg, 0.20 mmol) and DIEA (76.1 mg, 0.59 mmol) in DMF (5 mL) was added HATU (89.6 mg, 0.24 mmol) . After stirring at 20 °C for 6 h, the mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give N- [(3S) -1-azabicyclo [2.2.2] octan-3-yl] -2- {1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -2-oxoacetamide formate (25.0 mg, 32%) as a white solid.

[0344] MS (ESI) : mass calcd. for C₂₀H₂₃N₃O₂, 337.18, m/z found 338.1 [M+H]⁺.

[0345] ¹H NMR (400 MHz, DMSO-d₆) δ 8.81 (d, J = 8.0 Hz, 1H) , 8.28 (s, 1H) , 8.15-8.13 (m, 1H) , 7.47-7.44 (m, 1H) , 7.26-7.21 (m, 2H) , 4.19 (t, J = 8.0 Hz, 2H) , 3.96-3.94 (m, 1H) , 3.22-3.09 (m, 3H) , 2.90-2.84 (m, 1H) , 2.79-2.66 (m, 4H) , 2.62-2.55 (m, 2H) , 1.92-1.89 (m, 1H) , 1.78-1.75 (m, 1H) , 1.66-1.62 (m, 2H) , 1.41-1.35 (m, 1H) .

[0346] Example 9. Synthesis of I-19:



[0347] Experimental procedure:

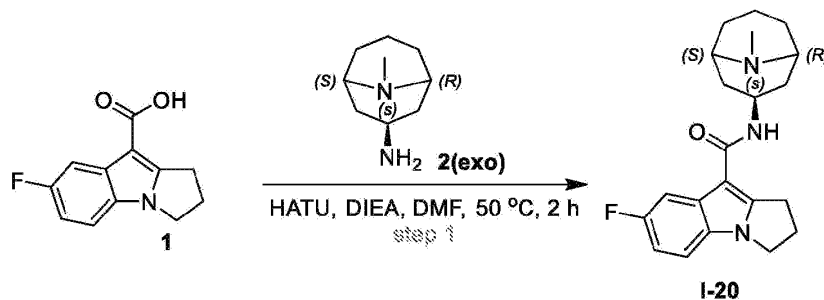
[0348] Step 1

[0349] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (50 mg, 0.25 mmol) , endo-9-methyl-9-azabicyclo [3.3.1] nonan-3-amine (38.3 mg, 0.25 mmol) and DIEA (96.4 mg, 0.75 mmol) in DMF (5 mL) was added HATU (113.4 mg, 0.30 mmol) . The reaction mixture was stirred at 20 °C for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 5um OBD 19*150mm, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 20 ml/min, wavelength: 214/254 nm) to give N- ((1R, 3r, 5S) -9-methyl-9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (46.8 mg, 56%) as a white solid.

[0350] MS (ESI) : mass calcd. for $C_{21}H_{27}N_3O$, 337.22, m/z found 338.2 $[M+H]^+$.

[0351] 1H NMR (400 MHz, DMSO- d_6) δ 8.21 (s, 0.8 H), 7.93-7.91 (m, 1H), 7.36-7.34 (m, 1H), 7.14-7.07 (m, 2H), 6.87 (d, J = 8.4 Hz, 1H), 4.43-4.35 (m, 1H), 4.11 (t, J = 7.2 Hz, 2H), 3.25-3.17 (m, 4H), 2.61-2.56 (m, 2H), 2.54 (s, 3H), 2.31-2.24 (m, 2H), 2.15-2.07 (m, 1H), 1.99-1.91 (m, 2H), 1.61-1.54 (m, 2H), 1.47-1.44 (m, 1H), 1.11-1.07 (m, 2H).

[0352] Example 10. Synthesis of I-20:



[0353] Experimental procedure:

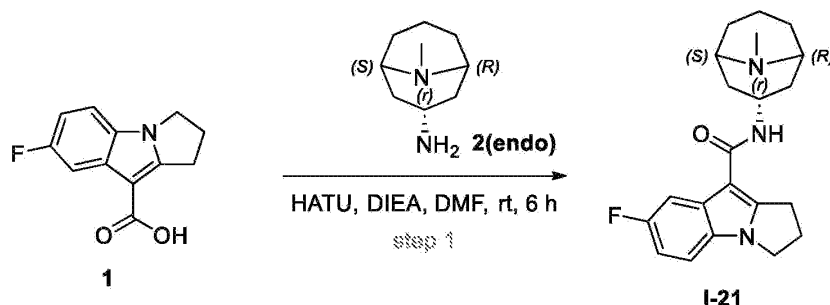
[0354] Step 1

[0355] To a mixture of 7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (50 mg, 0.23 mmol) in dimethylformamide (5 mL) were added HATU (130 mg, 0.34 mmol) and DIEA (88 mg, 0.68 mmol) at 0 °C under N_2 protection. After stirring for 30 minutes, 9-methyl-9-azabicyclo [3.3.1] nonan-3-amine (35 mg, 0.23 mmol) was added and the mixture was then stirred at 50 °C for 2 hours. The mixture was extracted with EA (10 mL $\times$ 3). The combined organic layer was washed with brine (10 mL $\times$ 2), dried over Na_2SO_4 and concentrated under reduced pressure to afford crude product which was purified by Prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA), B (Acetonitrile), 20~100% of B in A, 10.5 min, Flow rate: 30ml/min, wavelength: 214/254 nm) to give 7-fluoro-N- {9-methyl-9-azabicyclo [3.3.1] nonan-3-yl} -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide formate (26.9 mg, 33.2%) as white solid.

[0356] MS (ESI) : mass calcd. for $C_{21}H_{26}FN_3O$, 355.21, m/z found 356.2 $[M+H]^+$.

[0357] 1H NMR (400 MHz, DMSO) δ 8.25 (s, 1H), 7.64 (dd, J = 12.0, 4.0 Hz, 1H), 7.38 (dd, J = 8.0, 4.0 Hz, 1H), 7.00-6.91 (m, 2H), 4.72-4.64 (m, 1H), 4.11 (t, J = 8.0 Hz, 2H), 3.25-3.22 (m, 2H), 3.02-3.01 (m, 2H), 2.61-2.54 (m, 4H), 2.08-1.59 (m, 11H).

[0358] Example 11. Synthesis of I-21:



[0359] Experimental procedure:

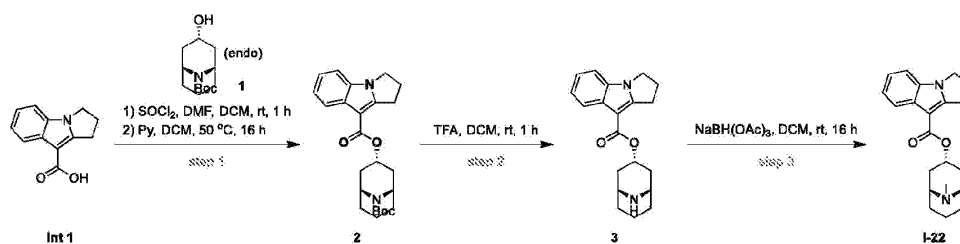
[0360] Step 1

[0361] To a mixture of 7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (50 mg, 0.23 mmol) , 9-methyl-9-azabicyclo [3.3.1] nonan-3-amine (35.2 mg, 0.23 mmol) and DIEA (88.4 mg, 0.68 mmol) in DMF (5 mL) was added HATU (104.1 mg, 0.27 mmol) . After stirring at room temperature for 6 h, the mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 5um OBD 19*150mm, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 20 ml/min, wavelength: 214/254 nm) to give 7-fluoro-N- ((1R, 3R, 5S) -9-methyl-9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (32.0 mg, 39%) as a white solid.

[0362] MS (ESI) : mass calcd. for C₂₁H₂₆FN₃O, 355.21, m/z found 356.2 [M+H]⁺.

[0363] ¹H NMR (400 MHz, DMSO-d₆) δ 8.22 (s, 1H) , 7.64 (dd, J = 10.4, 2.4 Hz, 1H) , 7.37 (dd, J = 8.8, 4.8 Hz, 1H) , 6.99-6.94 (m, 1H) , 6.83 (d, J = 8.8 Hz, 1H) , 4.37-4.32 (m, 1H) , 4.11 (t, J = 7.2 Hz, 2H) , 3.24 (t, J = 7.6 Hz, 2H) , 3.10 (d, J = 10.8 Hz, 2H) , 2.67-2.54 (m, 3H) , 2.50-2.48 (m, 2H) , 2.28-2.20 (m, 2H) , 2.14-2.08 (m, 1H) , 1.97-1.90 (m, 2H) , 1.57-1.43 (m, 3H) , 1.02 (d, J = 13.2 Hz, 2H) .

[0364] Example 12. Synthesis of I-22:



[0365] Experimental procedure:

[0366] Step 1

[0367] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (440 mg, 2.18 mmol) in DCM (5 mL) was added SOCl₂ (520 mg, 4.37 mmol) and a drop of DMF

at 0 °C. The reaction mixture was stirred at room temperature for 2 h under N₂. The mixture was concentrated under reduced pressure to give the crude product which was redissolved in DCM (5 mL). Pyridine (864 mg, 10.93 mmol) and endo-tert-butyl (1R, 3r, 5S) -3-hydroxy-9-azabicyclo [3.3.1] nonane-9-carboxylate (220 mg, 0.91 mmol) were added subsequently at room temperature. The reaction mixture was stirred at 50 °C for 16 h. The mixture was concentrated under reduced pressure to give the crude product which was purified by silica gel column chromatography (mobile phase A: PE, B: EA; 0 ~ 35% of B in A) to give (1R, 3r, 5S) -9- (tert-butoxycarbonyl) -9-azabicyclo [3.3.1] nonan-3-yl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate (250 mg, 26%) as an off-white solid.

[0368] MS (ESI) : mass calcd. for C₂₅H₃₂N₂O₄, 424.24, m/z found 447.2 [M+Na]⁺.

[0369] Step 2

[0370] To a mixture of endo- (1R, 3r, 5S) -9- (tert-butoxycarbonyl) -9-azabicyclo [3.3.1] nonan-3-yl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate (250 mg, 0.58 mmol) in DCM (6 mL) was added TFA (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The mixture was basified to pH 7 with NaHCO₃ aq. solution and extracted with EA (20 mL x 3). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give endo- (1R, 3r, 5S) -9-azabicyclo [3.3.1] nonan-3-yl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate (160 mg, 83%) as an off-white solid.

[0371] MS (ESI) : mass calcd. for C₂₀H₂₄N₂O₂, 324.18, m/z found 325.2 [M+H]⁺.

[0372] Step 3

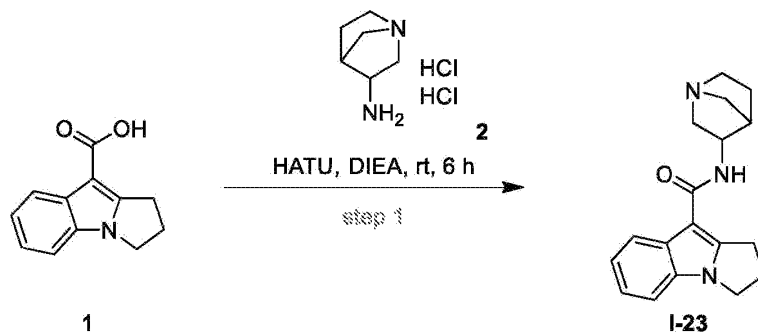
[0373] To a mixture of endo- (1R, 3r, 5S) -9-azabicyclo [3.3.1] nonan-3-yl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate (160 mg, 0.49 mmol) and formaldehyde aqueous solution (37%, 80 mg, 0.98 mmol) in DCM (5 mL) was added NaBH(OAc)₃ (313 mg, 1.47 mmol) at room temperature. The reaction mixture was stirred for 16 h. After reaction, the mixture was quenched with Na₂S₂O₃ aq. solution (20 mL) and extracted with EA (20 mL x 3). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um; mobile phase A: water (0.1%FA), B: Acetonitrile, 22 ~ 52%B in 10 min; flow rate: 30 mL/min; wavelength: 214/254 nm) to give endo- (1R, 3r, 5S) -9-methyl-9-azabicyclo [3.3.1] nonan-3-yl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate formate (93.8 mg, 56%) as a white solid.

[0374] MS (ESI) : mass calcd. for C₂₁H₂₆N₂O₂, 338.20, m/z found 339.2 [M+H]⁺.

[0375] ¹H NMR (400 MHz, CDCl₃) δ 8.63 (s, 0.67 H), 8.07-8.00 (m, 1H), 7.31-7.27 (m, 1H), 7.25-7.19 (m, 2H), 5.33-5.25 (m, 1H), 4.15 (t, J = 8.0 Hz, 2H), 3.42 (t, J = 4.0

Hz, 2H) , 3.31 (t, J = 8.0 Hz, 2H) , 2.91-2.75 (m, 5H) , 2.74-2.60 (m, 3H) , 2.33-2.19 (m, 2H) , 2.05 (d, J = 16.0 Hz, 2H) , 1.66 (dd, J = 16.0, 4.0 Hz, 2H) , 1.58-1.49 (m, 1H) .

[0376] Example 13. Synthesis of I-23:



[0377] Experimental procedure:

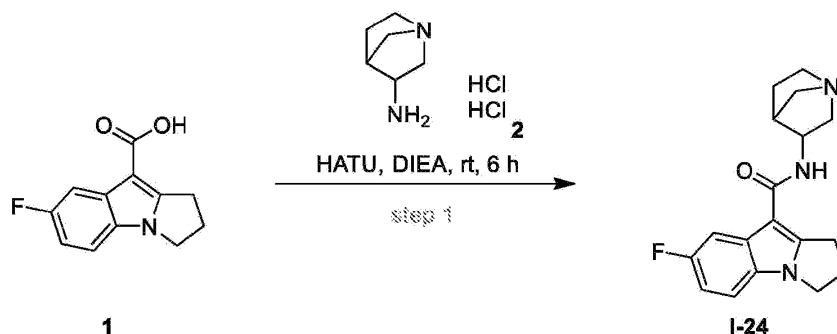
[0378] Step 1

[0379] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (30 mg, 0.15 mmol) , 1-azabicyclo [2.2.1] heptan-3-amine (16.7 mg, 0.15 mmol) and DIEA (57.8 mg, 0.45 mmol) in DMF (5 mL) was added HATU (68.0 mg, 0.18 mmol) and the reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give N- (1-azabicyclo [2.2.1] heptan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (15.7 mg, 36%) as a yellow solid.

[0380] MS (ESI) : mass calcd. for C₁₈H₂₁N₃O, 295.17, m/z found 296.1 [M+H]⁺.

[0381] ¹H NMR (400 MHz, MeOD) δ 8.49 (s, 1H) , 7.89-7.87 (m, 1H) , 7.35-7.32 (m, 1H) , 7.20-7.14 (m, 2H) , 4.59-4.12 (m, 3H) , 3.84-3.62 (m, 1H) , 3.48-3.30 (m, 2H) , 3.28-3.22 (m, 4H) , 3.15-3.04 (m, 2H) , 2.73-2.64 (m, 2H) , 2.25-1.76 (m, 2H) .

[0382] Example 14. Synthesis of I-24:



[0383] Experimental procedure:

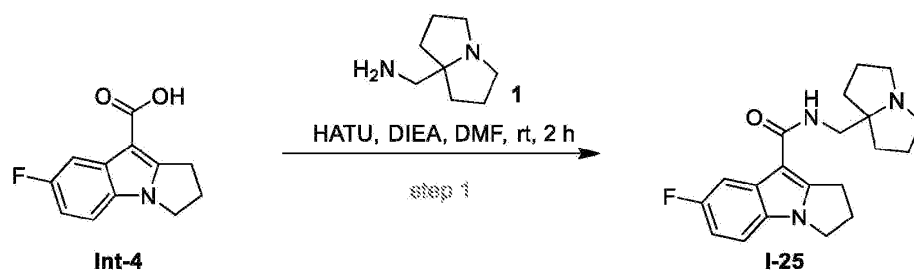
[0384] Step 1

[0385] To a mixture of 7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (30 mg, 0.14 mmol) , 1-azabicyclo [2.2.1] heptan-3-amine (15.4 mg, 0.14 mmol) and DIEA (53.1 mg, 0.41 mmol) in DMF (5 mL) was added HATU (62.5 mg, 0.16 mmol) . The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/ WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give N- (1-azabicyclo [2.2.1] heptan-3-yl) -7-fluoro-2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (14.4 mg, 34%) as a yellow solid.

[0386] MS (ESI) : mass calcd. for C₁₈H₂₀FN₃O, 313.16, m/z found 314.1 [M+H]⁺.

[0387] ¹H NMR (400 MHz, MeOD) δ 8.49 (s, 1H) , 7.59-7.57 (m, 1H) , 7.33-7.29 (m, 1H) , 6.97-6.91 (m, 1H) , 4.58-4.13 (m, 3H) , 3.83-3.60 (m, 1H) , 3.43-3.33 (m, 3H) , 3.30-3.24 (m, 3H) , 3.14-3.03 (m, 2H) , 2.73-2.65 (m, 2H) , 2.19-1.78 (m, 2H) .

[0388] Example 15. Synthesis of I-25:



[0389] Experimental procedure:

[0390] Step 1

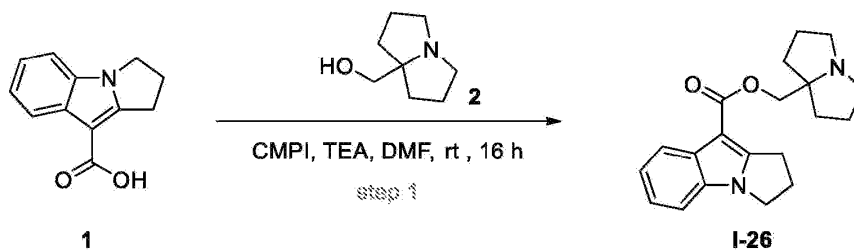
[0391] To a mixture of 7-fluoro-2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylic acid (86 mg, 0.39 mmol) and DIEA (230 mg, 1.78 mmol) in DMF (2 mL) was added HATU (142 mg, 0.37 mmol) in portions and the mixture was stirred at 25 °C for 30

min. Hexahydropyrrolizin-7a-ylmethanamine (50 mg, 0.35 mmol) was added at 0 °C and the mixture was stirred at 25 °C for 1 h. The mixture was diluted with water (50 mL) and extracted with EA (50 mL x 3). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um; mobile phase A: water (0.1%FA), B: Acetonitrile, 15 ~ 45%B in 10 min; flow rate: 30 mL/min; wavelength: 214/254 nm) to give 7-fluoro-N-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamide formate (97.3 mg, 79%) as a white solid.

[0392] MS (ESI): mass calcd. for C₂₀H₂₄FN₃O, 341.19, m/z found 342.2 [M+H]⁺.

[0393] ¹H NMR (400 MHz, DMSO) δ 8.31 (s, 1H), 7.72 (dd, J = 10.8, 2.8 Hz, 1H), 7.39 (dd, J = 8.8, 4.8 Hz, 1H), 7.32-7.23 (m, 1H), 7.02-6.95 (m, 1H), 4.13 (t, J = 7.2 Hz, 2H), 3.41 (d, J = 6.0 Hz, 2H), 3.26 (t, J = 7.6 Hz, 2H), 3.22-3.15 (m, 2H), 2.85-2.75 (m, 2H), 2.65-2.55 (m, 2H), 1.99-1.82 (m, 4H), 1.82-1.61 (m, 4H).

[0394] Example 16. Synthesis of I-26:



[0395] Experimental procedure:

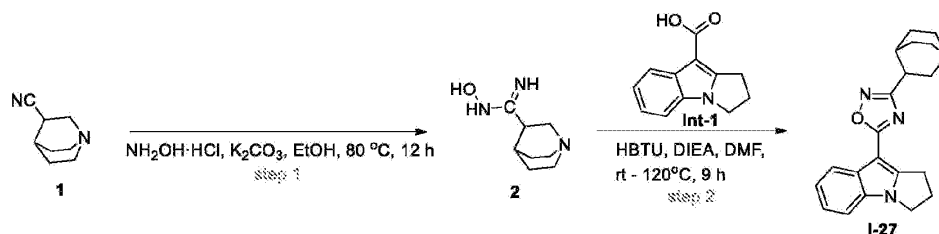
[0396] Step 1

[0397] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.50 mmol), hexahydropyrrolizin-7a-ylmethanol (70.2 mg, 0.50 mmol), 2-chloro-1-methylpyridinium iodide (CMPI) (165.1 mg, 0.65 mmol) and Et₃N (75.4 mg, 0.75 mmol) in DMF (10 mL) was added 4-DMAP (60.7 mg, 0.50 mmol) and the reaction mixture was stirred at room temperature for 16 h. After reaction, the mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile), flow rate: 30 ml/min, wavelength: 214/254 nm) to give (tetrahydro-1H-pyrrolizin-7a(5H)-yl)methyl 2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxylate formate (7 mg, 4%) as a white solid.

[0398] MS (ESI): mass calcd. for C₂₀H₂₄N₂O₂, 324.18, m/z found 325.2 [M+H]⁺.

[0399] ^1H NMR (400 MHz, DMSO- d_6) δ 8.39 (s, 0.3H) , 7.96-7.93 (m, 1H) , 7.42-7.40 (m, 1H) , 7.19-7.15 (m, 2H) , 4.16 (t, J = 8.0 Hz, 2H) , 3.91 (s, 2H) , 3.21 (t, J = 8.0 Hz, 2H) , 2.96 -2.91 (m, 2H) , 2.64-2.52 (m, 4H) , 1.92-1.86 (m, 2H) , 1.85-1.69 (m, 4H) , 1.62-1.56 (m, 2H) .

[0400] Example 17. Synthesis of I-27:



[0401] Experimental procedure:

[0402] Step 1

[0403] To a mixture of 1-azabicyclo [2.2.2] octane-3-carbonitrile (190 mg, 1.40 mmol) in EtOH (20 mL) were added $\text{NH}_2\text{OH} \cdot \text{HCl}$ (193.9 mg, 2.79 mmol) and K_2CO_3 (578.5 mg, 4.19 mmol) . The reaction mixture was stirred at 80 °C for 12 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give N-hydroxyquinuclidine-3-carboximidamide (100 mg, crude) as a yellow solid which was used directly for the next step.

[0404] MS (ESI) : mass calcd. for $\text{C}_8\text{H}_{15}\text{N}_3\text{O}$, 169.12, m/z found 170.1 $[\text{M}+\text{H}]^+$.

[0405] Step 2

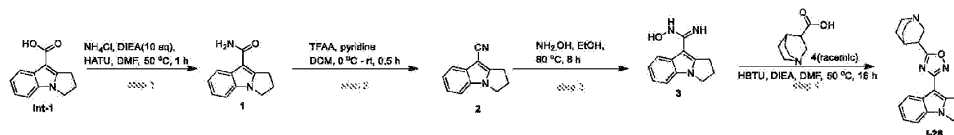
[0406] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (118.9 mg, 0.59 mmol) in DMF (10 mL) were added HBTU (246.5 mg, 0.65 mmol) and DIEA (229.1 mg, 1.77 mmol) . The mixture was stirred at room temperature for 1 h. N-hydroxy-1-azabicyclo [2.2.2] octane-3-carboximidamide (100 mg, 0.59 mmol) was added and the reaction mixture was stirred at 120 °C for 8 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 5um OBD 19*150mm, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 20 ml/min, wavelength: 214/254 nm) to give 5- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -3- (quinuclidin-3-yl) -1, 2, 4-oxadiazole trifluoroacetate (13.3 mg, 7%) as a yellow solid.

[0407] MS (ESI) : mass calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}$, 334.18, m/z found 335.1 $[\text{M}+\text{H}]^+$.

[0408] ^1H NMR (400 MHz, DMSO- d_6) δ 9.61 (s, 0.8H) , 8.06-8.04 (m, 1H) , 7.53-7.50 (m, 1H) , 7.29-7.24 (m, 2H) , 4.25 (t, J = 7.2 Hz, 2H) , 3.80-3.74 (m, 1H) , 3.68-3.62 (m,

2H) , 3.37-3.30 (m, 6H) , 2.72-2.65 (m, 2H) , 2.56-2.54 (m, 1H) , 2.09-1.97 (m, 2H) , 1.87-1.75 (m, 2H) .

[0409] Example 18. Synthesis of I-28:



[0410] Experimental procedure:

[0411] Step 1

[0412] To a solution of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (600 mg, 2.99 mmol) in DMF (12 mL) were added DIEA (3.85 g, 29.82 mmol) and HATU (1.70 g, 4.47 mmol) at room temperature. After stirring for 30 minutes, NH_4Cl (0.96 g, 17.89 mmol) was added, and the reaction mixture was stirred at 50 °C for 1 h. The mixture was concentrated to give a residue which was purified by silica gel column chromatography (DCM/MeOH=20: 1) to give 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (500 mg, 79%) as a white solid.

[0413] MS (ESI) : mass calcd. for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}$, 200.09, m/z found 201.1 $[\text{M}+\text{H}]^+$.

[0414] Step 2

[0415] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (500 mg, 2.50 mmol) and pyridine (1.97 g, 25 mmol) in DCM (50 mL) was added TFAA (1.84 g, 8.75 mmol) dropwise at 0 °C. After stirring at room temperature for 0.5 h, the reaction mixture was quenched with water and extracted with DCM (20 mL $\times$ 3) . The combined organic layer was washed with brine (10 mL $\times$ 2) , dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product which was purified by silica gel column chromatography (PE/EA =1: 1) to afford 1H, 2H, 3H-benzo [b] pyrrolizine-9-carbonitrile (350 mg, 73%) as a white solid.

[0416] MS (ESI) : mass calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_2$, 182.08, m/z found 183.1 $[\text{M}+\text{H}]^+$.

[0417] Step 3

[0418] To a solution of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carbonitrile (350 mg, 1.92 mmol) in EtOH (35 mL) was added $\text{NH}_2\text{OH}/\text{H}_2\text{O}$ (3.5 mL) dropwise at room temperature and the reaction mixture was stirred at 80 °C for 8 hours. The mixture was concentrated under reduced pressure to afford crude product (400 mg, crude) as a white solid.

[0419] MS (ESI) : mass calcd. for $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}$, 215.11, m/z found 216.1 $[\text{M}+\text{H}]^+$.

[0420] Step 4

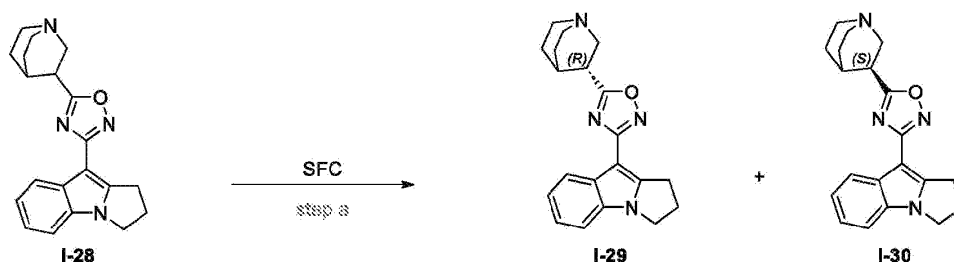
[0421] To a solution of (3S) -1-azabicyclo [2.2.2] octane-3-carboxylic acid (180 mg, 1.16 mmol) in dimethylformamide (8 mL) were added 2- (1H-benzotriazole-1-yl) -1, 1, 3, 3-tetramethyluronium tetrafluoroborate (410 mg, 1.28 mmol) and DIEA (450 mg,

3.48 mmol) at room temperature. After stirring for 1 h, N-hydroxy-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboximidamide (250 mg, 1.16 mmol) was added and the reaction mixture was stirred at 50 °C for 16 h. The reaction mixture was quenched with water and extracted with EA (20 mL× 3) . The combined organic layer was washed with brine (20 mL × 2) , dried over Na₂SO₄ and concentrated under reduced pressure to afford the crude product which was purified by prep-HPLC (Welch 10u C18 250 x 21.2 mm, Mobile Phase A: water (0.1%NH₃) , B (Acetonitrile) , 70~100%of B in A, 9 min, Flow rate: 30ml/min, wavelength: 214/254 nm) to give (3R) -3- (3- {1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -1, 2, 4-oxadiazol-5-yl) -1-azabicyclo [2.2.2] octane (33 mg, 8%) as a pink solid.

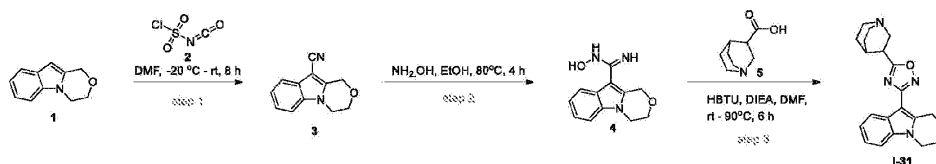
[0422] MS (ESI) : mass calcd. for C₂₀H₂₂N₄O, 334.18, m/z found 335.2 [M+H]⁺.

[0423] ¹H NMR (400 MHz, DMSO-d₆) δ 8.04-7.94 (m, 1H) , 7.50-7.39 (m, 1H) , 7.24-7.11 (m, 2H) , 4.18 (t, J = 8.0 Hz, 2H) , 3.30-3.26 (m, 5H) , 2.89-2.79 (m, 4H) , 2.67-2.59 (m, 2H) , 2.22-2.20 (m, 1H) , 1.79-1.52 (m, 3H) , 1.48 -1.39 (m, 1H) .

[0424] Example 19. Synthesis of I-29 &I-30:



- [0429] MS (ESI) : mass calcd. for $C_{20}H_{22}N_4O$, 334.18, m/z found 335.2 $[M+H]^+$.
- [0430] 1H NMR (400 MHz, DMSO) δ 9.63 (s, 1H) , 8.00-7.97 (m, 1H) , 7.48 -7.44 (m, 1H) , 7.23-7.17 (m, 2H) , 4.20 (t, J = 8.0 Hz, 2H) , 4.01-3.63 (m, 3H) , 3.38-3.35 (m, 1H) , 3.32-3.26 (m, 4H) , 2.71-2.60 (m, 2H) , 2.55-2.50 (m, 2H) , 2.10-2.08 (m, 1H) , 2.02-1.94 (m, 1H) , 1.84-1.81 (m, 2H) .
- [0431] I-30
- [0432] MS (ESI) : mass calcd. for $C_{20}H_{22}N_4O$, 334.18, m/z found 335.2 $[M+H]^+$.
- [0433] 1H NMR (400 MHz, DMSO) δ 9.63 (s, 1H) , 8.00-7.97 (m, 1H) , 7.48-7.44 (m, 1H) , 7.23-7.17 (m, 2H) , 4.20 (t, J = 8.0 Hz, 2H) , 4.01-3.63 (m, 3H) , 3.38-3.35 (m, 1H) , 3.32-3.26 (m, 4H) , 2.71-2.60 (m, 2H) , 2.55-2.50 (m, 2H) , 2.10-2.08 (m, 1H) , 2.02-1.94 (m, 1H) , 1.84-1.81 (m, 2H) .
- [0434] Example 20. Synthesis of I-31:



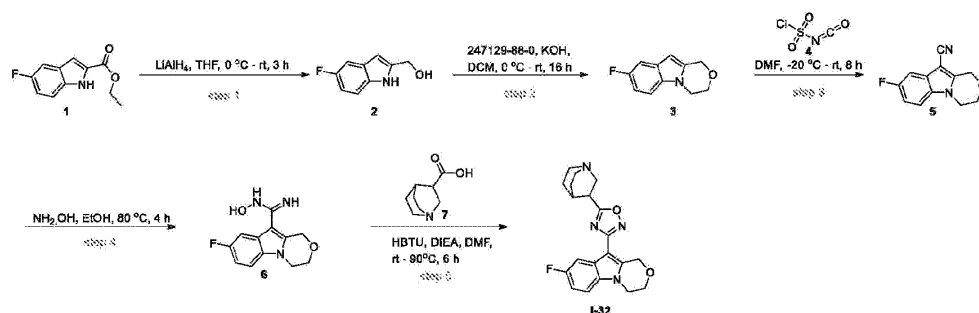
- [0435] Experimental procedure:
- [0436] Step 1
- [0437] To a mixture of 1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole (450 mg, 2.60 mmol) in DMF (10 mL) was added [(chlorosulfonyl) imino] methanone (441.2 mg, 3.12 mmol) at $-20^{\circ}C$ and the reaction mixture was then stirred at room temperature for 8 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give 1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carbonitrile (400 mg, 70%) as a yellow solid which was used for the next step directly.
- [0438] MS (ESI) : mass calcd. for $C_{12}H_{10}N_2O$, 198.08, m/z found 199.1 $[M+H]^+$.
- [0439] Step 2
- [0440] To a solution of 1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carbonitrile (350 mg, 1.77 mmol) in EtOH (10 mL) was added $NH_2OH \cdot H_2O$ (116.6 mg, 3.53 mmol) and the reaction mixture was heated to $80^{\circ}C$ and stirred for 4 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The combined organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give N-hydroxy-1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carboximidamide (350 mg, 69%) as a yellow solid which was used for the next step directly.
- [0441] MS (ESI) : mass calcd. for $C_{12}H_{13}N_3O_2$, 231.10, m/z found 232.1 $[M+H]^+$.
- [0442] Step 3

[0443] To a mixture of 1-azabicyclo [2.2.2] octane-3-carboxylic acid (67.1 mg, 0.43 mmol) in DMF (10 mL) were added HBTU (196.8 mg, 0.52 mmol) and DIEA (167.7 mg, 1.30 mmol) . The mixture was stirred at room temperature for 1 h. N-hydroxy-1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carboximidamide (100 mg, 0.43 mmol) was then added and the reaction mixture was heated to 90 °C and stirred for 5 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 5um OBD 19*150mm, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 20 ml/min, wavelength: 214/254 nm) to give 10- (5- (quinuclidin-3-yl) -1, 2, 4-oxadiazol-3-yl) -3, 4-dihydro-1H- [1, 4] oxazino [4, 3-a] indole formate (9.7 mg, 6%) as a white solid.

[0444] MS (ESI) : mass calcd. for C₂₀H₂₂N₄O₂, 350.17, m/z found 351.1 [M+H]⁺.

[0445] ¹H NMR (400 MHz, DMSO-d₆) δ 8.28 (s, 0.5H) , 8.09-8.07 (m, 1H) , 7.56-7.54 (m, 1H) , 7.30-7.24 (m, 2H) , 5.27 (s, 2H) , 4.21-4.09 (m, 4H) , 3.37-3.32 (m, 1H) , 3.28-3.26 (m, 2H) , 2.89-2.74 (m, 4H) , 2.20-2.19 (m, 1H) , 1.73-1.42 (m, 4H) .

[0446] Example 21. Synthesis of I-32:



[0447] Experimental procedure:

[0448] Step 1

[0449] To a solution of ethyl 5-fluoro-1H-indole-2-carboxylate (10.0 g, 48 mmol) in THF (200 mL) was added LiAlH₄ (2.2 g, 57.9 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with H₂O (6 mL) and 15%NaOH (9 mL) . The mixture was filtered, the filtrate was diluted with water (500 mL) and extracted with EA (300 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by flash chromatography (PE/EA =100/1 to 1/1) to give (5-fluoro-1H-indol-2-yl) methanol (7 g, 87%) as a yellow solid.

[0450] MS (ESI) : mass calcd. for C₉H₈FNO, 165.06, m/z found 166.1 [M+H]⁺.

[0451] Step 2

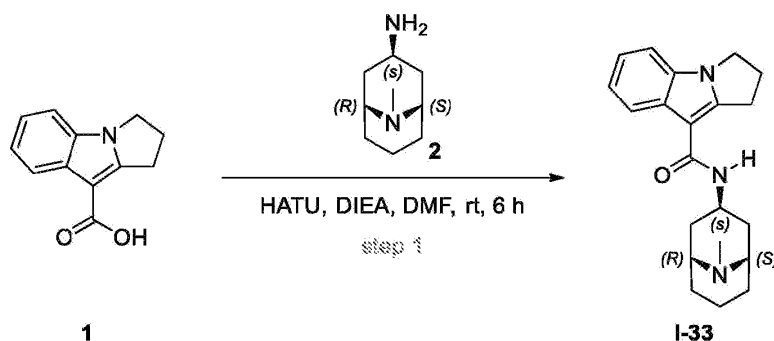
- [0452] To a solution of (5-fluoro-1H-indol-2-yl) methanol (2.0 g, 12.1 mmol) in DCM (40 mL) was added KOH (1.7 g, 30.2 mmol) at 0 °C and the mixture was stirred at this temperature for 0.5 h. Ethenyldiphenylsulfonium trifluoromethanesulfonate (5.26 g, 14.5 mmol) was added and the reaction mixture was warmed up and stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure to give the crude product which was purified by flash chromatography (PE/EA=100/1 to 10/1) to give 8-fluoro-1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole (1.2 g, 49%) as a yellow solid.
- [0453] MS (ESI) : mass calcd. for $C_{11}H_9FNO$, 191.07, m/z found 192.1 [M+H]⁺.
- [0454] Step 3
- [0455] To a solution of 8-fluoro-1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole (550 mg, 2.88 mmol) in DMF (10 mL) was added [(chlorosulfonyl) imino] methanone (407 mg, 2.88 mmol) at -20 °C. The reaction mixture was warmed up to room temperature and stirred for 8 h. The reaction mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue which was purified by silica gel column chromatography (PE/EA=100/1 to 5/1) to give 8-fluoro-1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carbonitrile (500 mg, 69%) as a yellow solid.
- [0456] MS (ESI) : mass calcd. for $C_{12}H_9FN_2O$, 216.07, m/z found 217.1 [M+H]⁺.
- [0457] Step 4
- [0458] To a solution of 8-fluoro-1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carbonitrile (450 mg, 2.08 mmol) in EtOH (10 mL) was added NH_2OH/H_2O (137 mg, 4.16 mmol) and the reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give 8-fluoro-N-hydroxy-1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carboximidamide (450 mg, crude) as a yellow solid.
- [0459] MS (ESI) : mass calcd. for $C_{12}H_{12}FN_3O_2$, 249.09, m/z found 250.1 [M+H]⁺.
- [0460] Step 5
- [0461] To a solution of 1-azabicyclo [2.2.2] octane-3-carboxylic acid (62 mg, 0.40 mmol) in DMF (10 mL) were added HBTU (183 mg, 0.48 mmol) and DIEA (156 mg, 1.20 mmol) . The mixture was stirred at room temperature for 1 h. 8-fluoro-N-hydroxy-1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carboximidamide (100 mg, 0.40 mmol) was added and the reaction mixture was stirred at 90 °C for 5 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude product which was purified by Prep-HPLC (Xbridge prep c18 5um

OBD 19*150mm, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 20 ml/min, wavelength: 214/254 nm) to give 8-fluoro-10- (5- (quinuclidin-3-yl) -1, 2, 4-oxadiazol-3-yl) -3, 4-dihydro-1H- [1, 4] oxazino [4, 3-a] indole formate (10.2 mg, 7%) as a white solid.

[0462] MS (ESI) : mass calcd. for $C_{20}H_{21}FN_4O_2$, 368.16, m/z found 369.1 $[M+H]^+$.

[0463] 1H NMR (400 MHz, DMSO- d_6) δ 8.26 (s, 1H) , 7.76-7.73 (m, 1H) , 7.61-7.58 (m, 1H) , 7.17-7.12 (m, 1H) , 5.25 (s, 2H) , 4.22-4.18 (m, 4H) , 3.38-3.32 (m, 1H) , 3.28-3.26 (m, 2H) , 2.84-2.80 (m, 4H) , 2.21-2.19 (m, 1H) , 1.74-1.42 (m, 4H) .

[0464] Example 22. Synthesis of I-33:



[0465] Experimental procedure:

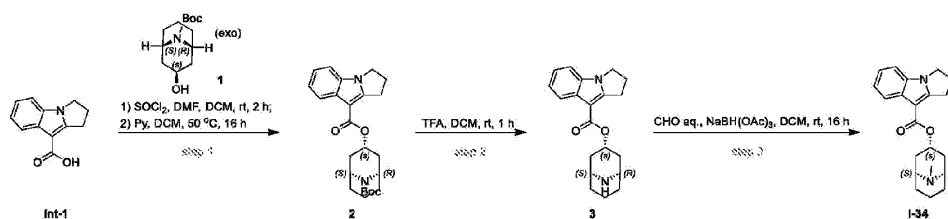
[0466] Step 1

[0467] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (50 mg, 0.25 mmol) , exo- (1R, 3S, 5S) -9-methyl-9-azabicyclo [3.3.1] nonan-3-amine (38.3 mg, 0.25 mmol) and DIEA (96.4 mg, 0.75 mmol) in DMF (5 mL) was added HATU (113.4 mg, 0.30 mmol) . After stirring at room temperature for 6 h, the reaction mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude product which was purified by prep-HPLC (Xbridge prep c18 5um OBD 19*150mm, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 20 ml/min, wavelength: 214/254 nm) to give N- ((1R, 3s, 5S) -9-methyl-9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (28.6 mg, 34%) as a white solid.

[0468] MS (ESI) : mass calcd. for $C_{21}H_{27}N_3O$, 337.22, m/z found 338.2 $[M+H]^+$.

[0469] 1H NMR (400 MHz, DMSO- d_6) δ 8.29 (s, 1H) , 7.92-7.90 (m, 1H) , 7.37-7.34 (m, 1H) , 7.14-7.07 (m, 2H) , 6.89 (d, J = 8.0 Hz, 1H) , 4.73-4.67 (m, 1H) , 4.11 (t, J = 7.2 Hz, 2H) , 3.22 (t, J = 7.2 Hz, 2H) , 3.01 (s, 2H) , 2.62-2.54 (m, 5H) , 2.08-1.97 (m, 4H) , 1.89-1.57 (m, 6H) .

[0470] Example 23. Synthesis of I-34:



[0471] Experimental procedure:

[0472] Step 1

[0473] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (200 mg, 0.99 mmol) in DCM (5 mL) at 0 °C was added SOCl₂ (236 mg, 1.98 mmol) followed by a drop of DMF dropwise. The reaction mixture was stirred at room temperature for 2 h under N₂. The mixture was concentrated under reduced pressure to give a crude product which was re-dissolved in DCM (5 mL). Pyridine (393 mg, 4.96 mmol) and tert-butyl (1R, 3s, 5S) -3-hydroxy-9-azabicyclo [3.3.1] nonane-9-carboxylate (96 mg, 0.39 mmol) were added at room temperature and the mixture was stirred at 50 °C for 16 h. The mixture was concentrated under reduced pressure to give the crude product which was purified by flash chromatography (mobile phase A: PE, B: EA; 0 ~ 25% of B in A) to give (1R, 3s, 5S) -9- (tert-butoxycarbonyl) -9-azabicyclo [3.3.1] nonan-3-yl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate (214 mg, 48%) as a yellow solid.

[0474] MS (ESI) : mass calcd. for C₂₅H₃₂N₂O₄, 424.24, m/z found 447.2 [M+Na]⁺.

[0475] Step 2

[0476] To a mixture of (1R, 3s, 5S) -9- (tert-butoxycarbonyl) -9-azabicyclo [3.3.1] nonan-3-yl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate (214 mg, 0.50 mmol) in DCM (6 mL) at 0 °C was added TFA (2 mL). The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was neutralized with NaHCO₃ (aq.) and extracted with EA (20 mL x 3). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give (1R, 3s, 5S) -9-azabicyclo [3.3.1] nonan-3-yl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate (159 mg, 97%) as an off-white solid.

[0477] MS (ESI) : mass calcd. for C₂₀H₂₄N₂O₂, 324.18, m/z found 325.2 [M+H]⁺.

[0478] Step 3

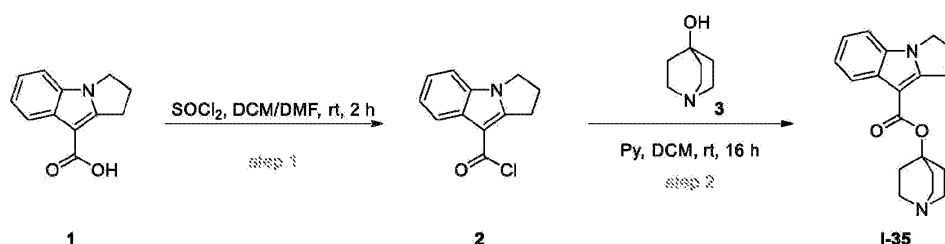
[0479] To a mixture of (1R, 5S) -9-azabicyclo [3.3.1] nonan-3-yl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate (169 mg, 0.52 mmol) and formaldehyde aqueous solution (37%, 85 mg, 1.04 mmol) in DCM (5 mL) was added NaBH(OAc)₃ (331 mg, 1.56 mmol) at room temperature. The reaction mixture was stirred for 16 h. The mixture was quenched with Na₂S₂O₃ aq. (20 mL) and extracted with EA (20 mL x 3). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated

under reduced pressure to give the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um; mobile phase A: water (0.1%FA) , B: Acetonitrile, 23 ~ 33%B in 10 min; flow rate: 30 mL/min; wavelength: 214/254 nm) to give (1R, 3s, 5S) -9-methyl-9-azabicyclo [3.3.1] nonan-3-yl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate formate (125.6 mg, 71%) as an off-white solid.

[0480] MS (ESI) : mass calcd. for $C_{21}H_{26}N_2O_2$, 338.20, m/z found 339.2 [M+H]⁺.

[0481] ¹H NMR (400 MHz, CDCl₃) δ 8.60 (s, 0.86H) , 8.10-7.99 (m, 1H) , 7.30-7.27 (m, 1H) , 7.25-7.18 (m, 2H) , 5.89-5.74 (m, 1H) , 4.14 (t, J = 8.0 Hz, 2H) , 3.55-3.47 (m, 2H) , 3.30 (t, J = 8.0 Hz, 2H) , 2.85 (s, 3H) , 2.73-2.62 (m, 2H) , 2.48-2.23 (m, 6H) , 2.00-1.74 (m, 4H) .

[0482] Example 24. Synthesis of I-35:



[0483] Experimental procedure:

[0484] Step 1

[0485] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.50 mmol) in dichloromethane (10 mL) and DMF (0.5 mL) was added SOCl₂ (118.3 mg, 0.99 mmol) . The reaction mixture was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure to give 1H, 2H, 3H-benzo [b] pyrrolizine-9-carbonyl chloride (110 mg, crude) as a yellow solid which was used directly for the next step.

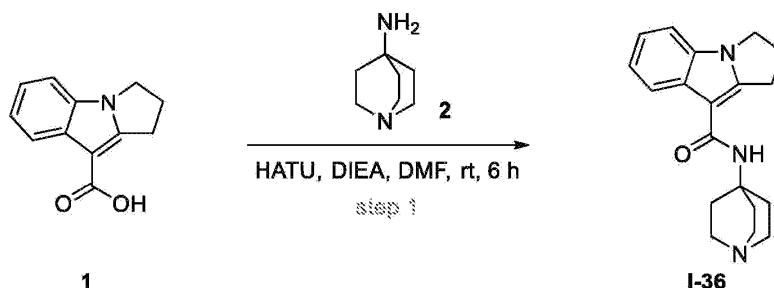
[0486] Step 2

[0487] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carbonyl chloride (100 mg, 0.46 mmol) in DCM (10 mL) were added pyridine (108.0 mg, 1.37 mmol) and 1-azabicyclo [2.2.2] octan-4-ol (57.9 mg, 0.46 mmol) . After stirring at room temperature for 16 h, the mixture was diluted with water (100 mL) and extracted with DCM (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by prep-HPLC (Xbridge prep c18 5um OBD 19*150mm, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 20 ml/min, wavelength: 214/254 nm) to give quinuclidin-4-yl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate trifluoroacetate (12.9 mg, 9%) as a grey solid.

[0488] MS (ESI) : mass calcd. for $C_{19}H_{22}N_2O_2$, 310.17, m/z found 311.2 [M+H]⁺.

[0489] ^1H NMR (400 MHz, DMSO- d_6) δ 9.62 (s, 0.80 H) , 7.88-7.86 (m, 1H) , 7.44-7.41 (m, 1H) , 7.20-7.15 (m, 2H) , 4.16 (t, J = 7.2 Hz, 2H) , 3.52-3.48 (m, 6H) , 3.18 (t, J = 7.6 Hz, 2H) , 2.67-2.55 (m, 2H) , 2.41-2.33 (m, 6H) .

[0490] Example 25. Synthesis of I-36:



[0491] Experimental procedure:

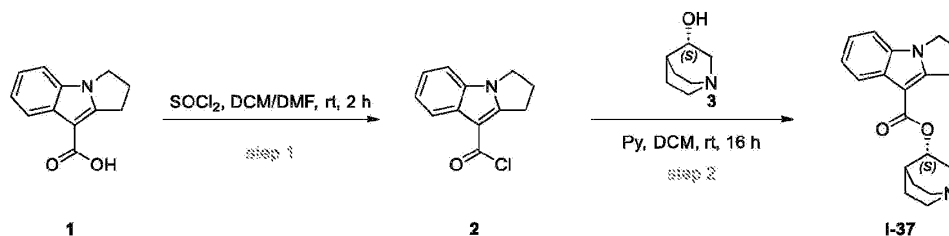
[0492] Step 1

[0493] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (50 mg, 0.25 mmol) , 1-azabicyclo [2.2.2] octan-4-amine (31.4 mg, 0.25 mmol) and DIEA (96.4 mg, 0.75 mmol) in DMF (5 mL) was added HATU (113.4 mg, 0.30 mmol) . After stirring at room temperature for 6 h, the mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give N- (quinuclidin-4-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (20.7 mg, 27%) as a yellow solid.

[0494] MS (ESI) : mass calcd. for $\text{C}_{19}\text{H}_{23}\text{N}_3\text{O}$, 309.18, m/z found 310.1 $[\text{M}+\text{H}]^+$.

[0495] ^1H NMR (400 MHz, DMSO- d_6) δ 8.31 (s, 1H) , 7.87-7.85 (m, 1H) , 7.36-7.34 (m, 1H) , 7.13-7.06 (m, 2H) , 6.50 (s, 1H) , 4.10 (t, J = 7.2 Hz, 2H) , 3.20 (t, J = 7.6 Hz, 2H) , 3.01-2.97 (m, 6H) , 2.61-2.54 (m, 2H) , 2.02-1.98 (m, 6H) .

[0496] Example 26. Synthesis of I-37:



[0497] Experimental procedure:

[0498] Step 1

[0499] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.50 mmol) in dichloromethane (10 mL) and DMF (0.5 mL) was added SOCl₂ (118.3 mg, 0.99 mmol) . The reaction mixture was stirred at 20 °C for 3 h. The mixture was concentrated under reduced pressure to give 1H, 2H, 3H-benzo [b] pyrrolizine-9-carbonyl chloride (110 mg, crude) as a yellow solid which was used directly for the next step.

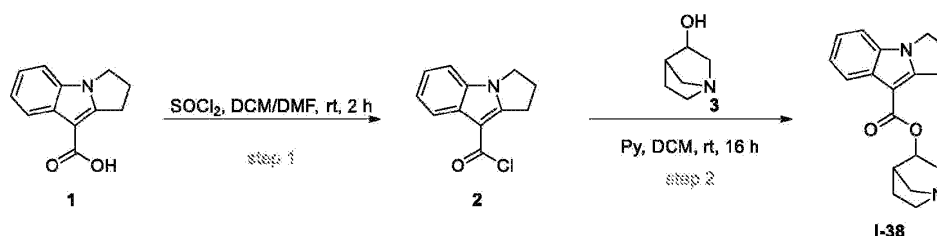
[0500] Step 2

[0501] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carbonyl chloride (100 mg, 0.46 mmol) in DCM (10 mL) were added pyridine (108.0 mg, 1.37 mmol) and (3S) -1-azabicyclo [2.2.2] octan-3-ol (57.9 mg, 0.46 mmol) . The reaction mixture was stirred at 20 °C for 16 h. The mixture was diluted with water (100 mL) and extracted with DCM (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give (S) -quinuclidin-3-yl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate formate (17.4 mg, 12%) as a white solid.

[0502] MS (ESI) : mass calcd. for C₁₉H₂₂N₂O₂, 310.17, m/z found 311.2 [M+H]⁺.

[0503] ¹H NMR (400 MHz, DMSO-d₆) δ 8.25 (s, 0.70 H) , 7.97-7.93 (m, 1H) , 7.43-7.40 (m, 1H) , 7.20-7.15 (m, 2H) , 4.94-4.92 (m, 1H) , 4.16 (t, J = 7.2 Hz, 2H) , 3.29-3.18 (m, 2H) , 2.88-2.85 (m, 2H) , 2.75-2.57 (m, 6H) , 1.91-1.89 (m, 1H) , 1.70-1.47 (m, 4H) .

[0504] Example 27. Synthesis of I-38:



[0505] Experimental procedure:

[0506] Step 1

[0507] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.50 mmol) in dichloromethane (10 mL) and DMF (0.5 mL) was added SOCl₂ (118.3 mg, 0.99 mmol) . The reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give 1H, 2H, 3H-benzo [b] pyrrolizine-9-carbonyl chloride (100 mg, crude) as a yellow solid which was used directly for the next step.

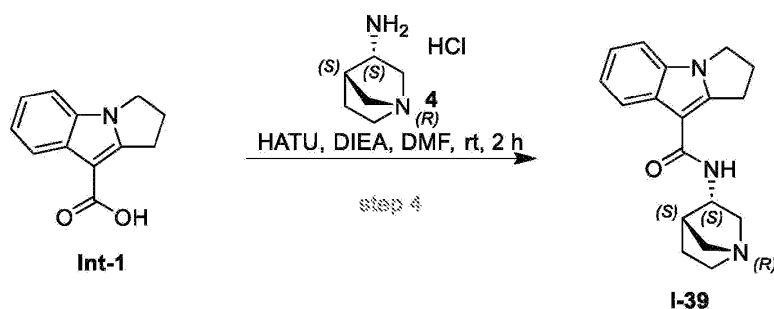
[0508] Step 2

[0509] To a solution of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carbonyl chloride (60 mg, 0.27 mmol) in DCM (5 mL) were added pyridine (64.8 mg, 0.82 mmol) and 1-azabicyclo [2.2.1] heptan-3-ol (30.9 mg, 0.27 mmol) . The reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with water (100 mL) and extracted with DCM (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give 1-azabicyclo [2.2.1] heptan-3-yl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate formate (17.5 mg, 21%) as a yellow solid.

[0510] MS (ESI) : mass calcd. for C₁₈H₂₀N₂O₂, 296.15, m/z found 297.2 [M+H]⁺.

[0511] ¹H NMR (400 MHz, DMSO-d₆) δ 8.27 (s, 1H) , 7.94-7.92 (m, 1H) , 7.43-7.40 (m, 1H) , 7.20-7.15 (m, 2H) , 5.17-5.14 (m, 1H) , 4.18-4.13 (m, 2H) , 3.25-3.10 (m, 3H) , 2.85-2.81 (m, 2H) , 2.64-2.57 (m, 4H) , 2.42-2.38 (m, 1H) , 2.33-2.24 (m, 1H) , 1.90-1.86 (m, 1H) , 1.52-1.48 (m, 1H) .

[0512] Example 28. Synthesis of I-39:



[0513] Experimental procedure:

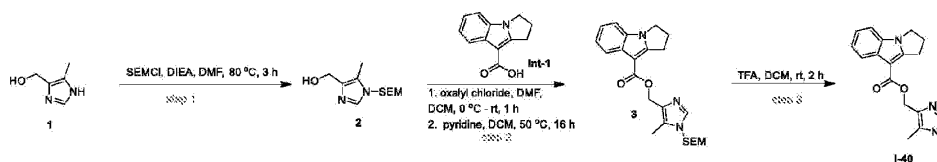
[0514] Step 1

[0515] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (54 mg, 0.26 mmol) and DIEA (157 mg, 1.21 mmol) in DMF (2 mL) was added HATU (97 mg, 0.25 mmol) in portion at 25 °C and the mixture was stirred for 30 min. (1R, 3S, 4S) -1-azabicyclo [2.2.1] heptan-3-amine hydrochloride (45 mg, 0.24 mmol) was added at 0 °C and the mixture was then stirred at 25 °C for 1 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3) . The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um; mobile phase A: water (0.1%FA) , B: Acetonitrile, 10 ~ 45%B in 10 min; flow rate: 30 mL/min; wavelength: 214/254 nm) to give N- ((1R, 3S, 4S) -1-azabicyclo [2.2.1] heptan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (53.7 mg, 74%) as a white solid.

[0516] MS (ESI) : mass calcd. for $C_{18}H_{21}N_3O$, 295.17, m/z found 296.2 $[M+H]^+$.

[0517] 1H NMR (400 MHz, DMSO) δ 8.17 (s, 0.23H) , 7.92-7.83 (m, 1H) , 7.47-7.32 (m, 2H) , 7.18-7.07 (m, 2H) , 4.49-4.38 (m, 1H) , 4.13 (t, J = 6.8 Hz, 2H) , 3.51 (t, J = 11.2 Hz, 1H) , 3.25 (t, J = 7.2 Hz, 2H) , 3.21-3.06 (m, 3H) , 3.03-2.94 (m, 2H) , 2.87-2.77 (m, 1H) , 2.64-2.55 (m, 2H) , 2.02-1.89 (m, 1H) , 1.85-1.77 (m, 1H) .

[0518] Example 29. Synthesis of I-40:



[0519] Experimental procedure:

[0520] Step 1

[0521] To a stirred solution of (5-methyl-1H-imidazol-4-yl) methanol (500 mg, 4.4591 mmol) in anhydrous DMF (13 mL) was added DIEA (1729.02 mg, 13.37 mmol) followed by SEMCl (892.11 mg, 5.35 mmol) . The resultant solution was heated to 80 °C for 3 h then cooled to room temperature. The reaction mixture was poured into brine (15 mL) and diluted with H_2O (6 mL) and EA (40 mL) . The organic phase was washed with brine (20 mL x 4) , dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the crude orange oil by flash chromatography on silica gel (DCM/MeOH/ NH_4OH , 95: 4: 1) provided (5-methyl-1-{ [2- (trimethylsilyl) ethoxy] methyl} imidazol-4-yl) methanol (450 mg, 39.4%) .

[0522] MS (ESI) : mass calcd. for $C_{11}H_{22}N_2O_2Si$, 242.15, m/z found 243.2 $[M+H]^+$.

[0523] Step 2

[0524] To a solution of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (130 mg, 0.646 mmol) in DCM (5mL) were added oxalyl chloride (246.03 mg, 1.9383 mmol) and DMF (9.44 mg, 0.1292 mmol) at 0 °C under N_2 . Then the mixture was stirred at room temperature under N_2 for 1 h. The mixture was concentrated to get the crude product. To the solution of the above crude product in DCM (5 mL) were added (5-methyl-1-{ [2-(trimethylsilyl) ethoxy] methyl} imidazol-4-yl) methanol (234.91 mg, 0.969 mmol) and TEA (130.76 mg, 1.2922 mmol) , then the mixture was stirred at 50 °C for 16 h under N_2 . The mixture was diluted with EtOAc and the precipitate was removed by filtering. The filtrate was washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product which was purified by silica gel chromatography column (DCM/MeOH =5: 1) to afford (5-methyl-1-{ [2- (trimethylsilyl) ethoxy] methyl} imidazol-4-yl) methyl 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylate (130 mg, 47%) as red oil.

[0525] MS (ESI) : mass calcd. for $C_{23}H_{31}N_3O_3Si$, 425.21, m/z found 426.2 $[M+H]^+$.

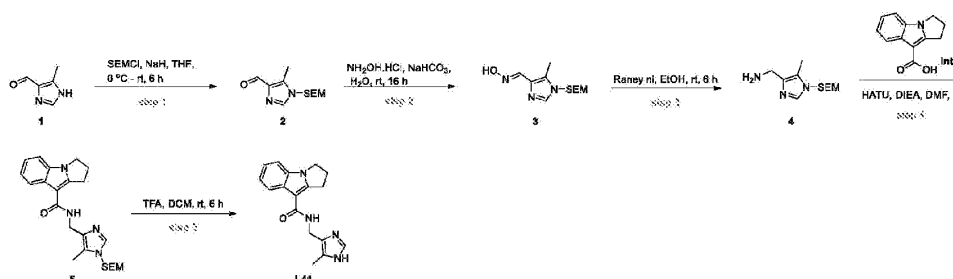
[0526] Step 3

[0527] To a solution of (5-methyl-1- { [2- (trimethylsilyl) ethoxy] methyl} imidazol-4-yl) methyl 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylate (130 mg, 0.3047 mmol) in DCM (1mL) was added TFA (2 ml) dropwise at 0 °C under N₂ and the mixture was stirred at room temperature under N₂ for 2 h. The mixture was concentrated under reduced pressure to afford a residue which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) , B (Acetonitrile) , 20~50% of B in A, 10 min, Flow rate: 30ml/min, wavelength: 214/254 nm) to afford (5-methyl-1H-imidazol-4-yl) methyl 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylate formate (16.8 mg, 18%) as a white solid.

[0528] MS (ESI) : mass calcd. for C₁₇H₁₇N₃O₂, 295.13, m/z found 296.1 [M+H]⁺.

[0529] ¹H NMR (400 MHz, DMSO) δ 8.17 (s, 1H) , 7.90-7.87 (m, 1H) , 7.50 (s, 1H) , 7.44-7.34 (m, 1H) , 7.21-7.08 (m, 2H) , 5.14 (s, 2H) , 4.14 (t, J = 8.0 Hz, 2H) , 3.14 (t, J = 8.0 Hz, 2H) , 2.60-2.54 (m, 2H) , 2.22 (s, 3H) .

[0530] Example 30. Synthesis of I-41:



[0531] Experimental procedure:

[0532] Step 1

[0533] To a solution of 5-methyl-1H-imidazole-4-carbaldehyde (1 g, 0.0091 mol) in DMF (20 mL) at 0 °C was added NaH (0.33 g, 0.014 mol) and the reaction mixture was stirred at 0 °C for 2 h. SEMCl (1.52 g, 9.1 mmol) was added, the reaction mixture was warmed to room temperature and stirred for 4 h. The mixture was diluted with water (200 mL) and extracted with EA (100 mL x 2) . The organic layer was concentrated to afford the crude product which was purified by silica gel column chromatography (PE: EA = 1: 1) to give 5-methyl-1- ((2- (trimethylsilyl) ethoxy) methyl) -1H-imidazole-4-carbaldehyde (1 g, 43%) as a yellow solid.

[0534] MS (ESI) : mass calcd. for C₁₁H₂₀N₂O₂Si, 240.13, m/z found 241.1 [M+H]⁺.

[0535] Step 2

[0536] To a mixture of 1- [(2-methoxyethyl) trimethyl-silyl] -5-methylimidazole-4-carbaldehyde (450 mg, 1.86 mmol) in H₂O (10 mL) were added NH₂OH. HCl (194.3 mg, 2.80 mmol) and Na₂CO₃ (592.8 mg, 5.59 mmol) . The

reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give (E)-5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-4-carbaldehyde oxime (450 mg, 75%) as a yellow solid which was used directly for the next step.

[0537] MS (ESI): mass calcd. for C₁₁H₂₁N₃O₂Si, 255.14, m/z found 256.2 [M+H]⁺.

[0538] Step 3

[0539] To a mixture of (E)-N-((1-((2-methoxyethyl)trimethylsilyl)-5-methylimidazol-4-yl)methylidene)hydroxylamine (400 mg, 1.56 mmol) in EtOH (10 mL) were added Raney-Ni (91.6 mg, 1.56 mmol) and NH₃·H₂O (54.7 mg, 1.56 mmol). The reaction mixture was stirred at room temperature under H₂ balloon for 6 h. After filtration, the filtrate was collected and concentrated in vacuo to give (5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)methanamine (200 mg, crude) as a yellow solid which was used directly for the next step.

[0540] MS (ESI): mass calcd. for C₁₁H₂₃N₃OSi, 241.16, m/z found 242.1 [M+H]⁺.

[0541] Step 4

[0542] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (120 mg, 0.60 mmol), (1-((2-methoxyethyl)trimethylsilyl)-5-methylimidazol-4-yl)methanamine (173.5 mg, 0.72 mmol) and DIEA (231.2 mg, 1.79 mmol) in DMF (10 mL) was added HATU (272.1 mg, 0.72 mmol). After stirring at room temperature for 6 h, the mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give N-((5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-4-yl)methyl)-2,3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (100 mg, 32%) as a yellow solid which was used directly for the next step.

[0543] MS (ESI): mass calcd. for C₂₃H₃₂N₄O₂Si, 424.23, m/z found 425.2 [M+H]⁺.

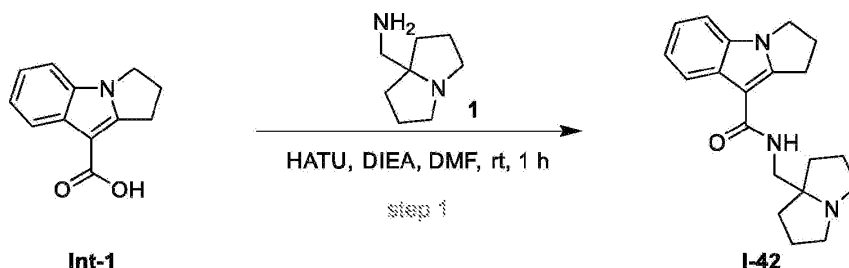
[0544] Step 5

[0545] A mixture of N-((1-((2-methoxyethyl)trimethylsilyl)-5-methylimidazol-4-yl)methyl)-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (100 mg, 0.24 mmol) in DCM/TFA=3/1 (12 mL) was stirred at room temperature for 6 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile), flow rate: 30 ml/min, wavelength: 214/254 nm) to give N-((5-methyl-1H-imidazol-4-yl)methyl)-2,3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (7.8 mg, 11%) as a white solid.

[0546] MS (ESI): mass calcd. for C₁₇H₁₈N₄O, 294.15, m/z found 295.2 [M+H]⁺.

[0547] ^1H NMR (400 MHz, DMSO- d_6) δ 11.42 (s, 1H) , 7.96-7.94 (m, 1H) , 7.45-7.08 (m, 5H) , 4.37-4.31 (m, 2H) , 4.10 (t, J = 7.2 Hz, 2H) , 3.21-3.19 (m, 2H) , 2.61-2.54 (m, 2H) , 2.19-2.12 (m, 3H) .

[0548] Example 31. Synthesis of I-42:



[0549] Experimental procedure:

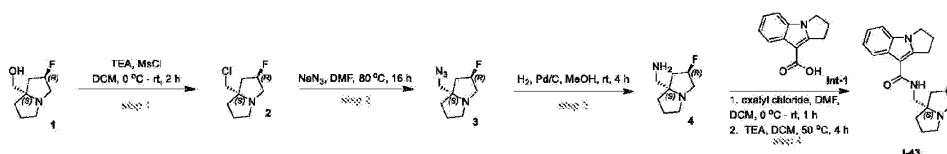
[0550] Step 1

[0551] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (142 mg, 0.70 mmol) and DIEA (414 mg, 3.20 mmol) in DMF (2 mL) was added HATU (256 mg, 0.67 mmol) in portions at room temperature. The mixture was stirred at room temperature for 30 min. To the mixture was added hexahydropyrrolizin-7a-ylmethanamine (90 mg, 0.64 mmol) at 0 °C and the mixture was stirred at 25 °C for 1 h. The mixture was diluted with water (50 mL) and extracted with EA (50 mL $\times$ 3) . The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue which was purified by prep-HPLC (WELCH Xtimate C18 21.2 $\times$ 250mm 10 μm ; mobile phase A: water (0.1%FA) , B: Acetonitrile, 20 ~ 50%B in 10 min; flow rate: 30 mL/min; wavelength: 214/254 nm) to give N- (hexahydropyrrolizin-7a-ylmethyl) -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide formate (134.3 mg, 64%) as a white solid.

[0552] MS (ESI) : mass calcd. for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}$, 323.20, m/z found 324.2 $[\text{M}+\text{H}]^+$.

[0553] ^1H NMR (400 MHz, DMSO- d_6) δ 8.35 (s, 1H) , 8.01-7.96 (m, 1H) , 7.41-7.34 (m, 1H) , 7.34-7.26 (t, J = 4.0 Hz, 1H) , 7.19-7.06 (m, 2H) , 4.12 (t, J = 8.0 Hz, 2H) , 3.44 (d, J = 4.0 Hz, 2H) , 3.30-3.15 (m, 4H) , 2.90-2.74 (m, 2H) , 2.66-2.25 (m, 2H) , 2.00-1.62 (m, 8H) .

[0554] Example 32. Synthesis of I-43:



[0555] Experimental procedure:

[0556] Step 1

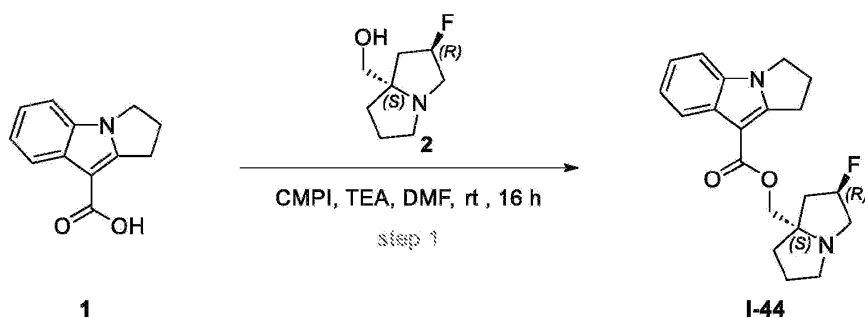
- [0557] To a mixture of [(2R, 7aS) -2-fluoro-hexahydropyrrolizin-7a-yl] methanol (2.0 g, 12.6 mmol) , Et₃N (3.82 g, 37.8 mmol) in DCM was added MsCl (1.88 g, 16.3 mmol) dropwise at 0 °C under N₂. The reaction mixture was stirred at room temperature under N₂ for 2 h. The mixture was diluted with water and extracted with DCM. The organic layer was washed with water, brine, dried over Na₂SO₄, filtered and concentrated to give (2R, 7aS) -7a-(chloromethyl) -2-fluorohexahydro-1H-pyrrolizine (2.2 g, crude) which was used in next step without further purification.
- [0558] MS (ESI) : mass calcd. for C₈H₁₃ClFN, 177.07, m/z found 178.1 [M+H]⁺.
- [0559] Step 2
- [0560] To a solution of (2R, 7aS) -7a- (chloromethyl) -2-fluoro-hexahydropyrrolizine (2 g, 11.3 mmol) in DMF (40 mL) was added NaN₃ (3.67 g, 56.5 mmol) at room temperature under N₂ protection and the reaction mixture was stirred at 80 °C for 16 h. The mixture was diluted with EA and filtered. The filtrate was washed with water, brine and dried over Na₂SO₄. The organic layer was concentrated to give a residue which was purified by silica gel column chromatography (PE/EA = 2: 1) to afford (2R, 7aS) -7a- (azidomethyl) -2-fluoro-hexahydropyrrolizine (1.6 g, 77%) as yellow oil.
- [0561] MS (ESI) : mass calcd. for C₈H₁₃FN₄, 184.11, m/z found 185.1 [M+H]⁺.
- [0562] Step 3
- [0563] To a solution of (2R, 7aS) -7a- (azidomethyl) -2-fluoro-hexahydropyrrolizine (200 mg, 1.09 mmol) in MeOH (10 mL) was added Pd/C (40 mg) and the reaction mixture was stirred at room temperature under H₂ for 4 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to give ((2R, 7aS) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methanamine (200 mg, crude) which was used in the next step directly.
- [0564] MS (ESI) : mass calcd. for C₈H₁₅FN₂, 158.12, m/z found 159.2 [M+H]⁺.
- [0565] Step 4
- [0566] To a solution of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.50 mmol) in DCM (5mL) was added oxalyl chloride (189 mg, 1.49 mmol) and one drop of DMF at 0 °C under N₂. Then the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated and redissolved in DCM and the solution was added to a mixture of [(2R, 7aS) -2-fluoro-hexahydropyrrolizin-7a-yl] methanamine (149 mg, 0.94 mmol) and TEA (286 mg, 2.83 mmol) . The reaction mixture was stirred at 50 °C for 4 h under N₂ protection. The mixture was then quenched with water and extracted with DCM and the combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a residue which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) , B (Acetonitrile) , 20

~100% of B in A, 11.5 min, Flow rate: 30ml/min, wavelength: 214/254 nm) to N- { [(2R, 7aS) -2-fluoro-hexahydropyrrolizin-7a-yl] methyl} -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (38 mg, 23%) as a white solid.

[0567] MS (ESI) : mass calcd. for $C_{20}H_{24}FN_3O$, 341.19, m/z found 342.2 [M+H]⁺.

[0568] ¹H NMR (400 MHz, DMSO-d₆) δ 7.87-7.85 (m, 1H), 7.36-7.34 (m, 1H), 7.17-7.03 (m, 2H), 6.44 (s, 1H), 4.87-4.74 (m, 1H), 4.10 (t, J = 8.0 Hz, 2H), 3.25-3.16 (m, 3H), 3.12-2.81 (m, 4H), 2.76-2.65 (m, 1H), 2.64-2.53 (m, 3H), 2.40-2.23 (m, 2H), 2.13-2.07 (m, 1H), 1.93-1.85 (m, 1H), 1.39-1.31 (m, 1H).

[0569] Example 33. Synthesis of I-44:



[0570] Experimental procedure:

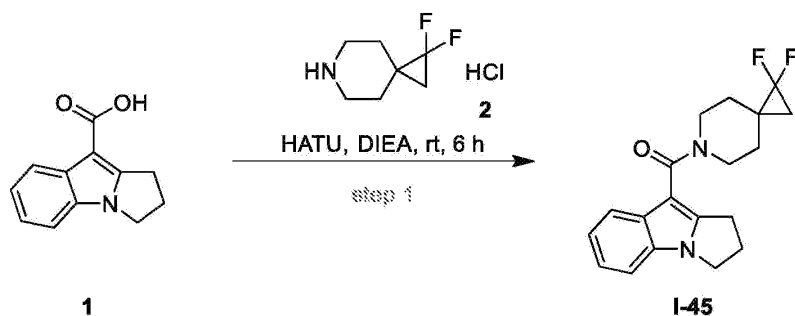
[0571] Step 1

[0572] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.50 mmol), [(2R, 7aS) -2-fluoro-hexahydropyrrolizin-7a-yl] methanol (79.1 mg, 0.50 mmol), CMPI (165.1 mg, 0.65 mmol) and Et₃N (75.4 mg, 0.75 mmol) in DMF (10 mL) was added 4-DMAP (60.7 mg, 0.50 mmol). The reaction mixture was stirred at 20 °C for 16 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile), flow rate: 30 ml/min, wavelength: 214/254 nm) to give ((2R, 7aS) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methyl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate formate (14.6 mg, 9%) as a white solid.

[0573] MS (ESI) : mass calcd. for $C_{20}H_{23}FN_2O_2$, 342.17, m/z found 343.1 [M+H]⁺.

[0574] ¹H NMR (400 MHz, DMSO-d₆) δ 8.39 (s, 0.2H), 7.96-7.92 (m, 1H), 7.43-7.39 (m, 1H), 7.20-7.15 (m, 2H), 5.34-5.21 (m, 1H), 4.16 (t, J = 8.0 Hz, 2H), 4.00-3.88 (m, 2H), 3.21 (t, J = 8.0 Hz, 2H), 3.11-3.09 (m, 2H), 3.04 -3.02 (m, 1H), 2.86-2.80 (m, 1H), 2.67-2.57 (m, 2H), 2.14-2.05 (m, 2H), 2.01-1.98 (m, 1H), 1.88-1.71 (m, 3H).

[0575] Example 34. Synthesis of I-45:



[0576] Experimental procedure:

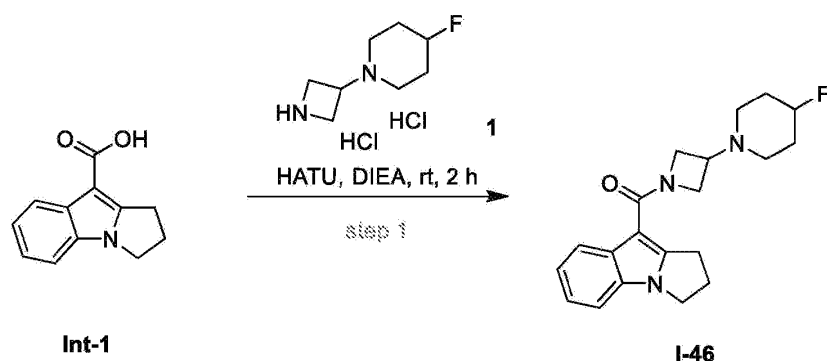
[0577] Step 1

[0578] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (40 mg, 0.20 mmol) , 1, 1-difluoro-6-azaspiro [2.5] octane (29.3 mg, 0.20 mmol) and DIEA (77.1 mg, 0.60 mmol) in DMF (5 mL) was added HATU (90.7 mg, 0.24 mmol) . The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/ WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give (1, 1-difluoro-6-azaspiro [2.5] octan-6-yl) (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) methanone (43.8 mg, 67%) as a white solid.

[0579] MS (ESI) : mass calcd. for C₁₉H₂₀F₂N₂O, 330.15, m/z found 331.1 [M+H]⁺.

[0580] ¹H NMR (400 MHz, DMSO-d₆) δ 7.55-7.53 (m, 1H) , 7.38-7.35 (m, 1H) , 7.14-7.06 (m, 2H) , 4.12 (t, J = 7.2 Hz, 2H) , 3.65-3.62 (m, 2H) , 3.52-3.44 (m, 2H) , 3.05 (t, J = 7.2 Hz, 2H) , 2.61-2.51 (m, 2H) , 1.70-1.63 (m, 2H) , 1.54-1.51 (m, 2H) , 1.34 (t, J = 8.4 Hz, 2H) .

[0581] Example 35. Synthesis of I-46:



[0582] Experimental procedure:

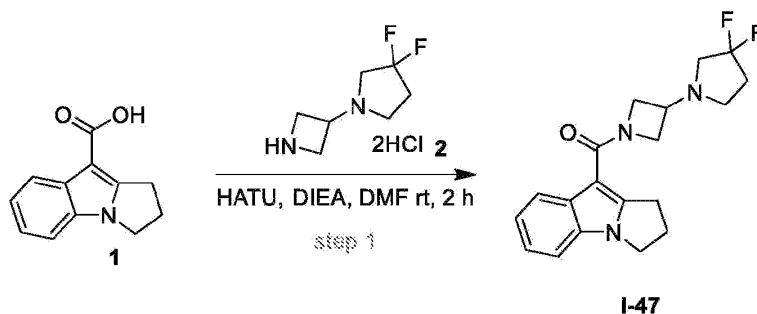
[0583] Step 1

[0584] To a mixture of 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylic acid (28 mg, 0.14 mmol) and DIEA (117 mg, 0.90 mmol) in DMF (1 mL) was added HATU (52 mg, 0.13 mmol) in portion at 25 °C. The mixture was stirred at 25 °C for 30 min. The mixture was added 1- (azetidin-3-yl) -4-fluoropiperidine dihydrochloride (30 mg, 0.12 mmol) at 25 °C. The mixture was stirred at 25 °C for 1 h. The mixture was diluted with water (20 mL) and extracted with EA (20 mL x 3) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product. The residue was purified by Prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um; mobile phase A: water (0.1%FA) , B: Acetonitrile, 15 ~ 55%B in 10 min; flow rate: 30 mL/min; wavelength: 214/254 nm) to give (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) (3- (4-fluoropiperidin-1-yl) azetidin-1-yl) methanone formate (43.0 mg, 96%) as a white solid.

[0585] MS (ESI) : mass calcd. for C₂₀H₂₄FN₃O, 341.19, m/z found 342.2 [M+H]⁺.

[0586] ¹H NMR (400 MHz, DMSO) δ 8.13 (s, 0.31H) , 7.74 (d, J=6.4 Hz, 1H) , 7.37 (d, J=6.8 Hz, 1H) , 7.24-7.00 (m, 2H) , 5.04-4.56 (m, 1H) , 4.38-4.02 (m, 5H) , 3.93-3.79 (m, 1H) , 3.20-2.96 (m, 3H) , 2.64-2.52 (m, 3H) , 2.45-2.36 (m, 1H) , 2.30-2.08 (m, 2H) , 1.96-1.59 (m, 4H) .

[0587] Example 36. Synthesis of I-47:



[0588] Experimental procedure:

[0589] Step 1

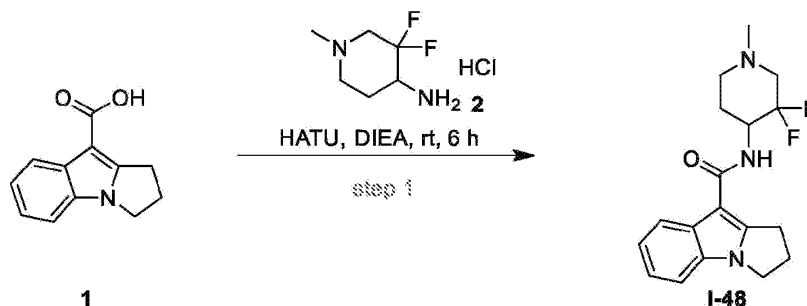
[0590] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (21 mg, 0.11 mmol) in dimethylformamide (5 mL) was added HATU (61 mg, 0.16 mmol) and DIEA (69 mg, 0.53 mmol) at 0 °C under N₂ protection. After stirring for 30 minutes, 1- (azetidin-3-yl) -3, 3-difluoropyrrolidine dihydrochloride (25 mg, 0.11 mmol) were added into the reaction mixture. The mixture was stirred at room temperature for 2 hours. LCMS showed the reaction was completed. The mixture was extracted with EA (10 mL× 3) . The combined organic layer was washed with brine (10 mL × 2) , dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product which was purified by Prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile phase A: H₂O (0.1%FA) , phase B: ACN,

35~65% of B in A, 10 min, Flow rate: 30ml/min, wavelength: 214/254 nm) to give 1-[1- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} carbonyl) azetidin-3-yl] -3, 3-difluoropyrrolidine formate (16.5 mg, 45%) as white solid.

[0591] MS (ESI) : mass calcd. for $C_{19}H_{21}F_2N_3O$, 345.17, m/z found 346.2 [M+H]⁺.

[0592] ¹H NMR (400 MHz, DMSO) δ 8.13 (s, 0.05 H) , 7.72 (dd, J = 8.0, 4.0 Hz, 1H) , 7.36 (dd, J = 8.0, 4.0 Hz, 1H) , 7.20-7.01 (m, 2H) , 4.12 (t, J = 8.0 Hz, 4H) , 3.94-3.92 (m, 2H) , 3.10 (t, J = 8.0 Hz, 2H) , 3.04-2.73 (m, 4H) , 2.61 -2.54 (m, 3H) , 2.30-2.23 (m, 2H) .

[0593] Example 37. Synthesis of I-48:



[0594] Experimental procedure:

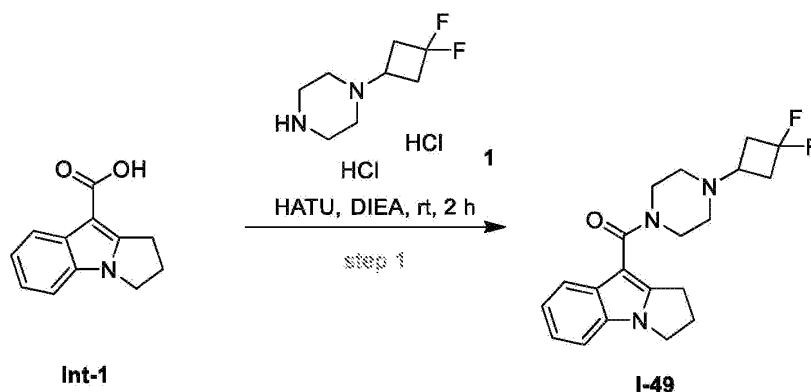
[0595] Step 1

[0596] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (40 mg, 0.20 mmol) , 3, 3-difluoro-1-methylpiperidin-4-amine (29.9 mg, 0.20 mmol) and DIEA (77.1 mg, 0.60 mmol) in DMF (5 mL) was added HATU (90.7 mg, 0.24 mmol) . The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give N- (3, 3-difluoro-1-methylpiperidin-4-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (36.5 mg, 52%) as a yellow solid.

[0597] MS (ESI) : mass calcd. for $C_{18}H_{21}F_2N_3O$, 333.17, m/z found 334.1 [M+H]⁺.

[0598] ¹H NMR (400 MHz, DMSO- d_6) δ 9.03 (s, 1H) , 8.14 (s, 0.1H) , 7.51 (d, J = 7.2 Hz, 1H) , 7.41 (d, J = 7.6 Hz, 1H) , 7.18-7.10 (m, 2H) , 4.45-4.40 (m, 1H) , 4.21 (d, J = 13.2 Hz, 1H) , 4.14 (t, J = 7.2 Hz, 2H) , 3.87-3.85 (m, 1H) , 3.72-3.61 (m, 1H) , 3.14-2.95 (m, 3H) , 2.67 2.57 (m, 5H) , 2.27-2.24 (m, 1H) , 1.75-1.65 (m, 1H) .

[0599] Example 38. Synthesis of I-49:



[0600] Experimental procedure:

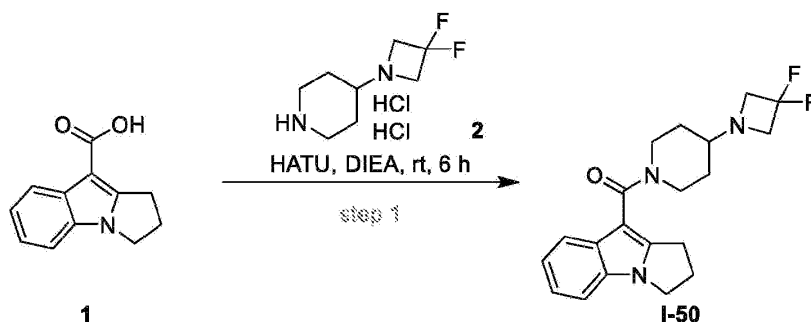
[0601] Step 1

[0602] To a mixture of 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylic acid (27 mg, 0.13 mmol) and DIEA (109 mg, 0.84 mmol) in DMF (1 mL) was added HATU (48 mg, 0.12 mmol) in portion at 25 °C. The mixture was stirred at 25 °C for 30 min. The mixture was added 1- (3, 3-difluorocyclobutyl) piperazine dihydrochloride (30 mg, 0.12 mmol) at 25 °C. The mixture was stirred at 25 °C for 1 h. The mixture was diluted with water (20 mL) and extracted with EA (20 mL x 3) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product. The residue was purified by Prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um; mobile phase A: water (0.1%FA) , B: Acetonitrile, 20 ~ 60%B in 10 min; flow rate: 30mL/min; wavelength: 214/254 nm) to give (4- (3, 3-difluorocyclobutyl) piperazin-1-yl) (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) methanone formate (29.9 mg, 68%) as a white solid.

[0603] MS (ESI) : mass calcd. for C₂₀H₂₃F₂N₃O, 359.42, m/z found 360.2 [M+H]⁺.

[0604] ¹H NMR (400 MHz, DMSO) δ 8.13 (s, 0.09H) , 7.52 (d, J= 7.2 Hz, 1H) , 7.36 (d, J=7.2 Hz, 1H) , 7.16-7.03 (m, 2H) , 4.12 (t, J = 7.2 Hz, 2H) , 3.54 (s, 4H) , 3.03 (t, J = 7.2 Hz, 2H) , 2.78-2.54 (m, 5H) , 2.48-2.26 (m, 6H) .

[0605] Example 39. Synthesis of I-50:



[0606] Experimental procedure:

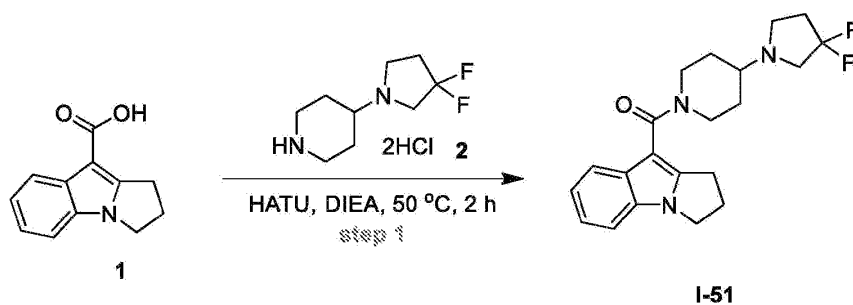
[0607] Step 1

[0608] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (40 mg, 0.20 mmol) , 4- (3, 3-difluoroazetidin-1-yl) piperidine (35.0 mg, 0.20 mmol) and DIEA (77.1 mg, 0.60 mmol) in DMF (5 mL) was added HATU (90.7 mg, 0.24 mmol) . The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give (4- (3, 3-difluoroazetidin-1-yl) piperidin-1-yl) (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) methanone formate (25.0 mg, 35%) as a white solid.

[0609] MS (ESI) : mass calcd. for C₂₀H₂₃F₂N₃O, 359.18, m/z found 360.1 [M+H]⁺.

[0610] ¹H NMR (400 MHz, DMSO-d₆) δ 8.14 (s, 0.15H) , 7.51-7.49 (m, 1H) , 7.36 (d, J = 7.2 Hz, 1H) , 7.13-7.06 (m, 2H) , 4.11 (t, J = 7.2 Hz, 2H) , 3.94-3.92 (m, 2H) , 3.58-3.56 (m, 3H) , 3.12-3.00 (m, 4H) , 2.59-2.53 (m, 2H) , 2.50-2.33 (m, 2H) , 1.75-1.69 (m, 2H) , 1.22-1.19 (m, 2H) .

[0611] Example 40. Synthesis of I-51:



[0612] Experimental procedure:

[0613] Step 1

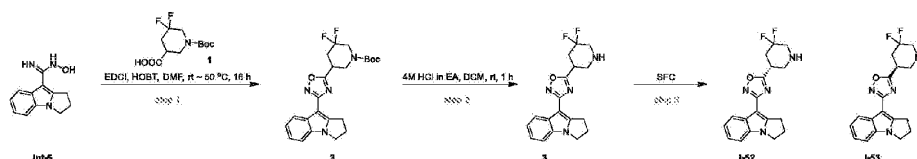
[0614] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (23 mg, 0.11 mmol) in dimethylformamide (5 mL) was added HATU (65 mg, 0.17 mmol) and DIEA (147 mg, 1.14 mmol) at 0 °C under N₂ protection. After stirring for 30 minutes, 4- (3, 3-difluoropyrrolidin-1-yl) piperidine hydrochloride (30 mg, 0.11 mmol) were added into the reaction mixture. The mixture was stirred at 50 °C for 2 hours. LCMS showed the reaction was completed. The mixture was extracted with EA (10 mL x 3) . The combined organic layer was washed with brine (10 mL x 2) , dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product which was purified by Prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) , B (Acetonitrile) , 20~60% of

B in A, 10 min, Flow rate: 30ml/min, wavelength: 214/254 nm) to give 1- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} carbonyl) -4- (3, 3-difluoropyrrolidin-1-yl) piperidine formate (27.0 mg, 63%) as light yellow solid.

[0615] MS (ESI) : mass calcd. for $C_{21}H_{25}F_2N_3O$, 373.20, m/z found 374.2 [M+H]⁺.

[0616] ¹H NMR (400 MHz, DMSO) δ 8.14 (s, 0.13H) , 7.52 (d, J = 8.0 Hz, 1H) , 7.38 (d, J = 8.0 Hz, 1H) , 7.19-7.06 (m, 2H) , 4.31-3.78 (m, 6H) , 3.57-3.48 (m, 2H) , 3.08-2.73 (m, 6H) , 2.62-2.54 (m, 3H) , 2.16-2.02 (m, 2H) , 1.53-1.41 (m, 2H) .

[0617] Example 41. Synthesis of I-52 & I-53:



[0618] Experimental procedure:

[0619] Step 1

[0620] To a mixture of 1- (tert-butoxycarbonyl) -5, 5-difluoropiperidine-3-carboxylic acid (150 mg, 0.56 mmol) and HOBt (114 mg, 0.84 mmol) and EDCI (162 mg, 0.84 mmol) in DMF (3 mL) was added N-hydroxy-2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboximidamide (146 mg, 0.67 mmol) at 25 °C. The reaction mixture was stirred at 50°C for 16 h under N₂. The mixture was diluted with water (20 mL) and extracted with EA (20 mL x 3) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product which was purified by flash chromatography (mobile phase A: PE, B: EA; 0 ~ 20% of B in A) to give tert-butyl 5- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3, 3-difluoropiperidine-1-carboxylate (120 mg, 42%) as a yellow solid. MS (ESI) : mass calcd. for $C_{23}H_{26}F_2N_4O_3$, 444.20, m/z found 467.2 [M+Na]⁺.

[0621] Step 2

[0622] To a mixture of tert-butyl 5- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3, 3-difluoropiperidine-1-carboxylate (115 mg, 0.26 mmol) in DCM (6 mL) was added 4M HCl in EA (2 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h under N₂. The mixture was concentrated under reduced pressure to give the crude product which was purified by reverse phase column (mobile phase A: H₂O (0.1% HCl) , B: ACN; 0 ~ 55% of B in A) to give 5- (5, 5-difluoropiperidin-3-yl) -3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazole (50 mg, 56%) as a white solid.

[0623] MS (ESI) : mass calcd. for $C_{18}H_{18}F_2N_4O$, 344.14, m/z found 345.1 [M+H]⁺.

[0624] Step 3

[0625] 5- (5, 5-difluoropiperidin-3-yl) -3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazole (50 mg) was separated via chiral prep-SFC (Daicel CHIRALCEL OJ, 250mm*30 mm I.D., 10 μ m; mobile phase A: CO₂, B: MeOH [0.2%NH₃ (7M Solution in MeOH)], A/B=65/35; flow rate: 70 g/min; wavelength: 214 nm; column temperature: 35 °C) to give (R) -5- (5, 5-difluoropiperidin-3-yl) -3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazole hydrochloride (peak 1, 20.1 mg, 40%) and (S) -5- (5, 5-difluoropiperidin-3-yl) -3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazole hydrochloride (peak 2, 21.4 mg, 42%) as white solids.

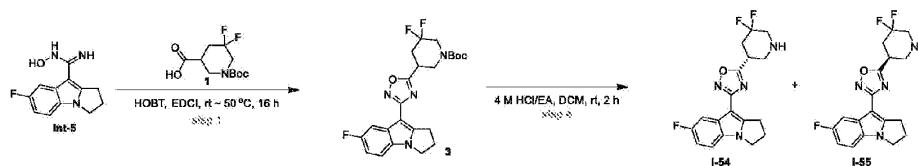
[0626] I-52 (peak 1)

[0627] MS (ESI) : mass calcd. for C₁₈H₁₈F₂N₄O, 344.14, m/z found 345.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 9.90 (br, 2H) , 8.03-7.96 (m, 1H) , 7.49-7.41 (m, 1H) , 7.24-7.14 (m, 2H) , 4.20 (t, J = 7.2 Hz, 2H) , 3.85-3.68 (m, 3H) , 3.63-3.44 (m, 2H) , 3.27 (t, J = 7.2 Hz, 2H) , 2.89-2.78 (m, 1H) , 2.70-2.55 (m, 3H) .

[0628] I-53 (peak 2)

[0629] MS (ESI) : mass calcd. for C₁₈H₁₈F₂N₄O, 344.14, m/z found 345.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 9.91 (br, 2H) , 8.03-7.97 (m, 1H) , 7.49-7.42 (m, 1H) , 7.25-7.14 (m, 2H) , 4.20 (t, J = 7.2 Hz, 2H) , 3.85-3.68 (m, 3H) , 3.63-3.45 (m, 2H) , 3.27 (t, J = 7.2 Hz, 2H) , 2.89-2.78 (m, 1H) , 2.70-2.55 (m, 3H) .

[0630] Example 42. Synthesis of I-54 & I-55:



[0631] Experimental procedure:

[0632] Step 1

[0633] To a solution of 1- [(tert-butoxy) carbonyl] -5, 5-difluoropiperidine-3-carboxylic acid (120 mg, 0.45 mmol) in dimethylformamide (4 mL) was added EDCI (130 mg, 0.68 mmol) and HOBT (92 mg, 0.68 mmol) at room temperature. After stirring for 1 h, 7-fluoro-N-hydroxy-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboximidamide (106 mg, 0.45 mmol) was added into the reaction mixture and the reaction mixture was stirred at room temperature for 1 h. Then the reaction mixture was stirred at 50 °C for 16 h. LCMS showed the reaction was completed. After reaction, the reaction mixture was quenched with water. The mixture was extracted with EA (20 mL×3) . The combined organic layer was washed with brine (20 mL × 2) , dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product which was purified by silica gel chromatography column (DCM/MeOH =20: 1) to afford tert-butyl 3, 3-difluoro-5- (3- {7-

fluoro-1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -1, 2, 4-oxadiazol-5-yl) piperidine-1-carboxylate (120 mg, 57.4%) as white solid.

[0634] MS (ESI) : mass calcd. for $C_{23}H_{25}F_3N_4O_3$, 462.19, m/z found 485.1 [M+Na]⁺.

[0635] Step 2

[0636] To a solution of tert-butyl 3, 3-difluoro-5- (3- {7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -1, 2, 4-oxadiazol-5-yl) piperidine-1-carboxylate (120 mg, 0.26 mmol) in DCM (2 mL) was added HCl in EA (4 M, 2 ml) at 0°C dropwise under N₂. Then the mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to afford crude product. The residue was purified by SFC (CHIRALCEL AD, 250mm × 30 mm I.D, 10μm, Mobile phase: CO₂/MeOH [0.2%NH₃ (7M Solution in MeOH)] = 45/55, Flow rate : 80 g/min, Wave length: UV 214 nm, Temperature: 35°C) to give (5R) -3, 3-difluoro-5- (3- {7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -1, 2, 4-oxadiazol-5-yl) piperidine (34 mg, 36.1%) as white solid and (5S) -3, 3-difluoro-5- (3- {7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -1, 2, 4-oxadiazol-5-yl) piperidine (34.6 mg, 36.8%) as white solid.

Rule 26,
11.12.2024

[0637] I-54

[0638] MS (ESI) : mass calcd. for $C_{18}H_{17}F_3N_4O$, 362.14, m/z found 363.1 [M+H]⁺.

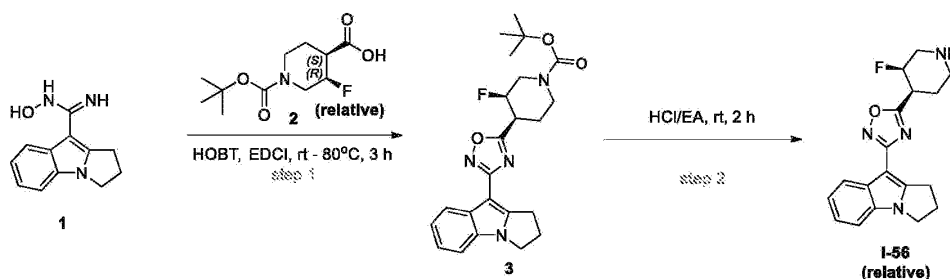
[0639] ¹H NMR (400 MHz, DMSO) δ 9.93 (s, 1H) , 7.68 (dd, J = 12.0, 4.0 Hz, 1H) , 7.51-7.49 (m, 1H) , 7.10-7.04 (m, 1H) , 4.21 (t, J = 8.0 Hz, 2H) , 3.92-3.66 (m, 3H) , 3.64-3.45 (m, 2H) , 3.27 (t, J = 8.0 Hz, 2H) , 2.88-2.79 (s, 1H) , 2.73-2.57 (m, 3H) .

[0640] I-55

[0641] MS (ESI) : mass calcd. for $C_{18}H_{17}F_3N_4O$, 362.14, m/z found 363.2 [M+H]⁺.

[0642] ¹H NMR (400 MHz, DMSO) δ 9.89 (s, 1H) , 7.68 (dd, J = 12.0, 4.0 Hz, 1H) , 7.51-7.46 (m, 1H) , 7.09-7.04 (m, 1H) , 4.21 (t, J = 8.0 Hz, 2H) , 3.88-3.69 (m, 3H) , 3.65-3.50 (m, 2H) , 3.27 (t, J = 8.0 Hz, 2H) , 2.88-2.79 (m, 1H) , 2.72-2.57 (m, 3H) .

[0643] Example 43. Synthesis of I-56:



[0644] Experimental procedure:

[0645] Step 1

[0646] To a mixture of (3R, 4S) -1- [(tert-butoxy) carbonyl] -3-fluoropiperidine-4-carboxylic acid (229.7 mg, 0.93 mmol) in ACN (10 mL) were added

HOBT (150.7 mg, 1.11 mmol) and EDCI (213.7 mg, 1.11 mmol). The mixture was stirred at room temperature for 1 h. N-hydroxy-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboximidamide (200 mg, 0.93 mmol) was added. The reaction mixture was stirred at 80 °C for 3 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was concentrated under reduced pressure to afford the crude product which was purified by silica gel column chromatography (PE: EA = 1: 1) to give tert-butyl (3R, 4S) -4- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3-fluoropiperidine-1-carboxylate (40 mg, 8%) as a yellow solid.

[0647] MS (ESI) : mass calcd. for $C_{23}H_{27}FN_4O_3$, 426.21, m/z found 449.2 [M+Na] .

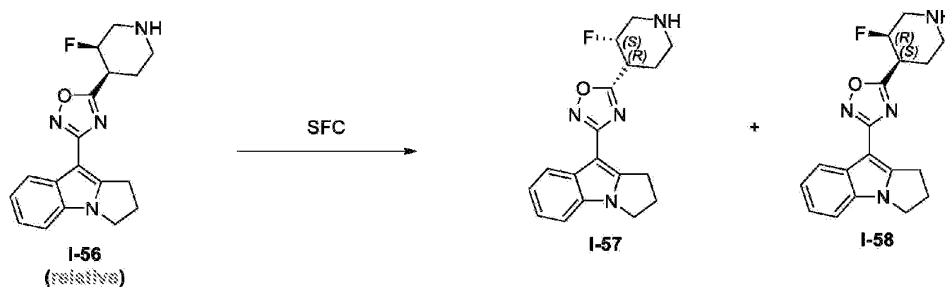
[0648] Step 2

[0649] To a mixture of tert-butyl (3R, 4S) -4- (3- {1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -1, 2, 4-oxadiazol-5-yl) -3-fluoropiperidine-1-carboxylate (40 mg, 0.094 mmol) in HCl/EA (4N) (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give 3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -5- ((3R, 4S) -3-fluoropiperidin-4-yl) -1, 2, 4-oxadiazole formate (10.4 mg, 32%) as a white solid.

[0650] MS (ESI) : mass calcd. for $C_{18}H_{19}FN_4O$, 326.15, m/z found 327.1 [M+H]⁺.

[0651] ¹H NMR (400 MHz, DMSO-d₆) δ 8.19 (s, 0.8H) , 8.01-7.98 (m, 1H) , 7.45-7.43 (m, 1H) , 7.22-7.16 (m, 2H) , 5.16-5.03 (m, 1H) , 4.18 (t, J = 7.2 Hz, 2H) , 3.68-3.56 (m, 2H) , 3.28-3.19 (m, 4H) , 3.10-3.06 (m, 1H) , 2.98-2.85 (m, 1H) , 2.69-2.62 (m, 2H) , 2.08-1.97 (m, 2H) .

[0652] Example 44. Synthesis of I-57 &I-58:



[0653] Experimental procedure:

[0654] Step 1

[0655] 3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -5- ((3R, 4S) -3-fluoropiperidin-4-yl) -1, 2, 4-oxadiazole (8 mg, 0.025 mmol) was split via prep-SFC (Daicel CHIRALCEL ID, 250mm×30 mm I.D., 10 um mobile phase A/B: CO₂/MeOH [0.2%NH₃ (7M Solution in MeOH)] = 50/50, flow rate: 80 g/min, column temp: 35

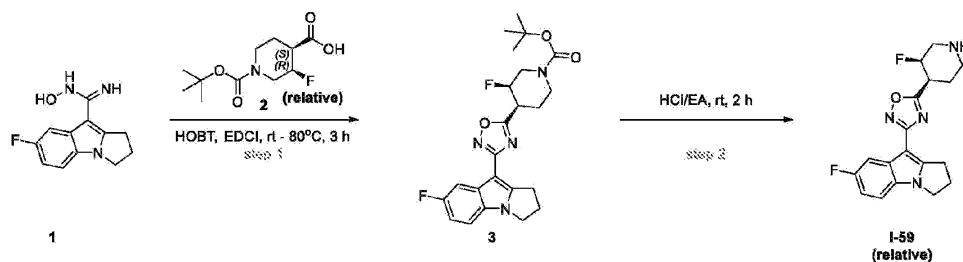
degree) to give 3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -5- ((3S, 4R) -3-fluoropiperidin-4-yl) -1, 2, 4-oxadiazole formate (1.3 mg, 16%) as a yellow solid and 3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -5- ((3R, 4S) -3-fluoropiperidin-4-yl) -1, 2, 4-oxadiazole formate (1.2 mg, 15%) as a yellow solid.

[0656] MS (ESI) : mass calcd. for $C_{18}H_{19}FN_4O$, 326.15, m/z found 327.1 $[M+H]^+$.

[0657] 1H NMR (400 MHz, MeOD) δ 8.51 (s, 1H) , 8.05-8.03 (m, 1H) , 7.35-7.33 (m, 1H) , 7.21-7.14 (m, 2H) , 5.48-5.36 (m, 1H) , 4.17 (t, J = 7.2 Hz, 2H) , 3.73-3.58 (m, 2H) , 3.47-3.43 (m, 2H) , 3.38-3.31 (m, 2H) , 3.16-3.06 (m, 1H) , 2.77-2.62 (m, 2H) , 2.50-2.29 (m, 2H) .

[0658] 1H NMR (400 MHz, MeOD) δ 8.50 (s, 1H) , 8.05-8.03 (m, 1H) , 7.35-7.33 (m, 1H) , 7.20-7.14 (m, 2H) , 5.46-5.34 (m, 1H) , 4.17 (t, J = 7.2 Hz, 2H) , 3.69-3.58 (m, 2H) , 3.48-3.42 (m, 2H) , 3.38-3.31 (m, 2H) , 3.12-3.05 (m, 1H) , 2.74-2.66 (m, 2H) , 2.49-2.31 (m, 2H) .

[0659] Example 45. Synthesis of I-59:



[0660] Experimental procedure:

[0661] Step 1

[0662] To a mixture of (3R, 4S) -1- [(tert-butoxy) carbonyl] -3-fluoropiperidine-4-carboxylic acid (265.0 mg, 1.07 mmol) in ACN (10 mL) were added HOBT (173.8 mg, 1.29 mmol) and EDCI (246.6 mg, 1.29 mmol) . The mixture was stirred at room temperature for 1 h. 7-fluoro-N-hydroxy-1H, 2H, 3H-benzopyrrolizine-9-carboximidamide (250 mg, 1.07 mmol) was added. The reaction mixture was stirred at 80 °C for 3 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was concentrated to afford the crude product which was purified by silica gel column chromatography (PE: EA = 1: 1) to give tert-butyl (3R, 4S) -3-fluoro-4- (3- (7-fluoro-2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) piperidine-1-carboxylate (60 mg, 10%) as a yellow solid.

[0663] MS (ESI) : mass calcd. for $C_{23}H_{26}F_2N_4O_3$, 444.20, m/z found 467.2 $[M+Na]^+$.

[0664] Step 2

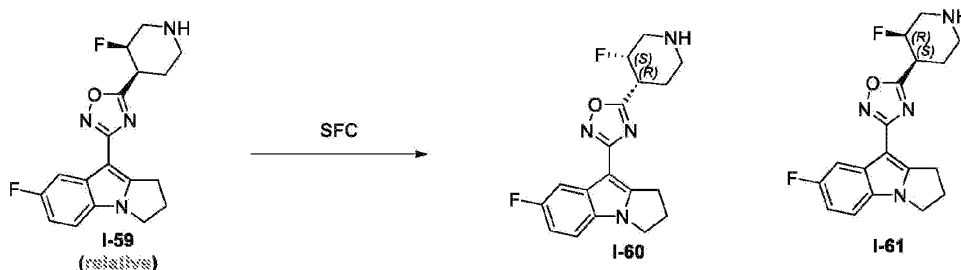
[0665] To a mixture of tert-butyl (3R, 4S) -3-fluoro-4- (3- {7-fluoro-1H, 2H, 3H-benzopyrrolizin-9-yl} -1, 2, 4-oxadiazol-5-yl) piperidine-1-carboxylate (60 mg, 0.14

mmol) in HCl/EA (4N) (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by Prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give 3- (7-fluoro-2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -5- ((3R, 4S) -3-fluoropiperidin-4-yl) -1, 2, 4-oxadiazole formate (31.3 mg, 65%) as a yellow solid.

[0666] MS (ESI) : mass calcd. for $C_{18}H_{18}F_2N_4O$, 344.14, m/z found 345.1 [M+H]⁺.

[0667] ¹H NMR (400 MHz, DMSO-d₆) δ 8.19 (s, 0.7H) , 7.67 (dd, J = 10.0, 2.4 Hz, 1H) , 7.48 (dd, J = 8.8, 4.4 Hz, 1H) , 7.06 (td, J = 9.2, 2.4 Hz, 1H) , 5.18-5.06 (m, 1H) , 4.19 (t, J = 7.2 Hz, 2H) , 3.70-3.59 (m, 2H) , 3.27-3.22 (m, 3H) , 3.12-3.08 (m, 1H) , 3.01-2.88 (m, 1H) , 2.72-2.62 (m, 3H) , 2.09-2.02 (m, 2H) .

[0668] Example 46. Synthesis of I-60 & I-61:



[0669] Experimental procedure:

[0670] Step 1

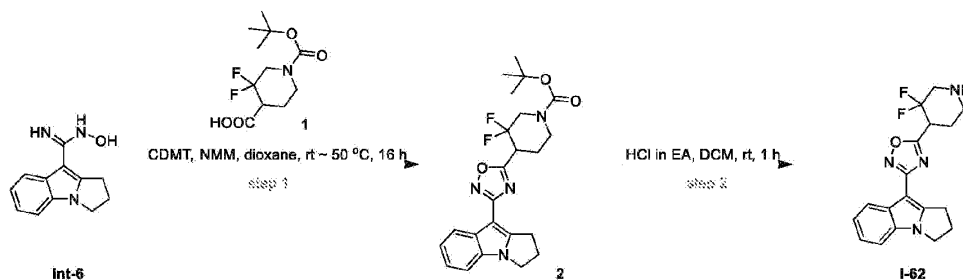
[0671] 3- (7-fluoro-2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -5- ((3R, 4S) -3-fluoropiperidin-4-yl) -1, 2, 4-oxadiazole (28 mg, 0.081 mmol) was split via prep-SFC (Daicel CHIRALCEL ID, 250mm×30 mm I.D., 10 um mobile phase A/B: CO₂/MeOH [0.2%NH₃ (7M Solution in MeOH)] = 50/50, flow rate: 80 g/min, column temp: 35 degree) to give 3- (7-fluoro-2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -5- ((3S, 4R) -3-fluoropiperidin-4-yl) -1, 2, 4-oxadiazole formate (1.0 mg, 4%) as a yellow solid and 3- (7-fluoro-2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -5- ((3R, 4S) -3-fluoropiperidin-4-yl) -1, 2, 4-oxadiazole formate (2.0 mg, 7%) as a yellow solid.

[0672] MS (ESI) : mass calcd. for $C_{18}H_{18}F_2N_4O$, 344.14, m/z found 345.1 [M+H]⁺.

[0673] ¹H NMR (400 MHz, MeOD) δ 8.51 (s, 1H) , 7.75-7.68 (m, 1H) , 7.34-7.31 (m, 1H) , 6.99-6.91 (m, 1H) , 5.36-5.24 (m, 1H) , 4.18 (t, J = 7.2 Hz, 2H) , 3.65-3.50 (m, 2H) , 3.35 3.31 (m, 3H) , 3.14-2.95 (m, 2H) , 2.74-2.67 (m, 2H) , 2.43-2.23 (m, 2H) .

[0674] ¹H NMR (400 MHz, MeOD) δ 8.56 (s, 1H) , 7.72-7.69 (m, 1H) , 7.33-7.30 (m, 1H) , 6.97-6.92 (m, 1H) , 5.41-5.29 (m, 1H) , 4.17 (t, J = 7.2 Hz, 2H) , 3.67-3.53 (m, 2H) , 3.40-3.31 (m, 3H) , 3.26-3.00 (m, 2H) , 2.73-2.66 (m, 2H) , 2.46-2.27 (m, 2H) .

[0675] Example 47. Synthesis of I-62:



[0676] Experimental procedure:

[0677] Step 1

[0678] To a mixture of CDMT (119 mg, 0.67 mmol) in dioxane (5 mL) was added NMM (171 mg, 1.69 mmol) at 25 °C. After 30 min, the reaction mixture was added 1- (tert-butoxycarbonyl) -3, 3-difluoropiperidine-4-carboxylic acid (150 mg, 0.56 mmol) and stirred at 25 °C for 1 h. The reaction mixture was added N-hydroxy-2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboximidamide (146 mg, 0.67 mmol) and stirred at 50 °C for 16 h under N₂. The mixture was concentrated under reduced pressure to give the crude product which was purified by Flash Chromatography (mobile phase A: PE, B: EA; 0 ~ 35% of B in A) to give tert-butyl 4- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3, 3-difluoropiperidine-1-carboxylate (150 mg, 53%) as a yellow solid.

[0679] MS (ESI) : mass calcd. for C₂₃H₂₆F₂N₄O₃, 444.20, m/z found 467.2 [M+Na]⁺.

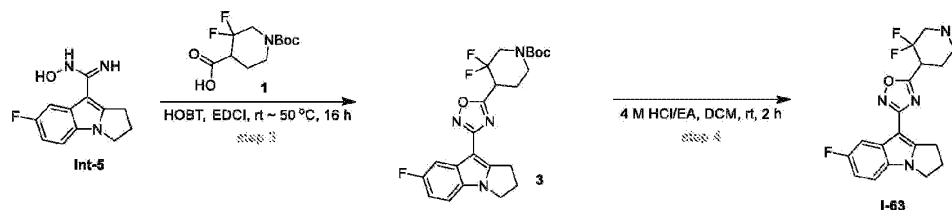
[0680] Step 2

[0681] To a mixture of tert-butyl 4- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3, 3-difluoropiperidine-1-carboxylate (120 mg, 0.27 mmol) in DCM (6 mL) was added 4M HCl in EA (2 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to give the crude product which was purified by Flash reverse (mobile phase A: H₂O (0.1% HCl) , B: ACN; 0 ~ 55% of B in A) to give 5- (3, 3-difluoropiperidin-4-yl) -3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazole hydrochloride (41.2 mg, 44%) as a white solid.

[0682] MS (ESI) : mass calcd. for C₁₈H₁₈F₂N₄O, 344.14, m/z found 345.1 [M+H]⁺.

[0683] ¹H NMR (400 MHz, DMSO) δ 10.57-9.00 (m, 2H) , 8.03-7.94 (m, 1H) , 7.50-7.41 (m, 1H) , 7.25-7.15 (m, 2H) , 4.39-4.24 (m, 1H) , 4.20 (t, J = 7.2 Hz, 2H) , 3.99-3.88 (m, 1H) , 3.79-3.64 (m, 1H) , 3.49-3.42 (m, 1H) , 3.26 (t, J = 7.6 Hz, 2H) , 3.22-3.11 (m, 1H) , 2.70-2.60 (m, 2H) , 2.57-2.52 (m, 1H) , 2.43-2.31 (m, 1H) .

[0684] Example 48. Synthesis of I-63:



[0685] Experimental procedure:

[0686] Step 1

[0687] To a solution of 1- [(tert-butoxy) carbonyl] -3, 3-difluoropiperidine-4-carboxylic acid (150 mg, 0.57 mmol) in dimethylformamide (5 mL) was added EDCI (163 mg, 0.85 mmol) and HOBt (115 mg, 0.85 mmol) at room temperature. After stirring for 1 h, 7-fluoro-N-hydroxy-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboximidamide (211 mg, 0.90 mmol) was added into the reaction mixture and the reaction mixture was stirred at room temperature for 1 h. Then the reaction mixture was stirred at 50°C for 16 h. LCMS showed the reaction was completed. After reaction, the reaction mixture was quenched with water. The mixture was extracted with EA (20 mL×3) . The combined organic layer was washed with brine (20 mL ×2) ,dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product which was purified by silica gel chromatography column (DCM/MEOH =20: 1) to afford tert-butyl 3, 3-difluoro-4- (3- {7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -1, 2, 4-oxadiazol-5-yl) piperidine-1-carboxylate (100 mg, 38%) as yellow solid.

[0688] MS (ESI) : mass calcd. for C₂₃H₂₅F₃N₄O₃, 462.19, m/z found 485.2 [M+Na]⁺.

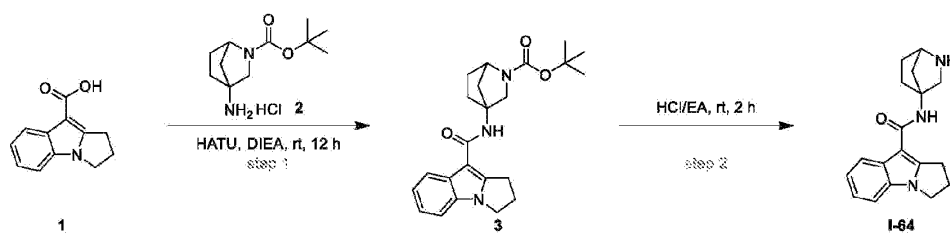
[0689] Step 2

[0690] To a solution of tert-butyl 3, 3-difluoro-4- (3- {7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -1, 2, 4-oxadiazol-5-yl) piperidine-1-carboxylate (100 mg, 0.22 mmol) in DCM (2 mL) was added HCl in EA (4 M, 2 ml) at 0 °C dropwise under N₂. Then the mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to afford crude product. The residue was purified by Prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) , B (Acetonitrile) , 20~100%of B in A, 10.5 min, Flow rate: 30ml/min, wavelength: 214/254 nm) to 3, 3-difluoro-4- (3- {7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -1, 2, 4-oxadiazol-5-yl) piperidine formate (35 mg, 43.5%) as white solid.

[0691] MS (ESI) : mass calcd. for C₁₈H₁₇F₃N₄O, 362.14, m/z found 363.2 [M+H]⁺.

[0692] ¹H NMR (400 MHz, DMSO) δ 8.14 (s, 1H) , 7.66 (dd, J = 12.0, 4.0 Hz, 1H) , 7.48 (dd, J = 8.0, 4.0 Hz, 1H) , 7.09-7.04 (m, 1H) , 4.20 (t, J = 8.0 Hz, 2H) , 4.08 -3.96 (m, 1H) , 3.29-3.15 (m, 4H) , 3.03-2.93 (m, 2H) , 2.75-2.58 (m, 3H) , 2.19-2.04 (m, 2H) .

[0693] Example 49. Synthesis of I-64:



[0694] Experimental procedure:

[0695] Step 1

[0696] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (40 mg, 0.20 mmol) , tert-butyl 4-amino-2-azabicyclo [2.2.1] heptane-2-carboxylate (42.2 mg, 0.20 mmol) and DIEA (77.1 mg, 0.60 mmol) in DMF (5 mL) was added HATU (90.7 mg, 0.60 mmol) . The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give tert-butyl 4- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamido) -2-azabicyclo [2.2.1] heptane-2-carboxylate (60 mg, crude) as a yellow solid which was used directly for the next step.

[0697] MS (ESI) : mass calcd. for C₂₃H₂₉N₃O₃, 395.22, m/z found 396.2 [M+H]⁺.

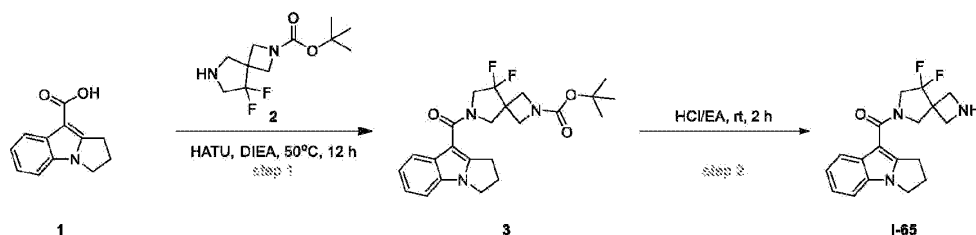
[0698] Step 2

[0699] To a mixture of tert-butyl 4- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamido) -2-azabicyclo [2.2.1] heptane-2-carboxylate (60 mg, 0.15 mmol) in HCl/EA (4N) (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give N- (2-azabicyclo [2.2.1] heptan-4-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (22.2 mg, 50%) as a white solid.

[0700] MS (ESI) : mass calcd. for C₁₈H₂₁N₃O, 295.17, m/z found 296.2 [M+H]⁺.

[0701] ¹H NMR (400 MHz, DMSO-d₆) δ 8.42 (s, 1H) , 7.91-7.89 (m, 1H) , 7.51 (s, 1H) , 7.38 -7.36 (m, 1H) , 7.15-7.08 (m, 2H) , 4.11 (t, J = 7.2 Hz, 2H) , 3.78 (s, 1H) , 3.36-3.17 (m, 4H) , 2.61-2.54 (m, 2H) , 2.09-2.03 (m, 2H) , 1.98-1.95 (m, 1H) , 1.87-1.85 (m, 3H) .

[0702] Example 50. Synthesis of I-65:



[0703] Experimental procedure:

[0704] Step 1

[0705] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (30 mg, 0.15 mmol) , tert-butyl 8, 8-difluoro-2, 6-diazaspiro [3.4] octane-2-carboxylate (37.0 mg, 0.15 mmol) and DIEA (57.8 mg, 0.45 mmol) in DMF (5 mL) was added HATU (68.0 mg, 0.18 mmol) . The reaction mixture was stirred at 50 °C for 12 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give tert-butyl 6- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carbonyl) -8, 8-difluoro-2, 6-diazaspiro [3.4] octane-2-carboxylate (40 mg, crude) as a yellow solid which was used directly for the next step.

[0706] MS (ESI) : mass calcd. for C₂₃H₂₇F₂N₃O₃, 431.20, m/z found 432.2 [M+H]⁺.

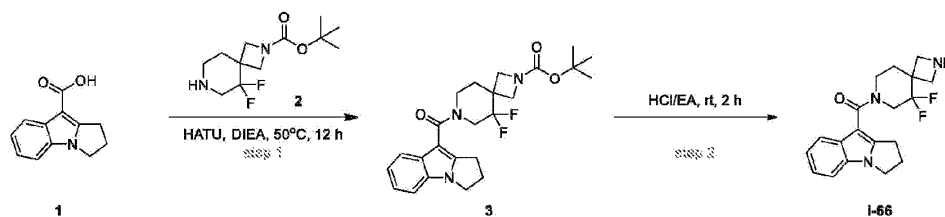
[0707] Step 2

[0708] To a mixture of tert-butyl 6- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} carbonyl) -8, 8-difluoro-2, 6-diazaspiro [3.4] octane-2-carboxylate (40 mg, 0.093 mmol) in HCl/EA (4N) (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give (8, 8-difluoro-2, 6-diazaspiro [3.4] octan-6-yl) (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) methanone formate (19.1 mg, 62%) as a white solid.

[0709] MS (ESI) : mass calcd. for C₁₈H₁₉F₂N₃O, 331.15, m/z found 332.1 [M+H]⁺.

[0710] ¹H NMR (400 MHz, DMSO-d₆) δ 8.233 (s, 0.7H) , 7.59 (d, J = 7.2 Hz, 1H) , 7.39 (d, J = 7.6 Hz, 1H) , 7.16-7.09 (m, 2H) , 4.13 (t, J = 7.2 Hz, 2H) , 3.98-3.89 (m, 4H) , 3.76-3.74 (m, 2H) , 3.43-3.41 (m, 2H) , 3.08 (t, J = 7.6 Hz, 2H) , 2.62-2.55 (m, 2H) .

[0711] Example 51. Synthesis of I-66:



[0712] Experimental procedure:

[0713] Step 1

[0714] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (30 mg, 0.15 mmol) , tert-butyl 5, 5-difluoro-2, 7-diazaspiro [3.5] nonane-2-carboxylate (39.1 mg, 0.15 mmol) and DIEA (57.8 mg, 0.45 mmol) in DMF (5 mL) was added HATU (68.0 mg, 0.18 mmol) . The reaction mixture was stirred at 50 °C for 12 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give tert-butyl 7- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carbonyl) -5, 5-difluoro-2, 7-diazaspiro [3.5] nonane-2-carboxylate (40 mg, crude) as a yellow solid which was used directly for the next step.

[0715] MS (ESI) : mass calcd. for C₂₄H₂₉F₂N₃O₃, 445.22, m/z found 446.2 [M+H]⁺.

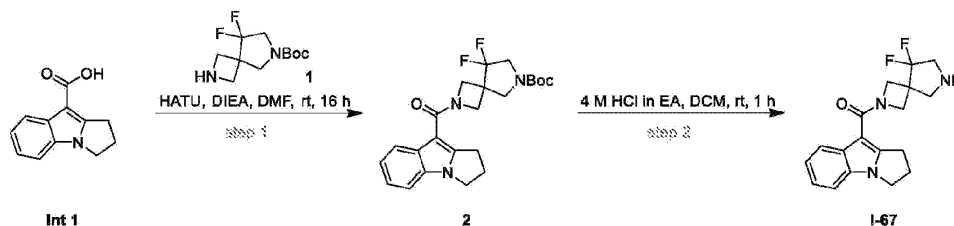
[0716] Step 2

[0717] To a mixture of tert-butyl 7- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} carbonyl) -5, 5-difluoro-2, 7-diazaspiro [3.5] nonane-2-carboxylate (40 mg, 0.090 mmol) in HCl/ EA (4N) (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give (5, 5-difluoro-2, 7-diazaspiro [3.5] nonan-7-yl) (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) methanone formate (18.2 mg, 57%) as a yellow solid.

[0718] MS (ESI) : mass calcd. for C₁₉H₂₁F₂N₃O, 345.17, m/z found 346.1 [M+H]⁺.

[0719] ¹H NMR (400 MHz, DMSO-d₆) δ 8.32 (s, 1H) , 7.48 (d, J = 7.2 Hz, 1H) , 7.38 (d, J = 7.6 Hz, 1H) , 7.16-7.08 (m, 2H) , 4.13 (t, J = 8.0 Hz, 2H) , 3.86 (t, J = 12.0 Hz, 4H) , 3.56-3.47 (m, 4H) , 3.01 (t, J = 7.2 Hz, 2H) , 2.61-2.54 (m, 2H) , 2.04-1.99 (m, 2H) .

[0720] Example 52. Synthesis of I-67:



[0721] Experimental procedure:

[0722] Step 1

[0723] To a mixture of 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylic acid (40 mg, 0.20 mmol) and DIEA (117 mg, 0.90 mmol) in DMF (2 mL) was added HATU (72 mg, 0.19 mmol) at 25 °C under N₂. After stirring for 30 min, tert-butyl 8, 8-difluoro-2, 6-diazaspiro [3.4] octane-6-carboxylate (45 mg, 0.18 mmol) was added into the reaction mixture. The mixture was stirred at 25 °C for 16 h. The mixture was diluted with water (20 mL) and extracted with EA (20 mL x 3) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product which was purified by Flash Chromatography (mobile phase A: PE, B: EA; 0 ~ 50% of B in A) to give tert-butyl 2- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carbonyl) -8, 8-difluoro-2, 6-diazaspiro [3.4] octane-6-carboxylate (78 mg, 89%) as a white solid.

[0724] MS (ESI) : mass calcd. for C₂₃H₂₇F₂N₃O₃, 431.20, m/z found 432.2 [M+H]⁺.

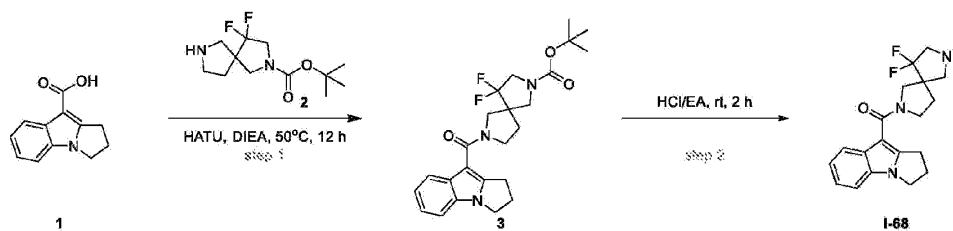
[0725] Step 2

[0726] To a mixture of tert-butyl 2- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carbonyl) -8, 8-difluoro-2, 6-diazaspiro [3.4] octane-6-carboxylate (73 mg, 0.17 mmol) in DCM (6 mL) was added 4M HCl in EA (2 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to give the crude product which was purified by Prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um; mobile phase A: water (0.1%TFA) , B: Acetonitrile, 15 ~ 45%B in 9 min; flow rate: 25 mL/min; wavelength: 214/254 nm) to give (8, 8-difluoro-2, 6-diazaspiro [3.4] octan-2-yl) (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) methanone trifluoroacetate (15.1 mg, 26%) as a white solid.

[0727] MS (ESI) : mass calcd. for C₁₈H₁₉F₂N₃O, 331.15, m/z found 332.1 [M+H]⁺.

[0728] ¹H NMR (400 MHz, DMSO) δ 9.43 (s, 1.77H) , 7.75-7.69 (m, 1H) , 7.43-7.36 (m, 1H) , 7.19-7.10 (m, 2H) , 4.23-4.10 (m, 6H) , 3.82-3.72 (m, 4H) , 3.10 (t, J = 7.2 Hz, 2H) , 2.63-2.55 (m, 2H) .

[0729] Example 53. Synthesis of I-68:



[0730] Experimental procedure:

[0731] Step 1

[0732] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (30 mg, 0.15 mmol) , tert-butyl 4, 4-difluoro-2, 7-diazaspiro [4.4] nonane-2-carboxylate (39.1 mg, 0.15 mmol) and DIEA (57.8 mg, 0.45 mmol) in DMF (5 mL) was added HATU (68.0 mg, 0.18 mmol) . The reaction mixture was stirred at 50 °C for 12 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give tert-butyl 7- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carbonyl) -4, 4-difluoro-2, 7-diazaspiro [4.4] nonane-2-carboxylate (40 mg, crude) as a yellow solid which was used directly for the next step.

[0733] MS (ESI) : mass calcd. for C₂₄H₂₉F₂N₃O₃, 445.22, m/z found 446.2 [M+H]⁺.

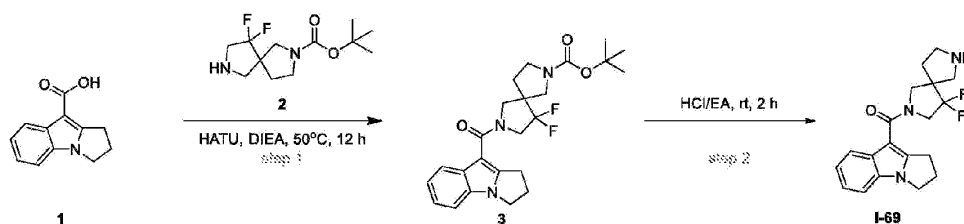
[0734] Step 2

[0735] To a mixture of tert-butyl 7- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} carbonyl) -4, 4-difluoro-2, 7-diazaspiro [4.4] nonane-2-carboxylate (40 mg, 0.090 mmol) in HCl/ EA (4N) (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1% HCl) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give (9, 9-difluoro-2, 7-diazaspiro [4.4] nonan-2-yl) (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) methanone hydrochloride (8.5 mg, 27%) as a white solid.

[0736] MS (ESI) : mass calcd. for C₁₉H₂₁F₂N₃O, 345.17, m/z found 346.2 [M+H]⁺.

[0737] ¹H NMR (400 MHz, DMSO-d₆) δ 10.28-10.13 (m, 1H) , 7.60 (d, J = 7.2 Hz, 1H) , 7.36 (d, J = 7.6 Hz, 1H) , 7.14-7.06 (m, 2H) , 4.12 (t, J = 7.2 Hz, 2H) , 3.84-3.75 (m, 3H) , 3.70-3.57 (m, 3H) , 3.52 (s, 2H) , 3.16-2.99 (m, 2H) , 2.62-2.55 (m, 2H) , 2.23-2.07 (m, 2H) .

[0738] Example 54. Synthesis of I-69:



[0739] Experimental procedure:

[0740] Step 1

[0741] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (30 mg, 0.15 mmol), tert-butyl 9, 9-difluoro-2, 7-diazaspiro [4.4] nonane-2-carboxylate (39.1 mg, 0.15 mmol) and DIEA (57.8 mg, 0.45 mmol) in DMF (5 mL) was added HATU (68.0 mg, 0.18 mmol). The reaction mixture was stirred at 50 °C for 12 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give tert-butyl 7- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carbonyl) -9, 9-difluoro-2, 7-diazaspiro [4.4] nonane-2-carboxylate (40 mg, crude) as a yellow solid which was used directly for the next step.

[0742] MS (ESI): mass calcd. for C₂₄H₂₉F₂N₃O₃, 445.22, m/z found 446.2 [M+H]⁺.

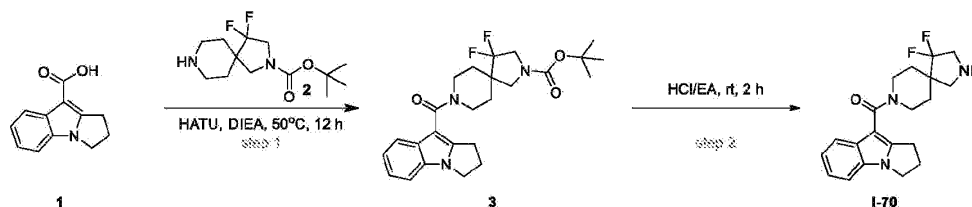
[0743] Step 2

[0744] To a mixture of tert-butyl 7- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) carbonyl -9, 9-difluoro-2, 7-diazaspiro [4.4] nonane-2-carboxylate (40 mg, 0.090 mmol) in HCl/EA (4N) (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile), flow rate: 25 ml/min, wavelength: 214/254 nm) to give (4, 4-difluoro-2, 7-diazaspiro [4.4] nonan-2-yl) (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) methanone formate (19.1 mg, 61%) as a yellow solid.

[0745] MS (ESI): mass calcd. for C₁₉H₂₁F₂N₃O, 345.17, m/z found 346.3 [M+H]⁺.

[0746] ¹H NMR (400 MHz, DMSO-d₆) δ 8.24 (s, 0.8H), 7.61 (d, J = 7.2 Hz, 1H), 7.38 (d, J = 7.2 Hz, 1H), 7.16-7.09 (m, 2H), 4.13 (t, J = 7.2 Hz, 2H), 4.05-3.94 (m, 2H), 3.74-3.65 (m, 2H), 3.26-2.71 (m, 6H), 2.63-2.55 (m, 2H), 2.04-1.68 (m, 2H).

[0747] Example 55. Synthesis of I-70:



[0748] Experimental procedure:

[0749] Step 1

[0750] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (30 mg, 0.15 mmol) , tert-butyl 4, 4-difluoro-2, 8-diazaspiro [4.5] decane-2-carboxylate (41.2 mg, 0.15 mmol) and DIEA (57.8 mg, 0.45 mmol) in DMF (5 mL) was added HATU (68.0 mg, 0.18 mmol) . The reaction mixture was stirred at 50 °C for 12 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give tert-butyl 8- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carbonyl) -4, 4-difluoro-2, 8-diazaspiro [4.5] decane-2-carboxylate (40 mg, crude) as a yellow solid which was used directly for the next step.

[0751] MS (ESI) : mass calcd. for C₂₅H₃₁F₂N₃O₃, 459.23, m/z found 460.2 [M+H]⁺.

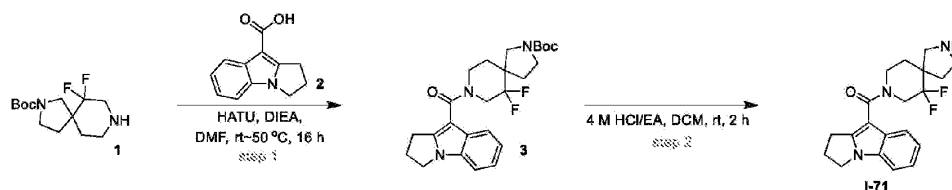
[0752] Step 2

[0753] To a mixture of tert-butyl 8- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} carbonyl) -4, 4-difluoro-2, 8-diazaspiro [4.5] decane-2-carboxylate (40 mg, 0.087 mmol) in HCl/EA (4N) (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate: 30 ml/min, wavelength: 214/254 nm) to give (4, 4-difluoro-2, 8-diazaspiro [4.5] decan-8-yl) (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) methanone formate (22.8 mg, 73%) as a white solid.

[0754] MS (ESI) : mass calcd. for C₂₀H₂₃F₂N₃O, 359.18, m/z found 360.1 [M+H]⁺.

[0755] ¹H NMR (400 MHz, DMSO-d₆) δ 8.19 (s, 0.15H) , 7.52-7.50 (m, 1H) , 7.37-7.35 (m, 1H) , 7.14-7.07 (m, 2H) , 4.12 (t, J = 7.2 Hz, 2H) , 4.00-3.97 (m, 2H) , 3.16-3.09 (m, 4H) , 3.04 (t, J = 7.2 Hz, 2H) , 2.98 (s, 2H) , 2.61-2.54 (m, 2H) , 1.62-1.55 (m, 4H) .

[0756] Example 56. Synthesis of I-71:



[0757] Experimental procedure:

[0758] Step 1

[0759] To a mixture of 1H, 2H, 3H-benzo[b]pyrrolizine-9-carboxylic acid (36 mg, 0.18 mmol) in dimethylformamide (3 mL) was added HATU (93 mg, 0.24 mmol) and DIEA (63 mg, 0.49 mmol) at 0 °C under N₂ protection. After stirring for 30 minutes, tert-butyl 6, 6-difluoro-2, 8-diazaspiro[4.5]decane-2-carboxylate (45 mg, 0.16 mmol)

were added and the reaction mixture was stirred at 50 °C for 16 hours. LCMS showed the reaction was completed. The mixture was extracted with EA (10 mL× 3) . The combined organic layer was washed with brine (10 mL × 2) , dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product which was purified by flash chromatography on silica gel (PE/EA=1: 1) to give tert-butyl 8- ((1H, 2H, 3H-benzo[b]pyrrolizin-9-yl) carbonyl) -6, 6-difluoro-2, 8-diazaspiro[4.5]decane-2-carboxylate (50.0 mg, 63%) as light yellow solid.

[0760] MS (ESI): mass calcd. for $C_5H_{31}F_3N_3O_3$, 459.23, m/z found 460.3 $[M+H]^+$.

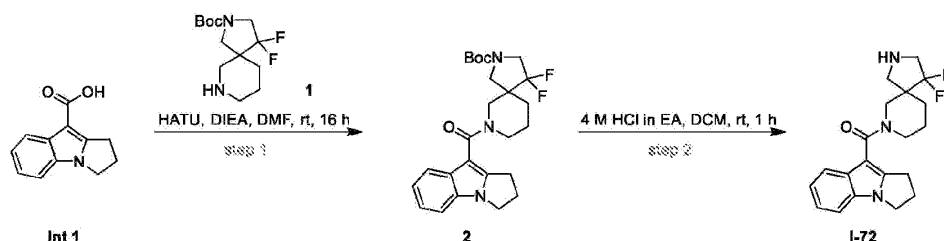
[0761] Step 2

[0762] To a solution of tert-butyl 8- ({ 1H, 2H, 3H-benzo[b]pyrrolizin-9-yl } carbonyl) -6, 6-difluoro-2, 8-diazaspiro[4.5]decane-2-carboxylate (50 mg, 0.10 mmol) in DCM (2 mL) was added HCl in EA (4 M, 2 ml) at 0 °C dropwise under N₂. Then the mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to afford crude product which was purified by Prep-HPLC (Welch 10u C18 250 x 21.2 mm, Mobile Phase A: water (0.05% NH₃) , B (Acetonitrile) , 37~47% of B in A, 9 min, Flow rate: 25ml/min, wavelength: 214/254 nm) to give 2- ({ 1H, 2H, 3H-benzo[b]pyrrolizin-9-yl } carbonyl) -5, 5-difluoro-2, 7-diazaspiro[3.5]nonane (25.5 mg, 43.0%) as light yellow solid.

[0763] MS (ESI): mass calcd. for $C_{20}H_{23}F_2N_3O$, 359.18, m/z found 360.1 $[M+H]^+$.

[0764] ¹H NMR (400 MHz, DMSO) δ 9.46 (s, 1H) , 9.21 (s, 1H) , 7.51 (d, J = 8.0 Hz, 1H) , 7.39 (d, J = 8.0 Hz, 1H) , 7.19-7.07 (m, 2H) , 4.14 (t, J = 8.0 Hz, 2H) , 4.09-3.87 (m, 2H) , 3.78-3.65 (m, 1H) , 3.60-3.50 (m, 1H) , 3.33-3.30 (m, 1H) , 3.22 (d, J = 1.6 Hz, 2H) , 3.08-2.97 (m, 2H) , 2.59-2.55 (m, 3H) , 2.30-2.19 (m, 1H) , 2.03-1.82 (m, 3H) .

[0765] Example 57. Synthesis of I-72:



[0766] Experimental procedure:

[0767] Step 1

[0768] To a mixture of 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylic acid (36 mg, 0.18 mmol) and DIEA (105 mg, 0.81 mmol) in DMF (2 mL) was added HATU (65 mg, 0.17 mmol) at 25 °C under N₂. After stirring for 30 min, tert-butyl 4, 4-difluoro-2, 7-diazaspiro [4.5] decane-2-carboxylate (45 mg, 0.16 mmol) was added into the reaction mixture. The mixture was stirred at 25 °C for 16 h. The mixture was diluted

with water (20 mL) and extracted with EA (20 mL x 3). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product which was purified by Flash Chromatography (mobile phase A: PE, B: EA; 0 ~ 50% of B in A) to give tert-butyl 7- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carbonyl) -4, 4-difluoro-2, 7-diazaspiro [4.5] decane-2-carboxylate (75 mg, 95%) as a white solid.

[0769] MS (ESI) : mass calcd. for C₂₃H₃₁F₂N₃O₃, 459.23, m/z found 460.2 [M+H]⁺.

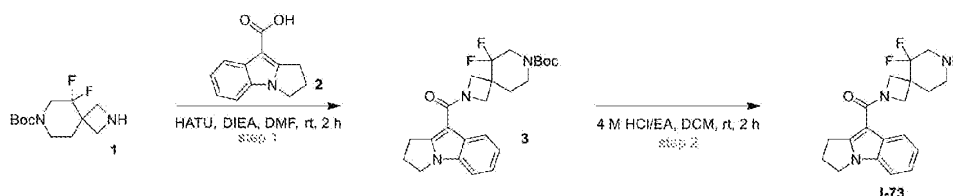
[0770] Step 2

[0771] To a mixture of tert-butyl 7- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carbonyl) -4, 4-difluoro-2, 7-diazaspiro [4.5] decane-2-carboxylate (70 mg, 0.15 mmol) in DCM (6 mL) was added 4M HCl in EA (2 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to give the crude product which was purified by Flash reverse (mobile phase A: H₂O (0.1% HCl), B: ACN; 0 ~ 35% of B in A) to give (4, 4-difluoro-2, 7-diazaspiro [4.5] decan-7-yl) (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) methanone hydrochloride (32.9 mg, 60%) as a white solid.

[0772] MS (ESI) : mass calcd. for C₂₀H₂₃F₂N₃O, 359.18, m/z found 360.3 [M+H]⁺.

[0773] ¹H NMR (400 MHz, DMSO) δ 9.83 (brs, 2H), 7.56-7.47 (m, 1H), 7.43-7.33 (m, 1H), 7.18-7.05 (m, 2H), 4.13 (t, J = 7.2 Hz, 2H), 4.05 (d, J = 13.2 Hz, 1H), 3.86-3.72 (m, 3H), 3.39-3.48 (m, 3H), 3.32-3.26 (m, 1H), 3.12-2.97 (m, 2H), 2.64-2.54 (m, 2H), 1.87-1.75 (m, 2H), 1.73-1.64 (m, 1H), 1.58-1.45 (m, 1H).

[0774] Example 58. Synthesis of I-73:



[0775] Experimental procedure:

[0776] Step 1

[0777] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (38 mg, 0.19 mmol) in dimethylformamide (3 mL) was added HATU (98 mg, 0.26 mmol) and DIEA (67 mg, 0.51 mmol) at 0°C under N₂ protection. After stirring for 30 minutes, tert-butyl 5, 5-difluoro-2, 7-diazaspiro [3.5] nonane-7-carboxylate (45 mg, 0.17 mmol) were added into the reaction mixture. The mixture was stirred at 25 °C for 2 hours. LCMS showed the reaction was completed. The mixture was extracted with EA (10 mL x 3). The combined organic layer was washed with brine (10 mL x 2), dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product which

was purified by flash chromatography on silica gel (PE/EA=1: 1) to give tert-butyl 2- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} carbonyl) -5, 5-difluoro-2, 7-diazaspiro [3.5] nonane-7-carboxylate (50.0 mg, 62%) as light yellow solid.

[0778] MS (ESI) : mass calcd. for $C_{24}H_{29}F_2N_3O_3$, 445.22, m/z found 446.3 [M+H]⁺.

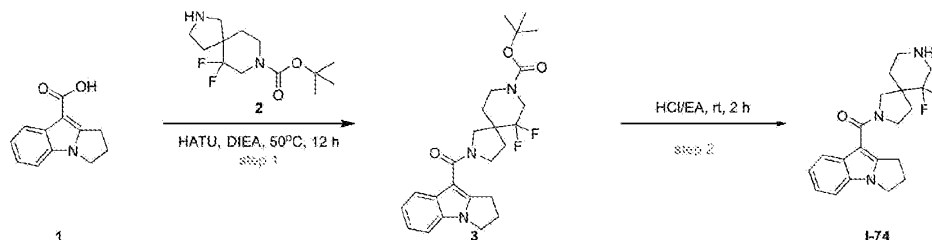
[0779] Step 2

[0780] To a solution of tert-butyl 2- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} carbonyl) -5, 5-difluoro-2, 7-diazaspiro [3.5] nonane-7-carboxylate (50 mg, 0.11 mmol) in DCM (2 mL) was added HCl in EA (4 M, 2 ml) at 0°C dropwise under N₂. Then the mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to afford crude product. The residue was purified by Prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) , B (Acetonitrile) , 15~45% of B in A, 10 min, Flow rate: 30ml/min, wavelength: 214/254 nm) to 2- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} carbonyl) -5, 5-difluoro-2, 7-diazaspiro [3.5] nonane formate (30 mg, 77.3%) as white solid.

[0781] MS (ESI) : mass calcd. for $C_{19}H_{21}F_2N_3O$, 345.17, m/z found 346.2 [M+H]⁺.

[0782] ¹H NMR (400 MHz, DMSO) δ 8.20 (s, 0.35H) , 7.76-7.69 (m, 1H) , 7.40-7.33 (m, 1H) , 7.17-7.07 (m, 2H) , 4.14-4.10 (m, 4H) , 3.81 (d, J = 8.0 Hz, 2H) , 3.11 (t, J = 8.0 Hz, 2H) , 2.84 (t, J = 12.0 Hz, 2H) , 2.63-2.51 (m, 5H) , 1.98-1.80 (m, 2H) .

[0783] Example 59. Synthesis of I-74:



[0784] Experimental procedure:

[0785] Step 1

[0786] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (30 mg, 0.15 mmol) , tert-butyl 6, 6-difluoro-2, 8-diazaspiro [4.5] decane-8-carboxylate (41.2 mg, 0.15 mmol) and DIEA (57.8 mg, 0.45 mmol) in DMF (5 mL) was added HATU (68.0 mg, 0.18 mmol) . The reaction mixture was stirred at 50 °C for 12 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give tert-butyl 2- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carbonyl) -6, 6-difluoro-2, 8-diazaspiro [4.5] decane-8-carboxylate (40 mg, crude) as a yellow solid which was used directly for the next step.

[0787] MS (ESI) : mass calcd. for $C_{25}H_{31}F_2N_3O_3$, 459.23, m/z found 460.2 $[M+H]^+$.

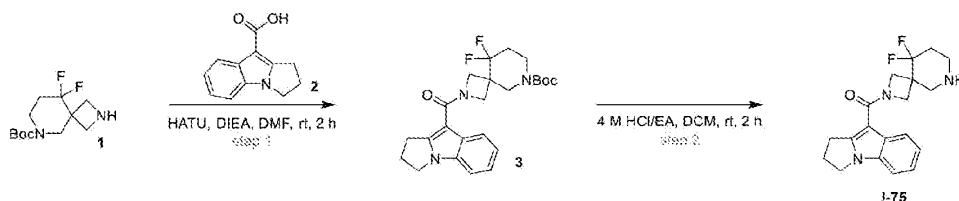
[0788] Step 2

[0789] To a mixture of tert-butyl 2- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl } carbonyl) -6, 6-difluoro-2, 8-diazaspiro [4.5] decane-8-carboxylate (40 mg, 0.087 mmol) in HCl/EA (4N) (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%TFA) B (acetonitrile) , flow rate : 25 ml/min, wavelength: 214/254 nm) to give (6, 6-difluoro-2, 8-diazaspiro [4.5] decan-2-yl) (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) methanone trifluoroacetate (13.6 mg, 43%) as a white solid.

[0790] MS (ESI) : mass calcd. for $C_{20}H_{23}F_2N_3O$, 359.18, m/z found 360.0 $[M+H]^+$.

[0791] 1H NMR (400 MHz, DMSO- d_6) δ 9.43 (s, 1H) , 7.57 (d, J = 7.2 Hz, 1H) , 7.37 (d, J = 7.6 Hz, 1H) , 7.14-7.06 (m, 2H) , 4.12 (t, J = 7.2 Hz, 2H) , 3.86-3.83 (m, 1H) , 3.69-3.62 (m, 4H) , 3.52-3.49 (m, 1H) , 3.20-3.16 (m, 2H) , 3.05 (t, J = 7.2 Hz, 2H) , 2.61-2.54 (m, 2H) , 2.23-2.16 (m, 1H) , 2.00-1.88 (m, 3H) .

[0792] Example 60. Synthesis of I-75:



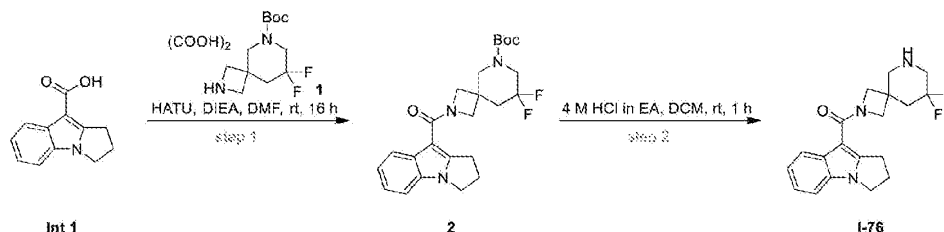
[0793] Experimental procedure:

[0794] Step 1

[0795] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (38 mg, 0.19 mmol) in dimethylformamide (3 mL) were added HATU (98 mg, 0.26 mmol) and DIEA (67 mg, 0.51 mmol) at 0°C under N_2 protection. After stirring for 30 minutes, tert-butyl 9, 9-difluoro-2, 6-diazaspiro [3.5] nonane-6-carboxylate (45 mg, 0.17 mmol) was added and the reaction mixture. was stirred at 25 °C for 2 hours. LCMS showed the reaction was completed. The mixture was extracted with EA (10 mL× 3) . The combined organic layer was washed with brine (10 mL × 2) , dried over Na_2SO_4 and concentrated under reduced pressure to afford crude product which was purified by flash chromatography on silica gel (PE/EA=3: 1) to give tert-butyl 2- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl } carbonyl) -9, 9-difluoro-2, 6-diazaspiro [3.5] nonane-6-carboxylate (50.0 mg, 62%) as a light yellow solid. MS (ESI) : mass calcd. for $C_{24}H_{29}F_2N_3O_3$, 445.22, m/z found 446.2 $[M+H]^+$.

[0796] Step 2

- [0797] To a solution of tert-butyl 2- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} carbonyl) -9, 9-difluoro-2, 6-diazaspiro [3.5] nonane-6-carboxylate (50 mg, 0.11 mmol) in DCM (2 mL) was added HCl in EA (4 M, 2 ml) at 0 °C dropwise under N₂. Then the mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to afford a residue which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) , B (Acetonitrile) , 15~45% of B in A, 10 min, Flow rate: 30ml/min, wavelength: 214/254 nm) to 2- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} carbonyl) -9, 9-difluoro-2, 6-diazaspiro [3.5] nonane formate (28 mg, 74%) as a white solid. MS (ESI) : mass calcd. for C₁₉H₂₁F₂N₃O, 345.17, m/z found 346.3 [M+H]⁺.
- [0798] ¹H NMR (400 MHz, DMSO) δ8.14 (s, 0.51H) , 7.73 -7.71 (m, 1H) , 7.38-7.36 (m, 1H) , 7.16-7.10 (m, 2H) , 4.18-3.98 (m, 4H) , 3.83-3.81 (m, 2H) , 3.10 (t, J = 8.0 Hz, 2H) , 3.01-2.97 (m, 2H) , 2.79-2.75 (m, 2H) , 2.63-2.52 (m, 3H) , 1.91-1.82 (m, 2H) .
- [0799] Example 61. Synthesis of I-76:



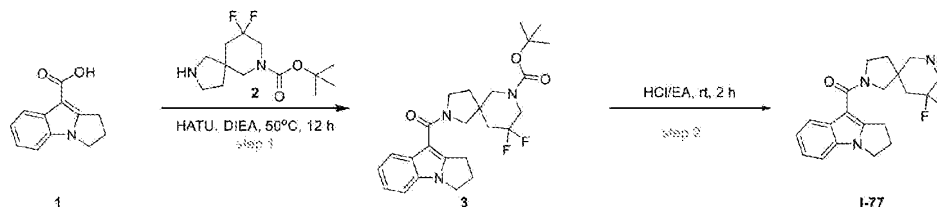
- [0800] Experimental procedure:
- [0801] Step 1
- [0802] To a mixture of 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylic acid (28 mg, 0.14 mmol) and DIEA (83 mg, 0.64 mmol) in DMF (2 mL) was added HATU (51 mg, 0.13 mmol) at 25 °C under N₂. After stirring for 30 min, tert-butyl 8, 8-difluoro-2, 6-diazaspiro [3.5] nonane-6-carboxylate oxalate (45 mg, 0.13 mmol) was added into the reaction mixture. The mixture was stirred at 25 °C for 16 h. The mixture was diluted with water (20 mL) and extracted with EA (20 mL x 3) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product which was purified by Flash Chromatography (mobile phase A: PE, B: EA; 0 ~ 75% of B in A) to give tert-butyl 2- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carbonyl) -8, 8-difluoro-2, 6-diazaspiro [3.5] nonane-6-carboxylate (57 mg, 90%) as a yellow solid.
- [0803] MS (ESI) : mass calcd. for C₂₄H₂₉F₂N₃O₃, 445.22, m/z found 446.2 [M+H]⁺.
- [0804] Step 2
- [0805] To a mixture of tert-butyl 2- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carbonyl) -8,8-difluoro-2, 6-diazaspiro [3.5] nonane-6-carboxylate (52 mg, 0.12 mmol) in DCM

(6 mL) was added 4M HCl in EA (2 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to give the crude product which was purified by Flash reverse (mobile phase A: H₂O (0.1% HCl), B: ACN; 0 ~ 35% of B in A) to give (8, 8-difluoro-2, 6-diazaspiro [3.5] nonan-2-yl) (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) methanone hydrochloride as a light yellow solid.

[0806] MS (ESI) : mass calcd. for C₁₉H₂₁F₂N₃O, 345.17, m/z found 346.1 [M+H]⁺.

[0807] ¹H NMR (400 MHz, DMSO) δ 9.84 (brs, 2H), 7.78-7.71 (m, 1H), 7.41-7.35 (m, 1H), 7.18-7.09 (m, 2H), 4.13 (t, 7.2 Hz, 2H), 4.05 (d, J = 9.2 Hz, 2H), 3.93 (d, J = 9.6 Hz, 2H), 3.54 (t, 11.6 Hz, 2H), 3.40 (s, 2H), 3.11 (t, J = 7.2 Hz, 2H), 2.63-2.56 (m, 2H), 2.55-2.52 (m, 1H), 2.48-2.44 (m, 1H).

[0808] Example 62. Synthesis of I-77:



[0809] Experimental procedure:

[0810] Step 1

[0811] To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (30 mg, 0.15 mmol), tert-butyl 9, 9-difluoro-2, 7-diazaspiro [4.5] decane-7-carboxylate (41.2 mg, 0.15 mmol) and DIEA (57.8 mg, 0.45 mmol) in DMF (5 mL) was added HATU (68.0 mg, 0.18 mmol). The reaction mixture was stirred at 50 °C for 12 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give tert-butyl 2- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carbonyl) -9, 9-difluoro-2, 7-diazaspiro [4.5] decane-7-carboxylate (40 mg, crude) as a yellow solid which was used directly for the next step.

[0812] MS (ESI) : mass calcd. for C₂₅H₃₁F₂N₃O₃, 459.23, m/z found 460.1 [M+H]⁺.

[0813] Step 2

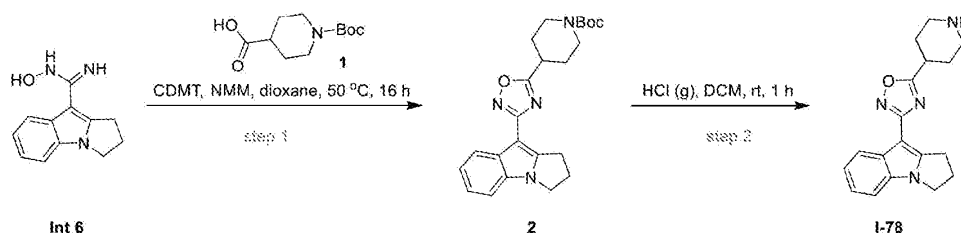
[0814] To a mixture of tert-butyl 2- ({ 1H, 2H, 3H-benzo [b] pyrrolizin-9-yl } carbonyl) -9, 9-difluoro-2, 7-diazaspiro [4.5] decane-7-carboxylate (40 mg, 0.087 mmol) in HCl/EA (4N) (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile), flow rate : 30 ml/min, wavelength: 214/254 nm) to give (9, 9-difluoro-2, 7-diazaspiro [4.5] decan-2-yl) (2, 3-

dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) methanone formate (15.3 mg, 48%) as a white solid.

[0815] MS (ESI) : mass calcd. for $C_{20}H_{23}F_2N_3O$, 359.18, m/z found 360.1 [M+H]⁺.

[0816] ¹H NMR (400 MHz, DMSO-d₆) δ 8.13 (s, 0.05H) , 7.59 (d, J = 7.2 Hz, 1H) , 7.35 (d, J = 7.6 Hz, 1H) , 7.14-7.03 (m, 2H) , 4.16-4.06 (m, 2H) , 3.56-3.29 (m, 4H) , 3.10-2.98 (m, 2H) , 2.93-2.86 (m, 2H) , 2.69-2.51 (m, 4H) , 2.09-1.97 (m, 2H) , 1.92-1.70 (m, 2H) .

[0817] Example 63. Synthesis of I-78:



[0818] Experimental procedure:

[0819] Step 1

[0820] To a mixture of CDMT (114 mg, 0.65 mmol) in dioxane (5 mL) was added NMM (165 mg, 1.63 mmol) at 25°C. After stirring for 30 min, 1- (tert-butoxycarbonyl) piperidine-4-carboxylic acid (125 mg, 0.54 mmol) was added into the reaction mixture. After stirring for 1 h, N-hydroxy-2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboximidamide (140 mg, 0.65 mmol) was added into the reaction mixture. The mixture was stirred at 50 °C for 16 h under N₂. The mixture was concentrated under reduced pressure to give the crude product which was purified by Flash Chromatography (mobile phase A: PE, B: EA; 0 ~ 35% of B in A) to give tert-butyl 4- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) piperidine-1-carboxylate (80 mg, 34%) as a light yellow solid.

[0821] MS (ESI) : mass calcd. for $C_{23}H_{28}N_4O_3$, 408.22, m/z found 431.0 [M+Na]⁺.

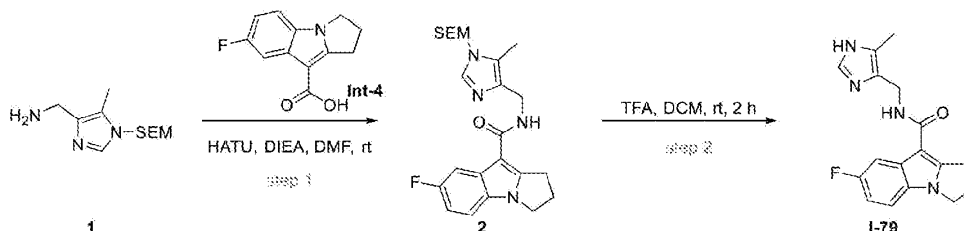
[0822] Step 2

[0823] To a mixture of tert-butyl 4- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) piperidine-1-carboxylate (80 mg, 0.19 mmol) in DCM (6 mL) was added 4M HCl in EA (2 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to give the crude product which was purified by Flash reverse (mobile phase A: H₂O (0.1%FA) , B: ACN; 0 ~ 35% of B in A) to give 3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -5- (piperidin-4-yl) -1, 2, 4-oxadiazole formate (42.2 mg, 69%) as a white solid.

[0824] MS (ESI) : mass calcd. for $C_{18}H_{20}N_4O$, 308.16, m/z found 309.1 [M+H]⁺.

[0825] ^1H NMR (400 MHz, DMSO) δ 8.33 (s, 1H) , 8.02-7.96 (m, 1H) , 7.47-7.40 (m, 1H) , 7.23-7.14 (m, 2H) , 4.18 (t, J = 7.2 Hz, 2H) , 3.50-3.22 (m, 3H) , 3.21-3.12 (m, 2H) , 2.89-2.76 (m, 2H) , 2.69-2.59 (m, 2H) , 2.17-2.05 (m, 2H) , 1.91-1.75 (m, 2H) .

[0826] Example 64. Synthesis of I-79:



[0827] Experimental procedure:

[0828] Step 1

[0829] To a mixture of 7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (150 mg, 0.68 mmol) , { 1- [(2-methoxyethyl) trimethyl- Si^{H} { 5 } -silyl] -5-methylimidazol-4-yl} methanamine (165.9 mg, 0.68 mmol) and DIEA (265.3 mg, 2.05 mmol) in DMF (10 mL) was added HATU (312.2 mg, 0.82 mmol) . The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give 7-fluoro-N- ((5-methyl-1- ((2- (trimethylsilyl) ethoxy) methyl) -1H-imidazol-4-yl) methyl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (100 mg, 26%) as a yellow solid which was used directly for the next step.

[0830] MS (ESI) : mass calcd. for $\text{C}_{23}\text{H}_{31}\text{FN}_4\text{O}_2\text{Si}$, 442.22, m/z found 443.2 $[\text{M}+\text{H}]^+$.

[0831] Step 2

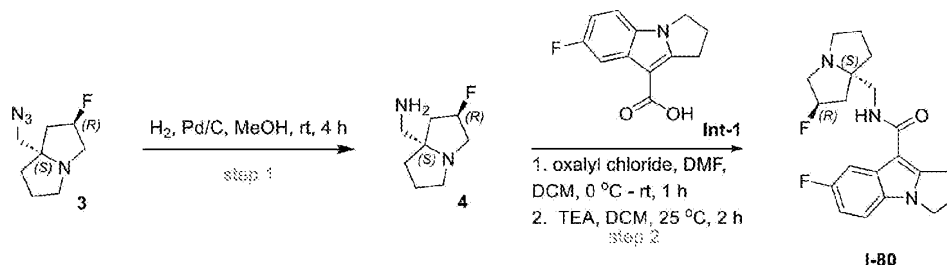
[0832] To a mixture of 7-fluoro-N- ({ 1- [(2-methoxyethyl) trimethyl- Si^{H} { 5 } -silyl] -5-methylimidazol-4-yl} methyl) -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (100 mg, 0.23 mmol) in DCM/TFA=3/1 (8 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (Xbridge prep c18 10um OBD 19*150mm/WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 30 ml/min, wavelength: 214/254 nm) to give 7-fluoro-N- ((5-methyl-1H-imidazol-4-yl) methyl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (5 mg, 7%) as a white solid.

[0833] MS (ESI) : mass calcd. for $\text{C}_{17}\text{H}_{17}\text{FN}_4\text{O}$, 312.14, m/z found 313.1 $[\text{M}+\text{H}]^+$.

[0834] ^1H NMR (400 MHz, DMSO- d_6) δ 11.64 (s, 1H) , 8.36 (s, 0.7H) , 7.70 (dd, J = 10.4, 2.4 Hz, 1H) , 7.42 (s, 1H) , 7.37 (dd, J = 8.4, 4.4 Hz, 1H) , 7.31-7.28 (m, 1H) , 6.97 (td,

$J = 9.2, 2.4 \text{ Hz, 1H}$, $4.32 \text{ (d, } J = 5.6 \text{ Hz, 2H)}$, $4.11 \text{ (t, } J = 7.2 \text{ Hz, 2H)}$, $3.22 \text{ (t, } J = 7.2 \text{ Hz, 2H)}$, $2.61\text{--}2.55 \text{ (m, 2H)}$, 2.16 (s, 3H) .

[0835] Example 65. Synthesis of I-80:



[0836] Experimental procedure:

[0837] Step 1

[0838] To a solution of (2R, 7aS)-7a-(azidomethyl)-2-fluoro-hexahydropyrrolizine (300 mg, 1.63 mmol) in MeOH (15 mL) was added Pd/C (60 mg) . Then the mixture was stirred at room temperature under H₂ for 4 h. Pd/C was removed by filtering and the filtrate was concentrated in vacuo to give the crude product (250 mg, crude) was used in the next step directly.

[0839] MS (ESI) : mass calcd. for C₈H₁₃FN₂, 158.12, m/z found 159.1 [M+H]⁺.

[0840] Step 2

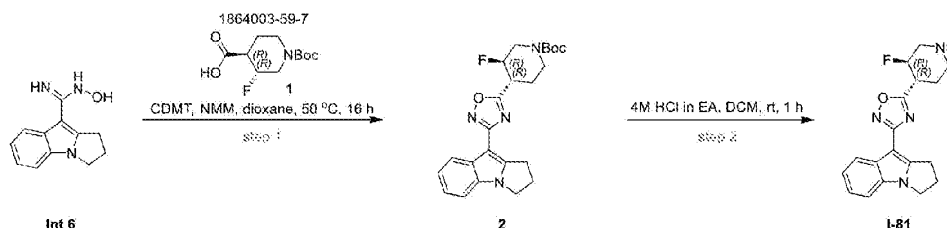
[0841] To a solution of 7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.456 mmol) in DCM (5mL) was added Oxalyl chloride (174 mg, 1.37 mmol) and DMF (6.67 mg, 0.0912 mmol) at 0°C dropwise under N₂. Then the mixture was stirred at room temperature for 0.5 h. The mixture was concentrated. The crude product was used in next step without further purification. To the solution of the above crude product in DCM (5mL) was added [(2R, 7aS)-2-fluoro-hexahydropyrrolizin-7a-yl] methanamine (144 mg, 0.912mmol) and TEA (92 mg, 0.913 mmol) , then the mixture was stirred at 25 °C for 2 h under N₂. The mixture was diluted with EA and the solid was removed by filtering, the filtrate was washed with water. The organic layer was washed with water, brine, dried over Na₂SO₄ and concentrated under reduced pressure to afford crude product. The residue was purified by Prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) , B (Acetonitrile) , 15~100%of B in A, 10 min, Flow rate: 25ml/min, wavelength: 214/254 nm) to N- { [(2R, 7aS)-2-fluoro-hexahydropyrrolizin-7a-yl] methyl} -7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide formate (45 mg, 26.6%) as white solid.

[0842] MS (ESI) : mass calcd. for C₂₀H₂₃F₂N₃O, 359.18, m/z found 360.2 [M+H]⁺.

[0843] ¹H NMR (400 MHz, DMSO) δ 8.21 (s, 0.15H) , 7.57 (dd, $J = 12.0, 4.0 \text{ Hz, 1H}$) , 7.37 (dd, $J = 8.0, 4.0 \text{ Hz, 1H}$) , 6.96 (td, $J = 8.0, 2.4 \text{ Hz, 1H}$) , 6.42 (s, 1H) , 4.93-4.62 (m, 1H) , 4.11 (t, $J = 8.0 \text{ Hz, 2H}$) , 3.27-3.14 (m, 3H) , 3.06-2.96 (m, 1H) , 2.91 (m, 1H) ,

2.84-2.81 (m, 2H) , 2.71 -2.66 (m, 1H) , 2.61 -2.54 (m, 3H) , 2.38-2.24 (m, 2H) , 2.14 -2.11 (m, 1H) , 1.91-1.83 (m, 1H) , 1.37-1.34 (m, 1H) .

[0844] Example 66. Synthesis of I-81:



[0845] Experimental procedure:

[0846] Step 1

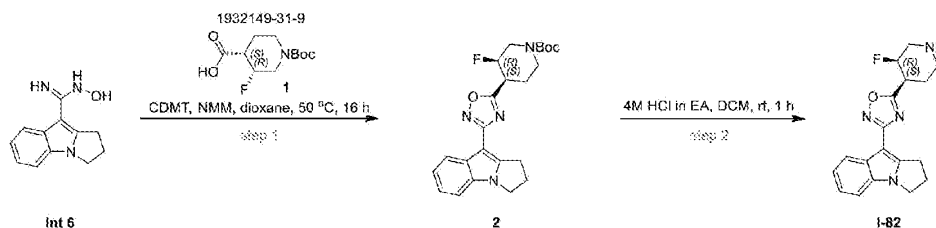
[0847] To a mixture of CDMT (85 mg, 0.48 mmol) in dioxane (6 mL) was added NMM (123 mg, 1.21 mmol) at 25 °C. After stirring for 30 min, (3R, 4R) -1- (tert-butoxy-carbonyl) -3-fluoropiperidine-4-carboxylic acid (100 mg, 0.40 mmol) was added into the reaction mixture. After stirring for 1 h, N-hydroxy-2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboximidamide (113 mg, 0.53 mmol) was added into the reaction mixture. The mixture was stirred at 50 °C for 16 h under N₂. The mixture was concentrated under reduced pressure to give the crude product which was purified by Flash Chromatography (mobile phase A: PE, B: EA; 0 ~ 20% of B in A) to give tert-butyl (3R, 4R) -4- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3-fluoropiperidine-1-carboxylate (78 mg, 42%) as a white solid. MS (ESI) : mass calcd. for C₂₃H₂₇FN₄O₃, 426.21, m/z found 449.1 [M+Na]⁺.

[0848] Step 2

[0849] To a mixture of tert-butyl (3R, 4R) -4- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3-fluoropiperidine-1-carboxylate (78 mg, 0.18 mmol) in DCM (6 mL) was added 4M HCl in EA (2 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 1 h under N₂. The mixture was concentrated under reduced pressure to give the crude product which was purified by reverse phase column (column: WELCH Xtimate C18 21.2*250 mm 10 um; mobile phase A: H₂O (0.1%FA) , B: ACN; 20 ~ 50% of B in A; flow rate: 30 mL/min; wavelength: 214 nm.) to give 3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -5-((3R, 4R) -3-fluoropiperidin-4-yl) -1, 2, 4-oxadiazole formate (30.2 mg, 50%) as a white solid. MS (ESI) : mass calcd. for C₁₈H₁₉FN₄O, 326.15, m/z found 327.1 [M+H]⁺.

[0850] ¹H NMR (400 MHz, DMSO) δ 8.43 (s, 0.18H) , 8.05 -7.93 (m, 1H) , 7.49-7.38 (m, 1H) , 7.24-7.14 (m, 2H) , 4.91-4.66 (m, 1H) , 4.19 (t, J = 6.8 Hz, 2H) , 3.48-3.40 (m, 1H) , 3.29-3.25 (m, 3H) , 2.94-2.86 (m, 1H) , 2.69-2.54 (m, 4H) , 2.12-2.00 (m, 1H) , 1.83-1.70 (m, 1H) .

[0851] Example 67. Synthesis of I-82:



[0852] Experimental procedure:

[0853] Step 1

[0854] To a mixture of CDMT (77 mg, 0.44 mmol) in dioxane (6 mL) was added NMM (110 mg, 1.09 mmol) at 25°C. After stirring for 30 min, (3R, 4S) -1- (tert-butoxy-carbonyl) -3-fluoropiperidine-4-carboxylic acid (90 mg, 0.36 mmol) was added into the reaction mixture. After stirring for 1 h, N-hydroxy-2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboximidamide (102 mg, 0.47 mmol) was added into the reaction mixture. The mixture was stirred at 50°C for 16 h under N₂. The mixture was concentrated under reduced pressure to give the crude product which was purified by Flash Chromatography (mobile phase A: PE, B: EA; 0 ~ 35% of B in A) to give tert-butyl (3R, 4S) -4- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3-fluoropiperidine-1-carboxylate (58 mg, 37%) as a white solid.

[0855] MS (ESI) : mass calcd. for $C_{23}H_{27}FN_4O_3$, 426.21, m/z found 449.2 $[M+Na]^+$.

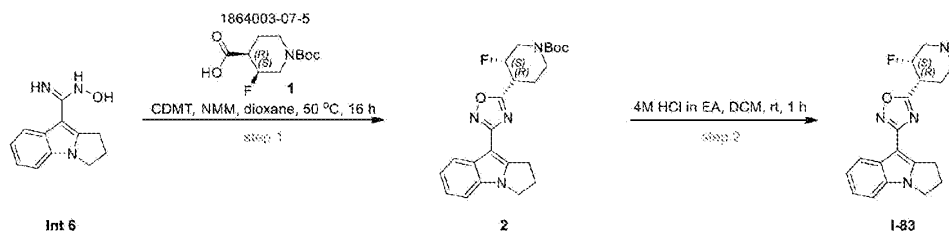
[0856] Step 2

[0857] To a mixture of tert-butyl (3R, 4S) -4- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3-fluoropiperidine-1-carboxylate (58 mg, 0.14 mmol) in DCM (3 mL) was added 4M HCl in EA (1 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 1 h under N₂. The mixture was concentrated under reduced pressure to give the crude product which was purified by Flash reverse (mobile phase A: H₂O (0.1% HCl) , B: ACN; 0 ~ 35% of B in A) to give 3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -5- ((3R, 4S) -3-fluoropiperidin-4-yl) -1, 2, 4-oxadiazole hydrochloride (32.3 mg, 72%) as a white solid.

[0858] MS (ESI) : mass calcd. for $C_{18}H_{19}FN_4O$, 326.15, m/z found 327.1 $[M+H]^+$.

[0859] ¹H NMR (400 MHz, DMSO+D₂O) δ 8.03-7.96 (m, 1H) , 7.52- 7.43 (m, 1H) , 7.29-7.18 (m, 2H) , 5.66- 5.47 (m, 1H) , 4.19 (t, J = 7.2 Hz, 2H) , 3.90- 3.67 (m, 2H) , 3.51- 3.34 (m, 2H) , 3.27 (t, J = 7.2 Hz, 2H) , 3.16 (td, J = 12.4, 4.0 Hz, 1H) , 2.70- 2.60 (m, 2H) , 2.43-2.32 (m, 2H) .

[0860] Example 68. Synthesis of I-83:



[0861] Experimental procedure:

[0862] Step 1

[0863] To a mixture of CDMT (77 mg, 0.44 mmol) in dioxane (6 mL) was added NMM (110 mg, 1.09 mmol) at 25 °C. After stirring for 30 min, (3S, 4R) -1- (tert-butoxycarbonyl) -3-fluoropiperidine-4-carboxylic acid (90 mg, 0.36 mmol) was added into the reaction mixture. After stirring for 1 h, N-hydroxy-2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboximidamide (102 mg, 0.47 mmol) was added into the reaction mixture. The mixture was stirred at 50°C for 16 h under N₂. The mixture was concentrated under reduced pressure to give the crude product which was purified by Flash Chromatography (mobile phase A: PE, B: EA; 0 ~ 35% of B in A) to give tert-butyl (3S, 4R) -4- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3-fluoropiperidine-1-carboxylate (57 mg, 36%) as a white solid.

[0864] MS (ESI) : mass calcd. for C₂₃H₂₇FN₄O₃, 426.21, m/z found 449.2 [M+Na]⁺.

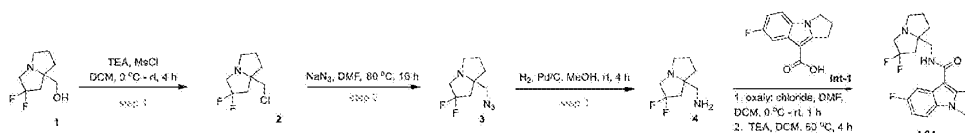
[0865] Step 2

[0866] To a mixture of tert-butyl (3S, 4R) -4- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3-fluoropiperidine-1-carboxylate (57 mg, 0.13 mmol) in DCM (3 mL) was added 4M HCl in EA (1 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 1 h under N₂. The mixture was concentrated under reduced pressure to give the crude product which was purified by Flash reverse (mobile phase A: H₂O (0.1% HCl), B: ACN; 0 ~ 35% of B in A) to give 3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -5- ((3S, 4R) -3-fluoropiperidin-4-yl) -1, 2, 4-oxadiazole hydrochloride (37.6 mg, 86%) as a white solid.

[0867] MS (ESI) : mass calcd. for C₁₈H₁₉FN₄O, 326.15, m/z found 327.1 [M+H]⁺.

[0868] ¹H NMR (400 MHz, DMSO-d₆) δ 8.03-7.96 (m, 1H), 7.50- 7.44 (m, 1H), 7.27-7.19 (m, 2H), 5.64- 5.47 (m, 1H), 4.19 (t, J = 7.2 Hz, 2H), 3.87- 3.66 (m, 2H), 3.51- 3.34 (m, 2H), 3.26 (t, J = 7.2 Hz, 2H), 3.16 (td, J = 12.4, 4.0 Hz, 1H), 2.70- 2.61 (m, 2H), 2.42-2.31 (m, 2H).

[0869] Example 69. Synthesis of I-84:



[0870] Experimental procedure:

[0871] Step 1

[0872] To a solution of (2, 2-difluoro-tetrahydro-1H-pyrrolizin-7a-yl) methanol (450 mg, 2.5 mmol) and Et₃N (771 mg, 7.6 mmol) in DCM (10 mL) was added MsCl (436 mg, 3.8 mmol) at 0 °C dropwise under N₂. Then the mixture was stirred at room temperature under N₂ for 4 h. The mixture was diluted with water (20 mL) and extracted with DCM (10 mL x 3). The organic layer was washed with water (50 mL x 2), brine (50 mL x 2), dried over Na₂SO₄, filtered and concentrated. The crude product (450 mg, crude) was used in next step without further purification.

[0873] MS (ESI): mass calcd. for C₈H₁₂ClF₂N, 195.06, m/z found 196.1 [M+H]⁺.

[0874] Step 2

[0875] To a solution of 7a- (chloromethyl) -2, 2-difluoro-tetrahydro-1H-pyrrolizine (450 mg, 2.3 mmol) in DMF (8 mL) was added NaN₃ (1.2 g, 18.4 mmol) at room temperature under N₂ protection. The reaction was stirred at 80 °C for 16 h. After reaction, the mixture was diluted with EA (50 mL) and the solid was removed by filtering, the filtrate was washed with water. The organic layer was washed with water (50 mL x 2), brine (50 mL x 2) and dried over Na₂SO₄. The crude product was purified by silica gel column chromatography (PE/EA = 2: 1) to afford 7a- (azidomethyl) -2, 2-difluoro-tetrahydro-1H-pyrrolizine (300 mg, 61.3%) as yellow oil.

[0876] MS (ESI): mass calcd. for C₈H₁₂F₂N₄, 202.10, m/z found 203.1 [M+H]⁺.

[0877] Step 3

[0878] To a solution of 7a- (azidomethyl) -2, 2-difluoro-tetrahydro-1H-pyrrolizine (270 mg, 1.33 mmol) in CH₃OH (10 mL) was added Pd/C (50 mg, wt%: 10%). Then the mixture was stirred at room temperature under H₂ for 4 h. Pd/C was removed by filtering and the filtrate was concentrated in vacuo to give the crude product was used in the next step directly.

[0879] MS (ESI): mass calcd. for C₈H₁₄F₂N₂, 176.11, m/z found 177.2 [M+H]⁺.

[0880] Step 4

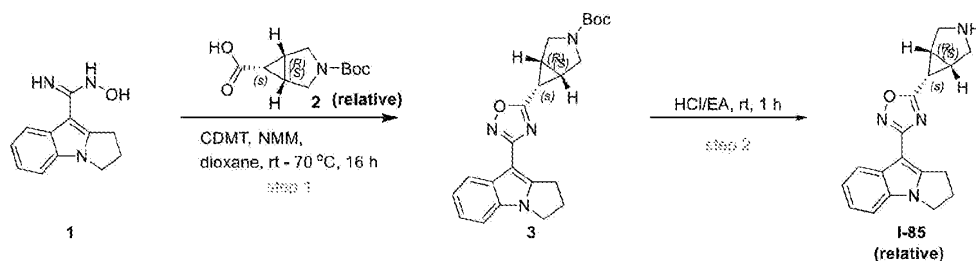
[0881] To a solution of 7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.46 mmol) in DCM (5mL) was added Oxalyl chloride (174 mg, 1.4 mmol) and DMF (6.67 mg, 0.09 mmol) at 0°C dropwise under N₂. Then the mixture was stirred at room temperature for 0.5 h. The mixture was concentrated. The crude product was used in next step without further purification. To the solution of the above crude product in DCM (5mL) was added (2, 2-difluoro-tetrahydro-1H-pyrrolizin-7a-yl) methanamine (161 mg, 0.912mmol) and TEA (138 mg, 1.37 mmol), then the mixture was stirred at 50°C for 2 h under N₂. The mixture was diluted with EA (50 mL). The organic layer was washed with water (50 mL x 2), brine (50 mL x 2), dried

over Na_2SO_4 and concentrated under reduced pressure to afford crude product. The residue was purified by Prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%TFA) , B (Acetonitrile) , 35~100%of B in A, 9.5 min, Flow rate: 25ml/min, wavelength: 214/254 nm) to N- [(2, 2-difluoro-tetrahydro-1H-pyrrolizin-7a-yl) methyl] -7-fluoro-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (80 mg, 46.5%) as white solid.

[0882] MS (ESI) : mass calcd. for $\text{C}_{20}\text{H}_{22}\text{F}_3\text{N}_3\text{O}$, 377.17, m/z found 378.2 $[\text{M}+\text{H}]^+$.

[0883] ^1H NMR (400 MHz, DMSO) δ 11.12 (s, 0.33H) , 7.56 (dd, $J = 8.0, 2.4$ Hz, 1H) , 7.41 (dd, $J = 8.0, 4.0$ Hz, 1H) , 7.05 (s, 1H) , 7.02- 6.92 (m, 1H) , 4.13 (t, $J = 8.0$ Hz, 2H) , 3.86-3.76 (m, 3H) , 3.31- 3.15 (m, 5H) , 3.06- 2.92 (m, 1H) , 2.75 -2.67 (m, 1H) , 2.62- 2.56 (m, 2H) , 2.22- 1.99 (m, 3H) , 1.79 -1.72 (m, 1H) .

[0884] Example 70. Synthesis of I-85:



[0885] Experimental procedure:

[0886] Step 1

[0887] Synthesis of tert-butyl (1R, 5S, 6s) -6- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3-azabicyclo [3.1.0] hexane-3-carboxylate. A mixture of CDMT (97.9 mg, 0.56 mmol) and NMM (141 mg, 1.39 mmol) in dioxane (10 mL) was stirred at room temperature for 0.5 h. (1R, 5S, 6S) -3- (tert-butyl-1, 2, 4-oxadiazol-5-yl) -3-azabicyclo [3.1.0] hexane-6-carboxylic acid (106 mg, 0.46 mmol) was added. The mixture was stirred at room temperature for 0.5 h. N-hydroxy-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboximidamide (100 mg, 0.46 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and stirred at 70°C for 16 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was concentrated to afford the crude product which was purified by silica gel column chromatography (PE: EA = 1: 1) to give tert-butyl (1R, 5S, 6s) -6- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3-azabicyclo [3.1.0] hexane-3-carboxylate (40 mg, 17%) as a yellow solid.

[0888] MS (ESI) : mass calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_4\text{O}_3$, 406.20, m/z found 407.1 $[\text{M}+\text{H}]^+$.

[0889] Step 2

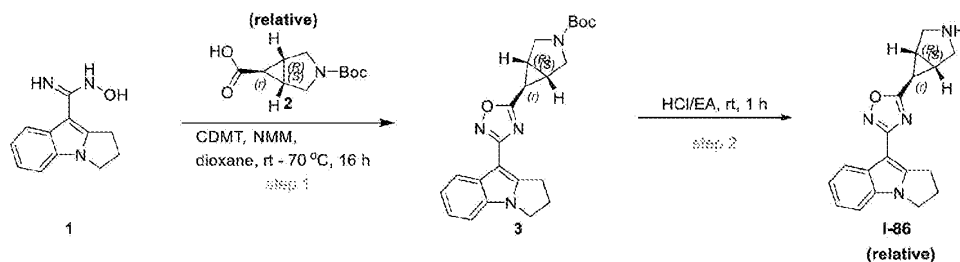
[0890] Synthesis of 5- ((1R, 5S, 6s) -3-azabicyclo [3.1.0] hexan-6-yl) -3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazole. A mixture of (1R, 5S, 6S) -6-

(3- {1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -1, 2, 4-oxadiazol-5-yl) -3-azabicyclo [3.1.0] hexan-3-yl tert-butyl formate (40 mg, 0.098 mmol) in HCl/EA (4N) (5 mL) was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 30 ml/min, wavelength: 214/254 nm) to give 5- ((1R, 5S, 6s) -3-azabicyclo [3.1.0] hexan-6-yl) -3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazole formate (9.4 mg, 31%) as a white solid.

[0891] MS (ESI) : mass calcd. for $C_{18}H_{18}N_4O$, 306.15, m/z found 307.1 [M+H]⁺.

[0892] ¹H NMR (400 MHz, DMSO-d₆) δ8.45 (s, 0.3H) , 8.01-7.89 (m, 1H) , 7.50-7.39 (m, 1H) , 7.25- 7.10 (m, 2H) , 4.17 (t, J = 7.2 Hz, 2H) , 3.22 (t, J = 7.6 Hz, 2H) , 3.10 (d, J = 10.8 Hz, 2H) , 2.95 (d, J = 10.8 Hz, 2H) , 2.70- 2.57 (m, 2H) , 2.26- 2.19 (m, 1H) , 2.15 -2.07 (m, 2H) .

[0893] Example 71. Synthesis of I-86



[0894] Experimental procedure:

[0895] Step 1

[0896] Synthesis of tert-butyl (1R, 5S, 6r) -6- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3-azabicyclo [3.1.0] hexane-3-carboxylate. A mixture of CDMT (97.9 mg, 0.56 mmol) and NMM (141.0 mg, 1.39 mmol) in dioxane (10 mL) was stirred at room temperature for 0.5 h. (1R, 5S, 6R) -3- (tert-butyl-oxo) -3-azabicyclo [3.1.0] hexane-6-carboxylic acid (106.1 mg, 0.46 mmol) was added. The mixture was stirred at room temperature for 0.5 h. N-hydroxy-1H, 2H, 3H-benzo [b] pyrrolizine-9-carboximidamide (100 mg, 0.46 mmol) was added. The reaction mixture was stirred at room temperature for 1 h and stirred at 70 °C for 16 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 2) . The organic layer was concentrated to afford the crude product which was purified by silica gel column chromatography (PE: EA = 1: 1) to give tert-butyl (1R, 5S, 6r) -6- (3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazol-5-yl) -3-azabicyclo [3.1.0] hexane-3-carboxylate (80 mg, 38%) as a yellow solid.

[0897] MS (ESI) : mass calcd. for $C_{23}H_{26}N_4O_3$, 406.20, m/z found 407.1 [M+H]⁺.

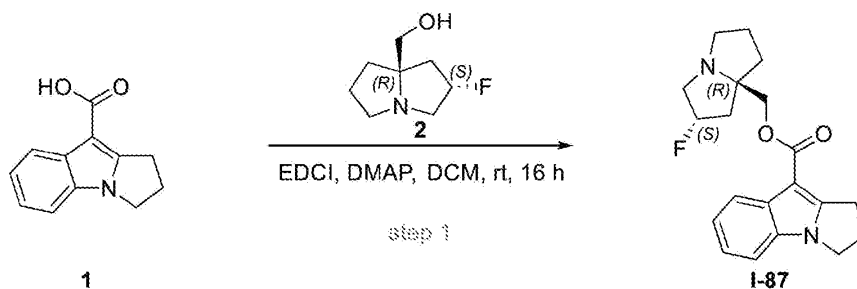
[0898] Step 2

[0899] Synthesis of 5- ((1R, 5S, 6r) -3-azabicyclo [3.1.0] hexan-6-yl) -3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1, 2, 4-oxadiazole. A mixture of (1R, 5S, 6R) -6- (3- {1H, 2H, 3H-benzo [b] pyrrolizin-9-yl} -1, 2, 4-oxadiazol-5-yl) -3-azabicyclo [3.1.0] hexan-3-yl tert-butyl formate (40 mg, 0.098 mmol) in HCl/EA (4N, 5 mL) was stirred at room temperature for 1 h. The mixture was concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 30 ml/min, wavelength: 214/254 nm) to give 5- ((1R, 5S, 6r) -3-azabicyclo [3.1.0] hexan-6-yl) -3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indol-9-yl) -1,2, 4-oxadiazole formate (22.8 mg, 73%) as a white solid.

[0900] MS (ESI) : mass calcd. for $C_{18}H_{18}N_4O$, 306.15, m/z found 307.1 $[M+H]^+$.

[0901] 1H NMR (400 MHz, DMSO- d_6) δ 8.20 (s, 0.8H) , 7.97-7.95 (m, 1H) , 7.43- 7.41 (m, 1H) , 7.22- 7.12 (m, 2H) , 4.17 (t, J = 7.2 Hz, 2H) , 3.23 (t, J = 7.6 Hz, 2H) , 3.07 (d, J = 11.6 Hz, 2H) , 2.82 (d, J = 11.6 Hz, 2H) , 2.67- 2.59 (m, 2H) , 2.35- 2.32 (m, 1H) , 2.20- 2.18 (m, 2H) .

[0902] Example 72. Synthesis of I-87:



[0903] Experimental procedure:

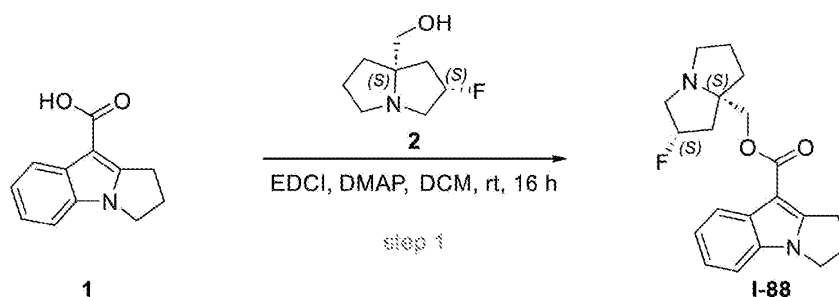
[0904] Step 1

[0905] Synthesis of ((2S, 7aR) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methyl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate. A mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.50 mmol) , [(2S, 7aR) -2-fluoro-hexahydropyrrolizin-7a-yl] methanol (79 mg, 0.50 mmol) , EDCI (143 mg, 0.75 mmol) and 4-DMAP (121 mg, 0.99 mmol) in DCM (10 mL) was stirred at room temperature for 16 h. The mixture was diluted with water (100 mL) and extracted with DCM (50 mL x 2) . The organic layer was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 30 ml/min, wavelength: 214/254 nm, Gradient: from 23%to 33%of B in A) to give ((2S, 7aR) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methyl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate formate (32.8 mg, 19%) as a white solid.

[0906] MS (ESI) : mass calcd. for $C_{20}H_{23}FN_2O_2$, 342.17, m/z found 343.1 $[M+H]^+$.

[0907] 1H NMR (400 MHz, DMSO- d_6) δ 8.32 (s, 0.2H) , 7.98- 7.90 (m, 1H) , 7.46- 7.38 (m, 1H) , 7.25- 7.13 (m, 2H) , 5.36- 5.21 (m, 1H) , 4.17 (t, $J = 7.2$ Hz, 2H) , 4.00- 3.89 (m, 2H) , 3.21 (t, $J = 7.6$ Hz, 2H) , 3.15- 3.10 (m, 2H) , 3.04- 3.02 (m, 1H) , 2.88- 2.80 (m, 1H) , 2.69-2.56 (m, 2H) , 2.15- 2.06 (m, 2H) , 2.02- 1.72 (m, 4H) .

[0908] Example 73. Synthesis of I-88:



[0909] Experimental procedure:

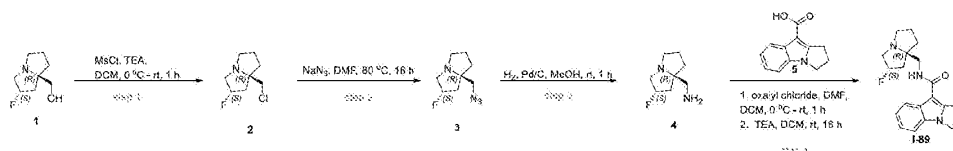
[0910] Step 1

[0911] Synthesis of ((2S, 7aS) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methyl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate. A mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.50 mmol) , [(2S, 7aS) -2-fluoro-hexahydro-pyrrolizin-7a-yl] methanol (79 mg, 0.50 mmol) , EDCI (143 mg, 0.75 mmol) and 4-DMAP (121 mg, 0.99 mmol) in DCM (10 mL) was stirred at room temperature for 16 h. The mixture was diluted with water (100 mL) and extracted with DCM (50 mL x 2) . The organic layer was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 30 ml/min, wavelength: 214/254 nm, Gradient: from 20%to 50%of B in A) to give ((2S, 7aS) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methyl 2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxylate formate (32.9 mg, 19%) as a white solid.

[0912] MS (ESI) : mass calcd. for $C_{20}H_{23}FN_2O_2$, 342.17, m/z found 343.2 $[M+H]^+$.

[0913] 1H NMR (400 MHz, DMSO- d_6) δ 8.40 (s, 0.2H) , 7.95- 7.93 (m, 1H) , 7.42- 7.40 (m, 1H) , 7.18- 7.16 (m, 2H) , 5.42- 5.29 (m, 1H) , 4.16 (t, $J = 7.2$ Hz, 2H) , 4.00 (q, $J = 10.4$ Hz, 2H) , 3.33- 3.26 (m, 1H) , 3.21 (t, $J = 7.6$ Hz, 2H) , 2.97- 2.76 (m, 2H) , 2.67- 2.55 (m, 3H) , 2.34- 2.25 (m, 1H) , 1.98- 1.67 (m, 5H) .

[0914] Example 74. Synthesis of I-89:



[0915] Experimental procedure:

[0916] Step 1

[0917] Synthesis of (2S, 7aR) -7a- (chloromethyl) -2-fluorohexahydro-1H-pyrrolizine. To a mixture of [(2S, 7aR) -2-fluoro-hexahydropyrrolizin-7a-yl] methanol (100 mg, 0.63 mmol) and Et₃N (190.7 mg, 1.88 mmol) in DCM (10 mL) was added MsCl (86.4 mg, 0.75 mmol) at 0°C under N₂. The reaction mixture was stirred at room temperature for 1 h under N₂. The mixture was diluted with water (50 mL) and extracted with DCM (30 mL x 2). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give (2S, 7aR) -7a- (chloromethyl) -2-fluorohexahydro-1H-pyrrolizine (100 mg, crude) as a colorless oil which was used directly for the next step. MS (ESI) : mass calcd. for C₈H₁₃ClFN, 177.07, m/z found 178.1 [M+H]⁺.

[0918] Step 2

[0919] Synthesis of (2S, 7aR) -7a- (azidomethyl) -2-fluorohexahydro-1H-pyrrolizine. To a solution of (2S, 7aR) -7a- (chloromethyl) -2-fluoro-hexahydropyrrolizine (100 mg, 0.56 mmol) in DMF (5 mL) was added NaN₃ (109.8 mg, 1.69 mmol). The reaction mixture was stirred at 80°C for 16 h under N₂. The mixture was diluted with EA (30 mL) and the solid was removed by filtering, the filtrate was washed with water. The organic layer was washed with water, brine, dried over Na₂SO₄, filtered and concentrated to afford the crude product which was purified by silica gel column chromatography (PE: EA = 3: 1) to give (2S, 7aR) -7a- (azidomethyl) -2-fluorohexahydro-1H-pyrrolizine (35 mg, 30%) as a colorless oil.

[0920] MS (ESI) : mass calcd. for C₈H₁₃FN₄, 184.11, m/z found 185.1 [M+H]⁺.

[0921] Step 3

[0922] Synthesis of ((2S, 7aR) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methanamine. To a solution of (2S, 7aR) -7a- (azidomethyl) -2-fluoro-hexahydropyrrolizine (35 mg, 0.19 mmol) in MeOH (5 mL) was added Pd/C (4.0 mg, 0.038 mmol) under nitrogen. The reaction mixture was stirred at room temperature for 1 h under H₂. The mixture was filtered and the filtrate was concentrated in vacuo to give ((2S, 7aR) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methanamine (30 mg, crude) as colorless oil which was used directly for the next step without further purification. MS (ESI) : mass calcd. for C₈H₁₅FN₂, 158.12, m/z found 159.1 [M+H]⁺.

[0923] Step 4

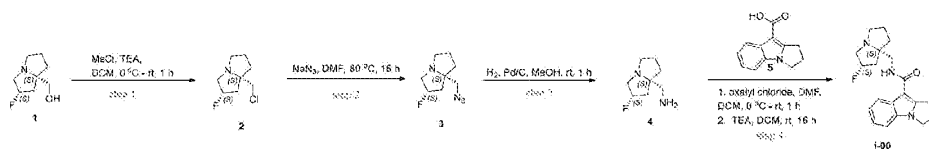
[0924] Synthesis of N- (((2S, 7aR) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methyl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide. To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (28 mg, 0.14 mmol) in DCM (10 mL) and DMF (0.5 mL) was added oxalyl chloride (26.5 mg, 0.21 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 h and then concentrated. The crude

product was used in next step without further purification. To a mixture of Et₃N (41.5 mg, 0.42 mmol) and [(2S, 7aR) -2-fluoro-hexahydropyrrolizin-7a-yl] methanamine (21.6 mg, 0.14 mmol) in DCM (10 mL) was added the above crude product in DCM (2 mL) . The reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with water (50 mL) and extracted with DCM (30 mL x 2) . The organic layer was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%NH₃) B (acetonitrile) , flow rate : 30 ml/min, Gradient: From 20%to 40%of B in A, wavelength: 214/254 nm) to give N- (((2S, 7aR) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methyl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (2 mg, 4%) as a white solid.

[0925] MS (ESI) : mass calcd. for C₂₀H₂₄FN₃O, 341.19, m/z found 342.2 [M+H]⁺.

[0926] ¹H NMR (400 MHz, MeOD) δ7.85- 7.78 (m, 1H) , 7.34- 7.27 (m, 1H) , 7.19- 7.08 (m, 2H) , 4.89- 4.74 (m, 1H) , 4.12 (t, J = 7.2 Hz, 2H) , 3.50- 3.34 (m, 2H) , 3.28- 3.22 (m, 2H) , 3.18- 3.04 (m, 2H) , 3.02- 2.91 (m, 2H) , 2.84- 2.55 (m, 4H) , 2.50- 2.40 (m, 1H) , 2.27- 2.20 (m, 1H) , 2.04- 1.96 (m, 1H) , 1.52- 1.47 (m, 1H) .

[0927] Example 75. Synthesis of I-90:



[0928] Experimental procedure:

[0929] Step 1

[0930] Synthesis of (2S, 7aS) -7a- (chloromethyl) -2-fluorohexahydro-1H-pyrrolizine. To a mixture of [(2S, 7aS) -2-fluoro-hexahydropyrrolizin-7a-yl] methanol (250 mg, 1.57 mmol) and Et₃N (476.7 mg, 4.71 mmol) in DCM (10 mL) was added MsCl (215.9 mg, 1.88 mmol) at 0°C under N₂. The reaction mixture was stirred at room temperature for 1 h under N₂. The mixture was diluted with water (100 mL) and extracted with DCM (50 mL x 2) . The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give (2S, 7aS) -7a- (chloromethyl) -2-fluorohexahydro-1H-pyrrolizine (250 mg, crude) as a colorless oil which was used directly for the next step. MS (ESI) : mass calcd. for C₈H₁₃ClFN, 177.07, m/z found 178.1 [M+H]⁺.

[0931] Step 2

[0932] Synthesis of (2S, 7aS) -7a- (azidomethyl) -2-fluorohexahydro-1H-pyrrolizine. To a solution of (2S, 7aS) -7a- (chloromethyl) -2-fluoro-hexahydropyrrolizine (250 mg, 1.41 mmol) in DMF (10 mL) was added NaN₃ (274.5 mg, 4.22 mmol) . The reaction mixture was stirred at 80°C for 16 h under N₂. The mixture was diluted with EA (30

mL) and the solid was removed by filtering, the filtrate was washed with water. The organic layer was washed with water, brine, dried over Na_2SO_4 , filtered and concentrated to afford the crude product which was purified by silica gel column chromatography (PE: EA = 3: 1) to give (2S, 7aS) -7a- (azidomethyl) -2-fluorohexahydro-1H-pyrrolizine (90 mg, 31%) as a colorless oil. MS (ESI) : mass calcd. for $\text{C}_8\text{H}_{13}\text{FN}_4$, 184.11, m/z found 185.1 $[\text{M}+\text{H}]^+$.

[0933] Step 3

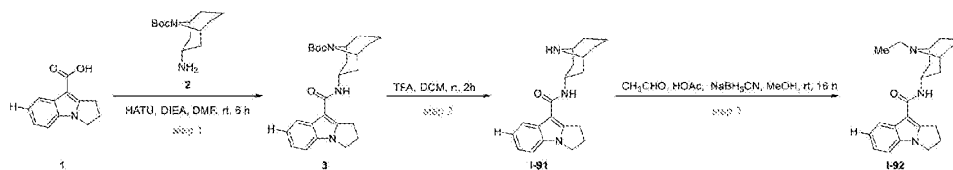
[0934] Synthesis of ((2S, 7aS) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methanamine. To a solution of (2S, 7aS) -7a- (azidomethyl) -2-fluoro-hexahydropyrrolizine (90 mg, 0.49 mmol) in MeOH (10 mL) was added Pd/C (10.4 mg, 0.10 mmol) under nitrogen protection. The reaction mixture was stirred at room temperature for 1 h under H_2 . The mixture was filtered and the filtrate was concentrated in vacuo to give ((2S, 7aS) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methanamine (75 mg, crude) as colorless oil which was used directly for the next step. MS (ESI) : mass calcd. for $\text{C}_8\text{H}_{15}\text{FN}_2$, 158.12, m/z found 159.1 $[\text{M}+\text{H}]^+$.

[0935] Step 4

[0936] Synthesis of N- ((2S, 7aS) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methyl)-2,3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide. To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (92 mg, 0.46 mmol) in DCM (10 mL) and DMF (0.5 mL) was added oxalyl chloride (87.0 mg, 0.69 mmol) at 0°C . The reaction mixture was stirred at room temperature for 1 h and the mixture was concentrated. The crude product was used in next step without further purification. To a mixture of Et_3N (138.2 mg, 1.37 mmol) and [(2S, 7aS) -2-fluoro-hexahydropyrrolizin-7a-yl] methanamine (72.0 mg, 0.46 mmol) in DCM (10 mL) was added the above crude product in DCM (3 mL) . The reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with water (100 mL) and extracted with DCM (50 mL x 2) . The organic layer was concentrated to afford the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) B (acetonitrile) , flow rate : 30 ml/min, Gradient: From 17%to 47%of B in A, wavelength: 214/254 nm) to give N- ((2S, 7aS) -2-fluorotetrahydro-1H-pyrrolizin-7a (5H) -yl) methyl)-2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (39.3 mg, 25%) as a white solid. MS (ESI) : mass calcd. for $\text{C}_{20}\text{H}_{24}\text{FN}_3\text{O}$, 341.19, m/z found 342.2 $[\text{M}+\text{H}]^+$.

[0937] ^1H NMR (400 MHz, DMSO- d_6) δ 8.23 (s, 1H) , 7.95- 7.93 (m, 1H) , 7.37- 7.35 (m, 1H) , 7.18- 7.06 (m, 2H) , 6.88- 6.86 (m, 1H) , 5.35- 5.22 (m, 1H) , 4.11 (t, J = 7.2 Hz, 2H) , 3.32- 3.18 (m, 4H) , 3.02- 2.84 (m, 2H) , 2.82- 2.54 (m, 4H) , 2.33- 2.17 (m, 1H) , 2.03-1.89 (m, 1H) , 1.87- 1.55 (m, 4H) .

[0938] Example 76. Synthesis of I-91 & I-92:



[0939] Experimental procedure:

[0940] Step 1

[0941] Synthesis of tert-butyl 3- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamido) -9-azabicyclo [3.3.1] nonane-9-carboxylate. To a mixture of 1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxylic acid (100 mg, 0.50 mmol) , tert-butyl 3-amino-9-azabicyclo [3.3.1] nonane-9-carboxylate (119.5 mg, 0.50 mmol) and DIEA (192.7 mg, 1.49 mmol) in DMF (10 mL) was added HATU (226.8 mg, 0.60 mmol) . The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL×3) . The combined organic layer was concentrated to afford the crude product which was purified by column chromatography (PE: EA = 1: 1) to give tert-butyl 3- (2, 3-dihydro-1H-pyrrolo [1, 2-a]indole-9-carboxamido) -9-azabicyclo [3.3.1] nonane-9-carboxylate (150 mg, 64%) as a yellow solid. MS (ESI) : mass calcd. for $C_{25}H_{33}N_3O_3$, 423.25, m/z found 368.2 [M-55] .

[0942] Step 2

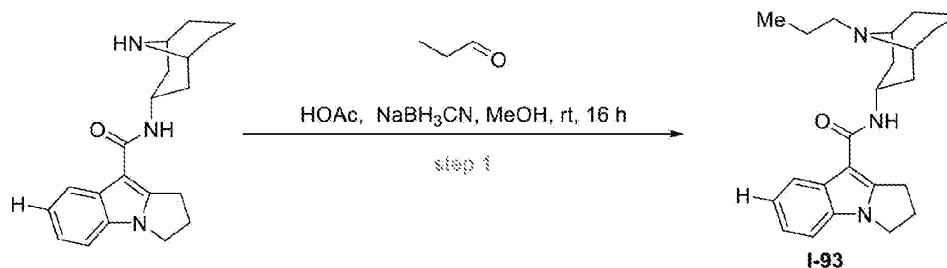
[0943] Synthesis of N- (9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a]indole-9-carboxamide formate. A mixture of tert-butyl 3- {1H, 2H, 3H-benzo [b] pyrrolizine-9-amido} -9-azabicyclo [3.3.1] nonane-9-carboxylate (50 mg, 0.12 mmol) in DCM/TFA=3/1 (8 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, Mobile phase A: water (0.1%FA) , B: acetonitrile, flow rate : 30 ml/min, gradient: from 20%to 40%of B in A, wavelength: 214/254 nm) to give N- (9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (26.4 mg, 69%) as a white solid. MS (ESI) : mass calcd. for $C_{20}H_{25}N_3O$, 323.20, m/z found 324.2 [M+H]⁺ . ¹H NMR (400 MHz, DMSO-d₆) δ8.40 (s, 0.75H) , 7.93- 7.91 (m, 1H) , 7.37 7.35 (m, 1H) , 7.17- 7.06 (m, 2H) , 6.95 (d, J = 8.4 Hz, 1H) , 4.35- 4.27 (m, 1H) , 4.11 (t, J = 7.2 Hz, 2H) , 3.64- 3.61 (m, 2H) , 3.23 (t, J = 7.6 Hz, 2H) , 2.62- 2.55 (m, 2H) , 2.27- 2.20 (m, 2H) , 2.10- 2.03 (m, 1H) , 1.79- 1.72 (m, 2H) , 1.60- 1.46 (m, 5H) .

[0944] Step 3

[0945] Synthesis of N- (9-ethyl-9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate. To a mixture of N- {9-azabicyclo [3.3.1] nonan-3-yl} -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (80 mg, 0.25 mmol)

and acetaldehyde (5.0M solution in THF, 0.1 mL) in MeOH (10 mL) was added HOAc (0.1 mL). The reaction mixture was stirred at room temperature for 4 h. NaBH₃CN (46.6 mg, 0.74 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, Mobile phase A: water (0.1%FA), B: acetonitrile, flow rate: 30 mL/min, gradient: from 15% to 45% of B in A, wavelength: 214/254 nm) to give N-(9-ethyl-9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (34.7 mg, 40%) as a white solid. MS (ESI) : mass calcd. for C₂₂H₂₉N₃O, 351.23, m/z found 352.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.16 (s, 0.55H), 7.93 -7.91 (m, 1H), 7.37 -7.35 (m, 1H), 7.16 -7.05 (m, 2H), 6.92 (d, J = 8.4 Hz, 1H), 4.46 -4.38 (m, 1H), 4.11 (t, J = 7.2 Hz, 2H), 3.41 -3.38 (m, 2H), 3.23 (t, J = 8.0 Hz, 2H), 2.94 -2.92 (m, 2H), 2.66 -2.54 (m, 2H), 2.31 -2.26 (m, 2H), 2.22 -2.09 (m, 1H), 1.97 -1.84 (m, 2H), 1.66 -1.61 (m, 2H), 1.49 -1.45 (m, 1H), 1.18 -1.15 (m, 2H), 1.19 (t, J = 7.2 Hz, 3H).

[0946] Example 77. Synthesis of I-93:



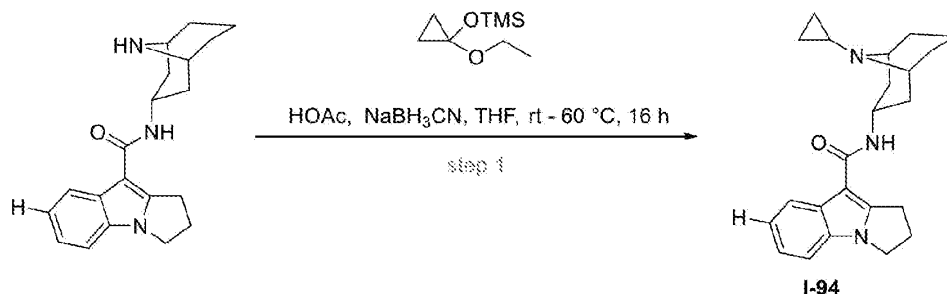
[0947] Experimental procedure:

[0948] Step 1

[0949] Synthesis of N-(9-propyl-9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate. To a mixture of N-(9-azabicyclo [3.3.1] nonan-3-yl) -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (80 mg, 0.25 mmol) and propionaldehyde (0.1 mL) in MeOH (10 mL) was added HOAc (0.1 mL). The reaction mixture was stirred at room temperature for 4 h. NaBH₃CN (46.6 mg, 0.74 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, Mobile phase A: water (0.1%FA), B: acetonitrile, flow rate: 30 mL/min, gradient: from 15% to 45% of B in A, wavelength: 214/254 nm) to give N-(9-propyl-9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (46.5 mg, 51%) as a white solid. MS (ESI) : mass calcd. for C₂₃H₃₁N₃O, 365.25, m/z found 366.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.14 (s, 0.27H), 7.99 -7.87 (m, 1H), 7.43 -7.31 (m, 1H), 7.19 -7.05 (m, 2H), 7.00 -6.98 (m, 1H), 4.48 (s, 1H), 4.11 (t, J = 7.2 Hz, 2H),

3.51 (s, 2H) , 3.24 (t, J = 7.2 Hz, 2H) , 2.96 (s, 2H) , 2.65- 2.55 (m, 2H) , 2.41- 2.29 (m, 2H) , 2.19- 2.12 (m, 1H) , 1.99- 1.93 (m, 2H) , 1.75- 1.63 (m, 2H) , 1.61 1.43 (m, 3H) , 1.29- 1.27 (m, 2H) , 0.92 (t, J = 8.0 Hz, 3H) .

[0950] Example 78. Synthesis of I-94:

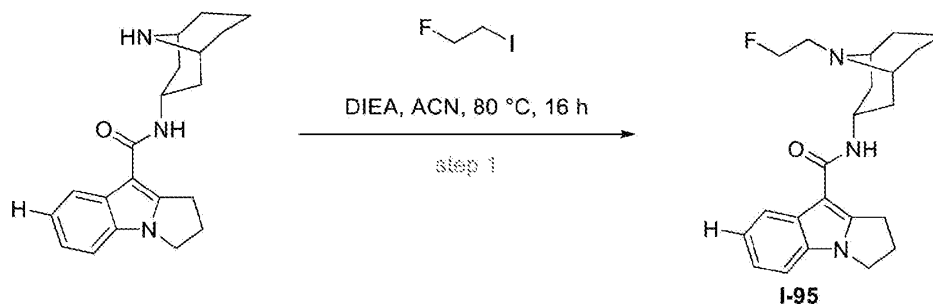


[0951] Experimental procedure:

[0952] Step 1

[0953] Synthesis of N-(9-cyclopropyl-9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide. To a mixture of N- {9-azabicyclo [3.3.1] nonan-3-yl} -1H,2H, 3H-benzo [b] pyrrolizine-9-carboxamide (70 mg, 0.22 mmol) , (1-ethoxycyclopropoxy) trimethylsilane (377.2 mg, 2.16 mmol) , HOAc (0.1 mL) and NaBH₃CN (68.0 mg, 1.08 mmol) in THF (10 mL) was stirred at 60 °C for 16 h. The mixture was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, Mobile phase A: water (0.1% NH₃) , B: acetonitrile, flow rate: 30 ml/min, gradient: from 65% to 95% of B in A, wavelength: 214/254 nm) to give N-(9-cyclopropyl-9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (11.9 mg, 15%) as a white solid. MS (ESI) : mass calcd. for C₂₃H₂₉N₃O, 363.23, m/z found 364.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.91- 7.89 (m, 1H) , 7.35-7.33 (m, 1H) , 7.16- 7.02 (m, 2H) , 6.76 (d, J = 8.8 Hz, 1H) , 4.22- 4.12 (m, 1H) , 4.10 (t, J = 7.2 Hz, 2H) , 3.22 (t, J = 7.6 Hz, 2H) , 3.15 (d, J = 10.4 Hz, 2H) , 2.60- 2.55 (m, 2H) , 2.37-2.32 (m, 1H) , 2.19- 2.12 (m, 2H) , 1.94- 1.88 (m, 2H) , 1.48- 1.43 (m, 3H) , 1.23 (s, 1H) , 1.03 (d, J = 12.4 Hz, 2H) , 0.49- 0.39 (m, 2H) , 0.29- 0.20 (m, 2H) .

[0954] Example 79. Synthesis of I-95:

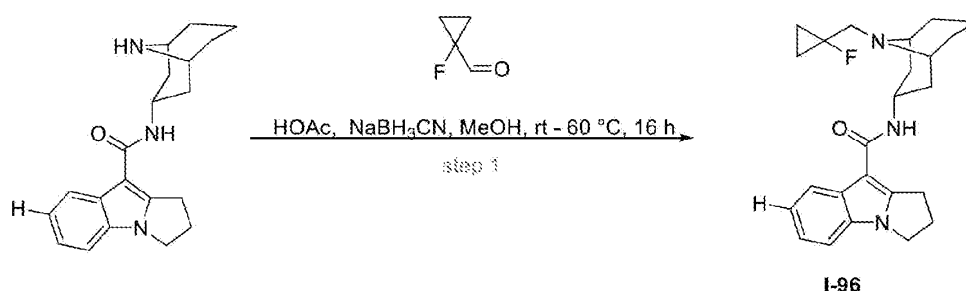


[0955] Experimental procedure:

[0956] Step 1

[0957] Synthesis of N- (9- (2-fluoroethyl) -9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide. To a mixture of N- {9-azabicyclo [3.3.1] nonan-3-yl} -1H,2H, 3H-benzo [b] pyrrolizine-9-carboxamide (50 mg, 0.15 mmol) and 1-fluoro-2-iodoethane (53.8 mg, 0.31 mmol) in ACN (10 mL) was added DIEA (60.0 mg, 0.46 mmol) . The reaction mixture was stirred at 80°C for 16 h. The mixture was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%NH₃) , B: acetonitrile, flow rate: 30 mL/min, gradient: from 55%to 85%of B in A, wavelength: 214/254 nm) to give N- (9- (2-fluoroethyl) -9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (18.5 mg, 31%) as a white solid. MS (ESI) : mass calcd. for C₂₂H₂₈FN₃O, 369.22, m/z found 370.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ7.93- 7.91 (m, 1H) , 7.36- 7.34 (m, 1H) , 7.15-7.04 (m, 2H) , 6.77 (d, J = 8.8 Hz, 1H) , 4.50- 4.36 (m, 2H) , 4.33- 4.23 (m, 1H) , 4.10 (t, J =7.2 Hz, 2H) , 3.23 (t, J = 7.6 Hz, 2H) , 3.10 (d, J = 10.8 Hz, 2H) , 2.95- 2.86 (m, 2H) , 2.61-2.54 (m, 2H) , 2.25- 2.06 (m, 3H) , 1.85- 1.75 (m, 2H) , 1.54- 1.39 (m, 3H) , 1.00 (d, J = 13.2 Hz, 2H) .

[0958] Example 80. Synthesis of I-96:



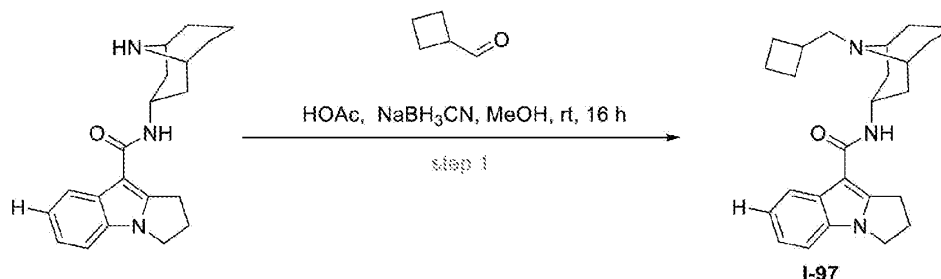
[0959] Experimental procedure:

[0960] Step 1

[0961] Synthesis of N- (9- ((1-fluorocyclopropyl) methyl) -9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide trifluoroacetate. To a mixture of N- {9-azabicyclo [3.3.1] nonan-3-yl} -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (80 mg, 0.25 mmol) and 1-fluorocyclopropane-1-carbaldehyde (43.6 mg, 0.50 mmol) in MeOH (10 mL) was added HOAc (0.1 mL) . The reaction mixture was stirred at room temperature for 4 h. NaBH₃CN (46.6 mg, 0.74 mmol) was then added, and the reaction mixture was stirred at 60 °C for 12 h. The mixture was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, mobile phase A: water (0.1%TFA) , B: acetonitrile, flow rate:

30 mL/min, gradient: from 22% to 40% of B in A, wavelength: 214/254 nm) to give N- (9- ((1-fluorocyclopropyl) methyl) -9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide trifluoroacetate (11.4 mg, 12%) as a white solid. MS (ESI) : mass calcd. for $C_{24}H_{30}FN_3O$, 395.24, m/z found 396.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.77 (s, 0.77H), 7.94-7.92 (m, 1H), 7.39- 7.37 (m, 1H), 7.25- 7.07 (m, 3H), 4.72- 4.35 (m, 1H), 4.13 (t, J = 7.2 Hz, 2H), 3.92- 3.80 (m, 4H), 3.25 (t, J = 7.6 Hz, 2H), 2.67- 2.54 (m, 4H), 2.28- 2.06 (m, 3H), 1.92- 1.75 (m, 2H), 1.57- 1.47 (m, 3H), 1.25- 1.19 (m, 2H), 1.08- 1.02 (m, 2H).

[0962] Example 81. Synthesis of I-97:

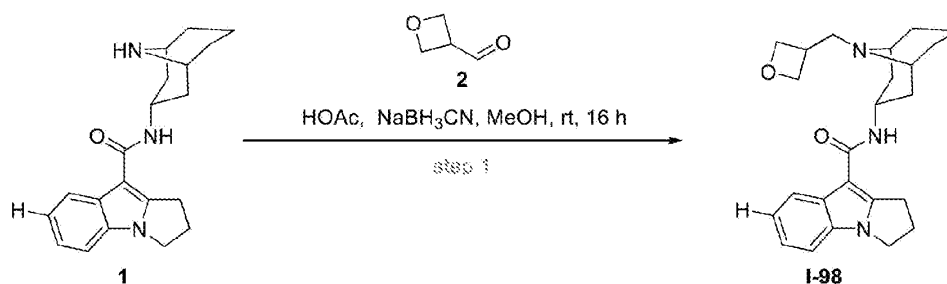


[0963] Experimental procedure:

[0964] Step 1

[0965] Synthesis of N- (9- (cyclobutylmethyl) -9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate. To a mixture of N- {9-azabicyclo [3.3.1] nonan-3-yl} -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (80 mg, 0.25 mmol) and cyclobutanecarboxaldehyde (41.6 mg, 0.50 mmol) in MeOH (10 mL) was added HOAc (0.1 mL). The reaction mixture was stirred at room temperature for 4 h. NaBH₃CN (46.6 mg, 0.74 mmol) was then added and the reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated to afford the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, mobile phase A: water (0.1%FA), B: acetonitrile, flow rate: 30 mL/min, gradient: from 20% to 60% of B in A, wavelength: 214/254 nm) to give N- (9- (cyclobutylmethyl) -9-azabicyclo [3.3.1] nonan-3-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (43.2 mg, 45%) as a white solid. MS (ESI) : mass calcd. for $C_{25}H_{33}N_3O$, 391.26, m/z found 392.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.14 (s, 0.5H), 7.93- 7.91 (m, 1H), 7.37- 7.35 (m, 1H), 7.17- 7.05 (m, 2H), 6.89 (d, J = 8.0 Hz, 1H), 4.46- 4.41 (m, 1H), 4.11 (t, J = 7.2 Hz, 2H), 3.23 (t, J = 8.0 Hz, 2H), 2.93 (s, 2H), 2.62- 2.54 (m, 3H), 2.32- 2.25 (m, 2H), 2.20- 2.08 (m, 1H), 2.02 1.97 (m, 3H), 1.94- 1.69 (m, 7H), 1.63- 1.57 (m, 2H), 1.48- 1.45 (m, 1H), 1.19- 1.16 (m, 2H).

[0966] Example 82. Synthesis of I-98:

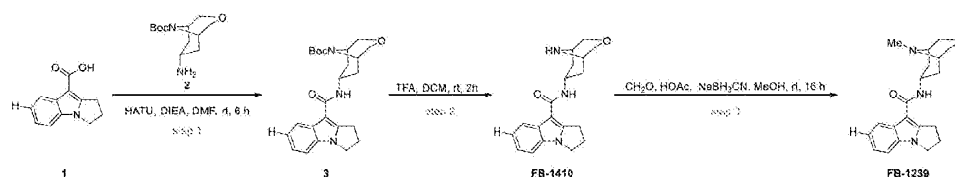


[0967] Experimental procedure:

[0968] Step 1

[0969] Synthesis of N-(9-(oxetan-3-ylmethyl)-9-azabicyclo[3.3.1]nonan-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamide. To a mixture of N-{9-azabicyclo[3.3.1]nonan-3-yl}-1H,2H,3H-benzo[b]pyrrolizine-9-carboxamide (80 mg, 0.25 mmol) and oxetane-3-carbaldehyde (42.6 mg, 0.50 mmol) in MeOH (10 mL) was added HOAc (0.1 mL). The reaction mixture was stirred at room temperature for 4 h. NaBH₃CN (46.6 mg, 0.74 mmol) was added and then the reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, mobile phase A: water (0.1% NH₃), B: acetonitrile, flow rate: 30 mL/min, gradient: from 45% to 75% of B in A, wavelength: 214/254 nm) to give N-(9-(oxetan-3-ylmethyl)-9-azabicyclo[3.3.1]nonan-3-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamide (43.5 mg, 45%) as a white solid. MS (ESI): mass calcd. for C₂₄H₃₁N₃O₂, 393.24, m/z found 394.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.92-7.90 (m, 1H), 7.36-7.33 (m, 1H), 7.17-7.04 (m, 2H), 6.75 (d, J = 8.8 Hz, 1H), 4.65-4.61 (m, 2H), 4.31-4.18 (m, 3H), 4.10 (t, J = 7.2 Hz, 2H), 3.22 (t, J = 7.6 Hz, 2H), 3.10-2.95 (m, 3H), 2.92-2.90 (m, 2H), 2.62-2.53 (m, 2H), 2.24-2.03 (m, 3H), 1.84-1.77 (m, 2H), 1.53-1.37 (m, 3H), 0.99-0.96 (m, 2H).

[0970] Example 83. Synthesis of I-99 & I-100:



[0971] Experimental procedure:

[0972] Step 1

[0973] Synthesis of tert-butyl 7-(2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamido)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate. To a mixture of 1H,2H,3H-benzo[b]pyrrolizine-9-carboxylic acid (400 mg, 1.99 mmol), tert-butyl 7-amino-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (481.7 mg, 1.99 mmol) and DIEA (770.8 mg,

5.96 mmol) in DMF (20 mL) was added HATU (907.0 mg, 2.39 mmol). The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (200 mL) and extracted with EA (100 mL×3). The combined organic layer was concentrated to afford the crude product which was purified by column chromatography (PE: EA = 1: 1) to give tert-butyl 7- (2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (500 mg, 47%) as a yellow solid. MS (ESI) : mass calcd. for $C_{24}H_{31}N_3O_4$, 425.23, m/z found 426.2 [M+H]⁺.

[0974] Step 2

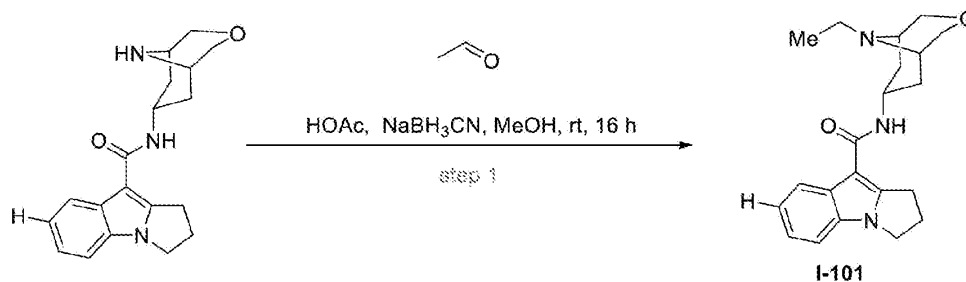
[0975] Synthesis of N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide. A mixture of tert-butyl 7- {1H, 2H, 3H-benzo [b] pyrrolizine-9-amido} -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (50 mg, 0.12 mmol) in DCM/TFA=3/1 (8 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, Mobile phase A: water (0.1%NH₃), B: acetonitrile, flow rate : 30 mL/min, gradient: from 33%to 43%of B in A, wavelength: 214/254 nm) to give N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (10.6 mg, 28%) as a white solid. MS (ESI) : mass calcd. for $C_{19}H_{23}N_3O_2$, 325.18, m/z found 326.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ8.17 (d, J = 10.4 Hz, 1H), 8.01 -7.99 (m, 1H), 7.36 -7.34 (m, 1H), 7.15 -7.04 (m, 2H), 4.59 -4.53 (m, 1H), 4.10 (t, J = 7.2 Hz, 2H), 3.90 -3.69 (m, 4H), 3.19 (t, J = 7.6 Hz, 2H), 2.84 -2.83 (m, 2H), 2.63 -2.55 (m, 2H), 2.26 -2.14 (m, 2H), 1.60 (d, J = 14.4 Hz, 2H).

[0976] Step 3

[0977] Synthesis of N- (9-methyl-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate. To a mixture of N- {3-oxa-9-azabicyclo [3.3.1] nonan-7-yl} -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (80 mg, 0.25 mmol) and CH₂O in H₂O (30%, 73.8 mg, 0.74 mmol) in MeOH (10 mL) was added HOAc (0.1 mL). The reaction mixture was stirred at room temperature for 4 h. NaBH₃CN (46.3 mg, 0.74 mmol) was then added and the reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, Mobile phase A: water (0.1%FA), B: acetonitrile, flow rate : 30 ml/min, gradient: from 10%to 40%of B in A, wavelength: 214/254 nm) to give N- (9-methyl-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide formate (49 mg, 59%) as a white solid. MS (ESI) : mass calcd. for $C_{20}H_{25}N_3O_2$, 339.19, m/z found 340.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆)

δ 8.14 (s, 0.4H) , 8.06 (d, J = 10.4 Hz, 1H) , 8.01 -7.99 (m, 1H) , 7.37 -7.34 (m, 1H) , 7.16 -7.05 (m, 2H) , 4.56 (dd, J = 17.2, 7.2 Hz, 1H) , 4.11 (t, J = 7.2 Hz, 2H) , 3.94 -3.80 (m, 4H) , 3.20 (t, J = 7.6 Hz, 2H) , 2.78 (s, 2H) , 2.63 -2.56 (m, 2H) , 2.54 (s, 3H) , 2.46 -2.41 (m, 2H) , 1.45 (d, J = 15.2 Hz, 2H) .

[0978] Example 84. Synthesis of I-101:

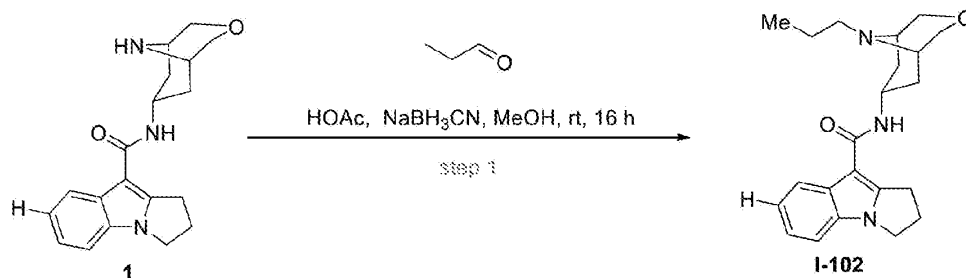


[0979] Experimental procedure:

[0980] Step 1

[0981] Synthesis of N- (9-ethyl-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide. To a mixture of N- {3-oxa-9-azabicyclo [3.3.1] nonan-7-yl} -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (80 mg, 0.25 mmol) and acetaldehyde (5.0M solution in THF, 0.1 mL) in MeOH (10 mL) was added HOAc (0.1 mL) . The reaction mixture was stirred at room temperature for 4 h. NaB-H₃CN (46.3 mg, 0.74 mmol) was then added and the reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, mobile phase A: water (0.1%NH₃) , B: acetonitrile, flow rate: 30 mL/min, gradient: from 38%to 48%of B in A, wavelength: 214/254 nm) to give N- (9-ethyl-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (33.5 mg, 38%) as a white solid. MS (ESI) : mass calcd. for C₂₁H₂₇N₃O₂, 353.21, m/z found 354.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.16 (d, J = 10.4 Hz, 1H) , 8.02-8.00 (m, 1H) , 7.36- 7.34 (m, 1H) , 7.16- 7.04 (m, 2H) , 4.55 (dd, J = 17.2, 7.2 Hz, 1H) , 4.10 (t, J = 7.2 Hz, 2H) , 3.85- 3.76 (m, 4H) , 3.20 (t, J = 7.6 Hz, 2H) , 2.73 (s, 2H) , 2.70- 2.64 (m, 2H) , 2.63 -2.56 (m, 2H) , 2.39- 2.30 (m, 2H) , 1.33 (d, J = 14.8 Hz, 2H) , 0.99 (t, J = 7.2 Hz, 3H) .

[0982] Example 85. Synthesis of I-102:

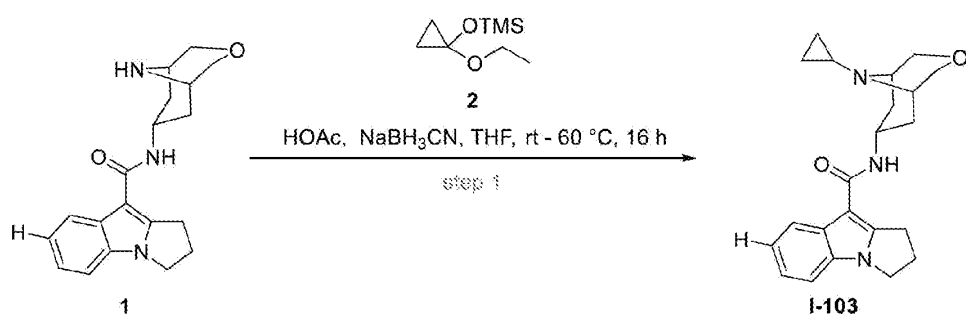


[0983] Experimental procedure:

[0984] Step 1

[0985] Synthesis of N-(9-propyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamide formate. To a mixture of N-{3-oxa-9-azabicyclo[3.3.1]nonan-7-yl}-1H, 2H, 3H-benzo[b]pyrrolizine-9-carboxamide (80 mg, 0.25 mmol) and propionaldehyde (0.1 mL) in MeOH (10 mL) was added HOAc (0.1 mL). The reaction mixture was stirred at room temperature for 4 h. NaBH₃CN (46.3 mg, 0.74 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, Mobile phase A: water (0.1%FA), B: acetonitrile, flow rate: 30 mL/min, gradient: From 17% to 47% of B in A, wavelength: 214/254 nm) to give N-(9-propyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamide formate (42 mg, 47%) as a white solid. MS (ESI): mass calcd. for C₂₂H₂₉N₃O₂, 367.20, m/z found 368.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.13 (s, 0.25H), 8.01-7.99 (m, 2H), 7.37-7.35 (m, 1H), 7.18-7.06 (m, 2H), 4.59-4.57 (m, 1H), 4.11 (t, J = 7.2 Hz, 2H), 3.92 (s, 4H), 3.20 (t, J = 7.6 Hz, 2H), 3.01-2.52 (m, 7H), 2.47-2.35 (m, 1H), 1.49 (s, 4H), 0.91 (t, J = 7.2 Hz, 3H).

[0986] Example 86. Synthesis of I-103:



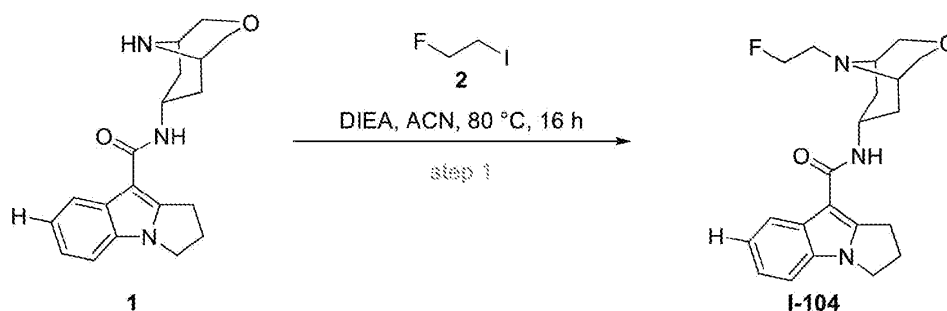
[0987] Experimental procedure:

[0988] Step 1

[0989] Synthesis of N-(9-cyclopropyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamide. To a mixture of N-{3-oxa-9-azabicyclo

[3.3.1] nonan-7-yl} -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (70 mg, 0.21 mmol) , (1-ethoxycyclopropoxy) trimethylsilane (374.9 mg, 2.15 mmol) , HOAc (0.1 mL) and NaBH₃CN (67.6 mg, 1.08 mmol) in THF (10 mL) was stirred at 60 °C for 16 h. The mixture was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, Mobile phase A: water (0.1%NH₃) , B: acetonitrile, flow rate : 30 ml/min, Gradient: fFrom 52%to 62%of B in A, wavelength: 214/254 nm) to give N- (9-cyclopropyl-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a]indole-9-carboxamide (7.2 mg, 9%) as a white solid. MS (ESI) : mass calcd. for C₂₂H₂₇N₃O₂, 365.21, m/z found 366.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ8.65 (d, J=10.4 Hz, 1H) , 8.00- 7.98 (m, 1H) , 7.32- 7.30 (m, 1H) , 7.19- 7.07 (m, 2H) , 4.73- 4.67 (m, 1H) , 4.13 (t, J = 7.2 Hz, 2H) , 3.95- 3.83 (m, 4H) , 3.29- 3.26 (m, 2H) , 2.88- 2.86 (m, 2H) , 2.71- 2.66 (m, 2H) , 2.64- 2.56 (m, 2H) , 2.55- 2.50 (m, 1H) , 1.57 (d, J = 15.2 Hz, 2H) , 0.58 -0.49 (m, 2H) , 0.42- 0.34 (m, 2H) .

[0990] Example 87. Synthesis of I-104:



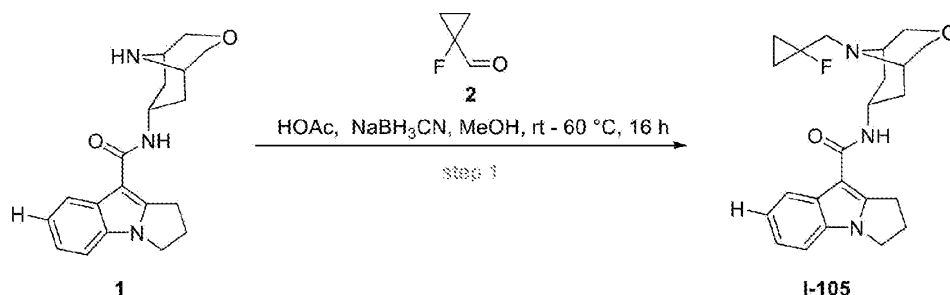
[0991] Experimental procedure:

[0992] Step 1

[0993] Synthesis of N- (9- (2-fluoroethyl))-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide. To a mixture of N- {3-oxa-9-azabicyclo [3.3.1] nonan-7-yl} -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (70 mg, 0.22 mmol) and 1-fluoro-2-iodoethane (74.8 mg, 0.43 mmol) in ACN (10 mL) was added DIEA (83.4 mg, 0.65 mmol) . The reaction mixture was stirred at 80 °C for 16 h. The mixture was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, Mobile phase A: water (0.1%FA) , B: acetonitrile, flow rate: 30 ml/min, gradient: from 10%to 40%of B in A, wavelength: 214/254 nm) to give N- (9- (2-fluoroethyl))-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (16.2 mg, 20%) as a white solid. MS (ESI) : mass calcd. for C₂₁H₂₆FN₃O₂, 371.20, m/z found 372.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ8.16 -8.13 (m, 1H) , 8.02- 7.99 (m, 1H) , 7.36- 7.34 (m, 1H) , 7.16- 7.06 (m, 2H) , 4.59- 4.55 (m, 2H) , 4.44- 4.42 (m, 1H) , 4.10

(t, $J = 7.2$ Hz, 2H), 3.88- 3.78 (m, 4H), 3.20 (t, $J = 7.6$ Hz, 2H), 2.99- 2.92 (m, 2H), 2.76 (s, 2H), 2.64- 2.55 (m, 2H), 2.45- 2.28 (m, 2H), 1.37 (d, $J = 14.8$ Hz, 2H).

[0994] Example 88. Synthesis of I-105:

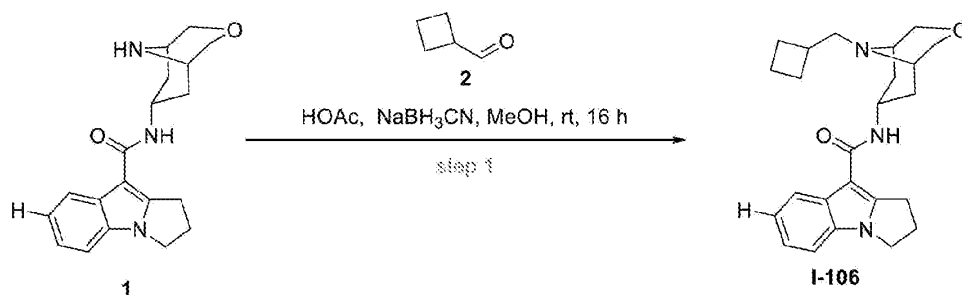


[0995] Experimental procedure:

[0996] Step 1

[0997] Synthesis of N-(9-((1-fluorocyclopropyl)methyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamide. To a mixture of N-{3-oxa-9-azabicyclo[3.3.1]nonan-7-yl}-1H,2H,3H-benzo[b]pyrrolizine-9-carboxamide (80 mg, 0.25 mmol) and 1-fluorocyclopropane-1-carbaldehyde (43.3 mg, 0.49 mmol) in MeOH (10 mL) was added HOAc (0.1 mL). The reaction mixture was stirred at room temperature for 4 h. NaBH₃CN (46.3 mg, 0.74 mmol) was added. The reaction mixture was stirred at 60 °C for 12 h. The mixture was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA), B: acetonitrile, flow rate: 30 mL/min, gradient: from 20% to 30% of B in A, wavelength: 214/254 nm) to give N-(9-((1-fluorocyclopropyl)methyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamide (18.4 mg, 19%) as a white solid. MS (ESI): mass calcd. for C₂₃H₂₈FN₃O₂, 397.22, m/z found 398.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.01- 7.99 (m, 1H), 7.82- 7.80 (m, 1H), 7.38- 7.36 (m, 1H), 7.18- 7.06 (m, 2H), 4.64- 4.62 (m, 1H), 4.47- 4.14 (m, 4H), 4.12 (t, $J = 7.2$ Hz, 2H), 4.06- 3.89 (m, 2H), 3.69 (s, 2H), 3.21 (t, $J = 7.6$ Hz, 2H), 2.79- 2.67 (m, 2H), 2.64- 2.58 (m, 2H), 2.08- 1.81 (m, 2H), 1.29- 1.24 (m, 2H), 1.03- 1.00 (m, 2H).

[0998] Example 89. Synthesis of I-106:

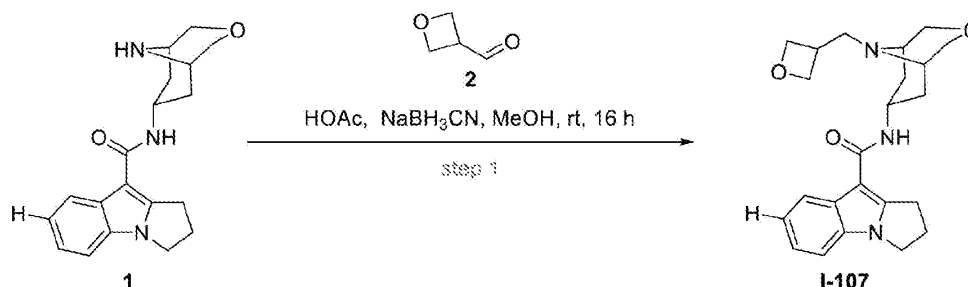


[0999] Experimental procedure:

[1000] Step 1

[1001] Synthesis of N- (9- (cyclobutylmethyl) -3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide. To a mixture of N- {3-oxa-9-azabicyclo [3.3.1] nonan-7-yl} -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (80 mg, 0.25 mmol) and Cyclobutanecarboxaldehyde (62.0 mg, 0.74 mmol) in MeOH (10 mL) was added HOAc (0.1 mL) . The reaction mixture was stirred at room temperature for 4 h. NaBH₃CN (46.3 mg, 0.74 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated to afford the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) , B: acetonitrile, flow rate: 30 mL/min, gradient: from 20%to 50%of B in A, wavelength: 214/254 nm) to give N- (9- (cyclobutylmethyl) -3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (17.7 mg, 18%) as a white solid. MS (ESI) : mass calcd. for C₂₄H₃₁N₃O₂, 393.24, m/z found 394.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ8.18 -8.08 (m, 1H) , 8.05 -7.95 (m, 1H) , 7.40 -7.30 (m, 1H) , 7.17 -6.99 (m, 2H) , 4.55 (dd, J = 16.8, 7.2 Hz, 1H) , 4.12 (t, J = 7.2 Hz, 2H) , 3.90 -3.75 (m, 4H) , 3.19 (t, J = 7.2 Hz, 2H) , 2.68 -2.67 (m, 2H) , 2.62 -2.56 (m, 2H) , 2.41 -2.33 (m, 2H) , 2.00 -1.96 (m, 3H) , 1.90 -1.77 (m, 4H) , 1.72 -1.65 (m, 2H) , 1.35 (d, J = 14.8 Hz, 2H) .

[1002] Example 90. Synthesis of I-107:



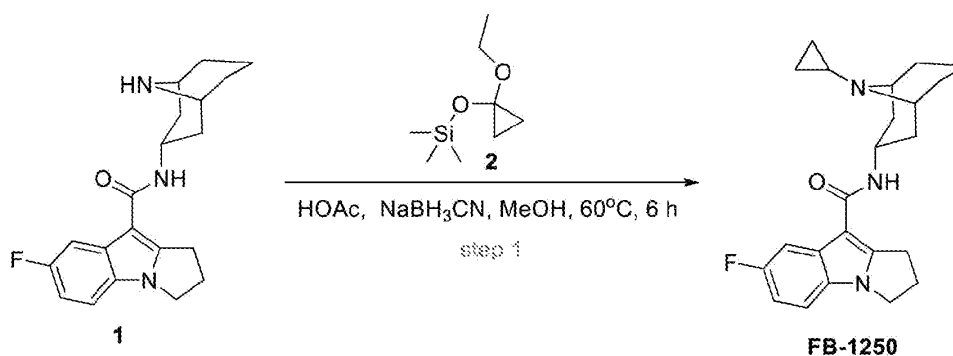
[1003] Experimental procedure:

[1004] Step 1

[1005] Synthesis of N- (9- (oxetan-3-ylmethyl) -3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide. To a mixture of N- {3-oxa-9-azabicyclo [3.3.1] nonan-7-yl} -1H, 2H, 3H-benzo [b] pyrrolizine-9-carboxamide (80 mg, 0.25 mmol) and oxetane-3-carbaldehyde (63.5 mg, 0.74 mmol) in MeOH (10 mL) was added HOAc (0.1 mL) . The reaction mixture was stirred at room temperature for 4 h. NaBH₃CN (46.3 mg, 0.74 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated to afford the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile

phase A: water (0.1%NH₃) , B: acetonitrile, flow rate: 30 mL/min, gradient: from 30%to 60%of B in A, wavelength: 214/254 nm) to give N- (9- (oxetan-3-ylmethyl) -3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (10.1 mg, 10%) as a white solid. MS (ESI) : mass calcd. for C₂₃H₂₉N₃O₃, 395.22, m/z found 396.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.13 (d, J = 10.4 Hz, 1H) , 8.01- 7.99 (m, 1H) , 7.36- 7.34 (m, 1H) , 7.16- 7.03 (m, 2H) , 4.63- 4.60 (m, 2H) , 4.55 (dd, J = 17.2, 7.2 Hz, 1H) , 4.28 (t, J = 6.0 Hz, 2H) , 4.10 (t, J = 7.2 Hz, 2H) , 3.83- 3.75 (m, 4H) , 3.19 (t, J = 7.6 Hz, 2H) , 3.13- 3.02 (m, 1H) , 2.95- 2.94 (m, 2H) , 2.67- 2.54 (m, 4H) , 2.40- 2.30 (m, 2H) , 1.35 (d, J = 14.8 Hz, 2H) .

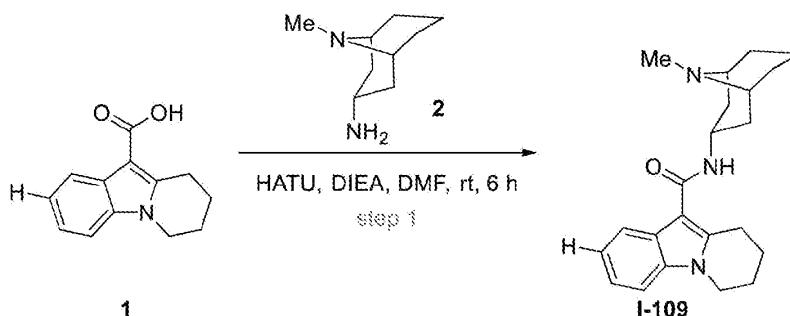
[1006] Example 91. Synthesis of I-108:



[1007] Step 1

[1008] Synthesis of N- (9-cyclopropyl-9-azabicyclo [3.3.1] nonan-3-yl) -7-fluoro-2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide. To a mixture of N- (9-azabicyclo [3.3.1] nonan-3-yl) -7-fluoro-2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (80 mg, 0.2 mmol) , CH₃COOH (36 mg, 0.6 mmol) and (1-ethoxycyclopropyl) trimethylsilane (245 mg, 1.4 mmol) in THF (5 mL) was added NaBH₃CN (88 mg, 1.4 mmol) and the mixture was stirred at 60 °C for 6 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL × 2) . The combined organic layer was dried over Na₂SO₄ and concentrated under vacuum to get a residue. The residue was purified by prep-HPLC (Column: Welch C18 21.2*250mm 10um, Mobile Phase A: water (0.1%NH₃) , B (acetonitrile) , flow rate: 25 ml/min, Gradient: From 60%to 90%of B in A, wavelength: 214/254 nm) to give N- (9-cyclopropyl-9-azabicyclo [3.3.1] nonan-3-yl) -7-fluoro-2, 3-dihydro-1H-pyrrolo [1, 2-a] indole-9-carboxamide (16.6 mg, 18%) as a white solid. MS (ESI) : mass calcd. for C₂₃H₂₈FN₃O, 381.22, m/z found 382.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 7.63 (dd, J = 12.0 Hz, 4.0 Hz, 1H) , 7.36 (dd, J = 8.0 Hz, 4.0 Hz, 1H) , 6.98-6.93 (m, 1H) , 6.74 (d, J = 8.0 Hz, 1H) , 4.21-4.09 (m, 3H) , 3.23- 3.14 (m, 4H) , 2.58-2.50 (m, 2H) , 2.37-2.33 (m, 1H) , 2.18-2.07 (m, 3H) , 1.94-1.88 (m, 2H) , 1.49- 1.42 (m, 3H) , 1.03 (d, J = 12.0 Hz, 2H) , 0.46- 0.41 (m, 2H) , 0.26 0.22 (m, 2H) .

[1009] Example 92. Synthesis of I-109:

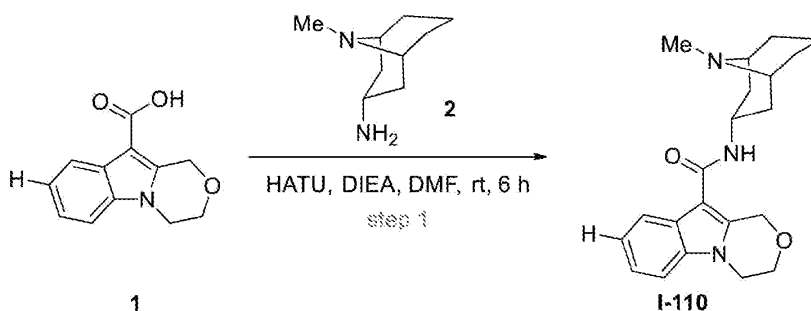


[1010] Experimental procedure:

[1011] Step 1

[1012] Synthesis of N-(9-methyl-9-azabicyclo [3.3.1] nonan-3-yl) -6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamide formate. To a mixture of 1H, 2H, 3H, 4H-pyrido [1, 2-a] indole-10-carboxylic acid (see Example 5) (75 mg, 0.35 mmol) , 9-methyl-9-azabicyclo [3.3.1] nonan-3-amine (53.7 mg, 0.35 mmol) and DIEA (135.1 mg, 1.05 mmol) in DMF (10 mL) was added HATU (159.0 mg, 0.42 mmol) . The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL×3) . The combined organic layer was concentrated to afford the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile phase A:water (0.1%FA) , B: acetonitrile, flow rate : 30 ml/min, Gradient: from 23%to 53%of B in A, wavelength: 214/254 nm) to give N-(9-methyl-9-azabicyclo [3.3.1] nonan-3-yl) -6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamide formate (42 mg, 34%) as a yellow solid. MS (ESI) : mass calcd. for $C_{22}H_{29}N_3O$, 351.23, m/z found 352.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d₆) δ 8.19 (s, 0.8H) , 7.83- 7.73 (m, 1H) , 7.45- 7.36 (m, 1H) , 7.17- 7.11 (m, 3H) , 4.44- 4.36 (m, 1H) , 4.07 (t, J = 6.0 Hz, 2H) , 3.18- 3.14 (m, 4H) , 2.54 (s, 3H) , 2.32- 2.24 (m, 2H) , 2.17- 1.89 (m, 5H) , 1.88- 1.77 (m, 2H) , 1.63- 1.50 (m, 2H) , 1.46-1.43 (m, 1H) , 1.09- 1.05 (m, 2H) .

[1013] Example 93. Synthesis of I-110:

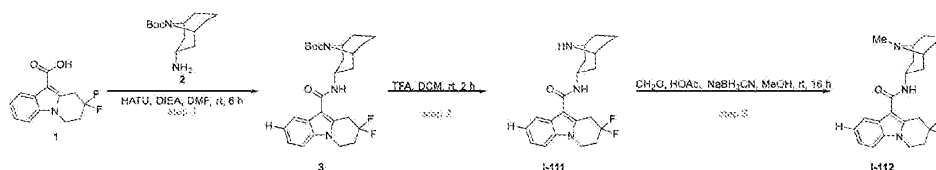


[1014] Experimental procedure:

[1015] Step 1

[1016] Synthesis of N- (9-methyl-9-azabicyclo [3.3.1] nonan-3-yl) -3, 4-dihydro-1H- [1, 4] oxazino [4, 3-a] indole-10-carboxamide formate. To a mixture of 1H, 3H, 4H- [1, 4] oxazino [4, 3-a] indole-10-carboxylic acid (See Example 3) (70 mg, 0.32 mmol) , 9-methyl-9-azabicyclo [3.3.1] nonan-3-amine (49.7 mg, 0.32 mmol) and DIEA (125.0 mg, 0.97 mmol) in DMF (10 mL) was added HATU (147.1 mg, 0.39 mmol) . The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL×3) . The combined organic layer was concentrated to afford the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, Mobile Phase A: water (0.1%FA) , B: acetonitrile, flow rate: 30 mL/min, gradient: from 20%to 50%of B in A, wavelength: 214/254 nm) to give N- (9-methyl-9-azabicyclo [3.3.1] nonan-3-yl) -3, 4-dihydro-1H- [1, 4] oxazino [4, 3-a] indole-10-carboxamide formate (47 mg, 41%) as a white solid. MS (ESI) : mass calcd. for $C_{21}H_{27}N_3O_2$, 353.21, m/z found 354.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.22 (s, 1H) , 7.87-7.84 (m, 1H) , 7.52- 7.45 (m, 1H) , 7.26- 7.14 (m, 3H) , 5.13 (s, 2H) , 4.43- 4.35 (m, 1H) , 4.13 (s, 4H) , 3.15- 3.12 (m, 2H) , 2.51 (s, 3H) , 2.27- 2.22 (m, 2H) , 2.18- 2.07 (m, 1H) , 1.98 -1.90 (m, 2H) , 1.66- 1.55 (m, 2H) , 1.46- 1.43 (m, 1H) , 1.07- 1.03 (m, 2H) .

[1017] Example 94. Synthesis of I-111 &I-112:

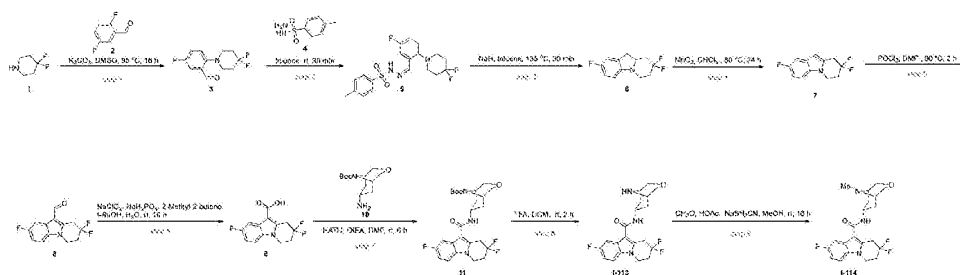


[1018] Step 1

[1019] Synthesis of tert-butyl 3- (8, 8-difluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamido) -9-azabicyclo [3.3.1] nonane-9-carboxylate. To a mixture of 2, 2-difluoro-1H, 3H, 4H-pyrido [1, 2-a] indole-10-carboxylic acid (190 mg, 0.76 mmol) , tert-butyl 3-amino-9-azabicyclo [3.3.1] nonane-9-carboxylate (181 mg, 0.76 mmol) and DIEA (293 mg, 2.27 mmol) in DMF (10 mL) was added HATU (345 mg, 0.90 mmol) . The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL×3) . The combined organic layer was concentrated to afford a crude product which was purified by column chromatography (PE: EA = 1: 1) to give tert-butyl 3- (8, 8-difluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamido) -9-azabicyclo [3.3.1] nonane-9-carboxylate (240 mg, 54%) as a yellow solid. MS (ESI) : mass calcd. for $C_{26}H_{33}F_2N_3O_3$, 473.25, m/z found 474.2 [M+H]⁺.

[1020] Step 2

- [1021] Synthesis of N- (9-azabicyclo [3.3.1] nonan-3-yl) -8, 8-difluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamide. To a mixture of tert-butyl 3- {2, 2-difluoro-1H, 3H, 4H-pyrido [1, 2-a] indole-10-amido} -9-azabicyclo [3.3.1] nonane-9-carboxylate (240 mg, 0.51 mmol) in DCM/TFA=3/1 (12 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford a crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250 mm 10 um, Mobile Phase A: water (0.1%FA) , B (acetonitrile) , flow rate: 30 ml/min, Gradient: from 22%to 32%of B in A, wavelength: 214/254 nm) to give N- (9-azabicyclo [3.3.1] nonan-3-yl) -8, 8-difluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamide (110 mg, 58%) as a white solid. MS (ESI) : mass calcd. for $C_{21}H_{23}F_2N_3O$, 373.20, m/z found 374.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 8.30 (s, 1H) , 7.83 (d, J = 7.2 Hz, 1H) , 7.50 (m, 2H) , 7.31 -7.16 (m, 2H) , 4.47 -4.36 (m, 1H) , 4.31 (t, J = 6.4 Hz, 2H) , 3.84 -3.77 (m, 4H) , 2.75 -2.60 (m, 2H) , 2.37 -2.25 (m, 2H) , 2.13 -2.01 (m, 1H) , 1.86 -1.61 (m, 4H) , 1.58 -1.52 (m, 3H) .
- [1022] Step 3
- [1023] Synthesis of 8, 8-difluoro-N- (9-methyl-9-azabicyclo [3.3.1] nonan-3-yl) -6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamide. To a solution of N- {9-azabicyclo [3.3.1] nonan-3-yl} -2, 2-difluoro-1H, 3H, 4H-pyrido [1, 2-a] indole-10-carboxamide (80 mg, 0.21 mmol) and CH₂O in H₂O (30%, 64 mg, 0.64 mmol) in MeOH (10 mL) was added AcOH (12.9 mg, 0.21 mmol) . The reaction mixture was stirred at room temperature for 4 h. NaBH₃CN (40.4 mg, 0.64 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated to afford a crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250 mm 10 um, Mobile Phase A: water (0.1%TFA) , B (acetonitrile) , flow rate: 30 mL/min, Gradient: from 25%to 35%of B in A, wavelength: 214/254 nm) to give 8, 8-difluoro-N- (9-methyl-9-azabicyclo [3.3.1] nonan-3-yl) -6,7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamide (22.5 mg, 27%) as a white solid. MS (ESI) : mass calcd. for $C_{22}H_{27}F_2N_3O$, 387.21, m/z found 388.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 8.98 (s, 1H) , 7.84- 7.81 (m, 1H) , 7.54- 7.51 (m, 2H) , 7.27- 7.20 (m, 2H) , 4.66-4.57 (m, 1H) , 4.32 (t, J = 6.4 Hz, 2H) , 3.81 (t, J = 14.8 Hz, 2H) , 3.67- 3.65 (m, 2H) , 2.91-2.83 (m, 3H) , 2.71- 2.62 (m, 2H) , 2.44- 2.38 (m, 2H) , 2.20- 2.00 (m, 3H) , 1.89- 1.78 (m, 2H) , 1.54- 1.42 (m, 3H) .
- [1024] Example 95. Synthesis of I-113 &I-114:



[1025] Experimental procedure:

[1026] Step 1

[1027] Synthesis of 2- (4, 4-difluoropiperidin-1-yl) -5-fluorobenzaldehyde. To a solution of 2, 5-difluorobenzaldehyde (40 g, 0.2815 mol) and 4, 4-difluoropiperidine hydrochloride (53.23 g, 0.34 mol) in DMSO (400 mL) was added K_2CO_3 (97.27 g, 0.71 mol). The reaction mixture was stirred at 95°C for 16 h. The mixture was diluted with water (1000 mL) and extracted with EA (500 mL×3). The combined organic layer was concentrated to afford a crude product which was purified by column chromatography (PE: EA = 10: 1) to give 2- (4, 4-difluoropiperidin-1-yl) -5-fluorobenzaldehyde (4 g, 7%) as a yellow solid. MS (ESI): mass calcd. for $C_{12}H_{12}F_3NO$, 243.09, m/z found 244.1 [M+H]⁺.

[1028] Step 2

[1029] Synthesis of (Z) -N'- (2- (4, 4-difluoropiperidin-1-yl) -5-fluorobenzylidene) -4-methylbenzenesulfonohydrazide. To a mixture of 2- (4, 4-difluoropiperidin-1-yl) -5-fluorobenzaldehyde (4 g, 0.016 mol) in toluene (50 mL) was added 4-methylbenzenesulfonohydrazide (3.67 g, 0.020 mol). The reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to give (Z) -N'- (2- (4, 4-difluoropiperidin-1-yl) -5-fluorobenzylidene) -4-methylbenzenesulfonohydrazide (6.77 g, crude) as a yellow solid which was used directly for the next step. MS (ESI): mass calcd. for $C_{19}H_{20}F_3N_3O_2S$, 411.12, m/z found 412.1 [M+H]⁺.

[1030] Step 3

[1031] Synthesis of 2, 8, 8-trifluoro-6, 7, 8, 9, 9a, 10-hexahydropyrido [1, 2-a] indole. To a mixture of N'- [(1Z) - [2- (4, 4-difluoropiperidin-1-yl) -5-fluorophenyl] methylidene] -4-methylbenzenesulfonohydrazide (6.77 g, 0.017 mol) in toluene (100 mL) was added NaH (0.44 g, 0.018 mol). The reaction mixture was stirred at 135°C for 0.5 h. The mixture was diluted with water (500 mL) and extracted with EA (200 mL×3). The combined organic layer was concentrated to afford a crude product which was purified by column chromatography (PE: EA = 10: 1) to give 2, 8, 8-trifluoro-6, 7, 8, 9, 9a, 10-hexahydropyrido [1, 2-a] indole (1.6 g, 37%) as a yellow solid. MS (ESI): mass calcd. for $C_{12}H_{12}F_3N$, 227.09, m/z found 228.1 [M+H]⁺.

[1032] Step 4

[1033] Synthesis of 2, 8, 8-trifluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole. To a mixture of 2,2, 8-trifluoro-1H, 3H, 4H, 10H, 10aH-pyrido [1, 2-a] indole (1.6 g, 0.007 mol) in chloroform (50 mL) was added MnO_2 (3.04 g, 0.035 mol). The reaction mixture was stirred at 80 °C for 24 h. The mixture was filtered through celite, and the filtrate was concentrated to afford a crude product which was purified by column chromatography (PE: EA = 3: 1) to give 2, 8, 8-trifluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole (0.7 g, 44%) as a yellow solid. MS (ESI): mass calcd. for $\text{C}_{12}\text{H}_{10}\text{F}_3\text{N}$, 225.08, m/z found 226.1 $[\text{M}+\text{H}]^+$.

[1034] Step 5

[1035] Synthesis of 2, 8, 8-trifluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carbaldehyde. To a mixture of 2, 2, 8-trifluoro-1H, 3H, 4H-pyrido [1, 2-a] indole (680 mg, 3.02 mmol) in DMF (20 mL) was added POCl_3 (1.39 g, 9.06 mmol). The reaction mixture was stirred at 90 °C for 2 h. The reaction mixture was quenched with ice water and adjusted to pH = 8 with sat. NaHCO_3 . The mixture was extracted with EA (100 mL x 2). The combined organic layer was concentrated to afford a crude product which was purified by column chromatography (PE: EA = 3: 1) to give 2, 8, 8-trifluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carbaldehyde (520 mg, 63%) as a yellow solid. MS (ESI): mass calcd. for $\text{C}_{13}\text{H}_{10}\text{F}_3\text{NO}$, 253.07, m/z found 254.1 $[\text{M}+\text{H}]^+$.

[1036] Step 6

[1037] Synthesis of 2, 8, 8-trifluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxylic acid. To a mixture of NaClO_2 (536 mg, 5.92 mmol) and NaH_2PO_4 (2369 mg, 19.75 mmol) in H_2O (5 mL) were added to 2, 2, 8-trifluoro-1H, 3H, 4H-pyrido [1, 2-a] indole-10-carbaldehyde (500 mg, 1.97 mmol) and 2-Methyl-2-butene (1385 mg, 19.75 mmol) in t-BuOH (15 mL). The reaction mixture was stirred at room temperature for 16 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL x 3). The combined organic layer was concentrated under reduced pressure to give 2, 8, 8-trifluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxylic acid (370 mg, crude) as a yellow solid which was used directly for the next step. MS (ESI): mass calcd. for $\text{C}_{13}\text{H}_{10}\text{F}_3\text{NO}_2$, 269.07, m/z found 270.0 $[\text{M}+\text{H}]^+$.

[1038] Step 7

[1039] Synthesis of tert-butyl 7- (2, 8, 8-trifluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate. To a mixture of 2, 2, 8-trifluoro-1H, 3H, 4H-pyrido [1, 2-a] indole-10-carboxylic acid (180 mg, 0.67 mmol), tert-butyl 7-amino-3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (162 mg, 0.67 mmol) and DIEA (259 mg, 2.01 mmol) in DMF (10 mL) was

added HATU (305 mg, 0.80 mmol). The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL×3). The combined organic layer was concentrated to afford a crude product which was purified by column chromatography (PE: EA = 1: 1) to give tert-butyl 7-(2, 8, 8-trifluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (250 mg, 66%) as a yellow solid. MS (ESI) : mass calcd. for $C_{25}H_{30}F_3N_3O_4$, 493.22, m/z found 494.2 [M+H]⁺.

[1040] Step 8

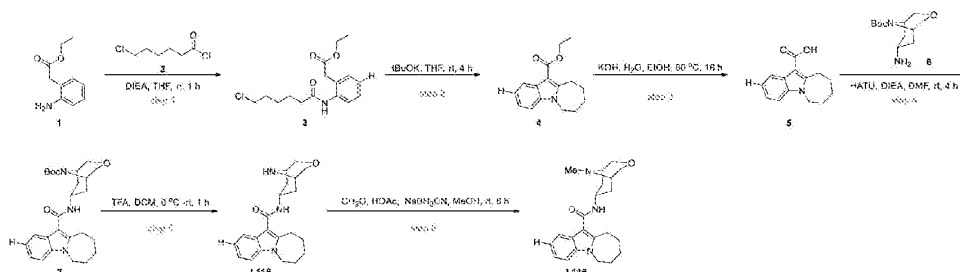
[1041] Synthesis of N-(3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 8, 8-trifluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamide. To a mixture of tert-butyl 7-(2, 2, 8-trifluoro-1H, 3H, 4H-pyrido [1, 2-a] indole-10-amido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (250 mg, 0.51 mmol) in DCM/TFA = 3/1 (12 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford a crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250 mm 10 um, Mobile Phase A: water (0.1%FA), B (acetonitrile), flow rate: 30 ml/min, Gradient: from 18% to 48% of B in A, wavelength: 214/254 nm) to give N-(3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2, 8, 8-trifluoro-6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamide (100 mg, 49%) as a white solid. MS (ESI) : mass calcd. for $C_{20}H_{22}F_3N_3O_2$, 393.17, m/z found 394.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 8.43 (s, 1H), 8.28 (s, 0.25 H), 7.56- 7.53 (m, 1H), 7.45 (dd, J = 8.8 Hz, 4.4 Hz, 1H), 7.03 (td, J = 9.2 Hz, 2.4 Hz, 1H), 4.77- 4.74 (m, 1H), 4.33 (t, J = 6.4 Hz, 2H), 4.18-4.07 (m, 4H), 3.80 (t, J = 14.4 Hz, 2H), 3.54- 3.52 (m, 2H), 2.69- 2.49 (m, 4H), 2.10 (d, J = 15.6 Hz, 2H).

[1042] Step 9

[1043] Synthesis of 2, 8, 8-trifluoro-N-(9-methyl-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamide. To a solution of 2, 2, 8-trifluoro-N-(3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -1H, 3H, 4H-pyrido [1, 2-a] indole-10-carboxamide (90 mg, 0.23 mmol) and CH₂O in H₂O (30%, 68 mg, 0.69 mmol) in MeOH (10 mL) was added AcOH (13.7 mg, 0.23 mmol). The reaction mixture was stirred at room temperature for 4 h. NaBH₃CN (43.1 mg, 0.69 mmol) was added, and the reaction mixture was stirred at room temperature for 12 h. The mixture was concentrated to afford a crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA), B: acetonitrile, flow rate: 30 mL/min, Gradient: from 18% to 48% of B in A, wavelength: 214/254 nm) to give 2, 8, 8-trifluoro-N-(9-methyl-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -6, 7, 8, 9-tetrahydropyrido [1, 2-a] indole-10-carboxamide (31.4 mg, 33%) as a white solid. MS (ESI) : mass calcd. for $C_{21}H_{24}F_3N_3O_2$, 407.18, m/z found 408.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 8.14 (s, 0.4H), 8.12- 8.10 (m, 1H), 7.62- 7.50 (m,

2H) , 7.10 (td, J = 9.2, 2.4 Hz, 1H) , 4.60- 4.54 (m, 1H) , 4.31 (t, J = 6.4 Hz, 2H) , 3.98- 3.78 (m, 6H) , 2.89 (s, 2H) , 2.72- 2.55 (m, 5H) , 2.46- 2.44 (m, 2H) , 1.58 (d, J = 13.2 Hz, 2H) .

[1044] Example 96. Synthesis of I-115 &I-116:



[1045] Experimental procedure:

[1046] Step 1

[1047] Synthesis of ethyl 2- (2- (6-chlorohexanamido) phenyl) acetate. To a mixture of ethyl 2- (2-aminophenyl) acetate (8.5 g, 0.047 mol) and DIEA (12.25 g, 0.095 mol) in THF (100 mL) was added 6-chlorohexanoyl chloride (8.01 g, 0.047 mol) . The reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with water (300 mL) and extracted with EA (200 mL×3) . The combined organic layer was concentrated to afford the crude product which was purified by column chromatography (PE: EA = 10: 1) to give ethyl 2- (2- (6-chlorohexanamido) phenyl) acetate (11.5 g, 74%) as a yellow solid. MS (ESI) : mass calcd. for $C_{16}H_{22}ClNO_3$, 311.13, m/z found 312.1 [M+H]⁺.

[1048] Step 2

[1049] Synthesis of ethyl 7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxylate. To a mixture of ethyl 2- [2- (6-chlorohexanamido) phenyl] acetate (11.5 g, 0.037 mol) in THF (200 mL) was added t-BuOK (10.35 g, 0.092 mol) . The reaction mixture was stirred at room temperature for 4 h. The mixture was diluted with water (300 mL) and extracted with EA (200 mL×3) . The combined organic layer was concentrated to afford the crude product which was purified by column chromatography (PE: EA = 3: 1) to give ethyl 7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxylate (0.9 g, 7%) as a yellow solid. MS (ESI) : mass calcd. for $C_{16}H_{19}NO_2$, 257.14, m/z found 258.1 [M+H]⁺.

[1050] Step 3

[1051] Synthesis of 7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxylic acid. To a solution of ethyl 7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxylate (230 mg, 0.89 mmol) in EtOH (20 mL) and H₂O (5 mL) was added KOH (180 mg, 3.21 mmol) . The reaction solution was stirred at 80 °C for 16 h. The reaction solution was diluted with water (50 mL) and extracted with EtOAc (20 mL x 2) . The water

phase was acidified with HCl (1N) to pH 2 ~3 and extracted with EtOAc (30 mL x 2). The combined organic layer was concentrated under reduced pressure to afford 7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxylic acid (140 mg, crude) as white solid.

[1052] MS (ESI) : mass calcd. for $C_{14}H_{15}NO_2$, 229.11, m/z found 230.2 [M+H]⁺.

[1053] Step 4

[1054] Synthesis of tert-butyl 7- (7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate. To a solution of 7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxylic acid (120 mg, 0.52 mmol) and tert-butyl 7-amino-3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (120 mg, 0.49 mmol) in DMF (10 mL) were added DIEA (310 mg, 2.56 mmol) and HATU (304 mg, 0.80 mmol), the reaction mixture was stirred at room temperature for 4 h. LCMS showed the reaction was completed. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford a residue which was purified by silica gel chromatography eluting with 50% of EA in PE to afford tert-butyl 7- (7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (140 mg, 59%) as yellow solid. MS (ESI) : mass calcd. for $C_{26}H_{35}N_3O_4$, 453.26, m/z found 454.2 [M+H]⁺.

[1055] Step 5

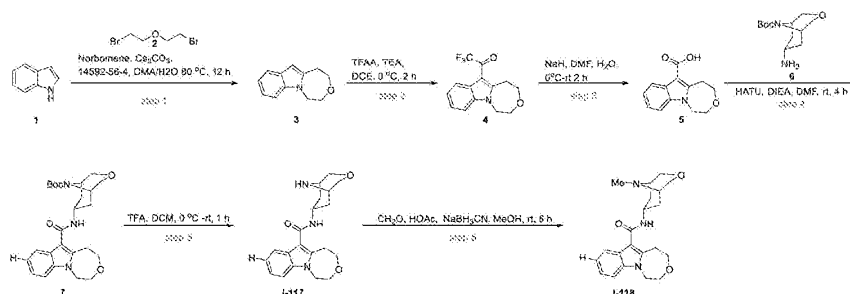
[1056] Synthesis of N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamide formate. To a solution of tert-butyl 7- (7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (140 mg, 0.31 mmol) in DCM (20 mL) was added TFA (2 mL) at 0 °C, the reaction mixture was stirred at room temperature for 1h. The mixture was concentrated to afford the crude product, which was purified by prep-HPLC (Column: WELCH Xtimate C18 21.2*250mm*10um, mobile phase A: water (0.1%FA), B: acetonitrile, flow rate: 30 mL/min, Gradient: from 15% to 45% of B in A, wavelength: 214/254 nm) to give N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamide formate (80 mg, 73%) as yellow solid. MS (ESI) : mass calcd. for $C_{21}H_{27}N_3O_2$, 353.21, m/z found 354.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 8.79 (s, 1H), 7.98 (d, J = 9.6 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.20 -7.05 (m, 2H), 4.63-4.57 (m, 1H), 4.34-4.22 (m, 2H), 4.02 -3.90 (m, 4H), 3.53- 3.51 (m, 2H), 3.30 -3.26 (m, 2H), 2.46- 2.41 (m, 2H), 1.94 -1.91 (m, 2H), 1.84- 1.80 (m, 2H), 1.67 -1.63 (m, 4H).

Rule 26,
11.12.2024

[1057] Step 6

- [1058] Synthesis of N- (9-methyl-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamide. To a mixture of N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamide (50 mg, 0.14 mmol) and HCHO (0.5 mL) in MeOH (10 mL) was added HOAc (0.1 mL) . The reaction mixture was stirred at room temperature for 1 h. NaB-H₃CN (30 mg, 0.44 mmol) was added. The reaction mixture was stirred at room temperature for 6 h. LCMS showed the reaction was completed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL x 2) . The combined organic layer was washed with brine, dried over Na₂SO₄, and concentrated to dryness in vacuo directly. The product was purified by prep-HPLC (Column: WELCH Xtimate C18 21.2*250mm*10um, mobile phase A: water (0.1%FA) , B: acetonitrile, flow rate: 30 mL/min, Gradient: from 15%to 45%of B in A, wavelength: 214/254 nm) to afford N- (9-methyl-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamide (26.2 mg, 47%) as a white solid. MS (ESI) : mass calcd. for C₂₂H₂₉N₃O₂, 367.23, m/z found 368.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ8.14 (s, 1H) , 7.733 (d, J = 8.0 Hz, 1H) , 7.52 (d, J = 8.0 Hz, 1H) , 7.18- 7.04 (m, 2H) , 4.57 (q, J = 8.0 Hz, 1H) , 4.33- 4.21 (m, 2H) , 3.96- 3.86 (m, 2H) , 3.83- 3.74 (m, 2H) , 3.32- 3.26 (m, 2H) , 2.83 (s, 2H) , 2.57 (s, 3H) , 2.49- 2.42 (m, 2H) , 1.87- 1.78 (m, 2H) , 1.73 1.59 (m, 4H) , 1.52 (d, J = 16.0 Hz, 2H) .

- [1059] Example 97. Synthesis of I-117 &I-118:



- [1060] Experimental procedure:

- [1061] Step 1

- [1062] Synthesis of 1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole. To a mixture of bis(1H-indole) (25 g, 0.21 mol) , Bis (acetonitrile) dichloropalladium (II) (5.54 g, 0.021 mol) , Norbornene (100.46 g, 1.07 mol) and Cs₂CO₃ (139.06 g, 0.43 mol) in DMF (300 mL) and H₂O (3 mL) was added 1-bromo-2- (2-bromoethoxy) ethane (123.73 g, 0.53 mol) . The reaction mixture was stirred at 80°C for 12 h under air. The mixture was diluted with water (1000 mL) and extracted with EA (500 mLx3) . The combined organic layer was concentrated to afford the crude product which was purified by column chromatography (PE: EA = 10: 1) to give 1, 2, 4, 5-tetrahydro- [1,

4] oxazepino [4, 5-a] indole (2.7 g, 5%) as a yellow solid. MS (ESI) : mass calcd. for $C_{12}H_{13}NO$, 187.10, m/z found 188.1 $[M+H]^+$.

[1063] Step 2

[1064] Synthesis of 2, 2, 2-trifluoro-1- (1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indol-11-yl)ethan-1-one. To a solution of 1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole (670 mg, 3.58 mmol) and TEA (435 mg, 4.3 mmol) in DCE (20 mL) was added TFAA (833 mg, 3.97 mmol) dropwise at 0°C. The reaction mixture was stirred for 2h at 0°C. LCMS showed the reaction was completed. The solution was diluted with water (30 mL) and extracted with DCM (20 mL × 2) . The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford 2, 2, 2-trifluoro-1- (1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indol-11-yl) ethan-1-one (550 mg, crude) as yellow solid. MS (ESI) : mass calcd. for $C_{14}H_{12}F_3NO_2$, 283.08, m/z found 284.1 $[M+H]^+$.

[1065] Step 3

[1066] Synthesis of 1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxylic acid. To a solution of 2, 2, 2-trifluoro-1- (1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indol-11-yl) ethan-1-one (540 mg, 1.91 mmol) in DMF (10 mL) was added NaH (483 mg, 12.08 mmol) at 0°C. H_2O (1 mL) was added to the solution at 0°C. The reaction mixture was stirred at room temperature for 2h. LCMS showed the reaction was completed. The reaction solution was diluted with water (50 mL) and extracted with EtOAc (20 mL × 2) . The water phase was acidified with HCl (1N) to pH 2 ~3 and extracted with EtOAc (30 mL × 2) . The combined organic layer was concentrated under reduced pressure to afford

[1067] 1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxylic acid (400 mg, crude) as yellow solid.

[1068] MS (ESI) : mass calcd. for $C_{13}H_{13}NO_3$, 231.09, m/z found 232.1 $[M+H]^+$.

[1069] Step 4

[1070] Synthesis of tert-butyl 7- (1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate. To a solution of 1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxylic acid (150 mg, 4.84 mmol) and tert-butyl 7-amino-3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (157 mg, 0.65 mmol) in DMF (20 mL) were added DIEA (418 mg, 3.24 mmol) and HATU (375 mg, 0.99 mmol) , the reaction mixture was stirred at room temperature for 4 h. LCMS showed the reaction was completed. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (20 mL × 3) . The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford a residue which was purified by silica gel chromatography eluting with 50% of EA in PE to afford tert-

butyl 7- (1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (250 mg, 85%) as yellow solid. MS (ESI) : mass calcd. for $C_{25}H_{33}N_3O_5$, 455.24, m/z found 456.2 [M+H]⁺.

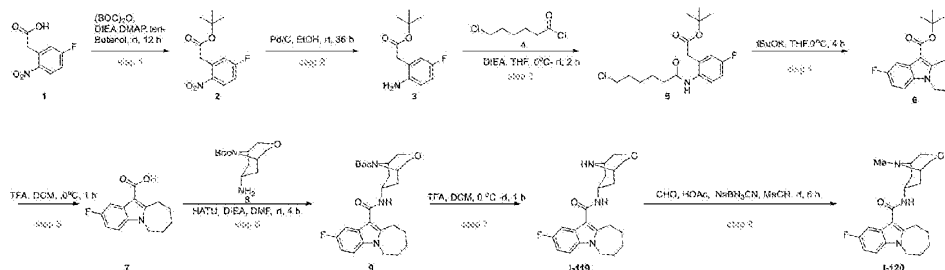
[1071] Step 5

[1072] Synthesis of N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxamide. To a solution of tert-butyl 7- (1, 2, 4, 5-tetrahydro-[1,4] oxazepino [4, 5-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (150 mg, 0.33 mmol) in DCM (20 mL) was added TFA (2 mL) at 0°C, the reaction mixture was stirred at room temperature for 1h. The mixture was concentrated to afford the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%NH₃) B (acetonitrile) , flow rate : 30 ml/min, Gradient: From 25%to 45%of B in A, wavelength: 214/254 nm) to give N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxamide (100 mg, 85%) as yellow solid. MS (ESI) : mass calcd. for $C_{20}H_{25}N_3O_3$, 355.19, m/z found 356.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.32 (d, J = 10.0 Hz, 1H) , 7.73 (d, J = 7.6 Hz, 1H) , 7.51 (d, J = 8.0 Hz, 1H) , 7.23- 7.04 (m, 2H) , 4.58- 4.52 (m, 1H) , 4.48 4.37 (m, 2H) , 3.90- 3.63 (m, 8H) , 3.61- 3.51 (m, 2H) , 2.85- 2.83 (m, 2H) , 2.28- 2.16 (m, 2H) , 1.64 (d, J = 14.4 Hz, 2H) .

[1073] Step 6

[1074] Synthesis of N- (9-methyl-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxamide. To a solution of N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxamide (100 mg, 0.28 mmol) and HCHO (0.1 mL) in MeOH (20 mL) was added HOAc (0.1 mL) . The reaction solution was stirred at room temperature for 1 h. NaBH₃CN (63 mg, 0.93 mmol) was added. The reaction mixture was stirred at room temperature for 6 h. LCMS showed the reaction was completed. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (30 mL x 3) . The combined organic layer was washed with brine, dried over Na₂SO₄, and concentrated to dryness in vacuo directly. The product was purified by prep-HPLC (Column: WELCH Xtimate C18 21.2*250mm*10um, mobile phase A: water (0.1%FA) , B: acetonitrile, flow rate: 30 mL/min, Gradient: from 30%to 50%of B in A, wavelength: 214/254 nm) to afford N- (9-methyl-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -1,2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxamide (22.3 mg, 22%) as a white solid. MS (ESI) : mass calcd. for $C_{21}H_{27}N_3O_3$, 369.21, m/z found 370.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.30 (d, J = 8.0 Hz, 1H) , 7.74 (d, J = 8.0 Hz, 1H) , 7.51 (d, J = 8.0 Hz, 1H) , 7.20- 7.08 (m, 2H) , 4.61- 4.51 (m, 1H) , 4.48- 4.34 (m, 2H) ,

[1075] Example 98. Synthesis of I-119 &I-120:



[1082] Synthesis of tert-butyl 2- (2- (6-chlorohexanamido) -5-fluorophenyl) acetate. To a solution of tert-butyl 2- (2-amino-5-fluorophenyl) acetate (12.4 g, 0.06 mol) and DIEA (21 g, 0.16 mol) in THF (200 mL) was added 6-chlorohexanoyl chloride (11.2 g, 0.07 mol) dropwise at 0°C. The reaction mixture was stirred at room temperature for 2h. LCMS showed the reaction was completed. The solution was diluted with water (300 mL) and extracted with EtOAc (200 mL x 3) . The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated to afford a residue which was purified by silica gel chromatography eluting with 10% of EtOAc in PE to afford tert-

butyl 2- (2- (6-chlorohexanamido) -5-fluorophenyl) acetate (14.3 g, 72.6%) as yellow oil. MS (ESI) : mass calcd. for $C_{18}H_{25}ClFNO_3$, 357.15, m/z found 302.1 [M-55]⁺.

[1083] Step 4

[1084] Synthesis of tert-butyl 2-fluoro-7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxylate. To a solution of tert-butyl 2- (2- (6-chlorohexanamido) -5-fluorophenyl) acetate (5 g, 14.01 mmol) in THF (100 mL) was added tBuOK (4 g, 35.71 mmol) at 0°C. The reaction mixture was stirred at 0 °C for 4 h. LCMS showed the reaction was completed. The solution was diluted with water (200 mL) and extracted with EtOAc (100 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford a residue which was purified by silica gel chromatography eluting with 30% of EA in PE to afford tert-butyl 2-fluoro-7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxylate (300 mg, 7%) as yellow solid. MS (ESI) : mass calcd. for $C_{18}H_{22}FNO_2$, 303.16, m/z found 304.2 [M+H]⁺.

[1085] Step 5

[1086] Synthesis of 2-fluoro-7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxylic acid. To a solution of tert-butyl 2-fluoro-7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxylate (200 mg, 0.66 mmol) in DCM (20 mL) was added TFA (0.5 mL) at 0°C, the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (50 mL) and extracted with DCM (20 mL × 2). The combined organic layer was washed with brine, dried over Na_2SO_4 , and concentrated to dryness in vacuo directly to give 2-fluoro-7,8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxylic acid (120 mg, crude) as yellow solid. MS (ESI) : mass calcd. for $C_{14}H_{14}FNO_2$, 247.10, m/z found 248.1 [M+H]⁺.

[1087] Step 6

[1088] Synthesis of tert-butyl 7- (2-fluoro-7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate. To a solution of 2-fluoro-7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxylic acid (120 mg, 0.49 mmol) and tert-butyl 7-amino-3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (140 mg, 0.58 mmol) in DMF (10 mL) were added DIEA (310 mg, 2.40 mmol) and HATU (284 mg, 0.75 mmol), the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford a residue which was purified by silica gel chromatography eluting with 50% of EtOAc in PE to afford tert-butyl 7- (2-fluoro-7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (140 mg, 61%) as yellow solid. MS (ESI) : mass calcd. for $C_{26}H_{34}FN_3O_4$, 471.25, m/z found 472.3 [M+H]⁺.

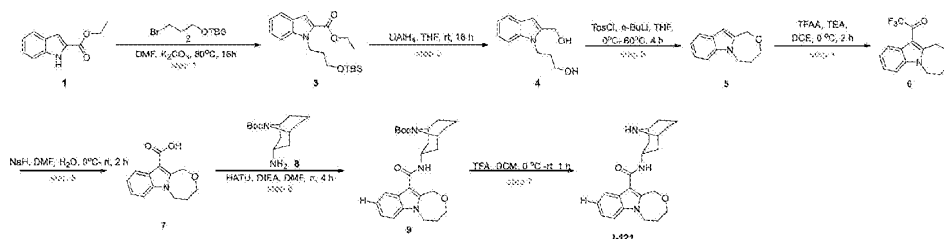
[1089] Step 7

[1090] Synthesis of N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2-fluoro-7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamide formate. To a solution of tert-butyl 7- (2-fluoro-7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (120 mg, 0.25 mmol) in DCM (20 mL) was added TFA (2 mL) at 0°C, the reaction mixture was stirred at room temperature for 1h. The mixture was concentrated to afford the crude product, which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, Mobile Phase A: water (0.1%FA) , B: acetonitrile, flow rate : 30 ml/min, Gradient: From 20%to 45%of B in A, wavelength: 214/254 nm) to give N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2-fluoro-7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a]indole-11-carboxamide formate (80 mg, 85%) as yellow solid. MS (ESI) : mass calcd. for $C_{21}H_{26}FN_3O_2$, 371.20, m/z found 372.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 8.26 (s, 0.45H) , 8.19 (d, J = 10.0 Hz, 1H) , 7.54 (dd, J = 9.2, 4.4 Hz, 1H) , 7.44 (dd, J = 10.0, 2.4 Hz, 1H) , 6.98 (td, J = 9.2, 2.4 Hz, 1H) , 4.55- 4.53 (m, 1H) , 4.32- 4.21 (m, 2H) , 3.77 (s, 4H) , 3.28- 3.26 (m, 2H) , 2.91- 2.89 (m, 2H) , 2.29- 2.16 (m, 2H) , 1.82- 1.80 (m, 2H) , 1.68-1.64 (m, 6H) .

[1091] Step 8

[1092] Synthesis of 2-fluoro-N- (9-methyl-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamide. To a solution of N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -2-fluoro-7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamide (50 mg, 0.13 mmol) and HCHO (0.5 mL) in MeOH (10 mL) was added HOAc (0.1 mL) . The reaction solution was stirred at room temperature for 1 h. NaBH₃CN (25 mg, 0.37 mmol) was added. The reaction mixture was stirred at room temperature for 6h. LCMS showed the reaction was completed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL x 2) . The combined organic layer was washed with brine, dried over Na₂SO₄, and concentrated to dryness in vacuo directly. The product was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm*10um, Mobile Phase A: water (0.1%FA) , B: acetonitrile, flow rate: 30 ml/min, Gradient: From 15%to 45%of B in A, wavelength: 214/254 nm) to afford 2-fluoro-N- (9-methyl-3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -7, 8, 9, 10-tetrahydro-6H-azepino [1, 2-a] indole-11-carboxamide (24.6 mg, 47%) as a white solid. MS (ESI) : mass calcd. for $C_{22}H_{28}FN_3O_2$, 385.22, m/z found 386.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.18 (d, J = 8.0 Hz, 1H) , 7.54 (dd, J = 8.0, 4.0 Hz, 1H) , 7.45 (dd, J = 8.0, 4.0 Hz, 1H) , 6.98 (td, J = 8.0, 4.0 Hz, 1H) , 4.54 (q, J = 8.0 Hz, 1H) , 4.32- 4.22 (m, 2H) , 3.89- 3.82 (m, 2H) , 3.75- 3.66 (m, 2H) , 3.30- 3.25 (m, 2H) , 2.65- 2.56 (m, 2H) , 2.44 (s, 3H) , 2.40 (dd, J = 16.0, 8.0 Hz, 2H) , 1.86- 1.78 (m, 2H) , 1.71- 1.59 (m, 4H) , 1.40 (d, J =16.0 Hz, 2H) .

[1093] Example 99. Synthesis of I-121:



[1094] Step 1

[1095] Synthesis of ethyl 1- (3- ((tert-butyldimethylsilyl) oxy) propyl) -1H-indole-2-carboxylate. To a mixture of ethyl 1H-indole-2-carboxylate (10 g, 52.91 mmol) and K_2CO_3 (21 g, 0.15 mol) in DMF (200 mL) was added (3-bromopropoxy) (tert-butyl) dimethylsilane (26 g, 102.77 mmol) dropwise. After stirring at 80°C for 16 h, the reaction mixture was diluted with water (500 mL) and extracted with EtOAc (200 mL $\times$ 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford a residue which was purified by silica gel chromatography eluting with 20% of EA in PE to afford ethyl 1- (3- ((tert-butyldimethylsilyl) oxy) propyl) -1H-indole-2-carboxylate (9 g, 47%) as yellow solid. MS (ESI) : mass calcd. for $C_{20}H_{31}NO_3Si$, 361.21, m/z found 362.2 $[M+H]^+$.

[1096] Step 2

[1097] Synthesis of 3- (2- (hydroxymethyl) -1H-indol-1-yl) propan-1-ol. To a solution of ethyl 1- (3- ((tert-butyldimethylsilyl) oxy) propyl) -1H-indole-2-carboxylate (9 g, 24.93 mmol) in THF (200 mL) was added $LiAlH_4$ (1.89 g, 49.74 mmol) dropwise at 0°C. The reaction mixture was stirred at room temperature for 16 h and then quenched with 1 M aqueous NaOH solution (10 mL) at 0°C. The mixture was filtered, and the filtrate was diluted with water (500 mL) and extracted with EtOAc (200 mL $\times$ 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford a residue which was purified by silica gel chromatography eluting with 50% of EtOAc in PE to afford 3- (2- (hydroxymethyl) -1H-indol-1-yl) propan-1-ol (4.8 g, 94%) as white solid. MS (ESI) : mass calcd. for $C_{12}H_{15}NO_2$, 205.11, m/z found 206.1 $[M+H]^+$.

[1098] Step 3

[1099] Synthesis of 4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole. To a solution of 3- (2- (hydroxymethyl) -1H-indol-1-yl) propan-1-ol (5 g, 24.39 mmol) in THF (100 mL) was added n-BuLi (12 mL, 30 mmol, 2.5M in hexane) dropwise at 0°C under N_2 . After stirring at 0°C for 0.5 h, TosCl (7.1 g, 37.37 mmol) in THF (50 mL) was added and the reaction mixture was stirred at 0°C for 2 h. n-BuLi (10 mL, 25 mmol, 2.5M in hexane) was added to the above solution at 0°C. The resulting mixture was stirred

at 60°C for 2 h under N₂. The mixture was quenched with aqueous NH₄Cl solution and extracted with EtOAc (200 mL × 3). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated to afford a residue which was purified by silica gel chromatography eluting with 20% of EtOAc in PE to afford 4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole (550 mg, 12%) as a yellow solid. MS (ESI) : mass calcd. for C₁₂H₁₃NO, 187.10, m/z found 188.1 [M+H]⁺.

[1100] Step 4

[1101] Synthesis of 1- (4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indol-11-yl) -2, 2, 2-trifluoroethan-1-one. To a solution of 4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole (550 mg, 2.94 mmol) and TEA (365 mg, 3.61 mmol) in DCE (20 mL) was added TFAA (704 mg, 3.35 mmol) dropwise at 0°C. After stirring at 0 °C for 2 h, the reaction mixture was diluted with water (30 mL) and extracted with DCM (20 mL × 2). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated to afford 1- (4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indol-11-yl) -2, 2, 2-trifluoroethan-1-one (800 mg, crude) as a yellow solid. MS (ESI) : mass calcd. for C₁₄H₁₂F₃NO₂, 283.08, m/z found 284.0 [M+H]⁺.

[1102] Step 5

[1103] Synthesis of 4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxylic acid. To a solution of 1- (4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indol-11-yl) -2, 2, 2-trifluoroethan-1-one (800 mg, 2.83 mmol) in DMF (20 mL) was added NaH (60%, 1.1 g, 11 mmol) at 0°C. H₂O (2 mL) was added to the solution at 0°C. The reaction mixture was stirred at room temperature for 2 h and then diluted with water (50 mL) and extracted with EtOAc (20 mL × 2). The aqueous phase was acidified with HCl (1N) to pH 2 ~ 3 and extracted with EtOAc (30 mL × 2). The combined organic layer was concentrated under reduced pressure to afford 4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxylic acid (560 mg, crude) as yellow solid. MS (ESI) : mass calcd. for C₁₃H₁₃NO₃, 231.09, m/z found 232.1 [M+H]⁺.

[1104] Step 6

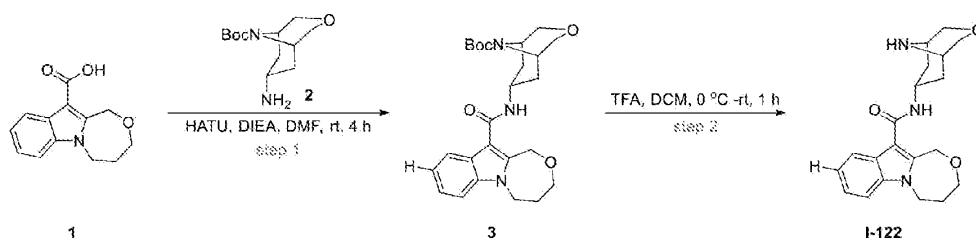
[1105] Synthesis of tert-butyl 3- (4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxamido) -9-azabicyclo [3.3.1] nonane-9-carboxylate. To a solution of 4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxylic acid (70 mg, 0.30 mmol) and tert-butyl 3-amino-9-azabicyclo [3.3.1] nonane-9-carboxylate (80 mg, 0.33 mmol) in DMF (20 mL) were added DIEA (127 mg, 0.98 mmol) and HATU (172 mg, 0.45 mmol), the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated to afford a residue which was purified by silica gel chromatography eluting with

50% of EA in PE to afford tert-butyl 3- (4, 5-dihydro-1H, 3H-[1, 4] oxazepino [4, 3-a] indole-11-carboxamido) -9-azabicyclo [3.3.1] nonane-9-carboxylate (100 mg, 73%) as yellow solid. MS (ESI) : mass calcd. for $C_{26}H_{35}N_3O_4$, 453.26, m/z found 398.1 [M-55]⁺.

[1106] Step 7

[1107] Synthesis of N- (9-azabicyclo [3.3.1] nonan-3-yl) -4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxamide. To a solution of tert-butyl 3- (4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxamido) -9-azabicyclo [3.3.1] nonane-9-carboxylate (100 mg, 0.22 mmol) in DCM (20 mL) was added TFA (2 mL) at 0°C, the reaction mixture was stirred at room temperature for 1h. The reaction mixture was diluted with water (50 mL) and extracted with DCM (20 mL x 2). The combined organic layer was washed with brine, dried over Na_2SO_4 , and concentrated to dryness in vacuo directly. The product was purified by prep-HPLC (Column: WELCH Xtimate C18 21.2*250mm*10um, Condition: mobile phase A water: (0.1% NH_3), B: acetonitrile, flow rate: 30 mL/min, gradient: from 45% to 70% of B in A, wavelength: 214/254 nm) to afford N- (9-azabicyclo [3.3.1] nonan-3-yl) -4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxamide (20.3 mg, 26%) as white solid. MS (ESI) : mass calcd. for $C_{21}H_{27}N_3O_2$, 353.21, m/z found 354.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO- d_6) δ 7.71 (d, J = 8.0 Hz, 1H), 7.64-7.46 (m, 2H), 7.21 (t, J = 8.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 5.02 (s, 2H), 4.58- 4.30 (m, 3H), 4.20- 3.94 (m, 3H), 3.21 (d, J = 8.0 Hz, 1H), 2.19- 1.93 (m, 3H), 1.88- 1.78 (m, 2H), 1.54- 1.24 (m, 7H).

[1108] Example 100. Synthesis of I-122:



[1109] Experimental procedure:

[1110] Step 1

[1111] Synthesis of tert-butyl 7- (4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate. To a solution of 4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxylic acid (90 mg, 0.39 mmol) and tert-butyl 7-amino-3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (113 mg, 0.47 mmol) in DMF (20 mL) were added DIEA (251 mg, 1.95 mmol) and HATU (222 mg, 0.58 mmol), the reaction mixture was stirred at room temperature for 4 h.

[1117] Synthesis of ethyl 1- (3- ((tert-butyldimethylsilyl) oxy) propyl) -5-fluoro-1H-indole-2-carboxylate. To a mixture of ethyl 5-fluoro-1H-indole-2-carboxylate

(1 g, 4.8 mmol) in DMF (20 mL) were added (3-bromopropoxy) (tert-butyl) dimethylsilane (2.43 g, 9.6 mmol) and K_2CO_3 (1.33 g, 9.6 mmol). The reaction mixture was stirred at 80 °C for 16 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL×3). The combined organic layer was concentrated to afford the crude product which was purified by column chromatography (PE: EA = 10: 1) to give ethyl 1- (3- ((tert-butyldimethylsilyl) oxy) propyl) -5-fluoro-1H-indole-2-carboxylate (1.4 g, 73%) as a yellow solid. MS (ESI) : mass calcd. for $C_{20}H_{30}FNO_3Si$, 379.20, m/z found 380.2 [M+H]⁺.

[1118] Step 2

[1119] Synthesis of 3- (5-fluoro-2- (hydroxymethyl) -1H-indol-1-yl) propan-1-ol. To a mixture of ethyl 1- {3- [(tert-butyldimethylsilyl) oxy] propyl} -5-fluoroindole-2-carboxylate (1.4 g, 3.7 mmol) in THF (20 mL) was added $LiAlH_4$ (0.17 g, 4.4 mmol) at 0°C. The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL×3). The combined organic layer was concentrated to afford the crude product which was purified by column chromatography (PE: EA = 1: 1) to give 3- (5-fluoro-2- (hydroxymethyl) -1H-indol-1-yl) propan-1-ol (0.5 g, 57%) as a yellow solid. MS (ESI) : mass calcd. for $C_{12}H_{14}FNO_2$, 223.10, m/z found 224.1 [M+H]⁺.

[1120] Step 3

[1121] Synthesis of 9-fluoro-4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole. To a solution of 3- [5-fluoro-2- (hydroxymethyl) indol-1-yl] propan-1-ol (350 mg, 1.57 mmol) in THF (10 mL) was added n-BuLi (2.5 M solution of THF, 0.69 mL, 1.72 mmol) at 0 °C under N_2 . The reaction mixture was stirred at 0 °C for 0.5 h. $TsCl$ (448.4 mg, 2.35 mmol) was added at 0 °C under N_2 . The reaction mixture was stirred at 0°C for 2 h. n-BuLi (2.5 M solution of THF, 0.69 mL, 1.72 mmol) was added at 0°C under N_2 . The reaction mixture was stirred at 60 °C for 3.5 h. The reaction mixture was quenched with saturated NH_4Cl . The mixture was diluted with water (100 mL) and extracted with EA (50 mL×3). The combined organic layer was concentrated to afford the crude product which was purified by column chromatography (PE: EA = 10: 1) to give 9-fluoro-4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole (50 mg, 16%) as a yellow solid. MS (ESI) : mass calcd. for $C_{12}H_{12}FNO$, 205.09, m/z found 206.1 [M+H]⁺.

[1122] Step 4

[1123] Synthesis of 2, 2, 2-trifluoro-1- (9-fluoro-4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indol-11-yl) ethan-1-one. To a solution of 9-fluoro-1H, 3H, 4H, 5H- [1, 4] oxazepino [4, 3-a] indole (50 mg, 0.24 mmol) and TEA (29.6 mg, 0.29 mmol) in DCE (10 mL) was added TFAA (56.3 mg, 0.27 mmol) at 0 °C. The reaction mixture was

stirred at 0 °C for 2 h. The mixture was diluted with water (100 mL) and extracted with DCM (50 mL×3). The combined organic layer was concentrated under reduced pressure to give 2, 2, 2-trifluoro-1- (9-fluoro-4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indol-11-yl) ethan-1-one (70 mg, crude) as a yellow solid which was used directly for the next step. MS (ESI) : mass calcd. for $C_{14}H_{11}F_4NO_2$, 301.07, m/z found 302.1 [M +H]⁺.

[1124] Step 5

[1125] Synthesis of 9-fluoro-4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxylic acid. To a solution of difluoromethyl 9-fluoro-1H, 3H, 4H, 5H- [1, 4] oxazepino [4, 3-a]indole-11-carbonyl fluoride (70 mg, 0.23 mmol) in DMF (5 mL) were added NaH (60%, 55.7 mg, 1.39 mmol) and H₂O (20.9 mg, 1.16 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was adjusted to pH = 2 with 1N HCl. The mixture was diluted with water (100 mL) and extracted with EA (50 mL×3). The combined organic layer was concentrated under reduced pressure to give 9-fluoro-4, 5-dihydro-1H, 3H-[1,4] oxazepino [4, 3-a] indole-11-carboxylic acid (40 mg, crude) as a yellow solid which was used directly for the next step. MS (ESI) : mass calcd. for $C_{13}H_{12}FNO_3$, 249.08, m/z found 250.1 [M+H]⁺.

[1126] Step 6

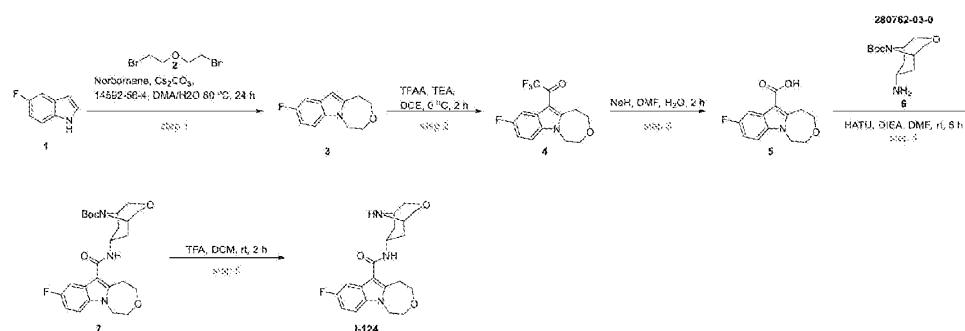
[1127] Synthesis of tert-butyl 7- (9-fluoro-4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate. To a mixture of 9-fluoro-1H, 3H, 4H, 5H- [1, 4] oxazepino [4, 3-a] indole-11-carboxylic acid (40 mg, 0.16 mmol), tert-butyl 7-amino-3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (38.9 mg, 0.16 mmol) and DIEA (62.2 mg, 0.48 mmol) in DMF (5 mL) was added HATU (73.2 mg, 0.20 mmol). The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL×3). The combined organic layer was concentrated to afford the crude product which was purified by column chromatography (PE: EA = 1: 1) to give tert-butyl 7- (9-fluoro-4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (50 mg, 53%) as a yellow solid. MS (ESI) : mass calcd. for $C_{25}H_{32}FN_3O_5$, 473.23, m/z found 474.2 [M+H]⁺.

[1128] Step 7

[1129] Synthesis of N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -9-fluoro-4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxamide trifluoroacetate. A mixture of tert-butyl 7- {9-fluoro-1H, 3H, 4H, 5H- [1, 4] oxazepino [4, 3-a] indole-11-amido} -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (50 mg, 0.11 mmol) in DCM/TFA=3/1 (8 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford

the crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250 mm 10um, Mobile Phase A: water (0.1%TFA) , B: acetonitrile, flow rate: 30 mL/min, Gradient: From 15%to 45%of B in A, wavelength: 214/254 nm) to give N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -9-fluoro-4, 5-dihydro-1H, 3H- [1, 4] oxazepino [4, 3-a] indole-11-carboxamide trifluoroacetate (24.4 mg, 61%) as a white solid. MS (ESI) : mass calcd. for $C_{20}H_{24}FN_3O_3$, 373.18, m/z found 374.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO-d₆) δ 9.03 (s, 1H) , 8.00 (d, J = 9.2 Hz, 1H) , 7.65 (dd, J = 9.2, 4.4 Hz, 1H) , 7.50 (dd, J = 10.2 Hz, 2.4 Hz, 1H) , 7.09 (td, J = 9.2 Hz, 2.4 Hz, 1H) , 5.12 (s, 2H) , 4.63- 4.42 (m, 3H) , 4.07- 4.04 (m, 2H) , 3.99- 3.93 (m, 4H) , 3.61- 3.59 (m, 2H) , 2.49- 2.41 (m, 2H) , 2.02- 1.98 (m, 2H) , 1.88- 1.84 (m, 2H) .

[1130] Example 102. Synthesis of I-124:



[1131] Step 1

[1132] Synthesis of 9-fluoro-1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole. To a mixture of 5-fluoro-1H-indole (25 g, 0.19 mol) , bis (acetonitrile) dichloropalladium (II) (4.8 g, 0.019 mol) , norbornene (87.09 g, 0.93 mol) and Cs_2CO_3 (120.55 g, 0.37 mol) in DMA (250 mL) and H_2O (2.5 mL) was added 1-bromo-2- (2-bromoethoxy) ethane (107.26 g, 0.4625 mol) . The reaction mixture was stirred at 80°C for 24 h under air. The mixture was diluted with water (1000 mL) and extracted with EA (500 mL×3) . The combined organic layer was concentrated to afford a crude product which was purified by column chromatography (PE: EA = 10: 1) to give 9-fluoro-1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole (3 g, 6%) as a yellow solid. MS (ESI) : mass calcd. for $C_{12}H_{12}FNO$, 205.09, m/z found 206.1 $[M+H]^+$.

[1133] Step 2

[1134] Synthesis of 2, 2, 2-trifluoro-1- (9-fluoro-1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indol-11-yl) ethan-1-one. To a solution of 9-fluoro-1H, 2H, 4H, 5H- [1, 4] oxazepino [4, 5-a] indole (360 mg, 1.75 mmol) and TEA (213 mg, 2.10 mmol) in DCE (10 mL) was added TFAA (405 mg, 1.93 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The mixture was diluted with water (100 mL) and extracted with DCM (50 mL×3) . The combined organic layer was concentrated to afford 2, 2,

2-trifluoro-1- (9-fluoro-1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indol-11-yl) ethan-1-one (450 mg, crude) as a yellow solid which was used directly for the next step. MS (ESI) : mass calcd. for $C_{14}H_{11}F_4NO_2$, 301.07, m/z found 302.0 [M+H]⁺.

[1135] Step 3

[1136] Synthesis of 9-fluoro-1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxylic acid. To a solution of difluoromethyl 9-fluoro-1H, 2H, 4H, 5H- [1, 4] oxazepino [4, 5-a]indole-11-carbonyl fluoride (450 mg, 1.49 mmol) in DMF (10 mL) were added NaH (214.4 mg, 8.93 mmol) and H₂O (134.1 mg, 7.44 mmol) . The reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL×3) . The combined organic layer was concentrated to afford 9-fluoro-1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxylic acid (100 mg, crude) as a yellow solid which was used directly for the next step. MS (ESI) : mass calcd. for $C_{13}H_{12}FNO_3$, 249.08, m/z found 250.1 [M+H]⁺.

[1137] Step 4

[1138] Synthesis of tert-butyl 7- (9-fluoro-1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate. To a mixture of 9-fluoro-1H, 2H, 4H, 5H- [1, 4] oxazepino [4, 5-a] indole-11-carboxylic acid (100 mg, 0.40 mmol) , tert-butyl 7-amino-3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (97.2 mg, 0.40 mmol) and DIEA (156 mg, 1.20 mmol) in DMF (5 mL) was added HATU (183 mg, 0.48 mmol) . The reaction mixture was stirred at room temperature for 6 h. The mixture was diluted with water (100 mL) and extracted with EA (50 mL×3) . The combined organic layer was concentrated to afford a crude product which was purified by column chromatography (PE: EA = 1: 1) to give tert-butyl 7- (9-fluoro-1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxamido) -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (120 mg, 51%) as a yellow solid. MS (ESI) : mass calcd. for $C_{25}H_{32}FN_3O_5$, 473.23, m/z found 474.2 [M+H]⁺.

[1139] Step 5

[1140] Synthesis of N- (3-oxa-9-azabicyclo [3.3.1] nonan-7-yl) -9-fluoro-1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxamide. A mixture of tert-butyl 7- {9-fluoro-1H, 2H, 4H, 5H- [1, 4] oxazepino [4, 5-a] indole-11-amido} -3-oxa-9-azabicyclo [3.3.1] nonane-9-carboxylate (120 mg, 0.25 mmol) in DCM/TFA=3/1 (8 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford a crude product which was purified by prep-HPLC (WELCH Xtimate C18 21.2*250mm 10um, Mobile Phase A: water (0.1%FA) , B (acetonitrile) , flow rate: 30 ml/min, Gradient: from 12%to 42%of B in A, wavelength: 214/254 nm) to give N- (3-oxa-9-

Rule 26,
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azabicyclo [3.3.1] nonan-7-yl) -9-fluoro-1, 2, 4, 5-tetrahydro- [1, 4] oxazepino [4, 5-a] indole-11-carboxamide (31.6 mg, 33%) as a white solid. MS (ESI) : mass calcd. for $C_{20}H_{24}FN_3O_3$, 373.18, m/z found 374.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 8.23 (s, 0.6H) , 8.18 (d, J = 10.0 Hz, 1H) , 7.54 (dd, J = 8.8, 4.4 Hz, 1H) , 7.45 (dd, J = 10.4, 2.4 Hz, 1H) , 7.03 (td, J = 9.2, 2.4 Hz, 1H) , 4.57- 4.51 (m, 1H) , 4.47 -4.41 (m, 2H) , 3.88- 3.68 (m, 8H) , 3.54 -3.52 (m, 2H) , 3.02-3.00 (m, 2H) , 2.33- 2.21 (m, 2H) , 1.71 (d, J = 14.4 Hz, 2H) .

[1141] Example 103. General methods for FLIPR in vitro screens for human & mouse 5-HT3A

[1142] HEK 293 cells stably transfected with either human 5-HT3A or mouse 5-HT3A receptors were used to evaluate inhibitory effect of compounds on serotonin-induced calcium responses. Calcium flux into the cells was measured using FLIPR®Tetra (Molecular Devices) . Cells were seeded in Poly-D-Lysine (PDL) coated, black-walled, clear-bottom, 384-well cell culture treated microplates at a cell density of 15000 cells/well in 50 μ L of cell growth medium (DMEM supplemented with 10% FBS, 100 U/mL penicillin and 100 μ g/mL streptomycin) . The microplate was incubated at 37°C, 5% CO₂ for cells to attach and grow. Two days after seeding, microplates were processed for FLIPR-based calcium flux assay. Firstly, spent medium was removed, cells were washed once with HBSS and then serum starved in HBSS containing 0.1% BSA and 1.2 mM calcium for 1 hour 30 minutes at 37°C, 5% CO₂. Compound stocks were prepared in DMSO and serially diluted to the desired concentrations using DMSO. Working stocks of compounds were prepared in assay buffer (HBSS containing 20 mM HEPES, 0.1% BSA and 1.2 mM calcium chloride) . Post serum starvation, medium was replaced with 20 μ L of assay buffer. Cells were loaded with dye by adding 20 μ L of FLIPR®calcium 6 assay reagent prepared in assay buffer supplemented with 4 mM probenecid (final conc. 2 mM) followed by incubation for 1 hour 15 minutes at 37°C and 5% CO₂. Then, test compounds (5 μ L) were added into respective wells 30 minutes before completion of dye loading. After completion of dye incubation, microplates were transferred to FLIPR®Tetra, 5 μ L of serotonin (final conc. 300 nM) was added. Fluorescence was recorded before and after addition of serotonin (λ -EX=485nm, λ -EM=525 nm) . Fluorescence (max-min) of each concentration of compound was normalized with that of 300 nM Serotonin (0% inhibition) and DMSO control (100% inhibition) to assess inhibitory effect. IC₅₀ was computed using GraphPad Prism 9. A: 0.1 nM < IC₅₀ ≤ 1 nM; B: 1 nM ≤ IC₅₀ ≤ 2 nM; C: 2 nM < IC₅₀; Cell: RPE MYC^{H2B-GFP}; Assay Time: 24~72 h.

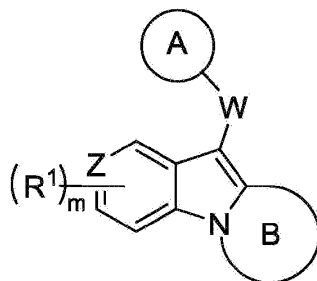
Syn	h5HT3A: IC50 (nM)	m5HT3A: IC50 (nM)
I-1	A	A
I-4	C	B
I-6	C	B
I-14	A	A
I-19	A	A
I-21	C	B
I-28	B	A
I-29	C	C
I-31	B	A
I-41	A	C
I-43	B	A
I-56	A	A
I-57	C, A	C, C
I-58	C, B	C, A
I-59	B	A
I-78	C	B
I-79	A	B
I-91	C	
I-92	C	

I-93	C	
I-94	C	
I-95	C	
I-96	C	
I-97	C	
I-98	C	
I-99	B	
I-100	A	
I-101	C	
I-102	C	
I-103	C	
I-104	B	
I-105	C	
I-106	C	
I-107	C	
I-108	C	
I-109	A	
I-110	B	
I-111	C	
I-112	C	
I-113	A	
I-114	A	
I-115	C	
I-116	A	
I-117	C	
I-118	A	
I-119	A	
I-120	A	
I-121	C	
I-122	B	
I-123	A	
I-124	A	

Claims

[Claim 1]

A compound of Formula (II) :



(I),

or a pharmaceutically acceptable salt thereof
wherein

Ring A is selected from the group consisting of 4-7 membered monocyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur, 7-10 membered bicyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur, or a 5-6 membered heteroaryl ring wherein Ring A may be substituted by one, two, or three R^3 ;

Ring B is 5-7 membered heterocyclyl ring containing 1-3 ring heteroatoms including the ring nitrogen to which it is attached, where the additional ring heteroatoms may each independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein Ring B may be substituted by one or two R^2 ;

W is selected from the group consisting of $-C(O)-$, $-C(O)O-$, $-C(O)N(H)-$, $-C(O)OCH_2-$, $-C(O)N(H)CH_2-$, and 5-membered heteroaryl ring having 1-3 ring heteroatoms;

Z is CR^1 or N;

R^1 for each occurrence is independently selected from the group consisting of hydrogen, halogen, $-OH$, C_1-C_3 alkyl (optionally substituted with one, two or three halogens), C_{3-7} -cycloalkyl; and 3-7 membered heterocyclyl ring containing 1-3 nitrogen atoms;

R^2 for each occurrence is independently selected from hydrogen, halogen, C_1-C_3 alkyl (optionally substituted with one, two or three halogens), $-C(O)-(C_1-C_3$ alkyl (optionally substituted with one, two

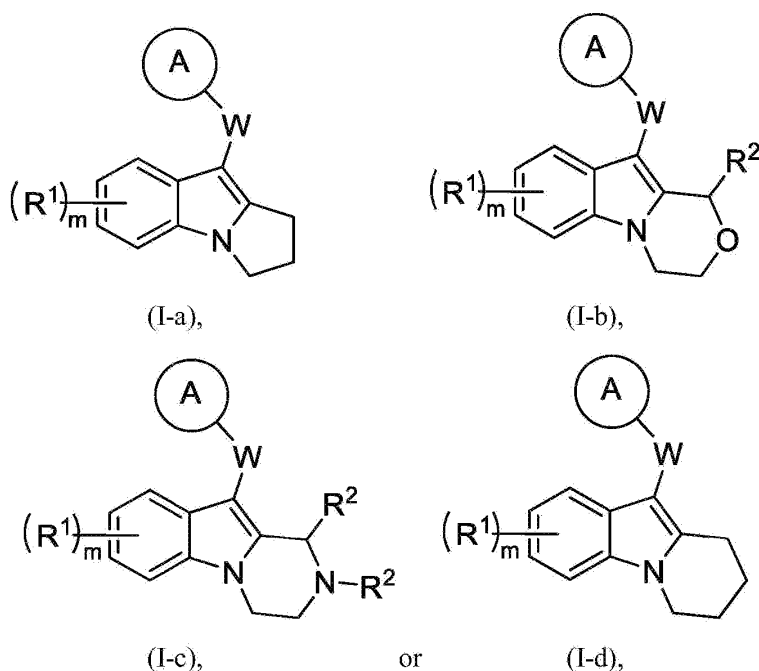
or three halogens)), and -C(O)O- (C₁-C₃ alkyl (optionally substituted with one, two or three halogens)) ;

R³ is independently for each occurrence selected from the group consisting of halogen, C₁-C₃ alkyl (optionally substituted with one, two or three halogens) , C₃₋₇cycloalkyl, 4-6 membered monocyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur (optionally substituted with one, two or three halogens) ; and

m is 1, 2, or 3.

[Claim 2]

The compound of claim 1, wherein the compound is of Formula (I-a) , (I-b) , (I-c) , or (I-d) :



or a pharmaceutical acceptable salt thereof.

[Claim 3]

The compound of claims 1-2, wherein Ring A is 7-9 membered bicyclic heterocyclyl ring containing 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur.

[Claim 4]

The compound of any one of claims 1-3, wherein Ring A is a bicyclo [2.2.2] heterocyclyl ring.

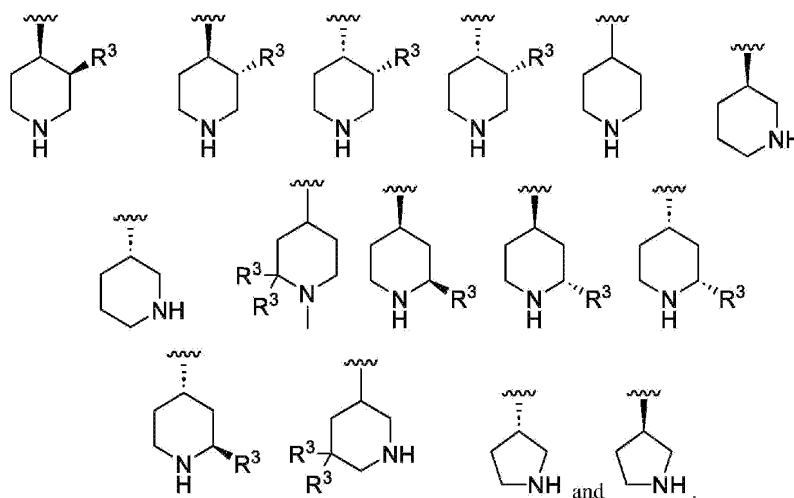
[Claim 5]

The compound of any one of claims 1-3, wherein Ring A is a bicyclo [4.4.0] heterocyclyl ring.

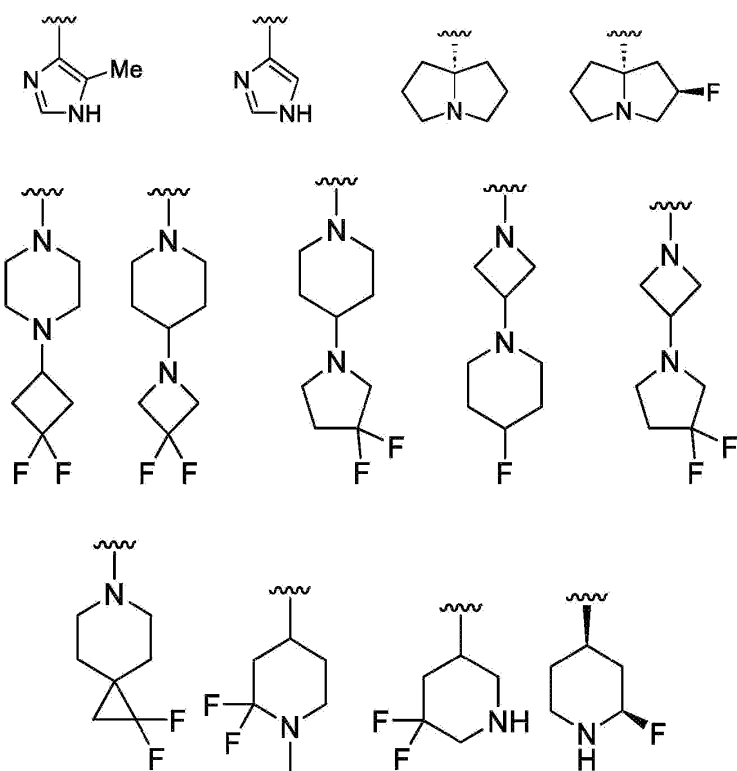
[Claim 6]

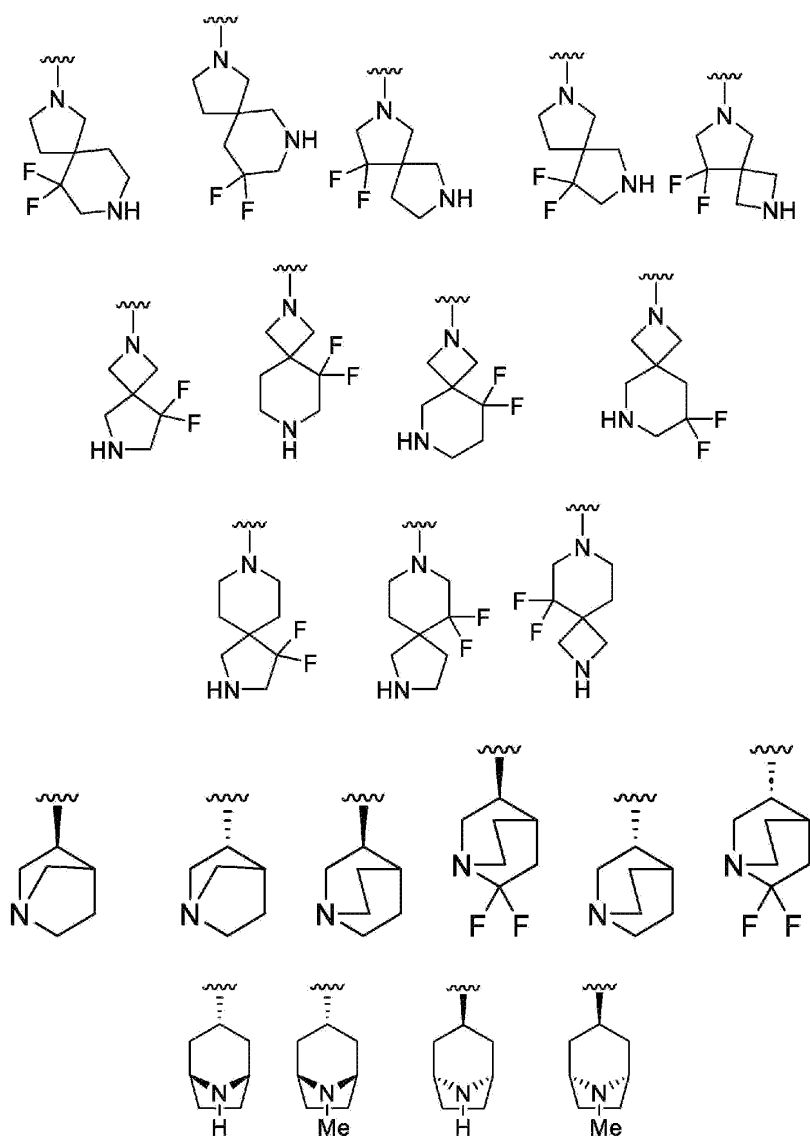
The compound of any one of claims 1-3, wherein Ring A is a bicyclo [3.3.1] heterocyclyl ring.

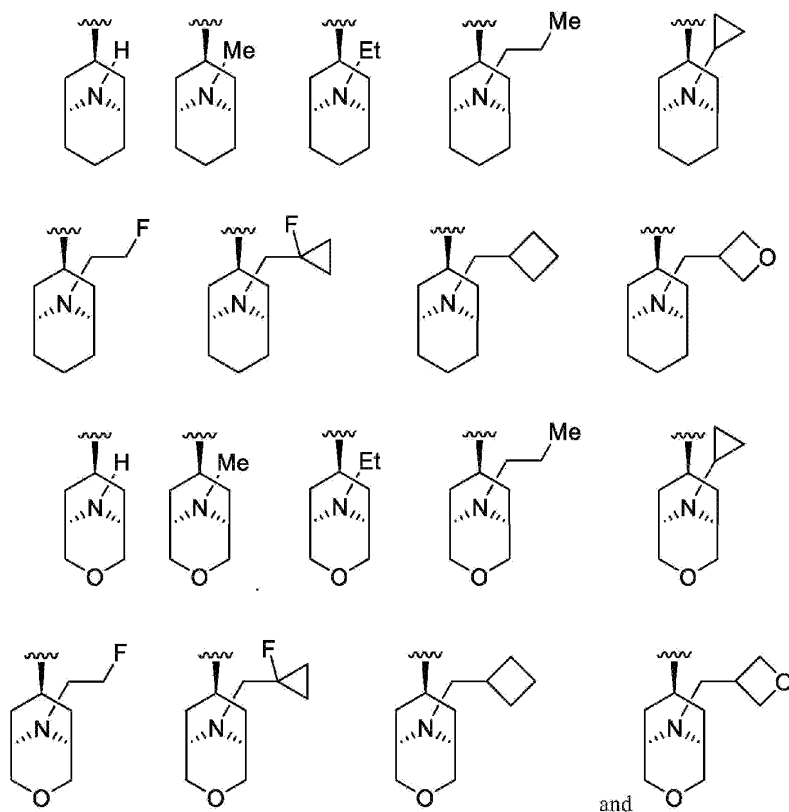
- [Claim 7] The compound of any one of claims 1-3 wherein Ring A is a bicyclo [2.2.1] heterocyclyl ring.
- [Claim 8] The compound of any one of claims 1-3, wherein Ring A is a bicyclo [3.2.1] heterocyclyl ring.
- [Claim 9] The compound of any one of claims 1-3, wherein Ring A is quinuclidinyl.
- [Claim 10] The compound of any one of claims 1-3, wherein Ring A is nortropanyl.
- [Claim 11] The compound of any one of claims 1-3, wherein Ring A is 3-oxa-9-azabicyclo [3.3.1] nonanyl.
- [Claim 12] The compound of any one of claims 1-3, wherein Ring A is of 4-7 membered monocyclic heterocyclyl ring having 1-3 ring heteroatoms each independently selected from the group consisting of nitrogen, oxygen, and sulfur.
- [Claim 13] The compound of claims 1, 2, or 12, wherein Ring A is selected from the group consisting of azetidiny, pyrrolidinyl, and piperidinyl, wherein Ring A may be substituted by one, two, or three R^3 .
- [Claim 14] The compound of claims 1, 2, or 12, wherein Ring A is selected from the group consisting of



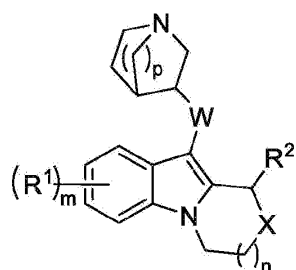
- [Claim 15] The compound of claims 1, 2, or 12, wherein Ring A is selected from the group consisting of







- [Claim 16] The compound of any of claims 1-15, wherein W is -C(O)-.
- [Claim 17] The compound of any of claims 1-15, wherein W is -C(O)O-.
- [Claim 18] The compound of any of claims 1-15, wherein W is -C(O)N(H)-.
- [Claim 19] The compound of any of claims 1-15, wherein W is -C(O)OCH₂-.
- [Claim 20] The compound of any of claims 1-15, wherein W is -C(O)N(H)CH₂-.
- [Claim 21] The compound of any of claims 1-15, wherein W is 5-membered heteroaryl ring having 1-3 ring heteroatoms.
- [Claim 22] The compound of claim 21, wherein W is oxadiazole.
- [Claim 23] A compound of Formula (II) :



(II),

or a pharmaceutically acceptable salt thereof

wherein

X is selected from the group consisting of -C(R'')₂-, -O-, and -N(H)-;

W is selected from the group consisting of -C(O)O-, -C(O)N(H)-, and a 5-membered heteroaryl ring having 1-3 ring heteroatoms;

R¹ for each occurrence is independently hydrogen or halogen

R² is hydrogen or C₁-C₃ alkyl;

R'' for each occurrence is independently selected from hydrogen, halogen, and methyl;

m is 1, 2, or 3;

n is 0, 1, 2, or 3; and

p is 0, 1, 2, 3.

[Claim 24]

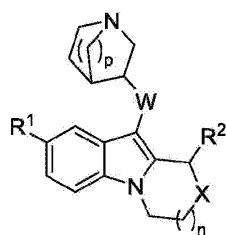
The compound of any of claims 1-23, wherein m is 1.

[Claim 25]

The compound of any of claims 1-23, wherein m is 2.

[Claim 26]

The compound of any of claims 1-23, wherein the compound is of Formula (II-a)

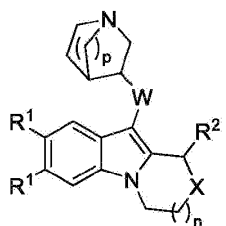


(II-a),

or a pharmaceutically acceptable salt thereof.

[Claim 27]

The compound of any of claims 1-23, wherein the compound is of Formula (II-a')



(II-a'),

or a pharmaceutically acceptable salt thereof,

wherein each R¹ may be the same or different.

[Claim 28]

The compound of any of claims 1-27, wherein R¹ is halogen.

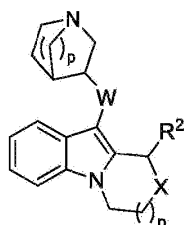
[Claim 29]

The compound of claim 28, wherein R¹ is fluoro.

[Claim 30]

The compound of any of claims 1-27, wherein R¹ is hydrogen.

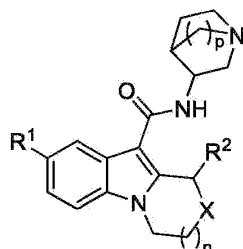
- [Claim 31] The compound of any of claims 1-27, wherein R^1 is C_1 - C_3 alkyl.
- [Claim 32] The compound of claim 31, wherein R^1 is methyl.
- [Claim 33] The compound of claim 23, wherein the compound is of Formula (II-a'')



(II-a''),

or a pharmaceutically acceptable salt thereof.

- [Claim 34] The compound of any of claims 1-33, wherein W is -C(O)O-.
- [Claim 35] The compound of any of claims 1-33, wherein W is -C(O)N(H)-.
- [Claim 36] The compound of any of claims 1-35, wherein W is a 5-membered heteroaryl ring having 1-3 ring heteroatoms.
- [Claim 37] The compound of claim 36, wherein W is selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, triazolyl, furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, and thiadiazolyl.
- [Claim 38] The compound of any of claims 1-32, wherein the compound is of Formula (II-b) :

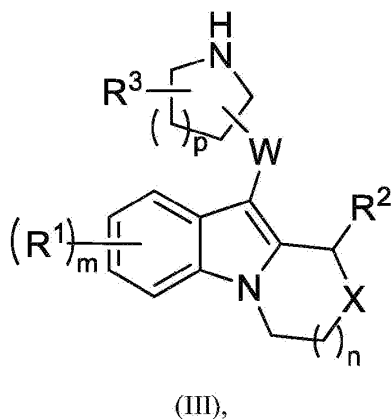


(II-b),

or a pharmaceutically acceptable salt thereof.

- [Claim 39] The compound of any of claims 1-38, wherein R^2 is hydrogen.
- [Claim 40] The compound of any of claims 1-38, wherein R^2 is C_1 - C_3 alkyl.
- [Claim 41] The compound of claim 40, wherein R^2 is methyl.
- [Claim 42] The compound of any of claims 23-41, wherein X is $-CH_2-$.
- [Claim 43] The compound of any of claims 23-41, wherein X is $-O-$.
- [Claim 44] The compound of any of claims 23-41, wherein X is $-N(H)-$.

- [Claim 45] The compound of any of claims 23-44, wherein n is 0.
 [Claim 46] The compound of any of claims 23-44, wherein n is 1.
 [Claim 47] The compound of any of claims 23-46, wherein p is 1.
 [Claim 48] The compound of any of claims 23-46, wherein p is 2.
 [Claim 49] The compound of any of claims 1-48, wherein R³ is halogen.
 [Claim 50] The compound of claim 49, wherein R³ is fluoro.
 [Claim 51] A compound of Formula (III) :



or a pharmaceutically acceptable salt thereof
 wherein

X is selected from the group consisting of -C(R'')₂-O-, and -N(H)-;

W is selected from the group consisting of -C(O)O-, -C(O)N(H)-, and a 5-membered heteroaryl ring having 1-3 ring heteroatoms;

R¹ for each occurrence is independently hydrogen or halogen

R² is hydrogen or C₁-C₃ alkyl;

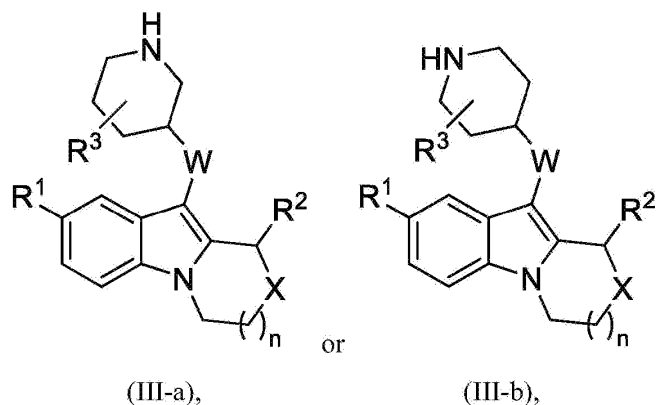
R³ is selected from the group consisting of hydrogen, halogen, and C₁-C₃ alkyl (optionally substituted with one, two or three halogens) ;

m is 1, 2, or 3;

n is 0, 1, 2, or 3; and

p is 0, 1, 2, 3.

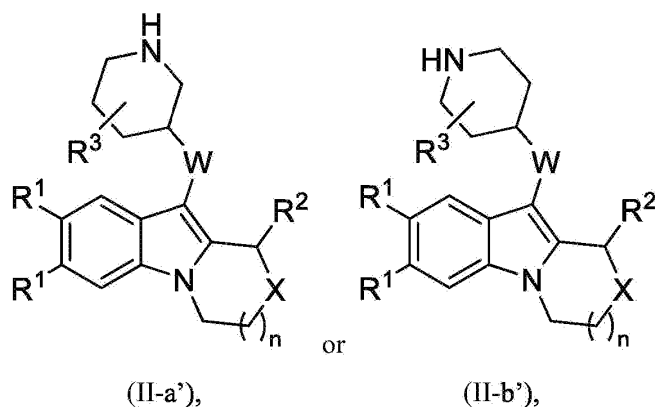
- [Claim 52] The compound of claim 51, wherein m is 1.
 [Claim 53] The compound of any of claims 51-52, wherein m is 2.
 [Claim 54] The compound of claim 51, wherein the compound is of Formula (III-a) or Formula (III-b)



or a pharmaceutically acceptable salt thereof.

[Claim 55]

The compound of claim 51, wherein the compound is of Formula (III-a') or Formula (III-b')



or a pharmaceutically acceptable salt thereof,

wherein each R¹ may be the same or different.

[Claim 56]

The compound of any of claims 51-55, wherein R¹ is halogen.

[Claim 57]

The compound of claim 56, wherein R¹ is fluoro.

[Claim 58]

The compound of any of claims 51-57, wherein R¹ is hydrogen.

[Claim 59]

The compound of any of claims 51-58, wherein R¹ is C₁-C₃ alkyl.

[Claim 60]

The compound of claim 59, wherein R¹ is methyl.

[Claim 61]

The compound of any of claims 51-60, wherein W is -C(O)O-.

[Claim 62]

The compound of any of claims 51-60, wherein W is -C(O)N(H)-.

[Claim 63]

The compound of any of claims 51-60, wherein W is a 5-membered heteroaryl ring having 1-3 ring heteroatoms.

[Claim 64]

The compound of claim 63, wherein W is selected from the group consisting of pyrrolyl, pyrazolyl, imidazolyl, triazolyl, furanyl,

oxazolyl, isoxazolyl, oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, and thiadiazolyl.

- [Claim 65] The compound of any of claims 51-64, wherein R^2 is hydrogen.
- [Claim 66] The compound of any of claims 51-64, wherein R^2 is C_1-C_3 alkyl.
- [Claim 67] The compound of claim 66, wherein R^2 is methyl.
- [Claim 68] The compound of any of claims 51-67, wherein X is $-CH_2-$.
- [Claim 69] The compound of any of claims 51-67, wherein X is $-O-$.
- [Claim 70] The compound of any of claims 51-67, wherein X is $-N(H)-$.
- [Claim 71] The compound of any of claims 51-70, wherein n is 0.
- [Claim 72] The compound of any of claims 51-70, wherein n is 1.
- [Claim 73] The compound of any of claims 51-72, wherein p is 1.
- [Claim 74] The compound of any of claims 51-72, wherein p is 2.
- [Claim 75] The compound of any of claims 51-74, wherein R^3 is halogen.
- [Claim 76] The compound of claim 75, wherein R^3 is fluoro.
- [Claim 77] A compound selected from the group consisting of those found in Table 1.
- [Claim 78] A pharmaceutical composition comprising a compound of any of claims 1-77 and a pharmaceutically acceptable adjuvant.
- [Claim 79] A method of treating, ameliorating or preventing a disease, disorder, or injury comprising administering a therapeutically effective amount of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 to a subject in need thereof.
- [Claim 80] The method of claim 79, wherein the disease, disorder, or injury is selected from the group consisting of pulmonary artery hypertension PAH, asthma, chronic obstructive pulmonary disease COPD, pulmonary fibrosis (e.g., idiopathic pulmonary fibrosis IPF, cystic fibrosis), a coronavirus infection (e.g., SARS-COV2 infection), acute lung injury, respiratory distress syndrome, respiratory failure, small cell lung cancer, interstitial lung disease, chronic obstructive pulmonary disease, and chronic thromboembolic pulmonary hypertension.
- [Claim 81] The method of claim 79, wherein the disease, disorder, or injury is pulmonary artery hypertension.
- [Claim 82] A method of treating, ameliorating or preventing cardiovascular disease, a cardiovascular disorder, or cardiac injury comprising administering a therapeutically effective amount of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 to a subject in need thereof.

- [Claim 83] The method of claim 82, wherein the ischemia-reperfusion injury is a result of myocardial infarction or ischemic stroke.
- [Claim 84] The method of any of claims 82-83, wherein the subject is at high risk of developing the disease or condition.
- [Claim 85] The method of claim 82, wherein the cardiovascular disease or cardiovascular disorder, is selected from the group consisting of: arrhythmia, aorta disease, cardiomyopathy, congenital heart disease, coronary artery disease, deep vein thrombosis, heart valve disease, hypertension, Marfan syndrome, pericardial disease, pulmonary embolism, rheumatic heart disease, vascular disease, and drug induced cardiotoxicity.
- [Claim 86] The method of any of claims 82-85, wherein the subject is expected to undergo coronary artery bypass grafting (CABG) surgery.
- [Claim 87] The method of any of claims 82-85, wherein the subject has undergone CABG surgery.
- [Claim 88] The method of any of claims 82-87, wherein the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 is administered to the subject by a route selected from the group consisting of: intravenous administration, intracardiac administration, and administration within a cardioplegic solution.
- [Claim 89] The method of any of claims 82-88, wherein, following administration of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 to a subject in need thereof, the subject has reduced symptoms selected from the group consisting of arrhythmias, microvascular dysfunction, myocardial stunning and myocyte death.
- [Claim 90] The method of any of claims 82-88, wherein cardiomyocytes of the subject exhibit reduced reactive oxygen species production following administration of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 compared to cardiomyocytes prior to administration of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 or compared to control samples of cardiomyocytes.
- [Claim 91] The method of any one of the above claims, wherein cardiomyocytes from the subject exhibit reduced release of Troponin I following administration of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 compared to cardiomyocytes or cardiac tissue prior to administration of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 or compared to control samples of cardiomyocytes or cardiac tissue from subjects that have not

- been administered the compound of any of claims 1-77, or the pharmaceutical composition of claim 78.
- [Claim 92] The method of any one of the above claims, wherein cardiomyocytes form the subject exhibit a cellular response selected from the group consisting of: reduced cell death, increased cell survival, decreased cell damage, and reduced oxidative stress, following administration of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 compared to cardiomyocytes prior to administration of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 or compared to control samples of cardiomyocytes, or cardiac tissue from subjects that have not been administered the compound of any of claims 1-77, or the pharmaceutical composition of claim 78.
- [Claim 93] The method of any one of the above claims, wherein administration of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 causes increased aortic velocity in the subject as compared to prior to administration of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 or subjects that have not been administered the compound of any of claims 1-77, or the pharmaceutical composition of claim 78.
- [Claim 94] The method of any one of the above claims, wherein administration of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 causes improved cardiac output in the subject as compared to prior to administration of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 or subjects that have not been administered the compound of any of claims 1-77, or the pharmaceutical composition of claim 78.
- [Claim 95] The method of any one of the above claims, wherein administration of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 causes a reduction of indicators of cardiovascular disease selected from the group consisting of: decreased collagen deposition, decreased fibroblast differentiation into myofibroblasts, increased or decreased expression of Smad Binding Elements (SBE) , increased cardiac contractile force generation or contractility, increased or enhanced maintenance of calcium handling, decreased hypertrophy (cell size) , and decreased expression of cardiac hypertrophic marker genes.
- [Claim 96] A method of treating a subject that has undergone myocardial infarction or cardiac arrest, and is in need of treatment, comprising: administering

- a therapeutically effective amount of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 to the subject after the myocardial infarction or cardiac arrest.
- [Claim 97] The method of claim 96, wherein the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 causes reduced infarct size in the heart tissue of the subject compared to a subject that was not administered the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 after myocardial infarction or cardiac arrest.
- [Claim 98] The method of claim 96 or 97, wherein the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 causes reduced cardiac tissue wall thinning after the myocardial infarction or cardiac arrest.
- [Claim 99] The method of claims 96-98, wherein the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 causes reduced granulation of cardiac tissue after the myocardial infarction or cardiac arrest.
- [Claim 100] The method of any one of claims 96-99, wherein the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 causes reduced neovascularization in cardiac tissue after the myocardial infarction or cardiac arrest.
- [Claim 101] The method of any one of claims 96-100, wherein the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 causes reduced neovascularization in cardiac tissue after the myocardial infarction or cardiac arrest.
- [Claim 102] The method of any one of the above claims, wherein the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 is administered in more than one dose.
- [Claim 103] The method of any one of the above claims, wherein the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 is administered in combination with at least one additional therapeutic agent.
- [Claim 104] A method of preventing or minimizing cardiac injury in a subject at risk of myocardial infarction or cardiac arrest, comprising: administering to the subject an effective amount of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 before the myocardial infarction or cardiac arrest, thereby preventing or ameliorating cardiovascular damage.

- [Claim 105] The method of claim 104, wherein the subject at risk of myocardial infarction or cardiac arrest has a cardiovascular disease or condition selected from the group consisting of: arrhythmia, aorta disease, cardiomyopathy, congenital heart disease, coronary artery disease, deep vein thrombosis, heart valve disease, hypertension, Marfan syndrome, pericardial disease, pulmonary embolism, rheumatic heart disease, and vascular disease.
- [Claim 106] The method of claim 104 or 105, wherein the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 is administered in more than one dose.
- [Claim 107] A method of reducing cardiac damage in a subject resulting from coronary artery bypass grafting (CABG) surgery, comprising administering to the subject, before, after and/or during the surgery, a therapeutically effective amount of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78.
- [Claim 108] A method of reducing cardiac damage in a subject resulting cardiopulmonary bypass surgery, comprising administering to the subject, before, after and/or during the surgery, a therapeutically effective amount of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78.
- [Claim 109] The method of claim 108, wherein the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 is administered in more than one dose.
- [Claim 110] The method of any one of claims 108-109, wherein the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 is administered prior to surgery, following surgery or both prior to and following surgery.
- [Claim 111] A method of treating a subject with cardiac tissue damage, and is in need of treatment, comprising: administering a sufficient amount of the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 to the subject, thereby ameliorating the cardiac tissue damage.
- [Claim 112] The method of claim 111, wherein the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 causes reduced neovascularization in the damaged cardiac tissue.
- [Claim 113] The method of any one of the above claims, wherein the compound of any of claims 1-77, or the pharmaceutical composition of claim 78 is administered in combination with at least one additional therapeutic agent.

- [Claim 114] The method of claim 113, wherein the at least one additional therapeutic agent is an agent selected from the group consisting of an agent that: reduces cholesterol, reduces low-density lipoprotein, reduces system blood pressure, and reduces blood glucose levels.
- [Claim 115] The method of any one of the above claims, wherein the method increases overall survival rate of the subjects compared to subjects that have not been administered the compound of any of claims 1-77, or the pharmaceutical composition of claim 78.
- [Claim 116] The method of claim 79, wherein the disease or disorder is a pulmonary disease or pulmonary disorder.
- [Claim 117] The method of claim 116, wherein the disease or disorder is an obstructive lung disease or a restrictive lung disease.
- [Claim 118] The method of claim 116, wherein the disease or disorder is selected from the group consisting of asthma, bronchiolitis obliterans organizing pneumonia (BOOP) , chronic obstructive pulmonary disease (COPD) , emphysema, pulmonary fibrosis, and sarcoidosis.
- [Claim 119] The method of claim 116, wherein the disease or disorder is selected from the group consisting of acute chest syndrome, acute respiratory distress syndrome, alpha-1 antitrypsin deficiency, asbestosis, aspergillosis, asthma, bronchiectasis, bronchiolitis, bronchiolitis obliterans, bronchitis, bronchopulmonary dysplasia, chronic cough, chronic obstructive pulmonary disease (COPD) , coccidioidomycosis, cryptogenic organizing pneumonia, cystic fibrosis, e-cigarette, or vaping product, use associated lung injury (EVALI) , emphysema, eosinophilic granulomatosis with polyangiitis (EGPA) , common cold, hantavirus pulmonary syndrome (HPS) , histoplasmosis, human metapneumovirus (hMPV) , hypersensitivity pneumonitis, idiopathic pulmonary fibrosis (IPF) , infectious lung diseases, influenza, interstitial lung disease (ILD) , Legionnaires' disease, lung cancer, LAM, MAC lung disease, mesothelioma, NTM lung disease, an occupational lung disease, pertussis, pneumonia, pneumothorax, primary ciliary dyskinesia (PCD) , pulmonary arterial hypertension (PAH) , pulmonary embolism, pulmonary fibrosis, pulmonary hypertension, respiratory syncytial virus, sarcoidosis, silicosis, sleep apnea, coronavirus related disease, and tuberculosis.
- [Claim 120] The method of claim 119, wherein bronchitis is acute bronchitis or chronic bronchitis.

[Claim 121]

The method of claim 116, wherein the disease or disorder is selected from the group consisting of aspergillosis, asthma, bronchiectasis, bronchitis, chronic cough, chronic obstructive pulmonary disease (COPD), common cold, croup, cystic fibrosis, hantavirus pulmonary syndrome (HPS), idiopathic pulmonary fibrosis (IPF), influenza, lung cancer, LAM, MAC lung disease, pertussis, pleurisy, pneumonia, pulmonary embolism, pulmonary hypertension, respiratory syncytial virus, sarcoidosis, sleep apnea, spirometry, sudden infant death syndrome, tobacco endgame, and tuberculosis.