

COMPOUNDS AS C5AR INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority benefit of PCT International Application No. PCT/CN2020/107800, filed August 7, 2020, the disclosure of which is hereby incorporated herein by reference in its entirety.

FIELD

[0002] The present disclosure relates to C5a receptor inhibitors, compositions thereof, methods of use thereof, and methods of preparation thereof.

BACKGROUND

[0003] C5a is a 74 amino acid peptide that is generated by the proteolysis of complement protein C5. Increased level of C5a has been associated with disorders such as autoimmune disorders and inflammatory disorders. The effects of C5a are believed to be mediated through its binding to the C5a receptor (C5aR). As such, there is a need for therapeutics that inhibit the activity of C5aR and thus inhibit the binding of C5a to C5aR. The present disclosure provides compounds that are C5aR inhibitors.

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] FIG. 1A shows the experimental design of the effect C5aR compounds have on C5a induced neutropenia in cyno monkeys.

[0005] FIG. 1B shows the *in vivo* rescue effect of compound Nos. 47 and 49 in human C5a induced neutropenia model in cyno monkeys.

[0006] FIG. 2A shows the experimental design of the effect C5aR compounds have on C5a induced neutropenia in human C5aR knocked-in mice.

[0007] FIG. 2B shows the *in vivo* rescue effect of compound No. 49 in human C5a induced neutropenia model in human C5aR knock-in mice.

[0008] FIG. 3 shows C5a induced CD11b upregulation on granulocytes in cyno monkey whole blood was blocked by orally pre-dosing compound Nos. 47 and 49 at 10mg/kg.

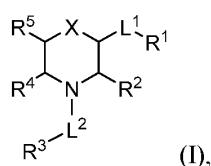
[0009] FIG. 4 shows C5a induced CD11b upregulation on neutrophil was blocked by compound No. 49 on neutrophil in mice whole blood by orally pre-dosing.

[0010] FIG. 5 shows C5a induced CD11b upregulation on neutrophil was blocked by compound Nos. 47 and 89 on neutrophil in human C5aR knock-in mice whole blood by orally pre-dosing.

[0011] FIG. 6 shows C5a induced CD11b upregulation on neutrophil was blocked by compound Nos. 47 and 49 on neutrophil in human C5aR knock-in mice whole blood by orally pre-dosing.

SUMMARY

[0012] In one aspect, provided is a compound of formula (I):



or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 , R^2 , R^3 , R^4 , R^5 , X , L^1 , and L^2 are as disclosed herein.

[0013] In another aspect, provided is a pharmaceutical composition comprising a compound as described herein and a pharmaceutically acceptable carrier or excipient. Also provided is a kit comprising a compound as described herein.

[0014] In another aspect, provided is a method of treating a C5a-mediated disorder in an individual in need thereof, comprising administering an therapeutically effective amount of a compound as described herein, or pharmaceutically acceptable salt thereof, to the individual. Also provided is use of a compound as described herein, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a C5a-mediated disease.

DETAILED DESCRIPTION

[0015] The following description sets forth exemplary embodiments of the present disclosure. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

Definitions

[0016] As used in the present specification, the following words, phrases and symbols are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0017] The term “about” refers to a variation of $\pm 1\%$, $\pm 3\%$, $\pm 5\%$, or $\pm 10\%$ of the value specified. For example, “about 50” can in some embodiments include a range of from 45 to 55. Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”.

[0018] The singular forms “a,” “an,” and “the” include plural references unless the context clearly dictates otherwise. Thus, e.g., reference to “the compound” includes a plurality of such compounds and includes reference to one or more compounds and equivalents thereof known to those skilled in the art.

[0019] “Alkyl” refers to an unbranched or branched saturated hydrocarbon chain. As used herein, alkyl has 1 to 10 carbon atoms (i.e., C_{1-10} alkyl or C_1-C_{10} alkyl), 1 to 8 carbon atoms (i.e., C_{1-8} alkyl or C_1-C_8 alkyl), 1 to 6 carbon atoms (i.e., C_{1-6} alkyl or C_1-C_6 alkyl), or 1 to 4 carbon atoms (i.e., C_{1-4} alkyl or C_1-C_4 alkyl). Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or identified by molecular formula, all positional isomers having that number of carbons may be encompassed; thus, for example, “butyl” includes n-butyl (i.e., $-(CH_2)_3CH_3$), sec-butyl (i.e., $-CH(CH_3)CH_2CH_3$), isobutyl (i.e., $-CH_2CH(CH_3)_2$) and tert-butyl (i.e., $-C(CH_3)_3$); and “propyl” includes n-propyl (i.e., $-(CH_2)_2CH_3$) and isopropyl (i.e., $-CH(CH_3)_2$).

[0020] “Alkylene” refers to a divalent alkyl group as defined herein.

[0021] “Haloalkyl” refers to an unbranched or branched alkyl group as defined above, wherein one or more hydrogen atoms are replaced by a halogen. For example, where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached. Dihaloalkyl and trihaloalkyl refer to alkyl substituted with two (“di”) or three (“tri”) halo groups, which may be, but are not necessarily, the same halogen. Examples of haloalkyl include difluoromethyl ($-CHF_2$) and trifluoromethyl ($-CF_3$).

[0022] “Heteroalkyl” refers to an alkyl group in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatomic group. The term “heteroalkyl” includes unbranched or branched saturated chain having carbon and heteroatoms. By way of example, 1, 2 or 3 carbon atoms may be independently replaced with the same or different heteroatomic group. Heteroatomic groups include, but are not limited to, -NH-, -O-, -S-, -S(O)-, -S(O)₂- and the like. As used herein, heteroalkyl includes 1 to 8 carbon atoms, or 1 to 4 carbon atoms; and 1 to 3 heteroatomic groups, 1 to 2 heteroatomic groups, or 1 heteroatomic group.

[0023] “Heteroalkylene” refers to a divalent heteroalkyl group as defined herein.

[0024] “Alkoxy” refers to the group “-O-alkyl”. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy and 1,2-dimethylbutoxy.

[0025] “Alkenyl” refers to an alkyl group containing at least one carbon-carbon double bond and having from 2 to 20 carbon atoms (i.e., C₂₋₂₀ alkenyl or C₂-C₂₀ alkenyl), 2 to 8 carbon atoms (i.e., C₂₋₈ alkenyl or C₂-C₈ alkenyl), 2 to 6 carbon atoms (i.e., C₂₋₆ alkenyl or C₂-C₆ alkenyl) or 2 to 4 carbon atoms (i.e., C₂₋₄ alkenyl or C₂-C₄ alkenyl). Examples of alkenyl groups include, but are not limited to, ethenyl, propenyl, and butadienyl (e.g., 1,2-butadienyl and 1,3-butadienyl).

[0026] “Alkynyl” refers to an alkyl group containing at least one carbon-carbon triple bond and having from 2 to 20 carbon atoms (i.e., C₂₋₂₀ alkynyl or C₂-C₂₀ alkynyl), 2 to 8 carbon atoms (i.e., C₂₋₈ alkynyl or C₂-C₈ alkynyl), 2 to 6 carbon atoms (i.e., C₂₋₆ alkynyl or C₂-C₆ alkynyl) or 2 to 4 carbon atoms (i.e., C₂₋₄ alkynyl or C₂-C₄ alkynyl). The term “alkynyl” also includes those groups having one triple bond and one double bond.

[0027] “Aryl” refers to an aromatic carbocyclic group having a single ring (e.g., monocyclic) or multiple rings (e.g., bicyclic or tricyclic) including fused systems. As used herein, aryl has 6 to 20 ring carbon atoms (i.e., C₆₋₂₀ aryl or C₆-C₂₀ aryl), 6 to 12 carbon ring atoms (i.e., C₆₋₁₂ aryl or C₆-C₁₂ aryl), or 6 to 10 carbon ring atoms (i.e., C₆₋₁₀ aryl or C₆-C₁₀ aryl). Examples of aryl groups include, but are not limited to, phenyl, naphthyl, fluorenyl and anthryl. Aryl, however, does not encompass or overlap in any way with heteroaryl defined below. If one or more aryl groups are fused with a heteroaryl, the resulting ring system is heteroaryl. If one or more aryl groups are fused with a heterocyclyl, the resulting ring system is heterocyclyl.

[0028] “Cycloalkyl” refers to a saturated or partially unsaturated cyclic alkyl group having a single ring or multiple rings including fused, bridged and spiro ring systems. The term “cycloalkyl” includes cycloalkenyl groups (i.e., the cyclic group having at least one double bond) and carbocyclic fused ring systems having at least one sp^3 carbon atom (i.e., at least one non-aromatic ring). As used herein, cycloalkyl has from 3 to 20 ring carbon atoms (i.e., C_{3-20} cycloalkyl or C_3-C_{20} cycloalkyl), 3 to 12 ring carbon atoms (i.e., C_{3-12} cycloalkyl or C_3-C_{12} cycloalkyl), 3 to 10 ring carbon atoms (i.e., C_{3-10} cycloalkyl or C_3-C_{10} cycloalkyl), 3 to 8 ring carbon atoms (i.e., C_{3-8} cycloalkyl or C_3-C_8 cycloalkyl), or 3 to 6 ring carbon atoms (i.e., C_{3-6} cycloalkyl or C_3-C_6 cycloalkyl). Monocyclic groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. Further, the term cycloalkyl is intended to encompass any non-aromatic ring which may be fused to an aryl ring, regardless of the attachment to the remainder of the molecule. Still further, cycloalkyl also includes “spirocycloalkyl” when there are two positions for substitution on the same carbon atom.

[0029] “Heteroaryl” refers to an aromatic group having a single ring, multiple rings or multiple fused rings, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. As used herein, heteroaryl includes 1 to 20 ring carbon atoms (i.e., C_{1-20} heteroaryl), 3 to 12 ring carbon atoms (i.e., C_{3-12} heteroaryl), or 3 to 8 carbon ring atoms (i.e., C_{3-8} heteroaryl) and 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. In certain instances, heteroaryl includes 5- to 14- membered ring systems, 5- to 12- membered ring systems, 5- to 10- membered ring systems, 5- to 7- membered ring systems, or 5- to 6- membered ring systems, each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur. Any aromatic ring, having a single or multiple fused rings, containing at least one heteroatom, is considered a heteroaryl regardless of the attachment to the remainder of the molecule (i.e., through any one of the fused rings). Heteroaryl does not encompass or overlap with aryl as defined above.

[0030] “Heterocyclyl” refers to a saturated or partially unsaturated cyclic alkyl group, with one or more ring heteroatoms independently selected from nitrogen, oxygen and sulfur. The term “heterocyclyl” includes heterocycloalkenyl groups (i.e., the heterocyclyl group having at least one double bond), bridged-heterocyclyl groups, fused-heterocyclyl groups and spiro-heterocyclyl groups. A heterocyclyl may be a single ring or multiple rings wherein the

multiple rings may be fused, bridged or spiro and may comprise one or more (e.g., 1 to 3) oxo (=O) or N-oxide (N⁺-O⁻) moieties. Any non-aromatic ring containing at least one heteroatom is considered a heterocyclyl, regardless of the attachment (i.e., can be bound through a carbon atom or a heteroatom). Further, the term heterocyclyl is intended to encompass any non-aromatic ring containing at least one heteroatom, which ring may be fused to an aryl or heteroaryl ring, regardless of the attachment to the remainder of the molecule. As used herein, heterocyclyl has 2 to 20 ring carbon atoms (i.e., C₂₋₂₀ or C₂-C₂₀ heterocyclyl), 2 to 12 ring carbon atoms (i.e., C₂₋₁₂ or C₂-C₁₂ heterocyclyl), 2 to 10 ring carbon atoms (i.e., C₂₋₁₀ or C₂-C₁₀ heterocyclyl), 2 to 8 ring carbon atoms (i.e., C₂₋₈ or C₂-C₈ heterocyclyl), 3 to 12 ring carbon atoms (i.e., C₃₋₁₂ or C₃-C₁₂ heterocyclyl), 3 to 8 ring carbon atoms (i.e., C₃₋₈ or C₃-C₈ heterocyclyl), or 3 to 6 ring carbon atoms (i.e., C₃₋₆ or C₃-C₆ heterocyclyl); having 1 to 5 ring heteroatoms, 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, sulfur or oxygen. In certain instances, heterocyclyl includes 3- to 14-membered ring systems, 3- to 12- membered ring systems, 5- to 10- membered ring systems, 5- to 7- membered ring systems, or 5- to 6- membered ring systems, each independently having 1 to 4 ring heteroatoms, 1 to 3 ring heteroatoms, 1 to 2 ring heteroatoms, or 1 ring heteroatom independently selected from nitrogen, oxygen and sulfur.

[0031] “Oxo” refers to =O.

[0032] “Halogen” or “halo” includes fluoro, chloro, bromo and iodo.

[0033] The terms “optional” or “optionally” means that the subsequently described event or circumstance may or may not occur. The term “optionally substituted” refers to any one or more (e.g., 1-5, 1-4, 1-3, 1-2, 2-5, 2-4, 2-3, 3-5, or 3-4) hydrogen atoms on the designated atom or group may or may not be replaced by a substituent atom or group commonly used in pharmaceutical chemistry. Each substituent can be the same or different.

[0034] “Individual” as used herein is a mammal, including humans. In some embodiments, individuals include pig, bovine, feline, canine, primate, rodent, or human. In some embodiments, the individual is human.

[0035] As used herein, “treatment” or “treating” is an approach for obtaining beneficial or desired results including clinical results. For purposes of this disclosure, beneficial or desired results include, but are not limited to, one or more of the following: decreasing one or more symptoms resulting from the disease or disorder, diminishing the extent of the disease

or disorder, stabilizing the disease or disorder (e.g., preventing or delaying the worsening of the disease or disorder), delaying the occurrence or recurrence of the disease or disorder, delaying or slowing the progression of the disease or disorder, ameliorating the disease or disorder state, providing a remission (whether partial or total) of the disease or disorder, decreasing the dose of one or more other medications required to treat the disease or disorder, enhancing the effect of another medication used to treat the disease or disorder, delaying the progression of the disease or disorder, increasing the quality of life, and/or prolonging survival of a patient. Also encompassed by “treatment” is a reduction of pathological consequence of the disease or disorder. The methods of this disclosure contemplate any one or more of these aspects of treatment.

[0036] The term “therapeutically effective amount” used herein refers to an amount of a compound or composition sufficient to treat a specified disorder, condition or disease such as ameliorate, palliate, lessen, and/or delay one or more of its symptoms. In reference to cancers or other unwanted cell proliferation, a therapeutically effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such as to suppress tumor growth) or to prevent or delay other unwanted cell proliferation. In some embodiments, a therapeutically effective amount is an amount sufficient to delay development. In some embodiments, a therapeutically effective amount is an amount sufficient to prevent or delay occurrence and/or recurrence. A therapeutically effective amount can be administered in one or more administrations.

[0037] The term “carrier,” as used herein, refers to relatively nontoxic chemical compounds or agents that facilitate the incorporation of a compound into cells or tissues.

[0038] As used herein, by “pharmaceutically acceptable” or “pharmacologically acceptable” is meant a material that is not biologically or otherwise undesirable, e.g., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any significant undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. Pharmaceutically acceptable carriers or excipients have preferably met the required standards of toxicological and manufacturing testing and/or are included on the Inactive Ingredient Guide prepared by the U.S. Food and Drug administration.

[0039] “Pharmaceutically acceptable salts” are those salts which retain at least some of the biological activity of the free (non-salt) compound, which are not biologically or

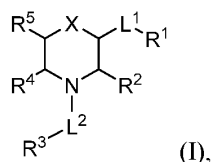
otherwise undesirable, and which can be administered as drugs or pharmaceuticals to an individual. Pharmaceutically acceptable salts may be pharmaceutically acceptable acid addition salts. Examples of pharmaceutically acceptable acid addition salts include, but are not limited to, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrate, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates. Pharmaceutically acceptable salts may be pharmaceutically acceptable base addition salts. Pharmaceutically acceptable base addition salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Pharmaceutically acceptable base addition salts derived from organic bases include, but are not limited to, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chlorprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, and *N*-ethylpiperidine.

[0040] The term “excipient” as used herein means an inert or inactive substance that may be used in the production of a drug or pharmaceutical, such as a tablet containing a compound of the disclosure as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a binder, disintegrant, coating, compression/encapsulation aid, cream or lotion, lubricant, solutions for parenteral administration, materials for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Binders include, e.g., carbomers, povidone, xanthan gum, etc.; coatings include, e.g., cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include, e.g., calcium carbonate, dextrose, fructose dc (dc=“directly compressible”), honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc.; disintegrants include, e.g., croscarmellose sodium, gellan gum, sodium starch glycolate, etc.; creams or lotions include, e.g., maltodextrin,

carrageenans, etc.; lubricants include, e.g., magnesium stearate, stearic acid, sodium stearyl fumarate, etc.; materials for chewable tablets include, e.g., dextrose, fructose dc, lactose (monohydrate, optionally in combination with aspartame or cellulose), etc.; suspending/gelling agents include, e.g., carrageenan, sodium starch glycolate, xanthan gum, etc.; sweeteners include, e.g., aspartame, dextrose, fructose dc, sorbitol, sucrose dc, etc.; and wet granulation agents include, e.g., calcium carbonate, maltodextrin, microcrystalline cellulose, etc.

Compounds

[0041] In one aspect, provided herein is a compound of formula (I):



or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

X is -O- or -CHR⁶-,

provided that when X is -O-, then L¹ is *-C(O)NH-** and L² is -C(O)-;

R¹ is C₃₋₁₂ cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, or C₆₋₁₄ aryl, each of which is independently optionally substituted with one or more R¹¹,

wherein each R¹¹ is independently oxo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1b}, -NO₂, -C(O)R^{1a}, -OC(O)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1a}R^{1b}, -OC(O)NR^{1a}R^{1b}, -NR^{1a}C(O)R^{1b}, -NR^{1a}C(O)OR^{1b}, -S(O)R^{1a}, -S(O)₂R^{1a}, -NR^{1a}S(O)R^{1b}, -C(O)NR^{1a}S(O)R^{1b}, -NR^{1a}S(O)₂R^{1b}, -C(O)NR^{1a}S(O)₂R^{1b}, -S(O)NR^{1a}R^{1b}, -S(O)₂NR^{1a}R^{1b}, -P(O)R^{1a}R^{1b}, C₃₋₆ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C₆₋₁₄ aryl, -(C₁₋₆ alkylene) NR^{1a}R^{1b}, -(C₁₋₆ alkylene) C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene) 3- to 12-membered heterocyclyl, -(C₁₋₆ alkylene) 5- to 12-membered heteroaryl, or -(C₁₋₆ alkylene) C₆₋₁₄ aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, hydroxyl, C₁₋₆ alkoxy, and -CN,

wherein R^{1a} and R^{1b} are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C₆₋₁₄ aryl, or

R^{1a} and R^{1b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, hydroxyl, C₁₋₆ alkoxy, and -CN;

R^2 is C₃₋₁₂ cycloalkyl, 3- to 12- membered heterocyclyl, or C₆₋₁₄ aryl, each of which is independently optionally substituted with one or more -Q-W, wherein:

Q is C₁₋₆ alkylene, -(N-L³-R^Q)- or -O-,

wherein R^Q is H, C₁₋₆ alkyl, 5- to 12-membered heteroaryl, or C₆₋₁₄ aryl, and L³ is -C(O)-, *-C(O)O-CH₂**, or a bond, wherein * indicates the point of attachment to N and ** indicates the point of attachment to R^Q,

W is H, C₃₋₁₂ cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, or C₆₋₁₄ aryl, each of which is independently optionally substituted with one or more R⁷;

R^3 is H, C₃₋₁₂ cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, or C₆₋₁₄ aryl, wherein the C₃₋₁₂ cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, and C₆₋₁₄ aryl are each independently optionally substituted with one or more R³¹,

wherein each R³¹ is independently oxo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, -CN, -OR^{3a}, -SR^{3a}, -NR^{3a}R^{3b}, -NO₂, -C(O)R^{3a}, -OC(O)R^{3a}, -C(O)OR^{3a}, -C(O)NR^{3a}R^{3b}, -OC(O)NR^{3a}R^{3b}, -NR^{3a}C(O)R^{3b}, -NR^{3a}C(O)OR^{3b}, -S(O)R^{3a}, -S(O)₂R^{3a}, -NR^{3a}S(O)R^{3b}, -C(O)NR^{3a}S(O)R^{3b}, -NR^{3a}S(O)₂R^{3b}, -C(O)NR^{3a}S(O)₂R^{3b}, -S(O)NR^{3a}R^{3b}, -S(O)₂NR^{3a}R^{3b}, -P(O)R^{3a}R^{3b}, C₃₋₆ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C₆₋₁₄ aryl, -(C₁₋₆ alkylene) NR^{3a}R^{3b}, -(C₁₋₆ alkylene)C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene) 3- to 12-membered heterocyclyl, -(C₁₋₆ alkylene) 5- to 12-membered heteroaryl, or -(C₁₋₆ alkylene) C₆₋₁₄ aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, hydroxyl, C₁₋₆ alkoxy, and -CN,

wherein R^{3a} and R^{3b} are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C₆₋₁₄ aryl, or

R^{3a} and R^{3b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, hydroxyl, C₁₋₆ alkoxy, and -CN; and

R⁴, R⁵, and R⁶ are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, -CN, hydroxyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C₆₋₁₄ aryl, wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, and C₆₋₁₄ aryl are each independently optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, hydroxyl, C₁₋₆ alkoxy, and -CN, and wherein,

R⁴ and R⁵ or R⁵ and R⁶ may be taken together with the carbon atoms to which they are attached to form a ring B which is independently optionally substituted with one or more R⁸, wherein ring B is C₃₋₁₂ cycloalkyl or 3- to 12- membered heterocyclyl, and

R⁴ may be taken with the carbon atom to which it is attached, the nitrogen atom adjacent to the carbon atom, L², and part of R³ to form a 6- to 8- membered heterocyclyl; each R⁷ is independently oxo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, -CN, -OR^{7a}, -SR^{7a}, -NR^{7a}R^{7b}, -NO₂, -C(O)R^{7a}, -OC(O)R^{7a}, -C(O)OR^{7a}, -C(O)NR^{7a}R^{7b}, -OC(O)NR^{7a}R^{7b}, -NR^{7a}C(O)R^{7b}, -NR^{7a}C(O)OR^{7b}, -S(O)R^{7a}, -S(O)₂R^{7a}, -NR^{7a}S(O)R^{7b}, -C(O)NR^{7a}S(O)R^{7b}, -NR^{7a}S(O)₂R^{7b}, -C(O)NR^{7a}S(O)₂R^{7b}, -S(O)NR^{7a}R^{7b}, -S(O)₂NR^{7a}R^{7b}, -P(O)R^{7a}R^{7b}, C₃₋₆ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C₆₋₁₄ aryl, -(C₁₋₆ alkylene) NR^{7a}R^{7b}, -(C₁₋₆ alkylene)C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene) 3- to 12-membered heterocyclyl, -(C₁₋₆ alkylene) 5- to 12-membered heteroaryl, or -(C₁₋₆ alkylene) C₆₋₁₄ aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, hydroxyl, C₁₋₆ alkoxy, and -CN, wherein

R^{7a} and R^{7b} are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C₆₋₁₄ aryl, or

R^{7a} and R^{7b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and -CN;

each R^8 is independently oxo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, -CN, $-OR^{8a}$, $-SR^{8a}$, $-NR^{8a}R^{8b}$, $-NO_2$, $-C(O)R^{8a}$, $-OC(O)R^{8a}$, $-C(O)OR^{8a}$, $-C(O)NR^{8a}R^{8b}$, $-OC(O)NR^{8a}R^{8b}$, $-NR^{8a}C(O)R^{8b}$, $-NR^{8a}C(O)OR^{8b}$, $-S(O)R^{8a}$, $-S(O)_2R^{8a}$, $-NR^{8a}S(O)R^{8b}$, $-C(O)NR^{8a}S(O)R^{8b}$, $-NR^{8a}S(O)_2R^{8b}$, $-C(O)NR^{8a}S(O)_2R^{8b}$, $-S(O)NR^{8a}R^{8b}$, $-S(O)_2NR^{8a}R^{8b}$, $-P(O)R^{8a}R^{8b}$, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C_{6-14} aryl, $-(C_{1-6} \text{ alkylene}) NR^{8a}R^{8b}$, $-(C_{1-6} \text{ alkylene}) C_{3-6}$ cycloalkyl, $-(C_{1-6} \text{ alkylene})$ 3- to 12-membered heterocyclyl, $-(C_{1-6} \text{ alkylene})$ 5- to 12-membered heteroaryl, or $-(C_{1-6} \text{ alkylene}) C_{6-14}$ aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and -CN, wherein

R^{8a} and R^{8b} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, or

R^{8a} and R^{8b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and -CN;

L^1 is $^*-C(O)NH-^{**}$, a bond, $-C(O)-$, $^*-CH_2-NH-^{**}$, or $^*-C(O)NH-CH_2-^{**}$, wherein * indicates the point of attachment to the carbon atom of the piperidine and ** indicates the point of attachment to R^1 ;

L^2 is $-C(O)-$, a bond, $-CH_2-$, $-S(O)_2-$, or $\#-S(O)_2-CH_2-##$, wherein # indicates the point of attachment to the nitrogen atom and ## indicates the point of attachment to R^3 ,

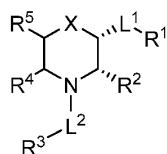
provided that when X is $-CHR^6-$ and R^4 , R^5 , and R^6 are all H, then at least one of the following conditions apply:

(1) L^1 is a bond, $-C(O)-$, $^*-CH_2-NH-^{**}$, or $^*-C(O)NH-CH_2-^{**}$,

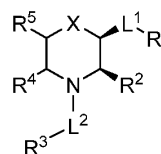
(2) L^2 is a bond, $-CH_2-$, $-S(O)_2-$, or $\#-S(O)_2-CH_2-##$, and

(3) R^2 is phenyl substituted with one or more $-Q-W$, wherein Q is $-(N-L^3-R^Q)-$ and R^Q is 5- to 12-membered heteroaryl or C_{6-14} aryl.

[0042] In some embodiments of a compound of formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, the compound is of formula (I-a) or formula (I-b), wherein R^1 , R^2 , R^3 , R^4 , R^5 , X , L^1 , and L^2 are detailed herein for formula (I). In some embodiments, the compound is of formula (I-a). In some embodiments, the compound is of formula (I-b).



(I-a)



(I-b)

[0043] Specific values described herein are values for a compound of formula (I) or any variation thereof where applicable, such as any one of formulae (I-a), (I-b), (II), (II-a)-(II-b), (III), (III-a), (III-b), (IV), (IV-a), (IV-b), (V), (V-a)-(V-k), (VI), (VI-a), (VI-b), (VII), (VII-a) and (VII-b). It is to be understood that two or more values may be combined. Thus, it is to be understood that any variable for a compound of formula (I) or any variation thereof may be combined with any other variable for a compound of formula (I) or any variation thereof of the same as if each and every combination of variables were specifically and individually listed.

[0044] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, X is $-O-$. In some embodiments, X is $-CHR^6-$.

[0045] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is $^*-C(O)NH-^{**}$. In some embodiments, L^1 is a bond. In some embodiments, L^1 is $-C(O)-$. In some embodiments, L^1 is $^*-CH_2-NH-^{**}$. In some embodiments, L^1 is $^*-C(O)NH-^{**}$, a bond, $-C(O)-$, or $^*-C(O)NH-CH_2-^{**}$. In some embodiments, L^1 is a bond, $-C(O)-$, or $^*-C(O)NH-CH_2-^{**}$. In some embodiments, L^1 is $^*-C(O)NH-^{**}$, a bond, $-C(O)-$, or $^*-C(O)NH-CH_2-^{**}$.

[0046] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, L^2 is a $-C(O)-$. In some embodiments, L^2 is a bond. In some embodiments, L^2 is $-S(O)_2-$. In some embodiments, L^2 is $-CH_2-$. In some embodiments, L^2 is $\#-S(O)_2-CH_2-\#$. In some embodiments, L^2 is $-C(O)-$, a bond, $-S(O)_2-$, or $\#-S(O)_2-CH_2-\#$. In some

embodiments, L^2 is a bond, $-S(O)_2-$, $-CH_2-$, or $^*-S(O)_2-CH_2-^{**}$. In some embodiments, L^2 is a bond, $-S(O)_2-$, or $\#-S(O)_2-CH_2-\#\#$.

[0047] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is $^*-C(O)NH-^{**}$, a bond, or $^*-CH_2-NH-^{**}$; and L^2 is $-C(O)-$, a bond, $-S(O)_2-$, $-CH_2-$, or $\#-S(O)_2-CH_2-\#\#$. In some embodiments, L^1 is $^*-C(O)NH-^{**}$, a bond, $-C(O)-$, or $^*-C(O)NH-CH_2-^{**}$; and L^2 is $-C(O)-$, a bond, $-S(O)_2-$, or $\#-S(O)_2-CH_2-\#\#$. In some embodiments, L^1 is $^*-C(O)NH-^{**}$ and L^2 is a bond. In some embodiments, L^1 is $^*-C(O)NH-^{**}$ and L^2 is $-S(O)_2-$. In some embodiments, L^1 is $^*-C(O)NH-^{**}$ and L^2 is $\#-S(O)_2-CH_2-\#\#$. In some embodiments, L^1 is $^*-C(O)NH-^{**}$ and L^2 is $-C(O)-$. In some embodiments, L^1 is a bond and L^2 is $-C(O)-$. In some embodiments, L^1 is $^*-CH_2-NH-^{**}$ and L^2 is $-C(O)-$. In some embodiments, L^1 is $-C(O)-$ and L^2 is $-C(O)-$.

[0048] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is H. In some embodiments, R^4 is C_{1-6} alkyl. In some embodiments, R^4 is C_{2-6} alkenyl. In some embodiments, R^4 is halogen. In some embodiments, R^4 is $-CN$. In some embodiments, R^4 is hydroxyl. In some embodiments, R^4 is C_{1-6} alkoxy. In some embodiments, R^4 is C_{3-6} cycloalkyl. In some embodiments, R^4 is 3- to 12-membered heterocyclyl. In some embodiments, R^4 is 5- to 12-membered heteroaryl. In some embodiments, R^4 is C_{6-14} aryl.

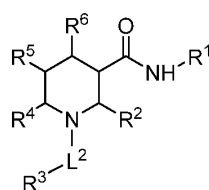
[0049] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, R^5 is H. In some embodiments, R^5 is C_{1-6} alkyl. In some embodiments, R^5 is C_{2-6} alkenyl. In some embodiments, R^5 is halogen. In some embodiments, R^5 is $-CN$. In some embodiments, R^5 is hydroxyl. In some embodiments, R^5 is C_{1-6} alkoxy. In some embodiments, R^5 is C_{3-6} cycloalkyl. In some embodiments, R^5 is 3- to 12-membered heterocyclyl. In some embodiments, R^5 is 5- to 12-membered heteroaryl. In some embodiments, R^5 is C_{6-14} aryl. In some embodiments, R^5 is H or hydroxyl.

[0050] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, R^6 is H. In some embodiments, R^6 is C_{1-6} alkyl. In some embodiments, R^6 is C_{2-6} alkenyl. In some embodiments, R^6 is halogen. In some embodiments, R^6 is $-CN$. In some

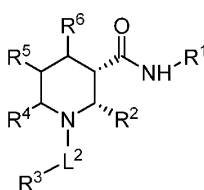
embodiments, R^6 is hydroxyl. In some embodiments, R^6 is C_{1-6} alkoxy. In some embodiments, R^6 is C_{3-6} cycloalkyl. In some embodiments, R^6 is 3- to 12-membered heterocyclyl. In some embodiments, R^6 is 5- to 12-membered heteroaryl. In some embodiments, R^6 is C_{6-14} aryl. In some embodiments, X is $-\text{CHR}^6-$; and R^6 is H.

[0051] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is H; R^5 is H or hydroxyl; X is $-\text{CHR}^6-$; and R^6 is H. In some embodiments, R^4 is H; R^5 is H; X is $-\text{CHR}^6-$; and R^6 is H. In some embodiments, R^4 is H; R^5 is H; X is $-\text{CHR}^6-$; R^6 is H; and L^1 is a bond, $-\text{C}(\text{O})-$, $^*-\text{CH}_2-\text{NH}-^{**}$, or $^*-\text{C}(\text{O})\text{NH}-\text{CH}_2-^{**}$. In some embodiments, R^4 is H; R^5 is H; X is $-\text{CHR}^6-$; R^6 is H; and L^1 is a bond, $-\text{C}(\text{O})-$, or $^*-\text{C}(\text{O})\text{NH}-\text{CH}_2-^{**}$. In some embodiments, R^4 is H; R^5 is H; X is $-\text{CHR}^6-$; R^6 is H; and L^2 is a bond, $-\text{CH}_2-$, $-\text{S}(\text{O})_2-$, or $\#-\text{S}(\text{O})_2-\text{CH}_2-\#$. In some embodiments, R^4 is H; R^5 is H; X is $-\text{CHR}^6-$; R^6 is H; and L^2 is a bond, $-\text{S}(\text{O})_2-$, or $\#-\text{S}(\text{O})_2-\text{CH}_2-\#$. In some embodiments, R^4 is H; R^5 is H; X is $-\text{CHR}^6-$; R^6 is H; and R^2 is phenyl substituted with one or more $-\text{Q}-\text{W}$, wherein Q is $-(\text{N}-\text{L}^3-\text{R}^Q)-$ and R^Q is 5- to 12-membered heteroaryl or C_{6-14} aryl.

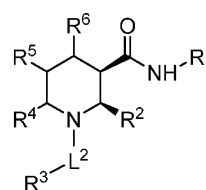
[0052] In some embodiments of a compound of formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, the compound is of formula (II), (II-a), or (II-b), wherein R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are detailed herein for formula (I); and L^2 is a bond, $-\text{CH}_2-$, $-\text{S}(\text{O})_2-$, or $\#-\text{S}(\text{O})_2-\text{CH}_2-\#$. In some embodiments, L^2 is a bond, $-\text{S}(\text{O})_2-$, or $\#-\text{S}(\text{O})_2-\text{CH}_2-\#$. In some embodiments, L^2 is a bond. In some embodiments, L^2 is $-\text{CH}_2-$. In some embodiments, L^2 is $-\text{S}(\text{O})_2-$. In some embodiments, L^2 is $\#-\text{S}(\text{O})_2-\text{CH}_2-\#$. In some embodiments, the compound is of formula (II). In some embodiments, the compound is of formula (II-a). In some embodiments, the compound is of formula (II-b).



(II)



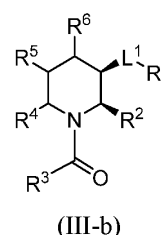
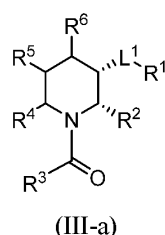
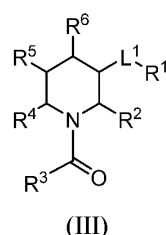
(II-a)



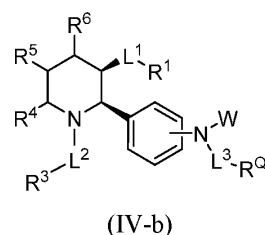
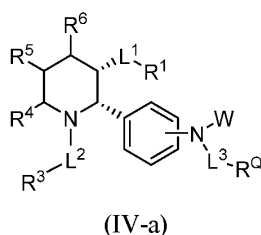
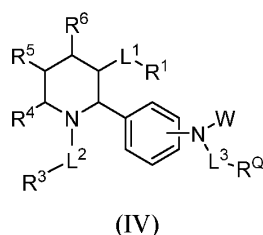
(II-b)

[0053] In some embodiments of a compound of formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, the compound is of formula (III), (III-a), or (III-b), wherein R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are detailed herein for formula (I); and L^1 is a bond, $-\text{C}(\text{O})-$, $^*-\text{CH}_2-\text{NH}-^{**}$, or $^*-\text{C}(\text{O})\text{NH}-\text{CH}_2-^{**}$. In some embodiments, L^1 is a

bond, -C(O)-, or *-C(O)NH-CH₂-*. In some embodiments, L¹ is a bond. In some embodiments, L¹ is -C(O)-. In some embodiments, L¹ is *-CH₂-NH-*. In some embodiments, L¹ is *-C(O)NH-CH₂-*. In some embodiments, the compound is of formula (III). In some embodiments, the compound is of formula (III-a). In some embodiments, the compound is of formula (III-b).

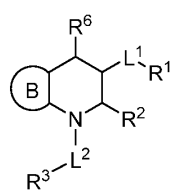


[0054] In some embodiments of a compound of formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, the compound is of formula (IV), (IV-a), or (IV-b), wherein R¹, R³, R⁴, R⁵, R⁶, W, L¹, and L² are detailed herein for formula (I); and R^Q is 5- to 12-membered heteroaryl or C₆₋₁₄ aryl. In some embodiments, the compound is of formula (IV). In some embodiments, the compound is of formula (IV-a). In some embodiments, the compound is of formula (IV-b).

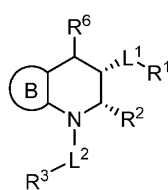


[0055] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, R⁴ and R⁵ are taken together with the carbon atoms to which they are attached to form a ring B which is optionally substituted with one or more R⁸, wherein ring B is C₃₋₁₂ cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, or C₆₋₁₄ aryl. In some embodiments, R⁵ and R⁶ are taken together with the carbon atoms to which they are attached to form a ring B which is optionally substituted with one or more R⁸, wherein ring B is C₃₋₁₂ cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, or C₆₋₁₄ aryl.

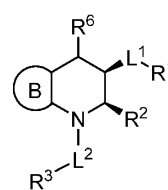
[0056] In some embodiments of a compound of formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, the compound is of formula (V), (V-a), (V-b), (VI), (VI-a), or (VI-b), wherein R^1 , R^2 , R^3 , R^4 , R^6 , L^1 , and L^2 are detailed herein for formula (I). In some embodiments, L^1 is $^*-C(O)NH-^{**}$ and L^2 is $-C(O)-$. In some embodiments, the compound is of formula (V). In some embodiments, the compound is of formula (V-a). In some embodiments, the compound is of formula (V-b). In some embodiments, the compound is of formula (VI). In some embodiments, the compound is of formula (VI-a). In some embodiments, the compound is of formula (VI-b).



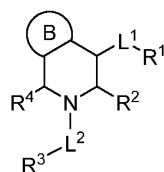
(V)



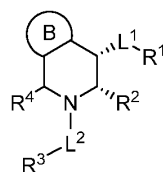
(V-a)



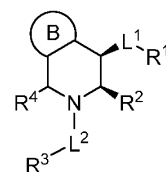
(V-b)



(VI)



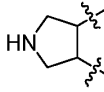
(VI-a)



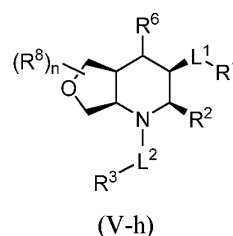
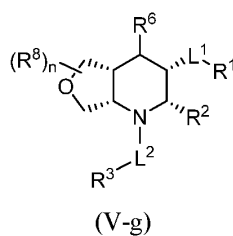
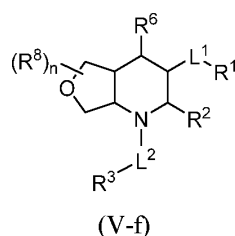
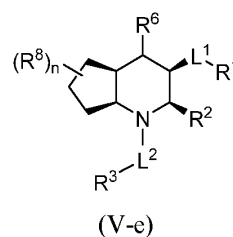
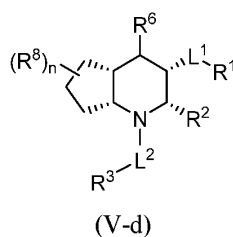
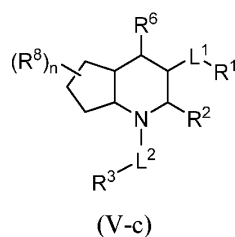
(VI-b)

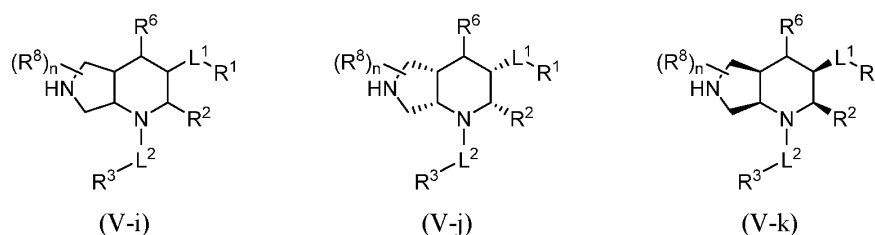
[0057] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, ring B is a C_{3-12} cycloalkyl, which is optionally substituted with one or more R^8 . In some embodiments, ring B is C_{3-6} cycloalkyl, which is optionally substituted with one or more R^8 . In some embodiments, ring B is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is independently optionally substituted with one or more R^8 . In some embodiments, ring B is cyclopentyl, which is optionally substituted with one or more R^8 . In some embodiments, ring B is a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more R^8 . In some embodiments, ring B is a 3- to 6- membered heterocyclyl, which is optionally substituted with one or more R^8 . In some embodiments, ring B is tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, each of which is independently optionally substituted with one or more R^8 . In some embodiments, ring B is tetrahydrofuranyl or pyrrolidinyl, each of which is

independently optionally substituted with one or more R^8 . In some embodiments, ring B is ring B is a C_{3-12} cycloalkyl or 3- to 12- membered heterocyclyl, each of which is optionally substituted with one or more R^8 . In some embodiments, ring B is cyclopentyl, tetrahydrofuranyl, or pyrrolidinyl, each of which is independently optionally substituted with one or more R^8 . In some embodiments, ring B is tetrahydrofuranyl, which is optionally substituted with one or more R^8 . In some embodiments, ring B is pyrrolidinyl, which is

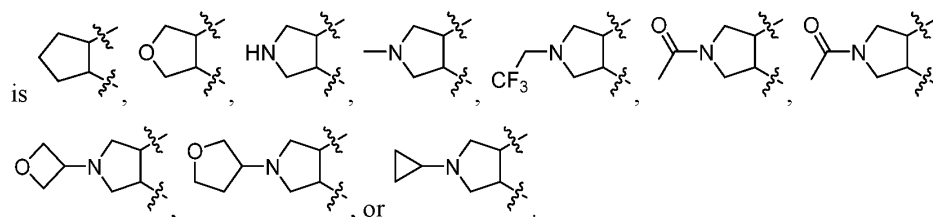
optionally substituted with one or more R^8 . In some embodiments, ring B is , , or , each of which is independently optionally substituted with one or more R^8 .

[0058] In some embodiments of a compound of formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, the compound is of formula (V-c), (V-d), (V-e), (V-f), (V-g), (V-h), (V-i), (V-j), or (V-k), wherein R^1 , R^2 , R^3 , R^6 , R^8 , L^1 , and L^2 are detailed herein for formula (I) and n is 0, 1, 2, or 3. In some embodiments, the compound is of formula (V-c). In some embodiments, the compound is of formula (V-d). In some embodiments, the compound is of formula (V-e). In some embodiments, the compound is of formula (V-f). In some embodiments, the compound is of formula (V-g). In some embodiments, the compound is of formula (V-h). In some embodiments, the compound is of formula (V-i). In some embodiments, the compound is of formula (V-j). In some embodiments, the compound is of formula (V-k).

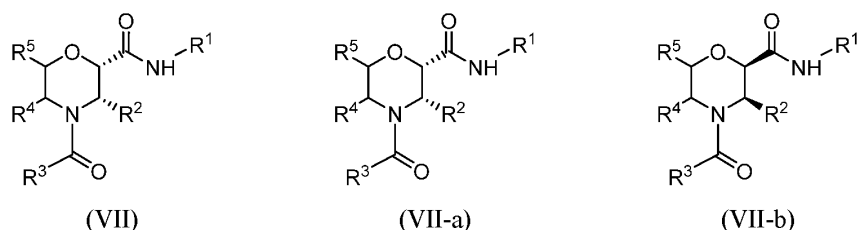




[0059] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, each R^8 is independently C_{1-6} alkyl, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, or $-C(O)R^{8a}$, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and $-CN$. In some embodiments, each R^8 is independently C_{1-6} alkyl, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, or $-C(O)R^{8a}$, each of which is independently optionally substituted with one or more halogen. In some embodiments, ring B



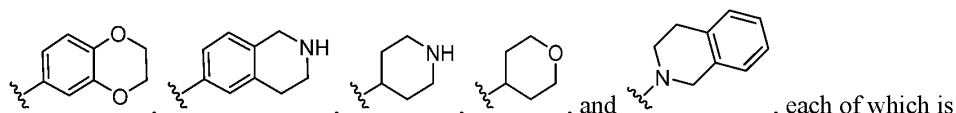
[0060] In some embodiments of a compound of formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, the compound is of formula (VII), (VII-a), or (VII-b), wherein R^1 , R^2 , R^3 , R^4 , and R^5 are detailed herein for formula (I). In some embodiments, the compound is of formula (VII). In some embodiments, the compound is of formula (VII-a). In some embodiments, the compound is of formula (VII-b).



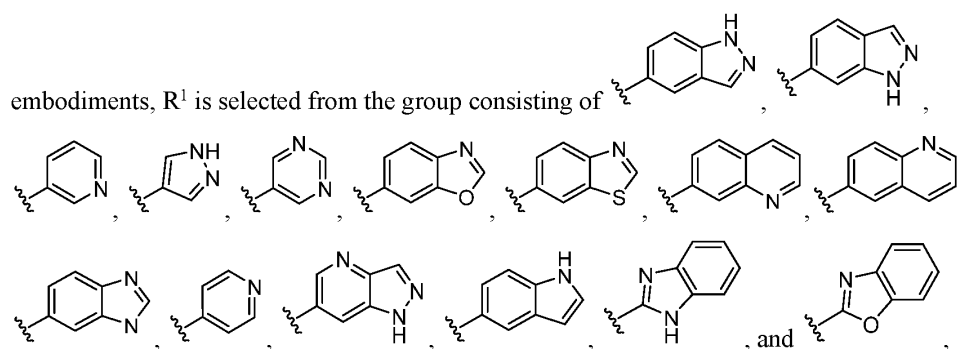
[0061] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, R^4 is taken with the carbon atom to which it is attached, the nitrogen atom

adjacent to the carbon atom, L^2 , and part of R^3 to form a 6- to 8- membered heterocyclyl. In some embodiments, R^4 is taken with the carbon atom to which it is attached, the nitrogen atom adjacent to the carbon atom, L^2 , and part of R^3 to form a 6-membered heterocyclyl. In some embodiments, R^4 is taken with the carbon atom to which it is attached, the nitrogen atom adjacent to the carbon atom, L^2 , and part of R^3 to form a 7-membered heterocyclyl. In some embodiments, R^4 is taken with the carbon atom to which it is attached, the nitrogen atom adjacent to the carbon atom, L^2 , and part of R^3 to form an 8-membered heterocyclyl.

[0062] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is C_{3-12} cycloalkyl, which is optionally substituted with one or more R^{11} . In some embodiments, R^1 is 3- to 12- membered heterocyclyl, which is optionally substituted with one or more R^{11} . In some embodiments, R^1 is selected from the group consisting of

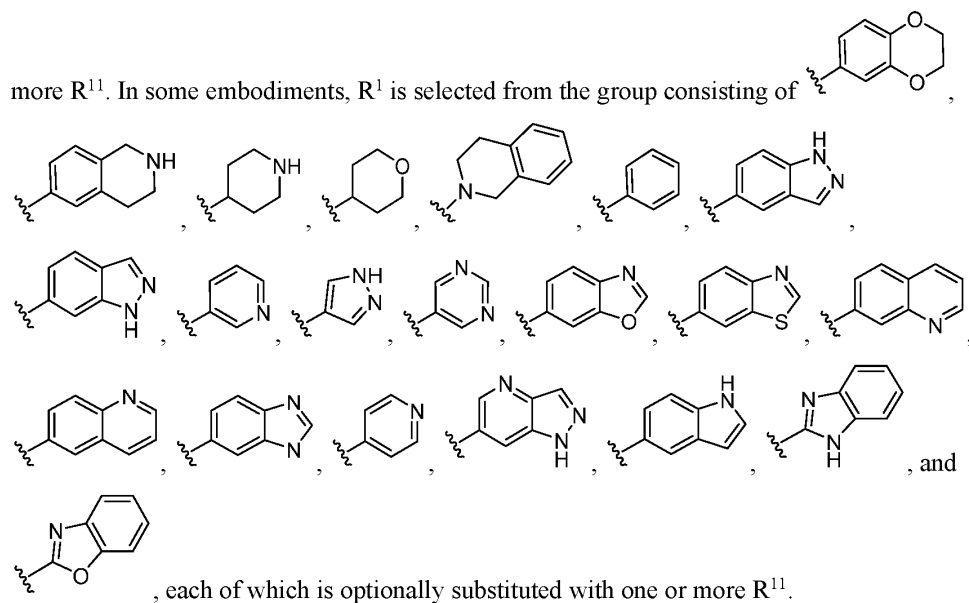


independently optionally substituted with one or more R^{11} . In some embodiments, R^1 is 5- to 12-membered heteroaryl, which is optionally substituted with one or more R^{11} . In some

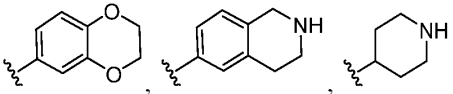
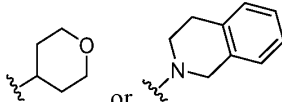
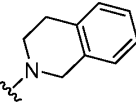


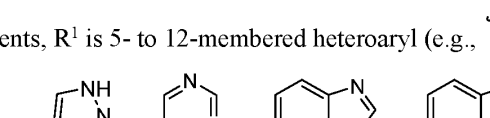
each of which is independently optionally substituted with one or more R^{11} . In some embodiments, R^1 is C_{6-14} aryl, which is optionally substituted with one or more R^{11} . In some embodiments, R^1 is phenyl, which is optionally substituted with one or more R^{11} . In some embodiments, R^1 is $-(C_{1-6}$ alkylene) C_{3-12} cycloalkyl, which is optionally substituted with one or more R^{11} . In some embodiments, R^1 is $-(C_{1-6}$ alkylene) 3- to 12- membered heterocyclyl, which is optionally substituted with one or more R^{11} . In some embodiments, R^1 is $-(C_{1-6}$ alkylene) 5- to 12-membered heteroaryl, which is optionally substituted with one or more R^{11} . In some embodiments, R^1 is $-(C_{1-6}$ alkylene) C_{6-14} aryl, which is optionally substituted

with one or more R^{11} . In some embodiments, R^1 is 3- to 12- membered heterocyclyl, C₆-14 aryl, or 5- to 12-membered heteroaryl, each of which is optionally substituted with one or

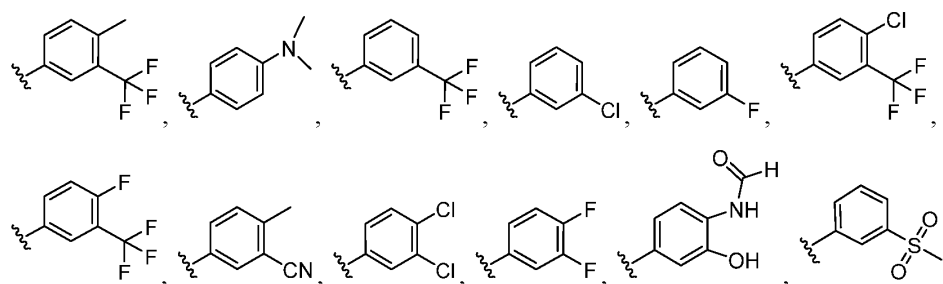


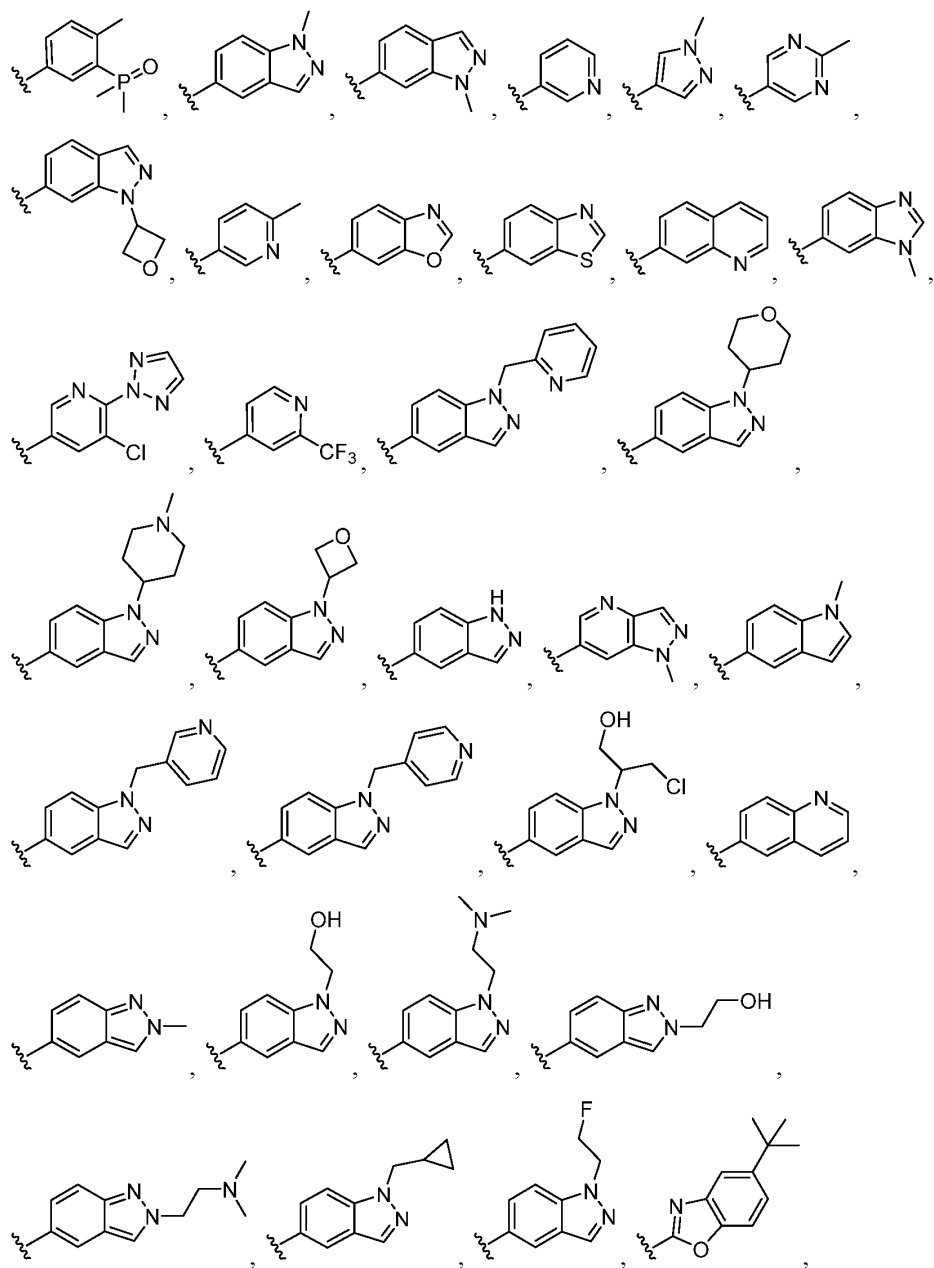
[0063] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, each R^{11} is independently C₁₋₆ alkyl, $-NR^{1a}R^{1b}$, halogen, $-CN$, $-OR^{1a}$, $-NR^{1a}C(O)R^{1b}$, $-S(O)_2R^{1a}$, $-P(O)R^{1a}R^{1b}$, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, $-(C_{1-6} \text{ alkylene})$ 5- to 12-membered heteroaryl, $-(C_{1-6} \text{ alkylene}) NR^{1a}R^{1b}$, or $-(C_{1-6} \text{ alkylene}) C_{3-6}$ cycloalkyl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, hydroxyl, C₁₋₆ alkoxy, and $-CN$. In some embodiments, each R^{11} is independently C₁₋₆ alkyl, $-NR^{1a}R^{1b}$, halogen, $-CN$, $-OR^{1a}$, $-NR^{1a}C(O)R^{1b}$, $-S(O)_2R^{1a}$, or $-P(O)R^{1a}R^{1b}$, each of which is independently optionally substituted with one or more halogen. In some embodiments, each R^{11} is independently C₁₋₆ alkyl, 3- to 12-membered heterocyclyl, halogen, 5- to 12-membered heteroaryl, $-(C_{1-6} \text{ alkylene})$ 5- to 12-membered heteroaryl, $-(C_{1-6} \text{ alkylene}) NR^{1a}R^{1b}$, $-(C_{1-6} \text{ alkylene}) C_{3-6}$ cycloalkyl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of halogen, C₁₋₆ alkyl, and hydroxyl. In some embodiments, each R^{11} is independently C₁₋₆ alkyl or halogen. In some embodiments,

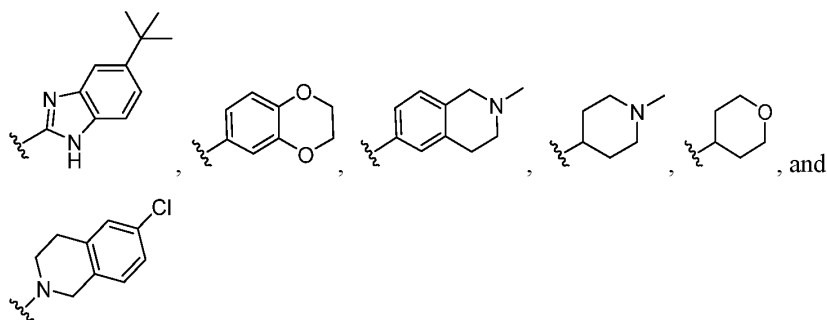
R^1 is 3- to 12-membered heterocyclyl (e.g., , , or ) optionally substituted with one or more R^{11} , wherein each R^{11} is independently C_{1-6} alkyl or halogen. In some embodiments, R^1 is C_{6-14} aryl (e.g., phenyl) optionally substituted with one or more R^{11} , wherein each R^{11} is independently C_{1-6} alkyl, $-NR^{1a}R^{1b}$, halogen, $-CN$, $-OR^{1a}$, $-NR^{1a}C(O)R^{1b}$, $-S(O)_2R^{1a}$, or $-P(O)R^{1a}R^{1b}$, each of which is independently optionally substituted with one or more halogen. In some

embodiments, R¹ is 5- to 12-membered heteroaryl (e.g., , optionally substituted with one or more R¹¹, wherein each R¹¹ is independently C₁₋₆ alkyl, 3- to 12-membered heterocyclyl, halogen, 5- to 12-membered heteroaryl, -(C₁₋₆ alkylene) 5- to 12-membered heteroaryl, -(C₁₋₆ alkylene) NR^{1a}R^{1b}, -(C₁₋₆ alkylene)C₃₋₆ cycloalkyl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of halogen, C₁₋₆ alkyl, and hydroxyl.

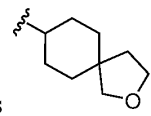
[0064] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, R¹ is selected from the group consisting of:



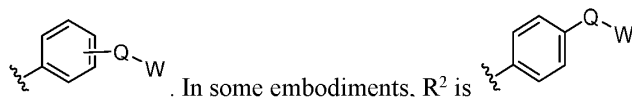




[0065] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{3-12} cycloalkyl, which is independently optionally substituted with one or more $-Q-W$. In some embodiments, R^2 is 3- to 12- membered heterocyclyl, which is



optionally substituted with one or more $-Q-W$. In some embodiments, R^2 is which is optionally substituted with one or more $-Q-W$. In some embodiments, R^2 is C_{6-14} aryl, which is optionally substituted with one or more $-Q-W$. In some embodiments, R^2 is phenyl, which is optionally substituted with one or more $-Q-W$. In some embodiments, R^2 is



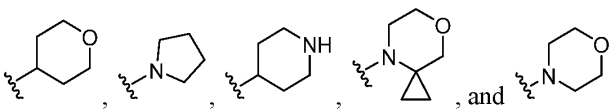
In some embodiments, R^2 is

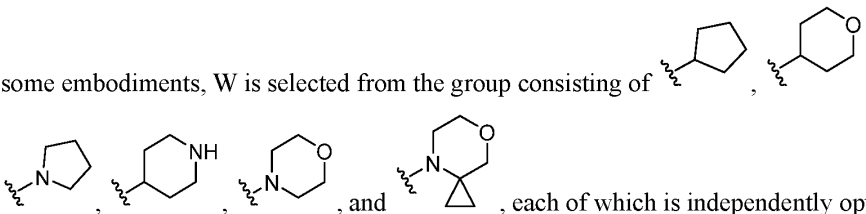
[0066] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, Q is C_{1-6} alkylene. In some embodiments, Q is $-CH_2-$. In some embodiments, Q is $-O-$. In some embodiments, Q is $-(N-L^3-R^Q)-$. In some embodiments, Q is $-NR^Q-$, wherein R^Q is H or C_{1-6} alkyl. In some embodiments, Q is $-NR^Q-$. In some embodiments, Q is $-NR^Q-$, wherein R^Q is H. In some embodiments, Q is $-(N-L^3-R^Q)-$, wherein R^Q is 5- to 12- membered heteroaryl or C_{6-14} aryl.

[0067] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, W is C_{3-12} cycloalkyl, which is independently optionally substituted with one or more R^7 . In some embodiments, W is C_{3-6} cycloalkyl, which is optionally substituted with

one or more R^7 . In some embodiments, W is , which is optionally substituted with

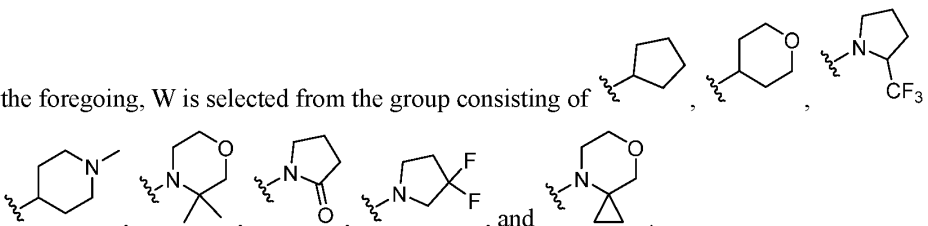
one or more R^7 . In some embodiments, W is 3- to 12- membered heterocyclyl, which is optionally substituted with one or more R^7 . In some embodiments, W is selected from the

group consisting of , each of which is independently optionally substituted with one or more R^7 . In some embodiments, W is 5- to 12-membered heteroaryl, which is optionally substituted with one or more R^7 . In some embodiments, W is C_{6-14} aryl, which is optionally substituted with one or more R^7 . In

some embodiments, W is selected from the group consisting of , each of which is independently optionally substituted with one or more R^7 .

[0068] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, each R^7 is independently oxo, C_{1-6} alkyl, or halogen, wherein the C_{1-6} alkyl is optionally substituted with one or more substituents selected from the group consisting of C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and $-CN$. In some embodiments, each R^7 is independently oxo, C_{1-6} alkyl, or halogen, wherein the C_{1-6} alkyl is optionally substituted with one or more halogen.

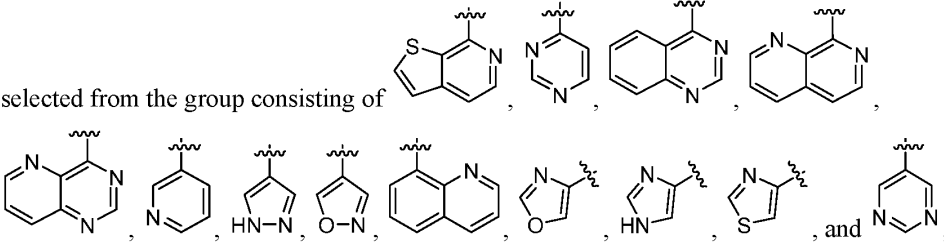
[0069] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of

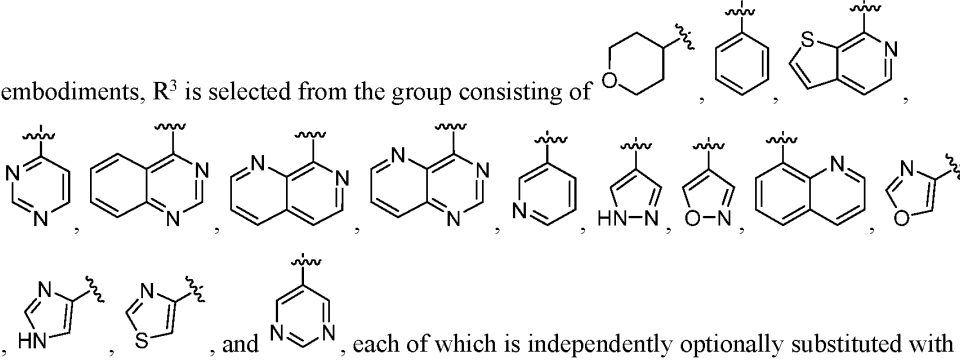
the foregoing, W is selected from the group consisting of .

[0070] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, R^3 is H. In some embodiments, R^3 is 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, each of which is independently optionally substituted

with one or more R^{31} . In some embodiments, R^3 is C_{6-14} aryl, which is optionally substituted with one or more R^{31} . In some embodiments, R^3 is phenyl, which is optionally substituted with one or more R^{31} . In some embodiments, R^3 is 3- to 12- membered heterocyclyl, which is

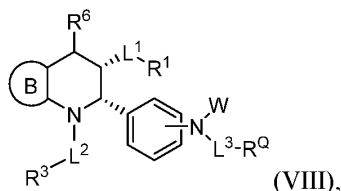
optionally substituted with one or more R^{31} . In some embodiments, R^3 is , which is optionally substituted with one or more R^{31} . In some embodiments, 5- to 12-membered heteroaryl, which is optionally substituted with one or more R^{31} . In some embodiments, R^3 is

selected from the group consisting of , each of which is independently optionally substituted with one or more R^{31} . In some

embodiments, R^3 is selected from the group consisting of , each of which is independently optionally substituted with one or more R^{31} .

[0071] In some embodiments of a compound of formula (I) or any variation thereof where applicable, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, each R^{31} is independently C_{1-6} alkyl, -CN, -NO₂, halogen, -OR^{3a}, -C(O)OR^{3a}, or -S(O)₂R^{3a}, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and -CN. In some embodiments, each R^{31} is independently C_{1-6} alkyl, -CN, -NO₂, halogen, -OR^{3a}, -C(O)OR^{3a}, or -S(O)₂R^{3a}, each of which is independently optionally substituted with one or more halogen. In some embodiments, each R^{31} is independently C_{1-6} alkyl or halogen. In some embodiments, R^3 is C_{6-14} aryl (e.g., phenyl) optionally substituted with one or more R^{31} , wherein each R^{31} is independently C_{1-}

[0073] In some embodiments of a compound of formula (I), or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, the compound is of formula (VIII),



wherein R^1 , R^3 , R^6 , B, W, L^1 , L^2 , L^3 , and R^Q are detailed herein for formula (I). In some embodiments, ring B is a C_{3-12} cycloalkyl, which is optionally substituted with one or more R^8 . In some embodiments, ring B is C_{3-6} cycloalkyl, which is optionally substituted with one or more R^8 . In some embodiments, ring B is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is independently optionally substituted with one or more R^8 . In some embodiments, ring B is cyclopentyl, which is optionally substituted with one or more R^8 . In some embodiments, ring B is a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more R^8 . In some embodiments, ring B is a 3- to 6- membered heterocyclyl, which is optionally substituted with one or more R^8 . In some embodiments, ring B is tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, each of which is independently optionally substituted with one or more R^8 . In some embodiments, ring B is tetrahydrofuranyl or pyrrolidinyl, each of which is independently optionally substituted with one or more R^8 . In some embodiments, ring B is ring B is a C_{3-12} cycloalkyl or 3- to 12- membered heterocyclyl, each of which is optionally substituted with one or more R^8 . In some embodiments, ring B is cyclopentyl, tetrahydrofuranyl, or pyrrolidinyl, each of which is independently optionally substituted with one or more R^8 . In some embodiments, ring B is tetrahydrofuranyl, which is optionally substituted with one or more R^8 . In some embodiments, ring B is pyrrolidinyl, which is

optionally substituted with one or more R^8 . In some embodiments, ring B is , , or , each of which is independently optionally substituted with one or more R^8 .

[0074] It is understood that every description, variation, embodiment or aspect of a moiety may be combined with every description, variation, embodiment or aspect of other moieties the same as if each and every combination of descriptions is specifically and individually listed. For example, every description, variation, embodiment or aspect provided herein with respect to R¹ of formula (I) may be combined with every description, variation, embodiment or aspect of R², R³, R⁴, R⁵, R⁶, L¹, and L² the same as if each and every combination were specifically and individually listed. It is also understood that all descriptions, variations, embodiments or aspects of formula (I), where applicable, apply equally to other formulae detailed herein (e.g., any one of formulae (I-a), (I-b), (II), (II-a)-(II-b), (III), (III-a), (III-b), (IV), (IV-a), (IV-b), (V), (V-a)-(V-k), (VI), (VI-a), (VI-b), (VII), (VII-a), (VII-b)) and (VIII) and are equally described, the same as if each and every description, variation, embodiment or aspect were separately and individually listed for all formulae.

[0075] Exemplary compounds provided by the present disclosure are shown in Table 1. In some embodiments, provided is a compound selected from the compounds in Table 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing. In some embodiments, provided is a compound selected from the compounds in Table 1, or a pharmaceutically acceptable salt thereof.

Table 1

Cmpd #	Name	Cmpd #	Name
1	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(thieno[2,3-c]pyridin-7-yl)piperidine-3-carboxamide	2	(2R,3S)-1-(2-chloropyrimidin-4-yl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
3	(2R,3R)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrimidin-4-yl)piperidine-3-carboxamide	4	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrimidin-4-yl)piperidine-3-carboxamide
5	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(quinazolin-4-yl)piperidine-3-carboxamide	6	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(1,7-naphthyridin-8-yl)piperidine-3-carboxamide
7	(2R,3R)-2-(4-(cyclopentylamino)phenyl)-N-(4-	8	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((3,5-dimethylisoxazol-4-yl)sulfonyl)-

	methyl-3-(trifluoromethyl)phenyl)-1-(pyrido[3,2-d]pyrimidin-4-yl)piperidine-3-carboxamide		N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
9	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2,4-dimethylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	10	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2,5-dimethylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
11	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2,6-dimethylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	12	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((3,5-dimethylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
13	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(mesitylsulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	14	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((2-nitrophenyl)sulfonyl)piperidine-3-carboxamide
15	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((4-fluoro-2-methylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	16	(2R,3S)-1-((3-chloro-2-methylphenyl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
17	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((5-fluoro-2-methylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	18	(2R,3S)-1-((3-fluoro-2-methylphenyl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
19	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2,6-difluorophenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	20	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2,6-dichlorophenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
21	methyl 2-(((2R,3S)-2-(4-(cyclopentylamino)phenyl)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)piperidin-1-yl)sulfonyl)-3-methylbenzoate	22	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(o-tolylsulfonyl)piperidine-3-carboxamide
23	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2-methoxyphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	24	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((2-(trifluoromethoxy)phenyl)sulfonyl)piperidine-3-carboxamide
25	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2-fluorophenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	26	(2R,3S)-1-((2-chlorophenyl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
27	(2R,3S)-1-((2-bromophenyl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-	28	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-

	methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide		1-((2-(trifluoromethyl)phenyl)sulfonyl)piperidine-3-carboxamide
29	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((2-(methylsulfonyl)phenyl)sulfonyl)piperidine-3-carboxamide	30	(2R,3S)-1-((2-cyanophenyl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
31	methyl 2-(((2R,3S)-2-(4-(cyclopentylamino)phenyl)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)piperidin-1-yl)sulfonyl)benzoate	32	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(naphthalen-2-ylsulfonyl)piperidine-3-carboxamide
33	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(naphthalen-1-ylsulfonyl)piperidine-3-carboxamide	34	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(phenylsulfonyl)piperidine-3-carboxamide
35	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyridin-3-ylsulfonyl)piperidine-3-carboxamide	36	(2R,3S)-1-((2-chloropyridin-3-yl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
37	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((perfluorophenyl)sulfonyl)piperidine-3-carboxamide	38	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((1,3,5-trimethyl-1H-pyrazol-4-yl)sulfonyl)piperidine-3-carboxamide
39	(2R,3S,4aS,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide	40	(2R,3S)-1-(benzylsulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
41	cis-4-(4-(cyclopentylamino)phenyl)-7-fluoro-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-1,2,3,4,6,11,12,12a-octahydrobenzo[e]pyrido[1,2-a]azepine-3-carboxamide	42	2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-5-hydroxy-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
43	cis-4-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-1,3,4,6,11,11a-hexahydro-2H-pyrido[1,2-b]isoquinoline-3-carboxamide	44	(3S,4R)-4-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-1,2,3,4,6,11,12,12a-octahydrobenzo[e]pyrido[1,2-a]azepine-3-carboxamide
45	(3R,4S)-4-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-1,2,3,4,6,11,12,12a-	46	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide

	octahydrobenzo[e]pyrido[1,2-a]azepine-3-carboxamide		
47	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	48	(2S,3R,4aS,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
49	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	50	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
51	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-N-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	52	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(tetrahydro-2H-pyran-4-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
53	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methylpiperidin-4-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	54	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazol-4-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
55	cis-N-(3-chlorophenyl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	56	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(3-fluorophenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
57	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(pyridin-3-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	58	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(2-methylpyrimidin-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
59	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(oxetan-3-yl)-1H-indazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	60	cis-N-(4-chloro-3-(trifluoromethyl)phenyl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
61	cis-2-(4-(cyclopentylamino)phenyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	62	cis-N-(3-cyano-4-methylphenyl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
63	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(6-methylpyridin-3-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	64	cis-2-(4-(cyclopentylamino)phenyl)-N-(3,4-dichlorophenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
65	cis-2-(4-(cyclopentylamino)phenyl)-N-(3,4-difluorophenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	66	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
67	cis-N-(benzo[d]oxazol-6-yl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-	68	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-

	6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide		formamido-3-hydroxyphenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
69	cis-N-(benzo[d]thiazol-6-yl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	70	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(3-(methylsulfonyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
71	cis-2-(4-(cyclopentylamino)phenyl)-N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	72	(cis-3-(6-chloro-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-2-(4-(cyclopentylamino)phenyl)octahydro-1H-cyclopenta[b]pyridin-1-yl)(2-fluoro-6-methylphenyl)methanone
73	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(quinolin-7-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	74	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-benzo[d]imidazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
75	cis-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	76	cis-2-(4-(cyclopentylamino)phenyl)-N-(3-(dimethylphosphoryl)-4-methylphenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
77	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	78	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
79	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(2-(trifluoromethyl)pyridin-4-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	80	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(pyridin-2-ylmethyl)-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
81	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(tetrahydro-2H-pyran-4-yl)-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	82	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(1-methylpiperidin-4-yl)-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
83	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(oxetan-3-yl)-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	84	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
85	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	86	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(pyridin-3-ylmethyl)-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
87	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(pyridin-4-ylmethyl)-1H-indazol-5-yl)octahydro-	88	cis-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-2-(4-((tetrahydro-2H-pyran-4-

	1H-cyclopenta[b]pyridine-3-carboxamide		yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
89	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	90	cis-1-(2-fluoro-6-methylbenzoyl)-N-(quinolin-7-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
91	(2S,3R,4aS,7aS)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	92	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(pyridin-2-ylmethyl)-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
93	(2R,3S,4aR,7aR)-N-(1-(1-chloro-3-hydroxypropan-2-yl)-1H-indazol-5-yl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	94	(2R,3S,4aR,7aR)-N-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
95	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(quinolin-6-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	96	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
97	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(2-methyl-2H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	98	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
99	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(oxetan-3-yl)-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	100	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(1-methylpiperidin-4-yl)-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
101	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(pyridin-4-ylmethyl)-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	102	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(2-hydroxyethyl)-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
103	(2R,3S,4aR,7aR)-N-(1-(2-(dimethylamino)ethyl)-1H-indazol-5-yl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	104	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(2-(2-hydroxyethyl)-2H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
105	(2R,3S,4aR,7aR)-N-(2-(2-(dimethylamino)ethyl)-2H-indazol-5-yl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-	106	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(tetrahydro-2H-pyran-4-yl)-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-

	yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide		yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
107	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(pyridin-3-ylmethyl)-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	108	(2R,3S,4aR,7aR)-N-(1-(cyclopropylmethyl)-1H-indazol-5-yl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
109	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(2-fluoroethyl)-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	110	cis-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(oxazole-4-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
111	cis-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(tetrahydro-2H-pyran-4-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	112	cis-2-(4-(cyclopentylamino)phenyl)-1-(1-methyl-1H-pyrazole-4-carbonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
113	cis-2-(4-(cyclopentylamino)phenyl)-1-(1-methyl-1H-imidazole-4-carbonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	114	cis-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(thiazole-4-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
115	cis-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrimidine-5-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	116	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((R)-2-(trifluoromethyl)pyrrolidin-1-yl)methyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
117	cis-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((1-methylpiperidin-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	118	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide
119	(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	120	(2S,3R,4aS,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide
121	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	122	(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-6-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide
123	(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	124	(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-N-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydrofuro[3,4-b]pyridine-3-carboxamide

125	(2S,3R,4aS,7aR)-2-(4-(cyclopentylamino)phenyl)-N-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	126	(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide
127	cis-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazol-4-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	128	cis-1-(2-fluoro-6-methylbenzoyl)-N-(pyridin-3-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide
129	cis-1-(2-fluoro-6-methylbenzoyl)-N-phenyl-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	130	cis-N-(3-(dimethylphosphoryl)-4-methylphenyl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide
131	cis-N-(benzo[d]oxazol-6-yl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	132	cis-N-(3-cyano-4-methylphenyl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide
133	cis-1-(2-fluoro-6-methylbenzoyl)-N-(2-methylpyrimidin-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	134	cis-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide
135	cis-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	136	cis-N-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide
137	(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(2-hydroxyethyl)-1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	138	(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide
139	(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	140	(2S,3R,4aS,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide
141	cis-2-(4-((3,3-dimethylmorpholino)methyl)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	142	(2R,3S,4aR,7aS)-2-(4-((3,3-dimethylmorpholino)methyl)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide
143	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-6-methyl-	144	cis-2-(4-(cyclopentyl(methyl)amino)phenyl)-1-(2-

	N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide		fluoro-6-methylbenzoyl)-6-methyl-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide
145	(2R,3S,4aS,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-(2,2,2-trifluoroethyl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide	146	(2R,3S,4aS,7aS)-6-acetyl-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide
147	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	148	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((2-oxopyrrolidin-1-yl)methyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
149	(2R,3S,4aR,7aR)-2-(4-((3,3-difluoropyrrolidin-1-yl)methyl)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	150	(2R,3S,4aR,7aR)-2-(4-((3,3-dimethylmorpholino)methyl)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
151	(2R,3S,4aR,7aR)-2-(4-((7-oxa-4-azaspiro[2.5]octan-4-yl)methyl)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	152	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-(oxetan-3-yl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide
153	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-6-cyclopropyl-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide	154	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-(tetrahydrofuran-3-yl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide
155	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	156	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-5-hydroxy-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
157	(2S,3R,4aS,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	158	cis-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
159	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	160	((2R,3R)-2-(4-(cyclopentylamino)phenyl)-3-(((4-methyl-3-(trifluoromethyl)phenyl)amino)methyl)piperidin-1-yl)(2-fluoro-6-methylphenyl)methanone
161	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-	162	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-

	(pyrido[3,2-d]pyrimidin-4-yl)piperidine-3-carboxamide		1-(pyrido[3,4-d]pyrimidin-4-yl)piperidine-3-carboxamide
163	benzyl cyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(quinazolin-4-yl)piperidin-2-yl)phenyl)carbamate	164	benzyl cyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(1,7-naphthyridin-8-yl)piperidin-2-yl)phenyl)carbamate
165	benzyl cyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(pyrido[3,4-b]pyrazin-5-yl)piperidin-2-yl)phenyl)carbamate	166	benzyl cyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(pyrido[3,2-d]pyrimidin-4-yl)piperidin-2-yl)phenyl)carbamate
167	benzyl cyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(pyrido[3,4-d]pyrimidin-4-yl)piperidin-2-yl)phenyl)carbamate	168	(2R,3S)-2-(4-(cyclopentyl(1,7-naphthyridin-8-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
169	(2R,3S)-2-(4-(cyclopentyl(thiazolo[4,5-c]pyridin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	170	(2S,3S)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-2-(2-oxaspiro[4.5]decan-8-yl)piperidine-3-carboxamide
171	(2R,3R)-2-(4-(cyclopentyl(1,7-naphthyridin-8-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	172	(2R,3S)-2-(4-(cyclopentyl(pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
173	(2R,3S)-2-(4-(cyclopentyl(thieno[2,3-c]pyridin-7-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	174	(2R,3R)-2-(4-(cyclopentyl(pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
175	(2R,3S)-2-(4-(cyclopentyl(isoquinolin-1-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	176	(2R,3S)-2-(4-(cyclopentyl(pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
177	(2R,3S)-2-(4-(cyclopentyl(quinazolin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	178	(2R,3S)-2-(4-(cyclopentyl(pyrido[3,4-d]pyrimidin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
179	(2R,3S)-2-(4-(cyclopentyl(phthalazin-1-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	180	((2R,3S)-3-(6-(tert-butyl)-1H-benzo[d]imidazol-2-yl)-2-(4-(cyclopentylamino)phenyl)piperidin-1-yl)(2-fluoro-6-methylphenyl)methanone
181	((2R,3S)-3-(5-(tert-butyl)benzo[d]oxazol-2-yl)-2-(4-(cyclopentylamino)phenyl)piperidin-1-yl)(2-fluoro-6-methylphenyl)methanone	182	((2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-

			cyclopenta[b]pyridin-3-yl)(6-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone
183	(2R,3S,4aR,7aR)-2-(4-(cyclopentyl(methyl)amino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	184	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1,2,3,4-tetrahydroisoquinolin-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
185	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)benzyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	186	tert-butyl 6-((2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamido)-3,4-dihydroisoquinoline-2(1H)-carboxylate
187	cis-3-(4-(cyclopentylamino)phenyl)-4-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)morpholine-2-carboxamide	188	(2R,3S)-2-(4-(N-cyclopentyl-2-fluoro-6-methylbenzamido)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
188	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(quinoline-8-carbonyl)piperidine-3-carboxamide	189	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide
190	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(3,5-dimethylisoxazole-4-carbonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	200	(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
201	cis-2-(4-(cyclopentyl(methyl)amino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	202	tert-butyl 6-cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamido)-3,4-dihydroisoquinoline-2(1H)-carboxylate
203	cis-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-2-(2-oxaspiro[4.5]decan-8-yl)piperidine-3-carboxamide	204	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-5-hydroxy-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide
205	cis-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-(((R)-2-(trifluoromethyl)pyrrolidin-1-yl)methyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	206	cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-(2,2,2-trifluoroethyl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide

[0076] Also provided are salts of compounds disclosed herein, such as pharmaceutically acceptable salts. The present disclosure also includes any or all of the stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of the compounds described. Thus, if a particular stereochemical form, such as a specific enantiomeric form or diastereomeric form, is depicted for a given compound, then it is understood that any or all stereochemical forms, including any enantiomeric or diastereomeric forms, and any tautomers or other forms of any of that same compound are herein described. Where tautomeric forms may be present for any of the compounds described herein, each and every tautomeric form is intended even though only one or some of the tautomeric forms may be explicitly depicted. The tautomeric forms specifically depicted may or may not be the predominant forms in solution or when used according to the methods described herein.

[0077] The disclosure also intends isotopically-labeled and/or isotopically-enriched forms of compounds described herein. The compounds herein may contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. In some embodiments, the compound is isotopically-labeled, such as an isotopically-labeled compound of the formula (I) or variations thereof described herein, where a fraction of one or more atoms are replaced by an isotope of the same element. Exemplary isotopes that can be incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{13}N , ^{15}O , ^{17}O , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl . Certain isotope labeled compounds (e.g. ^3H and ^{14}C) are useful in compound or substrate tissue distribution studies. Incorporation of heavier isotopes such as deuterium (^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life, or reduced dosage requirements and, hence may be preferred in some instances. Isotopically-labeled compounds described herein can generally be prepared by standard methods and techniques known to those skilled in the art or by procedures similar to those described in the accompanying Examples substituting appropriate isotopically-labeled reagents in place of the corresponding non-labeled reagent.

[0078] Solvates of a compound provided herein or a salt thereof are also contemplated. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent and are often formed during the process of crystallization. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol.

[0079] A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form. Unless otherwise stated, “substantially pure” intends a composition that contains no more than 35% impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a salt thereof. In some embodiments, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains no more than 25%, 20%, 15%, 10%, or 5% impurity. In some embodiments, a composition of substantially pure compound or a salt thereof is provided wherein the composition contains or no more than 3%, 2%, 1% or 0.5% impurity.

Compositions

[0080] In another aspect, provided herein is a pharmaceutical composition comprising a compound disclosed herein, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient. In some embodiments, the pharmaceutical composition is administered in any suitable form and by any suitable route, such as by enteral administration (e.g., oral administration, sublingual administration, or rectal administration) or parenteral administration (e.g., intravenous injection, intramuscular injection, subcutaneous injection, intravenous infusion, or inhalation/insufflation).

[0081] In certain embodiments, pharmaceutical compositions are formulated in any manner, including using one or more physiologically acceptable carriers comprising excipients and/or auxiliaries which facilitate processing of the active compounds into pharmaceutical compositions. In some embodiments, proper formulation is dependent upon the route of administration chosen. In various embodiments, any techniques, carriers and excipients are used as suitable.

[0082] In some embodiments, a compound or composition disclosed herein is administered by enteral administration. Exemplary routes of enteral administration include, without limitation, oral administration, sublingual administration, and rectal administration (e.g., through the rectum). In some embodiments, the enteral administration comprises oral administration. In some embodiments, the enteral administration comprises sublingual

administration. In some embodiments, the enteral administration comprises rectal administration.

[0083] In some embodiments, a compound or composition disclosed herein is administered by parenteral administration. Exemplary routes of parenteral administration include, without limitation, intravenous injection, intramuscular injection, subcutaneous injection, intravenous infusion, and inhalation/insufflation. In some embodiments, the parenteral administration comprises intravenous injection. In some embodiments, the parenteral administration comprises intramuscular injection. In some embodiments, the parenteral administration comprises subcutaneous injection. In some embodiments, the parenteral administration comprises intravenous infusion. In some embodiments, the parenteral administration comprises inhalation/insufflation.

[0084] In some embodiments, a compound or composition disclosed herein is administered by inhalation or insufflation. Exemplary types of preparations for inhalation and/or insufflation include, without limitation, sprays, aerosols, mists, capsules, powders, or cartridges for use in an inhaler or insufflator and solutions/suspensions for nebulization.

Methods of Use

[0085] In another aspect, provided is a method of inhibit the binding of C5a receptor ligand (e.g., C5a) to C5a receptor *in vitro* or *in vivo*, the method comprising contacting a C5a receptor with an effective amount of the compound or composition disclosed herein. In some embodiments, the binding of C5a receptor ligand (e.g., C5a) to C5a receptor is inhibited by at least about 99%, at least about 98%, at least about 97%, at least about 96%, at least about 95%, at least about 90%, at least about 80%, at least about 70%, at least about 60%, at least about 50%, at least about 40%, at least about 30%, or at least about 20%. In some embodiments, provided is a method of inhibit the binding receptor *in vitro* or *in vivo*, the method comprising contacting a C5a receptor with an effective amount of the compound or composition disclosed herein.

[0086] The compound or salt thereof described herein can be used in combination with other treatment modalities, such as anti-inflammatory therapies. Examples of anti-inflammatory therapies that can be used in combination with the methods of the invention include, for example, therapies that employ steroidal drugs, as well as therapies that employ non-steroidal drugs.

[0087] In another aspect, provided is a method of treating a disorder mediated by C5a in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound or composition disclosed herein to the subject. In some embodiments, the disorder is an inflammatory disease, a cardiovascular or cerebrovascular disease, or an autoimmune disease.

[0088] In some embodiments, the disorder is an autoimmune disorder. Examples of autoimmune disorders include, but are not limited to, Rheumatoid arthritis, systemic lupus erythematosus, Guillain-Barre syndrome, pancreatitis, lupus nephritis, lupus glomerulonephritis, psoriasis, Crohn's disease, vasculitis, irritable bowel syndrome, dermatomyositis, multiple sclerosis, bronchial asthma, pemphigus, pemphigoid, scleroderma, myasthenia gravis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage), immunovascularitis, tissue graft rejection, and hyperacute rejection of transplanted organs.

[0089] In some embodiments, the disorder is an inflammatory disorder or a related condition. Examples of inflammatory disorders and related conditions include, but are not limited to, Neutropenia, sepsis, septic shock, Alzheimer's disease, multiple sclerosis, stroke, inflammatory bowel disease (IBD), inflammation associated with severe burns, lung injury, and ischemia-reperfusion injury, osteoarthritis, as well as acute (adult) respiratory distress syndrome (ARDS), chronic pulmonary obstructive disorder (COPD), systemic inflammatory response syndrome (SIRS), atopic dermatitis, psoriasis, chronic urticaria and multiple organ dysfunction syndrome (MODS). Also included are pathologic sequellae associated with insulin-dependent diabetes mellitus (including diabetic retinopathy), lupus nephropathy, Heyman nephritis, membranous nephritis and other forms of glomerulonephritis, contact sensitivity responses, and inflammation resulting from contact of blood with artificial surfaces that can cause complement activation, as occurs, for example, during extracorporeal circulation of blood (e.g., during hemodialysis or via a heart-lung machine, for example, in association with vascular surgery such as coronary artery bypass grafting or heart valve replacement), or in association with contact with other artificial vessel or container surfaces (e.g., ventricular assist devices, artificial heart machines, transfusion tubing, blood storage bags, plasmapheresis, plateletpheresis, and the like).

[0090] In some embodiments, the disorder is a disorder related to ischemia/reperfusion injury. Examples of disorders related to ischemia/reperfusion injury include, but are not

limited to, those resulting from transplants, including solid organ transplant, and syndromes such as ischemic reperfusion injury, ischemic colitis and cardiac ischemia.

[0091] In some embodiments, the disorder is age-related macular degeneration.

[0092] In some embodiments, the disorder is a cardiovascular or cerebrovascular disorder. Examples of cardiovascular or cerebrovascular disorders include, but are not limited to, myocardial infarction, coronary thrombosis, vascular occlusion, post-surgical vascular reocclusion, atherosclerosis, traumatic central nervous system injury, and ischemic heart disease. In one embodiment, an effective amount of a compound of the invention may be administered to a patient at risk for myocardial infarction or thrombosis (i.e., a patient who has one or more recognized risk factor for myocardial infarction or thrombosis, such as, but not limited to, obesity, smoking, high blood pressure, hypercholesterolemia, previous or genetic history of myocardial infarction or thrombosis) in order to reduce the risk of myocardial infarction or thrombosis.

[0093] In some embodiments, the disorder is a vasculitic disease. Examples of vasculitic diseases include, but are not limited to, Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, Henoch-Schönlein purpura, polyarteritis nodosa, Rapidly Progressive Glomerulonephritis (RPGN), cryoglobulinaemia, giant cell arteritis (GCA), Behcet's disease and Takayasu's arteritis (TAK).

[0094] In some embodiments, the disorder is selected from: macular degeneration (MD), age-related macular degeneration (AMD), ischemia reperfusion injury, arthritis, rheumatoid arthritis, lupus, ulcerative colitis, stroke, post-surgery systemic inflammatory syndrome, asthma, allergic asthma, chronic obstructive pulmonary disease (COPD), paroxysmal nocturnal hemoglobinuria (PNH) syndrome, autoimmune hemolytic anemia (AIHA), Gaucher disease, myasthenia gravis, neuromyelitis optica (NMO), multiple sclerosis, delayed graft function, antibody-mediated rejection, atypical hemolytic uremic syndrome (aHUS), central retinal vein occlusion (CRVO), central retinal artery occlusion (CRAO), epidermolysis bullosa, sepsis, septic shock, organ transplantation, inflammation (including, but not limited to, inflammation associated with cardiopulmonary bypass surgery and kidney dialysis), C3 glomerulopathy, membranous nephropathy, IgA nephropathy, glomerulonephritis (including, but not limited to, anti-neutrophil cytoplasmic antibody (ANCA)-mediated glomerulonephritis, lupus nephritis, and combinations thereof), ANCA-mediated vasculitis, Shiga toxin induced HUS, and antiphospholipid antibody-induced

pregnancy loss, graft versus host disease (GVHD), bullous pemphigoid, hidradenitis suppurativa, dermatitis herpetiformis, sweets syndrome, pyoderma gangrenosum, palmo-plantar pustulosis & pustular psoriasis, rheumatoid neutrophilic dermatoses, subcorneal pustular dermatosis, bowel-associated dermatosis-arthritis syndrome, neutrophilic eccrine hidradenitis, linear IgA disease, or any combinations thereof.

[0095] In some embodiments, the disorder is HIV infection or AIDS.

[0096] In some embodiments, the compounds or salts thereof reduce neutropenia induced by human C5a in a subject. In some embodiments, the compounds or salts thereof reduce neutropenia induced by human C5a in a subject by reducing at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the neutrophil cell counts. In some embodiments, the subject is a human C5aR knock-in mice. In some embodiments, the subject is a cyno monkey. In some embodiments, the subject is a human. In some embodiments, the human C5a induced neutropenia is induced by intravitreal injection of human C5a. In some embodiments, the human C5a induced neutropenia is induced by oral dosing of human C5a.

[0097] In some embodiments, the compounds or salts thereof block human C5a induced CD11b upregulation on immune cells. In some embodiments, the immune cell is a granulocyte. In some embodiments, the immune cell is a neutrophil. In some embodiments, the compounds or salts thereof reduce CD11b upregulation induced by human C5a in a subject by reducing at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the CD11b expressed by granulocytes. In some embodiments, the compounds or salts thereof reduce CD11b upregulation induced by human C5a in a subject by reducing at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the CD11b expressed by neutrophils. In some embodiments, the subject is a human C5aR knock-in mice. In some embodiments, the subject is a cyno monkey. In some embodiments, the subject is a human. In some embodiments, the human C5a induced upregulation of CD11b is induced by intravitreal injection of human C5a. In some embodiments, the human C5a induced CD11b upregulation is induced by oral dosing of human C5a.

Dosing

[0098] Dosages and desired drug concentrations of pharmaceutical compositions of the present application may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary artisan. Animal experiments provide reliable guidance for the determination of effective

doses for human therapy. Interspecies scaling of effective doses can be performed following the principles laid down by Mordenti, J. and Chappell, W. "The Use of Interspecies Scaling in Toxicokinetics," In Toxicokinetics and New Drug Development, Yacobi et al., Eds, Pergamon Press, New York 1989, pp. 42-46.

[0099] Typically, dosages which may be administered in a method of the invention to a subject, in some embodiments a human, range in amount from 0.5 ng to about 50 mg per kilogram of body weight of the subject. While the precise dosage administered will vary depending upon any number of factors, including but not limited to, the type of subject and type of disease state being treated, the age of the subject and the route of administration. In some embodiments, the dosage of the compound will vary from about 1 µg to about 10 mg per kilogram of body weight of the subject. In other embodiments, the dosage will vary from about 3 µg to about 1 mg per kilogram of body weight of the subject.

[0100] A compound or composition disclosed herein may be administered to an individual in accordance with an effective dosing regimen for a desired period of time or duration, such as at least about one month, at least about 2 months, at least about 3 months, at least about 6 months, or at least about 12 months or longer, which in some variations may be for the duration of the individual's life. In one variation, the compound is administered on a daily or intermittent schedule. The compound can be administered to an individual continuously (for example, at least once daily) over a period of time. The dosing frequency can also be less than once daily, e.g., about a once weekly dosing. The dosing frequency can be more than once daily, e.g., twice or three times daily. The dosing frequency can also be intermittent, including a 'drug holiday' (e.g., once daily dosing for 7 days followed by no doses for 7 days, repeated for any 14 day time period, such as about 2 months, about 4 months, about 6 months or more). In some embodiments of a method disclosed herein, a compound or composition disclosed herein is administered four times a day, three times a day, twice a day, or once a day.

Articles of Manufacture and Kits

[0101] In another aspect, provided is an article of manufacture comprising a compound described herein or a composition described herein in suitable packaging. In some embodiments, the article of manufacture is for use in any of the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules,

bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

[0102] In another aspect, provided is a kit comprising a compound described herein or a composition described herein. The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for the treatment of any disorder disclosed herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

EXAMPLES

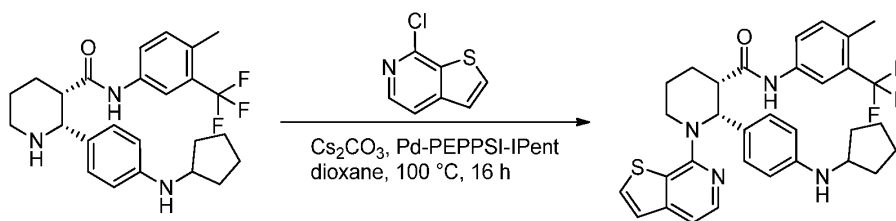
[0103] It is understood that the present disclosure has been made only by way of example, and that numerous changes in the combination and arrangement of parts can be resorted to by those skilled in the art without departing from the spirit and scope of the present disclosure.

[0104] Compounds of formula (I) or any sub-formula described herein can be synthesized using standard synthetic techniques known to those of skill in the art. For example, the synthesis of non-exemplified compounds according to the present disclosure can be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, or by making routine modifications of reaction conditions, reagents, and starting materials. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the present disclosure.

[0105] Where it is desired to obtain a particular enantiomer of a compound, this may be accomplished from a corresponding mixture of enantiomers using any suitable conventional procedure for separating or resolving enantiomers. Thus, for example, diastereomeric derivatives may be produced by reaction of a mixture of enantiomers, e.g. a racemate and an appropriate chiral compound. The diastereomers may then be separated by any convenient means, for example by crystallization and the desired enantiomer recovered. In another resolution process, a racemate may be separated using chiral High-Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described.

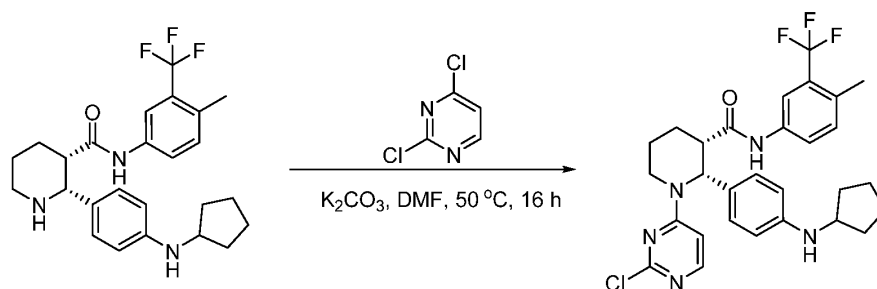
Synthetic Examples

Example S1: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoro-methyl)phenyl)-1-(thieno[2,3-c]pyridin-7-yl)piperidine-3-carboxamide (Compound No. 1)



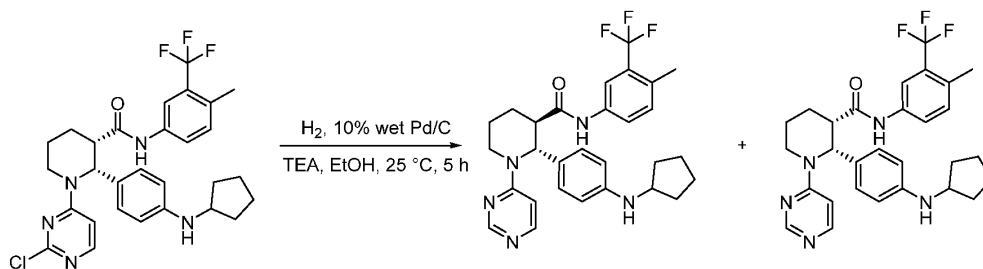
[0106] To a mixture of (2R,3S)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (50 mg, 95.39 μmol), 7-chloro-5-thienopyridine (32.36 mg, 190.79 μmol) and Cs_2CO_3 (93.24 mg, 286.18 μmol) in dioxane (1 mL) was added Pd-PEPPSI-IPent (7.57 mg, 9.54 μmol). The mixture was charged with N_2 , and then stirred at 100 °C for 16 h. The mixture combined with previous batches (38.16 μmol and 95.39 μmol) was filtered through a pad of Celite and rinsed with EtOAc (20 mL). The filtrate was concentrated to give the crude product (250 mg) as brown oil. The crude product was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% Dichloromethane: Methanol gradient @25 mL/min) to give a crude product (70 mg), which was further purified by prep-HPLC (column: Xtimate C18 10 μ 250 mm x50mm; mobile phase: [water(0.04% $\text{NH}_3\text{H}_2\text{O}$ +10mM NH_4HCO_3)-ACN]; B%: 70%-100%, 8min) to give the crude. The crude product was purified again by prep-TLC (Dichloromethane : Methanol = 10:1) to give (2R,3S)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-1-thieno[2,3-c]pyridin-7-yl-piperidine-3-carboxamide (5 mg, 7.95 μmol , 8.33% yield, 92% purity) as an off-white solid. ^1H NMR (400 MHz, CDCl_3) δ 1.23 - 1.48 (m, 6 H), 1.66 - 1.77 (m, 6 H), 1.87 - 2.04 (m, 4 H), 2.30 - 2.47 (m, 6 H), 3.27 (br d, $J=4.0$ Hz, 1 H), 3.58 - 3.76 (m, 3 H), 3.98 - 4.05 (m, 1 H), 6.07 (br s, 1 H), 6.49 (d, $J=8.5$ Hz, 2 H), 7.10 (d, $J=8.5$ Hz, 2 H), 7.20 (d, $J=8.5$ Hz, 1 H), 7.25 (s, 1 H), 7.30 - 7.41 (m, 2 H), 7.66 (d, $J=5.5$ Hz, 2 H), 7.80 (br d, $J=7.8$ Hz, 1 H), 8.13 (d, $J=5.5$ Hz, 1 H), 10.14 (br s, 1 H). LC-MS: (ES) m/z 579.2 ($\text{M}+\text{H}^+$).

Example S2: Synthesis of (2R,3S)-1-(2-chloropyrimidin-4-yl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 2)



[0107] A mixture of (2R,3S)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (300 mg, 572.37 μ mol), 2,4-dichloropyrimidine (170.54 mg, 1.14 mmol) and K_2CO_3 (237.32 mg, 1.72 mmol) in DMF (3 mL) was stirred at 50 °C for 16 h. The combined organic layers were washed with brine (15 mL x 4), dried over anhydrous Na_2SO_4 , filtered and concentrated to give the crude product (450 mg) as a brown gum. The crude product was diluted with MeCN (2.5 mL), filtered, and sent to be purified by prep-HPLC (column: Xtimate C18 10 μ 250 mm x 50mm; mobile phase: [water (0.04% NH_3H_2O +10mM NH_4HCO_3)-ACN]; B%: 70%-100%, 8 min). Compound (2R,3S)-1-(2-chloropyrimidin-4-yl)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (150 mg, 255.36 μ mol, 44.61% yield, 95% purity) was obtained as an off-white solid. 1H NMR (400 MHz, $CDCl_3$) δ 1.35 - 1.47 (m, 2 H), 1.53 - 1.75 (m, 8 H), 1.91 - 2.34 (m, 6 H), 2.42 (d, J =1.5 Hz, 3 H), 2.97 - 3.08 (m, 1 H), 3.21 - 3.34 (m, 1 H), 3.71 (quin, J =6.1 Hz, 1 H), 4.08 (br s, 1 H), 6.08 (br s, 1 H), 6.39 - 6.53 (m, 3 H), 7.09 - 7.23 (m, 3 H), 7.51 (dd, J =8.3, 2.0 Hz, 1 H), 7.58 (s, 1 H), 7.88 (br s, 1 H), 8.03 (d, J =6.0 Hz, 1 H). LC-MS: (ES) m/z 558.2 ($M+H^+$).

Example S3: Synthesis of (2R,3R)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrimidin-4-yl)piperidine-3-carboxamide and (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrimidin-4-yl)piperidine-3-carboxamide (Compound Nos. 3 and 4)

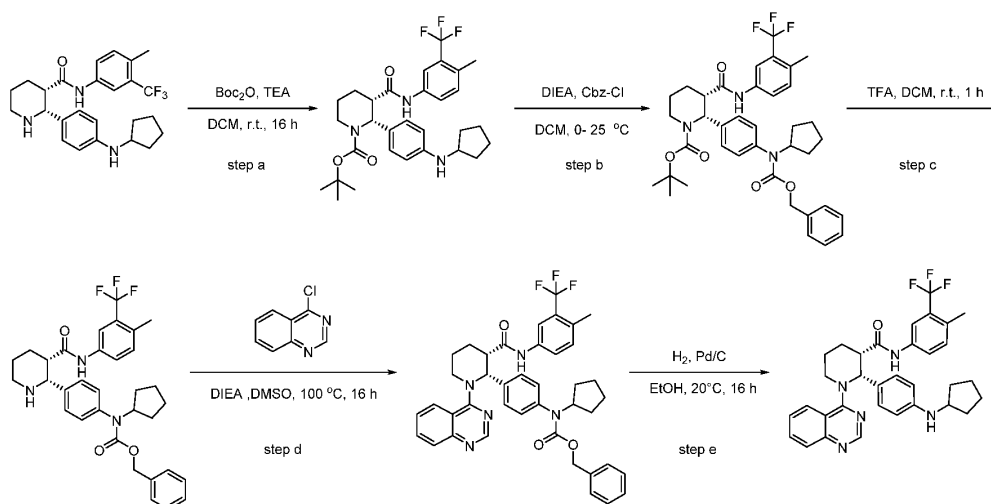


[0108] To a mixture of (2R,3S)-1-(2-chloropyrimidin-4-yl)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (150 mg, 268.80 μmol) and TEA (27.20 mg, 268.80 μmol , 37.41 μL) in EtOH (15 mL) was added Pd/C (10% wet basis) (60 mg, 10% purity) under Ar atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was filtered through a pad of celite, and the filtrate was concentrated to give the crude product (150 mg) as a gray gum. The crude product combined with the previous batch (50 mg, 89.6 μmol) was diluted with MeOH (3 mL), filtered, and sent to be purified by prep-HPLC. The product (100 mg) as a white solid was obtained from purification of prep-HPLC (column: Xtimate C18 10 μ 250 mm x50mm; mobile phase: [water(0.04% $\text{NH}_3\text{H}_2\text{O}$ +10mM NH_4HCO_3)-ACN];B%: 65%-95%, 8 min). Then the solid was further purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give two compounds.

(2R,3R)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-1-pyrimidin-4-yl-piperidine-3-carboxamide (5 mg, 9.55 μmol , 3.55% yield, 100% purity) was isolated as a gray solid. ^1H NMR (400 MHz, CDCl_3) δ 0.79 - 1.06 (m, 1 H), 0.79 - 1.06 (m, 1 H), 0.79 - 1.06 (m, 2 H), 1.18 - 1.35 (m, 3 H), 1.39 - 1.50 (m, 2 H), 1.64 - 1.82 (m, 6 H), 1.94 - 2.08 (m, 3 H), 2.32 (br dd, J =13.8, 4.3 Hz, 1 H), 2.42 (s, 3 H), 3.21 (td, J =12.7, 4.3 Hz, 1 H), 3.33 (br d, J =3.5 Hz, 1 H), 3.71 - 3.81 (m, 1 H), 4.05 (br d, J =9.8 Hz, 1 H), 6.35 (br s, 1 H), 6.53 - 6.63 (m, 3 H), 6.95 (d, J =8.5 Hz, 2 H), 7.20 (d, J =8.3 Hz, 1 H), 7.55 (br d, J =8.3 Hz, 1 H), 7.72 (s, 1 H), 8.26 (d, J =6.3 Hz, 1 H), 8.66 - 8.77 (m, 2 H). LC-MS: (ES) m/z 524.3 ($\text{M}+\text{H}^+$).

(2R,3S)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-1-pyrimidin-4-yl-piperidine-3-carboxamide (40 mg, 76.40 μmol , 28.42% yield, 100% purity) was obtained as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 1.43 (br d, J =4.8 Hz, 2 H), 1.54 - 1.73 (m, 6 H), 1.92 - 2.02 (m, 3 H), 2.11 (br d, J =10.0 Hz, 1 H), 2.26 (qd, J =13.0, 4.5 Hz, 1 H), 2.42 (d, J =1.3 Hz, 3 H), 3.00 (dt, J =12.9, 4.5 Hz, 1 H), 3.22 (td, J =13.4, 3.4 Hz, 1 H), 3.71 (quin, J =6.1 Hz, 1 H), 4.01 (br d, J =13.6 Hz, 1 H), 6.27 (br s, 1 H), 6.44 - 6.57 (m, 3 H), 7.10 - 7.24 (m, 3 H), 7.51 - 7.66 (m, 2 H), 8.03 (br s, 1 H), 8.19 (d, J =6.3 Hz, 1 H), 8.64 (s, 1 H). LC-MS: (ES) m/z 524.3 ($\text{M}+\text{H}^+$).

Example S4: Synthesis of benzyl cyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(quinazolin-4-yl)piperidin-2-yl)phenyl)carbamate (Compound No. 5)



[0109] Step a) To a mixture of (2R,3S)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (5 g, 9.54 mmol) and tert-butoxycarbonyl tert-butyl carbonate (2.08 g, 9.54 mmol, 2.19 mL) in DCM (50 mL) was added TEA (1.93 g, 19.08 mmol, 2.66 mL). The solution was stirred at 25 °C for 16 h. The reaction mixture was added to 30 mL of H₂O and extracted with DCM (50 mL x 2). The combined organic layers were washed with brine (50 mL), dried with anhydrous Na₂SO₄ and filtered. The filtrate was evaporated under vacuum to give crude product. The crude product was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/0 to 3:1) to give tert-butyl (2R,3S)-2-[4-(cyclopentyl amino)phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (4.2 g, 7.70 mmol, 80.69% yield) as a pale yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 1.22 - 1.52 (14 H, m) 1.53 - 1.66 (2 H, m) 1.67 - 1.87 (4 H, m) 1.89 - 2.02 (1 H, m) 2.32 (3 H, br d, *J*=1.22 Hz) 2.77 - 3.00 (2 H, m) 3.56 (1 H, t, *J*=6.16 Hz) 3.83 (1 H, br d, *J*=11.00 Hz) 5.28 - 5.76 (2 H, m) 6.35 (2 H, d, *J*=8.80 Hz) 6.96 (2 H, br d, *J*=8.31 Hz) 7.28 (1 H, d, *J*=8.31 Hz) 7.54 (1 H, br s) 7.81 (1 H, br s) 10.17 (1 H, br s). LC-MS: (ES) *m/z* 546.3 (M+H⁺).

[0110] Step b) To a mixture of tert-butyl (2R,3S)-2-[4-(cyclopentylamino)phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (2 g, 3.30 mmol) and DIEA (1.28 g, 9.90 mmol, 1.72 mL) in DCM (20 mL) was added CbzCl (1.13 g, 6.60 mmol, 937.95 μL) at 0 °C. Then the mixture was stirred at 25 °C for 12 h. The previous reaction mixture (100 mg batch) was combined with this batch. The combined mixture was quenched by addition of H₂O (20 mL) and extracted with DCM (30 mL). The organic phase separated

was concentrated in vacuo to give the crude product. The crude product was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min). The desired compound tert-butyl (2R,3S)-2-[4-[benzyloxycarbonyl (cyclopentyl)amino]phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (1.9 g, 100% purity) was obtained as white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.27 - 1.55 (m, 15 H), 1.56 - 1.72 (m, 1 H), 1.75 - 2.01 (m, 4 H), 2.05 - 2.21 (m, 1 H), 2.38 (d, *J*=1.51 Hz, 3 H), 3.06 (ddd, *J*=12.99, 6.21, 3.89 Hz, 1 H), 3.18 (br s, 1 H), 4.04 (br dd, *J*=13.68, 3.39 Hz, 1 H), 4.40 - 4.54 (m, 1 H), 4.99 - 5.06 (m, 2 H), 5.70 (br s, 1 H), 7.05 (d, *J*=8.28 Hz, 2 H), 7.14 (br s, 2 H), 7.18 - 7.29 (m, 4 H), 7.39 (br d, *J*=8.28 Hz, 2 H), 7.46 (br d, *J*=7.78 Hz, 1 H), 7.75 (d, *J*=1.51 Hz, 1 H). LC-MS: (ES) *m/z* 680.3 (M+H⁺).

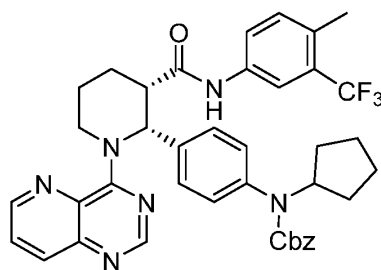
[0111] Step c) To a mixture of tert-butyl (2R,3S)-2-[4-[benzyloxycarbonyl(cyclopentyl)amino]phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (0.3 g, 441.33 μmol) in DCM (3 mL) was added TFA (1.54 g, 13.51 mmol, 1 mL). Then the mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with DCM (10 mL) and quenched by addition of saturated Na₂CO₃ solution to pH=9~10. The organic phase separated was dried, filtered and concentrated in vacuo to give the desired product benzyl N-cyclopentyl-N-[4-[(2R,3S)-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-piperidyl]phenyl]carbamate (0.24 g, 401.62 μmol, 91.00% yield, 97% purity) as off-white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.19 - 1.43 (m, 7 H), 1.71 - 1.82 (m, 2 H), 1.99 - 2.20 (m, 3 H), 2.36 (d, *J*=1.22 Hz, 3 H), 2.79 - 2.95 (m, 2 H), 3.36 (br d, *J*=11.49 Hz, 1 H), 4.08 (d, *J*=3.42 Hz, 1 H), 4.45 (quin, *J*=8.07 Hz, 1 H), 4.97 (s, 2 H), 7.07 (br d, *J*=8.31 Hz, 4 H), 7.15 - 7.26 (m, 4 H), 7.39 (d, *J*=8.31 Hz, 3 H), 7.72 (d, *J*=1.96 Hz, 1 H). LC-MS: (ES) *m/z* 580.3 (M+H⁺).

[0112] Step d) A mixture of benzyl N-cyclopentyl-N-[4-[(2R,3S)-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-piperidyl]phenyl]carbamate (150 mg, 258.78 μmol), 4-chloro quinazoline (60 mg, 364.54 μmol) and DIEA (100.33 mg, 776.33 μmol, 135.22 μL) in DMSO (0.5 mL) was stirred at 100 °C for 16 hr. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc 60 mL (30 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 35 mL/min) to give the crude benzyl N-cyclopentyl-N-[4-[(2R,3S)-3-[[4-methyl-3-

(trifluoromethyl)phenyl]carbonyl]-1-quinazolin-4-yl-2-piperidyl]phenyl]carbamate (94 mg, 99.61 μmol , 38.49% yield, 75% purity) as light yellow solid. The crude was further purified by prep-HPLC (basic condition) column: Xtimate C18 10 μ 250 mm x50mm; mobile phase: [water(0.04% $\text{NH}_3\text{H}_2\text{O}$ +10mM NH_4HCO_3)-ACN];B%: 80%-100%, 8 min) to give compound benzylN-cyclopentyl-N-[4-[(2R,3S)-3-[[4-methyl-3-(trifluoromethyl) phenyl]carbonyl]-1-quinazolin-4-yl-2-piperidyl]phenyl] carbamate (77 mg, 105.53 μmol , 79.46% yield, 97% purity) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 1.33 - 1.44 (m, 2 H), 1.49 (br s, 4 H), 1.82 - 1.96 (m, 3 H), 2.14 - 2.24 (m, 1 H), 2.30 - 2.41 (m, 1 H), 2.44 (d, J =1.25 Hz, 3 H), 3.40 - 3.53 (m, 2 H), 4.08 (br d, J =13.05 Hz, 1 H), 4.44 - 4.57 (m, 1 H), 5.09 (s, 2 H), 6.30 (br d, J =4.02 Hz, 1 H), 7.09 (d, J =8.53 Hz, 2 H), 7.16 (br s, 2 H), 7.20 - 7.26 (m, 4 H), 7.46 - 7.58 (m, 3 H), 7.64 (br d, J =8.28 Hz, 1 H), 7.76 - 7.84 (m, 2 H), 7.94 (dd, J =8.28, 5.02 Hz, 2 H), 8.41 (br s, 1 H), 8.78 (s, 1 H). LC-MS: (ES) m/z 708.3 ($\text{M}+\text{H}^+$).

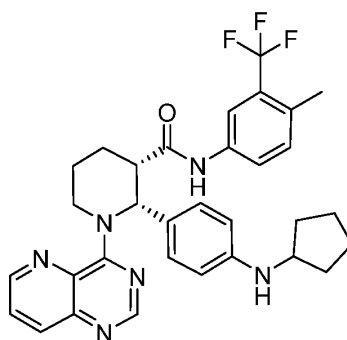
[0113] Step e) A mixture of benzyl N-cyclopentyl-N-[4-[(2R,3S)-3-[[4-methyl-3-(trifluoromethyl) phenyl] carbonyl]-1-quinazolin-4-yl-2-piperidyl]phenyl]carbamate (50 mg, 70.64 μmol) and Pd/C(wet) (20 mg, 10% purity) in EtOH (20 mL) was degassed and purged with H_2 (15 psi) 3 times. Then the mixture was stirred at 20 $^\circ\text{C}$ for 16 h under H_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (basic condition, column: Xtimate C18 10 μ 250 mm x50mm; mobile phase: [water (0.04% $\text{NH}_3\text{H}_2\text{O}$ +10 mM NH_4HCO_3)-ACN];B%: 70%-100%, 8 min) to give (2R,3S)- 2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-1-quinazolin-4-yl-piperidine-3-carboxamide (7 mg, 11.84 μmol , 16.76% yield, 97 % purity) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 1.40 - 1.50 (m, 2 H), 1.58 - 1.66 (m, 2 H), 1.68 - 1.76 (m, 2 H), 1.87 (br d, J =13.21 Hz, 1 H), 1.96 - 2.01 (m, 2 H), 2.10 - 2.18 (m, 1 H), 2.30 - 2.39 (m, 1 H), 2.43 (s, 3 H), 3.32 (dt, J =12.04, 4.00 Hz, 1 H), 3.47 - 3.60 (m, 1 H), 3.71 - 3.79 (m, 1 H), 4.09 (br d, J =13.21 Hz, 1 H), 6.23 (br d, J =4.16 Hz, 1 H), 6.54 (d, J =8.80 Hz, 2 H), 7.20 (d, J =8.31 Hz, 1 H), 7.30 (d, J =8.56 Hz, 2 H), 7.43 (t, J =7.58 Hz, 1 H), 7.63 (br d, J =8.31 Hz, 1 H), 7.73 (t, J =7.70 Hz, 1 H), 7.77 (s, 1 H), 7.87 (d, J =8.80 Hz, 2 H), 8.70 (s, 1 H), 8.78 (br s, 1 H). LC-MS: (ES) m/z 574.3 ($\text{M}+\text{H}^+$).

Example S5: Synthesis of benzyl cyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)-carbonyl)-1-(pyridof[3,2-d]pyrimidin-4-yl)piperidin-2-yl)phenyl)carbamate (Compound No. 166)



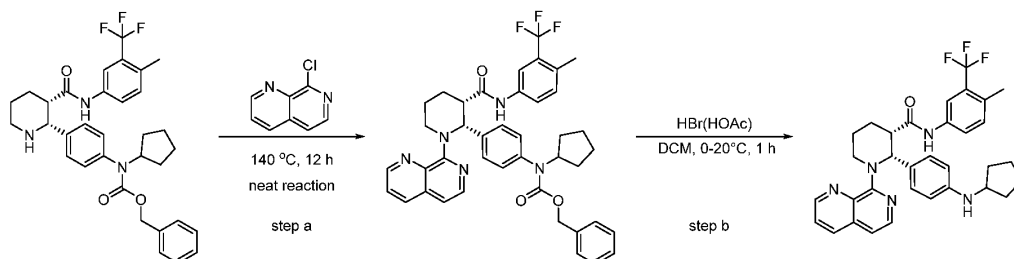
[0114] The title compound was synthesized in similar fashion as Example S4. ^1H NMR (400 MHz, CDCl_3) δ 1.31 - 1.43 (m, 2 H), 1.50 (br d, $J=4.02$ Hz, 4 H), 1.77 - 2.02 (m, 6 H), 2.21 (br d, $J=13.30$ Hz, 1 H), 2.36 - 2.54 (m, 4 H), 3.11 (br s, 1 H), 3.34 (br s, 1 H), 4.43 - 4.58 (m, 1 H), 5.03 - 5.13 (m, 2 H), 7.07 (d, $J=8.53$ Hz, 2 H), 7.13 (br s, 2 H), 7.18 - 7.26 (m, 4 H), 7.50 (br d, $J=7.78$ Hz, 2 H), 7.61 - 7.75 (m, 2 H), 7.81 (s, 1 H), 8.19 (br d, $J=8.03$ Hz, 1 H), 8.44 (br s, 1 H), 8.69 (s, 1 H), 8.80 (br d, $J=2.51$ Hz, 1 H). LC-MS: (ES) m/z 709.3 ($\text{M}+\text{H}^+$).

Example S6: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrido[3,2-d]pyrimidin-4-yl)piperidine-3-carboxamide (Compound No. 161)



[0115] The title compound was synthesized in a similar fashion as the compound in S4: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.40 (dt, $J=12.30, 6.15$ Hz, 2 H), 1.47 - 1.57 (m, 2 H), 1.60 - 1.70 (m, 2 H), 1.78 - 1.92 (m, 3 H), 1.92 - 2.10 (m, 2 H), 2.23 - 2.36 (m, 1 H), 2.38 (s, 3 H), 3.14 - 3.21 (m, 1 H), 3.33 (br t, $J=12.67$ Hz, 1 H), 3.58 - 3.70 (m, 1 H), 5.12 (br d, $J=6.53$ Hz, 1 H), 5.44 (br s, 1 H), 6.45 (d, $J=8.28$ Hz, 2 H), 7.22 (d, $J=8.53$ Hz, 2 H), 7.32 (br d, $J=8.53$ Hz, 2 H), 7.66 (br d, $J=8.28$ Hz, 1 H), 7.77 (dd, $J=8.53, 4.02$ Hz, 1 H), 7.89 (s, 1 H), 8.12 (d, $J=8.53$ Hz, 1 H), 8.58 (s, 1 H), 8.80 (dd, $J=4.14, 1.63$ Hz, 1 H), 9.74 (br s, 1 H). LC-MS: (ES) m/z 575.3 ($\text{M}+\text{H}^+$).

Example S7: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoro-methyl)phenyl)-1-(1,7-naphthyridin-8-yl)piperidine-3-carboxamide (Compound No. 6)

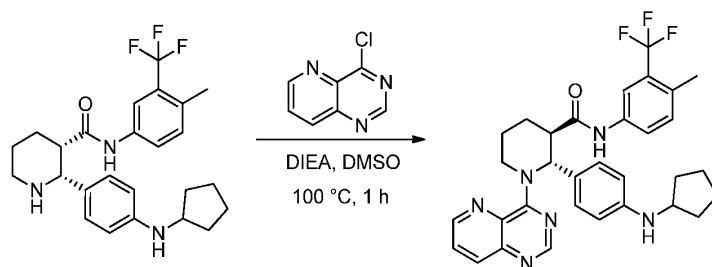


[0116] Step a) A solution of benzyl N-cyclopentyl-N-[4-[(2R,3S)-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-piperidyl]phenyl]carbamate (0.2 g, 345.04 μmol) and 8-chloro-1,7-naphthyridine (0.1 g, 607.56 μmol) in dioxane (1 mL) was concentrated in vacuo to give the residue. The residue was stirred at 140 °C for 12 h. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @18 mL/min) to give benzyl N-cyclopentyl-N-[4-[(2R,3S)-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-1-(1,7-naphthyridin-8-yl)-2-piperidyl]phenyl]carbamate (65 mg, 91.84 μmol , 26.62% yield, 100% purity) as light yellow solid. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.24 - 1.32 (m, 2 H), 1.40 (br d, $J=4.40$ Hz, 5 H), 1.75 (br d, $J=5.14$ Hz, 2 H), 1.90 (br dd, $J=8.44$, 4.28 Hz, 1 H), 2.09 - 2.27 (m, 2 H), 2.31 - 2.37 (m, 1 H), 2.41 (s, 3 H), 3.61 - 3.74 (m, 1 H), 3.87 (br s, 1 H), 4.32 - 4.46 (m, 1 H), 4.96 (s, 2 H), 6.09 (br s, 1 H), 6.85 (d, $J=8.31$ Hz, 2 H), 7.05 (br s, 2 H), 7.20 (br d, $J=3.18$ Hz, 3 H), 7.25 - 7.36 (m, 4 H), 7.66 - 7.77 (m, 2 H), 7.94 (d, $J=1.71$ Hz, 1 H), 8.01 (d, $J=5.62$ Hz, 1 H), 8.26 (dd, $J=8.31$, 1.71 Hz, 1 H), 9.02 (dd, $J=4.16$, 1.71 Hz, 1 H). LC-MS: (ES) m/z 708.3 ($\text{M}+\text{H}^+$).

[0117] Step b) To a solution of benzyl N-cyclopentyl-N-[4-[(2R,3S)-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-1-(1,7-naphthyridin-8-yl)-2-piperidyl]phenyl]carbamate (30 mg, 42.39 μmol) in DCM (2 mL) was added HBr (in HOAc) (89.40 mg, 364.62 μmol , 60.00 μL , 33% purity) at 0 °C. Then the mixture was stirred at 20 °C for 1 h. The reaction mixture was diluted with DCM (4 mL), alkalified to pH=9~10 by saturated NaHCO_3 solution and extracted with DCM (2 x 3 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give the residue. The residue was purified by prep-TLC (Petroleum ether/EtOAc=3/2) to give (2R,3S)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-

(trifluoromethyl)phenyl]-1-(1,7-naphthyridin-8-yl)piperidine-3-carboxamide (8 mg, 12.83 μ mol, 30.27% yield, 92% purity) as off-white solid. ^1H NMR (400 MHz, CDCl_3) δ 1.35 - 1.47 (m, 2 H), 1.53 - 1.64 (m, 5 H), 1.90 - 2.02 (m, 3 H), 2.34 - 2.50 (m, 5 H), 3.34 (br s, 1 H), 3.68 (quin, $J=6.15$ Hz, 1 H), 3.79 - 3.91 (m, 1 H), 4.26 (br d, $J=12.80$ Hz, 1 H), 6.45 (d, $J=8.53$ Hz, 2 H), 6.85 (s, 1 H), 7.05 (d, $J=8.28$ Hz, 2 H), 7.14 (d, $J=5.52$ Hz, 1 H), 7.21 (br d, $J=8.28$ Hz, 1 H), 7.55 (dd, $J=8.28, 4.27$ Hz, 1 H), 7.76 (s, 1 H), 7.87 (br d, $J=8.28$ Hz, 1 H), 8.10 (dd, $J=8.28, 1.51$ Hz, 1 H), 8.24 (d, $J=5.52$ Hz, 1 H), 8.77 (dd, $J=4.02, 1.51$ Hz, 1 H), 11.50 (s, 1 H). LC-MS: (ES) m/z 574.3 ($\text{M}+\text{H}^+$).

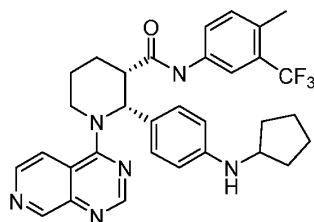
Example S8: (2*R*,3*R*)-2-(4-(cyclopentylamino)phenyl)-*N*-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrido[3,2-*d*]pyrimidin-4-yl)piperidine-3-carboxamide (Compound No. 7)



[0118] DIEA (116.18 mg, 898.95 μ mol, 156.58 μ L) was added to a solution of 4-chloro pyrido[3,2-*d*]pyrimidine (74.42 mg, 449.48 μ mol) and (2*R*,3*S*)-2-[4-(cyclopentylamino)phenyl]-*N*-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (150 mg, 299.65 μ mol) in DMSO (1 mL). The solution was stirred at 100 °C for 1 h. The reaction mixture was added to 2 mL of H_2O , and was extracted with DCM (5 mL $\times$ 2). The combined organic phase was dried with anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under vacuum to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=1/0 to 0:1) (plate, Petroleum ether/Ethyl acetate= 1:1). The resulting product was purified again by prep -TLC (Petroleum ether/Ethyl acetate=1:1) to give compound (2*R*,3*R*)-2-[4-(cyclopentylamino)phenyl]-*N*-[4-methyl-3-(trifluoromethyl)phenyl]-1-pyrido[3,2-*d*]pyrimidin-4-yl-piperidine-3-carboxamide (18 mg, 28.82 μ mol, 9.62% yield, 92% purity) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 0.60 - 0.93 (2 H, m), 1.06 - 1.43 (6 H, m), 1.44 - 1.78 (13 H, m), 1.80 - 2.05 (3 H, m), 2.26 - 2.52 (5 H, m), 3.37 - 3.55 (2 H, m), 3.58 - 3.71 (1 H, m), 5.02 (1 H, br s), 6.44 (2 H, br d, $J=7.58$ Hz),

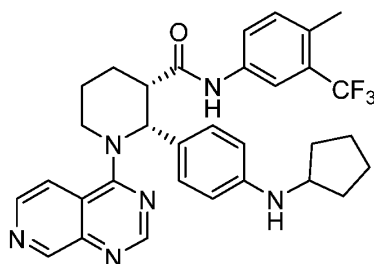
6.89 (2 H, br s), 7.10 (1 H, br d, $J=8.31$ Hz), 7.23 - 7.47 (1 H, m), 7.51 - 7.70 (3 H, m), 8.15 (1 H, br d, $J=8.31$ Hz), 8.70 (2 H, br s), 10.42 (1 H, br s). LC-MS: (ES) m/z 575.3 ($M+H^+$).

Example S9: (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrido[3,4-d]pyrimidin-4-yl)piperidine-3-carboxamide (Compound No. 162)



[0119] The title compound was synthesized in similar fashion as Example S8. ^1H NMR (400 MHz, CDCl_3) δ 1.47 (br dd, $J=12.55, 6.53$ Hz, 2 H), 1.61 - 1.66 (m, 2 H), 1.71 - 1.77 (m, 3 H), 1.86 (br s, 1 H), 1.95 - 2.06 (m, 2 H), 2.07 - 2.15 (m, 1 H), 2.31 (br s, 1 H), 2.43 (d, $J=1.00$ Hz, 3 H), 3.35 (br s, 1 H), 3.64 - 3.83 (m, 2 H), 4.06 - 4.30 (m, 1 H), 6.34 (br s, 1 H), 6.59 (br d, $J=8.53$ Hz, 2 H), 7.12 (d, $J=8.53$ Hz, 2 H), 7.20 - 7.25 (m, 1 H), 7.67 (br d, $J=8.53$ Hz, 1 H), 7.71 (s, 1 H), 7.76 (br d, $J=5.77$ Hz, 1 H), 8.54 - 8.60 (m, 1 H), 8.82 - 8.87 (m, 1 H), 9.34 - 9.38 (m, 1 H). LC-MS: (ES) m/z 575.3 ($M+H^+$).

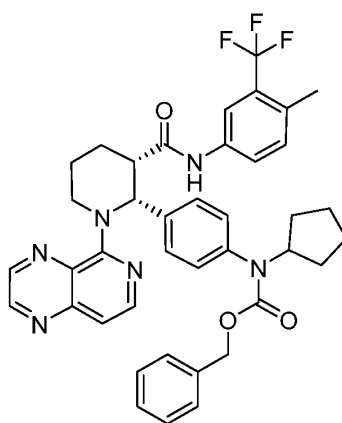
Example S10: Synthesis of benzyl cyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(pyrido[3,4-d]pyrimidin-4-yl)piperidin-2-yl)phenyl)carbamate (Compound 167)



[0120] The title compound was synthesized in similar fashion as Example S8. ^1H NMR (400 MHz, CDCl_3) δ 1.35 - 1.46 (m, 2 H), 1.50 (br s, 4 H), 1.74 - 1.80 (m, 1 H), 1.88 (br s, 2 H), 1.96 (br d, $J=13.45$ Hz, 1 H), 2.22 (br d, $J=13.21$ Hz, 1 H), 2.32 - 2.41 (m, 1 H), 2.44 (s, 3 H), 3.35 (dt, $J=12.23, 4.16$ Hz, 1 H), 3.43 - 3.53 (m, 1 H), 4.24 (br d, $J=13.21$ Hz, 1 H), 4.45 - 4.57 (m, 1 H), 5.10 (s, 2 H), 6.52 (br d, $J=4.16$ Hz, 1 H), 7.12 (d, $J=8.56$ Hz, 2 H), 7.17 (br

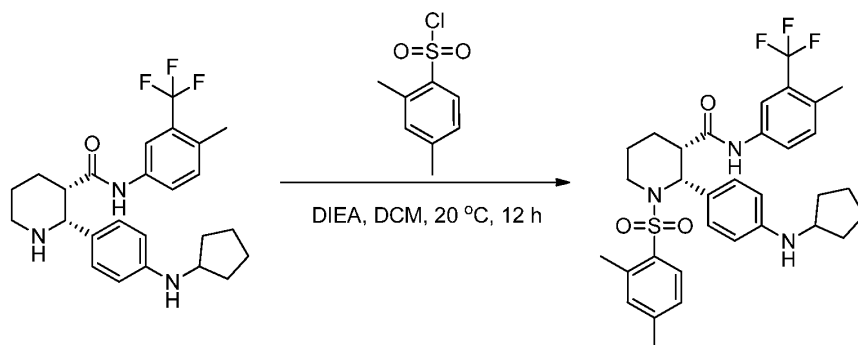
s, 2 H), 7.20 - 7.26 (m, 4 H), 7.52 (d, $J=8.31$ Hz, 2 H), 7.62 (br d, $J=9.29$ Hz, 1 H), 7.67 (d, $J=5.87$ Hz, 1 H), 7.75 (s, 1 H), 8.06 (s, 1 H), 8.59 (d, $J=5.62$ Hz, 1 H), 8.86 (s, 1 H), 9.36 (s, 1 H). LC-MS: (ES) m/z 709.3 ($M+H^+$).

Example S11: Synthesis of benzyl cyclopentyl(4-((2*R*,3*S*)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(pyrido[3,4-*b*]pyrazin-5-yl)piperidin-2-yl)phenyl)carbamate (Compound No. 165)



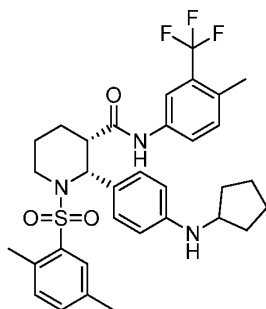
[0121] The title compound was synthesized in similar fashion as the above examples. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.30 - 1.36 (m, 2 H), 1.39 - 1.43 (m, 3 H), 1.79 (br s, 2 H), 1.87 - 2.16 (m, 4 H), 2.26 - 2.47 (m, 5 H), 3.30 - 3.36 (m, 1 H), 3.43 - 3.55 (m, 1 H), 4.41 (quin, $J=8.38$ Hz, 1 H), 4.50 - 4.62 (m, 1 H), 4.93 - 5.02 (m, 2 H), 6.76 (br d, $J=4.65$ Hz, 1 H), 6.97 (d, $J=8.31$ Hz, 2 H), 7.06 (br s, 2 H), 7.17 (br d, $J=2.93$ Hz, 3 H), 7.23 (d, $J=8.56$ Hz, 1 H), 7.27 (d, $J=5.87$ Hz, 1 H), 7.50 (d, $J=8.31$ Hz, 2 H), 7.57 (br d, $J=8.31$ Hz, 1 H), 7.83 (d, $J=1.71$ Hz, 1 H), 8.24 (d, $J=5.87$ Hz, 1 H), 8.82 (d, $J=1.47$ Hz, 1 H), 8.89 (d, $J=1.71$ Hz, 1 H). LC-MS: (ES) m/z 709.3 ($M+H^+$).

Example S12: Synthesis of (2*R*,3*S*)-2-(4-(cyclopentylamino)phenyl)-1-((2,4-dimethylphenyl)sulfonyl)-*N*-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 9)



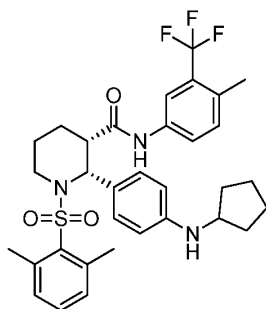
[0122] To a mixture of (2R,3S)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (50 mg, 112.23 μ mol) and DIEA (21.76 mg, 168.35 μ mol, 29.32 μ L) in DCM (1.5 mL) was added dropwise of a solution of 2,4-dimethylbenzenesulfonyl chloride (20.67 mg, 101.01 μ mol, 13.68 μ L) in DCM (0.5 mL) at 20 °C. Then the mixture was stirred at 20 °C for 12 h. The mixture was concentrated in vacuo to give the crude product. The crude product was purified by prep-HPLC (column: Agela ASB 150x25mmx5 μ m; mobile phase: [water(0.05% HCl)-ACN];B%: 50%-80%, 8 min) to give (2R,3S)-2-[4-(cyclopentylamino)phenyl]-1-((2,4-dimethylphenyl)sulfonyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (15 mg, 24.44 μ mol, 21.78% yield, 100% purity) as white solid. ¹H NMR (400 MHz, CDCl_3) δ 1.53 - 1.63 (m, 3 H), 1.65 - 1.83 (m, 4 H), 1.84 - 1.98 (m, 3 H), 2.04 - 2.13 (m, 1 H), 2.14 - 2.28 (m, 1 H), 2.36(s, 3 H), 2.39 (s, 3 H), 2.46 (s, 3 H), 3.00 - 3.12 (m, 1 H), 3.18 (dt, J =12.74, 4.67 Hz, 1 H), 3.67 (quin, J =6.15 Hz, 1 H), 3.77 (br d, J =11.29 Hz, 1 H), 5.38 (br, d, J =5.27 Hz, 1 H), 6.66 (br d, J =6.27 Hz, 2 H), 6.99 - 7.10 (m, 4 H), 7.14 (d, J =8.28 Hz, 1 H), 7.42 (br d, J =8.28 Hz, 1 H), 7.53 (s, 1 H), 7.67 (br s, 1 H), 7.79 - 7.88 (m, 1 H). LC-MS: (ES) m/z 614.3 ($\text{M}+\text{H}^+$).

Example S13: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2,5-dimethylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 10)



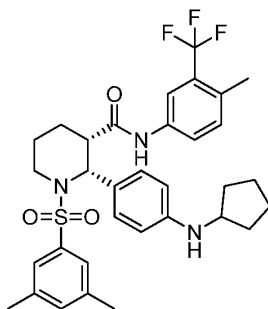
[0123] The title compound was synthesized in similar fashion as Example S12. ^1H NMR (400 MHz, CDCl_3) δ 1.46 (2 H, br s), 1.79 (11 H, br s), 1.95 - 2.12 (2 H, m), 2.27 (3 H, s), 2.39 (6 H, br d, $J=19.32$ Hz), 2.89 (1 H, br t, $J=13.45$ Hz), 3.13 (1 H, br s), 3.58 (1 H, br s), 3.76 (1 H, br d, $J=14.18$ Hz), 5.56 (1 H, br s), 7.11 (2 H, br d, $J=7.83$ Hz), 7.19 - 7.25 (2 H, m), 7.28 (2 H, br s), 7.43 (1 H, br d, $J=8.07$ Hz), 7.63 (1 H, br s), 7.79 (1 H, br s), 8.00 (1 H, br s), 10.99 (1 H, br s). LC-MS: (ES) m/z 614.3 ($\text{M}+\text{H}^+$).

Example S14: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2,6-dimethylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 11)



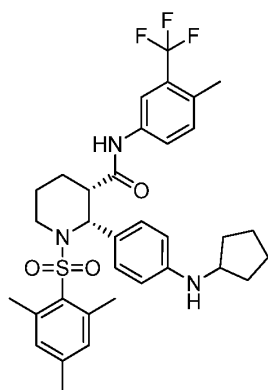
[0124] The title compound was synthesized in similar fashion as Example S12. ^1H NMR (400 MHz, CDCl_3) δ 1.35 - 1.57 (m, 5 H), 1.66 (br s, 2 H), 1.74 - 1.91 (m, 4 H), 2.16 (br d, $J=10.3$ Hz, 1 H), 2.35 (s, 3 H), 2.56 (s, 6 H), 3.05 - 3.15 (m, 1 H), 3.18 - 3.32 (m, 2 H), 3.65 (br s, 1 H), 5.36 (br s, 1 H), 6.20 - 6.74 (m, 1 H), 6.77 - 7.20 (m, 2 H), 7.23 (d, $J=7.8$ Hz, 2 H), 7.30 (d, $J=8.3$ Hz, 1 H), 7.36 - 7.43 (m, 1 H), 7.54 (br d, $J=8.3$ Hz, 1 H), 7.74 (d, $J=1.8$ Hz, 1 H), 10.10 (br s, 1 H). LC-MS: (ES) m/z 614.4 ($\text{M}+\text{H}^+$).

Example S15: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((3,5-dimethylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 12)



[0125] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, CDCl₃) δ 1.59 (br d, *J*=6.39 Hz, 5 H), 1.73 - 1.84 (m, 3 H), 1.86 - 2.04 (m, 4 H), 2.22 (s, 6 H), 2.39 (s, 3 H), 2.87 - 3.02 (m, 2 H), 3.65 (br t, *J*=5.73 Hz, 1 H), 3.82 (br d, *J*=10.14 Hz, 1 H), 5.73 (br s, 1 H), 6.61 (br s, 2 H), 7.00 - 7.18 (m, 4 H), 7.27 - 7.34 (m, 1 H), 7.43 (br d, *J*=7.72 Hz, 1 H), 7.53 (br s, 1 H), 7.96 (br s, 1 H). LC-MS: (ES) *m/z* 614.3 (M+H⁺).

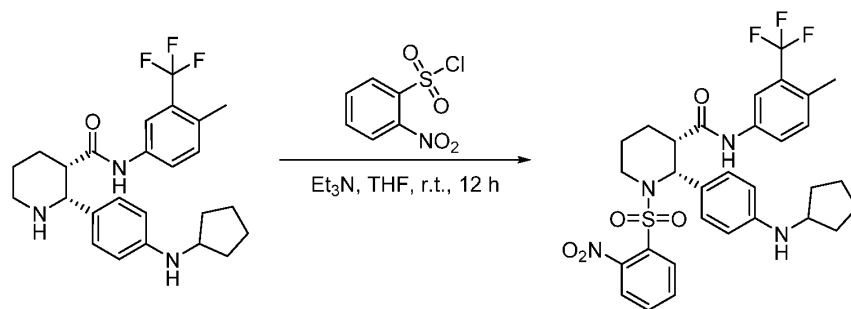
Example S16: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(mesitylsulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 13)



[0126] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.62 - 1.74 (m, 4 H), 1.82 (br s, 2 H), 1.95 (br d, *J*=6.75 Hz, 4 H), 2.24 (br d, *J*=12.51 Hz, 1 H), 2.31 (s, 3 H), 2.39 (s, 3 H), 2.59 (s, 6 H), 3.20 - 3.28 (m, 1 H), 3.42 (br d, *J*=8.38 Hz, 2 H), 3.89 (br t, *J*=6.63 Hz, 1 H), 4.82 (br s, 1 H), 5.48 (br d,

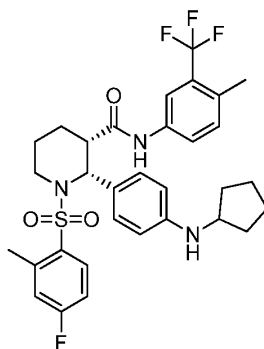
$J=6.25$ Hz, 1 H), 7.03 (s, 2 H), 7.21 - 7.31 (m, 3 H), 7.41 (br d, $J=8.25$ Hz, 1 H), 7.53 (br d, $J=7.88$ Hz, 2 H), 7.69 (s, 1 H), 10.06 (s, 1 H). LC-MS: (ES) m/z 628.3 ($M+H^+$).

Example S17: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((2-nitrophenyl)sulfonyl)piperidine-3-carboxamide (Compound No. 14)



[0127] The title compound was synthesized in similar fashion as Example S12. ^1H NMR (400 MHz, CDCl_3) δ 1.49 (br s, 2 H), 1.71 (br s, 2 H), 1.77 - 1.87 (m, 6 H), 1.94 - 2.09 (m, 2 H), 2.41 (s, 3 H), 3.00 - 3.15 (m, 2 H), 3.59 - 3.70 (m, 1 H), 3.88 (br d, $J=11.74$ Hz, 1 H), 5.71 (br d, $J=4.65$ Hz, 1 H), 7.19 (d, $J=8.07$ Hz, 1 H), 7.45 (br s, 3 H), 7.50 (br d, $J=7.83$ Hz, 1 H), 7.60 - 7.75 (m, 4 H), 7.98 (br d, $J=7.34$ Hz, 1 H), 8.15 (br s, 1 H), 11.06 (br s, 1 H). LC-MS: (ES) m/z 631.3 ($M+H^+$).

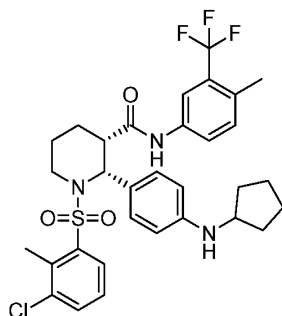
Example S18: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((4-fluoro-2-methylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 15)



[0128] The title compound was synthesized in similar fashion as Example S12. ^1H NMR (400 MHz, CDCl_3) δ 1.49 (br s, 2 H), 1.82 (br s, 8 H), 2.01 - 2.14 (m, 2 H), 2.41 (s, 3 H), 2.50

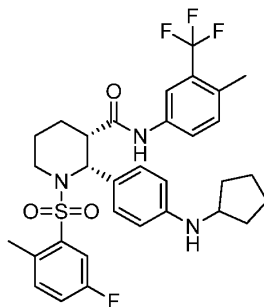
(s, 3 H), 2.91 - 3.05 (m, 1 H), 3.18 (br d, $J=4.52$ Hz, 1 H), 3.61 (br s, 1 H), 3.78 (br d, $J=11.29$ Hz, 1 H), 5.54 (br d, $J=4.52$ Hz, 1 H), 6.94 - 7.02 (m, 2 H), 7.18 (br d, $J=8.03$ Hz, 3 H), 7.31 (br s, 1 H), 7.42 (br d, $J=7.78$ Hz, 1 H), 7.62 (s, 1 H), 7.81 (br s, 1 H), 7.91 - 8.04 (m, 1 H), 10.85 (br s, 1 H). LC-MS: (ES) m/z 618.3 ($M+H^+$).

Example S19: Synthesis of (2R,3S)-1-((3-chloro-2-methylphenyl)sulfonyl)-2-(4-(cyclopentyl-amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 16)



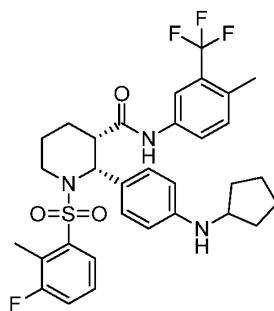
[0129] The title compound was synthesized in similar fashion to Example S12. ^1H NMR (400 MHz, CDCl_3) δ 1.51 (br s, 2 H), 1.74 (br d, $J=10.80$ Hz, 5 H), 1.83 - 1.95 (m, 3 H), 2.01 - 2.18 (m, 2 H), 2.40 (br s, 3 H), 2.51 (s, 3 H), 3.02 - 3.22 (m, 2 H), 3.64 (br t, $J=6.50$ Hz, 1 H), 3.80 (br d, $J=12.35$ Hz, 1 H), 5.45 (br d, $J=3.97$ Hz, 1 H), 7.09 (br s, 4 H), 7.14 - 7.24 (m, 2 H), 7.38 (br d, $J=8.38$ Hz, 1 H), 7.48 - 7.59 (m, 2 H), 7.70 (br s, 1 H), 7.87 (br d, $J=7.72$ Hz, 1 H). LC-MS: (ES) m/z 634.2 ($M+H^+$).

Example S20: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((5-fluoro-2-methylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 17)



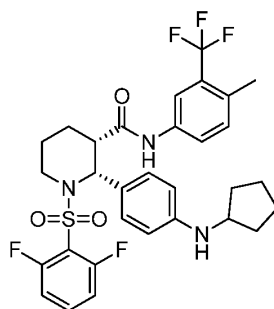
[0130] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.59 - 1.75 (m, 5 H), 1.82 (br s, 2 H), 1.89 - 2.08 (m, 4 H), 2.23 (qd, *J*=13.53, 3.91 Hz, 1 H), 2.39 (s, 3 H), 2.51 (s, 3 H), 3.22 (ddd, *J*=12.90, 6.30, 4.03 Hz, 1 H), 3.45 (td, *J*=13.14, 2.57 Hz, 1 H), 3.76 (br d, *J*=11.98 Hz, 1 H), 3.83 - 3.93 (m, 1 H), 5.58 (d, *J*=6.36 Hz, 1 H), 7.19 - 7.29 (m, 4 H), 7.29 - 7.35 (m, 1 H), 7.42 (dd, *J*=8.19, 1.83 Hz, 1 H), 7.46 - 7.56 (m, 3 H), 7.71 (d, *J*=1.96 Hz, 1 H). LC-MS: (ES) *m/z* 618.1 (M+H⁺).

Example S21: Synthesis of (2*R*,3*S*)-1-((3-fluoro-2-methylphenyl)sulfonyl)-2-(4-(cyclopentyl-amino)phenyl)-*N*-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 18)



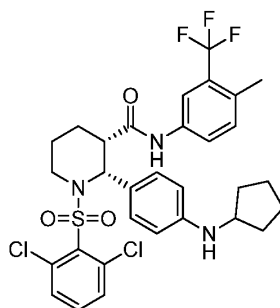
[0131] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, CDCl₃) δ 1.60 - 2.02 (m, 10 H), 2.12 (br s, 2 H), 2.44 (br s, 6 H), 3.18 (br s, 2 H), 3.57 - 4.02 (m, 2 H), 5.54 (br s, 1 H), 7.27 (br s, 7 H), 7.45 (br s, 1 H), 7.62 (br s, 1 H), 7.70 - 8.13 (m, 1 H). LC-MS: (ES) *m/z* 618.2 (M+H⁺).

Example S22: Synthesis of (2*R*,3*S*)-2-(4-(cyclopentylamino)phenyl)-1-((2,6-difluorophenyl)sulfonyl)-*N*-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 19)



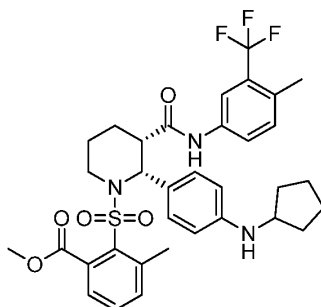
[0132] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, CDCl₃) δ 1.51 - 1.67 (m, 2 H), 1.73 - 1.94 (m, 8 H), 1.96 - 2.11 (m, 2 H), 2.38 (s, 3 H), 3.03 (br s, 1 H), 3.16 (br t, *J*=12.96 Hz, 1 H), 3.63 (br s, 1 H), 4.04 (br d, *J*=11.49 Hz, 1 H), 5.71 (br d, *J*=4.40 Hz, 1 H), 6.84 (br t, *J*=8.80 Hz, 2 H), 7.15 (br d, *J*=7.58 Hz, 1 H), 7.18 - 7.26 (m, 2 H), 7.28 - 7.31 (m, 1 H), 7.38 (br t, *J*=7.58 Hz, 2 H), 7.59 (s, 1 H), 7.98 (br s, 1 H), 10.12 - 11.64 (m, 1 H). LC-MS: (ES) *m/z* 622.3 (M+H⁺).

Example S23: Synthesis of (2*R*,3*S*)-2-(4-(cyclopentylamino)phenyl)-1-((2,6-dichlorophenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 20)



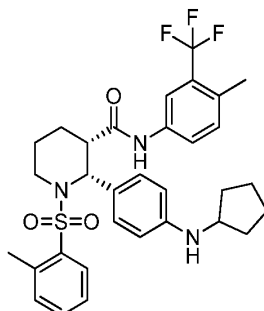
[0133] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, CDCl₃) δ 1.50 (br s, 2 H), 1.65 (br s, 2 H), 1.77 - 1.94 (m, 6 H), 2.04 (br d, *J*=16.54 Hz, 2 H), 2.40 (br s, 3 H), 3.09 - 3.27 (m, 2 H), 3.62 (br s, 1 H), 4.03 (br d, *J*=13.67 Hz, 1 H), 5.57 (br d, *J*=4.85 Hz, 1 H), 7.18 (br d, *J*=7.94 Hz, 3 H), 7.25 (br s, 1 H), 7.30 (s, 1 H), 7.35 - 7.46 (m, 3 H), 7.60 (s, 1 H), 7.72 (br s, 1 H), 9.53 - 11.11 (m, 1 H). LC-MS: (ES) *m/z* 654.1 (M+H⁺).

Example S24: Synthesis of methyl 2-(((2*R*,3*S*)-2-(4-(cyclopentylamino)phenyl)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)piperidin-1-yl)sulfonyl)-3-methylbenzoate (Compound No. 21)



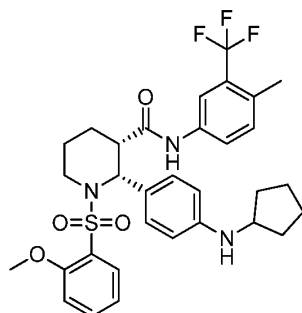
[0134] The title compound was synthesized in similar fashion as Example S12. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.59 - 1.73 (m, 5 H), 1.76 - 1.88 (m, 2 H), 1.89 - 2.03 (m, 4 H), 2.26 (qd, $J=13.55$, 4.02 Hz, 1 H), 2.39 (d, $J=1.51$ Hz, 3 H), 2.56 (s, 3 H), 3.24 (ddd, $J=13.05$, 6.02, 3.76 Hz, 1 H), 3.32 - 3.37 (m, 1 H), 3.82 - 3.91 (m, 1 H), 3.95 (s, 4 H), 5.57 (d, $J=6.27$ Hz, 1 H), 7.20 - 7.28 (m, 3 H), 7.34 (d, $J=7.03$ Hz, 1 H), 7.41 - 7.50 (m, 4 H), 7.54 - 7.60 (m, 1 H), 7.75 - 7.79 (m, 1 H), 9.82 (s, 1 H). LC-MS: (ES) m/z 680.1 (M+Na).

Example S25: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(o-tolylsulfonyl)piperidine-3-carboxamide (Compound No. 22)



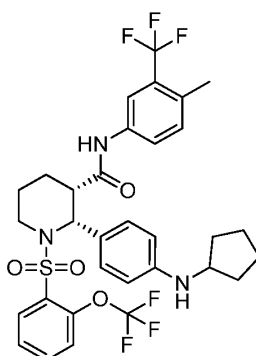
[0135] The title compound was synthesized in similar fashion as Example S12. ^1H NMR (400 MHz, CDCl_3) δ 1.56 - 1.89 (11 H, m) 2.03 (2 H, br s) 2.37 (3 H, s) 2.46 (3 H, s) 2.91 (1 H, br t, $J=12.96$ Hz) 3.15 (1 H, br s) 3.57 (1 H, br s) 3.79 (1 H, br d, $J=12.23$ Hz) 5.53 (1 H, br d, $J=4.16$ Hz) 7.15 (3 H, br d, $J=6.36$ Hz) 7.22 (1 H, s) 7.34 (2 H, br d, $J=7.34$ Hz) 7.41 (2 H, br t, $J=7.09$ Hz) 7.63 (1 H, s) 7.93 (1 H, br d, $J=7.83$ Hz) 8.06 (1 H, br s) 11.12 (1 H, br s). LC-MS: (ES) m/z 622.3 (M+Na).

Example S26: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2-methoxyphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 23)



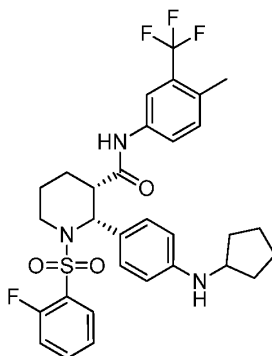
[0136] The title compound was synthesized in similar fashion as Example S12. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.64 (td, $J=12.84, 5.14$ Hz, 5 H), 1.81 (br d, $J=5.62$ Hz, 2 H), 1.89 - 2.06 (m, 4 H), 2.11 - 2.25 (m, 1 H), 2.38 (s, 3 H), 3.14 (ddd, $J=12.96, 6.24, 3.79$ Hz, 1 H), 3.44 - 3.55 (m, 1 H), 3.78 - 3.87 (m, 4 H), 3.99 - 4.09 (m, 1 H), 5.57 (d, $J=6.36$ Hz, 1 H), 6.89 - 6.99 (m, 2 H), 7.15 (br d, $J=8.07$ Hz, 2 H), 7.23 (d, $J=8.31$ Hz, 1 H), 7.38 - 7.49 (m, 4 H), 7.69 (d, $J=1.96$ Hz, 1 H), 7.78 (d, $J=8.07$ Hz, 1 H). LC-MS: (ES) m/z 616.2 ($\text{M}+\text{H}^+$).

Example S27: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoro-methyl)phenyl)-1-((2-(trifluoromethoxy)phenyl)sulfonyl)piperidine-3-carboxamide (Compound No. 24)



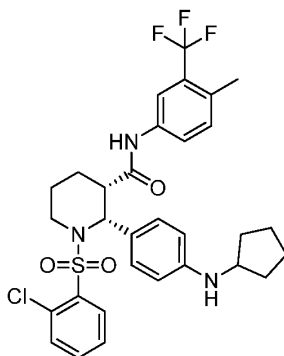
[0137] The title compound was synthesized in similar fashion as Example S12. ^1H NMR (400 MHz, CDCl_3) δ 1.48 (2 H, br s) 1.72 - 2.07 (11 H, m) 2.37 (3 H, br s) 2.91 - 3.09 (2 H, m) 3.58 (1 H, br s) 3.88 (1 H, br d, $J=12.47$ Hz) 5.61 (1 H, br d, $J=5.14$ Hz) 7.14 (1 H, br d, $J=8.07$ Hz) 7.22 (2 H, br s) 7.25 - 7.41 (4 H, m) 7.45 - 7.53 (1 H, m) 7.58 (1 H, s) 7.73 - 7.87 (2 H, m) 11.07 (1 H, br s). LC-MS: (ES) m/z 670.2 ($\text{M}+\text{H}^+$).

Example S28: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2-fluorophenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 25)



[0138] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, CDCl₃) δ 1.60 - 2.07 (12 H, m) 2.36 (3 H, s) 2.91 - 3.02 (1 H, m) 3.09 (1 H, br t, *J*=12.96 Hz) 3.61 (1 H, quin, *J*=6.48 Hz) 3.89 (1 H, br d, *J*=11.00 Hz) 5.64 (1 H, br d, *J*=5.14 Hz) 6.90 (2 H, br s) 7.01 - 7.19 (6 H, m) 7.34 - 7.46 (2 H, m) 7.54 (1 H, s) 7.68 (1 H, br t, *J*=7.09 Hz) 7.87 (1 H, br s). LC-MS: (ES) *m/z* 604.3 (M+H⁺).

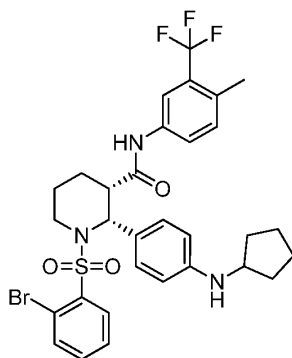
Example S29: Synthesis of (2R,3S)-1-((2-chlorophenyl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 26)



[0139] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, CDCl₃) δ 1.38 - 1.61 (2 H, m) 1.79 (9 H, br s) 1.98 (2 H, br s) 2.37 (3 H, s) 3.01 - 3.19 (2 H, m) 3.59 (1 H, br s) 3.85 (1 H, br d, *J*=11.25 Hz) 5.59 (1 H, br d, *J*=5.07 Hz) 7.15 (1 H, br d, *J*=8.16 Hz) 7.21 (1 H, br s) 7.26 - 7.34 (3 H, m) 7.36 - 7.46 (3 H, m) 7.59 (1 H, s)

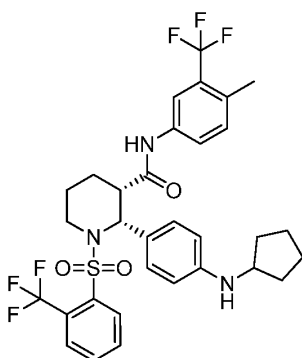
7.86 (1 H, br s) 8.01 (1 H, br d, $J=7.94$ Hz) 10.46 - 11.32 (1 H, m). LC-MS: (ES) m/z 620.2 ($M+H^+$).

Example S30: Synthesis of (2R,3S)-1-((2-bromophenyl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 27)



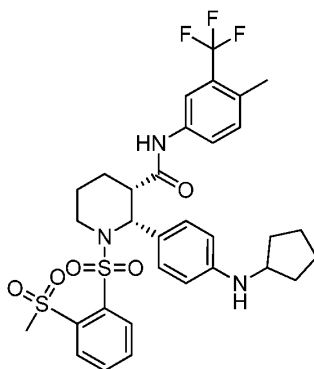
[0140] The title compound was synthesized in similar fashion as Example S12. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.60 - 1.73 (m, 5 H), 1.78 - 1.89 (m, 2 H), 1.90 - 2.03 (m, 4 H), 2.13 - 2.30 (m, 1 H), 2.38 (d, $J=1.25$ Hz, 3 H), 3.26 - 3.31 (m, 1 H), 3.54 (td, $J=13.30$, 2.51 Hz, 1 H), 3.78 (br dd, $J=13.55$, 3.26 Hz, 1 H), 3.83 - 3.93 (m, 1 H), 5.59 (d, $J=6.27$ Hz, 1 H), 7.22 - 7.29 (m, 3 H), 7.40 - 7.44 (m, 1 H), 7.44 - 7.53 (m, 4 H), 7.68 - 7.75 (m, 2 H), 8.11 (dd, $J=7.53$, 2.01 Hz, 1 H), 9.98 (s, 1 H). LC-MS: (ES) m/z 664.3 ($M+H^+$).

Example S31: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((2-(trifluoromethyl)phenyl)sulfonyl)piperidine-3-carboxamide (Compound No. 28)



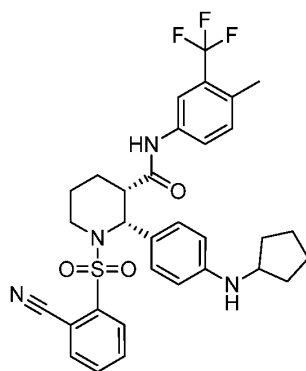
[0141] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.59 - 1.75 (m, 5 H), 1.82 (br s, 2 H), 1.88 - 2.07 (m, 4 H), 2.12 - 2.27 (m, 1 H), 2.39 (s, 3 H), 3.23 (ddd, *J*=12.90, 6.17, 3.91 Hz, 1 H), 3.41 - 3.56 (m, 1 H), 3.81 - 3.93 (m, 2 H), 5.64 (d, *J*=6.11 Hz, 1 H), 7.21 - 7.31 (m, 3 H), 7.44 (dd, *J*=8.19, 1.83 Hz, 1 H), 7.50 (br d, *J*=7.34 Hz, 2 H), 7.67 - 7.78 (m, 3 H), 7.89 (br d, *J*=7.34 Hz, 1 H), 8.10 (br d, *J*=7.09 Hz, 1 H). LC-MS: (ES) *m/z* 654.1 (M+H⁺).

Example S32: Synthesis of (2*R*,3*S*)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoro-methyl)phenyl)-1-((2-(methylsulfonyl)phenyl)sulfonyl)piperidine-3-carboxamide (Compound No. 29)



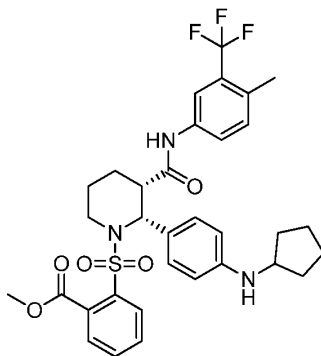
[0142] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, CDCl₃) δ 1.63 (br d, *J*=11.80 Hz, 4 H), 1.72 - 1.92 (m, 7 H), 1.95 - 2.11 (m, 1 H), 2.41 (s, 3 H), 2.70 - 2.81 (m, 1 H), 2.98 (br t, *J*=12.80 Hz, 1 H), 3.62 (s, 3 H), 3.65 - 3.71 (m, 1 H), 3.86 (br d, *J*=11.54 Hz, 1 H), 6.15 (d, *J*=4.52 Hz, 1 H), 7.19 (d, *J*=8.28 Hz, 1 H), 7.49 (br s, 1 H), 7.53 - 7.58 (m, 1 H), 7.65 (br d, *J*=8.28 Hz, 2 H), 7.83 (d, *J*=2.01 Hz, 1 H), 7.88 (quind, *J*=7.56, 7.56, 7.56, 7.56, 1.63 Hz, 2 H), 8.34 (dd, *J*=7.53, 1.51 Hz, 1 H), 8.50 (dd, *J*=7.53, 1.76 Hz, 1 H), 8.86 (s, 1 H), 11.10 (s, 1 H). LC-MS: (ES) *m/z* 664.4 (M+H⁺).

Example S33: Synthesis of (2*R*,3*S*)-1-((2-cyanophenyl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 30)



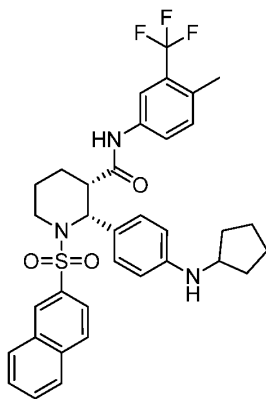
[0143] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, CDCl₃) δ 1.07 - 1.26 (1 H, m) 1.48 (2 H, br s) 1.69 - 2.05 (10 H, m) 2.40 (3 H, s) 3.14 (2 H, br t, *J*=11.03 Hz) 3.50 - 3.70 (2 H, m) 5.98 (1 H, br d, *J*=4.41 Hz) 7.18 (1 H, br d, *J*=8.16 Hz) 7.25 (1 H, s) 7.52 (3 H, br d, *J*=8.16 Hz) 7.63 - 7.79 (3 H, m) 7.89 (1 H, d, *J*=7.50 Hz) 8.09 (1 H, br d, *J*=7.50 Hz) 8.40 (1 H, s) 10.22 - 11.57 (1 H, m). LC-MS: (ES) *m/z* 611.3 (M+H⁺).

Example S34: Synthesis of methyl 2-(((2R,3S)-2-(4-(cyclopentylamino)phenyl)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)piperidin-1-yl)sulfonyl)benzoate (Compound No. 31)



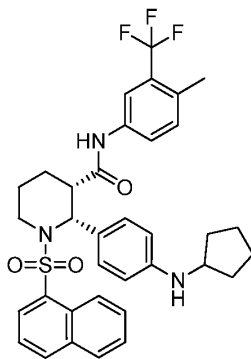
[0144] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.39 - 1.54 (m, 1 H), 1.61 - 1.74 (m, 4 H), 1.77 - 2.02 (m, 6 H), 2.02 - 2.18 (m, 1 H), 2.40 (d, *J*=1.22 Hz, 3 H), 2.99 (ddd, *J*=12.84, 5.62, 3.79 Hz, 1 H), 3.20 - 3.29 (m, 1 H), 3.84 - 3.94 (m, 1 H), 3.97 - 4.05 (m, 4 H), 5.76 (d, *J*=5.62 Hz, 1 H), 7.25 - 7.31 (m, 3 H), 7.50 - 7.64 (m, 5 H), 7.65 - 7.71 (m, 1 H), 7.82 (d, *J*=2.20 Hz, 1 H), 7.93 (d, *J*=7.83 Hz, 1 H), 9.86 (s, 1 H). LC-MS: (ES) *m/z* 666.2 (M+Na).

Example S35: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoro-methyl)phenyl)-1-(naphthalen-2-ylsulfonyl)piperidine-3-carboxamide (Compound No. 32)



[0145] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, CDCl₃) δ 1.46 (1 H, br s) 1.61 - 1.96 (13 H, m) 2.25 (3 H, s) 2.71 (1 H, br d, *J*=5.07 Hz) 2.95 (1 H, br t, *J*=12.68 Hz) 3.54 - 3.68 (1 H, m) 3.96 (1 H, br d, *J*=11.47 Hz) 6.06 (1 H, br s) 6.99 (1 H, br d, *J*=7.94 Hz) 7.16 (2 H, br d, *J*=8.16 Hz) 7.25 (1 H, s) 7.39 (1 H, br d, *J*=7.94 Hz) 7.47 - 7.64 (4 H, m) 7.81 - 7.92 (3 H, m) 8.27 (1 H, br s) 8.45 (1 H, br s). LC-MS: (ES) *m/z* 636.3 (M+H⁺).

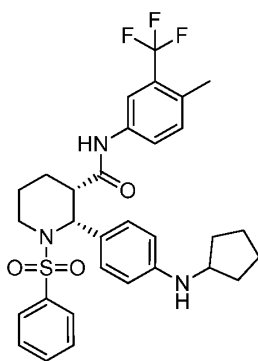
Example S36: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(naphthalen-1-ylsulfonyl)piperidine-3-carboxamide (Compound No. 33)



[0146] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.46 - 1.73 (m, 5 H), 1.77 - 1.99 (m, 6 H), 2.14 (qd, *J*=13.37,

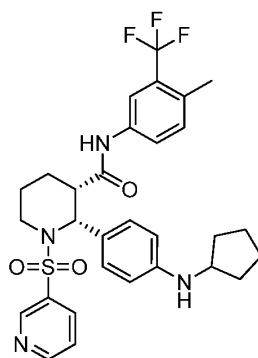
3.42 Hz, 1 H), 2.39 (s, 3 H), 3.17 (ddd, $J=12.90, 6.17, 3.91$ Hz, 1 H), 3.40 (td, $J=13.14, 2.32$ Hz, 1 H), 3.79 (quin, $J=6.91$ Hz, 1 H), 3.91 (br dd, $J=13.57, 3.06$ Hz, 1 H), 5.72 (d, $J=6.36$ Hz, 1 H), 7.10 (d, $J=8.56$ Hz, 2 H), 7.25 (d, $J=8.31$ Hz, 1 H), 7.37 (d, $J=8.56$ Hz, 2 H), 7.43 (dd, $J=8.31, 1.71$ Hz, 1 H), 7.51 (t, $J=7.83$ Hz, 1 H), 7.56 - 7.68 (m, 2 H), 7.71 (d, $J=1.71$ Hz, 1 H), 7.95 (d, $J=7.83$ Hz, 1 H), 8.10 (d, $J=8.07$ Hz, 1 H), 8.21 (d, $J=7.34$ Hz, 1 H), 8.58 (d, $J=8.31$ Hz, 1 H), 10.11 (s, 1 H). LC-MS: (ES) m/z 658.4 (M+Na).

Example S37: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoro-methyl)phenyl)-1-(phenylsulfonyl)piperidine-3-carboxamide (Compound No. 34)



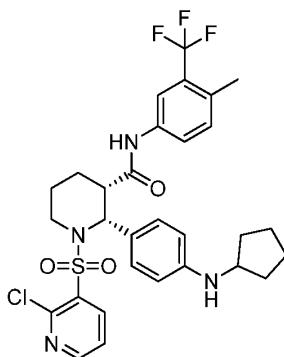
[0147] The title compound was synthesized in similar fashion as Example S12. ^1H NMR (400 MHz, CDCl_3) δ 1.41 - 1.55 (m, 2 H), 1.79 (br d, $J=12.57$ Hz, 6 H), 1.92 (br s, 4 H), 2.39 (br s, 3 H), 2.78 - 3.03 (m, 2 H), 3.67 (br s, 1 H), 3.86 (br d, $J=11.69$ Hz, 1 H), 5.85 (br s, 1 H), 6.98 (br s, 2 H), 7.14 (br s, 3 H), 7.35 - 7.52 (m, 4 H), 7.60 (br s, 1 H), 7.68 (br d, $J=7.06$ Hz, 2 H), 8.09 (br s, 1 H). LC-MS: (ES) m/z 608.3 (M+Na).

Example S38: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoro-methyl)phenyl)-1-(pyridin-3-ylsulfonyl)piperidine-3-carboxamide (Compound No. 35)



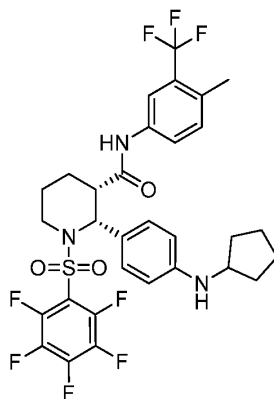
[0148] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.55 - 1.75 (4 H, m) 1.76 - 1.88 (3 H, m) 1.88 - 2.15 (5 H, m) 2.37 (3 H, s) 3.14 - 3.22 (1 H, m) 3.31 - 3.42 (1 H, m) 3.80 - 3.93 (1 H, m) 4.01 (1 H, br d, *J*=8.80 Hz) 5.70 (1 H, d, *J*=6.60 Hz) 7.19 - 7.28 (3 H, m) 7.40 (1 H, br d, *J*=8.56 Hz) 7.46 (2 H, d, *J*=8.31 Hz) 7.66 (1 H, dd, *J*=8.07, 5.14 Hz) 7.71 (1 H, s) 8.25 (1 H, br d, *J*=8.07 Hz) 8.67 - 8.76 (2 H, m). LC-MS: (ES) *m/z* 587.1 (M+H⁺).

Example S39: Synthesis of (2*R*,3*S*)-1-((2-chloropyridin-3-yl)sulfonyl)-2-(4-(cyclopentylamino)-phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No.36)



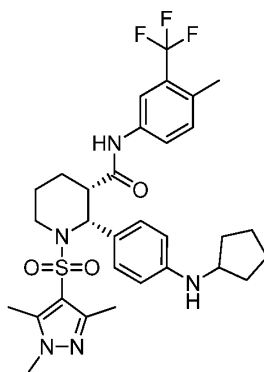
[0149] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.59 - 1.75 (m, 5 H), 1.82 (br d, *J*=4.89 Hz, 2 H), 1.90 - 2.01 (m, 3 H), 2.06 (br d, *J*=13.45 Hz, 1 H), 2.16 - 2.30 (m, 1 H), 2.38 (d, *J*=1.22 Hz, 3 H), 3.25 (ddd, *J*=12.96, 6.60, 4.16 Hz, 1 H), 3.65 (td, *J*=13.27, 2.81 Hz, 1 H), 3.80 - 3.91 (m, 1 H), 3.99 (br d, *J*=10.27 Hz, 1 H), 5.53 (d, *J*=6.60 Hz, 1 H), 7.23 (t, *J*=8.80 Hz, 3 H), 7.37 - 7.43 (m, 1 H), 7.45 - 7.51 (m, 3 H), 7.68 (d, *J*=1.96 Hz, 1 H), 8.37 - 8.50 (m, 2 H), 10.08 (s, 1 H). LC-MS: (ES) *m/z* 621.3 (M+H⁺).

Example S40: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoro-methyl)phenyl)-1-((perfluorophenyl)sulfonyl)piperidine-3-carboxamide (Compound No. 37)



[0150] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, METHANOL-*d*4) δ 1.53 - 1.71 (4 H, m) 1.72 - 1.99 (6 H, m) 2.05 - 2.16 (2 H, m) 2.37 (3 H, s) 3.17 (1 H, ddd, *J*=12.72, 6.36, 3.67 Hz) 3.59 (1 H, br t, *J*=12.84 Hz) 3.77 - 3.87 (1 H, m) 4.08 - 4.16 (1 H, m) 5.63 (1 H, d, *J*=6.60 Hz) 7.16 (2 H, br d, *J*=8.31 Hz) 7.23 (1 H, d, *J*=8.31 Hz) 7.38 (1 H, br d, *J*=8.31 Hz) 7.46 (2 H, d, *J*=8.56 Hz) 7.69 (1 H, d, *J*=1.71 Hz). LC-MS: (ES) *m/z* 676.2 (M+H⁺).

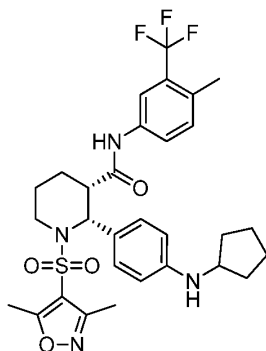
Example S41: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoro-methyl)phenyl)-1-((1,3,5-trimethyl-1H-pyrazol-4-yl)sulfonyl)piperidine-3-carboxamide (Compound No. 38)



[0151] The title compound was synthesized in similar fashion as Example S12. ¹H NMR (400 MHz, CDCl₃) δ 1.53 (br s, 1 H), 1.64 (br s, 2 H), 1.72 - 2.09 (m, 9 H), 2.25 (s, 3 H), 2.34

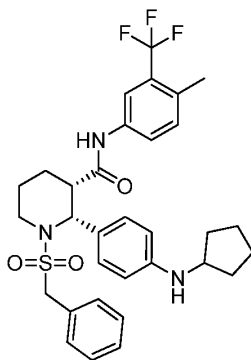
(s, 3 H), 2.41 (s, 3 H), 2.96 (br t, $J=12.55$ Hz, 1 H), 3.02 - 3.13 (m, 1 H), 3.66 (s, 4 H), 3.77 (br d, $J=12.30$ Hz, 1 H), 5.70 (br d, $J=4.27$ Hz, 1 H), 7.17 (br d, $J=8.28$ Hz, 1 H), 7.31 (br d, $J=8.28$ Hz, 2 H), 7.42 - 7.49 (m, 2 H), 7.67 (s, 1 H), 8.09 (br s, 1 H), 11.20 (br s, 1 H). LC-MS: (ES) m/z 640.4 (M+Na).

Example S42: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((3,5-dimethylisoxazol-4-yl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 8)



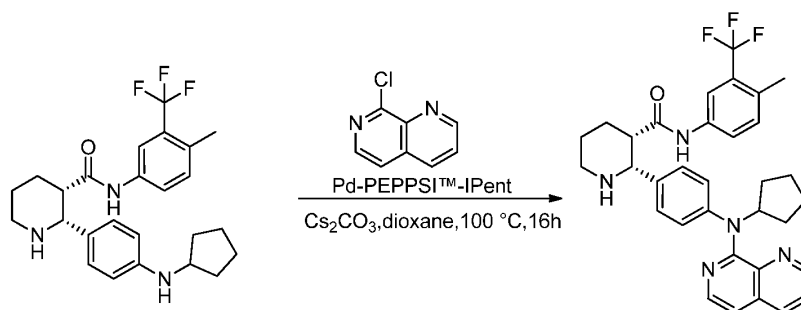
[0152] The title compound was synthesized in similar fashion as Example S12. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.58 - 1.74 (m, 5 H), 1.76 - 1.92 (m, 3 H), 1.92 - 2.04 (m, 2 H), 2.05 - 2.15 (m, 2 H), 2.21 (s, 3 H), 2.40 (s, 3 H), 2.47 (s, 3 H), 3.17 (ddd, $J=12.65$, 6.30, 3.79 Hz, 1 H), 3.56 (td, $J=12.90$, 2.57 Hz, 1 H), 3.83 - 3.97 (m, 2 H), 5.58 (d, $J=6.36$ Hz, 1 H), 7.27 (br d, $J=8.07$ Hz, 3 H), 7.42 - 7.47 (m, 1 H), 7.52 (d, $J=8.31$ Hz, 2 H), 7.75 (d, $J=1.96$ Hz, 1 H). LC-MS: (ES) m/z 627.2 (M+Na).

Example S43: Synthesis of (2R,3S)-1-(benzylsulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 40)



[0153] The title compound was synthesized in similar fashion as Example S12. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.57 - 1.74 (m, 5 H), 1.77 - 2.03 (m, 6 H), 2.12 - 2.25 (m, 1 H), 2.40 (s, 3 H), 3.09 - 3.17 (m, 1 H), 3.18 - 3.27 (m, 1 H), 3.55 - 3.65 (m, 1 H), 3.93 (quin, $J=6.97$ Hz, 1 H), 4.10 (br d, $J=13.69$ Hz, 1 H), 4.28 (d, $J=13.69$ Hz, 1 H), 5.55 (br d, $J=5.87$ Hz, 1 H), 7.23 - 7.31 (m, 3 H), 7.31 - 7.40 (m, 5 H), 7.44 (br d, $J=7.09$ Hz, 1 H), 7.65 (d, $J=8.56$ Hz, 2 H), 7.74 (s, 1 H). LC-MS: (ES) m/z 622.1 (M+Na).

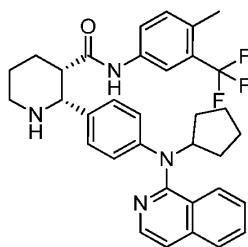
Example S44: Synthesis of (2R,3S)-2-(4-(cyclopentyl(1,7-naphthyridin-8-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 168)



[0154] (2R,3S)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-piperidine-3-carboxamide (150.00 mg, 286.18 μmol) and 8-chloro-1,7-naphthyridine (70.65 mg, 429.27 μmol) were dissolved in dioxane (6 mL), Pd-PEPPSI™-IPent (22.69 mg, 28.62 μmol) and Cs_2CO_3 (279.73 mg, 858.54 μmol) were added to the mixture. The mixture was stirred at 100°C under N_2 for 16 h. After cooled to 25°C, the reaction mixture was filtered, the filtrate was evaporated under vacuum to give crude product, which was purified by prep-HPLC (column: Agela ASB 150*25mm*5um; mobile phase: [water(0.05% HCl)-ACN]; B%: 30%-60%, 8 min). The result product from prep-HPLC was purified by prep-TLC (SiO_2 , DCM: MeOH = 10:1) to give (2R,3S)-2-[4-(cyclopentyl(1,7-naphthyridin-8-yl)amino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (6 mg, 8.95 μmol , 3.13% yield, 91% purity, HCl) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 0.73 - 0.85 (5 H, m), 1.13 - 1.34 (12 H, m), 1.51 - 1.68 (20 H, m), 1.79 - 1.89 (3 H, m), 1.89 - 2.02 (4 H, m), 2.16 - 2.24 (2 H, m), 2.33 (3 H, s), 2.80 - 2.91 (2 H, m), 3.36 (1 H, br d, $J=10.76$ Hz), 3.92 (1 H, d, $J=2.45$ Hz), 4.91 (1 H, br s), 6.86 - 6.93 (2 H, m), 6.96 (1 H, d, $J=5.38$ Hz), 6.99 - 7.07 (2 H, m), 7.10 (2 H, br d, $J=8.31$ Hz), 7.45 (1 H, br d, $J=8.07$ Hz),

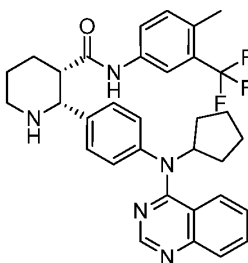
7.59 (1 H, s) 7.74 (1 H, d, $J=7.09$ Hz), 7.98 (1 H, br d, $J=2.69$ Hz), 8.09 (1 H, d, $J=5.62$ Hz), 10.75 (1 H, s). LCMS: m/z 574.3($M+H^+$).

Example S45: Synthesis of (2R,3S)-2-(4-(cyclopentyl(isoquinolin-1-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 175)



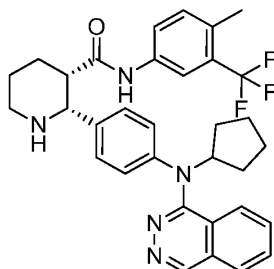
[0155] The title compound was synthesized in similar fashion as Example S46. 1H NMR (400 MHz, METHANOL- d_4) δ 1.43 - 1.73 (1 H, m) 1.43 - 1.70 (6 H, m) 1.85 - 2.03 (1 H, m) 2.13 (2 H, br s) 2.19 - 2.32 (3 H, m) 2.41 (3 H, d, $J=1.22$ Hz) 3.23 - 3.28 (2 H, m) 3.65 (1 H, br d, $J=11.25$ Hz) 4.61 (1 H, quin, $J=7.40$ Hz) 4.75 (1 H, d, $J=3.18$ Hz) 6.86 (1 H, t, $J=7.83$ Hz) 7.28 (1 H, d, $J=8.31$ Hz) 7.38 - 7.45 (3 H, m) 7.47 - 7.55 (2 H, m) 7.60 (3 H, d, $J=8.07$ Hz) 7.81 - 7.93 (3 H, m). LC-MS: (ES) m/z 573.3 ($M+H^+$).

Example S46: Synthesis of (2R,3S)-2-(4-(cyclopentyl(quinazolin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 177)



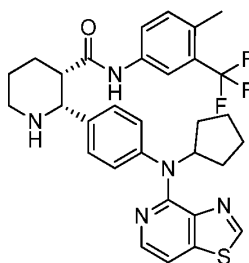
[0156] The title compound was synthesized in similar fashion as Example S46. 1H NMR (400 MHz, $CDCl_3$) δ 1.38 - 1.50 (m, 2 H), 1.58 (br d, $J=4.02$ Hz, 4 H), 1.72 (br d, $J=12.55$ Hz, 2 H), 1.98 - 2.09 (m, 3 H), 2.32 (br d, $J=12.30$ Hz, 1 H), 2.40 (s, 3 H), 2.91 - 3.05 (m, 2 H), 3.49 (br d, $J=10.79$ Hz, 1 H), 4.09 (d, $J=2.76$ Hz, 1 H), 5.17 - 5.29 (m, 1 H), 6.56 - 6.62 (m, 1 H), 6.65 - 6.72 (m, 1 H), 7.12 (br d, $J=8.28$ Hz, 3 H), 7.34 - 7.42 (m, 3 H), 7.52 (br d, $J=8.28$ Hz, 1 H), 7.65 - 7.74 (m, 2 H), 8.75 (s, 1 H), 10.73 (s, 1 H). LC-MS: (ES) m/z 574.2 ($M+H^+$).

Example S47: Synthesis of (2R,3S)-2-(4-(cyclopentyl(phthalazin-1-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 179)



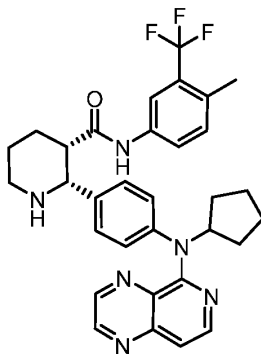
[0157] The title compound was synthesized in similar fashion as Example S46. ¹H NMR (400 MHz, CDCl₃) δ 1.22 - 1.30 (2 H, m), 1.80 - 1.98 (7 H, m), 2.04 (2 H, br s), 2.25 (1 H, br d, *J*=11.74 Hz), 2.39 (3 H, br s), 2.90 (2 H, br s), 3.42 (1 H, br d, *J*=11.98 Hz), 3.97 (1 H, br s), 4.92 (1 H, br s), 6.99 (2 H, br d, *J*=8.07 Hz), 7.10 (1 H, br d, *J*=8.31 Hz), 7.15 - 7.23 (3 H, m), 7.49 (3 H, br dd, *J*=18.83, 7.83 Hz), 7.60 (1 H, br s), 7.71 (1 H, br d, *J*=7.83 Hz), 9.11 (1 H, s), 10.73 (1 H, br s). LCMS: *m/z* 574.3 (M+H⁺).

Example S48: Synthesis of (2R,3S)-2-(4-(cyclopentyl(thiazolo[4,5-*c*]pyridin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 169)



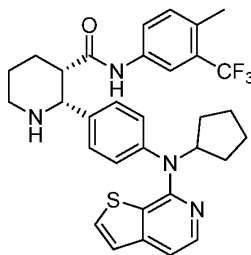
[0158] The title compound was synthesized in similar fashion as S46. ¹H NMR (400 MHz, CDCl₃) δ 0.65 - 0.94 (m, 1 H), 1.41 - 1.62 (m, 6 H), 1.66 - 2.05 (m, 8 H), 2.22 - 2.35 (m, 1 H), 2.40 (s, 3 H), 2.91 - 3.11 (m, 2 H), 3.48 (br d, *J*=11.0 Hz, 1 H), 4.08 (br s, 1 H), 5.16 - 5.31 (m, 1 H), 7.08 (d, *J*=8.3 Hz, 2 H), 7.14 (d, *J*=8.3 Hz, 1 H), 7.23 (d, *J*=5.5 Hz, 1 H), 7.30 (d, *J*=8.3 Hz, 2 H), 7.55 (dd, *J*=8.3, 1.5 Hz, 1 H), 7.66 (s, 1 H), 8.09 (d, *J*=5.5 Hz, 1 H), 8.21 (s, 1 H), 10.76 (br s, 1 H). LCMS: *m/z* 580.3 (M+H⁺).

Example S49: Synthesis of (2R,3S)-2-(4-(cyclopentyl(pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 172)



[0159] The title compound was synthesized in similar fashion as S46. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.36 - 1.56 (m, 2 H), 1.58 - 1.70 (m, 4 H), 1.86 - 1.94 (m, 1 H), 2.02 - 2.17 (m, 2 H), 2.19 - 2.25 (m, 2 H), 2.40 (s, 3 H), 3.19 (br s, 1 H), 3.60 (br d, *J*=12.47 Hz, 1 H), 4.33 - 4.44 (m, 1 H), 4.47 - 4.54 (m, 2 H), 4.72 (dd, *J*=4.03, 2.08 Hz, 1 H), 6.74 (dd, *J*=8.80, 7.34 Hz, 2 H), 6.92 (d, *J*=6.36 Hz, 1 H), 7.27 (d, *J*=8.31 Hz, 1 H), 7.37 (d, *J*=8.80 Hz, 2 H), 7.47 - 7.58 (m, 1 H), 7.67 - 7.72 (m, 1 H), 7.72 (d, *J*=2.93 Hz, 1 H), 7.93 (br d, *J*=8.31 Hz, 1 H), 10.14 (br d, *J*=2.93 Hz, 1 H). LC-MS: (ES) *m/z* 575.4 (M+H⁺).

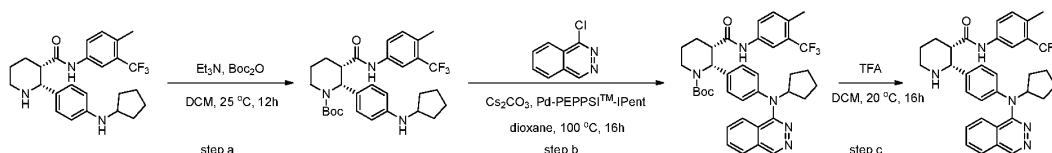
Example S50: Synthesis of (2R,3S)-2-(4-(cyclopentyl(thieno[2,3-*c*]pyridin-7-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 173)



[0160] The title compound was synthesized in similar fashion as S46. ¹H NMR (400 MHz, CDCl₃) δ 1.28 - 1.53 (m, 6 H), 1.72 (br d, *J*=13.8 Hz, 2 H), 1.85 - 2.08 (m, 5 H), 2.27 - 2.43 (m, 5 H), 2.91 - 3.08 (m, 2 H), 3.50 (br d, *J*=10.0 Hz, 1 H), 4.12 (d, *J*=2.5 Hz, 1 H), 5.10 - 5.26 (m, 1 H), 7.01 (s, 2 H), 7.05 (d, *J*=5.5 Hz, 1 H), 7.14 (d, *J*=8.5 Hz, 1 H), 7.23 (d, *J*=8.3

Hz, 2 H), 7.36 (d, $J=8.3$ Hz, 2 H), 7.56 (br d, $J=8.0$ Hz, 1 H), 7.71 (s, 1 H), 8.07 (d, $J=5.5$ Hz, 1 H), 10.77 (s, 1 H). LC-MS: (ES) m/z 579.23 ($M+H^+$).

Example S51: Synthesis of (2R,3S)-2-(4-(cyclopentyl(phthalazin-1-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 179)



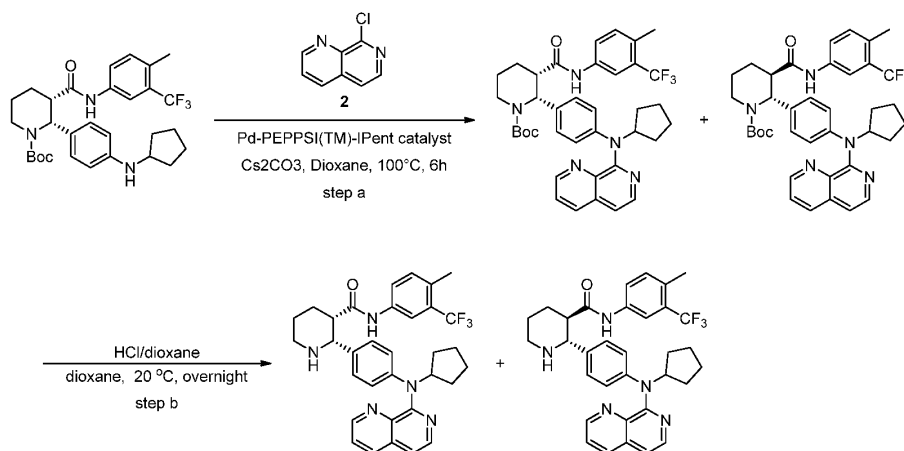
[0161] Step a) To a mixture of (2R,3S)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (1 g, 1.91 mmol) and Et_3N (386.12 mg, 3.82 mmol, 531.11 μL) in DCM (15 mL) was added Boc_2O (416.39 mg, 1.91 mmol, 438.31 μL) in one portion at 25 °C. The mixture was stirred at 25 °C for 12 hours. A light brown solution was noted. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give the residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, elution of 0~30% Ethyl acetate/Petroleum ether gradient @ 25 mL/min) to give a target product tert-butyl(2R,3S)-2-[4-(cyclopentylamino)phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (540 mg, 940.19 μmol , 49.28% yield, 95% purity) as white solid. ^1H NMR (400 MHz, CDCl_3) δ 1.36 - 1.45 (m, 2 H), 1.48 (s, 9 H), 1.46 - 1.51 (m, 1 H), 1.52 - 1.75 (m, 5 H), 1.83 (br d, $J=13.30$ Hz, 1 H), 1.90 - 1.99 (m, 3 H), 2.08 - 2.23 (m, 1 H), 2.39 (d, $J=1.51$ Hz, 3 H), 2.85 - 3.03 (m, 2 H), 3.57 - 3.75 (m, 2 H), 3.95 (br d, $J=14.05$ Hz, 1 H), 5.79 (br d, $J=5.27$ Hz, 1 H), 6.43 - 6.50 (m, 2 H), 7.08 - 7.21 (m, 3 H), 7.38 (dd, $J=8.28, 2.26$ Hz, 1 H), 7.59 (s, 1 H), 8.00 (br s, 1 H). LC-MS: (ES) m/z 546.3 ($M+H^+$).

[0162] Step b) Tert-butyl(2R,3S)-2-[4-(cyclopentylamino)phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (150 mg, 274.91 μmol) and 1-chlorophthalazine (67.87 mg, 412.36 μmol) were dissolved in dioxane (6 mL), Cs_2CO_3 (268.71 mg, 824.73 μmol) and Pd-PEPPSI™-IPent (21.80 mg, 27.49 μmol) were added to the mixture. The mixture was stirred at 100 °C under N_2 for 16h. The mixture was filtered, the filtrate was evaporated under vacuum to give crude product. The crude product was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=100/0 to 1:1) and prep-TLC (SiO_2 , Petroleum ether : Ethyl acetate= 1:1) to give the target product tert-butyl(2R,3S)-2-[4-(cyclopentyl(phthalazin-1-yl)amino)phenyl]-3-[[4-methyl-3-

(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (12 mg, 17.81 μ mol, 6.48% yield, 100% purity) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 1.19 - 1.33 (6 H, m) 1.56 (9 H, br s) 1.77 - 1.95 (7 H, m) 2.14 - 2.23 (1 H, m) 2.39 (3 H, s) 2.82 (1 H, br t, $J=13.08$ Hz) 2.89 - 3.00 (1 H, m) 3.93 (1 H, br d, $J=12.23$ Hz) 4.84 (1 H, br s) 5.28 (1 H, s) 5.78 (1 H, br s) 6.92 (2 H, br d, $J=8.31$ Hz) 7.11 (1 H, br d, $J=8.07$ Hz) 7.25 (2 H, s) 7.31 (1 H, br t, $J=7.83$ Hz) 7.45 (2 H, br d, $J=8.31$ Hz) 7.59 (1 H, t, $J=7.46$ Hz) 7.64 (1 H, s) 7.76 (1 H, d, $J=8.07$ Hz) 8.17 (1 H, br d, $J=13.94$ Hz) 9.15 (1 H, s). LC-MS: (ES) m/z 674.3 ($\text{M}+\text{H}^+$).

[0163] Step c) To a mixture of tert-butyl(2R,3S)-2-[4-[cyclopentyl(phthalazin-1-yl)amino]-phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (8 mg, 11.87 μ mol) in DCM (2 mL) was added TFA (154.00 mg, 1.35 mmol, 0.1 mL). The mixture was stirred at 25 $^\circ\text{C}$ for 1 h. A light yellow solution was noted. The reaction mixture was concentrated in vacuo to give the residue. The residue was diluted with DCM (10 mL) and alkalified to pH=8~9 by addition of saturated NaHCO_3 solution, washed with brine (2 x 5 mL), dried, filtered and concentrated in vacuo to give the crude product. The crude product was washed with mixed solvents (0.5 mL, Petroleum ether/EtOAc=10/1) and dried in vacuo to give the desired product to give the target product (2R,3S)-2-[4-[cyclopentyl(phthalazin-1-yl)amino]phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (4.5 mg, 7.77 μ mol, 65.41% yield, 99% purity) as light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 1.69 (br s, 2 H), 1.85 - 2.13 (m, 8 H), 2.17 - 2.32 (m, 2 H), 2.41 (s, 3 H), 2.86 - 2.98 (m, 2 H), 3.44 (br d, $J=11.49$ Hz, 1 H), 3.99 (d, $J=2.69$ Hz, 1 H), 4.93 (br s, 1 H), 5.24 - 5.49 (m, 1 H), 7.01 (d, $J=8.31$ Hz, 2 H), 7.12 (d, $J=8.07$ Hz, 1 H), 7.18 - 7.25 (m, 3 H), 7.28 - 7.37 (m, 1 H), 7.39 - 7.55 (m, 3 H), 7.63 (s, 1 H), 7.73 (d, $J=8.07$ Hz, 1 H), 9.12 (s, 1 H), 10.75 (s, 1 H). LC-MS: (ES) m/z 574.3 ($\text{M}+\text{H}^+$).

Example S52: Synthesis of (2R,3R)-2-(4-(cyclopentyl(1,7-naphthyridin-8-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide and (2R,3R)-2-(4-(cyclopentyl(1,7-naphthyridin-8-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound Nos. 168 and 171)



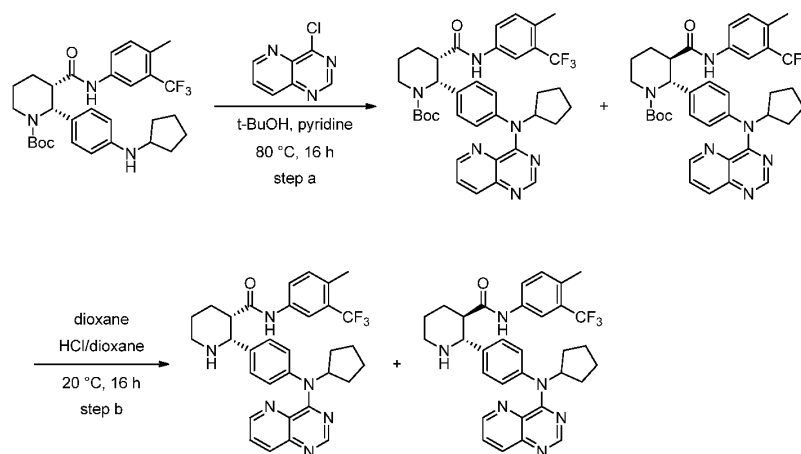
[0164] Step a) A mixture of tert-butyl(2R,3S)-2-[4-(cyclopentylamino)phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (200 mg, 366.55 μmol), 8-chloro-1,7-naphthyridine (75 mg, 455.67 μmol), Pd-PEPPSI(TM)-IPent catalyst (29.09 mg, 36.66 μmol) and Cs_2CO_3 (358.28 mg, 1.10 mmol) in dioxane (4 mL) was stirred at 100 °C for 6 h. A brown suspension was noted. The reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 x 3 mL), dried and concentrated in vacuo to give the crude product. The crude product was purified by prep-TLC. The desired compounds tert-butyl(2R,3S)-2-[4-[cyclopentyl(1,7-naphthyridin-8-yl)amino]phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (20 mg, 29.68 μmol , 6.67% yield, 100% purity) LC-MS: (ES) m/z 674.4 ($\text{M}+\text{H}^+$) and tert-butyl(2R,3R)-2-[4-[cyclopentyl(1,7-naphthyridin-8-yl)amino]phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (20 mg, 29.68 μmol , 6.67% yield, 100% purity) were obtained as light yellow gum. LC-MS: (ES) m/z 674.4 ($\text{M}+\text{H}^+$).

[0165] Step b) To a solution of tert-butyl(2R,3S)-2-[4-[cyclopentyl(1,7-naphthyridin-8-yl)amino]phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (20mg, 29.68 μmol) in DCM (0.5 mL) was added HCl/dioxane (4 M, 74.21 μL). Then the mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated in vacuo to give the crude product. The crude was washed with MTBE (3 * 1 mL) and dried in vacuo to give the desired product (HCl salt). The product was dissolved with H_2O (3 mL) and alkalified to pH=9~10, then the mixture was extracted with DCM (3 * 5 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give the desired product as light yellow gum, which was lyophilized. The desired compound (2R,3S)-2-[4-

[cyclopentyl(1,7-naphthyridin-8-yl)amino]phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (8 mg, 13.95 μ mol, 46.98% yield, 100% purity) was obtained as yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 1.63 - 1.71 (m, 2 H), 1.73 - 2.11 (m, 9 H), 2.27 (br d, $J=12.55$ Hz, 1 H), 2.41 (d, $J=1.51$ Hz, 3 H), 2.85 - 3.02 (m, 2 H), 3.43 (br d, $J=11.29$ Hz, 1 H), 4.00 (d, $J=2.76$ Hz, 1 H), 4.92 - 5.08 (m, 1 H), 6.99 (d, $J=8.53$ Hz, 2 H), 7.04 (d, $J=5.77$ Hz, 1 H), 7.10 (dd, $J=8.28$, 4.02 Hz, 1 H), 7.13 (d, $J=8.03$ Hz, 1 H), 7.18 (d, $J=8.28$ Hz, 2 H), 7.53 (dd, $J=8.28$, 2.01 Hz, 1 H), 7.67 (d, $J=1.76$ Hz, 1 H), 7.82 (dd, $J=8.28$, 1.76 Hz, 1 H), 8.06 (dd, $J=4.27$, 1.76 Hz, 1 H), 8.17 (d, $J=5.77$ Hz, 1 H), 10.83 (s, 1 H). LC-MS: (ES) m/z 574.4 ($\text{M}+\text{H}^+$).

[0166] Step b) To a solution of tert-butyl(2R,3R)-2-[4-[cyclopentyl(1,7-naphthyridin-8-yl)amino]phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (20.00 mg, 29.68 μ mol) in DCM (0.5 mL) was added HCl/dioxane (4 M, 0.1 mL). Then the mixture was stirred at 25 $^\circ\text{C}$ for 1 h. The reaction mixture was concentrated in vacuo to give the crude product. The crude product was washed with MTBE (3 * 1 mL) and dried in vacuo to give the desired product (HCl salt). The product was dissolved with H_2O (3 mL) and alkalinized to pH=9~10, then the mixture was extracted with DCM (3 * 5 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give the crude product. The product was further purified by prep-TLC (DCM/MeOH=10/1). The desired compound (2R,3R)-2-[4-[cyclopentyl(1,7-naphthyridin-8-yl)amino]phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (6.8 mg, 11.62 μ mol, 39.14% yield, 98% purity) was obtained as yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 1.61 (br s, 2 H), 1.68 - 1.81 (m, 2 H), 1.88 - 2.05 (m, 4 H), 2.15 - 2.37 (m, 4 H), 2.42 (s, 3 H), 2.56 (br t, $J=9.29$ Hz, 1 H), 2.85 (td, $J=11.55$, 3.55 Hz, 1 H), 3.20 (br d, $J=11.49$ Hz, 1 H), 3.90 (d, $J=10.03$ Hz, 1 H), 4.91 (br d, $J=6.85$ Hz, 1 H), 6.94 (d, $J=8.31$ Hz, 2 H), 7.03 (dd, $J=8.19$, 4.03 Hz, 1 H), 7.07 - 7.16 (m, 2 H), 7.29 - 7.40 (m, 4 H), 7.57 (s, 1 H), 7.85 (d, $J=7.58$ Hz, 1 H), 8.01 (br d, $J=3.42$ Hz, 1 H), 8.19 (d, $J=5.62$ Hz, 1 H). LCMS: m/z 574.4 ($\text{M}+\text{H}^+$).

Example S53: Synthesis of (2R,3S)-2-(4-(cyclopentyl(pyrido[3,2-d]pyrimidin-4-yl)amino)-phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide and (2R,3R)-2-(4-(cyclopentyl-(pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)-phenyl)piperidine-3-carboxamide (Compound Nos. 174 and 176)



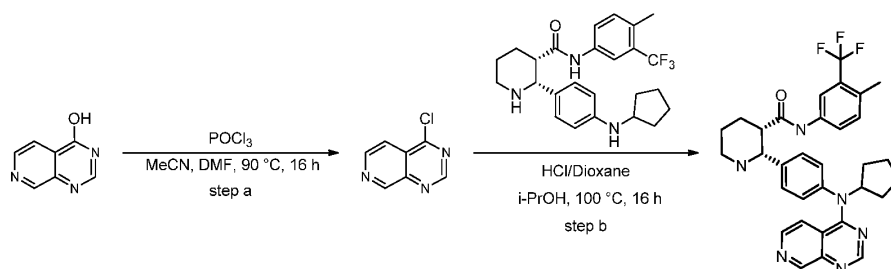
[0167] Step a) To a solution of tert-butyl (2R,3S)-2-[4-(cyclopentylamino)phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (120 mg, 219.93 μmol) in tert-butyl alcohol (1 mL) was added pyridine (17.40 mg, 219.93 μmol , 17.75 μL) and 4-chloropyrido[3,2-d]pyrimidine (33.14 mg, 200.13 μmol). The mixture was stirred at 80 $^{\circ}\text{C}$ for 16 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC to give tert-butyl(2R,3S)-2-[4-[cyclopentyl(pyrido-[3,2-d]pyrimidin-4-yl)amino]phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (12 mg, 16.36 μmol , 7.44% yield, 92% purity) as a light yellow solid (^1H NMR (400 MHz, CDCl_3) δ 1.49 (s, 9 H), 1.56 - 1.72 (m, 4 H), 1.92 (br s, 3 H), 1.98 - 2.06 (m, 3 H), 2.07 - 2.14 (m, 1 H), 2.15 - 2.27 (m, 1 H), 2.37 - 2.47 (m, 4 H), 2.93 - 3.01 (m, 1 H), 3.02 - 3.08 (m, 1 H), 4.06 (br d, $J=11.49$ Hz, 1 H), 5.40 - 5.53 (m, 1 H), 5.91 (br d, $J=4.40$ Hz, 1 H), 7.03 (d, $J=8.31$ Hz, 2 H), 7.15 (d, $J=8.31$ Hz, 1 H), 7.27 - 7.31 (m, 1 H), 7.39 (d, $J=8.31$ Hz, 2 H), 7.50 (br d, $J=8.31$ Hz, 1 H), 7.67 (s, 1 H), 7.97 (dd, $J=8.44$, 1.59 Hz, 1 H), 8.02 (dd, $J=3.91$, 1.47 Hz, 1 H), 8.67 (s, 1 H). LC-MS: (ES) m/z 675.3 ($\text{M}+\text{H}^+$)) and tert-butyl(2R,3R)-2-[4-[cyclopentyl (pyrido[3,2-d]pyrimidin-4-yl)amino]phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (53 mg, 76.98 μmol , 35.00% yield, 98% purity) as a yellow solid (^1H NMR (400 MHz, CDCl_3) δ 1.52 (s, 9 H), 1.56 - 1.73 (m, 8 H), 1.81 - 1.94 (m, 1 H), 2.09 (br d, $J=5.87$ Hz, 2 H), 2.41 (br s, 1 H), 2.45 (s, 3 H), 2.95 (td, $J=12.90$, 3.30 Hz, 1 H), 3.39 (br s, 1 H), 4.03 - 4.13 (m, 1 H), 5.51 - 5.62 (m, 1 H), 5.98 (br s, 1 H), 7.13 - 7.19 (m, 2 H), 7.25 (d, $J=8.31$ Hz, 3 H), 7.42 (dd, $J=8.44$, 4.03 Hz, 1 H), 7.80 - 7.89 (m, 2 H), 8.03 (dd, $J=8.44$, 1.34 Hz, 1 H), 8.23 (dd, $J=3.91$, 1.47 Hz, 1 H), 8.70 (s, 1 H), 8.95 (br s, 1 H). LC-MS: (ES) m/z 675.3 ($\text{M}+\text{H}^+$)).

[0168] Step b) To a solution of tert-butyl(2R,3S)-2-[4-[cyclopentyl(pyrido[3,2-d]pyrimidin-4-yl)amino]phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (12 mg, 17.78 μ mol) in dioxane (1 mL) was added HCl/dioxane (4 M, 44.46 μ L). The mixture was stirred at 20 °C for 16 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Then the residue was alkalized with aq. NaHCO₃ (3ml), then extracted with DCM 50 mL (25 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the product. The residue was purified by prep-HPLC (basic condition, column: Xtimate C18 10 μ 250 mm * 50 mm; mobile phase: [water (0.04% NH₃H₂O + 10 mM NH₄HCO₃)-ACN]; B%: 65%-95%, 8 min to give (2R,3S)-2-[4-[cyclopentyl(pyrido[3,2-d]pyrimidin-4-yl)amino]phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-piperidine-3-carboxamide (5 mg, 8.61 μ mol, 48.44% yield, 99% purity) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 1.44 (br d, *J*=6.60 Hz, 2 H), 1.52 - 1.62 (m, 5 H), 1.90 - 2.09 (m, 4 H), 2.32 (br d, *J*=12.23 Hz, 1 H), 2.39 (s, 3 H), 2.97 (br t, *J*=11.74 Hz, 1 H), 3.03 (br s, 1 H), 3.49 (br d, *J*=11.49 Hz, 1 H), 4.10 (br d, *J*=2.20 Hz, 1 H), 5.38 - 5.51 (m, 1 H), 7.07 (br d, *J*=8.07 Hz, 2 H), 7.13 (br d, *J*=8.31 Hz, 1 H), 7.21 (dd, *J*=8.19, 4.28 Hz, 1 H), 7.32 (br d, *J*=8.31 Hz, 2 H), 7.55 (br d, *J*=8.31 Hz, 1 H), 7.72 (s, 1 H), 7.84 - 7.96 (m, 2 H), 8.66 (s, 1 H), 10.83 (s, 1 H). LC-MS: (ES) *m/z* 575.3 (M+H⁺).

[0169] Step b) To a solution of tert-butyl (2R,3R)-2-[4-[cyclopentyl(pyrido[3,2-d]pyrimidin-4-yl)amino]phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]piperidine-1-carboxylate (50 mg, 74.10 μ mol) in dioxane (1 mL) was added HCl/dioxane (4 M, 185.25 μ L). The mixture was stirred at 20 °C for 16 hr. No further monitoring. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. Then the residue was alkalized with aq. NaHCO₃ (3ml), then extracted with DCM 50 mL (25 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the residue. The residue was purified by prep-HPLC (basic condition, column: Xtimate C18 10 μ 250 mm * 50 mm; mobile phase: [water (0.04% NH₃H₂O + 10 mM NH₄HCO₃)-ACN]; B%: 52%-82%, 8 min) to give (2R,3R)-2-[4-[cyclopentyl(pyrido[3,2-d]pyrimidin-4-yl)amino]phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (22 mg, 37.90 μ mol, 51.15% yield, 99% purity) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 1.25 - 1.42 (m, 4 H), 1.51 (br d, *J*=5.62 Hz, 2 H), 1.70 (q, *J*=12.88 Hz, 2 H), 1.95 - 2.05 (m, 3 H), 2.06 - 2.15 (m, 1 H), 2.41 (s, 3 H), 2.43 - 2.50 (m, 1 H), 2.87 - 2.96 (m, 1 H), 3.23 (br d, *J*=11.49 Hz, 1 H), 3.97 (d,

$J=9.54$ Hz, 1 H), 5.43 - 5.55 (m, 1 H), 7.05 (d, $J=8.31$ Hz, 2 H), 7.14 (dt, $J=8.19, 3.97$ Hz, 2 H), 7.25 (br s, 1 H), 7.40 - 7.49 (m, 3 H), 7.55 - 7.61 (m, 1 H), 7.58 (s, 1 H), 7.85 (br d, $J=2.45$ Hz, 1 H), 7.93 (dd, $J=8.44, 1.34$ Hz, 1 H), 8.61 (s, 1 H). LC-MS: (ES) m/z 575.3 ($M+H^+$).

Example S54: Synthesis of (2R,3S)-2-(4-(cyclopentyl(pyrido[3,4-d]pyrimidin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 178)

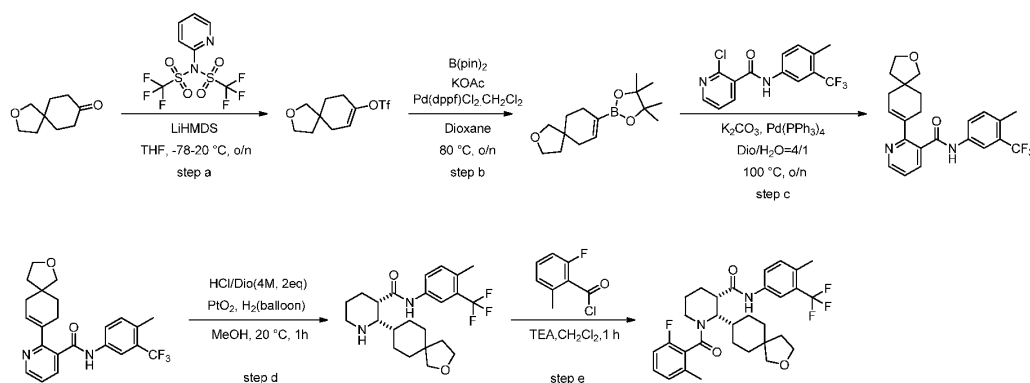


[0170] Step a) To a solution of pyrido[3,4-d]pyrimidin-4-ol (50 mg, 339.83 μ mol) in MeCN (1 mL) was added DMF (4.72 mg, 64.55 μ mol, 4.97 μ L), then the POCl₃ (2.57 g, 16.76 mmol, 1.56 mL) was added. The mixture was stirred at 90 °C for 16 hr. The reaction mixture was concentrated under reduced pressure to remove POCl₃. The residue was diluted with aq. NaHCO₃ 10 mL and extracted with EtOAc 60 mL (30 mL * 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the pure product. Compound 4-chloropyrido[3,4-d]pyrimidine (170 mg) was obtained as a gray solid. ¹H NMR (400 MHz, DMSO) δ 8.01 (d, $J=5.38$ Hz, 1 H), 8.27 (s, 1 H), 8.69 (d, $J=5.38$ Hz, 1 H), 9.11 (s, 1 H). LC-MS: (ES) m/z 166.0 ($M+H^+$).

[0171] Step b) To a solution of (2R,3S)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (150 mg, 336.69 μ mol) in isopropyl alcohol (1.2 mL) was added HCl/dioxane (4 M, 105.21 μ L) and then the 4-chloropyrido[3,4-d]pyrimidine (66.90 mg, 404.02 μ mol) was added. The mixture was stirred at 100 °C for 16 hr. The reaction mixture was alkalized with aq. NaHCO₃ 6 mL and extracted with EtOAc 50 mL. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (basic condition, column: Xtimate C18 10 μ 250 mm * 50 mm; mobile phase: [water (0.04% NH₃H₂O + 10 mM NH₄HCO₃)-ACN]; B%: 70%-100%, 8 min) to give (2R,3S)-2-[4-(cyclopentyl(pyrido[3,4-d]pyrimidin-4-yl)amino)phenyl]-N-[4-methyl-3-

(trifluoromethyl)phenyl]piperidine-3-carboxamide (20 mg, 33.76 μ mol, 10.03% yield, 97% purity) as a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 1.32 - 1.47 (m, 2 H), 1.51 - 1.62 (m, 4 H), 1.74 (br d, $J=12.80$ Hz, 2 H), 1.98 - 2.06 (m, 3 H), 2.33 (br d, $J=11.80$ Hz, 1 H), 2.39 (br d, $J=1.26$ Hz, 3 H), 2.95 - 3.05 (m, 2 H), 3.52 (br d, $J=11.29$ Hz, 1 H), 4.14 (d, $J=3.01$ Hz, 1 H), 5.21 - 5.31 (m, 1 H), 6.02 (d, $J=6.02$ Hz, 1 H), 7.13 - 7.21 (m, 3 H), 7.45 (d, $J=8.28$ Hz, 2 H), 7.53 (d, $J=2.01$ Hz, 1 H), 7.69 (dd, $J=8.28, 1.76$ Hz, 1 H), 7.86 (d, $J=6.02$ Hz, 1 H), 8.81 (s, 1 H), 9.13 (s, 1 H), 10.74 (s, 1 H). LC-MS: (ES) m/z 575.3 ($\text{M}+\text{H}^+$).

Example S55: Synthesis of (2S,3S)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)-phenyl)-2-(2-oxaspiro[4.5]decan-8-yl)piperidine-3-carboxamide (Compound No. 170)



[0172] Step a) To a solution of 2-oxaspiro[4.5]decan-8-one (300 mg, 1.95 mmol, 422.39 μ L) in THF (12 mL) was added LiHMDS (2M in THF/heptane) (2 M, 1.26 mL) at -78°C . After stirred for 30 min, the 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (1.04 g, 2.92 mmol) in THF (6 mL) was added. The mixture was stirred at 20°C for 15.5 hr. Saturated aqueous NaHCO_3 (20 mL) solution was added followed by dilution with EtOAc (80 mL). The organic layer was dried over Na_2SO_4 , filtered and the solvent removed under reduced pressure to give the residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=15/1 to 10:1) to give 2-oxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (430 mg, 1.50 mmol, 77.21% yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 1.73 - 1.84 (m, 4 H), 2.23 (br d, $J=3.18$ Hz, 2 H), 2.38 - 2.46 (m, 2 H), 3.55 (d, $J=1.47$ Hz, 2 H), 3.91 (t, $J=7.09$ Hz, 2 H), 5.75 (t, $J=4.03$ Hz, 1 H) LC-MS: (ES) m/z 287.05 ($\text{M}+\text{H}^+$).

[0173] Step b) A mixture of 2-oxaspiro[4.5]dec-7-en-8-yl trifluoromethanesulfonate (430 mg, 1.50 mmol), KOAc (294.83 mg, 3.00 mmol) and 4,4,5,5-tetramethyl-2-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (420 mg, 1.65 mmol) in dioxane (6 mL), after 5 min, the Pd(dppf)Cl₂.CH₂Cl₂ (61.33 mg, 75.10 μmol) was added. The mixture was degassed and purged with N₂ 3 times, and then the mixture was stirred at 80 °C for 15 h 55 min under N₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=20/1 to 10:1). Compound 4,4,5,5-tetramethyl-2-(2-oxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane (304 mg, 1.15 mmol, 76.61% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 1.27 (s, 12 H), 1.55 - 1.63 (m, 2 H), 1.65 - 1.77 (m, 2 H), 2.10 - 2.14 (m, 2 H), 2.16 - 2.24 (m, 2 H), 3.51 (s, 2 H), 3.82 - 3.91 (m, 2 H), 6.49 - 6.55 (m, 1 H). LC-MS: (ES) *m/z* 265.2 (M+H⁺).

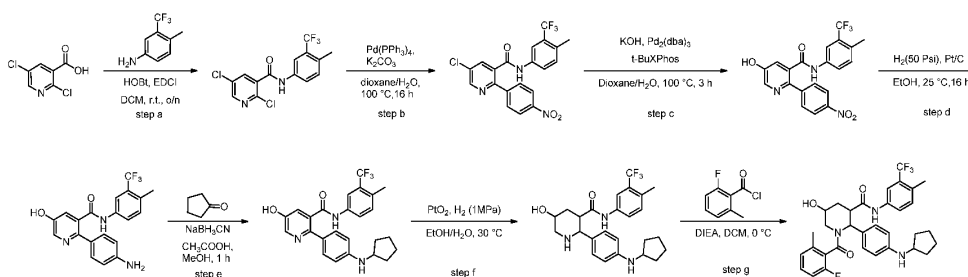
[0174] Step c) A mixture of 2-chloro-N-[4-methyl-3-(trifluoromethyl)phenyl]pyridine-3-carboxamide (130 mg, 413.11 μmol), 4,4,5,5-tetramethyl-2-(2-oxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane (140 mg, 529.97 μmol), Pd(PPh₃)₄ (95.47 mg, 82.62 μmol) and K₂CO₃ (2 M, 619.66 μL) in dioxane (3 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 100 °C for 16 h under an N₂ atmosphere. The reaction mixture was diluted with H₂O 10 mL and extracted with EtOAc 50 mL. The combined organic layers was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1/1 to 0:1) to give N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(2-oxaspiro[4.5]dec-7-en-8-yl)pyridine-3-carboxamide (153 mg, crude) as a colorless gum. LC-MS: (ES) *m/z* 417.2 (M+H⁺).

[0175] Step d) A mixture of N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(2-oxaspiro[4.5]dec-7-en-8-yl)pyridine-3-carboxamide (150 mg, 360.20 μmol), HCl/dioxane (4 M, 180.10 μL) and PtO₂ (16.36 mg, 72.04 μmol) in MeOH (10 mL) was degassed and purged with H₂ (15 psi) (726.09 μg, 360.20 μmol) for 3 times, and then the mixture was stirred at 20 °C for 3 h under H₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition, column: Waters Xbridge Prep OBD C18 150 * 30 10μ; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 35%-65%, 11 min) to give N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(2-oxaspiro[4.5]decan-8-yl)piperidine-3-carboxamide (70 mg, 148.41 μmol, 41.20% yield, 90% purity) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 0.88 - 1.17 (m, 2 H), 1.22 - 1.43 (m, 3 H), 1.46 - 1.65 (m, 4 H), 1.76 - 1.91 (m, 5 H), 2.17 (br d, *J*=13.55 Hz, 1 H), 2.44 (s, 4 H), 2.67 - 2.77 (m, 2 H), 3.29 (br d, *J*=11.29 Hz, 1 H), 3.39 -

3.46 (m, 1 H), 3.55 (q, $J=8.53$ Hz, 1 H), 3.83 (dt, $J=18.07$, 7.28 Hz, 2 H), 7.23 (d, $J=8.28$ Hz, 1 H), 7.70 (s, 1 H), 7.77 (br d, $J=8.28$ Hz, 1 H), 11.21 (br s, 1 H). LC-MS: (ES) m/z 425.3 ($M+H^+$).

[0176] Step e) To a solution of N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(2-oxaspiro[4.5]decan-8-yl) piperidine-3-carboxamide (50 mg, 117.79 μ mol) in DCM (6 mL) was added DIEA (53.28 mg, 412.25 μ mol, 71.81 μ L) and then the 2-fluoro-6-methyl-benzoyl chloride (60.98 mg, 353.36 μ mol) in DCM (1 mL) was added by dropwise at 0 °C. The mixture was stirred at 0 °C for 2 hr. The reaction mixture was quenched by addition H₂O 5 mL, and then extracted with DCM 40 mL (20 mL * 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue combined with previous batch (15 mg) was purified by prep-HPLC (HCl condition, column: Agela ASB 150 * 25 mm * 5 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 60%-90%, 8 min). The compound 1-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(2-oxaspiro[4.5]decan-8-yl)piperidine-3-carboxamide (50 mg, 96% purity) was obtained as a white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.04 - 1.59 (m, 5 H), 1.64 - 1.82 (m, 6 H), 1.88 (br d, $J=13.30$ Hz, 1 H), 2.00 - 2.17 (m, 2 H), 2.29 - 2.41 (m, 3 H), 2.44 (s, 3 H), 2.75 - 2.86 (m, 1 H), 3.03 - 3.18 (m, 1 H), 3.38 - 3.45 (m, 1 H), 3.49 - 3.59 (m, 1 H), 3.73 - 3.85 (m, 2 H), 4.98 - 5.08 (m, 1 H), 7.04 (q, $J=9.03$ Hz, 1 H), 7.11 - 7.22 (m, 1 H), 7.31 - 7.41 (m, 2 H), 7.63 - 7.73 (m, 1 H), 7.96 (s, 1 H), 10.31 (br d, $J=9.54$ Hz, 1 H). LC-MS: (ES) m/z 561.3 ($M+H^+$).

Example S56: Synthesis of 2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-5-hydroxy-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 42)



[0177] Step a) To a mixture of 2,5-dichloropyridine-3-carboxylic acid (5 g, 26.04 mmol, 31.27 μ L), 4-methyl-3-(trifluoromethyl)aniline (4.33 g, 24.74 mmol, 3.55 mL) in DCM (75 mL) was added successively with EDCI (5.99 g, 31.25 mmol) and HOBt (1.06 g, 7.81 mmol)

at 0 °C. Then the mixture was stirred at 15 °C for 12 h. The mixture was concentrated in vacuo to give the residue. The residue was dissolved with EtOAc (100 mL) and washed with saturated NaHCO₃ solution (2 x 10 mL), then acidified to pH=4~5 by addition of HCl (4 M) twice, dried, filtered and concentrated in vacuo to give the desired product 2,5-dichloro-N-[4-methyl-3-(trifluoromethyl)phenyl]pyridine-3-carboxamide (7.4 g, 21.20 mmol, 81.39% yield, 100% purity) as light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 2.49 (d, *J*=1.22 Hz, 3 H), 7.32 (d, *J*=8.31 Hz, 1 H), 7.75 (dd, *J*=8.19, 1.83 Hz, 1 H), 7.82 (d, *J*=1.71 Hz, 1 H), 8.15 (d, *J*=2.69 Hz, 1 H), 8.39 (br s, 1 H), 8.45 (d, *J*=2.69 Hz, 1 H). LC-MS: (ES) *m/z* 349.0 (M+H⁺).

[0178] **Step b)** To a mixture of 2,5-dichloro-N-[4-methyl-3-(trifluoromethyl)phenyl]pyridine-3-carboxamide (1 g, 2.86 mmol, 31.27 μL), (4-nitrophenyl)boronic acid (573.74 mg, 3.44 mmol, 3.55 mL) in dioxane (16 mL) was added successively with Pd(PPh₃)₄ (330.98 mg, 286.42 μmol) and K₂CO₃ (2 M, 4.30 mL) at 15 °C. Then the mixture was stirred at 100 °C for 12 h. The mixture was concentrated in vacuo to give the residue. The residue was dissolved with EtOAc (100 mL) and washed with H₂O (2 x 5 mL), dried, filtered and concentrated in vacuo to give the crude product. The crude was purified by prep-HPLC (column: Boston Prime C18 150 x 30 mm x 5 μm; mobile phase: [water (0.04% NH₃H₂O + 10 mM NH₄HCO₃)-ACN]; B%: 55%-85%, 8 min) to give 5-chloro-N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-nitrophenyl)pyridine-3-carboxamide (0.12 g, 269.86 μmol, 29.40% yield, 98% purity) as light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 2.45 (s, 3 H), 7.19 (s, 1 H), 7.25 (d, *J*=8.53 Hz, 1 H), 7.44 (br d, *J*=8.28 Hz, 1 H), 7.54 (d, *J*=1.76 Hz, 1 H), 7.92 (d, *J*=8.78 Hz, 2 H), 8.07 (d, *J*=2.51 Hz, 1 H), 8.31 (d, *J*=8.78 Hz, 2 H), 8.80 (d, *J*=2.26 Hz, 1 H). LC-MS: (ES) *m/z* 436.1 (M+H⁺).

[0179] **Step c)** A mixture of 5-chloro-N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-nitrophenyl) pyridine-3-carboxamide (1.8 g, 4.13 mmol), Pd₂(dba)₃ (189.12 mg, 206.52 μmol), t-Bu Xphos (175.40 mg, 413.05 μmol) and KOH (695.29 mg, 12.39 mmol) in dioxane (40 mL) / H₂O (20 mL) was stirred at 100 °C for 16 h. The mixture was diluted with EtOAc (50 mL) and acidified to pH=4~5 by addition of HCl (2 N). The mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried, filtered and concentrated in vacuo to give the residue. The residue was triturated with mixed solvents (22 mL, Petroleum ether/EtOAc=10/1) twice. The filter cake was dissolved with EtOAc (100 mL) and filtered through a pad of silica gel. The filtrate was concentrated in vacuo to give the pure product 5-hydroxy-N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-

nitrophenyl]pyridine-3-carboxamide (1.7 g, 3.95 mmol, 95.66% yield, 97% purity) as light brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.38 (s, 3 H), 7.38 (d, *J*=8.31 Hz, 1 H), 7.42 (d, *J*=2.69 Hz, 1 H), 7.66 (br d, *J*=8.31 Hz, 1 H), 7.82 (d, *J*=8.80 Hz, 2 H), 7.95 (d, *J*=1.22 Hz, 1 H), 8.24 (d, *J*=8.80 Hz, 2 H), 8.40 (d, *J*=2.69 Hz, 1 H), 10.73 (s, 1 H), 10.76 (s, 1 H). LC-MS: (ES) *m/z* 418.1 (M+H⁺).

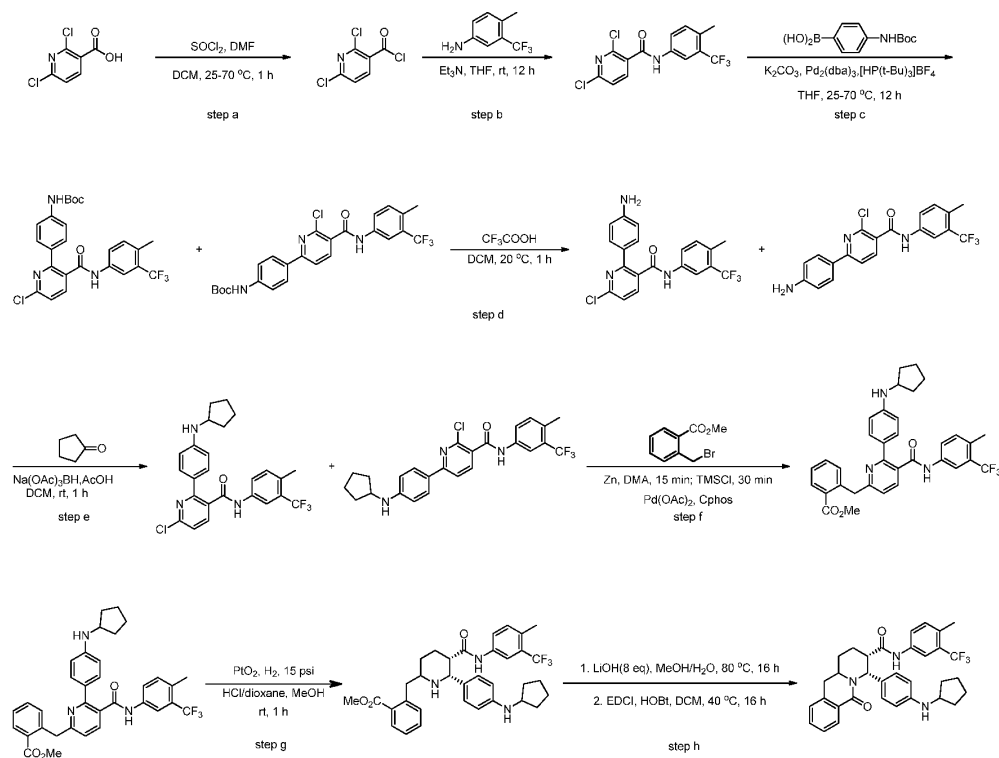
[0180] Step d) To a solution of 5-hydroxy-N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-nitrophenyl) pyridine-3-carboxamide (0.5 g, 1.20 mmol) in EtOH (15 mL) was added Pd/C (0.1 g, 10% purity) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 15°C for 16 h. The mixture was diluted with MeOH (20 mL) and filtered through a pad of Celite. The filtrate was concentrated in vacuo to give the desired compound 2-(4-aminophenyl)-5-hydroxy-N-[4-methyl-3-(trifluoromethyl)phenyl] pyridine-3-carboxamide (0.41 g, 1.01 mmol, 83.93% yield, 95% purity) as orange solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.38 (br s, 3 H), 5.22 (br s, 2 H), 6.49 (d, *J*=8.56 Hz, 2 H), 7.21 (d, *J*=2.69 Hz, 1 H), 7.30 (d, *J*=8.56 Hz, 2 H), 7.37 (br d, *J*=8.31 Hz, 1 H), 7.65 (br d, *J*=8.07 Hz, 1 H), 7.99 (s, 1 H), 8.25 (d, *J*=2.69 Hz, 1 H), 10.14 (s, 1 H), 10.49 (s, 1 H). LC-MS: (ES) *m/z* 388.1 (M+H⁺).

[0181] Step e) To a mixture of 2-(4-aminophenyl)-5-hydroxy-N-[4-methyl-3-(trifluoromethyl)-phenyl]pyridine-3-carboxamide (410.00 mg, 1.06 mmol) in MeOH (10 mL) was added cyclo-pentanone (89.03 mg, 1.06 mmol, 93.72 μL), HOAc (95.34 mg, 1.59 mmol, 90.80 μL) and NaBH₃CN (266.05 mg, 4.23 mmol) in one portion at 0 °C under N₂. The mixture was stirred at 30 °C for 16 h. The mixture was diluted with EtOAc (25 mL) and alkalinified to pH=8~9 and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and concentrated in vacuo to give the crude product. The crude product was purified by silica gel column chromatography (eluted with DCM/MeOH=100/1 to 10/1) to give 2-[4-(cyclopentylamino)-phenyl]-5-hydroxy-N-[4-methyl-3-(trifluoromethyl)phenyl]pyridine-3-carboxamide (450 mg, 948.47 μmol, 89.61% yield, 96% purity) as orange solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.39 (dt, *J*=12.17, 6.02 Hz, 2 H), 1.45 - 1.56 (m, 2 H), 1.58 - 1.70 (m, 2 H), 1.87 (dq, *J*=12.23, 6.03 Hz, 2 H), 2.38 (s, 3 H), 3.65 (dq, *J*=12.17, 5.97 Hz, 1 H), 5.72 (d, *J*=6.60 Hz, 1 H), 6.49 (d, *J*=8.80 Hz, 2 H), 7.21 (d, *J*=2.69 Hz, 1 H), 7.31 - 7.41 (m, 3 H), 7.67 (br d, *J*=8.31 Hz, 1 H), 7.97 (d, *J*=1.71 Hz, 1 H), 8.25 (d, *J*=2.69 Hz, 1 H), 10.14 (s, 1 H), 10.51 (s, 1 H). LC-MS: (ES) *m/z* 456.2 (M+H⁺).

[0182] Step f) To a solution of 2-[4-(cyclopentylamino)phenyl]-5-hydroxy-N-[4-methyl-3-(trifluoromethyl)phenyl]pyridine-3-carboxamide (0.45 g, 987.99 μmol) in EtOH (10 mL)/H₂O (5 mL) was added PtO₂ (112.17 mg, 493.99 μmol) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (1 MPa) at 30 °C for 32 h. The mixture was diluted with MeOH (20 mL) and filtered through a pad of Celite. The filtrate was concentrated in vacuo to give the crude. The crude was purified by prep-HPLC (column: Venusil ASB Phenyl 150 x 30 mm x 5 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 40%-70%, 10 min) to give 2-[4-(cyclopentylamino)phenyl]-5-hydroxy-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (120 mg, 260.01 μmol , 30.00% yield) as off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.31 (td, *J*=11.80, 6.24 Hz, 3 H), 1.49 (br s, 2 H), 1.60 (br s, 1 H), 1.81 (dt, *J*=12.29, 5.96 Hz, 2 H), 1.93 - 2.09 (m, 2 H), 2.34 (br s, 3 H), 2.79 (br d, *J*=14.18 Hz, 2 H), 2.99 (br d, *J*=12.47 Hz, 1 H), 3.53 - 3.61 (m, 1 H), 3.64 (br s, 1 H), 3.85 (br d, *J*=3.18 Hz, 1 H), 5.32 (br d, *J*=6.60 Hz, 1 H), 5.44 (br d, *J*=6.36 Hz, 1 H), 6.40 (br d, *J*=8.31 Hz, 2 H), 7.02 (br d, *J*=8.31 Hz, 2 H), 7.28 (br d, *J*=8.56 Hz, 1 H), 7.44 (br d, *J*=8.07 Hz, 1 H), 7.70 (s, 1 H), 10.33 (s, 1 H). LC-MS: (ES) *m/z* 462.3 (M+H⁺).

[0183] Step g) To a solution of 2-[4-(cyclopentylamino)phenyl]-5-hydroxy-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (10 mg, 19.93 μmol) and DIEA (5.15 mg, 39.87 μmol , 6.94 μL) in DCM (0.5 mL) was added dropwise of a solution of 2-fluoro-6-methyl-benzoyl chloride (3.27 mg, 18.94 μmol) in DCM (0.2 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min. The mixture was diluted with DCM (120 mL), washed with H₂O (2 x 10 mL), dried, filtered and concentrated in vacuo to give the crude product. The crude product was purified by prep-HPLC (column: Venusil ASB Phenyl 150 x 30 mm x 5 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 45%-75%, 9 min) to give 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-5-hydroxy-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (5 mg, 8.37 μmol , 41.97% yield, 100% purity) as white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.67 (br s, 4 H), 1.82 (br d, *J*=4.02 Hz, 2 H), 1.99 (br d, *J*=4.27 Hz, 2 H), 2.06 (s, 2 H), 2.12 - 2.26 (m, 1 H), 2.28 - 2.36 (m, 1 H), 2.36 - 2.48 (m, 5 H), 2.97 (dd, *J*=12.80, 11.04 Hz, 1 H), 3.24 - 3.30 (m, 1 H), 3.41 - 3.54 (m, 1 H), 3.71 - 3.87 (m, 1 H), 3.88 - 3.99 (m, 1 H), 6.44 - 6.52 (m, 1 H), 6.97 - 7.14 (m, 2 H), 7.19 (d, *J*=7.78 Hz, 1 H), 7.25 - 7.43 (m, 4 H), 7.46 - 7.58 (m, 1 H), 7.72 (dd, *J*=12.17, 8.66 Hz, 2 H), 7.78 - 7.88 (m, 1 H), 10.26 (d, *J*=10.79 Hz, 1 H). LC-MS: (ES) *m/z* 598.3 (M+H⁺).

Example S57: Synthesis of *cis*-4-(4-(cyclopentylamino)phenyl)-*N*-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-2,3,4,6,11,11a-hexahydro-1*H*-pyrido[1,2-*b*]isoquinoline-3-carboxamide (Compound No. 43)



[0184] Step a) To a mixture of 2,6-dichloropyridine-3-carboxylic acid (10 g, 52.08 mmol) and DMF (380.70 mg, 5.21 mmol, 400.73 μL) in DCM (20 mL) was added thionyl chloride (30.98 g, 260.42 mmol, 18.89 mL) in one portion at 25 °C. The mixture was stirred at 70 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a crude 2,6-dichloropyridine-3-carbonyl chloride (10.8 g, crude) as a light yellow solid. The crude product was used for the next step without further purification. LC-MS: (ES) m/z 206.1 ($\text{M}+\text{H}^+$).

[0185] Step b) To a mixture of 2,6-dichloropyridine-3-carbonyl chloride (10.8 g, 51.32 mmol) and 4-methyl-3-(trifluoromethyl)aniline (8.99 g, 51.32 mmol, 7.37 mL) in THF (30 mL) was added Et_3N (7.79 g, 76.98 mmol, 10.71 mL) in one portion at 0 °C. The mixture was stirred at 25 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography

(SiO₂, Petroleum ether/Ethyl acetate=100/0 to 10: 1) to give a crude product. The crude product was triturated with EtOAc (10 ml) and petroleum ether (50 ml) at 25 °C for 3 h to give the target product 2,6-dichloro-N-[4-methyl-3-(trifluoromethyl)-phenyl]pyridine-3-carboxamide (12.7 g, 36.38mmol, 70.88% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 2.50 (d, *J*=1.22 Hz, 3 H), 7.33 (d, *J*=8.31 Hz, 1 H), 7.77 (dd, *J*=8.07, 1.96 Hz, 1 H), 7.83 (d, *J*=1.71 Hz, 1 H), 8.21 (d, *J*=2.45 Hz, 1 H), 8.26 (br s, 1 H), 8.49 (d, *J*=2.69 Hz, 1 H). LC-MS: (ES) *m/z* 349.0 (M+H⁺).

[0186] Step c) To a mixture of [4-(tert-butoxycarbonylamino)phenyl]boronic acid (4.58 g, 19.33 mmol) and 2,6-dichloro-N-[4-methyl-3-(trifluoromethyl)phenyl]pyridine-3-carboxamide (10 g, 23.20 mmol) in THF (50 mL) and H₂O (5 mL) added Pd₂(dba)₃ (885.20 mg, 966.68 μmol), tritert-butylphosphonium; tetrafluoroborate (560.92 mg, 1.93 mmol) and KF (3.37 g, 58.00 mmol, 1.36 mL) in one portion at 25 °C under N₂. The mixture was stirred at 70 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with brine 50 mL and extracted with EtOAc 150 mL (50 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=100/1 to 5:1) to give the target product tert-butyl N-[4-[6-chloro-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-pyridyl]phenyl]carbamate and tert-butyl N-[4-[6-chloro-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-pyridyl]phenyl]carbamate (mixture, 7.5 g) as a light yellow solid. LC-MS: (ES) *m/z* 506.1 (M+H⁺).

[0187] Step d) To a mixture of tert-butyl N-[4-[6-chloro-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-pyridyl]phenyl]carbamate (14.82 mmol) and tert-butyl N-[4-[6-chloro-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-pyridyl]phenyl]carbamate in CH₂Cl₂ (3 mL) was added CF₃COOH (9.24 g, 81.04 mmol, 6 mL) in one portion at 0 °C. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a crude 2-(4-aminophenyl)-6-chloro-N-[4-methyl-3-(trifluoromethyl)phenyl]pyridine-3-carboxamide and 6-(4-aminophenyl)-2-chloro-N-[4-methyl-3-(trifluoromethyl)phenyl]pyridine-3-carboxamide (crude mixture 7.45g) as a light yellow oil. The crude was used for the next step without further purification. LC-MS: (ES) *m/z* 406.1 (M+H⁺).

[0188] Step e) To a mixture of cyclopentanone (3.11 g, 36.96 mmol, 3.27 mL) and 2-(4-aminophenyl)-6-chloro-N-[4-methyl-3-(trifluoromethyl)phenyl]pyridine-3-carboxamide and

6-(4-aminophenyl)-2-chloro-N-[4-methyl-3-(trifluoromethyl)phenyl]pyridine-3-carboxamide (7.45 g, mixture) in DCM (50 mL) was added AcOH (1.66 g, 27.72 mmol, 1.59 mL) and NaBH(OAc)₃ (3.92 g, 18.48 mmol) in one portion at 0 °C under N₂. The mixture was stirred at 30 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC: column: SANPONT C18, 250 x 50 mm x 10 µm, 100A; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 60%-90%, 25 min to give the target product 6-chloro-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(tri fluoromethyl)phenyl]pyridine-3-carboxamide (3.51 g, 7.41mmol, 40.07% yield) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 1.38 - 1.52 (m, 2 H), 1.60 - 1.67 (m, 2 H), 1.68 - 1.78 (m, 2 H), 2.01 (dq, *J*=12.7, 6.4 Hz, 2 H), 2.40 (d, *J*=1.0 Hz, 3 H), 3.80 (quin, *J*=6.2 Hz, 1 H), 3.97 (br s, 1 H), 6.60 (d, *J*=8.6 Hz, 2 H), 7.17 (d, *J*=8.3 Hz, 1 H), 7.22 (s, 1 H), 7.25 (s, 1 H), 7.26 - 7.33 (m, 2 H), 7.39 (br d, *J*=8.3 Hz, 1 H), 7.50 (d, *J*=8.6 Hz, 2 H), 8.07 (d, *J*=8.3 Hz, 1 H). LC-MS: (ES) *m/z* 474.1 (M+H⁺).

[0189] Step f) To a solution of zinc (363 mg, 5.55 mmol) in DMA (20 mL) was added 1,2-dibromoethane (63.42 mg, 337.61 µmol, 25.47 µL) by dropwise, then the mixture was stirred at 65 °C for 30 min. Later it was cooled to 25 °C. The chloro(trimethyl)silane (27.51 mg, 253.21 µmol, 32.14 µL) was added at 25 °C dropwise. The mixture was stirred at 25 °C for 30 min. Then the methyl 2-(bromomethyl)benzoate (1.0 g, 4.37 mmol) in DMA (5 mL) was added to the mixture dropwise. The reaction mixture was stirred at 25 °C for 1.5 h. The 6-chloro-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]pyridine-3-carboxamide (1 g, 2.11 mmol), Pd(OAc)₂ (47.37 mg, 211.01 µmol) and 2-(2-dicyclohexylphosphanylphenyl)-N1,N1,N3,N3-tetramethyl-benzene-1,3-diamine (92.13 mg, 211.01 µmol) in DMA (6 mL) was added to the mixture by dropwise. Then the mixture was stirred at 25 °C for 16 h under N₂ atmosphere. The reaction mixture was quenched by addition aq. NH₄Cl 50 mL, and then extracted with EtOAc 300 mL (150 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, eluent of 0~25% ethyl acetate/petroleum ether gradient @ 30 mL/min) to give methyl 2-[[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-pyridyl]methyl]benzoate (1.27 g, 2.10 mmol, 99.35% yield, 97% purity) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 1.48 (dt, *J*=12.17, 6.02 Hz, 2 H), 1.62 - 1.68 (m, 2 H), 1.72 - 1.79 (m, 2 H), 1.99 - 2.06 (m, 2 H), 2.42 (s, 3 H), 3.79 - 3.84 (m, 1 H), 3.85 (s, 3 H), 4.66 (s, 2 H),

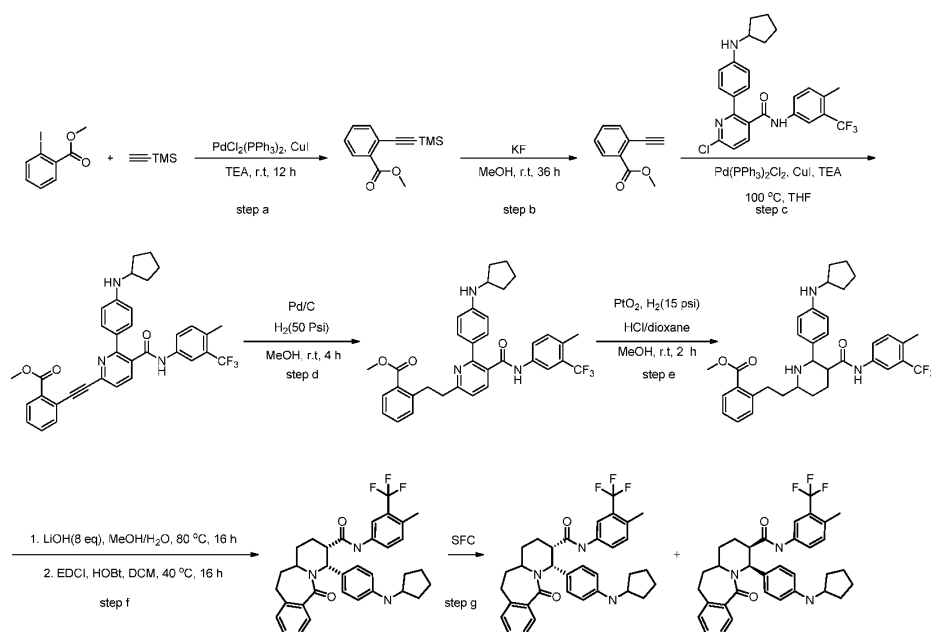
6.64 (d, $J=8.56$ Hz, 2 H), 7.05 (d, $J=8.07$ Hz, 1 H), 7.17 (br d, $J=11.25$ Hz, 2 H), 7.30 - 7.44 (m, 4 H), 7.47 - 7.53 (m, 3 H), 7.97 (dd, $J=7.95$, 1.10 Hz, 1 H), 8.04 (d, $J=7.83$ Hz, 1 H). LC-MS: (ES) m/z 588.24 ($M+H^+$).

[0190] Step g) A mixture of methyl 2-[[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(tri-fluoromethyl)phenyl]carbamoyl]-2-pyridyl]methyl]benzoate (500 mg, 850.88 μ mol), PtO_2 (101 mg, 444.78 μ mol) and HCl/dioxane (4 M, 426.00 μ L) in MeOH (15 mL) was degassed and purged with H_2 (15 psi) 3 times. Then the mixture was stirred at 20 °C for 7 h under H_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (HCl condition, column: Agela ASB 150 x 25 mm x 5 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 40%-70%, 8 min) to give cis-methyl 2-[[6-[4-(cyclopentylamino)-phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-piperidyl]methyl]benzoate (250 mg, 396.74 μ mol, 46.63% yield, 100% purity, HCl) as a white solid. 1H NMR (400 MHz, METHANOL- d_4) 1.59 - 1.75 (m, 4 H), 1.79 - 1.85 (m, 2 H), 1.88 - 1.99 (m, 2 H), 2.05 - 2.16 (m, 1 H), 2.20 (br s, 2 H), 2.40 (s, 3 H), 3.23 (br s, 1 H), 3.39 (br dd, $J=12.96$, 8.31 Hz, 1 H), 3.66 (dd, $J=12.96$, 5.62 Hz, 1 H), 3.87 (br d, $J=5.38$ Hz, 1 H), 3.92 - 3.96 (m, 1 H), 3.97 (s, 3 H), 4.81 (br s, 1 H), 7.28 (d, $J=8.31$ Hz, 1 H), 7.40 - 7.47 (m, 1 H), 7.47 - 7.54 (m, 2 H), 7.55 - 7.63 (m, 3 H), 7.77 (br d, $J=8.31$ Hz, 2 H), 7.88 (s, 1 H), 8.01 (d, $J=7.83$ Hz, 1 H), 10.18 (s, 1 H). LC-MS: (ES) m/z 594.3 ($M+H^+$).

[0191] Step h) To a solution of cis-methyl 2-[[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-piperidyl]methyl]benzoate (200 mg, 317.39 μ mol, HCl) in MeOH (10 mL) and H_2O (3 mL) was added LiOH (60.81 mg, 2.54 mmol). The mixture was stirred at 80 °C for 16 h. The reaction was concentrated and re-dissolved in DCM (15 mL). Then EDCI (182.53 mg, 952.17 μ mol), HOBt (42.89 mg, 317.39 μ mol) and 4-METHYLMORPHOLINE (122.00 mg, 1.21 mmol, 132.60 μ L) were added and the mixture was stirred at 40 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, eluent of 0~36% ethyl acetate/petroleum ether gradient @ 35mL/min). Compound cis-4-[4-(cyclopentyl-amino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-6-oxo-1,2,3,4,11,11a-hexahydrobenzo[b]-quinolizine-3-carboxamide (150 mg, 240.37 μ mol, 75.73% yield, 90% purity) was obtained as a white solid. 1H NMR (400 MHz, METHANOL- d_4) δ 1.39 - 1.51 (m, 2 H), 1.54 - 1.64 (m, 2 H), 1.67 - 1.84 (m, 3 H), 1.88 - 2.11 (m, 6 H), 2.44 (d, $J=1.25$ Hz, 3 H), 2.93 - 3.09 (m, 2 H), 3.72

(quin, $J=6.27$ Hz, 1 H), 3.97 - 4.10 (m, 1 H), 6.05 (d, $J=4.02$ Hz, 1 H), 6.55 (d, $J=8.53$ Hz, 2 H), 7.06 (d, $J=8.53$ Hz, 2 H), 7.25 - 7.39 (m, 3 H), 7.45 - 7.53 (m, 1 H), 7.62 (dd, $J=8.28$, 2.01 Hz, 1 H), 7.91 - 7.98 (m, 2 H). LC-MS: (ES) m/z 562.3(M+H⁺).

Example S58: Synthesis of (3S,4R)-4-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-1,2,3,4,6,11,12,12a-octahydrobenzo[e]pyrido[1,2-a]azepine-3-carboxamide and (3R,4S)-4-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-1,2,3,4,6,11,12,12a-octahydrobenzo[e]pyrido[1,2-a]azepine-3-carboxamide (Compound Nos. 44 and 45)



[0192] Step a) To a mixture of methyl 2-iodobenzoate (900 mg, 3.43 mmol, 505.62 μ L), CuI (32.71 mg, 171.73 μ mol, 0.05 eq) and dichloropalladium was added triphenylphosphane (120.53 mg, 171.73 μ mol) in TEA (40 mL) and ethynyl(trimethyl)silane (337.33 mg, 3.43 mmol, 475.79 μ L) in TEA (5 mL) at 20 °C under N₂. The mixture was filtered, washed with brine, and extracted with EtOAc (2 $\times$ 10mL). The combined extracts were dried over MgSO₄ and concentrated under vacuum to yield the residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=100/1 to 10:1) to give the target product methyl 2-(2-trimethylsilylethynyl)-benzoate (780 mg, 3.36mmol, 97.74% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 0.27 (s, 9 H), 3.83 - 3.98 (m, 4 H), 7.15 (td,

$J=7.7$, 1.8 Hz, 1 H), 7.32 - 7.47 (m, 2 H), 7.58 (d, $J=7.8$ Hz, 1 H), 7.79 (dd, $J=7.8$, 1.5 Hz, 1 H), 7.90 (dd, $J=7.8$, 0.8 Hz, 1 H), 7.99 (d, $J=7.8$ Hz, 1 H). LC-MS: (ES) m/z 233.1 ($M+H^+$).

[0193] Step b) To a mixture of methyl 2-(2-trimethylsilylethynyl)benzoate (780 mg, 3.36 mmol) in MeOH (3 mL) was added KF (390.06 mg, 6.71 mmol, 157.28 μ L) in one portion at 25 °C under N_2 . The mixture was stirred at 25 °C for 36 hours. The reaction mixture was concentrated under reduced pressure to remove MeOH (3 mL). The residue was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with 0.1M HCl (15 mL) and brine (15 mL x 3), dried over Na_2SO_4 , then filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=100/0 to 20:1) to give the target product methyl 2-ethynylbenzoate (280.5 mg, 1.75 mmol, 52.17% yield) as a brown oil. 1H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 1 H), 3.93 (s, 3 H), 7.37 - 7.43 (m, 1 H), 7.48 (td, $J=7.6$, 1.2 Hz, 1 H), 7.62 (d, $J=7.6$ Hz, 1 H), 7.94 (dd, $J=7.7$, 0.9 Hz, 1 H). LC-MS: (ES) m/z 161.05 ($M+H^+$).

[0194] Step c) To a solution of 6-chloro-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]pyridine-3-carboxamide (1.4 g, 2.95 mmol) and methyl 2-ethynylbenzoate (1.00 g, 6.24 mmol) in THF (40 mL) was added CuI (28.13 mg, 147.71 μ mol), PPh_3 (77.48 mg, 295.41 μ mol) and TEA (4.69 g, 46.34 mmol, 6.45 mL), then the mixture was stirred at 25 °C for 3 min. $Pd(PPh_3)_2Cl_2$ (100 mg, 142.47 μ mol) was added and the mixture was heated at 100 °C for 16 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with H_2O (100 mL) and extracted with EtOAc (300 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 , then filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 24 g SepaFlash® Silica Flash Column, Eluent of 0~30% ethyl acetate/petroleum ether gradient @ 30 mL/min). The compound methyl 2-[2-[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-pyridyl]ethynyl]benzoate (1.8 g, 2.71 mmol, 91.76% yield, 90% purity) was obtained as a brown gum. 1H NMR (400 MHz, $CDCl_3$) δ 1.48 (dt, $J=12.23$, 6.05 Hz, 2 H), 1.61 - 1.80 (m, 4 H), 1.98 - 2.05 (m, 2 H), 2.43 (s, 3 H), 3.79 - 3.87 (m, 1 H), 3.99 (s, 3 H), 6.65 (d, $J=8.53$ Hz, 2 H), 7.19 (br d, $J=8.28$ Hz, 1 H), 7.33 (s, 1 H), 7.40 - 7.48 (m, 2 H), 7.52 - 7.57 (m, 2 H), 7.60 (d, $J=8.03$ Hz, 1 H), 7.76 (d, $J=7.78$ Hz, 1 H), 8.03 (dd, $J=7.91$, 1.13 Hz, 1 H), 8.21 (d, $J=8.03$ Hz, 1 H). LC-MS: (ES) m/z 598.2 ($M+H^+$).

[0195] Step d) To a solution of methyl 2-[2-[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-pyridyl]ethynyl]benzoate (1.0 g, 1.67 mmol)

in MeOH (100 mL) was added Pd/C(wet) (400 mg, 10% purity). The mixture was degassed and purged with H₂ (15psi) 3 times, and then the mixture was stirred at 20 °C for 16 h under H₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a crude product (1.1 g). To a solution of the crude product (1.1 g) in MeOH (50 mL) was added Pd/C(wet) (700 mg, 10% purity). The mixture was degassed and purged with H₂ (50psi) 3 times, and then the mixture was stirred at 20 °C for another 4 hr under H₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; **20 g SepaFlash® Silica Flash Column, eluent of 0~25 % ethyl acetate/petroleum ether gradient @ 35 mL/min**) to give methyl 2-[2-[6-[4-(cyclopentylamino) phenyl]-5-[[4-methyl-3-(trifluoromethyl) phenyl]carbamoyl]-2-pyridyl]ethyl] benzoate (785 mg, 1.25 mmol, 68.07% yield, 96% purity) as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 1.48 (dq, *J*=12.23, 5.96 Hz, 2 H), 1.62 - 1.69 (m, 2 H), 1.71 - 1.81 (m, 2 H), 2.00 - 2.06 (m, 2 H), 2.42 (s, 3 H), 3.17 - 3.26 (m, 2 H), 3.45 (dd, *J*=9.29, 6.53 Hz, 2 H), 3.80 - 3.88 (m, 1 H), 3.92 (s, 3 H), 6.66 (d, *J*=8.53 Hz, 2 H), 7.17 - 7.23 (m, 3 H), 7.28 - 7.34 (m, 3H), 7.39 - 7.46 (m, 2 H), 7.51 (d, *J*=8.53 Hz, 2 H), 7.93 (d, *J*=7.78 Hz, 1 H), 8.09 (d, *J*=8.03 Hz, 1 H). LC-MS: (ES) *m/z* 602.3 (M+H⁺).

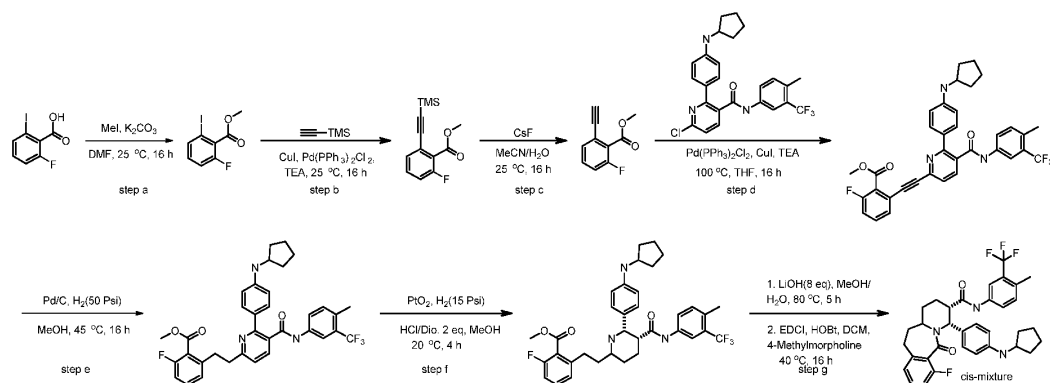
[0196] Step e) A mixture of methyl 2-[2-[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-pyridyl]ethyl]benzoate (400 mg, 664.83 μmol), PtO₂ (80.00 mg, 352.36 μmol) and HCl/dioxane (4 M, 334.00 μL) in MeOH (10 mL) was degassed and purged with H₂ (15 psi) 3 times, and then the mixture was stirred at 20 °C for 4 h under an H₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (HCl **condition**, column: Agela ASB 150 x 25 mm x 5 μm; mobile phase: [water (0.05%HCl)-ACN]; B%: 45%-75%, 8 min). The compound cis-methyl2-[2-[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-piperidyl]ethyl]benzoate (HCl) (270 mg, 95% purity) was obtained as a light yellow solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.64 (br d, *J*=3.18 Hz, 4 H), 1.80 (br s, 2 H), 1.87 - 1.98 (m, 2 H), 2.05 - 2.26 (m, 4 H), 2.26 - 2.35 (m, 2 H), 2.40 (s, 3 H), 2.97 - 3.09 (m, 1 H), 3.21 - 3.29 (m, 2 H), 3.48 - 3.59 (m, 1 H), 3.90 - 3.96 (m, 4 H), 4.80 (br s, 1 H), 7.27 (d, *J*=8.31 Hz, 1 H), 7.32 - 7.39 (m, 1 H), 7.42 (d, *J*=6.85 Hz, 1 H), 7.45 - 7.57 (m, 4 H), 7.77 (br d, *J*=8.31 Hz, 2 H), 7.86 (s, 1 H), 7.94 - 7.99 (m, 1 H), 10.19 (br s, 1 H). LC-MS: (ES) *m/z* 608.3 (M+H⁺).

[0197] Step f) To a solution of cis-methyl-2-[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-piperidyl]ethyl]benzoate (100 mg, 164.55 μmol) in MeOH (1 mL) and H₂O (0.3 mL) was added LiOH (31.53 mg, 1.32 mmol). The mixture was stirred at 80 °C for 16 h. The reaction was concentrated and re-dissolved in DCM (1.5 mL). Then EDCI (94.64 mg, 493.66 μmol), HOBt (22.24 mg, 164.55 μmol) and 4-methylmorpholine (63.25 mg, 625.30 μmol , 68.75 μL) were added and the mixture was stirred at 40 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% ethyl acetate/petroleum ether gradient @ 35 mL/min) to give cis-10-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-12-oxo-6,6a,7,8,9,10-hexahydro-5H-pyrido[1,2-b][2]benzazepine-9-carboxamide (40 mg, 64.62 μmol , 39.27% yield, 93% purity) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.38 (br d, $J=6.60$ Hz, 2 H), 1.52 - 1.61 (m, 2 H), 1.67 - 1.76 (m, 3 H), 1.88 - 1.99 (m, 4 H), 2.02 - 2.18 (m, 2 H), 2.33 (s, 3 H), 2.43 - 2.53 (m, 2 H), 2.60 - 2.73 (m, 1 H), 3.18 (dt, $J=11.55$, 5.84 Hz, 1 H), 3.58 (br s, 1 H), 3.63 - 3.71 (m, 1 H), 3.76 (br dd, $J=12.84$, 5.26 Hz, 1 H), 6.38 (d, $J=8.56$ Hz, 2 H), 6.76 (br d, $J=6.11$ Hz, 1 H), 7.01 (br d, $J=8.31$ Hz, 1 H), 7.07 (d, $J=7.09$ Hz, 1 H), 7.22 - 7.26 (m, 1 H), 7.28 - 7.35 (m, 2 H), 7.39 (s, 1 H), 7.50 (d, $J=8.56$ Hz, 2 H), 7.66 (d, $J=7.34$ Hz, 1 H), 8.80 (br s, 1 H). LC-MS: (ES) m/z 576.4 (M+H⁺).

[0198] Step g) The cis-10-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-12-oxo-6,6a,7,8,9,10-hexahydro-5H-pyrido[1,2-b][2]benzazepine-9-carboxamide (15 mg, 26.06 μmol) was separated by SFC (column: DAICEL CHIRALCEL OD-H (250 mm x 30 mm, 5 μm); mobile phase: [0.1% NH₃H₂O ETOH]; B%: 30%-30%, 8 min) to give (9S,10R)-10-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-12-oxo-6,6a,7,8,9,10-hexahydro-5H-pyrido[1,2-b][2]benzazepine-9-carboxamide (5 mg, 8.69 μmol , 33.33% yield, 100% purity) was obtained as a white solid (¹H NMR (400 MHz, CDCl₃) δ 1.34 - 1.41 (m, 2 H), 1.53 - 1.60 (m, 2 H), 1.69 - 1.78 (m, 3 H), 1.88 - 1.98 (m, 4 H), 2.02 - 2.14 (m, 2 H), 2.32 (s, 3 H), 2.44 - 2.52 (m, 2 H), 2.63 - 2.75 (m, 1 H), 3.20 (dt, $J=11.86$, 5.81 Hz, 1 H), 3.39 - 3.60 (m, 1 H), 3.65 (dt, $J=12.41$, 6.14 Hz, 1 H), 3.72 - 3.82 (m, 1 H), 6.35 (d, $J=8.80$ Hz, 2 H), 6.83 (d, $J=6.60$ Hz, 1 H), 6.97 (d, $J=8.31$ Hz, 1 H), 7.07 (d, $J=7.34$ Hz, 1 H), 7.23 - 7.26 (m, 1 H), 7.28 - 7.35 (m, 2 H), 7.36 (s, 1 H), 7.52 (d, $J=8.56$ Hz, 2 H), 7.68 (dd, $J=7.58$, 1.22 Hz, 1 H), 9.25 (br s, 1 H). LC-MS: (ES) m/z 576.3 (M+H⁺) and (9R,10S)-10-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-12-oxo-6,6a,7,8,9,10-hexahydro-5H-pyrido[1,2-b][2]benzazepine-9-carboxamide (5

mg, 8.43 μ mol, 32.33% yield, 97% purity) was obtained as a white solid (^1H NMR (400 MHz, CDCl_3) δ 1.37 (dt, $J=12.04$, 6.33 Hz, 2 H), 1.50 - 1.62 (m, 2 H), 1.68 - 1.76 (m, 3 H), 1.87 - 1.99 (m, 4 H), 2.01 - 2.14 (m, 2 H), 2.32 (s, 3 H), 2.44 - 2.53 (m, 2 H), 2.62 - 2.75 (m, 1 H), 3.21 (dt, $J=11.62$, 5.93 Hz, 1 H), 3.56 (br s, 1 H), 3.65 (quin, $J=6.24$ Hz, 1 H), 3.77 (br dd, $J=12.84$, 5.26 Hz, 1 H), 6.36 (d, $J=8.56$ Hz, 2 H), 6.83 (d, $J=6.60$ Hz, 1 H), 6.98 (d, $J=8.31$ Hz, 1 H), 7.07 (d, $J=7.58$ Hz, 1 H), 7.22 - 7.26 (m, 1 H), 7.31 (br dd, $J=7.46$, 1.10 Hz, 2 H), 7.34 - 7.37 (m, 1 H), 7.52 (d, $J=8.56$ Hz, 2 H), 7.68 (dd, $J=7.58$, 1.22 Hz, 1 H), 9.19 (br s, 1 H). LC-MS: (ES) m/z 576.3 ($\text{M}+\text{H}^+$)).

Example S59: Synthesis of *cis*-4-(4-(cyclopentylamino)phenyl)-7-fluoro-*N*-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-1,2,3,4,6,11,12,12a-octahydrobenzo[e]pyrido[1,2-*a*]azepine-3-carboxamide (Compound No. 41)



[0199] Step a) To a solution of 2-fluoro-6-iodo-benzoic acid (10 g, 37.59 mmol) in DMF (100 mL) was added K_2CO_3 (7.79 g, 56.39 mmol), then MeI (8.28 g, 58.33 mmol, 3.63 mL) was added. The mixture was stirred at 20 $^\circ\text{C}$ for 16 h. The reaction mixture was diluted with H_2O 100 mL and extracted with EtOAc 300 mL (150 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 20/1) to give methyl 2-fluoro-6-iodo-benzoate (10.4 g, 36.40 mmol, 96.81% yield, 98% purity) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 3.99 (s, 3 H), 7.09 - 7.16 (m, 2 H), 7.61 - 7.69 (m, 1 H). LC-MS: (ES) m/z 280.8 ($\text{M}+\text{H}^+$).

[0200] Step b) To a solution of methyl 2-fluoro-6-iodo-benzoate (11.1 g, 39.64 mmol) in TEA (80 mL) was added CuI (754.91 mg, 3.96 mmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (2.78 g, 3.96 mmol), then the ethynyl(trimethyl)silane (5.84 g, 59.46 mmol, 8.24 mL) in TEA (20 mL) was added by dropwise. The mixture was stirred at 20 $^\circ\text{C}$ for 16 h under N_2 atmosphere. The reaction

mixture was diluted with H₂O 100 mL and extracted with EtOAc 500 mL (250 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=20/1). The compound methyl 2-fluoro-6-(2-trimethylsilylethynyl) benzoate (9.9 g, 36.78 mmol, 92.78% yield, 93% purity) was obtained as a light brown oil. ¹H NMR (400 MHz, CDCl₃) δ 0.25 (s, 8 H), 3.95 (s, 3 H), 7.09 (ddd, *J*=9.35, 7.89, 1.59 Hz, 1 H), 7.28 - 7.39 (m, 2 H). LC-MS: (ES) *m/z* 251.1 (M+H⁺).

[0201] Step c) To a solution of methyl 2-fluoro-6-(2-trimethylsilylethynyl)benzoate (3 g, 11.98 mmol) in MeCN (80 mL) and H₂O (20 mL) was added CsF (7.28 g, 47.93 mmol, 1.77 mL). The mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove MeCN. The residue was extracted with ethyl acetate (250 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=30/1, plate 2) to give methyl 2-ethynyl-6-fluoro-benzoate (1.9 g, 10.56 mmol, 88.10% yield, 99% purity) as a light brown oil. ¹H NMR (400 MHz, CDCl₃) δ 3.29 (s, 1 H), 3.97 (s, 3 H), 7.10 - 7.17 (m, 1 H), 7.33 - 7.43 (m, 2 H). LC-MS: (ES) *m/z* 179.1 (M+H⁺).

[0202] Step d) To a solution of methyl 2-ethynyl-6-fluoro-benzoate (857.12 mg, 4.81 mmol) and 6-chloro-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]pyridine-3-carboxamide (760 mg, 1.60 mmol) in THF (50 mL) was added CuI (30.54 mg, 160.37 μmol), PPh₃ (42.06 mg, 160.37 μmol) and TEA (2.55 g, 25.16 mmol, 3.50 mL), then the mixture was stirred at 20 °C for 3 min. To the mixture was added Pd(PPh₃)₂Cl₂ (112.56 mg, 160.37 μmol) and the mixture was heated at 100 °C for 16 h under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with H₂O 100 mL and extracted with EtOAc (300 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% ethyl acetate/petroleum ether gradient @ 30 mL/min) to give 2-[2-[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-pyridyl]ethynyl]-3-fluoro-benzoate (720 mg, 1.09 mmol, 67.83% yield, 93% purity) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ 1.44 - 1.54 (m, 2 H), 1.61 - 1.69 (m, 2 H), 1.70 - 1.81 (m, 2 H), 1.98 - 2.12 (m, 2 H), 2.43 (s, 3 H), 3.77 - 3.88 (m, 1 H), 4.02 (s, 3 H), 6.65 (d,

$J=8.56$ Hz, 2 H), 7.15 - 7.26 (m, 3 H), 7.33 (s, 1 H), 7.44 (td, $J=8.01$, 5.50 Hz, 2 H), 7.48 - 7.55 (m, 4 H), 8.19 (d, $J=8.07$ Hz, 1 H). LC-MS: (ES) m/z 616.2 ($M+H^+$).

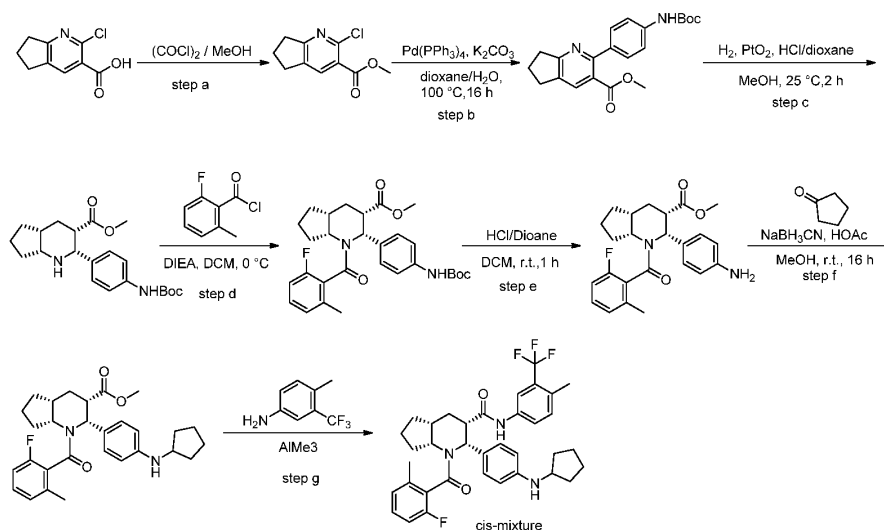
[0203] Step e) To a solution of methyl 2-[2-[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-pyridyl]ethynyl]-3-fluoro-benzoate (700 mg, 1.14 mmol) in MeOH (30 mL) was added Pd/C (wet) (100 mg, 10% purity). The mixture was degassed and purged with H_2 (50 psi) 3 times, and then the mixture was stirred at 45 °C for 4 h under H_2 atmosphere. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% ethyl acetate/petroleum ether gradient @ 35 mL/min) to give methyl 2-[2-[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-pyridyl]ethyl]-3-fluoro-benzoate (590 mg, 904.55 μ mol, 79.55% yield, 95% purity) as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ 1.43 - 1.53 (m, 2 H), 1.62 - 1.69 (m, 2 H), 1.71 - 1.80 (m, 2 H), 2.00 - 2.05 (m, 2 H), 2.42 (s, 3 H), 3.19 (s, 4 H), 3.69 - 3.77 (m, 1 H), 3.79 - 3.88 (m, 1 H), 3.94 (s, 3 H), 6.66 (d, $J=8.56$ Hz, 2 H), 6.99 (t, $J=8.93$ Hz, 1 H), 7.07 (dd, $J=17.12$, 7.83 Hz, 2 H), 7.16 - 7.24 (m, 2 H), 7.28 - 7.36 (m, 2 H), 7.42 (br d, $J=8.31$ Hz, 1 H), 7.51 (d, $J=8.56$ Hz, 2 H), 8.06 (d, $J=8.07$ Hz, 1 H). LC-MS: (ES) m/z 620.3 ($M+H^+$).

[0204] Step f) A mixture of methyl 2-[2-[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-pyridyl]ethyl]-3-fluoro-benzoate (580 mg, 936.02 μ mol), PtO_2 (106.28 mg, 468.01 μ mol) and HCl/dioxane (4 M, 470.24 μ L) in MeOH (20 mL) was degassed and purged with H_2 (15 psi) for 3 times, and then the mixture was stirred at 20 °C for 4 hr under H_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was alkalized with aqueous $NaHCO_3$ (10 mL) solution, then extracted with DCM 80 mL (40 mL $\times$ 2). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give a crude product. The crude product was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 0~2% ethyl acetate/petroleum ether gradient @ 35 mL/min) to give methyl 2-[2-[6-[4-(cyclopentylamino)-phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-piperidyl]ethyl]-3-fluoro-benzoate (520 mg, crude) as a brown gum. The crude product was further purified by prep-HPLC (HCl condition; column: Xtimate C18 150 $\times$ 40 mm $\times$ 10 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 30%-60%, 8 min) to give methyl 2-[2-[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-piperidyl]ethyl]-6-fluoro-benzoate (147 mg, 210.90 μ mol, 43.99% yield, 95% purity, HCl) as white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 1.45

(br d, $J=3.67$ Hz, 2 H), 1.57 - 1.78 (m, 6 H), 1.85 - 2.05 (m, 2 H), 2.12 (br s, 3 H), 2.34 (br s, 3 H), 2.65 - 2.87 (m, 2 H), 3.22 - 3.36 (m, 2 H), 3.73 - 3.81 (m, 2 H), 3.90 (s, 3 H), 4.67 (br d, $J=9.78$ Hz, 1 H), 7.18 - 7.35 (m, 4 H), 7.46 - 7.61 (m, 4 H), 7.98 (s, 1 H), 8.36 (br d, $J=10.76$ Hz, 1 H), 9.71 (br s, 1 H), 10.85 (s, 1 H). LC-MS: (ES) m/z 626.3 ($M+H^+$).

[0205] Step g) To a solution of methyl 2-[2-[6-[4-(cyclopentylamino)phenyl]-5-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-piperidyl]ethyl]-6-fluoro-benzoate (150 mg, 239.73 μ mol) in MeOH (3 mL) and H₂O (1 mL) was added LiOH (45.93 mg, 1.92 mmol). The mixture was stirred at 80 °C for 4 h. The reaction was concentrated and re-dissolved in DCM (5 mL). Then EDCI (137.87 mg, 719.20 μ mol), HOBt (32.39 mg, 239.73 μ mol) and 4-methylmorpholine (92.14 mg, 910.99 μ mol, 100.16 μ L) were added and the mixture was stirred at 40 °C for 16 h. The mixtures were concentrated under reduced pressure to remove DCM. The residue was diluted with H₂O 10 mL and extracted with DCM 50 mL (25 mL $\times$ 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crystallized solid was collected after re-crystallization from MeCN. The crystal was washed with MeCN 2 mL, filtered and the filter cake was dried under vacuum to give 10-[4-(cyclopentylamino)phenyl]-1-fluoro-N-[4-methyl-3-(trifluoromethyl)phenyl]-12-oxo-6,6a,7,8,9,10-hexahydro-5H-pyrido[1,2-b][2]benzazepine-9-carboxamide (45 mg, 74.29 μ mol, 30.99% yield, 98% purity) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.35 (br s, 2 H), 1.44 - 1.55 (m, 2 H), 1.56 - 1.68 (m, 3 H), 1.70 - 1.91 (m, 5 H), 2.08 - 2.18 (m, 1 H), 2.21 - 2.33 (m, 2 H), 2.34 (br s, 3 H), 2.53 - 2.61 (m, 2 H), 2.89 - 2.98 (m, 1 H), 3.57 (sxt, $J=6.11$ Hz, 1 H), 3.65 - 3.76 (m, 1 H), 5.47 (d, $J=6.36$ Hz, 1 H), 6.07 (d, $J=7.09$ Hz, 1 H), 6.35 (d, $J=8.56$ Hz, 2 H), 7.00 (d, $J=7.34$ Hz, 1 H), 7.13 (t, $J=9.17$ Hz, 1 H), 7.21 (d, $J=8.56$ Hz, 2 H), 7.29 (d, $J=8.31$ Hz, 1 H), 7.38 (td, $J=7.89, 5.75$ Hz, 1 H), 7.50 (br d, $J=8.07$ Hz, 1 H), 7.76 (d, $J=1.71$ Hz, 1 H), 10.23 (s, 1 H). LC-MS: (ES) m/z 594.4 ($M+H^+$).

Example S60: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 193)



[0206] Step a) To a mixture of 2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylic acid (485 mg, 2.45 mmol) in DCM (20 mL) was added oxalyl dichloride (467.26 mg, 3.68 mmol, 322.25 μL) and DMF (17.94 mg, 245.42 μmol , 18.88 μL). Then the mixture was stirred at 25°C for 15 min. The solvent was evaporated under vacuum. Then methanol (7.92 g, 247.12 mmol, 10 mL) was added. The reaction mixture was stirred at 25°C for another 15 min. The solvent was evaporated under vacuum to give methyl 2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylate (500 mg, crude) as a brown oil. LC-MS: (ES) m/z 212 ($\text{M}+\text{H}^+$).

[0207] Step b) $\text{Pd}(\text{PPh}_3)_4$ (545.99 mg, 472.49 μmol) was added to a mixture of methyl 2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylate (500 mg, 2.36 mmol), [4-(tert-butoxycarbonylamino)phenyl]boronic acid (840.06 mg, 3.54 mmol) and K_2CO_3 (979.54 mg, 7.09 mmol) in dioxane/ H_2O =1:1 (20 mL). The mixture was stirred at 100°C under N_2 for 3 h. The reaction mixture was extracted with EtOAc (30 mL x 2). The combined organic phase were washed with brine (30 mL), dried with anhydrous MgSO_4 and filtered. The filtrate was evaporated under vacuum to a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=100/0 to 3:1) to give methyl 2-[4-(tert-butoxycarbonylamino)phenyl]-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylate (480 mg, crude) as a white solid. LC-MS: (ES) m/z 369.2 ($\text{M}+\text{H}^+$).

[0208] Step c) PtO_2 (11.83 mg, 52.11 μmol) was added to a solution of methyl 2-[4-(tert-butoxycarbonylamino)phenyl]-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylate (480 mg, 1.30 mmol) and HCl (in H_2O) (12 M, 217.14 μL) in EtOH (10 mL). Then the mixture was

stirred at 25 °C under H₂ (15 psi) for 16 h. The reaction mixture was filtered. The filtrate was evaporated under vacuum. Then the mixture was added 10 mL of H₂O, alkalified with Na₂CO₃ solution and extracted with EtOAc (30 mL x 2). The combined organic phase were washed with brine (20 mL), dried with anhydrous MgSO₄ and filtered. The filtrate was evaporated under vacuum to give cis-methyl 2-[4-(tert-butoxycarbonylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (450 mg, 997.40 μmol, 76.56% yield, 83% purity) as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.35 - 1.52 (12 H, m) 1.54 - 1.90 (6 H, m) 2.00 - 2.09 (1 H, m) 2.81 - 2.97 (1 H, m) 3.15 (1 H, br d, *J*=5.62 Hz) 3.21 - 3.29 (3 H, m) 3.86 (1 H, br d, *J*=5.14 Hz) 7.16 (2 H, br d, *J*=8.07 Hz) 7.23 - 7.37 (2 H, m) 9.19 (1 H, br s). LC-MS: (ES) *m/z* 375.2 (M+H⁺).

[0209] **Step d)** 2-fluoro-6-methyl-benzoyl chloride (172.14 mg, 997.40 μmol) was added to a solution of cis-methyl-2-[4-(tert-butoxycarbonylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (450.00 mg, 997.40 μmol) and TEA (201.85 mg, 1.99 mmol, 277.65 μL) in DCM (10 mL). The mixture was stirred at 25 °C for 1 h. The reaction mixture was washed with 1N HCl (10 mL), H₂O (10 mL), brine (10 mL), dried with anhydrous Na₂SO₄ and filtered. The filtrate was evaporated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=100/0 to 3:1) to give cis-methyl 2-[4-(tert-butoxycarbonylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydro-cyclopenta[b]pyridine-3-carboxylate (440 mg, 766.95 μmol, 76.89% yield, 89% purity) as a white solid. LC-MS: (ES) *m/z* 511.2 (M+H⁺).

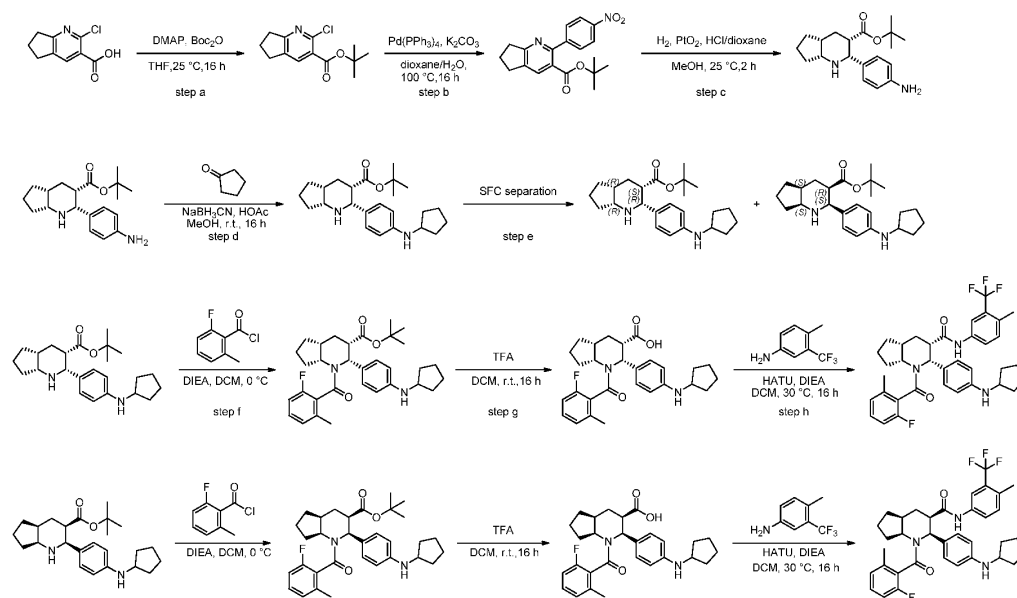
[0210] **Step e)** HCl/dioxane (4 M, 215.43 μL) was added to a solution of cis-methyl 2-[4-(tert-butoxycarbonylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydro-cyclopenta[b]pyridine-3-carboxylate (440 mg, 766.95 μmol) in DCM (10 mL). Then the solution was stirred at 25 °C for 1 h. The solvent was evaporated under vacuum to give cis-methyl 2-(4-amino phenyl)-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (390 mg, crude, HCl) as a brown oil. LC-MS: (ES) *m/z* 411.2 (M+H⁺).

[0211] **Step f)** To cyclopentanone (73.40 mg, 872.60 μmol, 77.26 μL) in DCM (10 mL) was added cis-methyl-2-(4-aminophenyl)-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydro-cyclopenta[b]pyridine-3-carboxylate (358.18 mg, 872.60 μmol, HCl), CH₃COOH (157.20 mg, 2.62 mmol, 149.71 μL) and HCl/dioxane (4 M, 283.59 μL), followed by NaBH(OAc)₃ (277.41 mg, 1.31 mmol). The mixture was stirred at 25 °C for 16 h. The reaction mixture was basified with Na₂CO₃ solution and extracted with DCM (30 mL x 2).

The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: Agela ASB 150 x 25 mm x 5 μm ; mobile phase: [water (0.05% HCl)- ACN]; B%: 42%-72%, 8 min) to give cis-methyl-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (200 mg, 417.89 μmol , 47.89% yield, 100% purity) as a light yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 0.96 - 1.21 (3 H, m), 1.23 - 1.46 (4 H, m), 1.47 - 1.59 (3 H, m), 1.59 - 1.72 (3 H, m), 1.74 - 1.95 (3 H, m), 1.95 - 2.11 (2 H, m), 2.23 - 2.36 (3 H, m), 2.88 - 3.04 (1 H, m), 3.50 - 3.71 (4 H, m), 5.53 - 5.61 (1 H, m), 6.38 - 6.44 (1 H, m), 6.48 (2 H, dd, $J=8.91, 2.38$ Hz), 6.99 (1 H, d, $J=8.53$ Hz), 7.04 - 7.16 (2 H, m), 7.30 - 7.40 (1 H, m). LC-MS: (ES) m/z 479.2 ($\text{M}+\text{H}^+$).

[0212] Step g) AlMe_3 (in toluene) (2 M, 156.71 μL) was added to a solution of 4-methyl-3-(trifluoromethyl)aniline (82.34 mg, 470.12 μmol) in DCE (6 mL). The mixture was stirred at 25 $^\circ\text{C}$ for 20 min. Then cis-methyl-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (150 mg, 313.42 μmol) was added to the mixture. The mixture was stirred at 85 $^\circ\text{C}$ for 3 h. The reaction mixture was basified with saturate NaHCO_3 solution. Then the mixture was extracted with EtOAc (50 mL x 2). The combined organic phase was washed with brine (50 mL), dried with anhydrous MgSO_4 and was filtered. The filtrate was evaporated under vacuum to give crude product. The crude product was purified by prep-HPLC (column: Xtimate C18 10 μ 250 mm x 50 mm; mobile phase: [water (0.04% $\text{NH}_3\text{H}_2\text{O}$ + 10 mM NH_4HCO_3)- ACN]; B%: 80%-100%, 8 min), then further purified by prep-HPLC (column: Agela ASB 150 x 25 mm x 5 μm ; mobile phase: [water (0.05% HCl)- ACN]; B%: 55%-85%, 8 min) to give cis-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxamide (58 mg, 92.36 μmol , 99% purity) as a white solid. (^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.07 - 1.30 (3 H, m) 1.50 - 1.61 (5 H, m) 1.63 - 1.76 (4 H, m) 1.88 (3 H, br d, $J=7.28$ Hz) 1.93 - 2.08 (2 H, m) 2.09 - 2.19 (2 H, m) 2.30 - 2.44 (6 H, m) 2.99 - 3.09 (1 H, m) 3.60 - 3.78 (1 H, m) 6.47 - 6.59 (1 H, m) 6.90 - 7.00 (2 H, m) 7.05 - 7.18 (2 H, m) 7.28 - 7.41 (2 H, m) 7.52 (2 H, dd, $J=16.56, 8.53$ Hz) 7.64 - 7.75 (1 H, m) 7.89 (1 H, dd, $J=14.81, 1.76$ Hz) 10.15 (1 H, br d, $J=8.78$ Hz). LC-MS: (ES) m/z 622.3 ($\text{M}+\text{H}^+$).

Example S61: Synthesis of (2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 48)



[0213] Step a) The DMAP (247.29 mg, 2.02 mmol) was added to a solution of 2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylic acid (800 mg, 4.05 mmol) and tert-butoxy carbonyl tert-butyl carbonate (1.77 g, 8.10 mmol, 1.86 mL) in THF (20 mL). The solution was stirred at 15 °C for 16 h. The reaction mixture was extracted with EtOAc (30 mL x 2). The combined organic phase was dried with anhydrous Na₂SO₄ and filtered. The filtrate was evaporated under vacuum to give residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=100:0 to 3:1) to give compound tert-butyl 2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylate (900 mg, 3.55 mmol, 87.62% yield, 100% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.58 (9 H, s), 2.15 (2 H, quin, *J*=7.58 Hz), 2.92 (2 H, t, *J*=7.46 Hz), 3.00 (2 H, t, *J*=7.70 Hz), 7.83 (1 H, s). LC-MS: (ES) *m/z* 254.0 (M+H⁺).

[0214] Step b) Pd(PPh₃)₄ (409.90 mg, 354.72 μmol) was added to a mixture of tert-butyl 2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylate (900.00 mg, 3.55 mmol), (4-nitrophenyl)boronic acid (769.75 mg, 4.61 mmol) and K₂CO₃ (1.47 g, 10.64 mmol) in dioxane/H₂O=1:1 (30 mL). The mixture was stirred at 100°C under N₂ for 16 h. The reaction mixture was extracted with EtOAc (30 mL x 2). The combined organic phase were washed

with brine (30 mL), dried with anhydrous MgSO_4 and filtered. The filtrate was evaporated under vacuum to a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=100/0 to 3:1) to give tert-butyl 2-(4-nitrophenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylate (935 mg, 2.75 mmol, 77.44% yield, 100% purity) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 1.29 (9 H, s), 2.20 (2 H, quin, $J=7.46$ Hz), 2.98 - 3.11 (4 H, m), 7.63 (2 H, br d, $J=7.58$ Hz), 7.94 (1 H, s), 8.27 (2 H, br d, $J=7.58$ Hz). LC-MS: (ES) m/z 341.1 ($\text{M}+\text{H}^+$).

[0215] Step c) To a solution of tert-butyl 2-(4-nitrophenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylate (1.1 g, 3.23 mmol) in MeOH (30 mL) was added PtO_2 (366.93 mg, 1.62 mmol) and HCl/dioxane (4 M, 1.62 mL) under N_2 . The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15psi) at 20 °C for 2 hours. LCMS showed ~80% of desired product was detected. The mixture was diluted with MeOH and filtered through a pad of Celite and concentrated in vacuo to give the residue. The residue was diluted with DCM (50 mL) and alkalified to pH=9~10. The organic layers separated was dried, filtered and concentrated in vacuo to give the residue. The crude residue was purified by column chromatography (SiO_2 , eluted with DCM/MeOH/ $\text{NH}_3\cdot\text{H}_2\text{O}$ =100/1/0.01 to 10/1/0.01) to give cis-tert-butyl 2-(4-aminophenyl)-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (0.6 g, 1.90 mmol, 66.67% yield, 100% purity) as light brown gum. ^1H NMR (400 MHz, CDCl_3) δ 1.18 (s, 9 H), 1.49 - 1.65 (m, 3 H), 1.68 - 1.82 (m, 2 H), 1.83 - 1.94 (m, 1 H), 1.99 - 2.09 (m, 2 H), 2.10 - 2.19 (m, 1 H), 2.80 (q, $J=6.02$ Hz, 1 H), 3.34 (td, $J=6.34, 2.89$ Hz, 1 H), 3.45 - 3.66 (m, 2 H), 3.93 (d, $J=5.52$ Hz, 1 H), 6.63 (d, $J=8.53$ Hz, 2 H), 7.15 (d, $J=8.28$ Hz, 2 H). LC-MS: (ES) m/z 317.2 ($\text{M}+\text{H}^+$).

[0216] Step d) To a mixture of cis-tert-butyl 2-(4-aminophenyl)-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (520.00 mg, 1.64 mmol) in MeOH (10 mL) was added cyclopentanone (179.70 mg, 2.14 mmol, 189.16 μL), HOAc (197.36 mg, 3.29 mmol, 187.96 μL) and NaBH_3CN (516.32 mg, 8.22 mmol) in one portion at 0 °C under N_2 . The mixture was stirred at 30 °C for 16 h. The mixture was diluted with DCM (30 mL) and alkalified to pH=8~9 and extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine, dried, filtered and concentrated in vacuo to give the desired compound tert-butyl 2-[4-(cyclopentylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (0.6 g, 1.50 mmol, 91.15% yield, 96% purity) was obtained as light brown gum. ^1H NMR (400 MHz, CDCl_3) δ 1.10 - 1.24 (m, 9 H), 1.39 - 1.47

(m, 2 H), 1.58 - 1.64 (m, 2 H), 1.66 - 1.77 (m, 4 H), 1.82 - 1.90 (m, 2 H), 1.98 - 2.11 (m, 6 H), 2.16 - 2.22 (m, 1 H), 2.78 (q, $J=6.11$ Hz, 1 H), 3.27 - 3.35 (m, 1 H), 3.78 (quin, $J=6.17$ Hz, 1 H), 3.92 (d, $J=5.62$ Hz, 1 H), 6.54 (d, $J=8.31$ Hz, 2 H), 7.13 (d, $J=8.31$ Hz, 2 H). LC-MS: (ES) m/z 385.3 ($M+H^+$).

[0217] Step e) The racemate cis-tert-butyl 2-[4-(cyclopentylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (850.00 mg, 2.21 mmol) was separated by SFC. (column: REGIS (s,s) WHELK-O1 (250 mm x 30 mm, 5 μ m); mobile phase: [0.1% $NH_3 \cdot H_2O$ ETOH]; B%: 30%-30%, 8 min). The compound tert-butyl (2S,3R,4aS,7aS)-2-[4-(cyclopentyl amino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta [b] pyridine-3-carboxylate (peak 1 showed on SFC spectrum, 0.37 g, 923.67 μ mol, 41.79% yield, 96% purity) was obtained as light yellow gum. 1H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9 H), 1.36 - 1.47 (m, 2 H), 1.48 - 1.64 (m, 5 H), 1.67 - 1.81 (m, 4 H), 1.82 - 1.89 (m, 1 H), 1.94 - 2.06 (m, 4 H), 2.07 - 2.16 (m, 1 H), 3.78 (quin, $J=6.24$ Hz, 1 H), 3.91 (d, $J=5.87$ Hz, 1 H), 5.31 (s, 1 H), 6.54 (d, $J=8.56$ Hz, 2 H), 7.13 (d, $J=8.31$ Hz, 2 H). LC-MS: (ES) m/z 385.3 ($M+H^+$). The compound tert-butyl (2R,3S,4aR,7aR)-2-[4-(cyclopentylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b] pyridine-3-carboxylate (peak 2 showed on SFC spectrum, 0.39 g, 953.31 μ mol, 43.13% yield, 94% purity) was obtained as light yellow gum. 1H NMR (400 MHz, $CHLOROFORM-d$) δ 1.17 (s, 9 H), 1.36 - 1.45 (m, 2 H), 1.50 - 1.63 (m, 5 H), 1.67 - 1.81 (m, 4 H), 1.83 - 1.92 (m, 1 H), 1.95 - 2.07 (m, 4 H), 2.08 - 2.16 (m, 1 H), 2.78 (q, $J=6.11$ Hz, 1 H), 3.30 (dt, $J=6.48, 3.36$ Hz, 1 H), 3.78 (quin, $J=6.17$ Hz, 1 H), 3.92 (d, $J=5.87$ Hz, 1 H), 6.54 (d, $J=8.31$ Hz, 2 H), 7.14 (d, $J=8.31$ Hz, 2 H). LC-MS: (ES) m/z 385.3 ($M+H^+$).

[0218] Step f) To a solution of tert-butyl(2S,3R,4aS,7aS)-2-[4-(cyclopentylamino)phenyl]-2,3,4,4a,5, 6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (0.25 g, 650.10 μ mol) and DIEA (168.04 mg, 1.30 mmol, 226.47 μ L) in DCM (10 mL) was added dropwise of a solution of 2-fluoro-6-methyl-benzoyl chloride (106.59 mg, 617.60 μ mol) in DCM (3 mL) at 0 $^{\circ}C$. The mixture was stirred at 0 $^{\circ}C$ for 10 min. The mixture was diluted with DCM (10 mL), washed with H_2O (2 x 2 mL), dried, filtered and concentrated in vacuo to give the crude product. The crude product was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 0~20% ethyl acetate/petroleum ether gradient @ 30 mL/min) to give the target compound tert-butyl (2R,3S,4aR,7aR) -2- [4-(cyclopentylamino) phenyl]-1-(2-fluoro-6-methyl- benzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carb oxylate (100% purity) as white

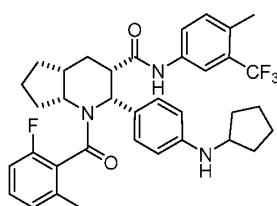
solid. ^1H NMR (400 MHz, DMSO-*d*₆) δ 1.06 - 1.21 (m, 4 H), 1.26 - 1.37 (m, 9 H), 1.38 - 1.46 (m, 2 H), 1.47 - 1.57 (m, 3 H), 1.59 - 1.69 (m, 2 H), 1.71 - 2.05 (m, 6 H), 2.18 - 2.35 (m, 3 H), 2.75 - 2.93 (m, 1 H), 3.47 - 3.71 (m, 2 H), 5.52 (br d, $J=6.27$ Hz, 1 H), 6.29 - 6.40 (m, 1 H), 6.43 - 6.53 (m, 2 H), 6.98 - 7.21 (m, 4 H), 7.33 (q, $J=7.45$ Hz, 1 H). LC-MS: (ES) m/z 521.3 ($\text{M}+\text{H}^+$).

[0219] Step g) To a solution of tert-butyl(2R,3S,4aR,7aR)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (0.28 g, 537.76 μmol) in DCM (6 mL) was added TFA (2.31 g, 20.26 mmol, 1.50 mL) at 10 °C. The mixture was stirred at 25 °C for 16 h. The mixture was concentrated in vacuo to give the residue. HCl/dioxane (4 M, 1 mL) was added to residue and the mixture was concentrated in vacuo to give the crude. The crude was triturated with MTBE (6 mL) at 15 °C for 0.5 h. The suspension was filtered. The filter cake was dried under vacuum to give the pure product (2R,3S,4aR,7aR)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (0.23 g, 485.18 μmol , 63.16% yield, 98% purity) as off-white solid. ^1H NMR (400 MHz, CDCl_3) δ 0.67 (br s, 1 H), 1.14 (br s, 1 H), 1.37 (br d, $J=10.76$ Hz, 2 H), 1.61 - 1.69 (m, 2 H), 1.74 - 2.19 (m, 11 H), 2.28 - 2.37 (m, 3 H), 2.85 - 3.07 (m, 1 H), 3.56 - 3.80 (m, 3 H), 6.54 - 6.65 (m, 1 H), 6.90 - 6.99 (m, 1 H), 7.04 (d, $J=7.58$ Hz, 1 H), 7.30 (br s, 1 H), 7.36 - 7.46 (m, 4 H). LC-MS: (ES) m/z 465.2 ($\text{M}+\text{H}^+$).

[0220] Step h) A mixture of (2R,3S,4aR,7aR)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (0.1 g, 215.25 μmol), HATU (98.21 mg, 258.30 μmol) and DIEA (69.55 mg) in DCM (2 mL) was stirred at 10 °C for 0.5 h. Then 4-methyl-3-(trifluoromethyl)aniline (45.24 mg, 258.30 μmol , 37.08 μL) was added and the mixture was stirred at 30 °C for another 16 h. The mixture from the batch (0.12 g) were combined with this batch. The combined mixture was diluted with DCM (10 mL), washed with HCl (1M, 2 x 0.25 mL), and then alkalified to pH=8~9 by addition of saturated NaHCO_3 solution. The organic layer was dried, filtered and concentrated in vacuo to give the crude. The crude was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 0~16% ethyl acetate/petroleum ether gradient @ 30 mL/min) to give target compound (2R,3S,4aR,7aR)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxamide (160 mg, 98% purity) as white solid. ^1H NMR (400 MHz, DMSO-*d*₆) δ 1.09 - 1.26 (m, 2 H),

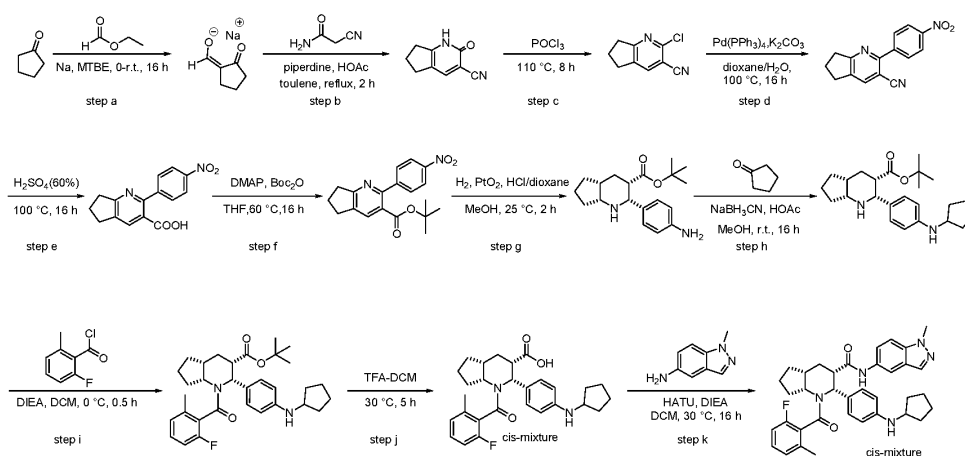
1.28 - 1.43 (m, 4 H), 1.46 - 1.55 (m, 3 H), 1.56 - 1.69 (m, 3 H), 1.79 - 1.98 (m, 4 H), 2.04 (br d, $J=8.03$ Hz, 1 H), 2.18 (s, 1 H), 2.30 (s, 2 H), 2.33 - 2.40 (m, 3 H), 2.89 - 2.98 (m, 1 H), 3.53 - 3.74 (m, 2 H), 5.46 - 5.53 (m, 1 H), 6.41 (d, $J=8.53$ Hz, 2 H), 6.44 - 6.53 (m, 1 H), 7.07 - 7.17 (m, 2 H), 7.25 (d, $J=8.78$ Hz, 1 H), 7.29 - 7.41 (m, 3 H), 7.65 - 7.80 (m, 1 H), 7.92 (dd, $J=8.78, 2.01$ Hz, 1 H), 10.34 (d, $J=13.55$ Hz, 1 H). LC-MS: (ES) m/z 622.3 ($M+H^+$).

Example S62: Synthesis of (2*S*,3*R*,4*aS*,7*aS*)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-*N*-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1*H*-cyclopenta[b]pyridine-3-carboxamide (Compound No. 47)



[0221] The title compound was synthesized in similar fashion as Example S62. ^1H NMR (400 MHz, DMSO- d_6) δ 1.01 - 1.24 (m, 2 H), 1.25 - 1.42 (m, 4 H), 1.43 - 1.54 (m, 3 H), 1.55 - 1.67 (m, 3 H), 1.78 - 1.96 (m, 4 H), 1.99 - 2.08 (m, 1 H), 2.17 (s, 1 H), 2.27 - 2.32 (m, 2 H), 2.32 - 2.38 (m, 3 H), 2.88 - 3.01 (m, 1 H), 3.53 - 3.73 (m, 2 H), 5.51 (br s, 1 H), 6.41 (d, $J=8.28$ Hz, 2 H), 6.47 (dd, $J=12.80, 5.77$ Hz, 1 H), 7.05 - 7.17 (m, 2 H), 7.24 (d, $J=8.78$ Hz, 1 H), 7.28 - 7.39 (m, 3 H), 7.66 - 7.79 (m, 1 H), 7.91 (dd, $J=8.78, 2.01$ Hz, 1 H), 10.34 (d, $J=13.55$ Hz, 1 H). LC-MS: (ES) m/z 622.3 ($M+H^+$).

Example S63: Synthesis of cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-*N*-(1-methyl-1*H*-indazol-5-yl)octahydro-1*H*-cyclopenta[b]pyridine-3-carboxamide (Compound No. 147)



[0222] Step a) To a flask charged with finely cut sodium (27.33 g, 1.19 mol, 28.18 mL) in MTBE (1.5 L) at 0 °C was added dropwise of a solution of cyclopentanone (50 g, 594.41 mmol, 52.63 mL) and ethyl formate (46.23 g, 624.14 mmol, 50.20 mL) in MTBE (500 mL). The mixture was stirred at 10 °C for 16 h. The precipitate was filtered, washed with MTBE and dried to give the desired compound [(Z)-(2-oxocyclopentylidene)methoxy]sodium (22 g, 164.05 mmol, 27.60% yield) as a yellow solid. ¹H NMR (400 MHz, D₂O) δ 1.61 (2 H, quin, J=7.52 Hz) 2.09 (2 H, t, J=7.83 Hz) 2.23 (2 H, t, J=7.21 Hz) 8.24 (1 H, s) 8.54 (1 H, s).

[0223] Step b) To a mixture of (2-oxocyclopentylidene)methoxysodium (22 g, 164.05 mmol) in toluene (600 mL) was added 2-cyanoacetamide (30.34 g, 360.90 mmol). Then a solution make up of HOAc (1 M, 73.82 mL) and piperadine (1 M, 73.82 mL) in DCM (73 mL) were added. The mixture was stirred at 120 °C for 16 h. The reaction mixture was added to 500 mL H₂O and extracted with DCM (500 mL x 2). The aqueous phase was acidified with 4 M HCl and was extracted with DCM (500 mL x 2). The combined organic phase was dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum to give target compound 2-oxo-1,5, 6,7-tetrahydrocyclopenta[b]pyridine-3-carbonitrile (3 g, crude) as a yellow solid.

[0224] Step c) 2-oxo-1,5,6,7-tetrahydrocyclopenta[b]pyridine-3-carbonitrile (17 g, 106.14 mmol) was added to POCl₃ (99.00 g, 645.67 mmol, 60 mL). The mixture was stirred at 110 °C for 16 h. The most of POCl₃ was evaporated under vacuum to give crude product. The crude product was added to 50 mL of H₂O and 50 mL of DCM, then the mixture was stirred at 20 °C for 1 h. The solution was basified by saturated NaHCO₃ solution and extracted with DCM (400 mL x 3). The combined organic phase was dried with anhydrous Na₂SO₄ and filtered through a pad of 100 g silica gel. The filtrate was evaporated under

vacuum to give 2-chloro-6,7-dihydro-5H-cyclopenta[b]-pyridine-3-carbonitrile (16 g) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 2.16 - 2.25 (2 H, m), 2.96 (2 H, t, *J*=7.61 Hz), 3.06 (2 H, t, *J*=7.83 Hz), 7.74 (1 H, s).

[0225] Step d) A solution of K₂CO₃ (36.03 g, 260.67 mmol) in H₂O (100 mL) was added to a mixture of 2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (16 g, 86.89 mmol), (4-nitrophenyl) boronic acid (18.86 g, 112.96 mmol) and Pd(PPh₃)₄ (10.04 g, 8.69 mmol) in dioxane (100 mL). The mixture was stirred at 100 °C under N₂ for 16 h. The result mixture was extracted with DCM (500 mL x 2). The combined organic phase was washed with brine (500 mL), dried with anhydrous Na₂SO₄, filtered and evaporated under vacuum to give crude product. The crude product was triturated with EtOAc (50 mL) at 20 °C for 5 min. The suspension was filtered. The filter cake was washed with EtOAc 50 (mL) and dried under vacuum to give compound 2-(4-nitrophenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (14 g, 52.78 mmol, 60.74% yield) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 2.27 (2 H, quin, *J*=7.65 Hz), 3.08 (2 H, t, *J*=7.40 Hz), 3.17 (2 H, t, *J*=7.78 Hz), 7.89 (1 H, s), 8.04 - 8.10 (2 H, m), 8.33 - 8.41 (2 H, m). LC-MS: (ES) *m/z* 266.1 (M+H⁺).

[0226] Step e) The 2-(4-nitrophenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (10 g, 37.70 mmol) was added a solution of H₂SO₄ (110.92 g, 1.13 mol, 60.28 mL) in H₂O (60 mL). The mixture was stirred at 110 °C for 16 h. The reaction was cooled to 20 °C, and was basified by 5M NaOH to pH=5. Then the white solid was formed. The solid was filtered, washed with 150 mL H₂O and evaporated under vacuum to give 2-(4-nitrophenyl)-6,7-dihydro-5H-cyclopenta [b] pyridine-3-carboxylic acid (10 g, 35.18 mmol, 93.32% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.09 (2 H, quin, *J*=7.52 Hz), 2.97 (4 H, br t, *J*=7.58 Hz), 7.70 (2 H, d, *J*=8.56 Hz), 8.00 (1 H, s), 8.24 (2 H, d, *J*=8.56 Hz), 13.13 (1 H, br s).

[0227] Step f) The tert-butoxycarbonyl tert-butyl carbonate (15.36 g, 70.36 mmol, 16.16 mL) was added to a mixture of 2-(4-nitrophenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylic acid (10 g, 35.18 mmol) and DMAP (4.30 g, 35.18 mmol) in THF (100 mL). The solution was stirred at 60 °C for 3h. Another portion of tert-butoxycarbonyl tert-butyl carbonate (7.68 g, 35.18 mmol, 8.08 mL) and DMAP (2.15 g, 17.59 mmol) were added and the mixture was stirred at 60 °C for another 16 h. Another portion of tert-butoxycarbonyl tert-butyl carbonate (7.68 g, 35.18 mmol, 8.08 mL) and DMAP (2.15 g, 17.59 mmol) were added and stirred at 60 °C for 3 h. The reaction mixture was added to 100 mL H₂O and extracted with EtOAc (100 mL x 2). The combined organic phase was washed with brine, dried with

anhydrous Na₂SO₄, filtered and evaporated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/Et-OAc=100:0 to 3:1) to give tert-butyl-2-(4-nitrophenyl)-6,7-dihydro-5H-cyclopenta[b]-pyridine-3-carboxylate (11.3 g, 33.20 mmol, 94.37% yield) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 1.29 (9 H, s), 2.20 (2 H, quin, *J*=7.64 Hz), 2.98 - 3.13 (4 H, m), 7.63 (2 H, d, *J*=8.56 Hz), 7.94 (1 H, s), 8.27 (2H, d, *J*=8.80 Hz). LC-MS: (ES) *m/z* 341.1 (M+H⁺).

[0228] Step g) PtO₂ (1.33 g, 5.88 mmol, 0.5 eq) was added to a solution of tert-butyl 2-(4-nitrophenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylate (4 g, 11.75 mmol) and HCl/dioxane (4 M, 5.88 mL) in MeOH (100 mL). The solution was stirred at 20 °C under H₂ (15 psi) for 2 h. The reaction mixture was filtered and the filtrate was evaporated under vacuum to give crude product. The crude product was added to 30 mL of H₂O and basified with saturate NaHCO₃ solution. The mixture was extracted with DCM (40 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, DCM : MeOH=100/0 to 100/1) to give compound cis-tert-butyl-2-(4-aminophenyl)-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (1.5 g, 4.65 mmol, 39.53% yield, 98% purity) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 1.09 (9 H, s), 1.52 - 1.81 (7 H, m), 1.91 - 2.00 (2 H, m), 2.01 - 2.08 (1 H, m), 2.70 (1 H, q, *J*=5.95 Hz), 3.20 (1 H, td, *J*=6.54, 2.81 Hz), 3.48 (2 H, br s), 3.82 (1 H, d, *J*=5.62 Hz), 6.55 (2 H, d, *J*=8.31 Hz), 7.06 (2 H, d, *J*=8.56 Hz). LC-MS: (ES) *m/z* 317.2 (M+H⁺).

[0229] Step h) To a mixture of cis-tert-butyl-2-(4-aminophenyl)-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (1.5 g, 4.74 mmol) and cyclopentanone (518.35 mg, 6.16 mmol, 545.64 μL) in MeOH (30 mL) was added HOAc (569.31 mg, 9.48 mmol, 542.20 μL) and NaBH₃CN (893.64 mg, 14.22 mmol) at 0°C. Then the mixture was stirred at 20 °C for 16 h. The reaction mixture was basified with NaHCO₃ solution and extracted with DCM (50 mL x 2). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by prep-HPLC (column: YMC-Triart Prep C18 150 x 40 mm x 7 μm; mobile phase: [water (0.1%TFA)-ACN]; B%: 20%-50%, 10 min). The pure fraction was basified with NaHCO₃ solution and extracted with DCM (500 mL x 2). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give compound cis-tert-butyl-2-[4-(cyclopentylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-

carboxylate (1.2 g, 3.12 mmol, 65.83% yield, 100% purity) as a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ pm 1.09 - 1.22 (9 H, m), 1.33 (2 H, br dd, $J=8.80, 3.91$ Hz), 1.39 - 1.79 (10 H, m), 1.85 - 2.10 (7 H, m), 2.11 - 2.25 (1 H, m), 2.83 (1 H, q, $J=5.54$ Hz), 3.49 (1 H, br s), 3.66 (1 H, quin, $J=6.11$ Hz), 4.16 (1 H, br d, $J=5.14$ Hz), 6.44 (2 H, d, $J=8.56$ Hz), 7.14 (2 H, d, $J=8.56$ Hz). LC-MS: (ES) m/z 385.3 ($\text{M}+\text{H}^+$).

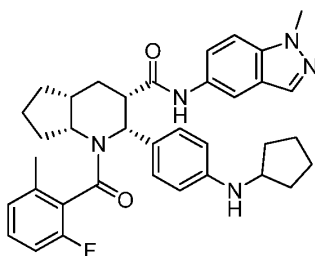
[0230] Step i) To a solution of *cis*-*tert*-butyl 2-[4-(cyclopentylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (800 mg, 2.08 mmol) and DIEA (537.73 mg, 4.16 mmol, 724.70 μL) in DCM (30 mL) was added dropwise of a solution of 2-fluoro-6-methyl-benzoyl chloride (359.03 mg, 2.08 mmol) in DCM (10 mL) at 0°C . The mixture was stirred at 0°C for 1 h. The reaction mixture was added 20 mL of H_2O and was extracted with DCM (2 x 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and evaporated under vacuum to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ EtOAc =100/0 to 3/1) to give compound *cis*-*tert*-butyl 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (1 g, 1.92 mmol, 92.32% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 0.81-0.97 (3 H, m), 0.99-1.19 (2 H, m), 1.28-1.38 (9 H, m), 1.39-1.50 (4 H, m), 1.58-1.76 (5 H, m), 1.92-2.10 (6 H, m), 2.28-2.40 (3 H, m), 2.68-2.99 (1 H, m), 3.43-3.80 (3 H, m), 6.32-6.52 (2 H, m), 6.57 (1 H, dd, $J=14.55, 5.26$ Hz), 6.86-6.94 (1 H, m), 6.96-7.01 (1 H, m) 7.16-7.23 (1 H, m) 7.30 (1 H, d, $J=8.31$ Hz). LC-MS: (ES) m/z 521.3 ($\text{M}+\text{H}^+$).

[0231] Step j) The *cis*-*tert*-butyl 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (1 g, 1.92 mmol) was dissolved in DCM (20 mL). Then TFA (6.48 g, 56.87 mmol, 4.21 mL) was added. The mixture was stirred at 15°C for 16 h. The reaction mixture was evaporated under vacuum to remove most of solvent. Then 20 mL H_2O was added. Then the mixture was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure to give *cis*-2-[4-(cyclopentylamino)-phenyl]-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (850 mg, 1.83 mmol, 95.27% yield) as a pale yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 0.75 - 1.01 (1 H, m), 1.13 - 1.31 (2 H, m), 1.36 - 1.53 (2 H, m), 1.58 - 2.06 (12 H, m), 2.20 (1 H, br d, $J=12.30$ Hz), 2.27 - 2.39 (3 H, m), 2.93 - 3.25 (1 H, m), 3.62 - 3.75 (1 H, m), 3.77 - 3.96 (2 H, m), 6.65 - 6.78 (1 H, m), 6.92

- 7.11 (2 H, m), 7.29 - 7.38 (2 H, m), 7.46 - 7.62 (2 H, m), 10.57 (1 H, br s). LC-MS: (ES) m/z 465.3 ($M+H^+$).

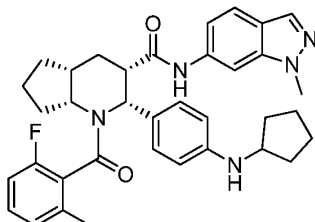
[0232] Step k) To a solution of cis-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (20 mg, 43.05 μ mol) in DCM (0.5 mL) was added HATU (20 mg, 52.60 μ mol) and DIEA (14.10 mg, 109.08 μ mol, 19 μ L). The mixture was stirred at 30 °C for 0.5 h. Then the 1-methylindazol-5-amine (8.24 mg, 55.97 μ mol, 5.36 μ L) was added and the mixture was stirred at 30 °C for another 15.5 hr. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (HCl condition, column: Agela DuraShell C18 150 x 25 mm x 5 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 35%-65%, 8 min) to give 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-N-(1-methylindazol-5-yl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]-pyridine-3-carboxamide (13 mg, 19.60 μ mol, 45.52% yield, 95% purity, HCl) as a light yellow solid. 1H NMR (400 MHz, METHANOL- d_4) δ 1.23 - 1.40 (m, 3 H), 1.68 (br s, 2 H), 1.83 (br s, 3 H), 1.91 - 2.04 (m, 3 H), 2.05 - 2.15 (m, 2 H), 2.17 - 2.21 (m, 1 H), 2.42 (s, 2 H), 3.19 - 3.27 (m, 1 H), 3.78 - 4.00 (m, 2 H), 4.02 - 4.06 (m, 3 H), 6.53 - 6.71 (m, 1 H), 7.05 (br t, $J=8.56$ Hz, 1 H), 7.11 - 7.21 (m, 1 H), 7.34 - 7.51 (m, 5 H), 7.86 - 7.98 (m, 4 H). LC-MS: (ES) m/z 594.3 ($M+H^+$).

Example S64: Synthesis of (2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 49)



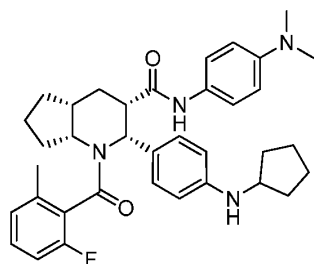
[0233] The title compound was synthesized in similar fashion as Example S63. 1H NMR (400 MHz, METHANOL- d_4) δ 1.20 - 1.47 (3 H, m), 1.48 - 1.89 (10 H, m), 1.90 - 2.05 (2 H, m), 2.06 - 2.16 (2 H, m), 2.17 - 2.35 (2 H, m), 2.37 - 2.49 (2 H, m), 3.19 - 3.29 (1 H, m), 3.76 - 4.01 (2 H, m), 4.02 - 4.10 (3 H, m), 6.54 - 6.74 (1 H, m), 7.01 - 7.11 (1 H, m), 7.11 - 7.23 (1 H, m), 7.34 - 7.56 (5 H, m), 7.81 - 8.01 (4 H, m). LC-MS: (ES) m/z 594.3 ($M+H^+$).

Example S65: (2*R*,3*S*,4*aR*,7*aR*)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)- *N*-(1-methyl-1*H*-indazol-6-yl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 66)



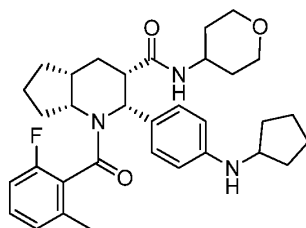
[0234] The title compound was synthesized in similar fashion as Example S63. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.23 - 1.47 (3 H, m), 1.50 - 1.90 (10 H, m), 1.90 - 2.04 (2 H, m), 2.05 - 2.39 (4 H, m), 2.44 (2 H, s), 3.22 - 3.31 (1H, m), 3.80 - 4.05 (5 H, m), 6.58 - 6.77 (1 H, m), 7.02 - 7.26 (3 H, m), 7.37 - 7.42 (1 H, m), 7.43 - 7.51 (2 H, m), 7.63 - 7.72 (1 H, m), 7.89 - 8.06 (4 H, m). LC-MS: (ES) *m/z* 594.3 (M+H⁺).

Example S66: (2*R*,3*S*,4*aR*,7*aR*)-2-(4-(cyclopentylamino)phenyl)-*N*-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 51)



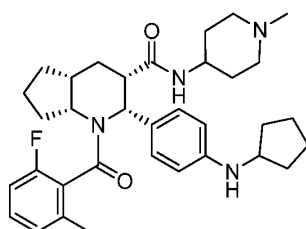
[0235] The title compound was synthesized in similar fashion as Example S63. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.15 - 1.40 (m, 4 H), 1.48 - 1.58 (m, 1 H), 1.66 - 1.77 (m, 5 H), 1.85 (br s, 2 H), 1.94 - 2.12 (m, 4 H), 2.17 - 2.31 (m, 2 H), 2.41 (s, 2 H), 3.19 - 3.27 (m, 7 H), 3.74 - 4.01 (m, 2 H), 6.55 - 6.70 (m, 1 H), 7.02 - 7.11 (m, 1 H), 7.11 - 7.21 (m, 1 H), 7.34 - 7.45 (m, 3 H), 7.53 - 7.61 (m, 2 H), 7.67 - 7.81 (m, 2 H), 7.84 - 7.92 (m, 2 H). LC-MS: (ES) *m/z* 583.4 (M+H⁺).

Example S67: Synthesis of (2*R*,3*S*,4*aR*,7*aR*)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)- *N*-(tetrahydro-2*H*-pyran-4-yl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 52)



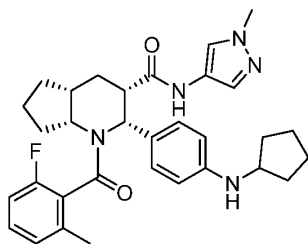
[0236] The title compound was synthesized in similar fashion as Example S63. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.10 - 1.62 (m, 7 H), 1.64 - 1.91 (m, 9 H), 1.94 - 2.09 (m, 4 H), 2.10 - 2.25 (m, 2 H), 2.36 (s, 2 H), 2.92 - 3.04 (m, 1 H), 3.34 - 3.51 (m, 2 H), 3.70 - 4.05 (m, 5 H), 6.44 - 6.60 (m, 1 H), 6.90 - 7.07 (m, 1 H), 7.09 - 7.19 (m, 1 H), 7.23 - 7.37 (m, 1 H), 7.38 - 7.49 (m, 2 H), 7.78 - 7.92 (m, 2 H). LC-MS: (ES) *m/z* 548.3 (M+H⁺).

Example S68: Synthesis of (2*R*,3*S*,4*aR*,7*aR*)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)- *N*-(1-methylpiperidin-4-yl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 53)



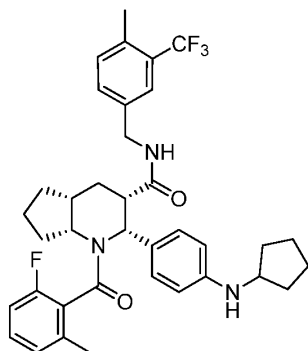
[0237] The title compound was synthesized in similar fashion as Example S63. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.04 - 1.37 (m, 3 H), 1.39 - 1.60 (m, 2 H), 1.61 - 1.81 (m, 7 H), 1.87 (br d, *J*=9.03 Hz, 3 H), 1.95 - 2.08 (m, 5 H), 2.14 - 2.25 (m, 2 H), 2.32 - 2.44 (m, 2 H), 2.76 - 2.90 (m, 3 H), 2.93 - 3.17 (m, 3 H), 3.32 - 3.65 (m, 3 H), 3.70 - 4.11 (m, 3 H), 6.48 - 6.63 (m, 1 H), 6.96 - 7.08 (m, 1 H), 7.10 - 7.20 (m, 1 H), 7.28 - 7.42 (m, 1 H), 7.44 - 7.54 (m, 2 H), 7.75 - 7.91 (m, 2 H). LC-MS: (ES) *m/z* 561.3 (M+H⁺).

Example S69: Synthesis of (2*R*,3*S*,4*aR*,7*aR*)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-*N*-(1-methyl-1*H*-pyrazol-4-yl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 54)



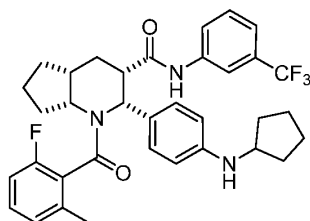
[0238] The title compound was synthesized in similar fashion as Example S63. LC-MS: (ES) m/z 544.3 ($M+H^+$).

Example S70: (2*R*,3*S*,4*aR*,7*aR*)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-*N*-(4-methyl-3-(trifluoromethyl)benzyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 185)



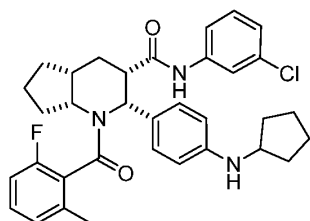
[0239] The title compound was synthesized in similar fashion as Example S64. 1H NMR (400 MHz, METHANOL- d_4) δ 0.98 - 1.34 (m, 3 H), 1.40 - 1.48 (m, 1 H), 1.71 (br s, 6 H), 1.87 (br s, 2 H), 1.93 - 2.11 (m, 4 H), 2.17 (td, $J=12.80, 6.78$ Hz, 1 H), 2.27 (s, 1 H), 2.37 (s, 2 H), 2.44 (br s, 3 H), 3.04 (br dd, $J=9.66, 4.89$ Hz, 1 H), 3.70 - 4.02 (m, 2 H), 4.24 - 4.52 (m, 2 H), 6.57 - 6.73 (m, 1 H), 7.05 (t, $J=8.91$ Hz, 1 H), 7.11 - 7.19 (m, 1 H), 7.23 - 7.42 (m, 5 H), 7.44 - 7.55 (m, 1 H), 7.67 - 7.84 (m, 2 H), 8.77 - 8.96 (m, 1 H). LC-MS: (ES) m/z 636.4 ($M+H^+$).

Example S71: *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-*N*-(3-(trifluoro-methyl)phenyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 46)



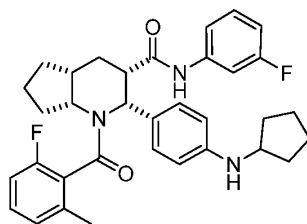
[0240] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.26 - 1.35 (m, 3 H), 1.66 (br s, 2 H), 1.74 - 1.85 (m, 3 H), 1.98 (br t, $J=16.14$ Hz, 2 H), 2.06 - 2.14 (m, 1 H), 2.17 - 2.27 (m, 2 H), 2.41 (s, 2 H), 3.19 (dt, $J=10.52, 5.26$ Hz, 1 H), 3.75 - 3.97 (m, 2 H), 6.53 - 6.67 (m, 1 H), 7.05 (td, $J=8.68, 3.91$ Hz, 1 H), 7.10 - 7.22 (m, 2 H), 7.25 (br d, $J=8.56$ Hz, 1 H), 7.34 - 7.41 (m, 2 H), 7.42 - 7.51 (m, 1 H), 7.56 - 7.72 (m, 1 H), 7.79 (d, $J=8.56$ Hz, 2 H), 7.89 - 8.00 (m, 1 H), 10.28 (br d, $J=4.65$ Hz, 1 H). LC-MS: (ES) m/z 608.3 ($\text{M}+\text{H}^+$).

Example S72: Synthesis of *cis*-N-(3-chlorophenyl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 55)



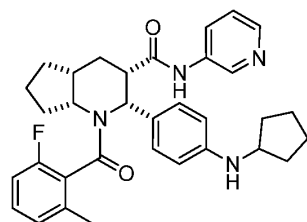
[0241] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.12 - 1.36 (3 H, m) 1.37 - 1.80 (10 H, m) 1.86 - 2.22 (5 H, m) 2.23 - 2.42 (3 H, m) 2.96 - 3.10 (1 H, m) 3.65 - 3.89 (2 H, m) 6.50 - 6.58 (2 H, m) 6.97 - 7.16 (3 H, m) 7.17 - 7.24 (1 H, m) 7.25 - 7.45 (4 H, m) 7.56 - 7.68 (1 H, m). LC-MS: (ES) m/z 574.2 ($\text{M}+\text{H}^+$).

Example S73: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(3-fluorophenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 56)



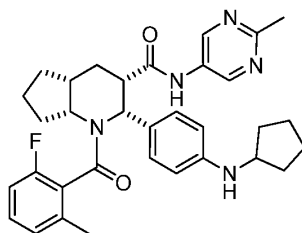
[0242] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.19 - 1.48 (m, 3 H), 1.56 - 1.77 (m, 6 H), 1.78 - 1.91 (m, 2 H), 1.92 - 2.11 (m, 4 H), 2.14 - 2.29 (m, 2 H), 2.33 - 2.43 (m, 2 H), 3.03 - 3.25 (m, 1 H), 3.72 - 4.03 (m, 2 H), 6.49 - 6.76 (m, 1 H), 6.77 - 6.98 (m, 1 H), 7.02 - 7.31 (m, 4 H), 7.33 - 7.54 (m, 4 H), 7.66 - 7.87 (m, 2 H). LC-MS: (ES) m/z 558.4 ($\text{M}+\text{H}^+$).

Example S74: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-*N*-(pyridin-3-yl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 57)



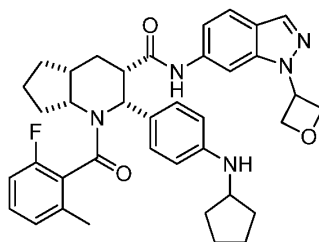
[0243] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.44 - 1.52 (m, 4 H), 1.56 - 1.64 (m, 4 H), 1.71 (br d, $J=5.62$ Hz, 4 H), 1.94 - 2.07 (m, 4 H), 2.13 - 2.22 (m, 2 H), 2.27 (s, 1 H), 2.39 (s, 2 H), 3.05 - 3.17 (m, 1 H), 3.69 - 3.78 (m, 2 H), 6.53 - 6.64 (m, 4 H), 7.01 - 7.08 (m, 1 H), 7.14 (dd, $J=11.00$, 7.83 Hz, 1 H), 7.33 - 7.41 (m, 3 H), 7.45 (d, $J=8.56$ Hz, 1 H), 7.92 - 8.05 (m, 1 H), 8.23 (ddd, $J=8.93$, 4.77, 1.22 Hz, 1 H), 8.63 - 8.72 (m, 1 H). LC-MS: (ES) m/z 541.3 ($\text{M}+\text{H}^+$).

Example S75: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-*N*-(2-methylpyrimidin-5-yl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 58)



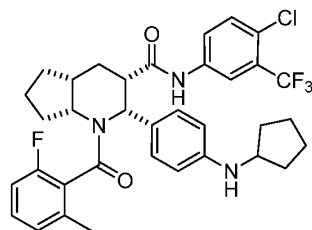
[0244] The title compound was synthesized in similar fashion as Example S63. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.16 - 1.42 (m, 3 H), 1.71 (br s, 6 H), 1.85 (br s, 3 H), 1.95 - 2.04 (m, 3 H), 2.12 - 2.28 (m, 3 H), 2.39 - 2.42 (m, 2 H), 2.72 - 2.82 (m, 3 H), 3.12 - 3.30 (m, 1 H), 3.82 - 4.08 (m, 2 H), 6.64 - 6.78 (m, 1 H), 7.04 - 7.22 (m, 2 H), 7.34 - 7.52 (m, 3 H), 7.82 - 7.94 (m, 2 H), 9.05 - 9.29 (m, 2 H). LC-MS: (ES) *m/z* 556.4 (M+H⁺).

Example S76: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(oxetan-3-yl)-1H-indazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 59)



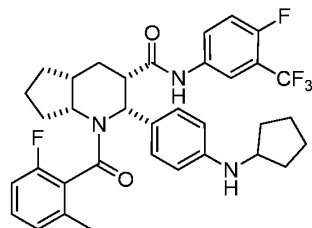
[0245] The title compound was synthesized in similar fashion as Example S63. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.14 - 1.52 (4 H, m), 1.61 - 1.92 (9 H, m), 1.92 - 2.27 (6 H, m), 2.28 - 2.54 (3 H, m), 3.11 - 3.31 (1 H, m), 3.78 - 4.16 (4 H, m), 5.09 - 5.29 (1 H, m), 6.57 - 6.78 (1 H, m), 7.03 - 7.25 (3 H, m), 7.36 - 7.54 (3 H, m), 7.61 - 7.78 (2 H, m), 7.89 - 8.13 (3 H, m). LC-MS: (ES) *m/z* 636.3 (M+H⁺).

Example S77: Synthesis of *cis*-N-(4-chloro-3-(trifluoromethyl)phenyl)-2-(4-(cyclopentylamino)-phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 60)



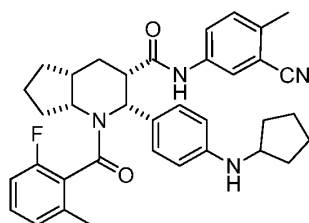
[0246] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.35 (br s, 3 H), 1.56 - 1.71 (m, 6 H), 1.79 (br d, $J=5.62$ Hz, 3 H), 1.93 - 2.11 (m, 4 H), 2.21 (s, 1 H), 2.40 (s, 2 H), 3.15 (br dd, $J=10.15, 5.50$ Hz, 1 H), 3.75 - 3.94 (m, 2 H), 6.52 - 6.67 (m, 1 H), 7.05 (br t, $J=8.56$ Hz, 2 H), 7.15 (br dd, $J=17.00, 7.46$ Hz, 2 H), 7.33 - 7.42 (m, 1 H), 7.47 - 7.57 (m, 1 H), 7.63 - 7.76 (m, 3 H), 8.00 - 8.10 (m, 1 H). LC-MS: (ES) m/z 642.3 ($\text{M}+\text{H}^+$).

Example S78: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-N-(4-fluoro-3-(trifluoromethyl)-phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 61)



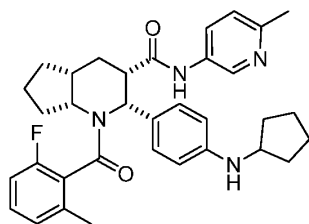
[0247] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.19 - 1.39 (m, 3 H), 1.54 - 1.76 (m, 6 H), 1.83 (br s, 3 H), 1.91 - 2.04 (m, 2 H), 2.04 - 2.15 (m, 2 H), 2.16 - 2.30 (m, 2 H), 2.40 (s, 2 H), 3.15 - 3.25 (m, 1 H), 3.76 - 4.01 (m, 2 H), 6.53 - 6.69 (m, 1 H), 7.02 - 7.10 (m, 1 H), 7.11 - 7.20 (m, 1 H), 7.27 (q, $J=9.70$ Hz, 1 H), 7.33 - 7.43 (m, 3 H), 7.62 - 7.77 (m, 1 H), 7.81 - 7.90 (m, 2 H), 7.94 - 8.08 (m, 1 H), 10.32 (s, 1 H). LC-MS: (ES) m/z 626.3 ($\text{M}+\text{H}^+$).

Example S79: Synthesis of *cis*-N-(3-cyano-4-methylphenyl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 62)



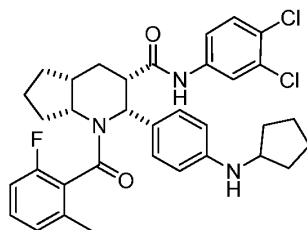
[0248] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.30 - 1.69 (8 H, m), 1.74 - 1.98 (5 H, m), 1.99 - 2.13 (2 H, m), 2.16 (1 H, s), 2.29 (1 H, s), 2.30 - 2.38 (3 H, m), 2.96 (1 H, br s), 3.57 - 3.82 (2 H, m), 4.53 (3 H, br s), 6.39 - 6.52 (2 H, m), 6.90 - 6.98 (1 H, m), 6.99 - 7.07 (1 H, m), 7.10 - 7.30 (3 H, m), 7.34 (1 H, d, $J=8.56$ Hz), 7.42 - 7.53 (1 H, m), 7.70 - 7.81 (1 H, m). LC-MS: (ES) m/z 579.3 ($\text{M}+\text{H}^+$).

Example S80: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-*N*-(6-methylpyridin-3-yl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 63)



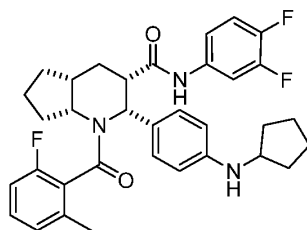
[0249] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.05 - 1.36 (m, 3 H), 1.47 - 1.57 (m, 1 H), 1.63 - 1.92 (m, 8 H), 1.99 (br s, 2 H), 2.07 - 2.21 (m, 2 H), 2.22 - 2.31 (m, 2 H), 2.41 (s, 2 H), 2.69 - 2.76 (m, 3 H), 3.25 - 3.30 (m, 1 H), 3.76 - 4.04 (m, 2 H), 6.67 - 6.81 (m, 1 H), 7.03 - 7.11 (m, 1 H), 7.13 - 7.22 (m, 1 H), 7.33 - 7.44 (m, 1 H), 7.45 - 7.53 (m, 2 H), 7.84 - 7.96 (m, 3 H), 8.37 - 8.51 (m, 1 H), 9.14 - 9.29 (m, 1 H). LC-MS: (ES) m/z 555.3 ($\text{M}+\text{H}^+$).

Example S81: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-*N*-(3,4-dichlorophenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 64)



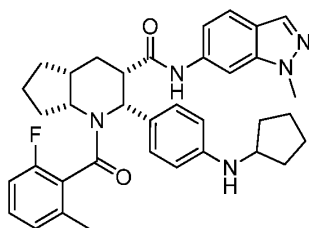
[0250] The title compound was synthesized in similar fashion as Example S63. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.28 - 1.33 (m, 3 H), 1.53 - 1.71 (m, 6 H), 1.72 - 1.85 (m, 3 H), 1.92 - 2.10 (m, 4 H), 2.17 - 2.25 (m, 2 H), 2.39 (s, 2 H), 3.07 - 3.19 (m, 1 H), 3.72 - 3.96 (m, 2 H), 6.48 - 6.68 (m, 1 H), 6.96 - 7.20 (m, 4 H), 7.29 - 7.46 (m, 3 H), 7.67 (br d, *J*=8.31 Hz, 2 H), 7.77 - 7.89 (m, 1 H). LC-MS: (ES) *m/z* 608.3 (M+H⁺).

Example S82: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-N-(3,4-difluorophenyl)-1-(2-fluoro-6-methyl benzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 65)



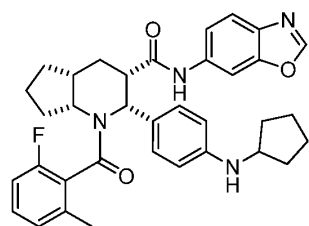
[0251] The title compound was synthesized in similar fashion as Example S63. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.18 - 1.58 (m, 3 H), 1.64 - 1.78 (m, 6 H), 1.84 (br s, 3 H), 1.93 - 2.10 (m, 4 H), 2.14 - 2.27 (m, 2 H), 2.38 - 2.43 (m, 2 H), 3.11 - 3.24 (m, 1 H), 3.76 - 4.02 (m, 2 H), 6.48 - 6.68 (m, 1 H), 7.04 - 7.24 (m, 4 H), 7.34 - 7.47 (m, 3 H), 7.50 - 7.66 (m, 1 H), 7.67 - 7.91 (m, 2 H). LC-MS: (ES) *m/z* 576.3 (M+H⁺).

Example S83: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 66)



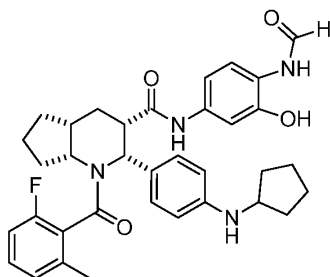
[0252] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.18 - 1.41 (m, 3 H), 1.55 - 1.75 (m, 6 H), 1.82 (br d, $J=6.11$ Hz, 3 H), 1.89 - 2.02 (m, 2 H), 2.07 - 2.16 (m, 2 H), 2.17 - 2.35 (m, 2 H), 2.42 (s, 2 H), 3.21 - 3.29 (m, 1 H), 3.77 - 3.96 (m, 2 H), 3.97 - 4.03 (m, 3 H), 6.51 - 6.76 (m, 1 H), 6.99 - 7.23 (m, 3 H), 7.32 - 7.49 (m, 3 H), 7.62 - 7.73 (m, 1 H), 7.85 - 8.03 (m, 4 H). LC-MS: (ES) m/z 594.4 ($\text{M}+\text{H}^+$).

Example S84: Synthesis of *cis*-*N*-(benzo[d]oxazol-6-yl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1*H*-cyclopenta[b]pyridine-3-carboxamide (Compound No. 67)



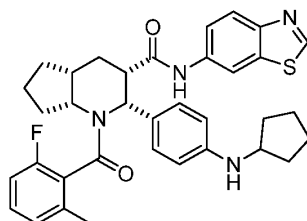
[0253] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.16 - 1.35 (m, 2 H), 1.37 - 1.52 (m, 4 H), 1.53 - 1.64 (m, 3 H), 1.70 (br d, $J=5.87$ Hz, 3 H), 1.89 - 2.08 (m, 3 H), 2.12 - 2.24 (m, 2 H), 2.27 (s, 1 H), 2.37 - 2.45 (m, 2 H), 3.04 - 3.18 (m, 1 H), 3.65 - 3.93 (m, 2 H), 6.49 - 6.68 (m, 3 H), 7.01 - 7.22 (m, 2 H), 7.29 - 7.51 (m, 4 H), 7.55 - 7.73 (m, 1 H), 7.93 - 8.13 (m, 1 H), 8.31 - 8.42 (m, 1 H). LC-MS: (ES) m/z 581.4 ($\text{M}+\text{H}^+$).

Example S85: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-*N*-(4-formamido-3-hydroxyphenyl)octahydro-1*H*-cyclopenta[b]pyridine-3-carboxamide (Compound No. 68)



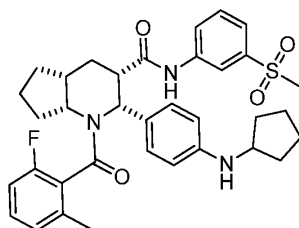
[0254] The title compound was synthesized in similar fashion as Example S63. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.22 - 1.38 (m, 2 H), 1.50 - 1.76 (m, 7 H), 1.78 - 1.90 (m, 3 H), 1.92 - 2.13 (m, 4 H), 2.15 - 2.31 (m, 2 H), 2.37 - 2.47 (m, 2 H), 3.11 - 3.22 (m, 1 H), 3.76 - 4.01 (m, 2 H), 6.49 - 6.66 (m, 1 H), 6.77 - 6.95 (m, 1 H), 7.02 - 7.09 (m, 1 H), 7.10 - 7.25 (m, 2 H), 7.32 - 7.46 (m, 3 H), 7.71 - 7.93 (m, 3 H), 8.19 - 8.26 (m, 1 H), 9.93 - 9.99 (m, 1 H). LC-MS: (ES) *m/z* 599.3 (M+H⁺).

Example S88: Synthesis of *cis*-N-(benzo[d]thiazol-6-yl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 69)



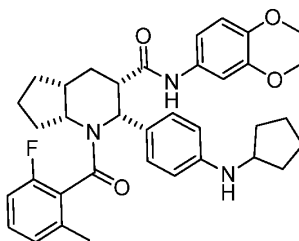
[0255] The title compound was synthesized in similar fashion as Example S63. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.27 - 1.40 (m, 3 H), 1.58 - 1.74 (m, 6 H), 1.82 (br s, 3 H), 1.96 (br s, 2 H), 2.07 - 2.14 (m, 2 H), 2.17 (s, 1 H), 2.20 - 2.37 (m, 1 H), 2.42 (s, 2 H), 3.19 - 3.28 (m, 1 H), 3.77 - 4.01 (m, 2 H), 6.55 - 6.70 (m, 1 H), 6.91 - 7.22 (m, 3 H), 7.32 - 7.59 (m, 4 H), 7.85 - 8.01 (m, 3 H), 8.28 - 8.46 (m, 1 H), 9.10 - 9.21 (m, 1 H). LC-MS: (ES) *m/z* 597.3 (M+H⁺).

Example S87: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(3-(methylsulfonyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 70)



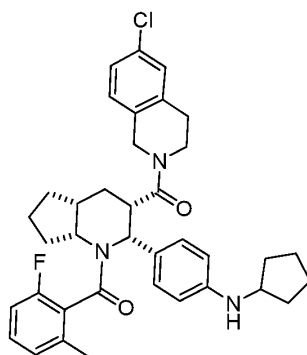
[0256] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.21 - 1.38 (m, 2 H), 1.63 - 1.79 (m, 7 H), 1.81 - 1.88 (m, 2 H), 1.92 - 2.12 (m, 5 H), 2.14 - 2.31 (m, 2 H), 2.37 - 2.44 (m, 2 H), 3.05 - 3.16 (m, 3 H), 3.19 - 3.28 (m, 1 H), 3.75 - 4.02 (m, 2 H), 5.94 - 6.14 (m, 0.3 H), 6.52 - 6.68 (m, 0.7 H), 7.04 - 7.20 (m, 2 H), 7.36 - 7.49 (m, 3 H), 7.53 - 7.71 (m, 3 H), 7.75 - 7.92 (m, 2 H), 8.11 - 8.29 (m, 1 H), 10.31 - 10.47 (m, 1 H). LC-MS: (ES) m/z 618.2 ($\text{M}+\text{H}^+$).

Example S88: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-*N*-(2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 71)



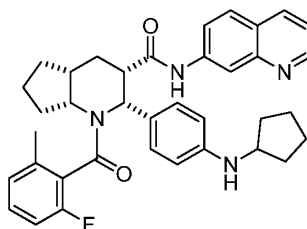
[0257] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.20 - 1.40 (m, 2 H), 1.42 - 1.62 (m, 2 H), 1.62 - 1.92 (m, 8 H), 1.93 - 2.10 (m, 4 H), 2.17 (s, 1 H), 2.19 - 2.48 (m, 3 H), 3.04 - 3.20 (m, 1 H), 3.72 - 3.87 (m, 1 H), 3.93 - 4.02 (m, 1 H), 4.09 - 4.27 (m, 4 H), 6.46 - 6.64 (m, 1 H), 6.68 - 6.75 (m, 1 H), 6.80 - 6.96 (m, 1 H), 7.01 - 7.05 (m, 1 H), 7.05 - 7.27 (m, 2 H), 7.31 - 7.45 (m, 2 H), 7.79 - 7.91 (m, 2 H). LC-MS: (ES) m/z 598.4 ($\text{M}+\text{H}^+$).

Example S89: Synthesis of *cis*-3-(6-chloro-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-2-(4-(cyclopentyl amino)phenyl)octahydro-1*H*-cyclopenta[*b*]pyridin-1-yl)(2-fluoro-6-methylphenyl)-methanone (Compound No. 72)



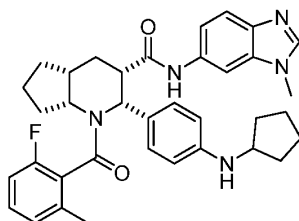
[0258] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, $\text{METHANOL-}d_4$) δ 1.18 - 1.59 (m, 3 H), 1.70 (br d, $J=4.16$ Hz, 6 H), 1.79 - 1.91 (m, 3 H), 1.92 - 2.05 (m, 3 H), 2.11 - 2.33 (m, 2 H), 2.38 - 2.55 (m, 2 H), 2.94 - 3.19 (m, 1 H), 3.43 - 3.83 (m, 2 H), 3.85 - 4.12 (m, 3 H), 4.54 - 4.86 (m, 3 H), 4.94 - 5.07 (m, 1 H), 6.32 - 6.59 (m, 1 H), 6.60 - 6.85 (m, 1 H), 6.95 - 7.45 (m, 8 H), 7.56 - 7.91 (m, 1 H). LC-MS: (ES) m/z 614.3 ($\text{M}+\text{H}^+$).

Example S90: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(quinolin-7-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 73)



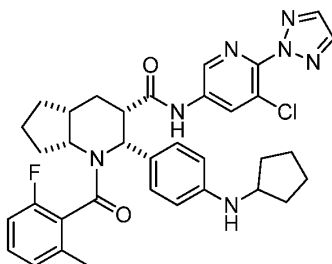
[0259] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, $\text{METHANOL-}d_4$) δ 1.13 - 1.48 (3 H, m), 1.49 - 1.87 (10 H, m), 1.89 - 2.10 (3 H, m), 2.12 - 2.29 (3 H, m), 2.30 - 2.53 (3 H, m), 3.34 - 3.41 (1 H, m), 3.78 - 4.07 (2 H, m), 6.66 - 6.84 (1 H, m), 7.03 - 7.24 (2 H, m), 7.26 - 7.54 (3 H, m), 7.82 - 7.98 (4 H, m), 8.16 - 8.31 (1 H, m), 8.81 - 9.09 (3 H, m). LC-MS: (ES) m/z 591.5 ($\text{M}+\text{H}^+$).

Example S91: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-benzod[imidazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 74)



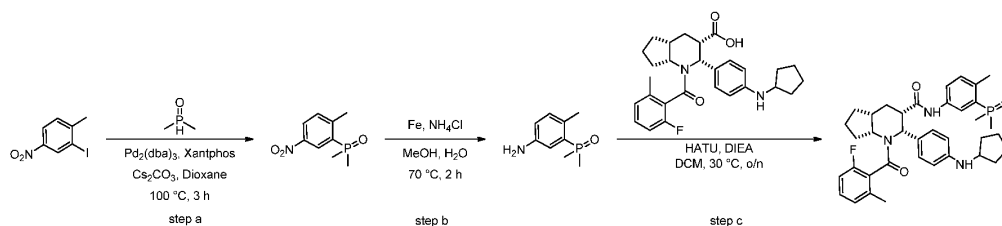
[0260] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.18 - 1.45 (4 H, m), 1.47 - 1.89 (10 H, m), 1.99 (2 H, br s), 2.09 - 2.26 (2 H, m), 2.26 - 2.50 (3 H, m), 3.12 - 3.29 (1 H, m), 3.74 - 3.96 (2 H, m), 3.97 - 4.15 (3 H, m), 6.62 - 6.78 (1 H, m), 7.03 - 7.24 (4 H, m), 7.34 - 7.45 (1 H, m), 7.57 - 7.70 (1 H, m), 7.72 - 7.88 (3 H, m), 8.27 - 8.43 (1 H, m), 9.25 (1 H, br s). LC-MS: (ES) m/z 594.3 ($\text{M}+\text{H}^+$).

Example S92: Synthesis of *cis-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide* (Compound No. 75)



[0261] The title compound was synthesized in similar fashion as Example S63. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.17 - 1.38 (3 H, m), 1.54 - 1.84 (10 H, m), 1.87 - 2.27 (6 H, m), 2.39 (2 H, s), 3.17 - 3.26 (1 H, m), 3.73 - 3.97 (2 H, m), 6.53 - 6.70 (1 H, m), 6.96 - 7.18 (2 H, m), 7.20 - 7.31 (2 H, m), 7.31 - 7.40 (1 H, m), 7.74 - 7.83 (2 H, m), 8.04 (2 H, br d, $J=7.09$ Hz), 8.35 - 8.50 (1 H, m). LC-MS: (ES) m/z 642.5 ($\text{M}+\text{H}^+$).

Example S93: Synthesis of *cis-2-(4-(cyclopentylamino)phenyl)-N-(3-(dimethylphosphoryl)-4-methylphenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide* (Compound No. 76)



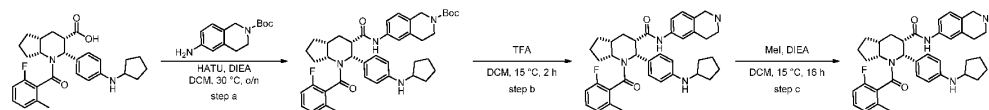
[0262] Step a) A solution of 2-iodo-1-methyl-4-nitro-benzene (0.5 g, 1.90 mmol), methylphos-phonoylmethane (296.73 mg, 3.80 mmol), $\text{Pd}_2(\text{dba})_3$ (87.03 mg, 95.00 μmol), Xantphos (109.99 mg, 190.00 μmol) and Cs_2CO_3 (929.03 mg, 2.85 mmol) in dioxane (3 mL) was stirred at 90 °C for 3 h. The mixture was quenched by addition of H_2O (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give the crude product. The crude product was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 0~30% ethyl acetate/petroleum ether gradient @25 mL/min, then 0~0.05% MeOH/DCM gradient) to give 2-dimethylphosphoryl-1-methyl-4-nitro-benzene (0.2 g, 881.93 μmol , 46.42% yield, 94% purity) as light orange solid. ^1H NMR (400 MHz, CDCl_3) δ 1.87 (s, 3 H), 1.90 (s, 3 H), 2.82 (s, 3 H), 7.47 (dd, $J=8.31, 3.67$ Hz, 1 H), 8.25 (dd, $J=8.44, 1.59$ Hz, 1 H), 8.46 (dd, $J=13.45, 2.20$ Hz, 1 H). LC-MS: (ES) m/z 214.1 ($\text{M}+\text{H}^+$).

[0263] Step b) To a mixture of 2-dimethylphosphoryl-1-methyl-4-nitro-benzene (0.2 g, 938.22 μmol) and NH_4Cl (100.37 mg, 1.88 mmol) in MeOH (8 mL)/ H_2O (1.5 mL) was added Fe (209.58 mg, 3.75 mmol). Then the mixture was stirred at 70 °C for 16 h. The mixture was diluted with MeOH (30 mL) and filtered through a pad of Celite. The filtrate was concentrated in vacuo to give the crude product. The crude product was purified by prep-TLC (DCM/MeOH=8/1) to give 3-dimethylphosphoryl-4-methyl-aniline (0.1 g, 491.30 μmol , 52.37% yield, 90% purity) as yellow semi-solid. LC-MS: (ES) m/z 184.2 ($\text{M}+\text{H}^+$).

[0264] Step c) A solution of cis-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (30 mg, 64.58 μmol), HATU (29.46 mg, 77.49 μmol) and DIEA (20.86 mg, 161.44 μmol , 28.12 μL) in DCM (0.75 mL) was stirred at 30 °C for 0.5 h. Then 3-dimethylphosphoryl-4-methyl-aniline (15.77 mg, 77.49 μmol) was added and the mixture was stirred at 30 °C for another 16 h. The mixture was concentrated in vacuo to give the crude product. The crude product was purified by prep-HPLC (column: Venusil ASB Phenyl 150 x 30 mm x 5 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 37%-67%, 10 min). The compound cis-2-[4-

(cyclopentylamino)phenyl]N-(3-dimethylphosphoryl-4-methyl-phenyl)-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxamide (25 mg, 36.78 μmol , 56.95% yield, 98% purity, HCl) was obtained as light yellow solid. ^1H NMR (400 MHz, $\text{METHANOL-}d_4$) δ 1.21 - 1.38 (m, 2 H), 1.51 - 1.60 (m, 1 H), 1.69 - 1.78 (m, 4 H), 1.85 (br s, 7 H), 1.99 - 2.14 (m, 3 H), 2.17 - 2.32 (m, 2 H), 2.37 - 2.46 (m, 2 H), 2.48 - 2.68 (m, 3 H), 3.15 - 3.25 (m, 1 H), 3.76 - 4.02 (m, 2 H), 6.55 - 6.80 (m, 1 H), 6.94 - 7.10 (m, 1 H), 7.11 - 7.20 (m, 1 H), 7.29 (br d, $J=8.28$ Hz, 1 H), 7.33 - 7.41 (m, 1 H), 7.45 (br d, $J=8.28$ Hz, 2 H), 7.55 - 7.71 (m, 1 H), 7.76 - 7.97 (m, 3 H). LC-MS: (ES) m/z 630.3 ($\text{M}+\text{H}^+$).

Example S94: Synthesis of *Synthesis of cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 77)*



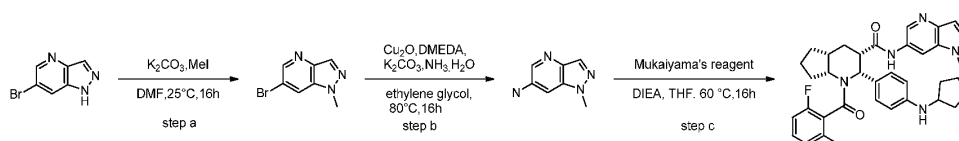
[0265] Step a) A solution of cis-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (0.1 g, 182.96 μmol), HATU (83.48 mg, 219.56 μmol) and DIEA (59.12 mg, 457.41 μmol , 79.67 μL) in DCM (1 mL) was stirred at 30 °C for 0.5 h. Then tert-butyl 6-amino-3,4-dihydro-1H-isoquinoline-2-carboxylate (54.52 mg, 219.56 μmol) was added and the mixture was stirred at 30 °C for another 16 h. The mixture was concentrated in vacuo to give the crude. The crude was purified by silica gel column chromatography to give cis-tert-butyl-6-[[2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carbonyl]amino]-3,4-dihydro-1H-isoquinoline-2-carboxylate (60 mg, 82.89 μmol , 45.31% yield, 96% purity) as light yellow solid. ^1H NMR (400 MHz, $\text{METHANOL-}d_4$) δ 1.23 - 1.39 (m, 3 H), 1.46 - 1.50 (m, 13 H), 1.55 - 1.64 (m, 3 H), 1.66 - 1.77 (m, 3 H), 1.96 - 2.04 (m, 2 H), 2.06 - 2.22 (m, 2 H), 2.27 (s, 1 H), 2.33 - 2.44 (m, 2 H), 2.71 - 2.83 (m, 2 H), 2.97 - 3.12 (m, 1 H), 3.56 - 3.64 (m, 2 H), 3.68 - 3.87 (m, 2 H), 4.49 (br s, 2 H), 6.51 - 6.62 (m, 3 H), 6.99 - 7.08 (m, 2 H), 7.10 - 7.17 (m, 1 H), 7.18 - 7.29 (m, 2 H), 7.30 - 7.34 (m, 1 H), 7.39 (d, $J=8.53$ Hz, 1 H), 7.45 (d, $J=8.78$ Hz, 1 H). LC-MS: (ES) m/z 695.5 ($\text{M}+\text{H}^+$).

[0266] Step b) To a solution of cis-tert-butyl-6-[[2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carbonyl]amino]-3,4-dihydro-1H-isoquinoline-2-carboxylate (55 mg, 79.15 μmol) in DCM (2

mL) was added TFA (264.69 mg, 2.32 mmol, 171.87 μ L). Then the mixture was stirred at 15 °C for 2 h. The mixture was concentrated in vacuo to give the crude. The crude was dissolved with DCM (20 mL) and alkalified to pH=8~9 by addition of saturated NaHCO₃ solution. The organic layer separated was dried, filtered and concentrated in vacuo to give the desired product cis-2-[4-(cyclopentylamino) phenyl]-1-(2-fluoro-6-methyl-benzoyl)-N-(1,2,3,4-tetrahydroisoquinolin-6-yl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]-pyridine-3-carboxamide (48 mg, 75.06 μ mol, 94.83% yield, 93% purity) as white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.27 - 1.37 (m, 3 H), 1.49 (br d, *J*=6.85 Hz, 3 H), 1.58 - 1.64 (m, 3 H), 1.68 - 1.75 (m, 3 H), 1.97 - 2.06 (m, 3 H), 2.12 - 2.22 (m, 2 H), 2.28 (s, 1 H), 2.40 (s, 2 H), 2.79 (br d, *J*=4.89 Hz, 3 H), 2.97 - 3.11 (m, 4 H), 3.69 - 3.79 (m, 2 H), 3.84 - 3.95 (m, 3 H), 6.54 - 6.62 (m, 3 H), 6.94 - 7.08 (m, 2 H), 7.12 - 7.21 (m, 2 H), 7.22 - 7.29 (m, 1 H), 7.35 - 7.42 (m, 2 H), 7.46 (d, *J*=8.80 Hz, 1 H). LC-MS: (ES) *m/z* 595.5 (M+H⁺).

[0267] Step c) To a solution of cis-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl- benzoyl)-N-(1,2,3,4-tetrahydroisoquinolin-6-yl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxamide (34 mg, 57.17 μ mol) and DIEA (14.78 mg, 114.33 μ mol, 19.91 μ L) in DCM (2 mL) was added dropwise of a solution of MeI (6.49 mg, 45.73 μ mol, 2.85 μ L) in DCM (1 mL). Then the mixture was stirred at 15 °C for 16 h. The mixture was concentrated in vacuo to give the residue. The residue was purified by prep-TLC (DCM/MeOH=10/1) to give cis-2-[4-(cyclopentyl amino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-N-(2-methyl-3,4-dihydro-1H-isoquinolin-6-yl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxamide (3 mg, 4.53 μ mol, 7.92% yield, 92% purity) as off-white solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.48 (br d, *J*=9.54 Hz, 3 H), 1.56 - 1.66 (m, 4 H), 1.68 - 1.77 (m, 3 H), 1.91 - 2.07 (m, 4 H), 2.10 - 2.23 (m, 2 H), 2.27 (s, 1 H), 2.33 - 2.45 (m, 3 H), 2.46 - 2.51 (m, 3 H), 2.72 - 2.81 (m, 2 H), 2.91 (q, *J*=7.09 Hz, 2 H), 3.03 (br d, *J*=10.76 Hz, 1 H), 3.53 - 3.62 (m, 2 H), 3.67 - 3.89 (m, 2 H), 6.50 - 6.61 (m, 3 H), 6.89 - 7.04 (m, 2 H), 7.05 - 7.20 (m, 2 H), 7.21 - 7.27 (m, 1 H), 7.29 - 7.38 (m, 2 H), 7.44 (d, *J*=8.80 Hz, 1 H). LC-MS: (ES) *m/z* 609.4 (M+H⁺).

Example S95: Synthesis of cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl- 1H-pyrazolo[4,3-b]pyridin-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 78)



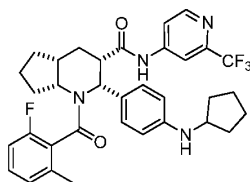
[0268] Step a) The K_2CO_3 (1.40 g, 10.10 mmol) and MeI (716.79 mg, 5.05 mmol, 314.38 μ L) were added to a solution of 6-bromo-1H-pyrazolo[4,3-b]pyridine (0.5 g, 2.52 mmol) in DMF (10 mL). The mixture was stirred at 25 °C for 16 h. The reaction mixture was added H_2O (20 mL) and was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine (25 mL), dried with anhydrous Na_2SO_4 , filtered, then the filtrate was evaporated under vacuum to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=100/0 to 3/1) to give compound 6-bromo-1-methyl-pyrazolo[4,3-b]pyridine (180 mg, 840.38 μ mol, 33.28% yield, 99% purity) as a pale yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ 4.07 (3 H, s) 7.94 (1 H, d, J =1.51 Hz) 8.20 (1 H, s) 8.60 (1 H, d, J =1.76 Hz). LCMS: m/z 214.0 ($M+H^+$).

[0269] Step b) The $NH_3 \cdot H_2O$ (2.10 g, 16.81 mmol, 2.31 mL, 28% purity) and Cu_2O (60.13 mg, 420.19 μ mol, 42.95 μ L) were added to a mixture of K_2CO_3 (116.15 mg, 840.38 μ mol), DMEDA (37.04 mg, 420.19 μ mol, 45.23 μ L) and 6-bromo-1-methyl-pyrazolo[4,3-b]pyridine (180 mg, 840.38 μ mol) in ethylene glycol (10 mL). The mixture was stirred at 80 °C for 16 h. The reaction mixture was added H_2O (10 mL) and was extracted with DCM:MeOH=10:1 (20 mL x 2). The combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4 , filtered, then the filtrate was evaporated under vacuum to give crude product. The crude product was purified by prep-TLC (plate: DCM: CH_3OH =15:1) to give compound 1-methylpyrazolo[4,3-b]pyridin-6-amine (40 mg, 261.87 μ mol, 31.16% yield, 97% purity) as a pale yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ 3.96 (3 H, s) 6.84 (1 H, d, J =1.25 Hz) 8.04 (1 H, s) 8.13 (1 H, br s). LCMS: m/z 149.2 ($M+H^+$).

[0270] Step c) The 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (20 mg, 43.05 μ mol) and 1-methylpyrazolo[4,3-b]pyridin-6-amine (7.65 mg, 51.66 μ mol) were dissolved in THF (2 mL). Then 2-chloro-1-methyl-pyridin-1-ium; iodide (16.50 mg, 64.58 μ mol) and DIEA (16.69 mg, 129.15 μ mol, 22.50 μ L) were added. The mixture was stirred at 60 °C for 16 h. The solvent was evaporated under vacuum to give crude product. The crude product was purified by prep-HPLC (column: Venusil ASB Phenyl 150 x 30 mm x 5 μ m; mobile phase: [water (0.05% HCl)- ACN]; B%: 45%-75%, 9 min) to give cis-2-[4-

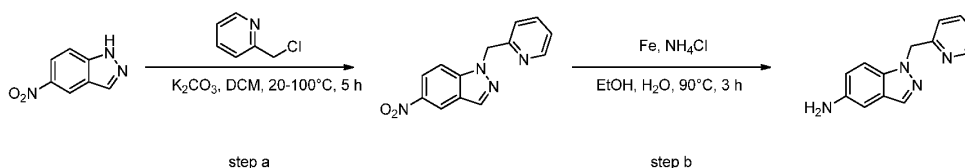
(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-N-(1-methylpyrazolo[4,3-b]pyridin-6-yl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxamide (8.5 mg, 13.47 μ mol, 31.28% yield, 100% purity, HCl) as a yellow solid. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.15 - 1.44 (3 H, m) 1.46 - 2.08 (13 H, m) 2.11 - 2.40 (4 H, m) 2.44 (2 H, s) 3.80 - 4.08 (2 H, m) 4.11 - 4.19 (3H, m) 6.66 - 6.84 (1 H, m) 7.00 - 7.14 (1 H, m) 7.15 - 7.30 (1 H, m) 7.36 - 7.45 (1 H, m) 7.48 (2 H, d, $J=8.53$ Hz) 7.88 - 8.01 (2 H, m) 8.15 - 8.28 (1 H, m) 8.63 - 8.86 (2 H, m). LCMS: m/z 595.5 (M+H $^+$).

Example S96: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(2-(trifluoromethyl)pyridin-4-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 79)



[0271] The title compound was synthesized in similar fashion as Example S95. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.23 - 1.34 (m, 2 H), 1.51 - 1.61 (m, 1 H), 1.67 (br s, 5 H), 1.82 (br s, 3 H), 1.86 - 2.00 (m, 3 H), 2.01 - 2.12 (m, 2 H), 2.12 - 2.21 (m, 2 H), 2.22 - 2.30 (m, 1 H), 2.35 - 2.44 (m, 2 H), 3.19 - 3.28 (m, 1 H), 3.74 - 4.02 (m, 2 H), 6.54 - 6.70 (m, 1 H), 7.01 - 7.09 (m, 1 H), 7.11 - 7.19 (m, 1 H), 7.31 - 7.43 (m, 3 H), 7.66 - 7.78 (m, 1 H), 7.82 - 7.91 (m, 2 H), 8.04 - 8.15 (m, 1 H), 8.41 - 8.57 (m, 1 H). LC-MS: (ES) m/z 609.3 (M+H $^+$).

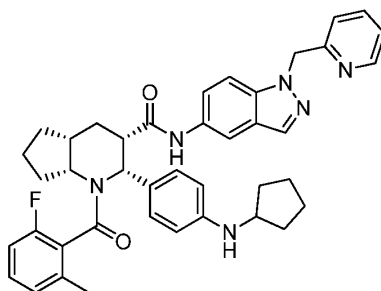
Example S97: Synthesis of (2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(pyridin-2-ylmethyl)-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 80)



[0272] Step a) To a mixture of 5-nitro-1H-indazole (2 g, 12.26 mmol) and 2-(chloromethyl)pyridine (2.41 g, 14.71 mmol, HCl) in DMF (10 mL) was added K_2CO_3 (4.24 g, 30.65 mmol) at 20°C under N_2 . The mixture was stirred at 100°C for 5 h. The reaction mixture was partitioned between EtOAc 100 mL and H_2O 100 mL. The organic phase was

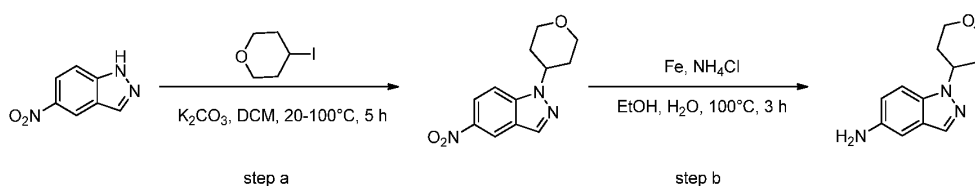
separated, dried, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=1/1 to 1/1). Compound 5-nitro-1-(2-pyridylmethyl)indazole (640 mg, 2.37 mmol, 19.30% yield, 94% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 5.75 (s, 2 H), 7.00 (d, *J*=7.83 Hz, 1 H), 7.20 (dd, *J*=6.97, 5.26 Hz, 1 H), 7.52 (d, *J*=9.05 Hz, 1 H), 7.60 (td, *J*=7.70, 1.71 Hz, 1 H), 8.22 (dd, *J*=9.29, 2.20 Hz, 1 H), 8.25 (d, *J*=0.73 Hz, 1 H), 8.56 (d, *J*=4.16 Hz, 1 H), 8.72 (d, *J*=1.71 Hz, 1 H) LCMS: (ES) *m/z* 255.1(M+H⁺).

[0273] Step b) A mixture of 5-nitro-1-(2-pyridylmethyl)indazole (400 mg, 1.57 mmol), Fe (702.88 mg, 12.59 mmol) and NH₄Cl (42.08 mg, 786.65 μmol) in EtOH (10 mL) and H₂O (2.5 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90°C for 3 h under N₂ atmosphere, filtered, then concentrated to get the desired product. Compound 1-(2-pyridylmethyl) indazol-5-amine (350 mg, 1.56 mmol, 99.20% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 5.62 - 5.76 (m, 2 H) 6.76 - 6.87 (m, 2 H) 6.96 (d, *J*=1.55 Hz, 1 H) 7.13 - 7.25 (m, 2 H) 7.54 (td, *J*=7.72, 1.61 Hz, 1 H) 7.88 (s, 1 H) 8.58 (d, *J*=4.53 Hz, 1 H) LCMS: (ES) *m/z* 225.4(M+H⁺).



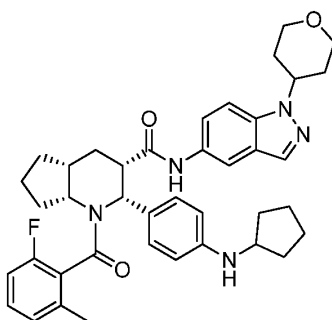
[0274] The title compound was synthesized in similar fashion as Example S95. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.25-1.41 (m, 4 H) 1.69 (br s, 3 H) 1.85 (br s, 4 H) 1.91-2.03 (m, 4 H) 2.06-2.23 (m, 4 H) 2.24-2.37 (m, 4H) 2.44 (s, 2 H) 3.21-3.29 (m, 1 H) 3.69 (br t, *J*=12.05 Hz, 2 H) 3.80-4.02 (m, 2 H) 4.13 (br d, *J*=7.28 Hz, 2 H) 4.73-4.85 (m, 1 H) 6.57-6.72 (m, 1 H) 7.04-7.12 (m, 1 H) 7.14-7.23 (m, 1 H) 7.35-7.46 (m, 4 H) 7.58-7.64 (m, 1 H) 7.90 (br d, *J*=8.78 Hz, 2 H) 7.95-7.98 (m, 2 H). LCMS: (ES) *m/z* 664.3(M+H⁺).

Exmaple S98: Synthesis of (2*R*,3*S*,4*aR*,7*aR*)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)- N-(1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indazol-5-yl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 81)



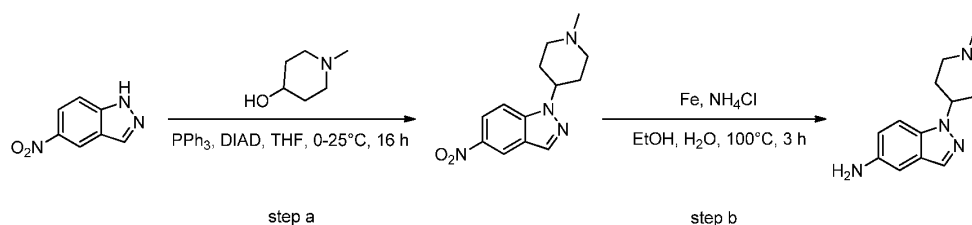
[0275] Step a) To a mixture of 5-nitro-1H-indazole (2 g, 12.26 mmol) and 1-methylpiperidin-4-ol (2.12 g, 18.39 mmol, 2.15 mL), PPh₃ (4.82 g, 18.39 mmol) in THF (20 mL) was added DIAD (1.96 M in toluene) (1.9 M, 9.68 mL) at 0°C under N₂. The mixture was stirred at 25°C for 16 h. The reaction solvent was concentrated to get a residue. The residue was purified by prep-HPLC: column: Welch Xtimate C18 150 * 40 mm * 10 μm; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 36%-46%, 8 min to give 1-(1-methyl-4-piperidyl)-5-nitro-indazole (900 mg, 3.46 mmol, 28.20% yield, 100% purity) was obtained as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.98 - 2.05 (m, 3 H) 2.15 - 2.27 (m, 2 H) 2.35 - 2.51 (m, 5 H) 3.06 (br d, *J*=12.05 Hz, 2 H) 4.46 (tt, *J*=11.61, 4.20 Hz, 1 H) 7.53 (d, *J*=9.29 Hz, 1 H) 8.21 (s, 1 H) 8.25 (dd, *J*=9.16, 2.13 Hz, 1 H) 8.72 (d, *J*=2.01 Hz, 1 H) LCMS: (ES) *m/z* 261.3(M+H⁺).

[0276] Step b) A mixture of 1-(1-methyl-4-piperidyl)-5-nitro-indazole (400 mg, 1.54 mmol), NH₄Cl (41.10 mg, 768.37 μmol) and Fe (686.55 mg, 12.29 mmol) in EtOH (10 mL) and H₂O (2.5 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90°C for 3 h under N₂ atmosphere, filtered, then concentrated to get the desired product. Compound 1-(1-methyl-4-piperidyl)indazol-5-amine (300 mg, 1.30 mmol, 84.76% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.15 (br s, 1 H) 2.26 - 2.41 (m, 4 H) 2.44 (br s, 3 H) 3.14 (br s, 2 H) 3.40 - 3.76 (m, 1 H) 4.41 (br s, 1 H) 6.86(dd, *J*=8.91, 2.13 Hz, 1 H) 6.95 (d, *J*=1.76 Hz, 1 H) 7.31 (d, *J*=8.78 Hz, 1 H) 7.78 (s, 1 H) LC-MS: (ES) *m/z* 231.3(M+H⁺).



[0277] The title compound was synthesized in similar fashion as Example S95. ¹H NMR (400 MHz, METHANOL-d₄) δ ppm 1.21 - 1.33 (m, 2 H) 1.49 - 1.59 (m, 1 H) 1.70 (br s, 6 H) 1.85 (br s, 3 H) 1.98 (br d, *J*=17.57 Hz, 3 H) 2.08 - 2.17(m, 2 H) 2.17 - 2.24 (m, 2 H) 2.28 (br d, *J*=13.55 Hz, 3 H) 2.44 (s, 2 H) 2.47 - 2.56 (m, 2 H) 2.92 - 3.04 (m, 4 H) 3.25 (br dd, *J*=10.16, 5.90 Hz, 2 H) 3.72 (brd, *J*=12.80 Hz, 2 H) 3.78 - 3.88 (m, 1 H) 3.93 - 4.02 (m, 1 H) 6.58 - 6.74 (m, 1 H) 7.04 - 7.12 (m, 1 H) 7.14 - 7.23 (m, 1 H) 7.37 - 7.50 (m, 4 H) 7.57 - 7.67 (m, 1 H) 7.88 - 8.05 (m, 4 H) LCMS: (ES) *m/z* 677.4 (M+H⁺).

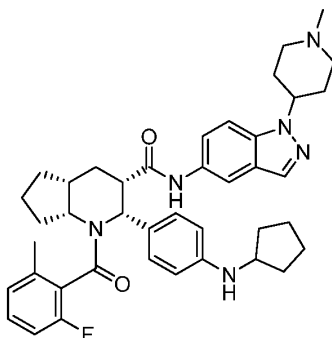
Example S99: Synthesis of (2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(1-methylpiperidin-4-yl)-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 82)



[0278] Step a) To a mixture of 5-nitro-1H-indazole (2 g, 12.26 mmol) and 1-methylpiperidin-4-ol (2.12 g, 18.39 mmol, 2.15 mL), PPh₃ (4.82 g, 18.39 mmol) in THF (20 mL) was added DIAD (1.96 M in toluene) (1.9 M, 9.68 mL) at 0°C under N₂. The mixture was stirred at 25°C for 16 h. The reaction solvent was concentrated to get a residue. The residue was purified by prep-HPLC: column: Welch Xtimate C18 150 * 40 mm * 10 µm; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 36%-46%, 8 min to give 1-(1-methyl-4-piperidyl)-5-nitro-indazole (900 mg, 3.46 mmol, 28.20% yield, 100% purity) was obtained as a light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 1.98 - 2.05 (m, 3 H) 2.15 - 2.27 (m, 2 H) 2.35 - 2.51 (m, 5 H) 3.06 (br d, *J*=12.05 Hz, 2 H) 4.46 (tt, *J*=11.61, 4.20 Hz, 1 H) 7.53 (d, *J*=9.29 Hz, 1 H) 8.21 (s, 1 H) 8.25 (dd, *J*=9.16, 2.13 Hz, 1 H) 8.72 (d, *J*=2.01 Hz, 1 H) LCMS: (ES) *m/z* 261.3(M+H⁺).

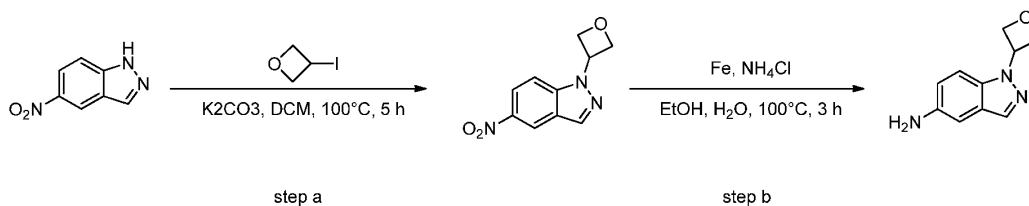
[0279] Step b) A mixture of 1-(1-methyl-4-piperidyl)-5-nitro-indazole (400 mg, 1.54 mmol), NH₄Cl (41.10 mg, 768.37 μmol) and Fe (686.55 mg, 12.29 mmol) in EtOH (10 mL) and H₂O (2.5 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90°C for 3 h under N₂ atmosphere, filtered, then concentrated to get the desired product. Compound 1-(1-methyl-4-piperidyl)indazol-5-amine (300 mg, 1.30 mmol, 84.76% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.15 (br s, 1 H)

2.26 - 2.41 (m, 4 H) 2.44 (br s, 3 H) 3.14 (br s, 2 H) 3.40 - 3.76 (m, 1 H) 4.41 (br s, 1 H)
6.86(dd, $J=8.91, 2.13$ Hz, 1 H) 6.95 (d, $J=1.76$ Hz, 1 H) 7.31 (d, $J=8.78$ Hz, 1 H) 7.78 (s, 1
H) LC-MS: (ES) m/z 231.3($M+H^+$).



[0280] The title compound was synthesized in similar fashion as Example S95. ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 1.21 - 1.33 (m, 2 H) 1.49 - 1.59 (m, 1 H) 1.70 (br s, 6 H) 1.85 (br s, 3 H) 1.98 (br d, $J=17.57$ Hz, 3 H) 2.08 - 2.17(m, 2 H) 2.17 - 2.24 (m, 2 H) 2.28 (br d, $J=13.55$ Hz, 3 H) 2.44 (s, 2 H) 2.47 - 2.56 (m, 2 H) 2.92 - 3.04 (m, 4 H) 3.25 (br dd, $J=10.16, 5.90$ Hz, 2 H) 3.72 (brd, $J=12.80$ Hz, 2 H) 3.78 - 3.88 (m, 1 H) 3.93 - 4.02 (m, 1 H) 6.58 - 6.74 (m, 1 H) 7.04 - 7.12 (m, 1 H) 7.14 - 7.23 (m, 1 H) 7.37 - 7.50 (m, 4 H) 7.57 - 7.67 (m, 1 H) 7.88 - 8.05 (m, 4 H) LCMS: (ES) m/z 677.4 ($M+H^+$).

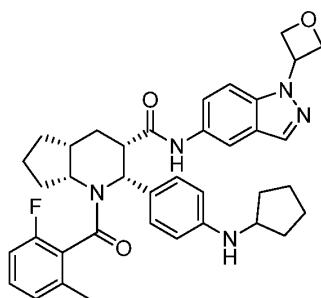
Example S100: Synthesis of (2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)- N-(1-(oxetan-3-yl)-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 83)



[0281] Step a) To a mixture of 5-nitro-1H-indazole (2 g, 12.26 mmol) and 3-iodooxetane (2.71 g, 14.71 mmol) in DMF (10mL) was added K_2CO_3 (3.39 g, 24.52 mmol) at 20°C under N_2 . The mixture was stirred at 100°C for 5 h. The reaction mixture was partitioned between EtOAc 100 mL and H_2O 100 mL. The organic phase was separated, dried, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC:(column: YMC-Triart Prep C18 150 * 40 mm* 7 μm ; mobile phase: [water (0.04%

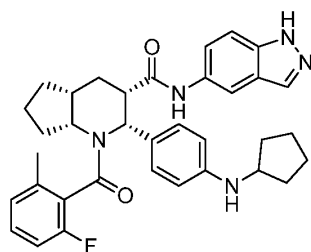
$\text{NH}_3\text{H}_2\text{O} + 10 \text{ mM } \text{NH}_4\text{HCO}_3\text{)-ACN}]$; B%: 32%-42%, 10 min) The compound 5-nitro-1-(oxetan-3-yl)indazole (350 mg, 1.56 mmol, 98% purity) was obtained as yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 5.13 - 5.23 (m, 2 H), 5.30 (t, $J=6.65$ Hz, 2 H), 5.76 - 5.92 (m, 1 H), 7.61 (d, $J=9.29$ Hz, 1 H), 8.26 - 8.37 (m, 2H), 8.76 (d, $J=2.01$ Hz, 1H) LCMS: (ES) m/z 220.1($\text{M}+\text{H}^+$).

[0282] Step b) A mixture of 5-nitro-1-(oxetan-3-yl)indazole (400 mg, 1.82 mmol), NH_4Cl (48.81 mg, 912.43 μmol) and Fe (815.27 mg, 14.60 mmol) in EtOH (10 mL) and H_2O (2.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90°C for 3 h under N_2 atmosphere. Filtered, then concentrated to get the desired product. Compound 1-(oxetan-3-yl) indazol-5-amine (335 mg, 1.77 mmol, 97.02% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 5.07 - 5.18 (m, 2 H) 5.28 (br t, $J=6.40$ Hz, 2 H) 5.72 (quin, $J=6.90$ Hz, 1 H) 6.90 (br d, $J=8.78$ Hz, 1 H) 6.96(s, 1 H) 7.37 (br d, $J=8.78$ Hz, 1 H) 7.88 (s, 1 H). LCMS: (ES) m/z 190.1($\text{M}+\text{H}^+$).



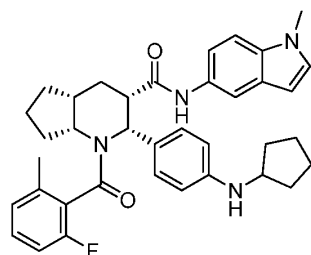
[0283] The title compound was synthesized in similar fashion as Example S95. ^1H NMR (400 MHz, $\text{METHANOL}-d_4$) δ ppm 1.31 (br s, 2 H) 1.42 - 1.66 (m, 6 H) 1.73 (br s, 2 H) 1.97 (br d, $J=11.29$ Hz, 3 H) 2.08 - 2.27 (m, 3 H) 2.30 (s, 1H) 2.39 - 2.46 (m, 2 H) 3.10 (br s, 1 H) 3.76 (br s, 2 H) 5.07 - 5.25 (m, 6 H) 5.96 (br d, $J=6.27$ Hz, 1 H) 6.58 - 6.67 (m, 3 H) 7.04 - 7.19 (m, 2 H) 7.41 - 7.60(m, 4 H) 7.86 - 8.11 (m, 2 H) LCMS: (ES) m/z 636.3 ($\text{M}+\text{H}^+$).

Example S101: Synthesis of (2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)- N-(1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 84)



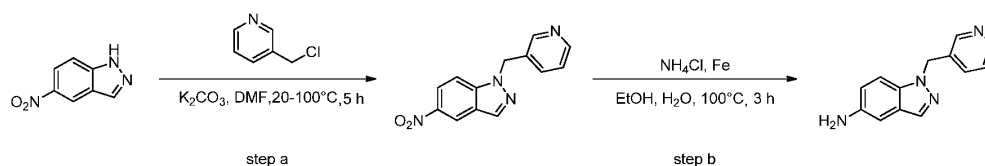
[0284] The title compound was synthesized in similar fashion as Example S95. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.24 - 1.43 (m, 3 H) 1.70 (br d, *J*=4.52 Hz, 6 H) 1.85 (br s, 4 H) 1.93 - 2.07 (m, 3 H) 2.07 - 2.18 (m, 2 H) 2.37 - 2.54 (m, 3 H) 3.18 - 3.30 (m, 1 H) 3.73 - 3.92 (m, 1 H) 3.93 - 4.06 (m, 1 H) 6.57 - 6.73 (m, 1 H) 7.03 - 7.12 (m, 1 H) 7.13 - 7.22 (m, 1 H) 7.34 - 7.57 (m, 6 H) 7.89 - 7.99 (m, 3 H) 8.00 - 8.04 (m, 1 H) LCMS: (ES) *m/z* 580.3(M+H⁺).

Example S102: Synthesis of (2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 85)



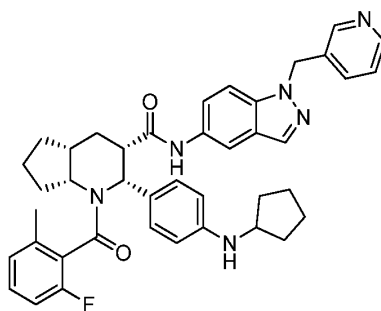
[0285] The title compound was synthesized in similar fashion as Example S95. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.32 (br d, *J*=13.05 Hz, 4 H) 1.44 - 1.56 (m, 2 H) 1.67 (br s, 6 H) 1.82 (br s, 4 H) 1.89 - 2.06 (m, 3 H) 2.11 (s, 1H) 2.20 - 2.29 (m, 2 H) 2.35 - 2.51 (m, 2 H) 3.19 (br d, *J*=14.56 Hz, 1 H) 3.72 - 3.79 (m, 1 H) 3.93 (s, 1 H) 6.34 - 6.40 (m, 1 H) 6.56 - 6.70 (m, 1 H) 7.04 - 7.25 (m, 6 H) 7.26 - 7.34 (m, 1 H) 7.36 - 7.44 (m, 1 H) 7.56 - 7.67 (m, 1 H) 7.80 (br s, 2 H) LCMS: (ES) *m/z* 593.3(M+H⁺).

Example S103: Synthesis of (2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(pyridin-3-ylmethyl)-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 86)



[0286] Step a) To a mixture of 5-nitro-1H-indazole (2 g, 12.26 mmol) and 3-(chloromethyl)-pyridine (2.41 g, 14.71 mmol, HCl) in DMF (10 mL) was added K_2CO_3 (5.08 g, 36.78 mmol) at 20°C under N_2 . The mixture was stirred at 100°C for 5 h. The reaction mixture was partitioned between EtOAc 100 mL and H_2O 100 mL. The organic phase was separated, dried, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC: column: Welch Xtimate C18 150 * 40 mm * 10 μm ; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 31%-51%, 8 min to give 5-nitro-1-(3-pyridylmethyl)indazole (300 mg, 1.18 mmol, 9.62% yield) was obtained as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ ppm 5.49 - 5.79 (m, 2 H) 7.25 - 7.31 (m, 2 H) 7.46 (d, $J=9.03$ Hz, 1 H) 7.51 - 7.58 (m, 1 H) 8.26 - 8.33 (m, 2 H) 8.57 - 8.65 (m, 2 H) 8.77 (d, $J=1.76$ Hz, 1 H) LCMS: (ES) m/z 255.1 ($M+H^+$).

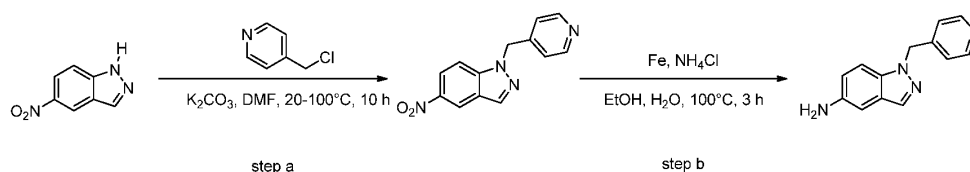
[0287] Step b) A mixture of 5-nitro-1-(3-pyridylmethyl)indazole (300 mg, 1.18 mmol), NH_4Cl (31.56 mg, 589.99 μmol) and Fe (527.16 mg, 9.44 mmol) in EtOH (10 mL) and H_2O (2.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90°C for 3 h under N_2 atmosphere, filtered, then concentrated to get the desired product. Compound 1-(3-pyridylmethyl)-indazol-5-amine (220 mg, 981.00 μmol , 83.14% yield) was obtained as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ ppm 5.55 (s, 2 H) 6.85 (dd, $J=8.78$, 2.01 Hz, 1 H) 6.96 (d, $J=1.76$ Hz, 1 H) 7.13 - 7.25 (m, 2 H) 7.44 (br d, $J=8.03$ Hz, 1 H) 7.85 (s, 1 H) 8.50 - 8.53 (m, 1 H) 8.56 (d, $J=1.51$ Hz, 1 H) LCMS: (ES) m/z 225.4 ($M+H^+$).



[0288] The title compound was synthesized in similar fashion as Example S95. 1H NMR (400 MHz, $METHANOL-d_4$) δ ppm 1.19 - 1.40 (m, 3 H) 1.45 - 1.63 (m, 2 H) 1.64 - 1.78 (m,

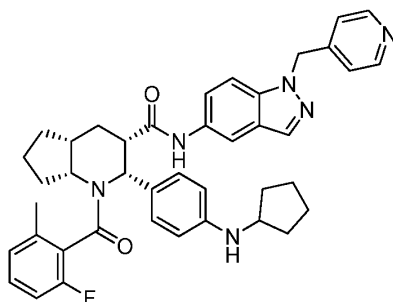
6 H) 1.84 (br d, $J=11.04$ Hz, 3 H) 2.00 (br s, 2 H) 2.08 -2.18 (m, 2 H) 2.21 - 2.34 (m, 2 H) 2.44 (s, 2 H) 3.21 - 3.27 (m, 1 H) 3.80 - 4.04 (m, 2 H) 5.91 - 6.01 (m, 2 H) 6.58 - 6.75 (m, 1 H) 7.04 - 7.23 (m, 2 H) 7.38 -7.53 (m, 5 H) 7.58 - 7.66 (m, 1 H) 7.86 (br t, $J=6.78$ Hz, 1 H) 7.92 - 8.00 (m, 2 H) 8.02 - 8.15 (m, 2 H) 8.35 (t, $J=8.03$ Hz, 1 H) 8.78 (br d, $J=5.77$ Hz, 1 H)
LCMS: m/z 671.3(M+H⁺).

Example S104: Synthesis of (2R,3S,4aR,7aR)-2-[4-(cyclopeantylamino)phenyl]-1-(2-fluoro-6-methyl-benzo yl)-N-[1-(4-pyridylmethyl)indazol-5-yl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta-[b]pyridine-3-carboxamide (Compound No. 87)



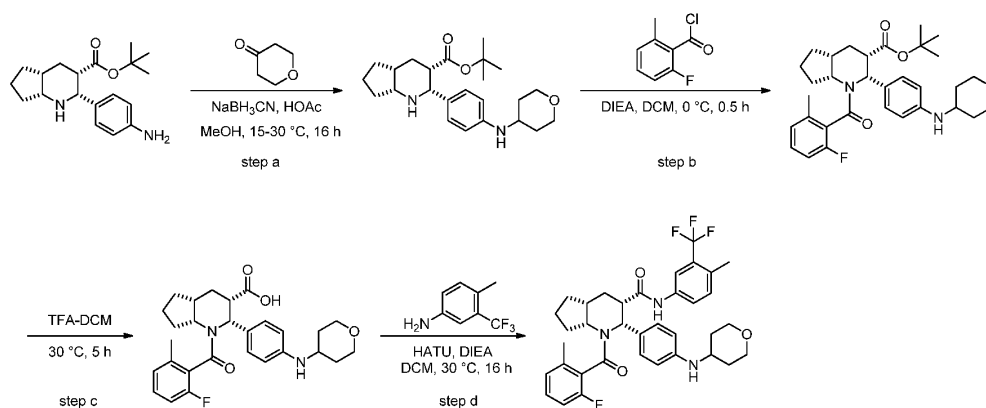
[0289] Step a) To a mixture of 5-nitro-1H-indazole (2 g, 12.26 mmol) and 4-(chloromethyl) pyridine (2.41 g, 14.71 mmol, HCl) in DMF (10 mL) was added K_2CO_3 (5.08 g, 36.78 mmol) at 20°C under N_2 . The mixture was stirred at 100°C for 5 h. The reaction mixture was partitioned between EtOAc 100 mL and H_2O 100 mL. The organic phase was separated, dried, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC: column: Welch Xtimate C18 150 * 40 mm * 10 μm ; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 31%-51%, 8 min. 5-nitro-1-(pyridin-4-yl)-1H-indazole (300 mg, 1.18 mmol, 9.62% yield) was obtained as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ ppm 5.67 (s, 2 H) 7.04 (d, $J=6.02$ Hz, 2 H) 7.38 (d, $J=9.29$ Hz, 1 H) 8.25 - 8.33 (m, 2 H) 8.55 - 8.61 (m, 2 H) 8.79(d, $J=2.01$ Hz, 1 H) LCMS: (ES) m/z 255.4 ($M+H^+$).

[0290] Step b) A mixture of 5-nitro-1-(pyridin-4-yl)-1H-indazole (300 mg, 1.18 mmol), NH₄Cl (31.56 mg, 589.99 μmol) and Fe (527.16 mg, 9.44 mmol) in EtOH (10 mL) and H₂O (2.5 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90°C for 3 h under N₂ atmosphere. Filtered, then concentrated to get the desired product. Compound 1-(pyridin-4-yl)-1H-indazol-5-amine (220 mg, 981.00 μmol, 83.14% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 5.54 (s, 2 H) 6.84 (dd, *J*=8.78, 2.01 Hz, 1 H) 6.97 (d, *J*=1.51 Hz, 1 H) 6.99 (d, *J*=5.77 Hz, 2 H) 7.10 (d, *J*=8.78 Hz, 1 H) 7.88 (d, *J*=0.75 Hz, 1 H) 8.51 (d, *J*=5.77 Hz, 2 H) LCMS: (ES) *m/z* 225.4 (M+H⁺).



[0291] The title compound was synthesized in similar fashion as Example S95. ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 1.33 (br d, $J=18.57$ Hz, 5 H) 1.50 (s, 1 H) 1.61 (br d, $J=4.77$ Hz, 3 H) 1.68 - 1.77 (m, 3 H) 1.96 - 2.06 (m, 3 H) 2.10 - 2.26 (m, 3 H) 2.29 (s, 1 H) 2.37 - 2.48 (m, 2 H) 3.10 (br s, 1 H) 3.66 - 3.81 (m, 2 H) 5.72 (d, $J=4.02$ Hz, 2 H) 6.57 - 6.68 (m, 3 H) 7.05 - 7.17 (m, 4 H) 7.34 - 7.51 (m, 5 H) 7.85 - 8.00 (m, 1 H) 8.07 (d, $J=9.54$ Hz, 1 H) 8.45 (br s, 2 H) LCMS: (ES) m/z 671.4 ($\text{M}+\text{H}^+$).

Example S105: Synthesis of *cis*-1-(2-fluoro-6-methylbenzoyl)-*N*-(4-methyl-3-(trifluoromethyl)-phenyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 88)



[0292] **Step a)** To a mixture of *cis*-tert-butyl 2-(4-aminophenyl)-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (0.1 g, 316.02 μmol) in MeOH (1.5 mL) was added tetrahydropyran-4-one (34.80 mg, 347.62 μmol , 31.93 μL), HOAc (37.95 mg, 632.04 μmol , 36.15 μL) and NaBH_3CN (119.15 mg, 1.90 mmol) in one portion at 15°C. The mixture was stirred at 30°C for 16 h. The mixture was diluted with DCM (15 mL) and alkalinized to pH=8~9 and extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried, filtered and concentrated in vacuo to give the crude. The

crude was purified by prep-HPLC(column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 μ m; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 20%-90%, 20 min) to give cis-tert-butyl 2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (80 mg, 199.72 μ mol, 68.38% yield) as colorless gum. LC-MS: (ES) m/z 401.3 ($\text{M}+\text{H}^+$).

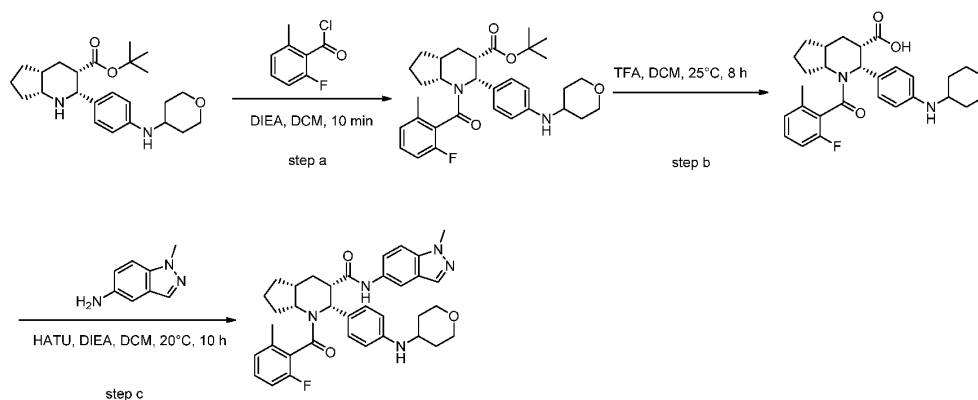
[0293] Step b) To a solution of cis-tert-butyl 2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (80 mg, 199.72 μ mol) and DIEA (51.62 mg, 399.45 μ mol, 69.58 μ L) in DCM (3 mL) was added dropwise of a solution of 2-fluoro-6-methyl-benzoyl chloride (34.47 mg, 199.72 μ mol) in DCM (2 mL) at 0°C. The mixture was stirred at 0 °C for 10 min. The mixture was diluted with DCM (20 mL), washed with H_2O (2 x 10 mL), dried, filtered and concentrated in vacuo to give the crude product. The crude product was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluent of 0~50% ethyl acetate/petroleum ether gradient @ 22 mL/min) to give cis-tert-butyl 1-(2-fluoro-6-methyl-benzoyl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (110 mg, 192.67 μ mol, 96.47% yield, 94% purity) as white solid. LC-MS: (ES) m/z 537.3 ($\text{M}+\text{H}^+$).

[0294] Step c) The cis-tert-butyl 1-(2-fluoro-6-methyl-benzoyl)-2-[4-(tetrahydropyran-4-yl-amino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (98 mg, 182.61 μ mol) was dissolved in DCM (5 mL). Then CF_3COOH (1.54 g, 13.51 mmol, 1 mL) was added. The mixture was stirred at 15 °C for 16 h. Then 10 mL of H_2O was added. Then the mixture was extracted with EtOAc (15 mL x 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure to give cis-1-(2-fluoro-6-methyl-benzoyl)-2-[4-(tetrahydropyran-4-yl amino) phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (85 mg, 168.03 μ mol, 92.02% yield, 95% purity) as white solid. LC-MS: (ES) m/z 481.2 ($\text{M}+\text{H}^+$).

[0295] Step d) The HATU (18.99 mg, 49.94 μ mol) and DIEA (13.45 mg, 104.04 μ mol, 18.12 μ L) were added to a mixture of cis-1-(2-fluoro-6-methyl-benzoyl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (20 mg, 41.62 μ mol) and 4-methyl-3-(trifluoromethyl)aniline (8.75 mg, 49.94 μ mol, 7.17 μ L) in DCM (0.5 mL). Then the mixture was stirred at 30 °C for 16 h. The reaction mixture was evaporated under vacuum to give the crude product. The crude product was purified by prep-HPLC (column: Venusil ASB Phenyl 150 x 30 mm x 5 μ m; mobile

phase: [water (0.05% HCl)-ACN]; B%: 60%-90%, 9 min) to give cis-1-(2-fluoro-6-methylbenzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxamide (6 mg, 8.45 μ mol, 20.32% yield, 95% purity, HCl) as white solid. ^1H NMR (400 MHz, METHANOL-*d*4) δ 1.18 - 1.40 (3 H, m), 1.41 - 1.91 (8 H, m), 1.94 - 2.12 (2 H, m), 2.13 - 2.30 (2 H, m), 2.32 - 2.48 (6 H, m), 3.09 - 3.22 (1 H, m), 3.38 (2 H, td, $J=11.92, 1.83$ Hz), 3.62 - 3.82 (1 H, m), 3.87 - 4.02 (2 H, m), 6.47 - 6.64 (1 H, m), 6.98 - 7.17 (2 H, m), 7.21 - 7.42 (4 H, m), 7.46 - 7.58 (1 H, m), 7.72 - 7.84 (2 H, m), 7.85 - 7.99 (1 H, m). LC-MS: (ES) m/z 638.3 ($\text{M}+\text{H}^+$).

Example S106: Synthesis of (2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 89)



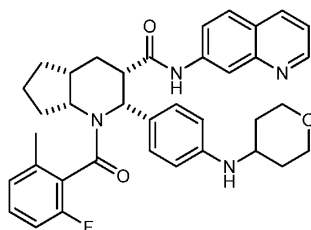
[0296] Step a) To a solution of (2R,3S,4aR,7aR)-tert-butyl 2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (800 mg, 2.00 mmol) and DIEA (516.26 mg, 3.99 mmol, 695.77 μ L) in DCM (15 mL) was added 2-fluoro-6-methylbenzoyl chloride (327.46 mg, 1.90 mmol) at 0°C, then the reaction mixture was stirred at 0°C for 10 min. The reaction mixture was quenched by addition MeOH (5 mL) at 25°C, then the mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=100/1 to 0/1). The compound (2R,3S,4aR,7aR)-tert-butyl 1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)-phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (1.06 g, 1.84 mmol, 91.97% yield, 93% purity) was obtained as white solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 1.15 - 1.24 (m, 3 H), 1.33 (s, 4 H), 1.39 (s, 5 H), 1.40 - 1.54 (m, 5 H), 1.94 - 2.09 (m, 6 H), 2.33 (d, $J=7.63$ Hz, 3 H), 3.47 - 3.57 (m, 4 H), 3.98 - 4.03 (m,

2 H), 6.50 - 6.62 (m, 3 H), 6.91 - 6.96 (m, 1 H), 7.01 (dd, $J=7.57$, 3.19 Hz, 1 H), 7.19 - 7.25 (m, 1 H), 7.29 (s, 1 H), 7.34 (d, $J=8.63$ Hz, 1 H). LC-MS: (ES) m/z 537.3 ($M+H^+$).

[0297] Step b) To a solution of (2R,3S,4aR,7aR)-tert-butyl 1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (1.06 g, 1.98 mmol) in DCM (5 mL) was added TFA (7.70 g, 67.53 mmol, 5 mL), then the reaction mixture was stirred at 25°C for 8 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was added HCl/dioxane at 25°C for 10 min. Then the residue was concentrated under reduced pressure to give a crude product. The compound (2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl) octahydro-1H-cyclopenta[b]pyridine-3-carboxylic acid (930 mg, 1.74 mmol, 88.34% yield, 97% purity, HCl) was obtained as yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.97 - 1.14 (m, 2 H), 1.20 - 1.41 (m, 2 H), 1.44 - 1.62 (m, 3 H), 1.69 - 1.87 (m, 3 H), 1.93 - 2.13 (m, 2 H), 2.20 - 2.33 (m, 3 H), 2.80 - 3.02 (m, 1 H), 3.27 - 3.40 (m, 2 H), 3.52 - 3.56 (m, 2 H), 3.59 - 3.70 (m, 1 H), 3.88 (br d, $J=11.51$ Hz, 2 H), 6.42 - 6.48 (m, 1 H), 6.92 - 7.22 (m, 5 H), 7.29 - 7.41 (m, 3 H). LC-MS: (ES) m/z 481.2 ($M+H^+$).

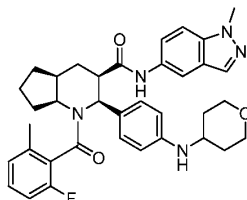
[0298] Step c) To a solution of (2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxylic acid, HATU (47.47 mg, 124.85 μmol) and DIEA (40.34 mg, 312.13 μmol , 54.37 μL) in DCM (3 mL) at 25°C for 10 min, then the 1-methylindazol-5-amine (22.97 mg, 156.06 μmol) was added, then the reaction mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated under reduced pressure to give a crude product. The crude product was purified by prep-HPLC. (column: Phenomenex Gemini-NX 150 * 30 mm * 5 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 30%-60%, 7 min). The compound (2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (17 mg, 25.52 μmol , 15.56% yield, 97% purity, HCl) was obtained as light yellow solid. ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 1.21 - 1.33 (m, 2 H), 1.55 (br t, $J=10.51$ Hz, 1 H), 1.66 - 1.92 (m, 6 H), 2.02 - 2.13 (m, 2 H), 2.15 - 2.35 (m, 2 H), 2.42 (s, 2 H), 3.18 - 3.30 (m, 2 H), 3.33 - 3.41 (m, 2 H), 3.67 - 3.84 (m, 2 H), 3.98 (br d, $J=11.88$ Hz, 2 H), 4.03 - 4.07 (m, 3 H), 6.54 - 6.72 (m, 1 H), 7.06 (t, $J=8.69$ Hz, 1 H), 7.14 - 7.21 (m, 1 H), 7.33 - 7.54 (m, 5 H), 7.84 - 7.99 (m, 4 H). LC-MS: (ES) m/z 610.3 ($M+H^+$).

Example S107: Synthesis of *cis*-1-(2-fluoro-6-methylbenzoyl)-N-(quinolin-7-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 90)



[0299] The title compound was synthesized in similar fashion as Example S106. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.17 - 1.46 (3 H, m), 1.47 - 1.93 (8 H, m), 2.07 - 2.37 (1 H, m), 2.10 - 2.22 (1 H, m), 2.23 - 2.38 (2 H, m), 2.45 (2 H, s), 3.36 - 3.47 (2 H, m), 3.67 - 3.89 (2 H, m), 3.92 - 4.04 (2 H, m), 6.67 - 6.91 (1 H, m), 7.02 - 7.14 (1 H, m), 7.15 - 7.24 (1 H, m), 7.33 - 7.46 (3 H, m), 7.85 - 8.02 (4 H, m), 8.25 - 8.34 (1 H, m), 8.88 - 9.15 (3 H, m). LC-MS: (ES) *m/z* 607.4 (M+H⁺).

Example S108: Synthesis of (2*S*,3*R*,4*aS*,7*aS*)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1*H*-indazol-5-yl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydro-1*H*-cyclopenta[b]pyridine-3-carboxamide (Compound No. 91)



[0300] Step a) To a solution of tert-butyl 2-(4-nitrophenyl)-6,7-dihydro-5*H*-cyclopenta[b]pyridine-3-carboxylate (1.2 g, 3.53 mmol), HCl/dioxane (4 M, 1.76 mL) in MeOH (25 mL) was added PtO₂ (160.11 mg, 705.11 μmol) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 20°C for 3 h. The previous batch (4 g) was combined with this batch, then concentrated under reduced pressure to remove solvent. The residue was diluted with sat. NaHCO₃(aq) 100 ml and extracted with EtOAc(100 mL * 3). The combined organic layers were dried, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, DCM:methanol=1/0 to 10/1) to get tert-butyl 2-(4-aminophenyl)-2,3,4,4*a*, 5,6,7,7*a*-octahydro-1*H*-cyclopenta[b]pyridine-3-carboxylate (2.4

g) as a light yellow gum. ^1H NMR (400 MHz, CDCl_3) δ ppm 1.17 (s, 9 H), 1.45 - 1.63 (m, 3 H), 1.75 - 1.91 (m, 3 H), 1.99 - 2.20 (m, 3 H), 2.78 (q, $J=6.05$ Hz, 1 H), 3.29 (td, $J=6.54$, 2.81 Hz, 1 H), 3.55 (br s, 2 H), 3.90 (d, $J=5.63$ Hz, 1 H), 6.62 (d, $J=8.38$ Hz, 2 H), 7.14 (d, $J=8.38$ Hz, 2 H). LC-MS: (ES) m/z 317.2 ($\text{M}+\text{H}^+$).

[0301] Step b) To a mixture of tert-butyl 2-(4-aminophenyl)-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (1.1 g, 3.48 mmol) and tetrahydropyran-4-one (417.63 mg, 4.17 mmol, 383.14 μL) in MeOH (15 mL) was added NaBH_3CN (655.36 mg, 10.43 mmol) at 0°C under N_2 . The mixture was stirred at 20°C for 6 h, then NaBH_3CN (436.90 mg, 6.95 mmol) and AcOH (313.13 mg, 5.21 mmol, 298.22 μL) were added to the mixture, and stirred at 20°C for another 6 h. The previous batch (1.5 g) was combined with this batch, and the mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with saturated NaHCO_3 (200 mL) and extracted with EtOAc (200 mL * 2). The combined organic layers were dried, filtered and concentrated under reduced pressure to give the tert-butyl 2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (5 g, crude) as a light yellow oil. The crude was purified by column chromatography (SiO_2 , DCM:methanol=1/0 to 10/1) to get a crude product (3.6 g, as a light yellow oil), then diluted with 1 M HCl(aq) 100 mL and washed with EtOAc (100 mL * 2). The liquid layer was added sat. NaHCO_3 (aq) (200 mL), then extracted with EtOAc (100 mL * 3), the combined organic layers were dried, filtered, and concentrated under reduced pressure to give tert-butyl 2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (2.0 g, 4.99 mmol, 40.00% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.12 - 1.24 (m, 9 H), 1.39 - 1.59 (m, 5 H), 1.69 - 1.92 (m, 4 H), 2.00 - 2.06 (m, 3 H), 2.10 - 2.18 (m, 1 H), 2.76 - 2.83 (m, 1 H), 3.30 (td, $J=6.57$, 2.87 Hz, 1 H), 3.44 - 3.56 (m, 3 H), 3.89 - 3.96 (m, 1 H), 3.97 - 4.05 (m, 1 H), 3.97 - 4.05 (m, 1 H), 6.50 - 6.61 (m, 2 H), 7.16 (d, $J=8.44$ Hz, 2 H). LC-MS: (ES) m/z 401.3 ($\text{M}+\text{H}^+$).

[0302] Step c) The tert-butyl 2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (2 g, 4.99 mmol) was purified by Prep-SFC: column: Phenomenex-Cellulose-2 (250 mm * 50 mm, 10 μm); mobile phase: [0.1% $\text{NH}_3\cdot\text{H}_2\text{O}$ EtOH]; B%: 45%-45%, 8 min to give tert-butyl (2S,3R,4aS,7aS)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (850 mg, 2.12 mmol, 42.46% yield) (800 mg, 2.00 mmol, 40.00% yield, 100% ee) as a white solid (^1H NMR (400 MHz, CDCl_3) δ ppm 1.16 (s, 9 H), 1.35 - 1.46 (m, 2 H),

1.67 - 1.90 (m, 6 H), 1.98 - 2.14 (m, 5 H), 2.73 - 2.82 (m, 1 H), 3.28 (td, $J=6.65$, 3.01 Hz, 1 H), 3.42 - 3.54 (m, 3 H), 3.89 (d, $J=6.02$ Hz, 1 H), 3.95 - 4.04 (m, 2 H), 6.55 (d, $J=8.53$ Hz, 2 H), 7.14 (d, $J=8.28$ Hz, 2 H). LC-MS: (ES) m/z 401.3 ($M+H^+$) and tert-butyl (2R,3S,4aR,7aR)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (800 mg, 2.00 mmol, 40.06% yield, 99% ee) as a white solid (1H NMR (400 MHz, $CDCl_3$) δ ppm 1.16 (s, 9 H), 1.51 - 1.58 (m, 2 H), 1.67 - 1.90 (m, 6 H), 1.97 - 2.19 (m, 5 H), 2.72 - 2.82 (m, 1 H), 3.29 (td, $J=6.65$, 2.76 Hz, 1 H), 3.41 - 3.55 (m, 3 H), 3.90 (d, $J=5.77$ Hz, 1 H), 3.95 - 4.04 (m, 2 H), 6.55 (d, $J=8.53$ Hz, 2 H), 7.15 (d, $J=8.28$ Hz, 2 H). LC-MS: (ES) m/z 401.3 ($M+H^+$)).

[0303] Step d) To a mixture of tert-butyl (2S,3R,4aS,7aS)-2-[4-(tetrahydropyran-4-ylamino)-phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (50.00 mg, 124.83 μ mol) and DIEA (32.27 mg, 249.65 μ mol, 43.48 μ L) in DCM (3 mL) was added 2-fluoro-6-methyl-benzoyl chloride (20.47 mg, 118.59 μ mol) at 0°C under N_2 . The mixture was stirred at 0°C for 10 min. The reaction mixture was concentrated to get a residue. The residue was purified by prep-TLC (SiO_2 , DCM:methanol=20:1). Tert-butyl (2S,3R,4aS,7aS)-1-(2-fluoro-6-methyl-benzoyl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (65 mg, 121.12 μ mol, 97.03% yield) was obtained as a colorless oil. LC-MS: (ES) m/z 537.3 ($M+H^+$).

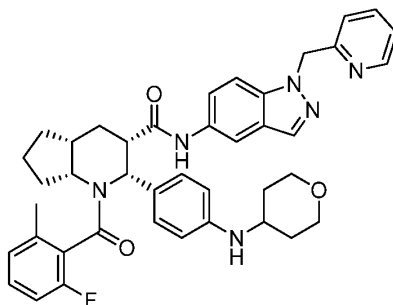
[0304] Step e) To a mixture of tert-butyl (2S,3R,4aS,7aS)-1-(2-fluoro-6-methyl-benzoyl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (65.00 mg, 121.12 μ mol) in DCM (5 mL) was added TFA (3.20 g, 28.10 mmol, 2.08 mL) at 25°C under N_2 . The mixture was stirred at 25 °C for 2.5 h. the mixture was concentrated to get a residue, then 4M HCl/dioxane (10 mL) was added, and stirred at 25°C for 10 min, then concentrated to get the desired product. Compound (2S,3R,4aS,7aS)-1-(2-fluoro-6-methyl-benzoyl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (60 mg, 116.05 μ mol, 95.82% yield, HCl) was obtained as a light yellow oil. LC-MS: (ES) m/z 481.2 ($M+H^+$).

[0305] Step f) To a mixture of (2S,3R,4aS,7aS)-1-(2-fluoro-6-methyl-benzoyl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (60 mg, 116.05 μ mol, HCl) in DCM (3 mL) was added DIEA (44.99 mg, 348.14 μ mol, 60.64 μ L) and HATU (52.95 mg, 139.26 μ mol) at 20°C under N_2 . The mixture was stirred at 20 °C for 10 min, then 1-methylindazol-5-amine (25.62 mg, 174.07 μ mol) was

added and the mixture was stirred at 20°C for 10 hr. The mixture was concentrated to get a residue. The residue was purified by Prep-HPLC: column: Phenomenex Gemini-NX 150 * 30 mm * 5 µm; mobile phase: [water (0.05% HCl)-ACN]; B%: 18%-58%, 10 min.

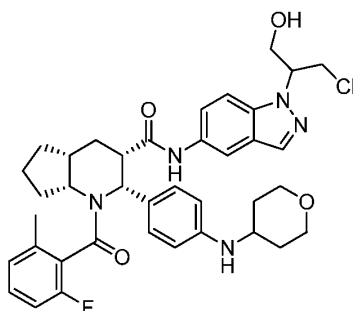
(2S,3R,4aS,7aS)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methylindazol-5-yl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxamide (20 mg, 31.82 µmol, 27.42% yield, 97% purity) was obtained as a light yellow solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.32 - 1.50 (m, 2 H), 1.58 - 1.65 (m, 1 H), 1.67 - 1.95 (m, 6 H), 2.03 - 2.17 (m, 2 H), 2.17 - 2.31 (m, 2 H), 2.34 - 2.51 (m, 2 H), 3.22 - 3.32 (m, 2 H), 3.35 - 3.45 (m, 2 H), 3.70 - 3.87 (m, 2 H), 4.00 (br d, *J*=11.88 Hz, 2 H), 4.03 - 4.09 (m, 3 H), 6.56 - 6.77 (m, 1 H), 7.03 - 7.14 (m, 1 H), 7.17 - 7.28 (m, 1 H), 7.35 - 7.55 (m, 5 H), 7.83 - 8.02 (m, 4 H). LC-MS: (ES) *m/z* 610.3 (M+H⁺).

Example S109: Synthesis of (2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-[1-(2-pyridylmethyl)indazol-5-yl]-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxamide (Compound No. 92)



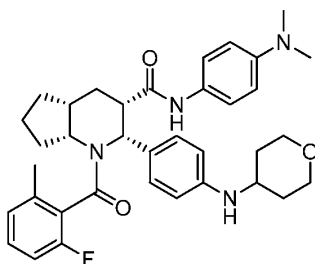
[0306] The title compound was synthesized in similar fashion as Example S108. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.26 - 1.36 (m, 2 H) 1.45 - 1.65 (m, 2 H) 1.66 - 1.90 (m, 6 H) 2.00 - 2.17 (m, 2 H) 2.18 - 2.33 (m, 2 H) 2.43 (s, 2H) 3.25 (br dd, *J*=10.49, 5.13 Hz, 1 H) 3.37 - 3.53 (m, 2 H) 3.75 - 3.84 (m, 1 H) 3.99 (br d, *J*=9.30 Hz, 2 H) 5.93 - 6.08 (m, 2 H) 6.56 - 6.77 (m, 1 H) 7.03 - 7.12 (m, 1 H) 7.14 - 7.22 (m, 1 H) 7.36 - 7.72 (m, 6 H) 7.89 - 8.01 (m, 3 H) 8.02 - 8.20 (m, 2 H) 8.36 - 8.46 (m, 1 H) 8.82 (br d, *J*=5.96 Hz, 1 H) LC-MS: (ES) *m/z* 687.3 (M+H⁺).

Example S110: Synthesis of (2R,3S,4aR,7aR)-N-[1-[1-(chloromethyl)-2-hydroxyethyl]indazol-5-yl]-1-(2-fluoro-6-methylbenzoyl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxamide (Compound No. 93)



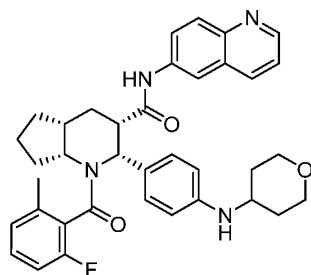
[0307] The title compound was synthesized in similar fashion as Example S108. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.31 (br s, 4 H) 1.70 (br d, *J*=11.44 Hz, 2 H) 1.75 - 1.85 (m, 3 H) 1.96 (s, 1 H) 2.04 - 2.15 (m, 2 H) 2.20 (s, 1 H) 2.26 (br d, *J*=9.06 Hz, 1 H) 2.43 (s, 2 H) 3.15 (s, 2 H) 3.69 - 3.88 (m, 2 H) 3.97 - 4.12 (m, 7 H) 6.54 - 6.71 (m, 1 H) 7.03 - 7.23 (m, 3 H) 7.36 - 7.45 (m, 4 H) 7.53 - 7.60 (m, 1 H) 7.92 - 7.96 (m, 2 H) 8.00 - 8.05 (m, 1 H) LC-MS: (ES) *m/z* 688.3 (M+H⁺).

Example S111: Synthesis of (2*R*,3*S*,4*aR*,7*aR*)-*N*-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 94)



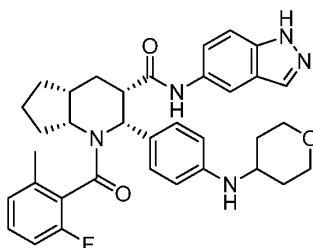
[0308] The title compound was synthesized in similar fashion as Example S108. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.22 - 1.34 (m, 2 H), 1.54 (br d, *J*=12.96 Hz, 1 H), 1.68 - 1.91 (m, 6 H), 2.01 - 2.15 (m, 2 H), 2.18 - 2.31 (m, 2 H), 2.41 (s, 2 H), 3.31 (dt, *J*=3.27, 1.60 Hz, 8 H), 3.37 - 3.46 (m, 2 H), 3.73 - 4.05 (m, 4 H), 6.53 - 6.70 (m, 1 H), 7.01 - 7.20 (m, 2 H), 7.37 - 7.48 (m, 3 H), 7.52 - 7.65 (m, 2 H), 7.69 - 7.82 (m, 2 H), 7.84 - 7.94 (m, 2 H). LC-MS: (ES) *m/z* 599.3 (M+H⁺).

Example S112: Synthesis of (2*R*,3*S*,4*aR*,7*aR*)-1-(2-fluoro-6-methylbenzoyl)-*N*-(quinolin-6-yl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 95)



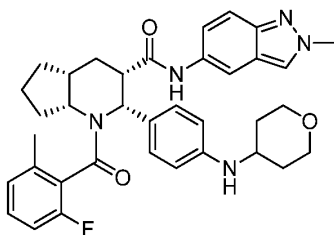
[0309] The title compound was synthesized in similar fashion as Example S108. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.33 (br s, 3 H), 1.62 - 1.86 (m, 6 H), 2.08 - 2.31 (m, 4 H), 2.45 (s, 2 H), 3.21 - 3.27 (m, 1 H), 3.36 - 3.55 (m, 2 H), 3.74 - 4.14 (m, 4 H), 6.59 - 6.87 (m, 1 H), 7.03 - 7.25 (m, 2 H), 7.34 - 7.59 (m, 3 H), 7.84 - 8.12 (m, 3 H), 8.18 - 8.36 (m, 2 H), 8.65 - 8.89 (m, 1 H), 8.96 - 9.21 (m, 2 H). LC-MS: (ES) *m/z* 607.3 (M+H⁺).

Example S113: (2*R*,3*S*,4*aR*,7*aR*)-1-(2-fluoro-6-methylbenzoyl)-*N*-(1*H*-indazol-5-yl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 96)



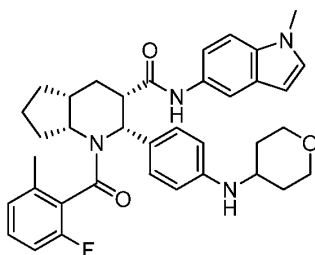
[0310] The title compound was synthesized in similar fashion as Example S108. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.25 - 1.37 (m, 2 H), 1.56 (br d, *J*=13.63 Hz, 1 H), 1.66 - 1.87 (m, 6 H), 2.05 - 2.16 (m, 2 H), 2.17 - 2.30 (m, 2 H), 2.42 (s, 2 H), 3.24 (br d, *J*=5.00 Hz, 2 H), 3.37 (br t, *J*=11.44 Hz, 2 H), 3.74 - 4.04 (m, 4 H), 6.55 - 6.72 (m, 1 H), 7.04 - 7.23 (m, 2 H), 7.36 - 7.58 (m, 5 H), 7.88 - 7.98 (m, 2 H), 8.02 - 8.13 (m, 1 H), 8.22 - 8.30 (m, 1 H). LC-MS: (ES) *m/z* 596.3 (M+H⁺).

Example S114: (2*R*,3*S*,4*aR*,7*aR*)-1-(2-fluoro-6-methylbenzoyl)-*N*-(2-methyl-2*H*-indazol-5-yl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 97)



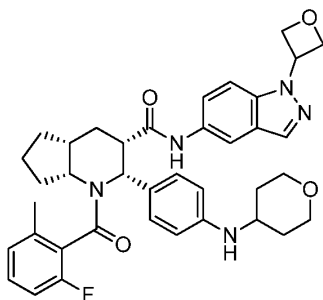
[0311] The title compound was synthesized in similar fashion as Example S108. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.28 (br d, *J*=7.50 Hz, 2 H), 1.43 - 1.64 (m, 2 H), 1.66 - 1.91 (m, 6 H), 2.04 - 2.16 (m, 2 H), 2.18 - 2.31 (m, 2 H), 2.42 (s, 2 H), 3.18 - 3.28 (m, 1 H), 3.34 - 3.41 (m, 2 H), 3.72 - 4.04 (m, 4 H), 4.21 - 4.30 (m, 3 H), 6.55 - 6.71 (m, 1 H), 7.03 - 7.20 (m, 2 H), 7.35 - 7.49 (m, 4 H), 7.52 - 7.61 (m, 1 H), 7.87 - 7.96 (m, 2 H), 7.97 - 8.13 (m, 1 H), 8.30 - 8.40 (m, 1 H). LC-MS: (ES) *m/z* 610.3 (M+H⁺).

Example S115: (2*R*,3*S*,4*aR*,7*aR*)-1-(2-fluoro-6-methylbenzoyl)-*N*-(1-methyl-1*H*-indol-5-yl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 98)



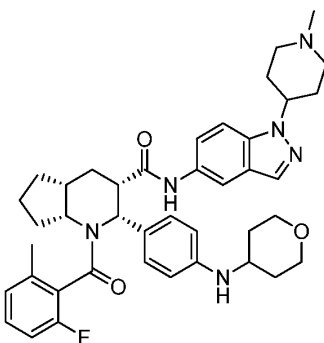
[0312] The title compound was synthesized in similar fashion as Example S108. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.31 (br d, *J*=13.01 Hz, 2 H), 1.56 - 1.88 (m, 8 H), 2.04 - 2.14 (m, 2 H), 2.15 - 2.26 (m, 2 H), 2.39 - 2.44 (m, 2 H), 3.16 - 3.26 (m, 1 H), 3.36 - 3.42 (m, 2 H), 3.67 - 3.84 (m, 5 H), 3.95 (br s, 2 H), 6.51 - 6.68 (m, 1 H), 7.03 - 7.19 (m, 4 H), 7.24 - 7.45 (m, 5 H), 7.53 - 7.78 (m, 1 H), 7.82 - 7.95 (m, 2 H). LC-MS: (ES) *m/z* 609.3 (M+H⁺).

Example S116: (2*R*,3*S*,4*aR*,7*aR*)-1-(2-fluoro-6-methylbenzoyl)-*N*-(1-(oxetan-3-yl)-1*H*-indazol-5-yl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 99)



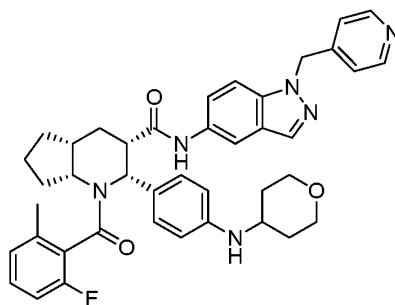
[0313] The title compound was synthesized in similar fashion as Example S108. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.28 (br d, *J*=4.05 Hz, 2 H), 1.37 - 1.58 (m, 6 H), 1.70 (br s, 1 H), 1.95 (br d, *J*=11.44 Hz, 2 H), 2.12 - 2.31 (m, 3 H), 2.35 - 2.45 (m, 2 H), 3.09 (br s, 1 H), 3.40 - 3.57 (m, 3 H), 3.75 - 4.00 (m, 3 H), 4.59 (br s, 1 H), 5.10 - 5.21 (m, 4 H), 5.85 - 6.01 (m, 1 H), 6.55 - 6.66 (m, 3 H), 6.97 - 7.19 (m, 2 H), 7.35 - 7.53 (m, 4 H), 7.82 - 8.13 (m, 2 H). LC-MS: (ES) *m/z* 652.3 (M+H⁺).

Example S117: (2*R*,3*S*,4*aR*,7*aR*)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(1-methylpiperidin-4-yl)-1*H*-indazol-5-yl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydro-1*H*-cyclopenta[*b*]-pyridine-3-carboxamide (Compound No. 100)



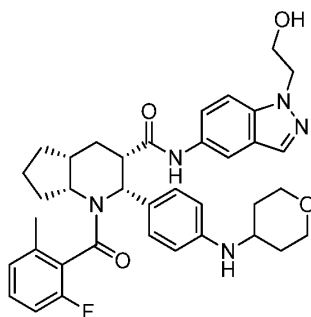
[0314] The title compound was synthesized in similar fashion as Example S108. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.23 - 1.41 (m, 3 H), 1.55 - 1.85 (m, 7 H), 2.04 - 2.15 (m, 2 H), 2.26 (br d, *J*=13.83 Hz, 3 H), 2.42 (s, 3 H), 2.46 - 2.56 (m, 2 H), 2.95 - 3.00 (m, 3 H), 3.23 (br dd, *J*=10.19, 5.66 Hz, 1 H), 3.32 - 3.42 (m, 4 H), 3.51 - 3.90 (m, 5 H), 3.95 (br s, 2 H), 6.56 - 6.77 (m, 1 H), 6.97 - 7.26 (m, 3 H), 7.27 - 7.39 (m, 1 H), 7.45 (d, *J*=8.58 Hz, 2 H), 7.58 - 7.66 (m, 1 H), 7.87 - 8.03 (m, 4 H). LC-MS: (ES) *m/z* 693.4 (M+H⁺).

Example S118: (2*R*,3*S*,4*aR*,7*aR*)-1-(2-fluoro-6-methylbenzoyl)-*N*-(1-(pyridin-4-ylmethyl)-1*H*-indazol-5-yl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydro-1*H*-cyclopenta[*b*]-pyridine-3-carboxamide (Compound No. 101)



[0315] The title compound was synthesized in similar fashion as Example S108. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.21 - 1.39 (m, 3 H), 1.48 - 1.90 (m, 8 H), 2.00 - 2.13 (m, 2 H), 2.14 - 2.27 (m, 2 H), 2.27 - 2.63 (m, 3 H), 3.23 (dt, *J*=10.73, 5.36 Hz, 1 H), 3.33 - 3.43 (m, 2 H), 3.68 - 4.02 (m, 4 H), 5.95 - 6.07 (m, 2 H), 6.57 - 6.79 (m, 1 H), 7.02 - 7.19 (m, 2 H), 7.36 - 7.54 (m, 4 H), 7.69 - 7.76 (m, 2 H), 7.88 - 8.01 (m, 2 H), 8.08 (br s, 1 H), 8.11 - 8.18 (m, 1 H), 8.75 - 8.79 (m, 2 H). LC-MS: (ES) *m/z* 687.3 (M+H⁺).

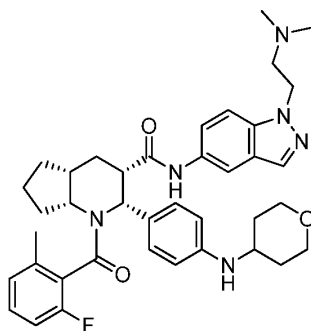
Example S119: (2*R*,3*S*,4*aR*,7*aR*)-1-(2-fluoro-6-methylbenzoyl)-*N*-(1-(2-hydroxyethyl)-1*H*-indazol-5-yl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydro-1*H*-cyclopenta[*b*]-pyridine-3-carboxamide (Compound No. 102)



[0316] The title compound was synthesized in similar fashion as Example S108. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.26 - 1.48 (m, 2 H), 1.53 - 1.62 (m, 1 H), 1.69 - 1.94 (m, 6 H), 2.03 - 2.15 (m, 2 H), 2.18 - 2.33 (m, 2 H), 2.44 (s, 2 H), 3.24 (br d, *J*=9.66 Hz, 2 H),

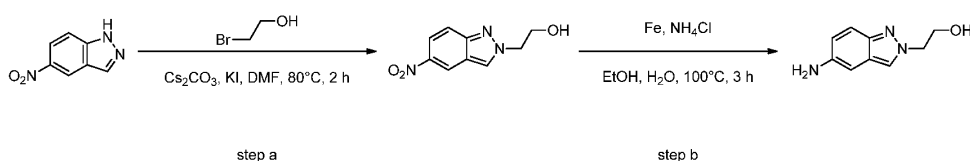
3.36 - 3.50 (m, 2 H), 3.76 - 4.08 (m, 6 H), 4.40 - 4.56 (m, 2 H), 6.53 - 6.76 (m, 1 H), 7.05 - 7.25 (m, 2 H), 7.36 - 7.65 (m, 5 H), 7.87 - 8.08 (m, 4 H) LC-MS: (ES) m/z 640.3 ($M+H^+$).

Example S120: (2*R*,3*S*,4*aR*,7*aR*)-*N*-(1-(2-(dimethylamino)ethyl)-1*H*-indazol-5-yl)-1-(2-fluoro-6- methylbenzoyl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 103)



[0317] The title compound was synthesized in similar fashion as Example S108. ^1H NMR (400 MHz, METHANOL-*d*4) δ ppm 1.35 (br s, 2 H), 1.55 (br s, 1 H), 1.66 - 1.97 (m, 6 H), 2.13 (br d, $J=9.66$ Hz, 2 H), 2.20 - 2.35 (m, 2 H), 2.40 - 2.52 (m, 2 H), 3.01 (s, 6 H), 3.25 (br s, 2 H), 3.36 - 3.50 (m, 2 H), 3.66 - 4.18 (m, 6 H), 4.64 - 4.81 (m, 2 H), 6.44 - 6.81 (m, 1 H), 7.04 - 7.27 (m, 2 H), 7.35 - 7.77 (m, 5 H), 7.83 - 8.19 (m, 4 H) LC-MS: (ES) m/z 667.4 ($M+H^+$).

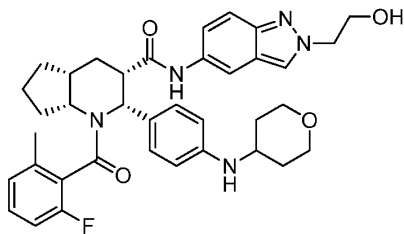
Example S121: ((2*R*,3*S*,4*aR*,7*aR*)-1-(2-fluoro-6- methylbenzoyl)-*N*-(2-(2-hydroxyethyl)-2*H*-indazol-5-yl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 104)



[0318] **Step a)** To a solution of 5-nitro-1*H*-indazole (1.4 g, 8.58 mmol) and 2-bromoethanol (1.39 g, 11.16 mmol, 792.14 μL) in DMF (15 mL) was added Cs_2CO_3 (5.59 g, 17.16 mmol) and KI (142.46 mg, 858.19 μmol) at 20°C under N_2 . The mixture was stirred at 80°C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=100/1 to 0/1). The compound 2-(5-nitroindazol-2-yl)ethanol (520 mg, 2.51 mmol,

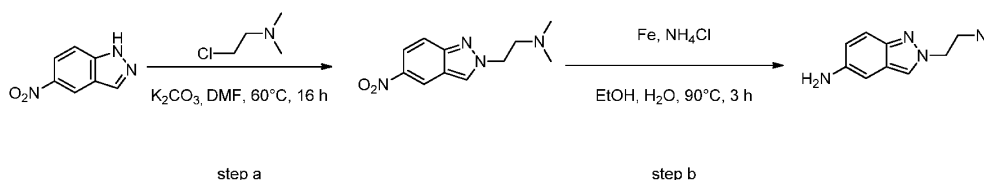
29.25% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 2.88 (br s, 1 H), 4.19 (br s, 2 H), 4.57 - 4.73 (m, 2 H), 7.76 (d, $J=9.38$ Hz, 1 H), 8.13 (dd, $J=9.51$, 2.13 Hz, 1 H), 8.31 (s, 1 H), 8.75 (d, $J=2.13$ Hz, 1 H) LC-MS: (ES) m/z 208.1 ($\text{M}+\text{H}^+$).

[0319] Step b) To a solution of 2-(5-nitroindazol-2-yl)ethanol (470 mg, 2.27 mmol) in EtOH (10 mL) and H_2O (2 mL) was added Fe (1.01 g, 18.15 mmol) and NH_4Cl (60.67 mg, 1.13 mmol). The mixture was stirred at 100°C for 3 hr. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , DCM:methanol =100/1 to 10/1). The Compound 2-(5-aminoindazol-2-yl)ethanol (310 mg, 1.75 mmol, 77.12% yield, 100% purity) was obtained as a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 3.44 - 3.69 (m, 2 H), 4.06 - 4.13 (m, 2 H), 4.44 - 4.50 (m, 2 H), 6.78 (d, $J=1.51$ Hz, 1 H), 6.85 (dd, $J=9.03$, 2.01 Hz, 1 H), 7.54 (d, $J=9.03$ Hz, 1 H), 7.70 (s, 1 H) LC-MS: (ES) m/z 178.1 ($\text{M}+\text{H}^+$).



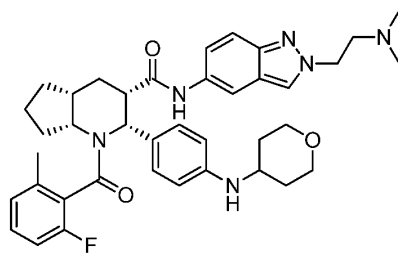
[0320] The title compound was synthesized in similar fashion as Example S108. ^1H NMR (400 MHz, $\text{METHANOL}-d_4$) δ ppm 1.24 - 1.33 (m, 2 H), 1.56 (br d, $J=15.77$ Hz, 1 H), 1.68 - 1.93 (m, 6 H), 2.02 - 2.16 (m, 2 H), 2.17 - 2.29 (m, 2 H), 2.42 (s, 2 H), 3.18 - 3.30 (m, 2 H), 3.34 - 3.43 (m, 2 H), 3.75 - 4.10 (m, 6 H), 4.54 - 4.70 (m, 2 H), 6.56 - 6.74 (m, 1 H), 7.03 - 7.20 (m, 2 H), 7.36 - 7.67 (m, 5 H), 7.88 - 8.01 (m, 2 H), 8.10 - 8.24 (m, 1 H), 8.57 (br s, 1 H). LC-MS: (ES) m/z 640.3 ($\text{M}+\text{H}^+$).

Example S122: (2R,3S,4aR,7aR)-N-(2-(2-(dimethylamino)ethyl)-2H-indazol-5-yl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 105)



[0321] **Step a)** To a solution of 5-nitro-1H-indazole (1.65 g, 10.10 mmol) in DMF (20 mL) was added K_2CO_3 (4.33 g, 31.32 mmol), after 30 min, the 2-chloro-N,N-dimethylethanamine (2.33 g, 16.16 mmol, HCl) was added. The mixture was stirred at 60°C for 16 h showed the desired product was detected. The reaction mixture was diluted with H_2O 20 mL and extracted with EA 100 mL (50 mL * 2). The combined organic layers were washed with brine 20 mL, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC. (column: Welch Xtimate C18 150 * 40 mm * 10 μm ; mobile phase: [water (10 mM NH_4HCO_3)-CAN]; B%: 39%-47%, 7.2 min). The compound N,N-dimethyl-2-(5-nitroindazol-2-yl)ethanamine (0.42 g, 1.79 mmol, 17.72% yield, 100% purity) was obtained as a yellow solid. 1H NMR (400 MHz, METHANOL- d_4) δ ppm 2.27 - 2.34 (m, 6 H), 2.98 (t, $J=6.40$ Hz, 2 H), 4.64 (t, $J=6.53$ Hz, 2 H), 7.73 (d, $J=9.29$ Hz, 1 H), 8.10 (dd, $J=9.54$, 2.26 Hz, 1 H), 8.66 (s, 1 H), 8.81 (d, $J=1.76$ Hz, 1 H). LC-MS: (ES) m/z 235.1 ($M+H^+$).

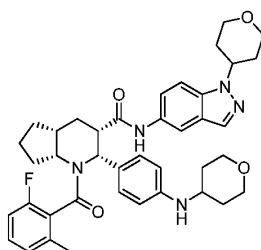
[0322] **Step b)** To a solution of N,N-dimethyl-2-(5-nitroindazol-2-yl)ethanamine (0.4 g, 1.71 mmol), Fe (534 mg, 9.56 mmol) and NH_4Cl (32 mg, 598.23 μmol) in EtOH (10 mL) and H_2O (2.5 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 90°C for 3 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove EtOH and H_2O . The residue was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% ethylacetate/petroleum ether gradient @ 35 mL/min). The compound 2-[2-(dimethylamino)ethyl]indazol-5-amine (310 mg, 1.50 mmol, 99% purity) were obtained as a brown gum. 1H NMR (400 MHz, $CDCl_3$) δ ppm 2.30 (s, 6 H), 2.89 (t, $J=6.75$ Hz, 2 H), 4.45 (t, $J=6.82$ Hz, 2 H), 6.77 (d, $J=2.00$ Hz, 1 H), 6.82 (dd, $J=9.01$, 2.13 Hz, 1 H), 7.55 (d, $J=9.13$ Hz, 1 H), 7.74 (s, 1 H). LC-MS: (ES) m/z 205.1 ($M+H^+$).



[0323] The title compound was synthesized in similar fashion as Example S108. 1H NMR (400 MHz, METHANOL- d_4) δ ppm 1.26 - 1.36 (m, 2 H), 1.53 - 1.59 (m, 1 H), 1.70 - 1.90

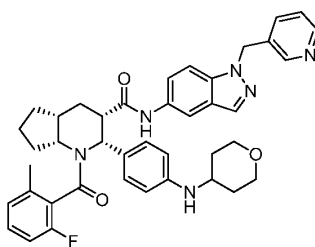
(m, 6 H), 2.04 - 2.14 (m, 2 H), 2.18 - 2.32 (m, 2 H), 2.42 (s, 2 H), 2.98 - 3.05 (m, 6 H), 3.14 - 3.29 (m, 2 H), 3.33 - 3.42 (m, 2 H), 3.76 - 4.04 (m, 6 H), 4.74 (br s, 2 H), 6.56 - 6.71 (m, 1 H), 6.99 - 7.18 (m, 2 H), 7.23 - 7.58 (m, 5 H), 7.89 - 8.04 (m, 3 H), 8.24 - 8.36 (m, 1 H). LC-MS: (ES) m/z 667.4 ($M+H^+$).

Example S123: (2*R*,3*S*,4*aR*,7*aR*)-1-(2-fluoro-6-methyl-benzoyl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-*N*-(1-tetrahydropyran-4-ylindazol-5-yl)-2,3,4,4*a*,5,6,7,7*a*-octahydro-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 106)



[0324] The title compound was synthesized in similar fashion as Example S108. ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 1.26 - 1.42 (m, 3 H) 1.47 - 1.56 (m, 1 H) 1.70 (br d, $J=8.94$ Hz, 2 H) 1.75 - 1.85 (m, 3 H) 1.94 (br d, $J=12.99$ Hz, 2 H) 2.08 - 2.16 (m, 2 H) 2.20 (s, 1 H) 2.25 - 2.33 (m, 3 H) 2.40 - 2.50 (m, 2 H) 3.14 - 3.28 (m, 2 H) 3.38 (br s, 2 H) 3.69 (br t, $J=12.10$ Hz, 3 H) 3.79 - 3.89 (m, 1 H) 3.96 - 4.15 (m, 5 H) 6.56 - 6.70 (m, 1 H) 7.01 - 7.23 (m, 3 H) 7.36 - 7.45 (m, 4 H) 7.58 - 7.64 (m, 1 H) 7.88 - 7.98 (m, 4 H) LC-MS: (ES) m/z 680.3 ($M+H^+$).

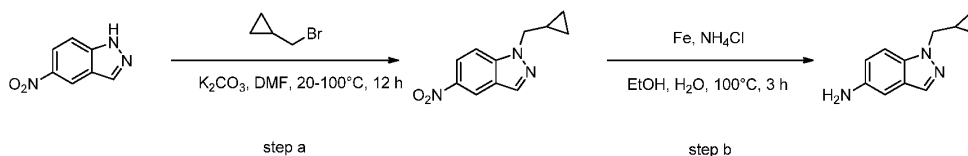
Example S124: Synthesis of (2*R*,3*S*,4*aR*,7*aR*)-1-(2-fluoro-6-methyl-benzoyl)-*N*-[1-(3-pyridylmethyl)indazol-5-yl]-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4*a*,5,6,7,7*a*-octahydrocyclopenta[*b*]pyridine-3-carboxamide (Compound No. 107)



[0325] The title compound was synthesized in similar fashion as Example S108. ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 1.24 - 1.37 (m, 3 H) 1.57 (br d, $J=17.64$ Hz, 1 H) 1.65 - 1.80 (m, 4 H) 1.82 - 1.89 (m, 2 H) 2.06 - 2.17 (m, 2 H) 2.18 - 2.29 (m, 2 H) 2.39 - 2.47 (m, 2

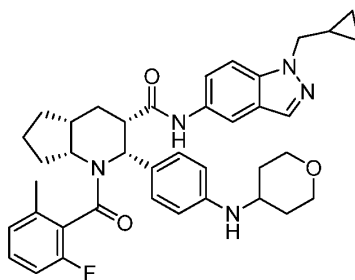
H) 3.20 - 3.27 (m, 1 H) 3.35 - 3.46 (m, 2 H) 3.69 - 3.90 (m, 2 H) 3.97 (br s, 2 H) 5.91 (br d, $J=3.46$ Hz, 2 H) 6.57 - 6.72 (m, 1 H) 6.58 - 6.72 (m, 1 H) 7.01 - 7.11 (m, 1 H) 7.14 - 7.21 (m, 1 H) 7.37 - 7.52 (m, 4 H) 7.61 - 7.70 (m, 1 H) 7.91 - 7.98 (m, 2 H) 7.99 - 8.08 (m, 2 H) 8.08 - 8.14 (m, 1 H) 8.38 - 8.45 (m, 1 H) 8.75 - 8.83 (m, 2 H). LC-MS: (ES) m/z 687.3 ($M+H^+$).

Example S125: Synthesis of (2R,3S,4aR,7aR)-N-[1-(cyclopropylmethyl)indazol-5-yl]-1-(2-fluoro-6-methyl-benzoyl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-cyclopenta[b]pyridine-3-carboxamide (Compound No. 108)



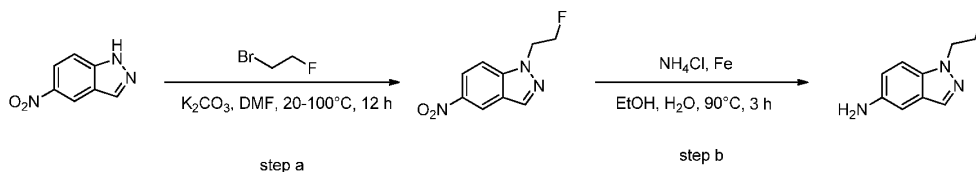
[0326] Step a) To a mixture of bromomethylcyclopropane (1.99 g, 14.71 mmol, 1.41 mL) and 5-nitro-1H-indazole (2.00 g, 12.26 mmol) in DMF (10 mL) was added K_2CO_3 (5.08 g, 36.78 mmol) at 20°C under N_2 . The mixture was stirred at 100°C for 12 h. The reaction mixture was partitioned between EtOAc 100 mL and H_2O 100 mL. The organic phase was separated, dried, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (column: YMC-Triart Prep C18 150 * 40 mm * 7 μm ; mobile phase: [water (0.04% NH_3H_2O + 10 mM NH_4HCO_3)-ACN]; B%: 40%-70%, 10 min) to give 1-(cyclopropylmethyl)-5-nitro-indazole (1.3 g, 5.98 mmol, 48.81% yield) as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ ppm 0.36 - 0.51 (m, 2 H) 0.54 - 0.69 (m, 2 H) 1.29 - 1.44 (m, 1 H) 4.32 (d, $J=7.03$ Hz, 2 H) 7.49 (d, $J=9.29$ Hz, 1H) 8.21 (s, 1 H) 8.27 (d, $J=9.29$ Hz, 1 H) 8.73 (s, 1 H) LCMS: (ES) m/z 218.3($M+H^+$).

[0327] Step b) A mixture of 1-(cyclopropylmethyl)-5-nitro-indazole (500 mg, 2.30 mmol, 1 eq), Fe (1.03 g, 18.41 mmol, 8 eq) and NH_4Cl (61.56 mg, 1.15 mmol, 0.5 eq) in EtOH (10 mL) and H_2O (2.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90°C for 3 h under N_2 atmosphere. Filtered, then concentrated to get the desired product. 1-(cyclopropyl-methyl)indazol-5-amine (400 mg, 2.14 mmol, 92.81% yield) was obtained as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ ppm 0.33 - 0.48 (m, 2 H) 0.50 - 0.64 (m, 2 H) 1.23 - 1.40 (m, 1 H) 3.09 (br s, 3 H) 4.22 (d, $J=6.78$ Hz, 2 H) 6.90 (br d, $J=8.53$ Hz, 1 H) 6.98 (s, 1 H) 7.26 - 7.31 (m, 1 H) 7.81 (s, 1 H) LCMS: (ES) m/z 188.3($M+H^+$).



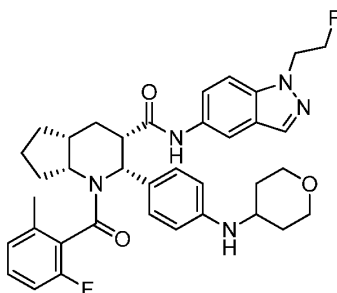
[0328] The title compound was synthesized in similar fashion as Example S108. ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 0.42 (br d, $J=5.02$ Hz, 2 H) 0.56 (br d, $J=8.28$ Hz, 2 H) 1.26 - 1.48 (m, 5 H) 1.51 - 1.89 (m, 8 H) 2.12 (br d, $J=8.28$ Hz, 2 H) 2.20 (s, 1 H) 2.28 (s, 1 H) 2.44 (s, 2 H) 3.13 - 3.30 (m, 1 H) 3.77 (br d, $J=7.03$ Hz, 2 H) 3.98 (br s, 3 H) 4.26 - 4.33 (m, 2 H) 6.54 - 6.72 (m, 1H) 7.00 - 7.32 (m, 3 H) 7.37 - 7.48 (m, 4 H) 7.52 - 7.58 (m, 1 H) 7.90 - 7.99 (m, 4 H) LCMS:(ES) m/z 687.3($M+H^+$).

Example S126: Synthesis of (2R,3S,4aR,7aR)-N-[1-(2-fluoroethyl)indazol-5-yl]-1-(2-fluoro-6-methyl-benzoyl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta-[b]pyridine-3-carboxamide (Compound No. 109)



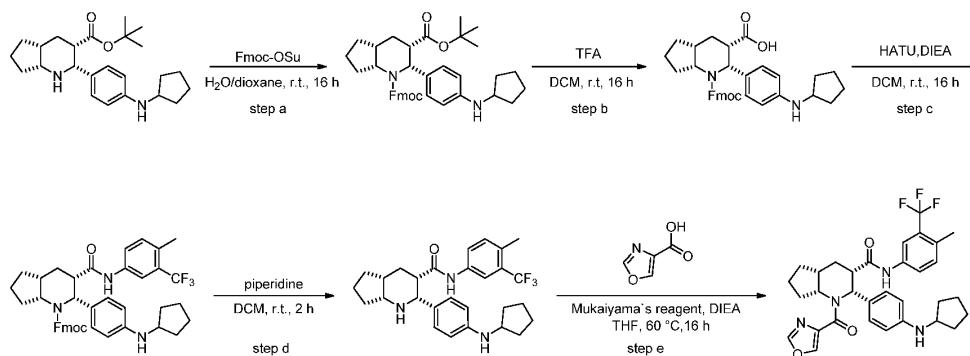
[0329] Step a) To a mixture of 1-bromo-2-fluoro-ethane (1.87 g, 14.71 mmol) and 5-nitro-1H-indazole (2.00 g, 12.26 mmol) in DMF (10 mL) was added K_2CO_3 (3.39 g, 24.52 mmol) at 20°C under N_2 . The mixture was stirred at 100°C for 12 h. The reaction mixture was partitioned between EtOAc 100 mL and H_2O 100 mL. The organic phase was separated, dried, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (column: Welch Xtimate C18 150 * 40 mm * 10 μm ; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 35%-55%, 8 min) to give 1-(2-fluoroethyl)-5-nitro-indazole (1.4 g, 6.69 mmol, 54.59% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 4.69 - 4.75 (m, 1 H) 4.78 (t, $J=4.64$ Hz, 1 H) 4.82 - 4.87 (m, 1 H) 4.96 (t, $J=4.64$ Hz, 1 H) 7.56 (d, $J=9.29$ Hz, 1 H) 8.28 (d, $J=0.75$ Hz, 1 H) 8.32 (dd, $J=9.16$, 2.13 Hz, 1 H) 8.76 (d, $J=1.51$ Hz, 1 H) LCMS: (ES) m/z 210.6($M+H^+$).

[0330] **Step b)** A mixture of 1-(2-fluoroethyl)-5-nitro-indazole (400 mg, 1.91 mmol), NH_4Cl (51.14 mg, 956.13 μmol) and Fe (854.32 mg, 15.30 mmol) in EtOH (10 mL) and H_2O (2.5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90°C for 3 h under N_2 atmosphere, filtered, then concentrated to get the desired product. 1-(2-fluoroethyl)indazol-5-amine (300 mg, 1.67 mmol, 87.55% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 4.58 (t, $J=4.89$ Hz, 1 H) 4.64 (t, $J=4.89$ Hz, 1 H) 4.77 (t, $J=5.02$ Hz, 1 H) 4.88 (t, $J=5.02$ Hz, 1 H) 6.86 - 6.96(m, 2 H) 7.29 (d, $J=8.78$ Hz, 1 H) 7.83 (s, 1 H) LCMS: (ES) m/z 180.1($\text{M}+\text{H}^+$).



[0331] The title compound was synthesized in similar fashion as Example S108. ^1H NMR (400 MHz, $\text{METHANOL}-d_4$) δ ppm 1.30 - 1.48 (m, 3 H) 1.52 - 1.65 (m, 2 H) 1.67 - 1.77 (m, 3 H) 1.78 - 1.88 (m, 3 H) 2.06 - 2.17 (m, 2 H) 2.20 (s, 1H) 2.24 - 2.37 (m, 1 H) 2.43 - 2.48 (m, 2 H) 3.22 - 3.28 (m, 1 H) 3.35 - 3.42 (m, 2 H) 3.72 - 4.01 (m, 4 H) 4.62 - 4.79 (m, 4 H) 6.56 - 6.70 (m, 1 H) 7.01 - 7.11 (m, 1 H) 7.14 - 7.21 (m, 1 H) 7.37 - 7.46 (m, 4 H) 7.51 - 7.58 (m, 1 H) 7.92 - 8.02 (m, 4 H) LCMS: (ES) m/z 643.3($\text{M}+\text{H}^+$).

Example S127: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)-phenyl)-1-(oxazole-4-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 110)



[0332] Step a) A solution of NaHCO_3 (290.54 mg, 3.46 mmol, 134.51 μL) in H_2O (20 mL) was added to a solution of *cis*-*tert*-butyl 2-[4-(cyclopentylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (700 mg, 1.73 mmol) in dioxane (20 mL) and Fmoc-OSu (583.34 mg, 1.73 mmol) was added. The mixture was stirred at 15 °C for 16 h. The reaction mixture was extracted with EtOAc (30 mL x 2). The combined organic phase were washed with brine, dried with anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under vacuum to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=100/0 to 3/1) to give compound *cis*-3-*tert*-butyl 1-(9H-fluoren-9-ylmethyl) 2-[4-(cyclopentylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-1,3-dicarboxylate (1 g, 1.65 mmol, 95.30% yield, 100% purity) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 0.94 (1 H, br s) 1.23 (8 H, s) 1.40 (5 H, dt, $J=12.11, 5.87$ Hz) 1.47 - 1.80 (8 H, m) 1.87 (3 H, br s) 2.68 (1 H, br s) 3.55- 3.84 (2 H, m) 4.25 - 4.37 (1 H, m) 4.43 - 4.68 (2 H, m) 5.48 (2 H, d, $J=6.53$ Hz) 6.36 (2 H, br d, $J=7.78$ Hz) 6.77 (2 H, br d, $J=7.53$ Hz) 7.23 - 7.47 (4 H, m) 7.64 (2 H, br d, $J=7.03$ Hz) 7.83 - 7.93 (2 H, m). LC-MS: (ES) m/z 607.4 ($\text{M}+\text{H}^+$).

[0333] Step b) The *cis*-3-*tert*-butyl 1-(9H-fluoren-9-ylmethyl) 2-[4-(cyclopentylamino)phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-1,3-dicarboxylate (1 g, 1.65 mmol) was dissolved in DCM (20 mL). Then CF_3COOH (1.88 g, 16.48 mmol, 1.22 mL) was added. And the mixture was stirred at 15 °C for 2 h. The mixture was evaporated under vacuum to give crude product. The crude product was added H_2O (20 mL), extracted with EtOAc (30 mL x 2). The combined organic phase was washed with brine, dried with anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under vacuum to give compound *cis*-2-[4-(cyclopentylamino)phenyl]-1-(9H-fluoren-9-ylmethoxycarbonyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (900 mg, 1.63 mmol, 99.17% yield) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 0.78 (1 H, br s), 1.31 - 1.67 (6 H, m), 1.68 - 2.12 (10 H, m), 2.80 (1 H, br s), 3.62 - 4.05 (2 H, m), 4.23 (1 H, br s), 4.47 - 4.80 (2 H, m), 5.37 - 5.96 (1 H, m), 6.99 - 7.20 (4 H, m), 7.25 - 7.41 (4 H, m), 7.53 (2 H, br d, $J=7.34$ Hz), 7.72 (2 H, br d, $J=7.34$ Hz), 9.43 (1 H, br s). LC-MS: (ES) m/z 551.3 ($\text{M}+\text{H}^+$).

[0334] Step c) The *cis*-2-[4-(cyclopentylamino)phenyl]-1-(9H-fluoren-9-ylmethoxycarbonyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (0.9 g, 1.63 mmol) and 4-methyl-3-(trifluoromethyl)aniline (343.50 mg, 1.96 mmol, 281.56 μL) were dissolved in DCM (20 mL). Then DIEA (528.05 mg, 4.09 mmol, 711.66 μL , 2.5 *eq*) and

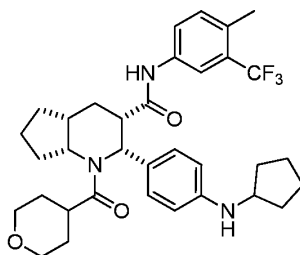
HATU (745.70 mg, 1.96 mmol, 1.2 *eq*) were added. The mixture was stirred at 20 °C for 16 h. The reaction mixture was added to H₂O (20 mL) and was extracted with DCM (20 mL x 2). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na₂SO₄ and filtered. The filtrate was evaporated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=100/0 to 2/1) to give compound cis-9H-fluoren-9-ylmethyl 2-[4-(cyclopentyl-amino)phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2,3,4,4a,5,6,7,7a-octahydro-cyclopenta[b]pyridine-1-carboxylate (1 g, 1.41 mmol, 86.44% yield, 100% purity) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.34 - 1.51 (5 H, m), 1.53 - 1.75 (8 H, m), 1.79 - 2.02 (5 H, m), 2.41 (3 H, br s), 2.77 (1 H, br s), 3.51 - 3.77 (2 H, m), 4.25 (2 H, br s), 4.50 - 4.70 (2 H, m), 5.42 - 5.88 (1 H, m), 6.40 (2 H, d, *J*=8.53 Hz), 6.88 - 7.10 (2 H, m), 7.17 (1 H, br d, *J*=8.03 Hz), 7.28 - 7.60 (8 H, m), 7.73 (2 H, br d, *J*=6.02 Hz). LC-MS: (ES) *m/z* 708.3 (M+H⁺).

[0335] Step d) The cis-9H-fluoren-9-ylmethyl 2-[4-(cyclopentylamino)phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-1-carboxylate (1 g, 1.41 mmol) was dissolved in DCM (10 mL). Then piperidine (862.20 mg, 10.13 mmol, 1 mL) was added. The mixture was stirred at 20 °C for 2 h. Then another portion of piperidine (862.20 mg, 10.13 mmol, 1 mL) was added and the mixture was stirred at 20 °C for another 1 h. The reaction mixture was diluted with H₂O 10 mL and extracted with DCM (10 mL x 2). The combined organic layers were washed with brine 10 mL, dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, DCM:methanol=100/0 to 100/1) to give cis-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (550 mg, 1.09 mmol, 76.97% yield, 96% purity) as a pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 1.32 - 1.45 (2 H, m), 1.59 - 1.94 (1 H, m), 1.94 (1 H, dt, *J*=12.65, 6.27 Hz), 2.04 - 2.16 (1 H, m), 2.17 - 2.34 (2 H, m), 2.38 (3 H, d, *J*=1.22 Hz), 2.76 - 2.83 (1 H, m), 3.40 (1 H, br t, *J*=4.03 Hz), 3.58 (1 H, br s), 3.64 - 3.74 (1 H, m), 3.89 (1 H, d, *J*=2.69 Hz), 6.49 (2 H, d, *J*=8.56 Hz), 7.06 (2 H, d, *J*=8.56 Hz), 7.10 - 7.17 (1 H, m), 7.55 (1 H, dd, *J*=8.31, 1.71 Hz), 7.64 (1 H, d, *J*=1.96 Hz), 11.17 (1 H, s). LC-MS: (ES) *m/z* 486.3 (M+H⁺).

[0336] Step e) The cis-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (30 mg, 61.78 μmol) and oxazole-4-carboxylic acid (6.99 mg, 61.78 μmol) were dissolved in THF (1 mL). Then 2-chloro-1-methyl-pyridin-1-ium iodide (23.68 mg, 92.67 μmol) and DIEA (23.95 mg,

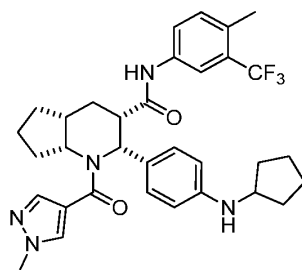
185.34 μ mol, 32.28 μ L) were added. The mixture was stirred at 60 °C for 16 h. The solvent was evaporated under vacuum to give crude product. The crude product was purified by prep-HPLC(column: Venusil ASB Phenyl 150 x 30 mm x 5 μ m; mobile phase: [water (0.05% HCl) -ACN]; B%: 50%-80%, 9 min) to give compound *cis*-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-1-(oxazole-4-carbonyl)-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxamide (13 mg, 18.81 μ mol, 30.44% yield, 84% purity) as a white solid. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.29 - 1.45 (1 H, m), 1.49 - 1.75 (9 H, m), 1.77 - 2.15 (1 H, m), 1.77 - 2.15 (8 H, m), 2.30 (1 H, br s), 2.43 (4 H, d, $J=1.25$ Hz), 3.09 - 3.25 (1 H, m), 3.92 (1 H, br t, $J=6.90$ Hz), 4.76 - 4.88 (1 H, m), 6.55 (1 H, br s), 7.22 - 7.33 (3 H, m), 7.56 (1 H, br d, $J=8.28$ Hz), 7.66 (2 H, brs), 7.86 (1 H, d, $J=2.26$ Hz), 8.29 (1 H, s), 8.40 (1 H, br s), 10.12 (1 H, br s). LC-MS: (ES) m/z 581.3 ($\text{M}+\text{H}^+$).

Example S128: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(tetrahydro-2H-pyran-4-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 111)



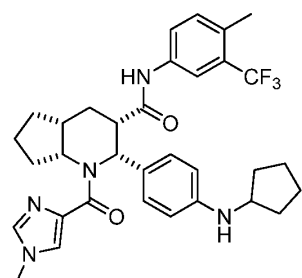
[0337] The title compound was synthesized in similar fashion as Example S127. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.67 (br s, 5 H), 1.81 (br d, $J=12.55$ Hz, 6 H), 1.93 - 2.11 (m, 5 H), 2.25 - 2.61 (m, 7 H), 3.00 - 3.27 (m, 2 H), 3.46 - 3.62 (m, 2 H), 3.90 (br d, $J=7.78$ Hz, 1 H), 3.98 (br s, 2 H), 4.17 - 4.49 (m, 1 H), 4.51 - 4.80 (m, 1 H), 6.25 (br d, $J=5.77$ Hz, 1 H), 7.23 - 7.29 (m, 1 H), 7.30 - 7.45 (m, 3 H), 7.46 - 7.58 (m, 2 H), 7.59 - 7.76 (m, 2 H), 7.79 - 7.91 (m, 1 H), 10.01 - 10.32 (m, 1 H). LC-MS: (ES) m/z 598.4 ($\text{M}+\text{H}^+$).

Example S129: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(1-methyl-1H-pyrazole-4-carbonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 112)



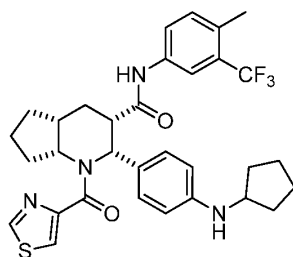
[0338] The title compound was synthesized in similar fashion as Example S127. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 0.78 (2 H, br s), 1.28 - 1.33 (2 H, m), 1.42 - 1.52 (5 H, m), 1.67 - 1.78 (5 H, m), 2.12 - 2.25 (2 H, m), 2.31 (3 H, d, *J*=1.22 Hz), 2.90 - 3.00 (1 H, m), 3.60 (1 H, quin, *J*=6.24 Hz), 3.72 (3 H, s), 4.22 - 4.32 (1 H, m), 4.50 (1 H, br s), 5.17 - 5.25 (1 H, m), 6.46 (2 H, d, *J*=8.56 Hz), 6.85 (2 H, d, *J*=8.56 Hz), 7.18 (1 H, d, *J*=8.31 Hz), 7.44 - 7.53 (1 H, m), 7.57 (1 H, s), 7.72 (1 H, d, *J*=1.71 Hz), 7.76 (1 H, s). LC-MS: (ES) *m/z* 594.3 (M+H⁺).

Example S130: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(1-methyl-1H-imidazole-4-carbonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 113)



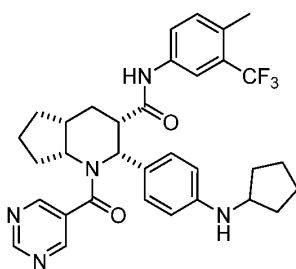
[0339] The title compound was synthesized in similar fashion as Example S127. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 0.65 - 0.90 (6 H, m), 1.19 (7 H, br s), 1.78 - 1.91 (4 H, m), 1.96 - 2.15 (3 H, m), 2.30 (3 H, d, *J*=0.98 Hz), 2.98 (1 H, br s), 3.54 - 3.62 (1 H, m), 3.66 (3 H, s), 4.50 (1 H, s), 4.56 - 4.71 (1 H, m), 6.32 - 6.46 (3 H, m), 7.04 (1 H, br s), 7.17 (1 H, d, *J*=8.31 Hz), 7.38 (1 H, br s), 7.45 (1 H, br d, *J*=8.31 Hz), 7.58 (1 H, br s), 7.71 (1 H, s). LC-MS: (ES) *m/z* 594.4 (M+H⁺).

Example S131: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(thiazole-4-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 114)



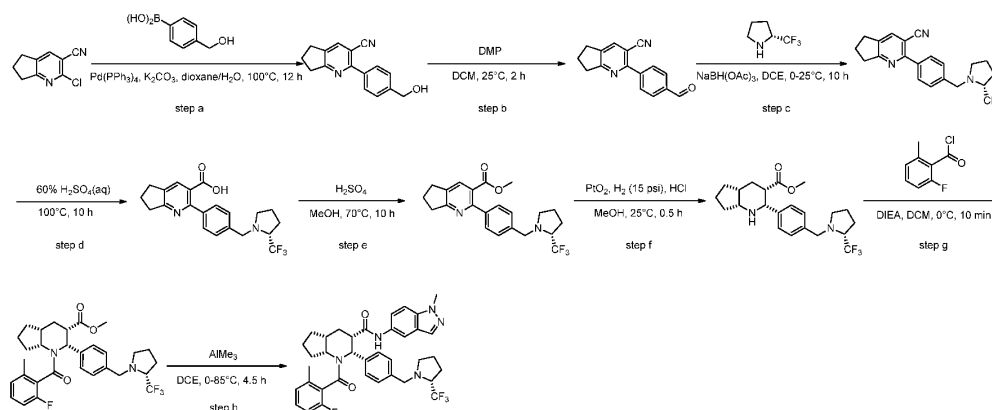
[0340] The title compound was synthesized in similar fashion as Example S127. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.21 - 1.63 (13 H, m), 1.76 - 2.20 (5 H, m), 2.30 (3 H, d, J =1.47 Hz), 2.99 (1 H, br s), 3.17 - 3.27 (2 H, m), 3.60 (1 H, br t, J =6.11 Hz), 4.14 (1 H, br s), 6.41 (3 H, br s), 7.15 (3 H, br d, J =8.31 Hz), 7.42 (1 H, br d, J =7.34 Hz), 7.68 (1 H, br s), 8.95 (1 H, d, J =1.96 Hz). LC-MS: (ES) m/z 597.3 (M+H⁺).

Example S132: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)-phenyl)-1-(pyrimidine-5-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide (Compound No. 115)



[0341] The title compound was synthesized in similar fashion as Example S127. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.29 - 1.42 (1 H, m), 1.44 - 1.64 (4 H, m), 1.71 (7 H, br s), 1.86 (4 H, br s), 2.01 (4 H, br s), 2.42 (5 H, s), 3.19 - 3.27 (2 H, m), 3.97 (1 H, br s), 7.30 (1 H, d, J =8.03 Hz), 7.43 (3 H, br d, J =7.28 Hz), 7.55 (2 H, br d, J =6.78 Hz), 7.61 - 7.96 (3 H, m), 10.10 (1 H, br s). LC-MS: (ES) m/z 592.3 (M+H⁺).

Example S133: Synthesis of (2*R*,3*S*,4*aR*,7*aR*)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1*H*-indazol-5-yl)-2-(4-(((*R*)-2-(trifluoromethyl)pyrrolidin-1-yl)methyl)phenyl)octahydro-1*H*-cyclopenta[b]pyridine-3-carboxamide (Compound No. 116)



[0342] Step a) To a solution of 2-chloro-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (1 g, 5.60 mmol), [4-(hydroxymethyl)phenyl]boronic acid (1.11 g, 7.28 mmol), Pd(PPh₃)₄ (646.94 mg, 559.85 μmol) and K₂CO₃ (2.32 g, 16.80 mmol) in dioxane (15 mL) and H₂O (15 mL), then the reaction mixture was stirred at 100 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was filtered with EtOAc (100 ml) and filtrate was concentrated under reduced pressure to give a crude product. The crude product was added H₂O (20 mL) and acidized with HCl to pH=5, then extracted with DCM (50 mL * 2). Then the aqueous phase was adjust to pH=8 with saturated Na₂CO₃ (aq) (50 ml) and extracted with DCM (50 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the desired product. The compound 2-[4-(hydroxymethyl)phenyl]-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (1.2 g, 4.70 mmol, 83.92% yield, 98% purity) was obtained as white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.14 - 2.31 (m, 3 H), 3.04 (t, *J*=7.58 Hz, 2 H), 3.14 (t, *J*=7.83 Hz, 2 H), 4.76 (s, 2 H), 7.48 (d, *J*=8.31 Hz, 2 H), 7.77 - 7.91 (m, 3 H). LC-MS: (ES) *m/z* 251.1 (M+H⁺).

[0343] Step b) To a mixture of 2-[4-(hydroxymethyl)phenyl]-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (600 mg, 2.40 mmol) in DCM (20 mL) was added DMP (1.53 g, 3.60 mmol, 1.11 mL) at 0°C under N₂. The mixture was stirred at 25°C for 2 h. The reaction mixture was quenched by addition Na₂S₂O₃(aq) 20mL at 25°C, and then diluted with NaHCO₃(aq) 20 mL and extracted with DCM (20 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the desired product. Compound 2-(4-formylphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile

(590 mg, 2.26 mmol, 94.18% yield, 95% purity) was obtained as a light yellow solid. LC-MS: (ES) m/z 249.1 ($M+H^+$).

[0344] Step c) To a mixture of 2-(4-formylphenyl)-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (380 mg, 1.53 mmol) and (2R)-2-(trifluoromethyl)pyrrolidine (425.85 mg, 3.06 mmol) in DCE (10 mL) was added $NaBH(OAc)_3$ (973.15 mg, 4.59 mmol) at 0°C under N_2 . The mixture was stirred at 25°C for 10 h. The reaction mixture was quenched by addition sat. $Na_2S_2O_3$ solution 20 mL at 25°C, and then diluted with a saturated $NaHCO_3$ solution (20 mL) and extracted with DCM (20 mL * 3). The combined organic layers were dried, filtered and concentrated under reduced pressure to give the residue. The residue was purified by column chromatography (SiO_2 , DCM:methanol = 100/1 to 5/1) and 2-[4-[(2R)-2-(trifluoromethyl)pyrrolidin-1-yl]methyl]phenyl]-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (300 mg, 807.76 μ mol, 52.78% yield) was obtained as a light yellow solid. 1H NMR (400 MHz, METHANOL- d_4) δ ppm 0.85 - 0.92 (m, 1 H) 1.27 (br s, 1 H) 1.73 - 1.92 (m, 1 H) 1.75 - 1.92 (m, 2 H) 1.96 - 2.09 (m, 2 H) 2.24 (quin, $J=7.64$ Hz, 2 H) 2.35 - 2.46 (m, 1 H) 3.00 - 3.06 (m, 2 H) 3.11 - 3.21 (m, 2 H) 3.26 - 3.34 (m, 1 H) 3.69 (d, $J=13.45$ Hz, 1 H) 4.26 (d, $J=13.69$ Hz, 1 H) 7.48 (d, $J=8.07$ Hz, 2 H) 7.67 - 7.95 (m, 3 H). LC-MS: (ES) m/z 372.2 ($M+H^+$).

[0345] Step d) To a solution of 2-[4-[(2R)-2-(trifluoromethyl)pyrrolidin-1-yl]methyl]phenyl]-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carbonitrile (280 mg, 753.91 μ mol) in H_2SO_4 (3 mL) and H_2O (3 mL), then the reaction mixture was stirred at 100°C for 10 h. The reaction was adjusted to pH=4 with saturated $NaHCO_3$ solution and the reaction mixture was lyophilized. Then was added MeOH (20 mL), added filtered to get the filtrate. The filtrate was concentrated under reduced pressure to remove MeOH to give a crude product. Compound 2-[4-[(2R)-2-(trifluoromethyl)pyrrolidin-1-yl]methyl]phenyl]-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylic acid (500 mg, crude, contains Na_2SO_4) was obtained as a yellow solid. LC-MS: (ES) m/z 391.2 ($M+H^+$).

[0346] Step e) To a solution of 2-[4-[(2R)-2-(trifluoromethyl)pyrrolidin-1-yl]methyl]phenyl]-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylic acid (400 mg, 1.02 mmol) in MeOH (10 mL), Then the H_2SO_4 (20.51 mg, 204.92 μ mol, 11.15 μ L, 98% purity) was added at 25°C, then the reaction mixture was stirred at 70°C for 10 h. The reaction mixture was partitioned between EtOAc (100 mL) and saturated $NaHCO_3$ (aq) (100 mL). The organic phase was separated, dried, filtered and concentrated under reduced pressure to give the crude. The compound methyl 2-[4-[(2R)-2-(tri-fluoromethyl)pyrrolidin-1-

yl)methyl]phenyl]-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylate (201 mg, crude) was obtained as a yellow oil. LC-MS: (ES) m/z 405.2 ($M+H^+$).

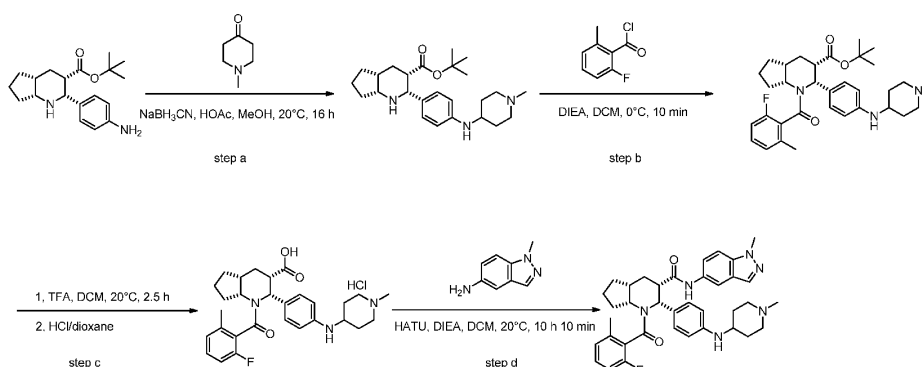
[0347] Step f) To a solution of methyl 2-[4-[(2R)-2-(trifluoromethyl)pyrrolidin-1-yl)methyl]phenyl]-6,7-dihydro-5H-cyclopenta[b]pyridine-3-carboxylate (180 mg, 445.08 μmol) in MeOH (10 mL) was added HCl (4 M, 222.54 μL), then the PtO_2 (30.32 mg, 133.52 μmol) was added. Then the reaction mixture was stirred at 25°C for 0.5 h under H_2 (15 Psi). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified by prep-TLC (SiO_2 , DCM: MeOH = 20:1). Compound methyl 2-[4-[(2R)-2-(trifluoromethyl)pyrrolidin-1-yl)methyl]phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (100 mg, crude) was obtained as a light yellow oil. LC-MS: (ES) m/z 411.2 ($M+H^+$).

[0348] Step g) To a mixture of methyl 2-[4-[(2R)-2-(trifluoromethyl)pyrrolidin-1-yl)methyl]phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1H-cyclopenta[b]pyridine-3-carboxylate (99 mg, 241.19 μmol) and 2-fluoro-6-methyl-benzoyl chloride (49.95 mg, 289.42 μmol) in DCM (3 mL) was added DIEA (62.34 mg, 482.37 μmol , 84.02 μL) at 0°C under N_2 . The mixture was stirred at 0°C for 10 min. The reaction was concentrated to get a residue. The residue was purified by prep-TLC (SiO_2 , DCM: MeOH = 20:1). The compound methyl 1-(2-fluoro-6-methyl-benzoyl)-2-[4-[(2R)-2-(trifluoromethyl)pyrrolidin-1-yl)methyl]phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (130 mg, crude) was obtained as a colorless oil. LC-MS: (ES) m/z 547.3 ($M+H^+$).

[0349] Step h) To a solution of 1-methylindazol-5-amine (43.75 mg, 297.30 μmol) in DCE (1 mL) was added $\text{Al}(\text{CH}_3)_3$ (in toluene) (2 M, 178.38 μL) at 0°C. After stirring for 30 min, a solution of methyl 1-(2-fluoro-6-methyl-benzoyl)-2-[4-[(2R)-2-(trifluoromethyl)pyrrolidin-1-yl)methyl]phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (65 mg, 118.92 μmol) in DCE (1 mL) was added. The mixture was stirred at 85°C for 4 h. The reaction was concentrated to get a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 80 * 40 mm * 3 μm ; mobile phase: [water (0.05% $\text{NH}_3\text{H}_2\text{O}$ + 10 mM NH_4HCO_3)-CA N]; B%: 60%-90%, 8 min). 1-(2-fluoro-6-methyl-benzoyl)-N-(1-methylindazol-5-yl)-2-[4-[(2R)-2-(trifluoromethyl)pyrrolidin-1-yl)methyl]phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxamide (10 mg, 14.81 μmol , 12.45% yield, 98% purity) was obtained as a white solid. ^1H NMR (400 MHz, $\text{METHANOL-}d_4$) δ ppm 1.15 - 1.38 (m, 2 H), 1.39 - 1.62 (m, 2 H), 1.64 - 1.84 (m, 3 H), 1.87 - 2.32 (m, 6 H), 2.34 - 2.49 (m,

3 H), 2.80 - 2.92 (m, 1 H), 3.16 (br dd, $J=9.79, 5.52$ Hz, 1 H), 3.34 (br s, 2 H), 3.48 - 3.67 (m, 1 H), 3.72 - 3.97 (m, 1 H), 3.98 - 4.17 (m, 4 H), 6.65 - 6.84 (m, 1 H), 7.01 - 7.21 (m, 2 H), 7.29 (br d, $J=8.28$ Hz, 2 H), 7.34 - 7.58 (m, 3 H), 7.63 - 7.87 (m, 2 H), 7.93 (d, $J=11.80$ Hz, 1 H). LC-MS: (ES) m/z 662.3 ($M+H^+$).

Example S134: Synthesis of *cis*-1-(2-fluoro-6-methylbenzoyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-2-(4-((1-methylpiperidin-4-yl)amino)phenyl)octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxamide (Compound No. 117)



[0350] Step a) To a mixture of tert-butyl 2-(4-aminophenyl)-2,3,4,4a,5,6,7,7a-octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxylate (150 mg, 474.03 μ mol) and 1-methylpiperidin-4-one (64.37 mg, 568.83 μ mol, 66.15 μ L) in MeOH (5 mL) was added AcOH (28.47 mg, 474.03 μ mol, 27.11 μ L) and NaBH_3CN (89.37 mg, 1.42 mmol) at 20 °C under N_2 , the mixture was stirred at 20 °C for 16 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with saturated $\text{NaHCO}_3(\text{aq})$ (20 mL) and extracted with EtOAc (20 mL * 2). The combined organic layers were dried, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2 , DCM:methanol: $\text{NH}_3 \cdot \text{H}_2\text{O}$ = 10:1:0.1) to get tert-butyl 2-[4-[(1-methyl-4-piperidyl)amino]phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxylate (75 mg, 172.27 μ mol, 36.34% yield, 95% purity) as a light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ ppm 1.18 (s, 9 H), 1.39 - 1.64 (m, 6 H), 1.72 - 1.95 (m, 10 H), 1.99 - 2.09 (m, 5 H), 2.11 - 2.20 (m, 3 H), 2.31 (s, 3 H), 2.76 - 2.88 (m, 3 H), 3.22 - 3.38 (m, 2 H), 3.91 (d, $J=5.50$ Hz, 1 H), 6.54 (d, $J=8.63$ Hz, 2 H), 7.14 (d, $J=8.38$ Hz, 2 H). LC-MS: (ES) m/z 414.3 ($M+H^+$).

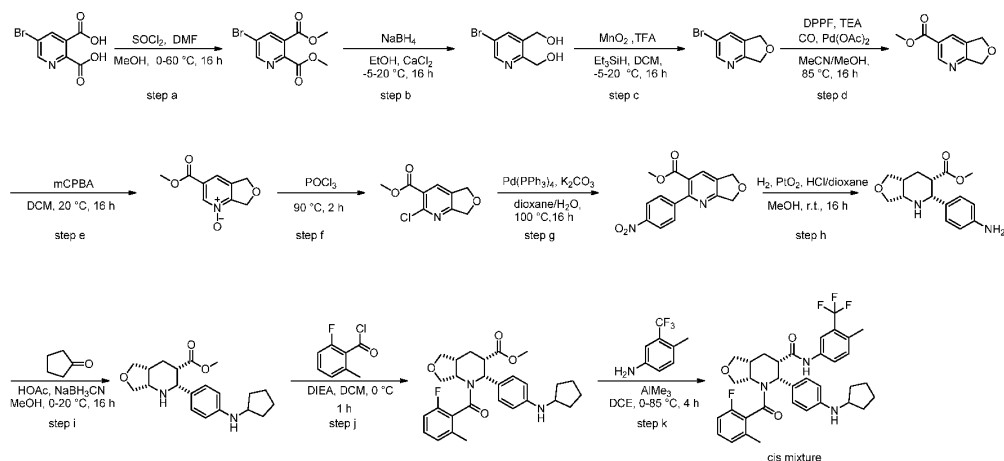
[0351] Step b) To a mixture of tert-butyl 2-[4-[(1-methyl-4-piperidyl)amino]phenyl]-2,3,4,4a,5,6,7,7a-octahydro-1*H*-cyclopenta[*b*]pyridine-3-carboxylate (70 mg, 169.25 μ mol)

and DIEA (43.75 mg, 338.50 μmol , 58.96 μL) in DCM (3 mL) was added 2-fluoro-6-methyl-benzoyl chloride (27.75 mg, 160.79 μmol) at 0°C under N_2 . The mixture was stirred at 0 °C for 10 min. The reaction mixture was concentrated to get a residue. The residue was purified by prep-TLC (SiO_2 , DCM:methanol: $\text{NH}_3 \cdot \text{H}_2\text{O}$ =10:1:0.1) to give tert-butyl 1-(2-fluoro-6-methyl-benzoyl)-2-[4-[(1-methyl-4-piperidyl)amino]phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (64 mg, 116.42 μmol , 68.79% yield, 100% purity) as a colorless oil. LC-MS: (ES) m/z 550.3 ($\text{M}+\text{H}^+$).

[0352] Step c) To a mixture of tert-butyl 1-(2-fluoro-6-methyl-benzoyl)-2-[4-[(1-methyl-4-piperidyl)amino]phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylate (64 mg, 116.42 μmol) in DCM (5 mL) was added TFA (3.08 g, 27.01 mmol, 2 mL) at 20°C under N_2 . The mixture was stirred at 20 °C for 2.5 h. The mixture was concentrated to get a residue, then 10 mL (4M HCl/dioxane) was added, and stirred at 20°C for 10 min, then concentrated to get 1-(2-fluoro-6-methyl-benzoyl)-2-[4-[(1-methyl-4-piperidyl)amino]phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta-[b]pyridine-3-carboxylic acid (60 mg, 113.19 μmol , 97.22% yield, HCl) as a light yellow oil. LC-MS: (ES) m/z 494.3 ($\text{M}+\text{H}^+$).

[0353] Step d) To a mixture of 1-(2-fluoro-6-methyl-benzoyl)-2-[4-[(1-methyl-4-piperidyl)amino]phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxylic acid (60 mg, 113.19 μmol , HCl) in DCM (3 mL) was added HATU (51.65 mg, 135.83 μmol) and DIEA (43.89 mg, 339.58 μmol , 59.15 μL) at 20°C under N_2 . The mixture was stirred at 20°C for 10 min, then 1-methylindazol-5-amine (24.99 mg, 169.79 μmol) was added and the mixture was stirred at 20°C for 10 hr. The mixture was concentrated to get a residue. The residue was purified by Prep-HPLC (column: Phenomenex Gemini-NX 150 * 30 mm * 5 μm ; mobile phase: [water (0.05% HCl) -ACN]; B%: 18%-58%, 10 min to give 1-(2-fluoro-6-methyl-benzoyl)-N-(1-methylindazol-5-yl)-2-[4-[(1-methyl-4-piperidyl)amino]phenyl]-2,3,4,4a,5,6,7,7a-octahydrocyclopenta[b]pyridine-3-carboxamide (20 mg, 30.34 μmol , 26.80% yield, 100% purity, HCl) as a brown solid. ^1H NMR (400 MHz, $\text{METHANOL}-d_4$) δ ppm 1.18 - 1.45 (m, 3 H), 1.48 - 1.64 (m, 2 H), 1.78 (br s, 1 H), 2.01 - 2.16 (m, 4 H), 2.22 - 2.35 (m, 3 H), 2.44 (s, 2 H), 2.88 (s, 3 H), 3.04 - 3.16 (m, 2 H), 3.18 - 3.28 (m, 1 H), 3.51 - 3.70 (m, 3 H), 3.77 - 3.96 (m, 2 H), 4.05 - 4.11 (m, 3 H), 6.58 - 6.74 (m, 1 H), 7.03 - 7.22 (m, 2 H), 7.36 - 7.58 (m, 5 H), 7.75 - 8.11 (m, 4 H). LC-MS: (ES) m/z 623.3 ($\text{M}+\text{H}^+$).

Example S135: Synthesis of *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-*N*-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-*b*]pyridine-3-carboxamide (Compound No. 118)



[0354] Step a) To a solution of 5-bromopyridine-2,3-dicarboxylic acid (50 g, 203.24 mmol) in MeOH (500 mL) was added SOCl₂ (145.08 g, 1.22 mol, 88.46 mL) and DMF (2.97 g, 40.65 mmol, 3.13 mL) at 0 °C. The mixture was stirred at 60 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=10/1 to 4/1) to give compound dimethyl 5-bromopyridine-2,3-dicarboxylate (47.5 g, 173.31 mmol, 85.28% yield, 100% purity) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 4.53 (br s, 2 H), 4.64 (d, *J*=4.89 Hz, 2 H), 5.17 (br s, 1 H), 5.43 (br t, *J*=5.50 Hz, 1 H), 7.94 - 8.02 (m, 1 H), 8.50 (d, *J*=2.20 Hz, 1 H). LC-MS: (ES) *m/z* 273.9 (M+H⁺).

[0355] Step b) To a solution of dimethyl 5-bromopyridine-2,3-dicarboxylate (42 g, 153.25 mmol) in EtOH (500 mL) was slowly added NaBH₄ (28.99 g, 766.23 mmol) at -5 °C. Then the CaCl₂ (15.31 g, 137.92 mmol) in EtOH (150 mL) was added dropwise slowly at -5 °C. The mixture was stirred for at 20 °C for 16 h. The mixture was quenched by slow addition of aqueous 2 N HCl solution (500 mL, pH~2-3). After stirring for 2 h, the mixture was concentrated to give the residue. Saturated aqueous sodium bicarbonate solution was added to the residue until pH=7. The aqueous mixture was extracted with EtOAc 900 mL (450 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography (SiO₂, DCM:methanol:NH₃·H₂O= 50:1:0.1 to 10:1:0.1, plate 2)

to give [5-bromo-2-(hydroxymethyl)-3-pyridyl]methanol (22 g, 100.90 mmol, 65.84% yield) as a light yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 4.53 (s, 2 H), 4.64 (s, 2 H), 7.99 (d, $J=1.71$ Hz, 1 H), 8.50 (d, $J=2.20$ Hz, 1 H). LC-MS: (ES) m/z 217.9 ($\text{M}+\text{H}^+$).

[0356] Step c) To a solution of [5-bromo-2-(hydroxymethyl)-3-pyridyl]methanol (21 g, 96.31 mmol) in DCM (500 mL) was added MnO_2 (41.87 g, 481.55 mmol) at -5°C , then TFA (164.72 g, 1.44 mol, 106.96 mL) was added. Then triethylsilane (50.39 g, 433.39 mmol, 69.22 mL) was added dropwise over 15 min. Then the mixture was stirred at 0°C for 1 h. The mixture was stirred at 20°C for 14 h and 45 min. 50 mL of H_2O was added to the reaction mixture, then filtered and concentrated under reduced pressure to give a residue. The residue was alkalified with aqueous NaHCO_3 (200 mL) to pH~7-8 and extracted with DCM (500 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=3/1 to 0/1, plate 2) to give 3-bromo-5,7-dihydrofuro[3,4-b]pyridine (4.7 g, 22.56 mmol, 23.42% yield, 96% purity) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 5.02 (d, $J=1.71$ Hz, 2 H), 5.15 (d, $J=0.73$ Hz, 2 H), 7.69 (s, 1 H), 8.54 (d, $J=0.98$ Hz, 1 H). LC-MS: (ES) m/z 200.0 ($\text{M}+\text{H}^+$).

[0357] Step d) A mixture of 3-bromo-5,7-dihydrofuro[3,4-b]pyridine (5.7 g, 28.50 mmol), DPPF (4.74 g, 8.55 mmol), TEA (8.65 g, 85.49 mmol, 11.90 mL) and $\text{Pd}(\text{OAc})_2$ (959.62 mg, 4.27 mmol) in MeOH (20 mL) and MeCN (50 mL) was degassed and purged with CO (50 psi) 3 times, and then the mixture was stirred at 80°C for 32 h under CO atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=3/1 to 3/2) to give methyl 5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate (4.3 g, 23.04 mmol, 80.85% yield, 96% purity) as a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 3.97 (s, 3 H), 5.12 (t, $J=1.83$ Hz, 2 H), 5.21 (s, 2 H), 8.17 (s, 1 H), 9.12 (s, 1 H). LC-MS: (ES) m/z 180.1 ($\text{M}+\text{H}^+$).

[0358] Step e) To a solution of methyl 5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate (4.3 g, 24.00 mmol) in DCM (70 mL) was added m-CPBA (9.01 g, 44.40 mmol, 85% purity) at 0°C . The mixture was stirred at 20°C for 16 h. The reaction mixture was quenched by addition of Na_2SO_3 (10 %) 45 mL at 0°C , and then extracted with DCM (100 mL x 2). The combined organic layers were washed with aqueous NaHCO_3 40 mL, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give the residue methyl 1-oxido-5,7-dihydrofuro[3,4-b]pyridin-1-ium-3-carboxylate (4.8 g, crude) as light yellow solid, which

was used in next step without further purification. ^1H NMR (400 MHz, CDCl_3) δ 3.98 (s, 3 H), 5.24 - 5.30 (m, 4 H), 7.74 (s, 1 H), 8.70 (s, 1 H). LC-MS: (ES) m/z 196.1 ($\text{M}+\text{H}^+$).

[0359] Step f) The methyl 1-oxido-5,7-dihydrofuro[3,4-b]pyridin-1-ium-3-carboxylate (2 g, 8.20 mmol) was added to POCl_3 (27.90 g, 181.93 mmol, 16.91 mL). The mixture was stirred at 90 °C for 2 h. The reaction mixture was concentrated under reduced pressure to remove POCl_3 . The residue was alkalified with aqueous NaHCO_3 (80 mL) and extracted with EtOAc (150 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, eluent of 0~20% ethyl acetate/petroleum ether gradient @ 35 mL/min) to give methyl 2-chloro-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate (750 mg, 3.44 mmol, 41.97% yield, 98% purity) as light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 3.97 (s, 3 H), 5.07 (t, $J=1.83$ Hz, 2 H), 5.18 (s, 2 H), 8.05 (s, 1 H). LC-MS: (ES) m/z 214.1 ($\text{M}+\text{H}^+$).

[0360] Step g) A mixture of methyl 2-chloro-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate (2.1 g, 9.83 mmol), (4-nitrophenyl)boronic acid (2.95 g, 17.70 mmol), $\text{Pd}(\text{PPh}_3)_4$ (1.14 g, 983.07 μmol) and K_2CO_3 (2 M, 17.20 mL) in dioxane (50 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 100 °C for 16 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove dioxane and then extracted with EtOAc 160 mL (80 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=5/1 to 2/1, plate 2) to give methyl 2-(4-nitrophenyl)-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate (2.6 g, 6.93 mmol, 70.47% yield, 80% purity) as a light brown solid. ^1H NMR (400 MHz, CDCl_3) δ 3.74 (s, 3 H), 5.16 (d, $J=1.47$ Hz, 2 H), 5.28 (s, 2 H), 7.67 - 7.69 (m, 2 H), 8.11 (s, 1 H), 8.32 (d, $J=8.80$ Hz, 2H). LC-MS: (ES) m/z 301.1 ($\text{M}+\text{H}^+$).

[0361] Step h) A mixture of methyl 2-(4-nitrophenyl)-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate (1.68 g, 4.76 mmol), PtO_2 (431.98 mg, 1.90 mmol) and HCl/dioxane (4 M, 2.38 mL) in MeOH (50 mL) was degassed and purged with H_2 (15 psi) 3 times, and then the mixture was stirred at 20 °C for 4 h under H_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was alkalified with aqueous NaHCO_3 10 mL and extracted with DCM (50 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give

a crude product. The crude product combined with previous batch was purified by column chromatography (SiO₂, DCM:methanol: NH₃·H₂O=100:1:0.1-20:1:0.1) to give cis-methyl 2-(4-amino phenyl)-1,2,3,4,4a,5,7,7a-octahydrofuro[3,4-b] pyridine-3-carboxyl ate (90% purity) (1.67 g) as a light yellow gum. ¹H NMR (400 MHz, CDCl₃) δ 2.12 - 2.20 (m, 2 H), 2.21 - 2.28 (m, 1 H), 2.87 - 2.93 (m, 1 H), 3.38 (s, 3 H), 3.50 - 3.55 (m, 2 H), 3.70 - 3.81 (m, 2 H), 3.85 - 3.93 (m, 1 H), 3.96 - 4.04 (m, 2 H), 6.61 - 6.67 (m, 2 H), 7.05 - 7.13 (m, 2 H). LC-MS: (ES) *m/z* 277.2 (M+H⁺).

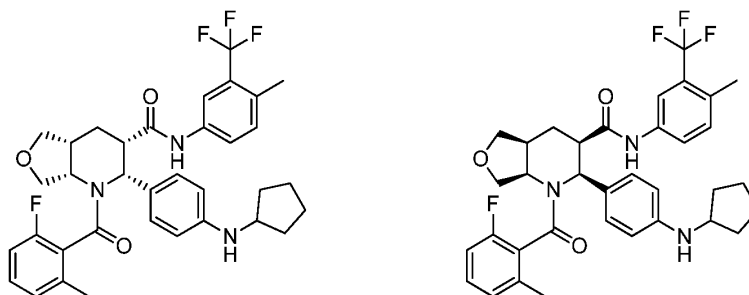
[0362] Step i) To a solution of cis-methyl 2-(4-aminophenyl)-1,2,3,4,4a,5,7,7a-octahydrofuro-[3,4-b] pyridine-3-carboxylate (800 mg, 2.90 mmol) and cyclopentanone (304.00 mg, 3.61 mmol, 320.00 μL) in MeOH (20 mL) was added CH₃COOH (208.63 mg, 3.47 mmol, 198.69 μL, 1.2 eq) and NaBH₃CN (727.73 mg, 11.58 mmol) at 0 °C. The mixture was stirred at 20 °C for 16 h. Another portion of NaBH₃CN (181.93 mg, 2.90 mmol) and CH₃COOH (105.00 mg, 1.75 mmol, 100 μL) were added to the mixture, then stirred at 20 °C for another 4 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was alkalinified with aqueous NaHCO₃ (10 mL) and extracted with DCM (50 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, DCM:methanol=100/1, plate 2) to give cis-methyl 2-[4-(cyclopentylamino)phenyl]-1,2,3,4,4a,5,7,7a-octahydrofuro[3,4-b]pyridine-3-carboxylate (820 mg, 2.14 mmol, 74.01% yield, 90% purity) as a light yellow gum. ¹H NMR (400 MHz, CDCl₃) δ 1.44 (br dd, *J*=11.74, 6.11 Hz, 2 H), 1.59 - 1.64 (m, 2 H), 1.69 - 1.73 (m, 2 H), 1.95 - 2.06 (m, 3 H), 2.11 - 2.19 (m, 2 H), 2.20 - 2.28 (m, 1 H), 2.89 (q, *J*=5.95 Hz, 1 H), 3.37 (s, 3 H), 3.51 - 3.55 (m, 1 H), 3.73 - 3.80 (m, 3 H), 3.86 - 3.92 (m, 1 H), 3.96 - 4.04 (m, 2 H), 6.51 - 6.57 (m, 2 H), 7.11 (d, *J*=8.56 Hz, 2 H). LC-MS: (ES) *m/z* 345.2 (M+H⁺).

[0363] Step j) To a solution of cis-methyl 2-[4-(cyclopentylamino)phenyl]-1,2,3,4,4a,5,7,7a-octahydrofuro[3,4-b]pyridine-3-carboxylate (200 mg, 580.64 μmol) in DCM (10 mL) was added DIEA (262.65 mg, 2.03 mmol, 353.98 μL), then the 2-fluoro-6-methyl-benzoyl chloride (100.21 mg, 580.64 μmol) in DCM (1 mL) was added dropwise. The mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched by addition of H₂O (10 mL), and then extracted with DCM (30 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, DCM:methanol=50/1, plate 2) to give the crude product. The crude product was further purified by prep-HPLC

(HCl condition; column: Phenomenex Gemini-NX 150 x 30mm x 5 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 25%-55%, 7 min). The eluent was alkalified with aqueous NaHCO_3 (10 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give the pure product cis-methyl 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-3,4,4a,5,7,7a-hexahydro-2H-furo[3,4-b]pyridine-3-carboxylate (110 mg, 224.32 μ mol, 38.63% yield, 98% purity) as light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 0.82 - 0.93 (m, 2 H), 1.45 (ddd, $J=19.45, 13.05, 6.15$ Hz, 3 H), 1.62 (br d, $J=5.27$ Hz, 2 H), 1.68 - 1.76 (m, 2 H), 2.02 (br dd, $J=12.92, 6.15$ Hz, 2 H), 2.29 - 2.38 (m, 3 H), 2.85 - 3.06 (m, 1 H), 3.08 - 3.18 (m, 1 H), 3.31 (br t, $J=8.53$ Hz, 1 H), 3.43 (s, 1 H), 3.68 (s, 1 H), 3.71 - 3.74 (m, 2 H), 3.74 - 3.86 (m, 2 H), 3.91 - 4.10 (m, 1 H), 4.16 - 4.29 (m, 1 H), 4.95 - 5.03 (m, 1 H), 6.30 - 6.40 (m, 1 H), 6.49 - 6.60 (m, 2 H), 6.63 - 6.81 (m, 1 H), 6.92 - 7.07 (m, 1 H), 6.92 - 7.07 (m, 1 H), 7.15 - 7.26 (m, 2 H). LC-MS: (ES) m/z 481.3 ($\text{M}+\text{H}^+$).

[0364] Step k) To a solution of 4-methyl-3-(trifluoromethyl)aniline (111.57 mg, 624.26 μ mol, 91.45 μ L) in DCE (1 mL) was added $\text{Al}(\text{CH}_3)_3$ (in toluene) (2 M, 364.15 μ L) at 0 $^\circ\text{C}$, after 20 min, the cis-methyl 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-3,4,4a,5,7,7a-hexahydro-2H-furo[3,4-b]pyridine-3-carboxylate (100 mg, 208.09 μ mol) in DCE (1 mL) was added. The mixture was stirred at 85 $^\circ\text{C}$ for 3 hr 40 min. The reaction mixture was diluted with aq. NaHCO_3 8 mL and extracted with DCM 80 mL (40 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=200/1) to give the crude product. The crude product was further purified by prep-HPLC (HCl condition, column: Phenomenex Gemini-NX 150 x 30 mm x 5 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 35%-65%, 7 min) to give cis-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-3,4,4a,5,7,7a-hexahydro-2H-furo[3,4-b]pyridine-3-carboxamide (40 mg, 59.38 μ mol, 28.54% yield, 98% purity, HCl) as a white solid. ^1H NMR (400 MHz, $\text{METHANOL}-d_4$) δ 1.27 - 1.42 (m, 2 H), 1.57 - 1.73 (m, 4 H), 1.81 (br s, 2 H), 1.91 - 2.07 (m, 3 H), 2.08 - 2.21 (m, 1 H), 2.25 - 2.47 (m, 5 H), 2.66 (s, 1 H), 3.11 - 3.26 (m, 1 H), 3.44 - 3.74 (m, 1 H), 3.75 - 3.95 (m, 2 H), 3.98 - 4.13 (m, 1 H), 4.20 - 4.33 (m, 1 H), 6.29 - 6.52 (m, 1 H), 6.73 - 6.88 (m, 1 H), 6.94 (br d, $J=8.07$ Hz, 1 H), 7.00 - 7.44 (m, 5 H), 7.46 - 7.60 (m, 1 H), 7.65 - 7.87 (m, 1 H), 9.66 - 9.82 (m, 0.4 H), 10.25 (s, 0.3 H). LC-MS: (ES) m/z 624.3 ($\text{M}+\text{H}^+$).

Example S136: Synthesis of (2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide and (2S,3R,4aS,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound Nos. 119 and 120)



[0365] The cis-methyl-2-[4-(cyclopentylamino)phenyl]-1,2,3,4,4a,5,7,7a-octahydrofuro[3,4-b]pyridine-3-carboxylate (800 mg, 2.32 mmol) was separated by SFC (column: DAICEL CHIRALPAK IG (250 mm x 30mm x 10 μ m); mobile phase: [0.1% $\text{NH}_3 \cdot \text{H}_2\text{O}$ ETOH]; B%: 40%-40%, 8 min). The compound methyl(2R,3S,4aR,7aS)-2-[4-(cyclopentylamino)phenyl]-1,2,3,4,4a,5,7,7a-octahydrofuro[3,4-b]pyridine-3-carboxylate (peak 1 on SFC spectrum, 245 mg, 704.17 μ mol, 30.32% yield, 99% purity) was obtained as a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 1.39 - 1.50 (m, 2 H), 1.54 - 1.66 (m, 2 H), 1.66 - 1.77 (m, 2 H), 1.95 - 2.06 (m, 2 H), 2.12 - 2.19 (m, 2 H), 2.20 - 2.29 (m, 1 H), 2.89 (q, $J=5.79$ Hz, 1 H), 3.51 - 3.57 (m, 1 H), 3.72 - 3.82 (m, 3 H), 3.86 - 3.93 (m, 1 H), 3.96 - 4.04 (m, 2 H), 6.54 (d, $J=8.56$ Hz, 2 H), 7.11 (d, $J=8.56$ Hz, 2 H). LC-MS: (ES) m/z 345.2 ($\text{M}+\text{H}^+$). The compound methyl(2S,3R,4aS,7aR)-2-[4-(cyclopentylamino)phenyl]-1,2,3,4,4a,5,7,7a-octahydrofuro[3,4-b]pyridine-3-carboxylate (peak 2, 310 mg, 890.99 μ mol, 38.36% yield, 99% purity) was obtained as light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 1.45 (dt, $J=12.41$, 6.14 Hz, 2 H), 1.54 - 1.65 (m, 2 H), 1.66 - 1.77 (m, 2 H), 2.00 (dt, $J=12.47$, 6.24 Hz, 2 H), 2.16 (q, $J=5.87$ Hz, 2 H), 2.22 - 2.31 (m, 1 H), 2.89 (q, $J=5.87$ Hz, 1 H), 3.38 (s, 3 H), 3.51 - 3.57 (m, 1 H), 3.71 - 3.81 (m, 3 H), 3.86 - 3.93 (m, 1 H), 3.97 - 4.04 (m, 2 H), 6.54 (d, $J=8.56$ Hz, 2 H), 7.11 (d, $J=8.56$ Hz, 2 H). LC-MS: (ES) m/z 345.2 ($\text{M}+\text{H}^+$).

[0366] The title compounds were synthesized in similar fashion as Example S135.

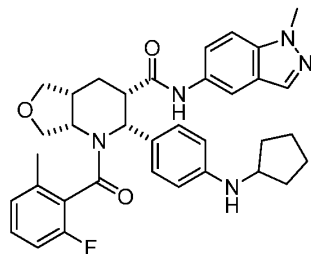
(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide.

¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.39 (s, 1 H), 1.68 (br s, 4 H), 1.83 (br s, 2 H), 1.93 - 2.05 (m, 3 H), 2.08 - 2.27 (m, 1 H), 2.34 - 2.47 (m, 5 H), 2.77 (br d, *J*=7.09 Hz, 1 H), 3.12 - 3.26 (m, 1 H), 3.34 - 3.58 (m, 1 H), 3.63 - 3.79 (m, 1 H), 3.81 - 3.97 (m, 2 H), 3.98 - 4.12 (m, 1 H), 4.20 - 4.39 (m, 1 H), 5.04 - 5.33 (m, 1 H), 6.39 - 6.54 (m, 0.5 H), 6.68 - 6.77 (m, 0.5 H), 6.88 - 7.18 (m, 4 H), 7.20 - 7.25 (m, 1 H), 7.26 - 7.50 (m, 3 H), 7.51 - 7.65 (m, 1 H), 7.70 - 7.83 (m, 1 H), 9.76 - 9.90 (m, 0.3 H), 10.29 (s, 0.2 H). *m/z* 624.4 (M+H⁺).

(2S,3R,4aS,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide.

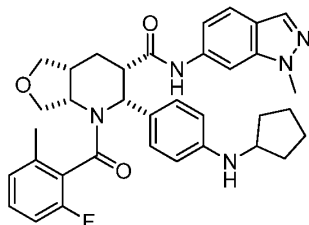
¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.39 (s, 1 H), 1.68 (br s, 4 H), 1.83 (br s, 2 H), 1.87 - 2.07 (m, 4 H), 2.07 - 2.30 (m, 1 H), 2.34 - 2.56 (m, 5 H), 2.58 - 2.93 (m, 1 H), 3.12 - 3.27 (m, 1 H), 3.68 - 3.81 (m, 1 H), 3.82 - 3.97 (m, 2 H), 3.97 - 4.13 (m, 1 H), 4.18 - 4.36 (m, 1 H), 5.07 - 5.28 (m, 1 H), 6.28 - 6.57 (m, 1 H), 6.67 - 6.95 (m, 1 H), 6.97 - 7.44 (m, 7 H), 7.45 - 7.66 (m, 1 H), 7.69 - 7.88 (m, 1 H), 9.74 - 9.96 (m, 0.4 H), 10.29 (s, 0.2 H); LC-MS: (ES) *m/z* 624.4 (M+H⁺).

Example S137: Synthesis of (2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 126)



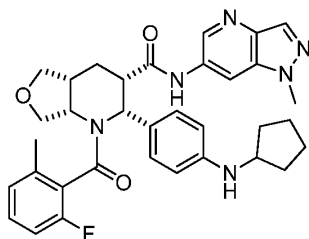
[0367] The title compound was synthesized in similar fashion as Examples S135 and S136. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.59 - 1.76 (m, 4 H), 1.82 (br s, 2 H), 1.94 (br d, *J*=16.06 Hz, 2 H), 2.03 - 2.10 (m, 1 H), 2.11 - 2.31 (m, 1 H), 2.45 (d, *J*=13.05 Hz, 2 H), 2.53 - 2.85 (m, 1 H), 3.19 - 3.28 (m, 1 H), 3.34 - 3.59 (m, 1 H), 3.69 - 3.82 (m, 1 H), 3.85 - 3.97 (m, 2 H), 3.98 - 4.05 (m, 4 H), 4.06 - 4.14 (m, 1 H), 4.21 - 4.35 (m, 1 H), 6.34 - 6.78 (m, 1 H), 7.02 - 7.23 (m, 3 H), 7.23 - 7.35 (m, 2 H), 7.36 - 7.54 (m, 3 H), 7.62 (d, *J*=7.78 Hz, 1 H), 7.78 - 7.96 (m, 2 H). LC-MS: (ES) *m/z* 596.3 (M+H⁺).

Example S138: Synthesis of (2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-6-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 122)



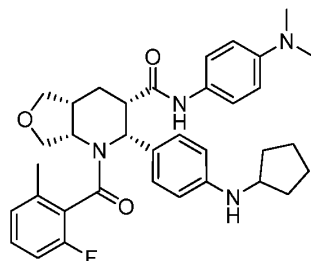
[0368] The title compound was synthesized in similar fashion as Examples S135 and S136. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.66 (br s, 4 H), 1.82 (br s, 2 H), 1.97 (br s, 2 H), 2.03 - 2.11 (m, 1 H), 2.15 - 2.31 (m, 1 H), 2.46 (d, *J*=14.92 Hz, 2 H), 2.56 - 2.84 (m, 1 H), 3.20 - 3.29 (m, 1 H), 3.35 - 3.59 (m, 1 H), 3.69 - 3.84 (m, 1 H), 3.84 - 3.93 (m, 3 H), 3.93 - 4.05 (m, 3 H), 4.05 - 4.15 (m, 1 H), 4.21 - 4.35 (m, 1 H), 6.33 - 6.76 (m, 1 H), 6.90 - 7.07 (m, 2 H), 7.07 - 7.34 (m, 4 H), 7.35 - 7.62 (m, 2 H), 7.64 - 7.70 (m, 1 H), 7.77 - 7.95 (m, 2 H). LC-MS: (ES) *m/z* 596.3 (M+H⁺).

Example S139: Synthesis of (2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazolo[4,3-*b*]pyridin-6-yl)octahydrofuro[3,4-*b*]pyridine-3-carboxamide (Compound No. 123)



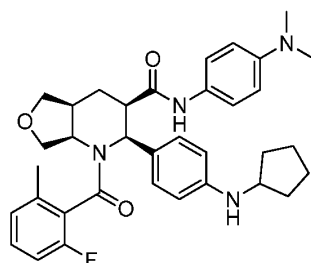
[0369] The title compound was synthesized in similar fashion as Examples S135 and S136. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.69 (br s, 4 H), 1.84 (br s, 2 H), 1.97 (br s, 2 H), 2.06 - 2.15 (m, 1 H), 2.19 - 2.36 (m, 1 H), 2.43 - 2.52 (m, 2 H), 2.53 - 2.89 (m, 1 H), 3.33 - 3.41 (m, 2 H), 3.69 - 4.06 (m, 4 H), 4.06 - 4.11 (m, 2 H), 4.12 - 4.19 (m, 2 H), 4.23 - 4.35 (m, 1 H), 4.99 - 5.23 (m, 1 H), 6.43 - 6.79 (m, 1 H), 7.05 - 7.17 (m, 2 H), 7.18 - 7.34 (m, 2 H), 7.38 - 7.50 (m, 2 H), 7.84 (br d, *J*=8.56 Hz, 1 H), 8.20 - 8.30 (m, 1 H), 8.39 - 8.89 (m, 2 H). LC-MS: (ES) *m/z* 597.3 (M+H⁺).

Example S140: Synthesis of (2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-N-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 124)



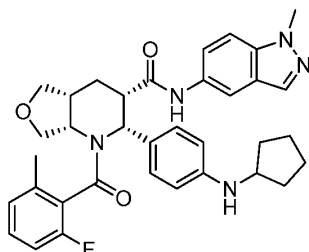
[0370] The title compound was synthesized in similar fashion as Examples S135 and S136. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.39 (s, 1 H), 1.71 (br s, 4 H), 1.86 (br s, 2 H), 1.92 - 2.06 (m, 3 H), 2.07 - 2.49 (m, 3 H), 2.50 - 2.83 (m, 1 H), 3.23 (s, 3 H), 3.27 (s, 3 H), 3.34 - 3.53 (m, 1 H), 3.64 - 4.13 (m, 4 H), 4.19 - 4.47 (m, 1 H), 5.12 (d, *J*=6.1 Hz, 1 H), 6.31 - 6.78 (m, 1 H), 6.96 - 7.15 (m, 2 H), 7.17 - 7.34 (m, 2 H), 7.34 - 7.63 (m, 5 H), 7.64 - 7.81 (m, 2 H); LC-MS: (ES) *m/z* 585.4 (M+H⁺).

Example S141: Synthesis of (2S,3R,4aS,7aR)-2-(4-(cyclopentylamino)phenyl)-N-(4-(dimethyl-amino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 125)



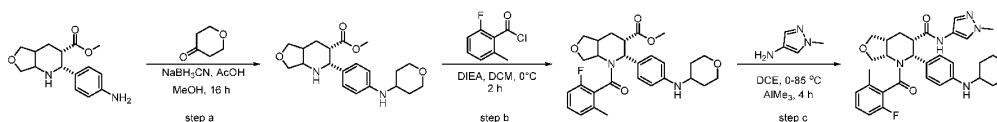
[0371] The title compound was synthesized in similar fashion as Examples S135 and S136. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.39 (s, 1 H), 1.71 (br s, 4 H), 1.85 (br s, 2 H), 1.92 - 2.06 (m, 3 H), 2.08 - 2.50 (m, 3 H), 2.51 - 2.83 (m, 1 H), 3.22 (s, 3 H), 3.27 (s, 3 H), 3.32 - 3.52 (m, 1 H), 3.67 - 4.14 (m, 4 H), 4.16 - 4.48 (m, 1 H), 4.97 - 5.35 (m, 1 H), 6.30 - 6.79 (m, 1 H), 6.94 - 7.16 (m, 2 H), 7.17 - 7.30 (m, 2 H), 7.30 - 7.63 (m, 5 H), 7.63 - 7.81 (m, 2 H); LC-MS: (ES) *m/z* 585.4 (M+H⁺).

Example S142: Synthesis of (2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 126)



[0372] The title compound was synthesized in similar fashion as Examples S135 and S136. ¹H NMR (400 MHz, METHANOL-d₄) δ ppm 1.42 - 1.50 (m, 3 H), 1.57 - 1.63 (m, 2 H), 1.71 (br d, J=5.52 Hz, 2 H), 1.89 - 2.02 (m, 3 H), 2.14 - 2.21 (m, 1 H), 2.29 - 2.54 (m, 3 H), 3.05 - 3.18 (m, 1 H), 3.70 - 3.77 (m, 2 H), 3.99 - 4.04 (m, 4 H), 4.19 - 4.35 (m, 1 H), 4.91 - 4.97 (m, 2 H), 6.40 (t, J=8.16 Hz, 1 H), 6.55 - 6.59 (m, 2 H), 6.72 - 6.82 (m, 1 H), 7.05 - 7.25 (m, 3 H), 7.36 - 7.45 (m, 3 H), 7.79 - 7.95 (m, 2 H). LC-MS: (ES) *m/z* 596.3 (M+H⁺).

Example S143: Synthesis of cis-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazol-4-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 127)



[0373] **Step a)** To a solution of cis-methyl 2-(4-aminophenyl)-1,2,3,4,4a,5,7,7a-octahydrofuro-[3,4-b]pyridine-3-carboxylate (780 mg, 2.82 mmol) and tetrahydropyran-4-one (352.78 mg, 3.52 mmol, 323.65 μL) in MeOH (20 mL) was added CH₃COOH (254.26 mg, 4.23 mmol, 242.15 μL) and NaBH₃CN (886.90 mg, 14.11 mmol) at 0 °C. The mixture was stirred at 20 °C for 16 h. After 16 h, NaBH₃CN (200 mg, 3.18 mmol) and CH₃COOH (52.50 mg, 874.24 μmol, 50 μL) were added to the reaction mixture, and it was stirred at 20 °C for another 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was alkalinized with aqueous NaHCO₃ (10 mL) and extracted with DCM (50 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a pure product. The residue was purified by column chromatography (SiO₂, DCM:methanol=100/1) to give cis-methyl 2-[4-

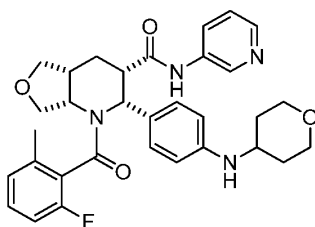
(tetrahydropyran-4-ylamino) phenyl]-1,2,3,4,4a,5,7,7a-octahydrofuro[3,4-b]pyridine-3-carboxylate (330 mg, 732.43 μ mol, 25.95% yield, 80% purity) as a light yellow gum. ^1H NMR (400 MHz, CDCl_3) δ 1.35 - 1.49 (m, 1 H), 1.35 - 1.49 (m, 1 H), 1.95 - 2.05 (m, 2 H), 2.14 (q, $J=5.95$ Hz, 2 H), 2.18 - 2.27 (m, 1 H), 2.83 - 2.91 (m, 1 H), 3.35 (s, 3 H), 3.41 - 3.54 (m, 5 H), 3.68 - 3.78 (m, 2 H), 3.86 (t, $J=8.31$ Hz, 1 H), 3.93 - 4.01 (m, 4 H), 6.53 (d, $J=8.56$ Hz, 2 H), 6.60 (d, $J=8.31$ Hz, 1 H), 7.06 - 7.13 (m, 2 H). LC-MS: (ES) m/z 361.2 ($\text{M}+\text{H}^+$).

[0374] Step b) To a solution of cis-methyl 2-[4-(tetrahydropyran-4-ylamino)phenyl]-1,2,3,4,4a,5,7,7a-octahydrofuro[3,4-b]pyridine-3-carboxylate (399 mg, 1.11 mmol) in DCM (15 mL) was added DIEA (500.72 mg, 3.87 mmol, 674.83 μ L), then the 2-fluoro-6-methylbenzoyl chloride (200.60 mg, 1.16 mmol) in DCM (5 mL) was added dropwise. The mixture was stirred at 0 $^\circ\text{C}$ for 3 h. The reaction mixture was quenched by addition H_2O (10 mL), and then extracted with DCM (30 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , DCM:methanol=50/1) to give cis-methyl 1-(2-fluoro-6-methylbenzoyl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-3,4,4a,5,7,7a-hexahydro-2H-furo[3,4-b]pyridine-3-carboxylate (510 mg, 821.64 μ mol, 74.22% yield, 80% purity) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ 1.47 (br d, $J=9.54$ Hz, 2 H), 1.54 (s, 1 H), 2.02 (br s, 2 H), 2.15 - 2.39 (m, 5 H), 2.84 - 3.06 (m, 1 H), 3.07 - 3.33 (m, 1 H), 3.43 - 3.58 (m, 5 H), 3.61 - 3.89 (m, 4 H), 3.95 - 4.06 (m, 3 H), 6.32 - 6.42 (m, 1 H), 6.51 - 6.58 (m, 1 H), 6.59 - 6.67 (m, 1 H), 6.72 - 6.81 (m, 1 H), 6.92 - 7.08 (m, 2 H), 7.17 - 7.27 (m, 2 H). LC-MS: (ES) m/z 497.3 ($\text{M}+\text{H}^+$).

[0375] Step c) To a solution of 1-methylpyrazol-4-amine (23.47 mg, 241.66 μ mol, 11.03 μ L) in DCE (1.5 mL) was added $\text{Al}(\text{CH}_3)_3$ (2 M, 140.97 μ L), the mixture stirred at 30 $^\circ\text{C}$ for 0.5 h. Then the cis-methyl 1-(2-fluoro-6-methylbenzoyl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-3,4,4a,5,7,7a-hexahydro-2H-furo[3,4-b]pyridine-3-carboxylate (40 mg, 80.55 μ mol) in DCE (1 mL) was added and stirred at 85 $^\circ\text{C}$ for 3.5 h. The reaction mixture was diluted with aqueous NaHCO_3 (8 mL) and extracted with DCM (30 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (HCl condition, column: Phenomenex Gemini-NX 150 x 30 mm x 5 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 25%-55%, 7 min) to give cis-1-(2-fluoro-6-methylbenzoyl)-N-(1-methylpyrazol-4-yl)-2-[4-(tetrahydropyran-4-ylamino)phenyl]-3,4,4a,5,7,7a-hexahydro-2H-furo[3,4-b]pyridine-3-carboxamide (12 mg, 20.06 μ mol, 24.91% yield, 100% purity, HCl) as

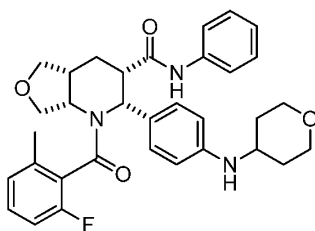
a yellow solid. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.27 - 1.41 (m, 2 H), 1.69 - 1.80 (m, 2 H), 1.85 (br s, 1 H), 1.97 - 2.10 (m, 2 H), 2.14 - 2.29 (m, 1 H), 2.35 - 2.49 (m, 2 H), 2.52 - 2.84 (m, 1 H), 3.12 - 3.25 (m, 1 H), 3.34 - 3.45 (m, 2 H), 3.65 - 3.76 (m, 2 H), 3.80 - 3.90 (m, 3 H), 3.95 - 4.12 (m, 3 H), 4.18 - 4.44 (m, 1 H), 4.99 - 5.37 (m, 1 H), 6.32 - 6.77 (m, 1 H), 6.94 - 7.36 (m, 5 H), 7.37 - 7.50 (m, 2 H), 7.60 - 8.00 (m, 2 H). LC-MS: (ES) m/z 562.3 ($\text{M}+\text{H}^+$).

Example S144: Synthesis of *cis*-1-(2-fluoro-6-methylbenzoyl)-*N*-(pyridin-3-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 128)



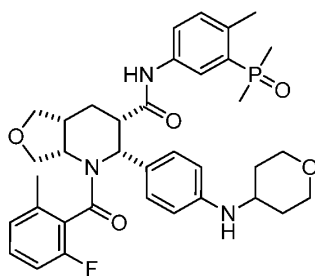
[0376] The title compound was synthesized in similar fashion as Example S143. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.28 - 1.41 (m, 2 H), 1.71 (br s, 2 H), 1.86 (br s, 2 H), 2.00 - 2.12 (m, 1 H), 2.22 - 2.36 (m, 1 H), 2.40 - 2.51 (m, 2 H), 2.51 - 2.86 (m, 1 H), 3.37 - 3.47 (m, 2 H), 3.67 - 3.91 (m, 3 H), 3.97 - 4.13 (m, 3 H), 4.22 - 4.46 (m, 1 H), 4.96 - 5.36 (m, 1 H), 6.42 - 6.77 (m, 1 H), 6.97 - 7.32 (m, 4 H), 7.34 - 7.46 (m, 2 H), 7.79 (br d, $J=8.25$ Hz, 1 H), 7.91 - 8.12 (m, 1 H), 8.31 - 8.65 (m, 2 H), 8.92 - 9.62 (m, 1 H). LC-MS: (ES) m/z 559.3 ($\text{M}+\text{H}^+$).

Example S145: Synthesis of *cis*-1-(2-fluoro-6-methylbenzoyl)-*N*-phenyl-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 129)



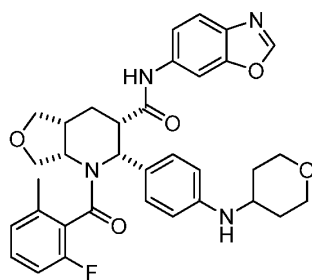
[0377] The title compound was synthesized in similar fashion as Example S143. ¹H NMR (400 MHz, METHANOL-*d*₄) 1H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.26 - 1.40 (m, 2 H), 1.67 - 1.87 (m, 3 H), 1.99 - 2.05 (m, 1 H), 2.12 - 2.24 (m, 1 H), 2.44 (d, *J*=12.13 Hz, 2 H), 2.51 - 2.82 (m, 1 H), 3.13 - 3.27 (m, 1 H), 3.34 - 3.44 (m, 2 H), 3.50 - 3.91 (m, 3 H), 3.96 - 4.14 (m, 3 H), 4.20 - 4.46 (m, 1 H), 4.94 - 5.17 (m, 1 H), 6.27 - 6.76 (m, 1 H), 6.97 - 7.16 (m, 3 H), 7.18 - 7.32 (m, 5 H), 7.35 - 7.48 (m, 3 H), 7.73 - 7.83 (m, 1 H). LC-MS: (ES) *m/z* 558.3 (M+H⁺).

Example S146: Synthesis of *cis*-N-(3-(dimethylphosphoryl)-4-methylphenyl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 130)



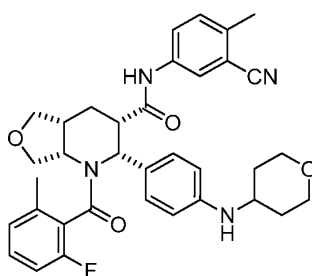
[0378] The title compound was synthesized in similar fashion as Example S143. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.27 - 1.41 (m, 5 H), 1.79 - 1.87 (m, 6 H), 1.98 - 2.09 (m, 2 H), 2.22 (br dd, *J*=19.44, 7.70 Hz, 1 H), 2.44 (d, *J*=11.49 Hz, 2 H), 2.50 - 2.66 (m, 4 H), 2.78 (br s, 1 H), 3.22 (br d, *J*=9.05 Hz, 1 H), 3.34 - 3.48 (m, 3 H), 3.66 - 3.91 (m, 3 H), 3.94 - 4.12 (m, 3 H), 4.20 - 4.34 (m, 1 H), 5.08 - 5.38 (m, 1 H), 6.30 - 6.76 (m, 1 H), 7.00 - 7.17 (m, 3 H), 7.18 - 7.35 (m, 4 H), 7.38 - 7.48 (m, 1 H), 7.53 - 7.62 (m, 1 H), 7.75 - 7.87 (m, 1 H). LC-MS: (ES) *m/z* 648.4 (M+H⁺).

Example S147: Synthesis of *cis*-N-(benzo[d]oxazol-6-yl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 131)



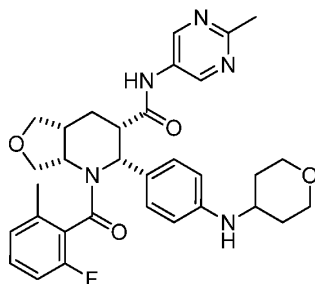
[0379] The title compound was synthesized in similar fashion as Example S143. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.36 - 1.44 (m, 3 H), 1.83 - 2.08 (m, 4 H), 2.12 - 2.26 (m, 2 H), 2.29 - 2.48 (m, 2 H), 3.05 - 3.25 (m, 1 H), 3.41 - 3.57 (m, 3 H), 3.83 - 4.10 (m, 4 H), 4.14 - 4.33 (m, 1 H), 5.16 - 5.37 (m, 1 H), 6.40 (br d, $J=7.83$ Hz, 1 H), 6.47 - 6.79 (m, 3 H), 7.02 - 7.13 (m, 2 H), 7.13 - 7.30 (m, 1 H), 7.32 - 7.43 (m, 2 H), 7.53 - 7.68 (m, 2 H), 8.36 - 8.42 (m, 1 H). LC-MS: (ES) m/z 599.3 ($\text{M}+\text{H}^+$).

Example S148: Synthesis of cis-N-(3-cyano-4-methylphenyl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 132)



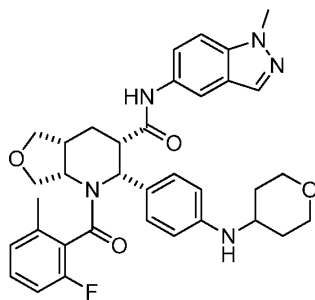
[0380] The title compound was synthesized in similar fashion as Example S143. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.31 (br d, $J=15.41$ Hz, 1 H), 1.58 (s, 1 H), 1.61 - 1.75 (m, 2 H), 1.76 - 1.95 (m, 3 H), 2.06 (br s, 1 H), 2.28 - 2.53 (m, 5 H), 2.64 - 2.92 (m, 1 H), 3.34 - 3.48 (m, 2 H), 3.61 - 3.91 (m, 3 H), 3.93 - 4.11 (m, 3 H), 4.47 - 4.78 (m, 1 H), 5.21 - 5.31 (m, 1 H), 6.49 - 6.70 (m, 1 H), 7.01 - 7.14 (m, 3 H), 7.15 - 7.37 (m, 4 H), 7.45 (br dd, $J=16.51$, 8.19 Hz, 1 H), 7.52 - 7.69 (m, 1 H), 7.77 - 7.92 (m, 1 H). LC-MS: (ES) m/z 597.4 ($\text{M}+\text{H}^+$).

Example S149: Synthesis of *cis*-(2*R*,3*S*,4*aR*,7*aS*)-1-(2-fluoro-6-methylbenzoyl)-*N*-(2-methyl-pyrimidin-5-yl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-*b*]pyridine-3-carboxamide (Compound No. 133)



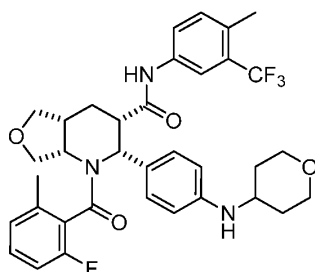
[0381] The title compound was synthesized in similar fashion as Example S143. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.25 - 1.42 (m, 2 H), 1.66 - 1.95 (m, 2 H), 1.97 - 2.06 (m, 1 H), 2.14 - 2.31 (m, 1 H), 2.34 - 2.62 (m, 3 H), 2.66 - 2.83 (m, 3 H), 3.35 - 3.50 (m, 3 H), 3.71 - 3.91 (m, 2 H), 3.95 - 4.14 (m, 3 H), 4.19 - 4.34 (m, 1 H), 5.03 - 5.19 (m, 1 H), 6.38 - 6.78 (m, 1 H), 7.01 - 7.16 (m, 2 H), 7.17 - 7.34 (m, 2 H), 7.35 - 7.53 (m, 1 H), 7.80 (br d, *J*=6.85 Hz, 1 H), 8.83 (br s, 1 H), 9.02 - 9.15 (m, 1 H). LC-MS: (ES) *m/z* 574.4 (M+H⁺).

Example S150: Synthesis of *cis*-1-(2-fluoro-6-methylbenzoyl)-*N*-(1-methyl-1*H*-indazol-5-yl)-2-(4-((tetrahydro-2*H*-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-*b*]pyridine-3-carboxamide (Compound No. 134)



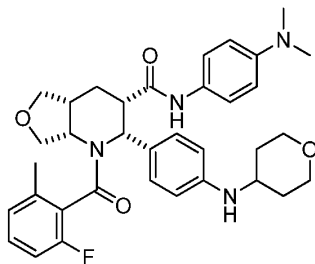
[0382] The title compound was synthesized in similar fashion as Example S143. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.25 - 1.42 (m, 2 H), 1.56 - 1.96 (m, 6 H), 1.99 - 2.27 (m, 2 H), 2.29 - 2.54 (m, 2 H), 2.62 - 3.10 (m, 1 H), 3.56 - 3.92 (m, 4 H), 3.93 - 4.12 (m, 6 H), 5.13 - 5.38 (m, 1 H), 6.45 - 6.76 (m, 1 H), 7.01 - 7.20 (m, 3 H), 7.20 - 7.31 (m, 2 H), 7.31 - 7.38 (m, 1 H), 7.39 - 7.53 (m, 2 H), 7.60 - 7.99 (m, 3 H). LC-MS: (ES) *m/z* 612.4 (M+H⁺).

Example S151: Synthesis of *cis*-1-(2-fluoro-6-methylbenzoyl)-*N*-(4-methyl-3-(trifluoromethyl)-phenyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-*b*]pyridine-3-carboxamide (Compound No. 135)



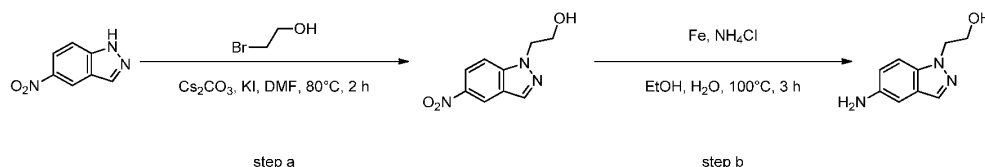
[0383] The title compound was synthesized in similar fashion as Example S143. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.27 - 1.34 (m, 2 H), 1.59 - 1.75 (m, 2 H), 1.76 - 1.92 (m, 2 H), 1.99 - 2.10 (m, 2 H), 2.36 - 2.46 (m, 5 H), 3.11 - 3.27 (m, 1 H), 3.34 - 3.44 (m, 3 H), 3.62 - 3.91 (m, 3 H), 3.93 - 4.13 (m, 3 H), 4.20 - 4.34 (m, 1 H), 5.05 - 5.38 (m, 1 H), 6.27 - 6.77 (m, 1 H), 6.89 - 7.26 (m, 5 H), 7.26 - 7.43 (m, 3 H), 7.43 - 7.63 (m, 1 H), 7.70 - 7.88 (m, 1 H). LC-MS: (ES) *m/z* 640.3 (M+H⁺).

Example S152: Synthesis of *cis*-*N*-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-*b*]pyridine-3-carboxamide (Compound No. 136)



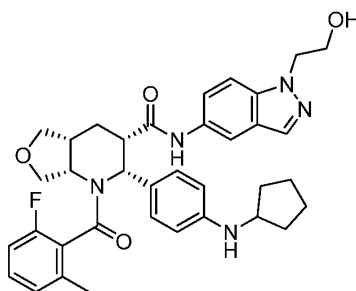
[0384] The title compound was synthesized in similar fashion as Example S143. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.26 - 1.43 (m, 2 H), 1.57 - 1.77 (m, 2 H), 1.79 - 1.95 (m, 2 H), 1.97 - 2.32 (m, 3 H), 2.38 - 2.47 (m, 2 H), 2.49 - 2.82 (m, 1 H), 3.22 (s, 3 H), 3.26 (s, 3 H), 3.36 - 3.47 (m, 2 H), 3.59 - 3.92 (m, 2 H), 3.95 - 4.13 (m, 3 H), 4.19 - 4.33 (m, 1 H), 4.89 - 5.11 (m, 1 H), 6.29 - 6.78 (m, 1 H), 6.85 - 7.00 (m, 1 H), 7.01 - 7.16 (m, 2 H), 7.16 - 7.24 (m, 1 H), 7.25 - 7.50 (m, 4 H), 7.53 - 7.60 (m, 1 H), 7.65 - 7.78 (m, 2 H), 9.89 - 10.02 (m, 0.2 H), 10.40 (s, 0.3 H). LC-MS: (ES) *m/z* 601.3 (M+H⁺).

Example S153: Synthesis of (2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(2-hydroxyethyl)-1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 137)



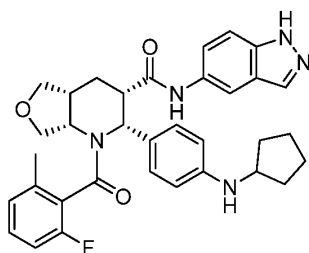
[0385] Step a) To a solution of 5-nitro-1H-indazole (1.4 g, 8.58 mmol) and 2-bromoethanol (1.39 g, 11.16 mmol, 792.14 μ L) in DMF (15 mL) was added Cs_2CO_3 (5.59 g, 17.16 mmol), KI (142.46 mg, 858.19 μ mol) at 20°C under N_2 . The mixture was stirred at 80°C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=100/1 to 0/1 Plate 1). The compound 2-(5-nitroindazol-1-yl)ethanol (1 g, 4.83 mmol, 56.24% yield) was obtained as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 2.58 (t, J =5.82 Hz, 1 H), 4.13 - 4.26 (m, 2 H), 4.46 - 4.64 (m, 2 H), 7.56 (d, J =9.26 Hz, 1 H), 8.26 (s, 1 H), 8.31 (dd, J =9.26, 2.00 Hz, 1 H), 8.76 (d, J =2.00 Hz, 1 H). LC-MS: (ES) m/z 208.1 ($\text{M}+\text{H}^+$).

[0386] Step b) To a solution of 2-(5-nitroindazol-1-yl)ethanol (0.9 g, 4.34 mmol), iron (1.94 g, 34.75 mmol) and NH_4Cl (116.18 mg, 2.17 mmol) in EtOH (20 mL) and H_2O (4 mL) was degassed and purged with N_2 3 times, and then the mixture was stirred at 100°C for 3 h under a N_2 atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 0~3% DCM:methanol @ 30 mL/min). The compound 2-(5-aminoindazol-1-yl)ethanol (700 mg, 3.95 mmol, 90.94% yield, 100% purity) was obtained as a light yellow solid. ^1H NMR (400 MHz, CDCl_3) δ ppm 3.56 (br s, 2 H), 4.07 - 4.14 (m, 2 H), 4.40 - 4.46 (m, 2 H), 6.91 (dd, $J=8.78, 2.01$ Hz, 1 H), 6.96 (d, $J=1.76$ Hz, 1 H), 7.29 (s, 1 H), 7.83 (s, 1 H). LC-MS: (ES) m/z 178.1 ($\text{M}+\text{H}^+$).



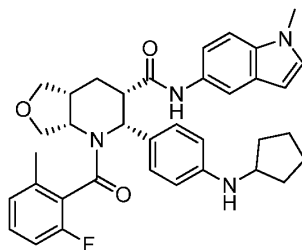
[0387] The title compound was synthesized in similar fashion as Example S143. ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 1.68 (br s, 4 H), 1.82 (br s, 2 H), 1.94 (br s, 2 H), 2.02 - 2.17 (m, 2 H), 2.32 - 2.51 (m, 2 H), 2.55 - 2.85 (m, 1 H), 3.26 (br d, $J=9.03$ Hz, 2 H), 3.33 - 3.40 (m, 1 H), 3.70 - 3.83 (m, 1 H), 3.86 - 3.99 (m, 4 H), 4.00 - 4.12 (m, 1 H), 4.24 - 4.52 (m, 3 H), 6.45 - 6.76 (m, 1 H), 7.02 - 7.18 (m, 3 H), 7.21 - 7.31 (m, 2 H), 7.33 - 7.53 (m, 3 H), 7.54 - 7.66 (m, 1 H), 7.82 - 7.97 (m, 2 H). LC-MS: (ES) m/z 626.3 ($\text{M}+\text{H}^+$).

Example S154: Synthesis of (2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 138)



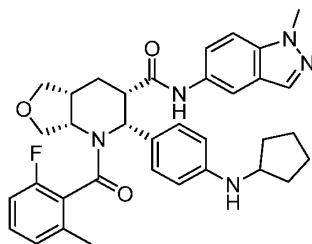
[0388] The title compound was synthesized in similar fashion as Example S143. ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 1.67 (br d, $J=3.76$ Hz, 4 H), 1.82 (br s, 2 H), 1.96 (s, 2 H), 2.08 - 2.32 (m, 2 H), 2.45 (d, $J=12.05$ Hz, 2 H), 2.65 - 2.84 (m, 1 H), 3.23 (br s, 2 H), 3.32 - 3.37 (m, 2 H), 3.67 - 3.96 (m, 3 H), 4.03 - 4.34 (m, 1 H), 5.18 (br d, $J=6.27$ Hz, 1 H), 6.46 - 6.77 (m, 1 H), 7.07 - 7.16 (m, 2 H), 7.27 (dd, $J=8.41, 1.88$ Hz, 2 H), 7.41 - 7.45 (m, 2 H), 7.65 (br d, $J=2.51$ Hz, 1 H), 7.82 (d, $J=8.78$ Hz, 1 H), 7.92 - 8.00 (m, 2 H). LC-MS: (ES) m/z 582.3 ($\text{M}+\text{H}^+$).

Example S155: Synthesis of (2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 139)



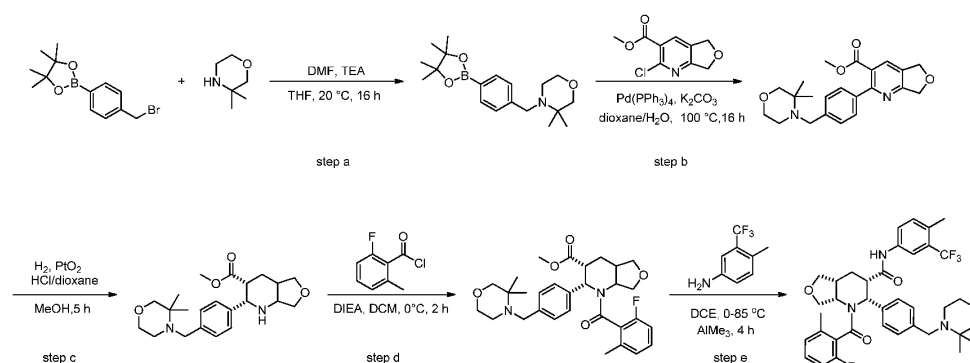
[0389] The title compound was synthesized in similar fashion as Example S143. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.64 - 1.72 (m, 4 H), 1.81 (br s, 2 H), 1.95 - 2.06 (m, 3 H), 2.14 - 2.29 (m, 1 H), 2.42 - 2.45 (m, 1 H), 2.60 (br d, *J*=17.88 Hz, 1 H), 3.13 - 3.25 (m, 2 H), 3.35 - 3.49 (m, 1 H), 3.73 - 3.81 (m, 4 H), 3.89 - 4.11 (m, 3 H), 4.22 - 4.30 (m, 1 H), 6.28 - 6.49 (m, 1 H), 6.71 - 6.97 (m, 2 H), 7.03 - 7.16 (m, 4 H), 7.19 - 7.32 (m, 4 H), 7.39 - 7.42 (m, 1 H), 7.73 - 7.84 (m, 1 H). LC-MS: (ES) *m/z* 595.3 (M+H⁺).

Example S156: Synthesis of (2*S*,3*R*,4*aS*,7*aR*)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)- *N*-(1-methyl-1*H*-indazol-5-yl)octahydrofuro[3,4-*b*]pyridine-3-carboxamide (Compound No. 140)



[0390] The title compound was synthesized in similar fashion as Example S143. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.69 (br s, 4 H), 1.84 (br s, 2 H), 1.99 - 2.32 (m, 4 H), 2.47 (d, *J*=11.80 Hz, 2 H), 2.64 - 2.90 (m, 1 H), 3.14 - 3.31 (m, 2 H), 3.38 - 3.61 (m, 1 H), 3.90 (br dd, *J*=9.03, 4.77 Hz, 1 H), 4.02 - 4.08 (m, 4 H), 4.09 - 4.21 (m, 1 H), 4.26 - 4.46 (m, 1 H), 4.98 - 5.27 (m, 1 H), 6.32 - 6.80 (m, 1 H), 7.04 - 7.24 (m, 4 H), 7.26 - 7.36 (m, 2 H), 7.38 - 7.68 (m, 4 H), 7.79 - 7.98 (m, 3 H). LC-MS: (ES) *m/z* 596.3 (M+H⁺).

Example S157: Synthesis of *cis*-2-(4-((3,3-dimethylmorpholino)methyl)phenyl)-1-(2-fluoro-6-methylbenzoyl)-*N*-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-*b*]pyridine-3-carboxamide (Compound No. 141)



[0391] Step a) A mixture of 2-[4-(bromomethyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.9 g, 3.03 mmol), 3,3-dimethylmorpholine (523.52 mg, 4.55 mmol) and TEA (1.23 g, 12.12 mmol, 1.69 mL) in THF (12 mL) and DMF (1 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 20 °C for 16 h under a N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with brine (10 mL) and extracted with ethyl acetate (50 mL). The combined organic layers was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=5/1) to give 3,3-dimethyl-4-[[4-(4,4,5,5-tetra methyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]morpholine (585 mg, 1.68 mmol, 55.36% yield, 95% purity) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.12 (s, 6 H), 1.35 (s, 12 H), 2.35 - 2.42 (m, 2 H), 3.40 (s, 2 H), 3.53 (br s, 2 H), 3.60 - 3.65 (m, 2 H), 7.36 (d, *J*=7.83 Hz, 2 H), 7.76 (d, *J*=7.83 Hz, 2 H). LC-MS: (ES) *m/z* 332.3 (M+H⁺).

[0392] Step b) A mixture of methyl 2-chloro-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate (400 mg, 1.87 mmol), 3,3-dimethyl-4-[[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]morpholine (744.34 mg, 2.25 mmol), Pd(PPh₃)₄ (216.38 mg, 187.25 μmol) and K₂CO₃ (2 M, 3.28 mL) in dioxane (10 mL) was degassed and purged with N₂ 3 times, and then the mixture was stirred at 100 °C for 16 h under a N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to remove dioxane and then extracted with EtOAc 160 mL (80 mL x 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, eluent of 0~30 % ethyl acetate/petroleum ether gradient @ 35 mL/min) to give compound methyl 2-[4-[(3,3-dimethylmorpholin-4-

yl)methyl]phenyl]-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate (860 mg, 1.80 mmol, 96.07% yield, 80% purity) as a light yellow gum. ¹H NMR (400 MHz, CDCl₃) δ 1.14 (s, 6 H), 2.37 - 2.44 (m, 2 H), 3.38 - 3.43 (m, 2 H), 3.58 (br s, 2 H), 3.61 - 3.67 (m, 2 H), 3.71 (s, 3 H), 5.14 (t, *J*=1.63 Hz, 2 H), 5.24 (s, 2 H), 7.41 - 7.48 (m, 4 H), 7.97 (s, 1 H). LC-MS: (ES) *m/z* 383.2 (M+H⁺).

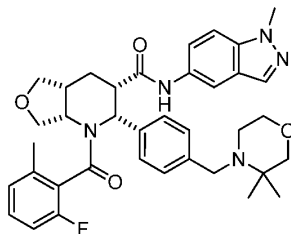
[0393] Step c) To a solution of methyl 2-[4-[(3,3-dimethylmorpholin-4-yl)methyl]phenyl]-5,7-dihydrofuro[3,4-b]pyridine-3-carboxylate (0.8 g, 1.78 mmol) and HCl/dioxane (4 M, 889.00 μL) in MeOH (15 mL) was added PtO₂ (121.12 mg, 533.40 μmol). Then the mixture was degassed and purged with H₂ (15 psi) 3 times, and then the mixture was stirred at 20 °C for 3 h under H₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was alkalinized with aqueous NaHCO₃ 10 mL and extracted with DCM 100 mL (50 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=100/1 to 10/1, plate 2) to give cis-methyl 2-[4-[(3,3-dimethylmorpholin-4-yl)methyl]phenyl]-1,2,3,4,4a,5,7,7a-octahydrofuro[3,4-b]pyridine-3-carboxylate (430 mg, 996.14 μmol, 56.03% yield, 90% purity) as a light yellow gum. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.13 (s, 6 H), 2.14 (dt, *J*=14.07, 4.28 Hz, 1 H), 2.25 - 2.36 (m, 2 H), 2.37 - 2.44 (m, 2 H), 2.91 - 2.99 (m, 1 H), 3.32 - 3.33 (m, 3 H), 3.37 (s, 2 H), 3.48 - 3.54 (m, 3 H), 3.58 - 3.63 (m, 2 H), 3.73 (t, *J*=8.50 Hz, 1 H), 3.78 (dd, *J*=9.51, 1.50 Hz, 1 H), 3.83 - 3.89 (m, 1 H), 3.96 (dd, *J*=9.51, 5.13 Hz, 1 H), 4.05 (d, *J*=5.13 Hz, 1 H), 7.24 - 7.32 (m, 4 H). LC-MS: (ES) *m/z* 389.4 (M+H⁺).

[0394] Step d) To a solution of cis-methyl 2-[4-[(3,3-dimethylmorpholin-4-yl)methyl]phenyl]-1,2,3,4,4a,5,7,7a-octahydrofuro[3,4-b]pyridine-3-carboxylate (400 mg, 1.03 mmol) in DCM (15 mL) was added DIEA (399.20 mg, 3.09 mmol, 538.00 μL), then the 2-fluoro-6-methyl-benzoyl chloride (213.23 mg, 1.24 mmol) in DCM (2 mL) was added at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 0~3% ethyl acetate/petroleum ether gradient @ 30 mL/min) to give cis-methyl 2-[4-[(3,3-dimethylmorpholin-4-yl)methyl]phenyl]-1-(2-fluoro-6-methyl-benzoyl)-3,4,4a,5,7,7a-hexahydro-2H-furo[3,4-b]pyridine-3-carboxylate (280 mg, 97% purity) as a light yellow gum. ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.95 - 1.08 (m, 6 H), 1.24 (s, 1 H), 1.73 - 1.96 (m, 1

H), 2.18 - 2.38 (m, 4 H), 2.58 - 2.86 (m, 1 H), 3.00 - 3.10 (m, 1 H), 3.11 - 3.22 (m, 1 H), 3.27 (br d, $J=7.38$ Hz, 2 H), 3.30 - 3.33 (m, 3 H), 3.36 - 3.40 (m, 1 H), 3.41 - 3.55 (m, 4 H), 3.57 - 3.68 (m, 2 H), 3.69 - 3.90 (m, 1 H), 4.70 - 4.94 (m, 1 H), 6.40 - 6.79 (m, 2 H), 7.06 - 7.21 (m, 3 H), 7.22 - 7.43 (m, 2 H) LC-MS: (ES) m/z 525.3 ($M+H^+$).

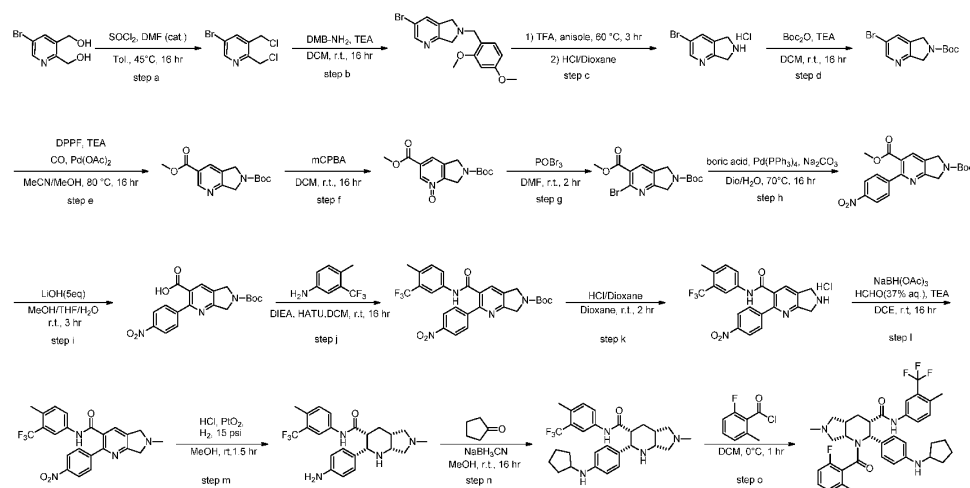
[0395] Step e) To a solution of 4-methyl-3-(trifluoromethyl)aniline (40.06 mg, 228.74 μ mol, 32.84 μ L) in DCE (1.5 mL) was added $Al(CH_3)_3$ (in toluene) (2 M, 133.43 μ L) at 0 °C, after 20 min, the cis-methyl-2-[4-[(3,3-dimethylmorpholin-4-yl)methyl]phenyl]-1-(2-fluoro-6-methyl-benzoyl)-3,4,4a,5,7,7a-hexahydro-2H-furo[3,4-b]pyridine-3-carboxylate (40 mg, 76.25 μ mol) in DCE (1 mL) was added. The mixture was stirred at 85 °C for 3 h 40 min. The reaction mixture was diluted with aqueous $NaHCO_3$ 8 mL and extracted with DCM (30 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (HCl condition; column: Phenomenex Gemini-NX 150 x 30 mm x 5 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 25% - 55%, 7 min) to give cis-2-[4-[(3,3-dimethylmorpholin-4-yl)methyl]phenyl]-1-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-3,4,4a,5,7,7a-hexahydro-2H-furo[3,4-b]pyridine-3-carboxamide (30 mg, 44.93 μ mol, 58.93% yield, 100% purity) as a light yellow solid. 1H NMR (400 MHz, $METHANOL-d_4$) δ 1.26 - 1.37 (m, 2 H), 1.45 - 1.51 (m, 3 H), 1.54 - 1.57 (m, 3 H), 1.99 - 2.10 (m, 1 H), 2.14 - 2.30 (m, 1 H), 2.38 (s, 1 H), 2.40 - 2.47 (m, 3 H), 2.51 - 2.83 (m, 1 H), 2.98 - 3.27 (m, 2 H), 3.33 - 3.47 (m, 1 H), 3.55 - 3.65 (m, 2 H), 3.69 - 3.80 (m, 2 H), 3.83 - 4.14 (m, 4 H), 4.20 - 4.47 (m, 1 H), 4.59 - 4.72 (m, 1 H), 4.93 - 5.13 (m, 1 H), 6.31 - 6.76 (m, 1 H), 6.91 - 6.99 (m, 1 H), 7.01 - 7.16 (m, 1 H), 7.17 - 7.34 (m, 3 H), 7.35 - 7.42 (m, 1 H), 7.48 (br d, $J=6.78$ Hz, 1 H), 7.53 - 7.92 (m, 3 H). LC-MS: (ES) m/z 668.4 ($M+H^+$).

Example S158: Synthesis of (2R,3S,4aR,7aS)-2-(4-((3,3-dimethylmorpholino)methyl)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide (Compound No. 142)



[0396] The title compound was synthesized in similar fashion as Example S143. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.31 - 1.40 (m, 1 H), 1.43 - 1.57 (m, 6 H), 1.97 - 2.34 (m, 3 H), 2.41 - 2.48 (m, 1 H), 2.54 - 2.84 (m, 1 H), 2.88 - 3.15 (m, 1 H), 3.18 - 3.28 (m, 1 H), 3.36 - 3.66 (m, 3 H), 3.68 - 3.80 (m, 2 H), 3.81 - 3.91 (m, 1 H), 3.94 - 4.06 (m, 5 H), 4.07 - 4.32 (m, 2 H), 4.58 - 4.72 (m, 1 H), 4.93 - 5.18 (m, 1 H), 6.32 - 6.77 (m, 1 H), 6.96 - 7.26 (m, 3 H), 7.28 - 7.55 (m, 5 H), 7.63 - 7.99 (m, 3 H). LC-MS: (ES) *m/z* 640.3 (M+H⁺).

Example S159: Synthesis *cis*-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-6-methyl-*N*-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1*H*-pyrrolo[3,4-*b*]pyridine-3-carboxamide (Compound No. 143)



[0397] **Step a)** To a mixture of [5-bromo-2-(hydroxymethyl)-3-pyridyl]methanol (10 g, 45.86 mmol) in toluene (120 mL) was added DMF (670.44 mg, 9.17 mmol, 705.73 μ L) and SOCl₂ (43.65 g, 366.89 mmol, 26.62 mL) at 15 °C. Then the mixture was stirred at 45 °C for 3 h. The mixture was concentrated under vacuum to give the residue. The residue was dissolved with EtOAc (100 mL)/H₂O (50 mL). The mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with saturated NaHCO₃ (3 x 50 mL), brine (2 x 30 mL), dried, filtered and concentrated in vacuo to give the desired compound 5-bromo-2,3-bis(chloromethyl)pyridine (12 g, 44.72 mmol, 97.50% yield, 95% purity) as brown oil. ¹H NMR (400 MHz, CDCl₃) δ 4.71 (s, 2 H), 4.77 (s, 2 H), 7.93 (d, *J*=1.96 Hz, 1 H), 8.61 (d, *J*=2.20 Hz, 1 H). LC-MS: (ES) *m/z* 253.9 (M+H⁺).

[0398] **Step b)** To a solution of 5-bromo-2,3-bis(chloromethyl)pyridine (12 g, 44.72 mmol) and (2,4-dimethoxyphenyl)methanamine (7.85 g, 46.95 mmol, 7.07 mL) in DCM (150

mL) was added DIEA (18.55 g, 143.53 mmol, 25 mL) at 0 °C. Then the mixture was stirred at 25 °C for 16 h. The mixture was diluted with DCM (50 mL) and washed with brine (2 x 50 mL), dried, filtered and concentrated in vacuo to give the residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, eluent of 0~40% ethyl acetate/petroleum ether gradient @ 85 mL/min) to give 3-bromo-6-[(2,4-dimethoxy phenyl)methyl]-5,7-dihydropyrrolo[3,4-b]pyridine (11 g, 29.92 mmol, 66.92% yield, 95% purity) as light brown gum. ¹H NMR (400 MHz, CDCl₃) δ 3.83 (d, *J*=4.27 Hz, 6 H), 3.89 (s, 2 H), 3.97 (s, 4 H), 6.49 (dq, *J*=4.42, 2.29 Hz, 2 H), 7.23 - 7.27 (m, 1 H), 7.58 (d, *J*=2.01 Hz, 1 H), 8.43 (d, *J*=2.01 Hz, 1 H). LC-MS: (ES) *m/z* 351.1 (M+H⁺).

[0399] Step c) To a mixture of 3-bromo-6-[(2,4-dimethoxyphenyl)methyl]-5,7-dihydropyrrolo [3,4-b]pyridine (11 g, 29.92 mmol) in TFA (95.29 g, 835.71 mmol, 61.88 mL) was added anisole (20.52 g, 189.77 mmol, 20.63 mL). Then the mixture was stirred at 60 °C for 2 h. The mixture was concentrated in vacuo to give the residue. HCl/dioxane (4 M, 80 mL) was added the residue and the mixture was stirred at 20 °C for 0.5 h. Then the mixture was concentrated to give the residue. The residue was triturated with EtOAc (50 mL) for 15 min at 20 °C. The suspension was filtered and the filter cake was dried to give the desired compound 3-bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine (7.5 g, 27.03 mmol, 90.31% yield, 98% purity, 2HCl) as light orange solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ 4.57 (s, 2 H), 4.72 (s, 2 H), 8.10 (s, 1 H), 8.66 (s, 1 H). LC-MS: (ES) *m/z* 199.1 (M+H⁺).

[0400] Step d) To a solution of 3-bromo-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine (7.5 g, 27.03 mmol, 2HCl) in DCM (80 mL) was added TEA (13.67 g, 135.13 mmol, 18.81 mL) and Boc₂O (8.85 g, 40.54 mmol, 9.31 mL) at 0 °C. Then the mixture was stirred at 20 °C for 12 h. The mixture was filtered and the filter cake was eluted with DCM (2 x 20 mL). The filtrate was washed with brine (3 x 30 mL), dried, filtered and concentrated in vacuo to give the residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~8% ethyl acetate/petroleum ether gradient @ 40 mL/min) to give tert-butyl 3-bromo-5,7-dihydropyrrolo[3,4-b]pyridine-6-carboxylate (7.8 g, 25.55 mmol, 94.55% yield, 98% purity) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.52 (s, 9 H), 4.55 - 4.74 (m, 4 H), 7.63 - 7.77 (m, 1 H), 8.54 (br s, 1 H). LC-MS: (ES) *m/z* 299.1 (M+H⁺).

[0401] Step e) A mixture of tert-butyl-3-bromo-5,7-dihydropyrrolo[3,4-b]pyridine-6-carboxylate (7.8 g, 25.55 mmol), Pd(OAc)₂ (573.65 mg, 2.56 mmol), DPPF (2.83 g, 5.11 mmol) and TEA (7.76 g, 76.65 mmol, 10.67 mL) in MeCN (80 mL)/MeOH (80 mL) was

stirred at 80 °C for 16 h under CO (50 psi). The mixture was diluted with EtOAc (200 mL) and filtered. The filtrate was washed with brine (3 x 50 mL), dried, filtered and concentrated in vacuo to give the crude product. The crude product was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, eluent of 0~30% ethyl acetate/petroleum ether gradient @ 40 mL/min) to give 6-tert-butyl-3-methyl 5,7-dihydropyrrolo[3,4-b]pyridine-3,6-dicarboxylate (6.6 g, 23.72 mmol, 92.81% yield, 100% purity) as off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.46 (s, 9 H), 3.89 (s, 3 H), 4.53 - 4.72 (m, 4 H), 8.26 (br d, *J*=8.07 Hz, 1 H), 8.96 (s, 1 H). LC-MS: (ES) *m/z* 279.1 (M+H⁺).

[0402] Step f) To a solution of 6-tert-butyl-3-methyl 5,7-dihydropyrrolo[3,4-b]pyridine-3,6-dicarboxylate (6 g, 21.56 mmol) in DCM (120 mL) was added *m*-CPBA (9.30 g, 43.12 mmol, 80% purity) at 0 °C. Then the mixture was stirred at 25 °C for 12 h. The mixture was diluted with DCM (50 mL) and quenched by addition of Na₂S₂O₃ solution (50 mL). After stirring for 10 min, The organic layer separated was washed with saturated NaHCO₃ solution (3 x 50 mL), dried, filtered and concentrated in vacuo to give 6-tert-butyl-3-methyl 1-oxido-5,7-dihydropyrrolo[3,4-b]pyridine-3,6-dicarboxylate (6.1 g, 19.69 mmol, 91.33% yield, 95% purity) as light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 1.52 (s, 9 H), 3.97 (s, 3 H), 4.74 - 4.88 (m, 4 H), 7.68 - 7.80 (m, 1 H), 8.71 (s, 1 H). LC-MS: (ES) *m/z* 295.2 (M+H⁺).

[0403] Step g) To a solution of 6-tert-butyl-3-methyl 1-oxido-5,7-dihydropyrrolo[3,4-b]pyridine-3,6-dicarboxylate (6 g, 19.16 mmol) in DMF (180 mL) was added POBr₃ (8.24 g, 28.75 mmol, 2.92 mL) at 0 °C. Then the mixture was stirred at 25 °C for 2 h. The mixture was diluted with EtOAc (500 mL) and carefully added to a solution of NaHCO₃ solution (10%, 400 mL). The mixture was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried, filtered and concentrated in vacuo to give the residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, eluent of 0~25% ethyl acetate/petroleum ether gradient @ 80 mL/min) to give 6-tert-butyl-3-methyl 2-bromo-5,7-dihydropyrrolo[3,4-b]pyridine-3,6-dicarboxylate (0.7 g, 1.96 mmol, 10.23% yield, 100% purity) as light yellow gum. ¹H NMR (400 MHz, CDCl₃) δ 1.53 (s, 9 H), 3.95 - 4.00 (m, 3 H), 4.62 - 4.77 (m, 4 H), 7.90 - 8.05 (m, 1 H). LC-MS: (ES) *m/z* 357.1 (M+H⁺).

[0404] Step h) To a mixture of 6-tert-butyl-3-methyl 2-bromo-5,7-dihydropyrrolo[3,4-b]pyridine-3,6-dicarboxylate (0.5 g, 1.40 mmol), (4-nitrophenyl)boronic acid (280.39 mg, 1.68 mmol) and Pd(PPh₃)₄ (323.51 mg, 279.96 μmol) in dioxane (16 mL) was added a

solution of Na_2CO_3 (2 M, 2.10 mL) in at 25 °C. Then the mixture was stirred at 70 °C for 12 h. The mixture was diluted with EtOAc (50 mL)/ H_2O (50 mL). The mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (3 x 15 mL), dried, filtered and concentrated in vacuo to give the residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 0~25% ethyl acetate/petroleum ether gradient @ 20 mL/min) to give 6-tert-butyl-3-methyl 2-(4-nitrophenyl)-5,7-dihydropyrrolo[3,4-b]pyridine-3,6-dicarboxylate (0.42 g, 1.05 mmol, 70.00% yield) as yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 1.54 (d, $J=5.02$ Hz, 9 H), 3.74 (d, $J=4.77$ Hz, 3 H), 4.72 - 4.87 (m, 4 H), 7.62 - 7.69 (m, 2 H), 8.06 - 8.17 (m, 1 H), 8.31 (d, $J=8.78$ Hz, 2 H). LC-MS: (ES) m/z 400.1 ($\text{M}+\text{H}^+$).

[0405] Step i) To a mixture of 6-tert-butyl 3-methyl 2-(4-nitrophenyl)-5,7-dihydropyrrolo[3,4-b] pyridine-3,6-dicarboxylate (0.23 g, 575.87 μmol) in MeOH (5 mL) / THF (2 mL) was added a solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ (120.83 mg, 2.88 mmol, 413.12 μL) in H_2O (0.5 mL) at 25 °C. Then the mixture was stirred at 25 °C for 3 h. The mixture was concentrated in vacuo to give the residue. The residue was diluted with MTBE (30 mL) and acidified to pH=4~5 by addition of citric acid aqueous solution. The mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give the target compound 6-tert-butoxycarbonyl-2-(4-nitrophenyl)-5,7-dihydropyrrolo[3,4-b]pyridine-3-carboxylic acid (220 mg, 570.88 μmol , 99.13% yield) as off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 1.48 (d, $J=4.27$ Hz, 9 H), 4.66 (br d, $J=11.29$ Hz, 2 H), 4.72 (br d, $J=12.30$ Hz, 2 H), 7.77 (dd, $J=8.78$, 2.01 Hz, 2 H), 8.23 (d, $J=9.03$ Hz, 1 H), 8.30 (d, $J=8.53$ Hz, 2 H). LC-MS: (ES) m/z 386.1 ($\text{M}+\text{H}^+$).

[0406] Step j) To a mixture of 6-tert-butoxycarbonyl-2-(4-nitrophenyl)-5,7-dihydropyrrolo[3,4-b] pyridine-3-carboxylic acid (200 mg, 518.98 μmol , 31.27 μL), HATU (236.80 mg, 622.78 μmol) in DCM (5 mL) was added successively with DIEA (134.15 mg, 1.04 mmol, 180.79 μL), 4-methyl-3-(trifluoromethyl)aniline (109.08 mg, 622.78 μmol , 89.41 μL). Then the mixture was stirred at 25 °C for 12 h. The reaction mixture was diluted with DCM (30 mL) and washed with H_2O (2 x 10 mL). The organic layer was dried, filtered and concentrated in vacuo to give the residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluent of 0~35% ethyl acetate/petroleum ether gradient @ 20 mL/min) to give tert-butyl 3-[[4-methyl-3-(trifluoromethyl)phenyl]carbonyl]-2-(4-nitrophenyl)-5,7-dihydropyrrolo[3,4-b]pyridine-6-carboxylate (0.3 g, 497.69 μmol , 95.90% yield, 90% purity) as light yellow solid. ^1H NMR

(400 MHz, CDCl_3) δ 1.54 (d, $J=5.77$ Hz, 9 H), 2.44 (s, 3 H), 2.79 (s, 7 H), 4.77 (br d, $J=15.06$ Hz, 4 H), 7.24 (br d, $J=8.28$ Hz, 1 H), 7.47 (br dd, $J=19.95$, 7.65 Hz, 1 H), 7.56 (br s, 1 H), 7.87 - 7.98 (m, 3 H), 8.29 (d, $J=8.78$ Hz, 2 H). LC-MS: (ES) m/z 543.2 ($\text{M}+\text{H}^+$).

[0407] Step k) To a mixture of tert-butyl 3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-(4-nitrophenyl)-5,7-dihydropyrrolo[3,4-b]pyridine-6-carboxylate (0.3 g, 497.69 μmol) in Dioxane (3 mL) was added HCl/dioxane (4 M, 1.87 mL). Then the mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated in vacuo to give the desired compound N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-nitrophenyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxamide (0.22 g, 450.24 μmol , 90.47% yield, 98% purity, HCl) as light brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.38 (d, $J=1.00$ Hz, 3 H), 4.64 (br s, 2 H), 4.70 (br s, 2 H), 7.39 (d, $J=8.53$ Hz, 1 H), 7.62 - 7.68 (m, 1 H), 7.86 - 7.90 (m, 2 H), 7.91 (d, $J=2.01$ Hz, 1 H), 8.20 (s, 1 H), 8.30 (d, $J=9.03$ Hz, 2 H), 10.23 (br s, 2 H), 10.91 (s, 1 H). LC-MS: (ES) m/z 443.1 ($\text{M}+\text{H}^+$).

[0408] Step l) To a solution of N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-nitrophenyl)-6,7-dihydro-5H-pyrrolo[3,4-b]pyridine-3-carboxamide (110 mg, 229.72 μmol , HCl) and HCHO (in H_2O) (55.93 mg, 689.15 μmol , 51.31 μL) in DCE (5 mL) was added successively TEA (46.49 mg, 459.43 μmol , 63.95 μL) and $\text{NaBH}(\text{OAc})_3$ (146.06 mg, 689.15 μmol). Then the mixture was stirred at 25 °C for 12 h. The mixture was diluted with DCM (30 mL) and alkalified to pH=8~9 and extracted with DCM (3 x 20 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give the desired compound 6-methyl-N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-nitrophenyl)-5,7-dihydropyrrolo[3,4-b]pyridine-3-carboxamide (110 mg, 216.91 μmol , 94.42% yield, 90% purity) as light brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 2.38 (d, $J=1.25$ Hz, 3 H), 2.56 (s, 3 H), 3.96 (s, 2 H), 3.99 (s, 2 H), 7.38 (d, $J=8.28$ Hz, 1 H), 7.65 (br d, $J=8.03$ Hz, 1 H), 7.84 - 7.89 (m, 2 H), 7.91 (d, $J=2.01$ Hz, 1 H), 8.00 (s, 1 H), 8.25 - 8.30 (m, 2 H), 10.73 (s, 1 H). LC-MS: (ES) m/z 457.1 ($\text{M}+\text{H}^+$).

[0409] Step m) To a solution of 6-methyl-N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-nitrophenyl)-5,7-dihydropyrrolo[3,4-b]pyridine-3-carboxamide (110 mg, 216.91 μmol) in MeOH (8 mL) was added successively with HCl/dioxane (4 M, 108.45 μL) and PtO_2 (24.63 mg, 108.45 μmol) under N_2 . The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25 °C for 1.5 h. The mixture was diluted with MeOH (30 mL) and filtered through a pad of Celite and the filtrate was concentrated in vacuo to give the residue. The residue was diluted with DCM (50 mL) and

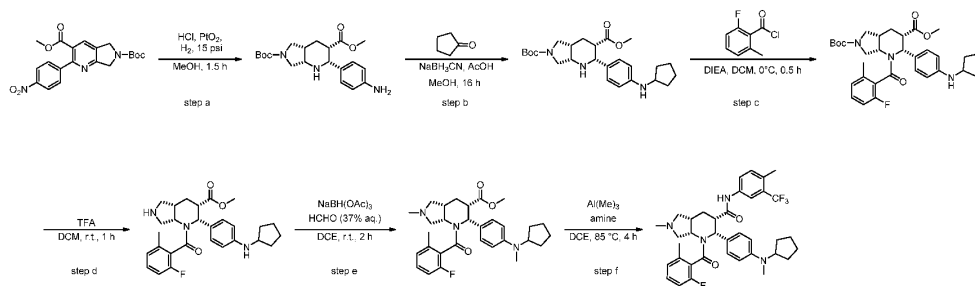
alkalified to pH=9~10 by saturated NaHCO₃ solution. The organic layers separated was dried, filtered and concentrated in vacuo to give the desired compound cis-2-(4-aminophenyl)-6-methyl-N-[4-methyl-3-(trifluoro methyl)phenyl]-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3-carboxamide (100 mg, crude) as light brown gum. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.35 (br s, 4 H), 2.90 (br s, 3 H), 3.91 - 4.19 (m, 2 H), 4.60 (br s, 1 H), 6.57 (br d, *J*=6.78 Hz, 2 H), 7.18 (br d, *J*=7.78 Hz, 2 H), 7.32 (br d, *J*=7.28 Hz, 1 H), 7.40 - 7.55 (m, 1 H), 7.81 - 7.93 (m, 1 H). LC-MS: (ES) *m/z* 433.1 (M+H⁺).

[0410] Step n) To a mixture of cis-2-(4-aminophenyl)-6-methyl-N-[4-methyl-3-(trifluoro-methyl)phenyl]-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3-carboxamide (90 mg, 166.48 μmol) in MeOH (4.5 mL) was added cyclopentanone (16.80 mg, 199.78 μmol, 17.69 μL), HOAc (15.00 mg, 249.72 μmol, 14.28 μL) and NaBH₃CN (31.39 mg, 499.44 μmol) in one portion at 0 °C under N₂. The mixture was stirred at 25 °C for 16 h. The mixture was diluted with DCM (30 mL) and alkalified to pH=8~9 by saturated NaHCO₃ solution and extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine, dried, filtered and concentrated in vacuo to give the crude product. The crude product was purified by silica gel column chromatography (eluted with DCM/MeOH/NH₃·H₂O from 100/1/0.1 to 20/1/0.02) to give cis-2-[4-(cyclopentylamino)phenyl]-6-methyl-N-[4-methyl-3-(trifluoromethyl)phenyl]-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3-carboxamide (60 mg, 113.86 μmol, 68.39% yield, 95% purity) as light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.28 - 1.39 (m, 2 H), 1.40 - 1.55 (m, 3 H), 1.56 - 1.66 (m, 2 H), 1.77 - 1.89 (m, 2 H), 1.92 - 1.99 (m, 1 H), 2.00 - 2.08 (m, 1 H), 2.26 (s, 3 H), 2.34 - 2.37 (m, 3 H), 2.57 - 2.69 (m, 3 H), 2.73 - 2.80 (m, 1 H), 3.52 - 3.65 (m, 1 H), 3.80 (br d, *J*=4.52 Hz, 1 H), 5.35 (d, *J*=6.53 Hz, 1 H), 6.40 (d, *J*=8.53 Hz, 2 H), 6.99 - 7.04 (m, 2 H), 7.28 (d, *J*=8.53 Hz, 1 H), 7.58 (br d, *J*=8.03 Hz, 1 H), 7.76 (s, 1 H), 11.29 (br s, 1 H). LC-MS: (ES) *m/z* 501.2 (M+H⁺).

[0411] Step o) To a solution of cis-2-[4-(cyclopentylamino)phenyl]-6-methyl-N-[4-methyl-3-(trifluoromethyl)phenyl]-2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3-carboxamide (60 mg, 119.86 μmol) and DIEA (30.98 mg, 239.71 μmol, 41.75 μL) in DCM (5 mL) was added dropwise of a solution of 2-fluoro-6-methyl-benzoyl chloride (20.69 mg, 119.86 μmol) in DCM (3 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min. The mixture was diluted with DCM (30 mL), washed with H₂O (2 x 10 mL), dried, filtered and concentrated in vacuo to give the crude product. The crude product was purified by prep-HPLC (column: Phenomenex Gemini-NX 150 x 30 mm x 5 μm; mobile phase: [water (0.05%

HCl)-ACN]; B%: 21%-41%, 9 min) to give cis-2-[4-(cyclopentyl-amino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-6-methyl-N-[4-methyl-3-(trifluoromethyl)phenyl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b]pyridine-3-carboxamide (20 mg, 29.12 μ mol, 24.29% yield, 98% purity, HCl) as light yellow solid. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.44 (br s, 1 H), 1.67 (br s, 5 H), 1.76 - 2.06 (m, 5 H), 2.22 - 2.55 (m, 6 H), 2.62 - 2.99 (m, 3 H), 3.02 - 3.25 (m, 3 H), 3.62 (br s, 1 H), 3.77 - 4.23 (m, 3 H), 5.24 (br s, 1 H), 6.32 - 6.81 (m, 1 H), 6.98 (br s, 1 H), 7.05 - 7.34 (m, 5 H), 7.35 - 7.81 (m, 3 H), 7.87 (br s, 1 H), 9.93 - 10.44 (m, 1 H). LC-MS: (ES) m/z 637.23(M+H $^+$).

Example S160: Synthesis of cis-2-(4-(cyclopentyl(methyl)amino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-6-methyl-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide (Compound No. 144)



[0412] Step a) To a solution of 6-tert-butyl-3-methyl-2-(4-nitrophenyl)-5H-pyrrolo[3,4-b]pyridine-3,6(7H)-dicarboxylate (500 mg, 1.25 mmol) in MeOH (25 mL) was added successively with HCl/dioxane (4 M, 625.94 μ L) and PtO₂ (142.14 mg, 625.94 μ mol) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 25°C for 1.5 hours. The mixture was diluted with MeOH and filtered through a pad of Celite and the filtrate was concentrated in vacuo to give the residue. The residue was diluted with DCM (50 mL) and alkalified to pH=9~10 by addition of saturated NaHCO₃ aqueous solution. The organic layer separated was dried, filtered and concentrated in vacuo to give the crude product. The crude product was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluent of 0~10% MeOH/DCM gradient @ 20 mL/min) to give cis-6-tert-butyl 3-methyl 2-(4-aminophenyl)-1,2,3,4,4a,5,7,7a-octahydropyrrolo [3,4-b]pyridine-3,6-dicarboxylate (0.2 g, 511.37 μ mol, 40.85% yield, 96% purity) as light brown gum. ^1H NMR (400 MHz, CDCl₃) δ 1.47 (s, 9 H), 2.23 (br dd, J =13.45, 3.67 Hz, 3 H), 2.89 (br d, J =4.16 Hz, 1 H), 3.37 - 3.51 (m,

6 H), 3.54 - 3.66 (m, 2 H), 3.90 (br d, $J=4.40$ Hz, 1 H), 6.64 (d, $J=8.31$ Hz, 2 H), 7.03 - 7.15 (m, 2 H). LC-MS: (ES) m/z 376.3 ($M+H^+$).

[0413] Step b) To a mixture of cis-6-tert-butyl 3-methyl-2-(4-aminophenyl)-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3,6-dicarboxylate (200 mg, 532.68 μ mol) in MeOH (8 mL) was added cyclopentanone (53.77 mg, 639.21 μ mol, 56.60 μ L), HOAc (47.98 mg, 799.02 μ mol, 45.70 μ L) and $NaBH_3CN$ (100.42 mg, 1.60 mmol) in one portion at 0 °C. The mixture was stirred at 25 °C for 16 h. The mixture was diluted with DCM (30 mL) and alkalified to pH=8~9 and extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine, dried, filtered and concentrated in vacuo to give the desired compound cis-6-tert-butyl-3-methyl 2-[4-(cyclopentyl-amino)phenyl]-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3,6-dicarboxylate (0.23 g, 492.59 μ mol, 92.47% yield, 95% purity) as light yellow gum. 1H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 1.71 (br d, $J=7.09$ Hz, 2 H), 1.94 - 2.02 (m, 4 H), 2.12 - 2.28 (m, 5 H), 2.89 (br d, $J=4.40$ Hz, 1 H), 3.36 - 3.53 (m, 7 H), 3.55 - 3.65 (m, 1 H), 3.72 - 3.82 (m, 1 H), 3.89 (br d, $J=4.89$ Hz, 1 H), 6.55 (d, $J=8.31$ Hz, 2 H), 7.08 - 7.16 (m, 2 H). LC-MS: (ES) m/z 444.3 ($M+H^+$).

[0414] Step c) To a solution of cis-6-tert-butyl-3-methyl 2-[4-(cyclopentylamino)phenyl]-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3,6-dicarboxylate (0.23 g, 492.59 μ mol) and DIEA (127.32 mg, 985.17 μ mol, 171.60 μ L) in DCM (10 mL) was added dropwise of a solution of 2-fluoro-6-methyl-benzoyl chloride (80.76 mg, 467.96 μ mol) in DCM (5 mL) at 0 °C. The mixture was stirred at 0 °C for 20 min. The mixture was diluted with DCM (30 mL), washed with H_2O (2 x 10 mL), dried, filtered and concentrated in vacuo to give the crude product. The crude product was purified by prep-HPLC (column: YMC Triart C18 150 x 25 mm x 5 μ m; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 63%-93%, 9.5 min) to give cis-6-tert-butyl-3-methyl-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b]pyridine-3,6-dicarboxylate (0.16 g, 220.80 μ mol, 32.00% yield, 80% purity) as off-white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 1.13 - 1.37 (m, 9 H), 1.38 - 1.45 (m, 2 H), 1.49 - 1.69 (m, 3 H), 1.80 - 1.93 (m, 2 H), 2.16 - 2.36 (m, 4 H), 2.95 - 3.26 (m, 2 H), 3.58 - 3.70 (m, 3 H), 3.88 - 4.01 (m, 1 H), 5.63 (br s, 1 H), 6.40 - 6.53 (m, 2 H), 6.94 (d, $J=8.56$ Hz, 1 H), 7.09 - 7.22 (m, 2 H), 7.30 - 7.43 (m, 1 H). LC-MS: (ES) m/z 480.2 ($M+H^+$).

[0415] Step d) To a solution of cis-6-tert-butyl-3-methyl-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b]pyridine-3,6-dicarboxylate (160.00 mg, 220.80 μ mol) in DCM (4 mL) was added TFA (616.08 mg, 5.40

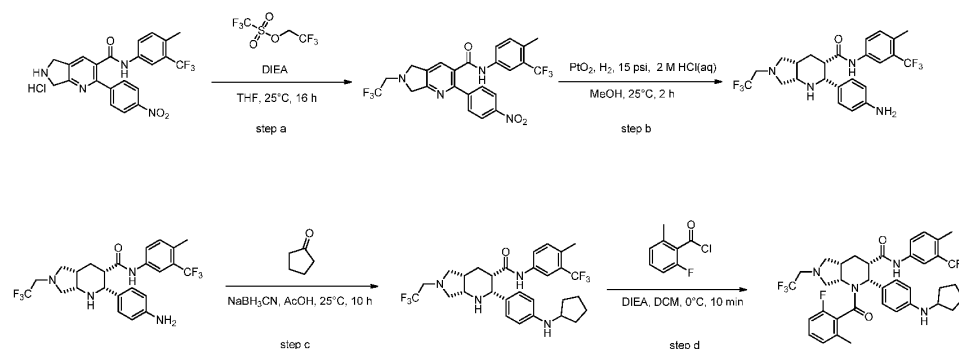
mmol, 400.05 μL). Then the mixture was stirred at 25 °C for 1 h. The mixture was concentrated in vacuo to give the residue. The residue was dissolved in DCM (30 mL) and alkalified to pH=8~9. The organic layer separated was dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo to give cis-methyl 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydropyrrolo-[3,4-b]pyridine-3-carboxylate (120 mg, 200.17 μmol , 90.66% yield, 80% purity) as light yellow gum. LC-MS: (ES) m/z 480.2 ($\text{M}+\text{H}^+$).

[0416] Step e) To a solution of cis-methyl-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-2,3,4,4a,5,6,7,7a-octahydropyrrolo[3,4-b]pyridine-3-carboxylate (110 mg, 229.37 μmol) and HCHO (in H_2O) (11.17 mg, 137.62 μmol , 10.25 μL) in DCE (4 mL) was added $\text{NaBH}(\text{OAc})_3$ (145.84 mg, 688.10 μmol). Then the mixture was stirred at 25 °C for 1 h. The mixture was diluted with DCM (30 mL) and alkalified to pH=8~9 and extracted with DCM (3 x 10 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give the crude product. The crude product was purified by prep-HPLC (column: Phenomenex Gemini-NX 150 x 30 mm x 5 μm ; mobile phase: [water (0.1%TFA)-ACN]; B%: 6%-36%, 10 min). The eluent was alkalified to pH=8~9 and extracted with DCM (3 x 20 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give cis-methyl 2-[4-[cyclopentyl(methyl)amino]phenyl]-1-(2-fluoro-6-methyl-benzoyl)-6-methyl-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b]pyridine-3-carboxylate (60 mg, 117.01 μmol , 51.02% yield, 99% purity) as white solid. LC-MS: (ES) m/z 508.3 ($\text{M}+\text{H}^+$).

[0417] Step f) To a solution of 4-methyl-3-(trifluoromethyl)aniline (51.75 mg, 295.49 μmol , 42.42 μL) in DCE (1 mL) was added $\text{Al}(\text{CH}_3)_3$ (in toluene) (2 M, 177.29 μL) at 0 °C. After stirring for 30 min at 25 °C, a solution of cis-methyl 2-[4-[cyclopentyl(methyl)amino]phenyl]-1-(2-fluoro-6-methyl-benzoyl)-6-methyl-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b]pyridine-3-carboxylate (60 mg, 118.19 μmol) in DCE (1 mL) was added. The mixture was stirred at 85 °C for 3 h 30 min. The mixture was diluted with DCM (30 mL), and quenched by addition of saturated NaHCO_3 solution (10 mL). After stirring for 15 min at RT, the mixture was extracted with DCM (3 x 10 mL). The combined organic layers were dried, filtered and concentrated in vacuo to give the crude product. The crude was purified by prep-HPLC (column: Phenomenex Gemini-NX 150 x 30 mm x 5 μm ; mobile phase: [water (0.05%HCl)-ACN]; B%: 13%-53%, 10 min) to give target compound cis-2-[4-[cyclopentyl(methyl)amino]phenyl]-1-(2-fluoro-6-methyl-benzoyl)-6-methyl-N-[4-methyl-3-(trifluoromethyl)phenyl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b]pyridine-3-

carboxamide (42 mg, 59.89 μmol , 50.67% yield, 98% purity, HCl) as white solid. ^1H NMR (400 MHz, METHANOL- d_4) δ 1.44 - 1.53 (m, 1 H), 1.61 - 2.06 (m, 7 H), 2.08 - 2.32 (m, 2 H), 2.33 - 2.47 (m, 5 H), 2.49 (s, 1 H), 2.73 - 2.80 (m, 1 H), 2.82 - 2.93 (m, 1 H), 3.01 (br d, $J=8.28$ Hz, 1 H), 3.12 (s, 1 H), 3.18 - 3.23 (m, 2 H), 3.25 (br d, $J=2.76$ Hz, 1 H), 3.31 (s, 2 H), 3.50 - 3.74 (m, 1 H), 3.84 - 4.01 (m, 1 H), 4.03 - 4.24 (m, 2 H), 5.28 (br d, $J=7.03$ Hz, 1 H), 6.43 - 6.63 (m, 0.5 H), 6.68 - 6.78 (m, 0.5 H), 7.06 (br t, $J=8.41$ Hz, 1 H), 7.12 - 7.19 (m, 1 H), 7.22 - 7.36 (m, 3 H), 7.37 - 7.54 (m, 2 H), 7.54 - 7.64 (m, 1 H), 7.65 - 7.73 (m, 1 H), 7.84 - 8.01 (m, 1 H). LC-MS: (ES) m/z 651.4 ($\text{M}+\text{H}^+$).

Example S161: Synthesis of (2R,3S,4aS,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-(2,2,2-trifluoroethyl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide (Compound No. 145)



[0418] Step a) To a mixture of N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-nitrophenyl)-6-(2,2,2-trifluoroethyl)-5,7-dihydropyrrolo[3,4-b]pyridine-3-carboxamide (120 mg, 232.87 μmol , 2HCl) in THF (5 mL) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (108.10 mg, 465.74 μmol) and DIEA (60.19 mg, 465.74 μmol , 81.12 μL) at 25°C under N_2 . The mixture was stirred at 25°C for 16 h. Then concentrated to get a residue. The residue was purified by prep-TLC (SiO_2 , petroleum ether/ethyl acetate=1/1). N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-nitrophenyl)-6-(2,2,2-trifluoroethyl)-5,7-dihydropyrrolo[3,4-b]pyridine-3-carboxamide (120 mg, 228.83 μmol , 98.26% yield) was obtained as a white solid. LC-MS: (ES) m/z 525.1 ($\text{M}+\text{H}^+$). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.48 - 1.74 (m, 22 H), 2.45 (br s, 3 H), 3.35 - 3.62 (m, 2 H), 4.36 (br s, 4 H), 7.13 (br s, 1 H), 7.39 (br s, 1 H), 7.52 (br s, 1 H), 7.92 (br s, 3 H), 8.24 - 8.40 (m, 2 H).

[0419] Step b) To a solution of N-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-nitrophenyl)-6-(2,2,2-trifluoroethyl)-5,7-dihydropyrrolo[3,4-b]pyridine-3-carboxamide (120

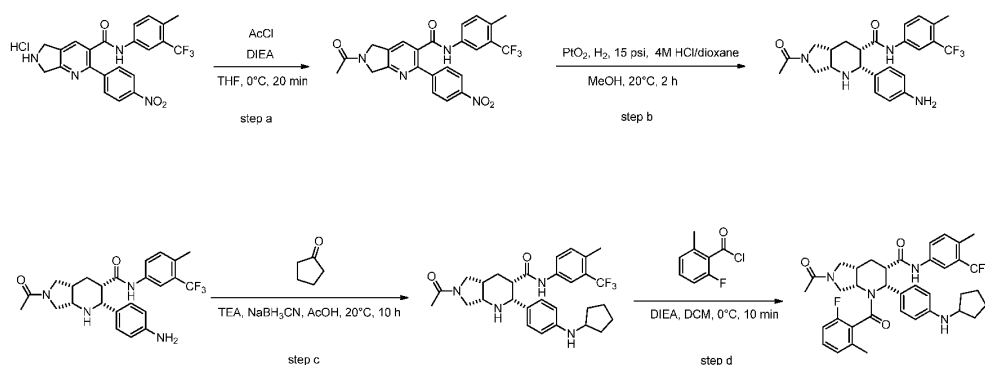
mg, 228.83 μmol), PtO_2 (25.98 mg, 114.41 μmol) in MeOH (5 mL) was added HCl(aq) (2 M, 228.83 μL) under N_2 . The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 20 °C for 2 h. The mixture was filtered and concentrated under reduced pressure to give the residue. The residue was purified by prep-TLC (SiO_2 , DCM:MeOH = 10:1). 2-(4-aminophenyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-6-(2,2,2-trifluoroethyl)-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3-carboxamide (45 mg, 84.52 μmol , 36.94% yield, 94% purity) was obtained as a light yellow oil. LC-MS: (ES) m/z 501.2 ($\text{M}+\text{H}^+$).

[0420] Step c) To a mixture of 2-(4-aminophenyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-6-(2,2,2-trifluoroethyl)-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3-carboxamide (45 mg, 89.91 μmol) and cyclopentanone (9.08 mg, 107.90 μmol , 9.55 μL) in MeOH (2 mL) was added NaBH_3CN (16.95 mg, 269.74 μmol) at 20°C under N_2 . Then AcOH (10.80 mg, 179.83 μmol , 10.28 μL) was added to the mixture, the mixture was stirred at 20°C for 10 h. The reaction mixture was partitioned between saturated NaHCO_3 (aq) (20 mL) and DCM (20 mL). The organic phase was separated, dried filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2 , DCM:MeOH = 10:1). 2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-6-(2,2,2-trifluoroethyl)-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3-carboxamide (25 mg, 43.97 μmol , 48.90% yield, 100% purity) was obtained as a light yellow oil. LC-MS: (ES) m/z 567.3 ($\text{M}+\text{H}^+$).

[0421] Step d) To a mixture of 2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoro-methyl)phenyl]-6-(2,2,2-trifluoroethyl)-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3-carboxamide (25 mg, 43.97 μmol), DIEA (11.36 mg, 87.94 μmol , 15.32 μL) in DCM (1 mL) was added 2-fluoro-6-methyl-benzoyl chloride (7.59 mg, 43.97 μmol) at 0°C under N_2 . The mixture was stirred at 0°C for 10 min, then concentrated to get a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 150 * 30 mm * 5 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 36%-66%, 7 min). 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-6-(2,2,2-trifluoroethyl)-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b]pyridine-3-carboxamide (3 mg, 4.05 μmol , 9.21% yield, 100% purity, HCl) was obtained as a light yellow solid. LC-MS: (ES) m/z 705.3 ($\text{M}+\text{H}^+$). ^1H NMR (400 MHz, METHANOL- d_4) δ ppm 1.28 - 1.48 (m, 5 H), 1.52 (br d, $J=3.76$ Hz, 1 H), 1.87 - 2.08 (m, 2 H), 2.21 - 2.34 (m, 4 H), 2.37 - 2.56 (m, 1 H), 2.37 - 2.56 (m, 4 H), 2.84 - 2.98 (m, 2 H), 3.09 (br d, $J=2.76$ Hz, 2

H), 3.19 (br d, $J=10.29$ Hz, 1 H), 3.26 - 3.31 (m, 1 H), 3.43 - 3.54 (m, 1 H), 3.90 - 4.05 (m, 1 H), 4.64 (d, $J=3.51$ Hz, 1 H), 6.31 - 6.44 (m, 1 H), 6.47 - 6.58 (m, 1 H), 6.65 - 6.79 (m, 1 H), 7.25 - 7.38 (m, 3 H), 7.39 - 7.57 (m, 3 H), 7.83 - 7.94 (m, 1 H).

Example S162: Synthesis of (2*R*,3*S*,4*aS*,7*aS*)-6-acetyl-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-*N*-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1*H*-pyrrolo[3,4-*b*]pyridine-3-carboxamide (Compound No. 146)



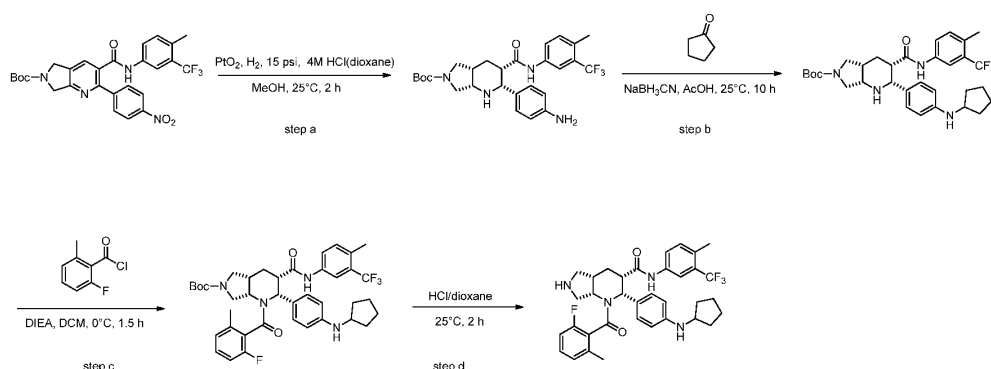
[0422] Step a) To a mixture of *N*-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-nitrophenyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridine-3-carboxamide (100 mg, 194.06 μ mol, 2HCl), TEA (58.91 mg, 582.17 μ mol, 81.03 μ L) in DCM (1 mL) was added acetyl chloride (30.47 mg, 291.09 μ mol, 27.70 μ L) at 0°C under N₂. The mixture was stirred at 0°C for 20 min. The reaction mixture was concentrated under reduced pressure to give the residue. The residue was purified by prep-TLC (SiO₂, DCM: MeOH = 10:1). 6-acetyl-*N*-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-nitrophenyl)-5,7-dihydropyrrolo[3,4-*b*]pyridine-3-carboxamide (85 mg, 175.47 μ mol, 90.42% yield, 100% purity) was obtained as a light yellow gum. LC-MS: (ES) m/z 485.1 (M+H⁺).

[0423] Step b) To a solution of 6-acetyl-*N*-[4-methyl-3-(trifluoromethyl)phenyl]-2-(4-nitrophenyl)-5,7-dihydropyrrolo[3,4-*b*]pyridine-3-carboxamide (85 mg, 175.47 μ mol), PtO₂ (19.92 mg, 87.73 μ mol) in MeOH (5 mL) was added HCl/dioxane (4 M, 87.73 μ L) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 20°C for 2 h. The desired product was detected. The mixture was filtered and concentrated under reduced pressure to give the desired product. 6-acetyl-2-(4-aminophenyl)-*N*-[4-methyl-3-(trifluoromethyl)phenyl]-1,2,3,4,4*a*,5,7,7*a*-octahydropyrrolo[3,4-*b*]pyridine-3-carboxamide (80 mg, crude) was obtained as a light yellow oil. LC-MS: (ES) m/z 461.2 (M+H⁺).

[0424] Step c) To a mixture of 6-acetyl-2-(4-aminophenyl)-N-[4-methyl-3-(trifluoromethyl)-phenyl]-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3-carboxamide (80 mg, 160.98 μmol , HCl) and cyclopentanone (14.90 mg, 177.08 μmol , 15.68 μL) in MeOH (2 mL) was added TEA (32.58 mg, 321.96 μmol , 44.81 μL) and AcOH (19.33 mg, 321.96 μmol , 18.41 μL) at 20°C under N_2 . Then NaBH_3CN (30.35 mg, 482.94 μmol) was added to the mixture and the mixture was stirred at 20°C for 10 h. The reaction mixture was partitioned between saturated NaHCO_3 (aq) (20 mL) and DCM (20 mL). The organic phase was separated, dried filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2 , DCM: MeOH = 10:1, plate 1). 6-acetyl-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3-carboxamide (20 mg, crude) was obtained as a light yellow oil. LC-MS: (ES) m/z 529.3 ($\text{M}+\text{H}^+$).

Step d) To a mixture of 6-acetyl-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-3-carboxamide (20 mg, 37.84 μmol), DIEA (9.78 mg, 75.67 μmol , 13.18 μL) in DCM (1 mL) was added 2-fluoro-6-methyl-benzoyl chloride (6.53 mg, 37.84 μmol) at 0°C under N_2 . The mixture was stirred at 0°C for 10 min, then concentrated to get a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX 150 * 30 mm * 5 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 25%-55%, 7 min). 6-acetyl-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b]pyridine-3-carboxamide (3 mg, 4.15 μmol , 10.97% yield, 97% purity, HCl) was obtained as a light yellow solid. LC-MS: (ES) m/z 665.3 ($\text{M}+\text{H}^+$). ^1H NMR (400 MHz, $\text{METHANOL}-d_4$) δ ppm 1.26 - 1.61 (m, 6 H), 1.90 - 2.05 (m, 2 H), 2.07 - 2.22 (m, 3 H), 2.26 (d, $J=16.06$ Hz, 3 H), 2.30 - 2.39 (m, 1 H), 2.39 - 2.50 (m, 4 H), 2.51 - 2.65 (m, 1 H), 2.91 - 3.20 (m, 2 H), 3.66 - 3.83 (m, 2 H), 3.89 - 4.04 (m, 2 H), 4.05 - 4.21 (m, 1 H), 4.69 (br s, 1 H), 6.26 - 6.60 (m, 1 H), 6.72 (br s, 1 H), 7.26 - 7.39 (m, 3 H), 7.40 - 7.56 (m, 3 H), 7.58 - 8.09 (m, 2 H).

Example S163: Synthesis of (2R,3S,4aS,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide (Compound No. 39)



[0425] Step a) To a solution of tert-butyl 3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-2-(4-nitrophenyl)-5,7-dihydropyrrolo[3,4-b]pyridine-6-carboxylate (50 mg, 92.17 μmol), PtO_2 (10.46 mg, 46.08 μmol) in MeOH (5 mL) was added HCl/dioxane (4 M, 46.08 μL) under N_2 . The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 20°C for 2 h. The mixture was filtered and concentrated under reduced pressure to give the residue. The residue was purified by column chromatography (SiO_2 , Dichloromethane : Methanol=1/0 to 10/1). Tert-butyl 2-(4-aminophenyl)-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-6-carboxylate (100 mg, crude) was obtained as a light yellow oil. LC-MS: (ES) m/z 519.3 ($\text{M}+\text{H}^+$).

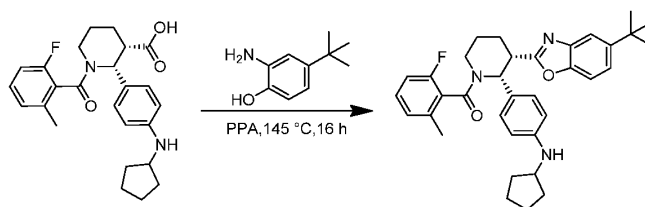
[0426] Step b) To a mixture of tert-butyl 2-(4-aminophenyl)-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-6-carboxylate (40 mg, 77.14 μmol) and cyclopentanone (7.14 mg, 84.85 μmol , 7.51 μL) in MeOH (2 mL) was added NaBH_3CN (14.54 mg, 231.41 μmol) at 20°C under N_2 . Then AcOH (9.26 mg, 154.27 μmol , 8.82 μL) was added to the mixture and the mixture was stirred at 20°C for 10 h. The reaction mixture was partitioned between saturated NaHCO_3 (aq) (20 ml) and DCM (20 mL). The organic phase was separated, dried filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2 , EtOAc: MeOH = 50:1). Tert-butyl 2-[4-(cyclopentylamino)phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-6-carboxylate (25 mg, crude) was obtained as a light yellow oil. LC-MS: (ES) m/z 587.3 ($\text{M}+\text{H}^+$).

[0427] Step c) To a mixture of tert-butyl 2-[4-(cyclopentylamino)phenyl]-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-1,2,3,4,4a,5,7,7a-octahydropyrrolo[3,4-b]pyridine-6-

carboxylate (25 mg, 42.61 μmol), DIEA (11.01 mg, 85.22 μmol , 14.84 μL) in DCM (1 mL) was added 2-fluoro-6-methyl-benzoyl chloride (7.35 mg, 42.61 μmol) at 0 °C under N_2 . The mixture was stirred at 0 °C for 1.5 h. Then the mixture was concentrated to get a crude product. The crude was purified by prep-HPLC (column: Venusil ASB Phenyl 150 * 30 mm * 5 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 25%-55%, 12.5 min). Tert-butyl 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b]pyridine-6-carboxylate (15 mg, 19.76 μmol , 17.85% yield, HCl) was obtained as a light yellow solid. LC-MS: (ES) m/z 723.4 ($\text{M}+\text{H}^+$).

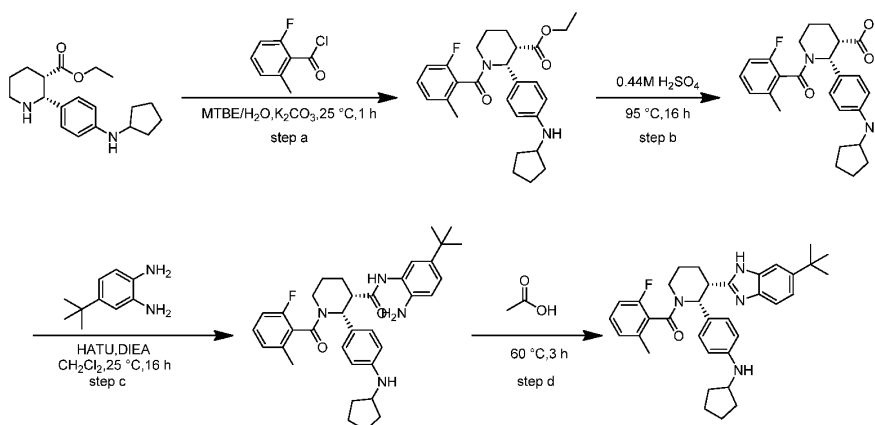
[0428] Step d) Tert-butyl 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-3-[[4-methyl-3-(trifluoromethyl)phenyl]carbamoyl]-3,4,4a,5,7,7a-hexahydro-2H-pyrrolo[3,4-b]pyridine-6-carboxylate (15 mg, 20.75 μmol) in HCl/dioxane (4 M, 15.00 mL) was stirred at 20 °C for 2 h. Then the mixture was concentrated to get a crude product and purified by prep-HPLC (column: Venusil ASB Phenyl 150 * 30 mm * 5 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 25%-55%, 12 min). 2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-2,3,4,4a,5,6,7,7a-octahydropyrrolo[3,4-b]pyridine-3-carboxamide (7 mg, 10.62 μmol , 43.75% yield, 100% purity, HCl) was obtained as a light yellow solid. ^1H NMR (400 MHz, $\text{METHANOL}-d_4$) δ ppm 1.33 (br s, 4 H), 1.50 (br d, $J=6.08$ Hz, 2 H), 1.87 - 2.08 (m, 2 H), 2.26 (d, $J=13.83$ Hz, 3 H), 2.33 - 2.51 (m, 5 H), 2.55 - 2.69 (m, 1 H), 2.92 (br s, 1 H), 3.07 - 3.17 (m, 1 H), 3.48 - 3.65 (m, 1 H), 3.76 - 3.84 (m, 1 H), 3.84 - 3.99 (m, 2 H), 4.33 (br s, 1 H), 4.78 (br s, 1 H), 6.23 - 6.38 (m, 1 H), 6.44 - 6.62 (m, 1 H), 6.68 - 6.79 (m, 1 H), 7.23 - 7.39 (m, 3 H), 7.40 - 7.53 (m, 3 H), 7.64 - 7.90 (m, 1 H). LC-MS: (ES) m/z 623.3 ($\text{M}+\text{H}^+$).

Example S164: Synthesis of ((2R,3S)-3-(5-(tert-butyl)benzo[d]oxazol-2-yl)-2-(4-(cyclopentyl-amino)phenyl) piperidin-1-yl)(2-fluoro-6-methylphenyl)methanone (Compound No. 181)



[0429] To a mixture of (2R,3S)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl) piperidine-3-carboxylic acid (500 mg, 1.18 mmol) and 2-amino-4-tert-butyl-phenol (389.23 mg, 2.36 mmol) in PPA (3 mL). The mixture was stirred at 145 °C for 16 h. The reaction mixture was cooled to 20 °C, basified with saturated NaHCO₃ solution, then the mixture was extracted with ethyl acetate (50 mL x 2). The combined organic phase was washed with brine (50 mL), dried with anhydrous MgSO₄ and was filtered. The filtrate was evaporated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=100/0 to 3:1). The result product was purified by prep-HPLC (column: Agela ASB 150 * 25 mm * 5 μm; mobile phase: [water (0.05% HCl)-ACN]; B%: 55%-85%, 8 min) to give [(2R,3S)-3-(5-tert-butyl-1,3-benzoxazol-2-yl)-2-[4-(cyclopentylamino)phenyl]-1-piperidyl]-(2-fluoro-6-methyl-phenyl)-methanone (45 mg, 80.46 μmol, 6.83% yield, 99% purity) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.36 (9 H, s), 1.46 (1 H, br d, *J*=6.60 Hz), 1.55 (3 H, br s), 1.80 - 1.99 (9 H, m), 2.02 (3 H, s), 2.30 - 2.45 (2 H, m), 3.06 - 3.23 (1 H, m), 3.41 (1 H, br d, *J*=12.47 Hz), 3.74 (1 H, br d, *J*=6.36 Hz), 3.97 - 4.11 (1 H, m), 6.74 - 6.85 (1 H, m), 6.87 - 7.00 (2 H, m), 7.14 - 7.23 (1H, m), 7.33 - 7.39 (1 H, m), 7.39 - 7.44 (1 H, m), 7.44 - 7.55 (2 H, m), 7.59 (1 H, br s), 7.66 - 7.75 (1 H, m). LCMS: *m/z* 554.4 (M+H⁺).

Example S165: Synthesis of ((2R,3S)-3-(6-(tert-butyl)-1H-benzo[d]imidazol-2-yl)-2-(4-(cyclopentylamino)phenyl)piperidin-1-yl)(2-fluoro-6-methylphenyl)methanone (Compound No. 180)



[0430] **Step a)** K₂CO₃ (3.84 g, 27.81 mmol) was dissolved in H₂O (30 mL). After cooling to 25°C, MTBE (40 mL) was added, then ethyl(2R,3S)-2-[4-(cyclopentylamino)phenyl]piperidine-3- carboxylate (4.4 g, 13.90 mmol, L-DTTA) was

added. The mixture was stirred at 25°C for 0.5 h. 2-fluoro-6-methyl-benzoyl chloride (719.92 mg, 4.17 mmol) was dissolved in MTBE (40 mL) and added to the mixture dropwise. Then the mixture was stirred at 25 °C for 0.5 h. The reaction mixture was extracted with MTBE (40 mL * 2), the combined organic phase was washed with brine (40 mL) and dried with anhydrous MgSO₄. Then the mixture was filtered. The filtrate was evaporated under vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=100/0 to 3:1) (petroleum ether: ethyl acetate=3:1) to obtain ethyl(2R,3S)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl) piperidine-3-carboxylate (1.7 g, 3.76 mmol, 27.02% yield) as a white solid. LC-MS: (ES) *m/z* 453.3 (M+H⁺).

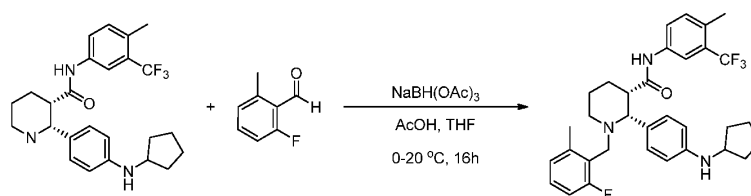
[0431] Step b) The ethyl (2R,3S)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)piperidine-3-carboxylate (1.7 g, 3.76 mmol) was added to H₂SO₄ (0.44 M, 15.39 mL). The mixture was stirred at 95°C for 16 h. The reaction mixture was cooled to 20°C, basified with saturated NaHCO₃ solution, then the mixture was extracted with ethyl acetate (50 mL * 2). The combined organic phase was washed with brine (50 mL), dried with anhydrous MgSO₄ and was filtered. The filtrate was evaporated under vacuum to give (2R,3S)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)piperidine-3-carboxylic acid (1.5 g, 3.22 mmol, 85.60% yield, 91% purity) as a white solid. LCMS: *m/z* 425.2(M+H⁺).

[0432] Step c) To a mixture of (2R,3S)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl) piperidine-3-carboxylic acid (700 mg, 1.50 mmol) and 4-tert-butylbenzene-1,2-diamine (246.46 mg, 1.50 mmol) in DCM (10 mL) was added HATU (570.56 mg, 1.50 mmol) and DIEA (775.75 mg, 6.00 mmol, 1.05 mL). The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=100/0 to 1:1) to obtain (2R,3S)-N-(2-amino-5-tert-butyl-phenyl)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)piperidine-3-carboxamide (0.8 g, 981.19 μmol, 65.39% yield, 70% purity) as a brown oil. LCMS: *m/z* 571.3 (M+H⁺).

[0433] Step d) The (2R,3S)-N-(2-amino-5-tert-butyl-phenyl)-2-[4-(cyclopentylamino)phenyl]-1-(2-fluoro-6-methyl-benzoyl)piperidine-3-carboxamide (800 mg, 981.19 μmol) was dissolved in CH₃COOH (11.76 g, 195.83 mmol, 11.20 mL). The solution was stirred at 60 °C for 3 h. The solvent was evaporated under vacuum to give crude product. The crude product was purified by prep-HPLC (column: Agela ASB 150 * 25 mm * 5 μm; mobile phase: [water (0.05% HCl)-ACN]; B%: 32%-62%, 8 min) to give [(2R,3S)-3-

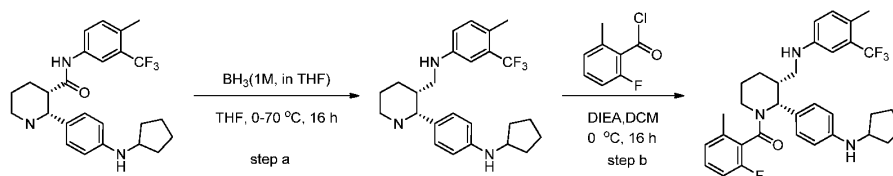
(6-tert-butyl-1H-benzimidazol-2-yl)-2-[4-(cyclopentylamino)phenyl]-1-piperidyl]-(2-fluoro-6-methyl-phenyl)methanone (35 mg, 63.32 μmol , 6.45% yield, 100% purity) as a white solid. ^1H NMR (400 MHz, DMSO-*d*₆) δ 1.25 (2 H, s), 1.30 (10 H, d, $J=3.42$ Hz), 1.43 (7 H, br d, $J=10.52$ Hz), 1.56 - 1.77 (7 H, m), 1.89 - 2.02 (3 H, m), 2.34 (3 H, s), 2.52 - 2.66 (2 H, m), 3.96 - 4.10 (1 H, m), 6.59 (1 H, br t, $J=6.11$ Hz), 7.03 - 7.10 (2 H, m), 7.15 - 7.22 (2 H, m), 7.27 - 7.37 (2 H, m), 7.54 - 7.60 (2 H, m), 7.61 - 7.67 (1 H, m). LCMS: m/z 553.4 ($\text{M}+\text{H}^+$).

Example S166: Synthesis of (2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide (Compound No. 159)



[0434] To a solution of (2R,3S)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (100 mg, 224.46 μmol) and 2-fluoro-6-methyl-benzaldehyde (46.51 mg, 336.69 μmol) in THF (5 mL) was added $\text{NaBH}(\text{OAc})_3$ (95.14 mg, 448.91 μmol) and AcOH (13.48 mg, 224.46 μmol , 12.84 μL) at 0 °C. The mixture was stirred at 20 °C for 16 hr. The reaction mixture was quenched by addition aqueous NaHCO_3 (10 mL), and then extracted with DCM (30 mL * 2). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (HCl condition, column: Agela ASB 150 * 25 mm * 5 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 55%-85%, 8 min) to give (2R,3S)-2-[4-(cyclopentylamino)phenyl]-1-[(2-fluoro-6-methyl-phenyl)methyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (80 mg, 140.93 μmol , 62.79% yield, 100% purity) as a light yellow solid. ^1H NMR (400 MHz, METHANOL-*d*₄) δ 1.65 (br s, 4 H), 1.80 (br s, 2 H), 1.98 (br d, $J=9.29$ Hz, 3 H), 2.18 - 2.37 (m, 3 H), 2.41 (s, 3 H), 2.45 (s, 3 H), 3.26 - 3.30 (m, 1 H), 3.41 - 3.53 (m, 1 H), 3.55 - 3.63 (m, 1 H), 3.87 - 3.96 (m, 1 H), 4.21 (br d, $J=13.69$ Hz, 1 H), 4.33 - 4.41 (m, 1 H), 5.01 (br s, 1 H), 7.10 - 7.20 (m, 2 H), 7.27 - 7.46 (m, 4 H), 7.69 (br dd, $J=15.28, 8.44$ Hz, 3 H), 7.91 (s, 1 H). LC-MS: (ES) m/z 568.3 ($\text{M}+\text{H}^+$).

Example S167: Synthesis of ((2R,3R)-2-(4-(cyclopentylamino)phenyl)-3-(((4-methyl-3-(trifluoro-methyl)phenyl)amino)methyl)piperidin-1-yl)(2-fluoro-6-methylphenyl)methanone (Compound No. 160)

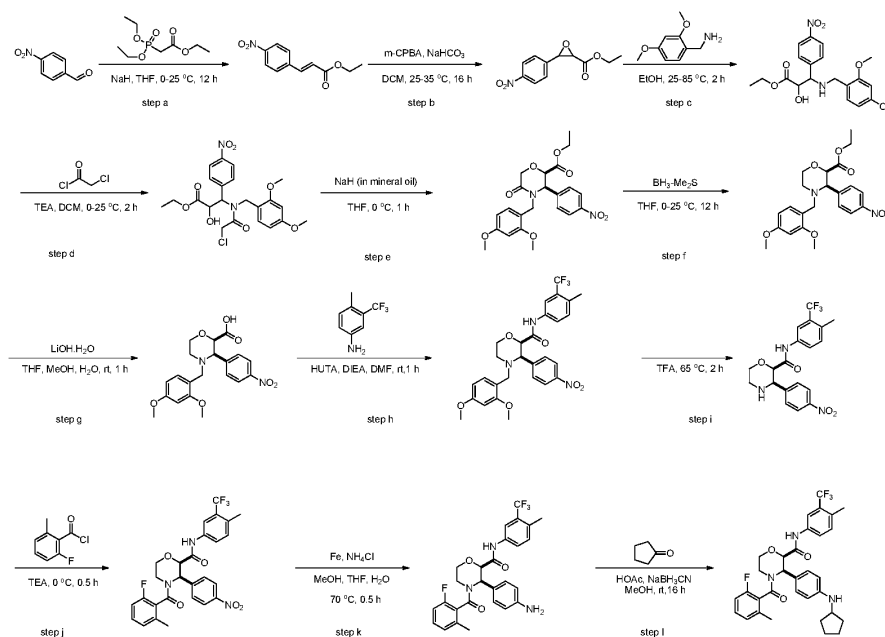


[0435] Step a) To a solution of (2R,3S)-2-[4-(cyclopentylamino)phenyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (200 mg, 448.91 μmol) in THF (10 mL) was added BH_3 (in THF) (1 M, 1.80 mL) at 0 °C under N_2 atmosphere. The mixture was stirred under N_2 at 70 °C for 16 h. The reaction mixture was quenched by addition MeOH 10 mL, and then 3N HCl was added, stirred and refluxed for 1 h, then diluted with aqueous NaHCO_3 (20 mL) and extracted with ethyl acetate (40 mL * 2). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition, column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 μm ; mobile phase: [water (0.04% $\text{NH}_3 \cdot \text{H}_2\text{O}$ + 10mM NH_4HCO_3)-ACN]; B%: 60%-90%, 10 min) to give N-[(2R,3R)-2-[4-(cyclopentylamino)phenyl]-3-piperidyl]methyl-4-methyl-3-(trifluoromethyl)aniline (50 mg, 114.71 μmol , 25.55% yield, 99% purity) as a light yellow gum. LC-MS: (ES) m/z 432.3 ($\text{M}+\text{H}^+$).

[0436] Step b) To a solution of N-[(2R,3R)-2-[4-(cyclopentylamino)phenyl]-3-piperidyl]methyl-4-methyl-3-(trifluoromethyl)aniline (50 mg, 115.87 μmol) in DCM (2 mL) was added DIEA (29.95 mg, 231.73 μmol , 40.36 μL) and then 2-fluoro-6-methylbenzoyl chloride (20.00 mg, 115.87 μmol , 1 eq) in DCM (1 mL) was added by dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by addition H_2O (1 mL), and then extracted with DCM 20 mL (10 mL * 2). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (HCl condition, column: Agela DuraShell C18 150 * 25 mm * 5 μm ; mobile phase: [water (0.05% HCl)-ACN]; B%: 55%-82%, 7 min) to give [(2R,3R)-2-[4-(cyclopentylamino)phenyl]-3-[[4-methyl-3-(trifluoromethyl)anilino]methyl]-1-piperidyl]-(2-fluoro-6-methylphenyl)methanone (35 mg, 55.04 μmol , 47.50% yield, 95% purity, HCl) as a white solid. ^1H NMR (400 MHz,

METHANOL-*d*₄) δ 1.69 - 1.77 (m, 4 H), 1.87 (s, 2 H), 1.85 - 1.89 (m, 1 H), 1.97 - 2.06 (m, 4 H), 2.39 (br d, $J=17.85$ Hz, 5 H), 2.48 - 2.62 (m, 1 H), 3.07 - 3.26 (m, 2 H), 3.33 - 3.46 (m, 2 H), 3.99 (quin, $J=6.91$ Hz, 1 H), 6.21 (dd, $J=8.93$, 6.24 Hz, 1 H), 6.87 - 7.07 (m, 2 H), 7.09 - 7.24 (m, 2H), 7.26 - 7.44 (m, 4 H), 7.52 (t, $J=8.44$ Hz, 2 H), 7.84 (dd, $J=16.87$, 8.56 Hz, 2 H). LC-MS: (ES) m/z 568.4 (M+H⁺).

Example S168: Synthesis of *cis*-3-(4-(cyclopentylamino)phenyl)-4-(2-fluoro-6-methylbenzoyl)-*N*-(4-methyl-3-(trifluoromethyl)phenyl)morpholine-2-carboxamide (Compound No. 187)



[0437] Step a) To a mixture of NaH (3.97 g, 99.26 mmol, 60% purity) in THF (200 mL) was added a solution of 4-nitrobenzaldehyde (10 g, 66.17 mmol) in THF (50 mL) slowly at 0 °C. The reaction mixture was stirred at 0 °C for 20 min. Ethyl 2-diethoxyphosphorylacetate (14.83 g, 66.17 mmol, 13.13 mL) was added in small portions. The reaction mixture was stirred at 25 °C for another 12 hr. The reaction mixture was quenched by addition of NH₄Cl at 25 °C, and then diluted with water (50 mL) and extracted with EtOAc 300 mL (100 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/0 to 10:1) to give ethyl (E)-3-(4-nitrophenyl)prop-2-enoate (7 g, 31.64 mmol, 47.82% yield) as a light yellow solid. ¹H NMR (400 MHz,

DMSO-*d*₆): δ 1.24 (t, $J=7.1$ Hz, 3 H), 4.18 (q, $J=7.1$ Hz, 2 H), 6.82 (d, $J=16.1$ Hz, 1 H), 7.72 (d, $J=16.1$ Hz, 1 H), 7.98 (d, $J=8.8$ Hz, 2 H), 8.20 (d, $J=9.0$ Hz, 2 H).

[0438] Step b) To a solution of ethyl (E)-3-(4-nitrophenyl)prop-2-enoate (7 g, 31.64 mmol) in DCM (160 mL) was added NaHCO₃ (saturated aqueous solution) (160 mL) and m-CPBA (20.48 g, 94.93 mmol, 80% purity) at 25 °C. Then the mixture was stirred at 35 °C for 16 h. The mixture was quenched by addition of saturated Na₂S₂O₃ solution (150 mL) and extracted with DCM (3 x 50 mL), and the combined organic layers was dried, filtered and concentrated in vacuo to give the crude. The crude was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, eluent of 0~10% ethyl acetate/petroleum ether gradient @ 40 mL/min) to give ethyl 3-(4-nitrophenyl)oxirane-2-carboxylate (4 g, 16.86 mmol, 53.29% yield) as yellow gum. ¹H NMR (400 MHz, CDCl₃) δ 1.35 (t, $J=7.2$ Hz, 3 H), 3.50 (d, $J=1.5$ Hz, 1 H), 4.21 (d, $J=1.5$ Hz, 1 H), 4.25 - 4.39 (m, 2 H), 7.49 (d, $J=8.5$ Hz, 2 H), 8.19 - 8.28 (m, 2 H).

[0439] Step c) To a solution of ethyl 3-(4-nitrophenyl)oxirane-2-carboxylate (0.8 g, 3.37 mmol) in EtOH (4 mL) was added (2,4-dimethoxyphenyl)methanamine (563.91 mg, 3.37 mmol, 508.03 μ L) at 25 °C. Then the mixture was stirred at 85 °C for 12 h. The mixture was concentrated in vacuo to give the crude. The crude was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, eluent of 0~30% ethyl acetate/petroleum ether gradient @ 45 mL/min) to give ethyl 3-[(2,4-dimethoxyphenyl)methylamino]-2-hydroxy-3-(4-nitrophenyl) propanoate (0.3 g, 741.82 μ mol, 22.00% yield) as light yellow solid. LC-MS: (ES) m/z 405.2 (M+H⁺).

[0440] Step d) To a solution of ethyl 3-[(2,4-dimethoxyphenyl) methylamino]-2-hydroxy-3-(4-nitro phenyl)propanoate (0.3 g, 741.82 μ mol) and TEA (82.57 mg, 816.00 μ mol, 113.58 μ L) in DCM (5 mL) was added 2-chloroacetyl chloride (83.78 mg, 741.82 μ mol, 59.00 μ L) at 0 °C. Then the mixture was stirred at 25 °C for 2 h. The mixture was diluted with DCM (20 mL), washed with H₂O (2 x 20 mL), brine (2 x 20 mL), dried, filtered and concentrated in vacuo to give the crude ethyl 3-[(2-chloroacetyl)-[(2,4-dimethoxyphenyl) methyl] amino]-2-hydroxy-3-(4-nitro phenyl) propanoate (0.36 g, crude) as light yellow gum. The crude product was used directly in the next step without further purification. LC-MS: (ES) m/z 481.2 (M+H⁺).

[0441] Step e) To a solution of ethyl 3-[(2-chloroacetyl)-[(2,4-dimethoxyphenyl) methyl] amino]-2-hydroxy-3-(4-nitrophenyl) propanoate (0.36 g, 748.60 μ mol) in THF (30 mL) was

added NaH (60% dispersion in mineral oil) (31 mg, 775.07 μmol , 60% purity) at 0 °C. Then the mixture was stirred at 0 °C for 1 h. The mixture was poured into saturated NH_4Cl solution (30 mL) carefully and extracted with EtOAc (2 x 20 mL). The combined organic phase separated was washed with brine, dried, filtered and concentrated in vacuo to give the crude. The crude was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 0~60% ethyl acetate/petroleum ether gradient @20 mL/min) to give cis-ethyl 4-[(2,4-dimethoxyphenyl)methyl]-3-(4-nitrophenyl)-5-oxo-morpholine-2-carboxylate (0.19 g, 427.51 μmol , 57.11% yield) as light yellow gum. ^1H NMR (400 MHz, CDCl_3) δ 1.07 (t, $J=7.1$ Hz, 3 H), 3.76 (s, 3 H), 3.79 - 3.87 (m, 4 H), 3.93 - 4.09 (m, 2 H), 4.42 (d, $J=16.9$ Hz, 1 H), 4.64 (d, $J=3.4$ Hz, 1 H), 4.68 (d, $J=16.9$ Hz, 1 H), 4.86 (d, $J=3.4$ Hz, 1 H), 5.01 (d, $J=14.4$ Hz, 1 H), 6.39 (d, $J=2.2$ Hz, 1 H), 6.46 (dd, $J=8.3, 2.2$ Hz, 1 H), 7.20 (d, $J=8.3$ Hz, 1 H), 7.39 (d, $J=8.6$ Hz, 2 H), 8.18 (d, $J=8.8$ Hz, 2 H). LC-MS: (ES) m/z 445.2 ($\text{M}+\text{H}^+$).

[0442] Step f) To a solution of cis-ethyl 4-[(2,4-dimethoxyphenyl)methyl]-3-(4-nitrophenyl)-5-oxo-morpholine-2-carboxylate (0.16 g, 360.01 μmol) in THF (2 mL) was added $\text{BH}_3\text{-Me}_2\text{S}$ (10 M, 108.00 μL) at 0 °C. Then the mixture was stirred at 25 °C for 12 h. The mixture was quenched with H_2O (10 mL) carefully and extracted with EtOAc (2 x 20 mL). The combined organic phase separated was washed with brine, dried, filtered and concentrated in vacuo to give the crude. The crude was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluent of 0~50% ethyl acetate/petroleum ether gradient @ 20 mL/min) to give the target product cis-ethyl 4-[(2,4-dimethoxyphenyl)methyl]-3-(4-nitrophenyl)morpholine-2-carboxylate (125 mg, 290.39 μmol , 80.66% yield) as light yellow gum. ^1H NMR (400 MHz, acetonitrile- d_3) δ 0.88 (t, $J=7.1$ Hz, 3 H), 2.42 (d, $J=12.7$ Hz, 1 H), 2.72 - 2.81 (m, 1 H), 3.15 (d, $J=13.4$ Hz, 1 H), 3.49 (d, $J=13.7$ Hz, 1 H), 3.74 (s, 3 H), 3.75 - 3.82 (m, 4 H), 3.86 (q, $J=7.1$ Hz, 2 H), 4.14 - 4.25 (m, 2 H), 4.61 (d, $J=3.7$ Hz, 1 H), 6.50 - 6.57 (m, 2 H), 7.31 (d, $J=8.1$ Hz, 1 H), 7.70 (d, $J=8.6$ Hz, 2 H), 8.17 (d, $J=8.8$ Hz, 2 H). LC-MS: (ES) m/z 431.2 ($\text{M}+\text{H}^+$).

[0443] Step g) To a solution of cis-ethyl 4-[(2,4-dimethoxyphenyl)methyl]-3-(4-nitrophenyl)morpholine-2-carboxylate (417 mg, 968.75 μmol) in THF (2.5 mL) / MeOH (2.5 mL) / H_2O (1 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (60.98 mg, 1.45 mmol, 726.57 μL). Then the mixture was stirred at 25 °C for 1 h. The mixture was quenched with brine (1 mL) carefully and acidified to pH=4~5 by addition of HCl (2 M), then extracted with EtOAc (5 x 10 mL). The combined organic phase separated was washed with brine (3 x 5 mL), dried, filtered and

concentrated in vacuo to give cis-4-[(2,4-dimethoxyphenyl)methyl]-3-(4-nitrophenyl)morpholine-2-carboxylic acid (380 mg, 944.34 μmol , 97.48% yield) as yellow solid. ^1H NMR (400 MHz, acetonitrile- d_3) δ 2.73 (br d, $J=13.1$ Hz, 1 H), 3.03 (t, $J=10.5$ Hz, 1 H), 3.45 (br d, $J=13.1$ Hz, 1 H), 3.70 (s, 3 H), 3.74 - 3.83 (m, 4 H), 3.97 - 4.06 (m, 1 H), 4.14 - 4.23 (m, 1 H), 4.64 (br s, 1 H), 5.02 (br s, 1 H), 6.51 (d, $J=2.3$ Hz, 1 H), 6.55 (dd, $J=8.3, 2.5$ Hz, 1 H), 7.49 (d, $J=8.5$ Hz, 1 H), 7.86 (br d, $J=8.5$ Hz, 2 H), 8.23 (d, $J=9.0$ Hz, 2 H).

[0444] Step h) To a solution of cis-4-[(2,4-dimethoxyphenyl)methyl]-3-(4-nitrophenyl)morpholine-2-carboxylic acid (385 mg, 956.77 μmol), 4-methyl-3-(trifluoromethyl)aniline (217.85 mg, 1.24 mmol, 178.57 μL) and DIEA (370.97 mg, 2.87 mmol, 499.95 μL) in DMF (5 mL) was added HATU (545.69 mg, 1.44 mmol). Then the mixture was stirred at 25 °C for 1 h. The mixture was quenched with H_2O (3 mL) carefully and extracted with EtOAc (2 x 10 mL). The combined organic phase separated was washed with brine, dried, filtered and concentrated in vacuo to give the crude product. The crude product was purified by prep-TLC to give cis-4-[(2,4-dimethoxyphenyl)methyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-3-(4-nitrophenyl)morpholine-2-carboxamide (510 mg, 911.48 μmol , 95.27% yield) as light yellow gum. ^1H NMR (400 MHz, acetonitrile- d_3) δ 2.36 (d, $J=1.2$ Hz, 3 H), 2.48 (dd, $J=12.8, 2.3$ Hz, 1 H), 2.79 - 2.86 (m, 1 H), 3.11 (d, $J=13.7$ Hz, 1 H), 3.58 (d, $J=13.7$ Hz, 1 H), 3.73 (s, 3 H), 3.80 (s, 3 H), 3.91 (td, $J=11.6, 3.2$ Hz, 1 H), 4.24 (dd, $J=11.4, 3.1$ Hz, 1 H), 4.34 (d, $J=3.4$ Hz, 1 H), 4.62 (d, $J=3.7$ Hz, 1 H), 6.50 - 6.57 (m, 2 H), 7.21 (d, $J=8.1$ Hz, 1 H), 7.34 (d, $J=8.1$ Hz, 1 H), 7.41 - 7.51 (m, 1 H), 7.64 - 7.76 (m, 3 H), 8.12 (d, $J=8.8$ Hz, 2 H), 8.77 (s, 1 H). LC-MS: (ES) m/z 560.2 ($\text{M}+\text{H}^+$).

[0445] Step i) A mixture of cis-4-[(2,4-dimethoxyphenyl)methyl]-N-[4-methyl-3-(trifluoromethyl)phenyl]-3-(4-nitrophenyl)morpholine-2-carboxamide (0.19 g, 339.57 μmol) in TFA (4 mL) was stirred at 65 °C for 2 h. The mixture was diluted with DCM (6 mL) and alkalinized to pH=8~9 by addition of saturated NaHCO_3 solution. The organic layer was separated to give a solution of cis-N-[4-methyl-3-(trifluoromethyl)phenyl]-3-(4-nitrophenyl)morpholine-2-carboxamide (assumed in quantitative yield (139.01 mg) obtained) in DCM (6 mL), and the organic phase was used directly in the next step.

[0446] Step j) To a solution of cis-N-[4-methyl-3-(trifluoromethyl)phenyl]-3-(4-nitrophenyl)morpholine-2-carboxamide (139.01 mg, 339.58 μmol) in DCM (6 mL) was added TEA (51.54 mg, 509.37 μmol , 70.90 μL) and 2-fluoro-6-methyl-benzoyl chloride (58.61 mg, 339.58 μmol) at 0 °C. Then the mixture was stirred at 0 °C for 0.5 h. The mixture was diluted with DCM (20 mL), washed with brine (2 x 10 mL), dried, filtered and

concentrated in vacuo to give the crude. The crude was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/DCM gradient @ 18 mL/min) to give cis-4-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]-3-(4-nitrophenyl)morpholine-2-carboxamide (160 mg, 269.85 µmol, 79.47% yield, 92% purity) as light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.86 - 2.02 (m, 3 H), 2.33 - 2.43 (m, 5 H), 3.11 - 3.22 (m, 1 H), 3.29 - 3.45 (m, 1 H), 3.73 - 3.90 (m, 2 H), 4.15 - 4.28 (m, 1 H), 4.65 - 4.83 (m, 1 H), 6.26 (br s, 1 H), 6.96 - 7.19 (m, 3 H), 7.28 - 7.40 (m, 2 H), 7.68 (br d, *J*=7.78 Hz, 1 H), 7.85 (d, *J*=2.01 Hz, 1 H), 7.92 (dd, *J*=17.82, 8.78 Hz, 2 H), 8.12 - 8.23 (m, 2 H), 9.86 (br d, *J*=14.81 Hz, 1 H). LC-MS *R*_t (retention time): 0.93 min; MS: (ES) *m/z* 546.2 (M+H⁺).

[0447] Step k) To a mixture of cis-4-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoromethyl) phenyl]-3-(4-nitrophenyl)morpholine-2-carboxamide (120 mg, 219.99 µmol) and NH₄Cl (11.77 mg, 219.99 µmol) in MeOH (2.5 mL) / THF (2.5 mL) / H₂O (1 mL) was added Fe (73.71 mg, 1.32 mmol). Then the mixture was stirred at 70 °C for 0.5 h. The mixture was diluted with EtOAc (20mL) and alkalified to pH=8~9 by addition of saturated NaHCO₃ solution. The organic phase separated was washed with brine, dried, filtered and concentrated in vacuo to give the crude cis-3-(4-aminophenyl)-4-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoro methyl)phenyl]morpholine-2-carboxamide (100 mg, 180.41 µmol, 82.01% yield, 93% purity) as light yellow solid. LC-MS: (ES) *m/z* 516.2 (M+H⁺).

[0448] Step l) To a mixture of cis-3-(4-aminophenyl) -4-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3- (trifluoromethyl)phenyl]morpholine-2-carboxamide (100 mg, 193.99 µmol) in MeOH (3 mL) was added cyclopentanone (19.58 mg, 232.78 µmol, 20.61 µL), HOAc (11.65 mg, 193.99 µmol, 11.09 µL) and NaBH₃CN (30.48 mg, 484.97 µmol) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched with H₂O (10 mL) and extracted with DCM (3 x 15 mL). The combined organic layers were washed with brine (2 x 5 mL), dried, filtered and concentrated in vacuo to give the crude. The crude was purified by prep-HPLC (column: Agela Durashell C18 150x30 5µ; mobile phase: [water (0.05% HCl)-ACN]; B%: 42%-72%, 8 min) to give the target product cis-3-[4-(cyclopentyl amino) phenyl]-4-(2-fluoro-6-methyl-benzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]morpholine-2-carboxamide (0.1 g, 171.35 µmol) (45 mg, 98% purity) as light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 1.29 - 1.48 (m, 3 H), 1.63 - 1.74 (m, 3 H), 1.87 - 2.00 (m, 2 H), 2.01 - 2.09 (m, 3 H), 2.35 - 2.49 (m, 4 H), 3.12 (br d, *J*=13.80

Hz, 1 H), 3.38 - 3.53 (m, 1 H), 3.56 - 3.76 (m, 2 H), 3.81 - 4.00 (m, 1 H), 4.16 (br d, $J=11.04$ Hz, 1 H), 4.35 - 4.49 (m, 1 H), 4.52 - 4.58 (m, 1 H), 4.63 (dd, $J=14.05, 3.01$ Hz, 1 H), 4.92 (d, $J=3.51$ Hz, 1 H), 6.36 - 6.42 (m, 1 H), 6.50 (d, $J=8.53$ Hz, 1 H), 6.82 - 6.99 (m, 2 H), 6.99 - 7.16 (m, 2 H), 7.18 - 7.25 (m, 1 H), 7.32 (td, $J=7.97, 6.15$ Hz, 1 H), 7.37 - 7.51 (m, 1 H), 7.52 - 7.59 (m, 1 H), 7.69 (br d, $J=8.03$ Hz, 1 H), 8.13 - 8.45 (m, 1 H). LC-MS: (ES) m/z 584.3 ($M+H^+$).

Biological examples

Example B1: Inhibition of C5a-C5aR binding

[0449] U937 cells were originally obtained from the American Type Culture Collection (ATCC) and transfected with human C5a receptor (C5aR). U937/C5aR cells were cultured at 37 °C, 5% CO₂ in RPMI1640(Gibco) supplemented with 10% FBS(Gibco) and 350μg/ml Geneticin (Gibco) and passaged every 3 days to maintain the density range from 1x10⁵ to 2x10⁶ cells/ml.

[0450] Human C5a biotinylation was performed according to the procedure provided by manufacturer (Thermo Scientific, A39257). 10mM solution of Sulfo-NHS-LC-Biotin was prepared by adding 180μl ultrapure H₂O to the 1mg vial immediately. 12μl 10mM biotin reagent was added to 200μg human C5a solution, gently pipetted for 3 seconds, and incubated on ice for 2 hours. Amicon ultra-0.5 centrifuge filter device (Millipore, UFC5003BK) was pre-rinsed with Milli-Q H₂O, centrifuged at 14000g for 5min immediately before use. Up to 500μl sample (diluted by PBS) was added to the device and capped. The device was spun at 14000g for approximately 5min. 250μl PBS was added to the filter device, spun at 14000g for 5min, and repeatedly washed 6 times. The filter device was separated from the microcentrifuge tube and placed upside down in a clean microcentrifuge tube, spun for 2min at 1000g to transfer the concentrated sample from the device to the tube.

[0451] U937/C5aR cells were collected and washed twice by PBS, cells were suspended in PBS+0.1% BSA buffer at the density of 3x10⁶ cells/ml. 100μl cell suspension was added to a 96 well microplate. 50μl compound diluted in assay buffer and 50μl biotinylated ligand human C5a (30nM) were added to corresponding wells in order and the plate was incubated on ice for 120min and then centrifuged at 1000rpm for 3-5min at 4 °C. Supernatant was removed and cells were washed by pre-cold PBS twice. 100μl FITC conjugated streptavidin

was added to cells, incubated on ice for another 30min, and then centrifuged at 1000rpm for 3-5min at 4 °C. Supernatant was removed and cells were washed by pre-cold PBS twice. 150µl PBS was added to suspend the cells and signals were detected by FACS (Beckman, Cytotflex). IC₅₀ values were calculated by GraphPad Prism software and provided in Table B1.

Table B1

Compound No./name	IC ₅₀ (nM)	Compound No./name	IC ₅₀ (nM)
2	+	47	+++
4	+	49	++++
5	+++	50	++++
6	++	51	++++
7	+	52	+
8	+	54	+++
9	+	55	+++
10	++	56	++++
11	++	57	+++
13	+	58	+++
14	+	59	+++
15	+	60	+
16	+	61	+
17	++	62	+++
18	+	63	++++
19	+	64	++
20	+	65	+++
22	++	66	++++
23	+	67	++++
24	+	68	+
25	++	69	+++
26	+	70	++
27	+	71	++++
28	+	73	+++
29	+	74	+
30	+	76	+
32	+	77	+
33	+	78	+++
34	+	79	+
35	+	83	+
36	++	84	++++
38	+	88	+++
40	++++	89	++++
41	++	90	+++
42	++++	92	+
44	+++	94	++++
46	+++	95	++

Compound No./name	IC ₅₀ (nM)
96	++++
97	++
98	++++
99	+
102	+
103	+
104	+
105	+
107	+
109	++
110	+++
111	+++
113	+
114	++++
115	+++
118	++++
119	++++
121	+++
122	+
123	+++
124	+++
126	++++
126	++++
129	+
134	+

Compound No./name	IC ₅₀ (nM)
135	+++
136	+
138	+++
139	++++
141	+++
142	+
144	+++
144	++
147	++++
155	++
158	++++
161	+++
162	+++
166	+
170	++
180	+
184	+
187	+++
188	++++
189	+++
190	++
200	—
201	—
202	—

—: IC₅₀ > 5000nM in migration assay; or IC₅₀ > 10000nM in Ca²⁺ flux assay

+: 5000 nM ≥ IC₅₀ ≥ 2000 nM in migration assay (compound shows weak activity at 2000nM and the % inhibition is less than 50%) or 10000 nM ≥ IC₅₀ ≥ 2000 nM

++: 500 nM ≤ IC₅₀ < 2000 nM;

+++; 50 nM ≤ IC₅₀ < 500 nM;

++++; IC₅₀ < 50 nM.

Example B2: Inhibition of C5a-C5aR binding determined by cell migration assays

[0452] Migration assay was performed by using polycarbonate membrane with 3.0μm pore (Corning). U937/C5aR cells were collected and washed twice by PBS; cells were suspended in Hank's balanced salt solution (HBSS)+ 1% FBS buffer at the density of 6×10⁶ cells/ml. Cells were premixed with compound and added to insert well, ligand human C5a and compound were added to bottom well in order, gently mix, incubate for 30min at 37°C, 5% CO₂. Put insert plate into bottom well, migrate for 180min at 37°C, 5% CO₂. Gently remove the insert well, add 50μl CellTiter-Glo (Promega), gently shaking for 5min at room temperature, transfer 150μl mixture to black plate and read luminescence intensity by

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microplate reader (BioTek). IC₅₀ value was calculated by GraphPad Prism software and provided in Table B2.

Table B2

Compound Name	Compound No.	IC ₅₀ (nM)
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(quinazolin-4-yl)piperidine-3-carboxamide	5	+++
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(quinoline-8-carbonyl)piperidine-3-carboxamide	188	++++
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrido[3,4-d]pyrimidin-4-yl)piperidine-3-carboxamide	162	++
benzyl cyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(1,7-naphthyridin-8-yl)piperidin-2-yl)phenyl)carbamate	164	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((perfluorophenyl)sulfonyl)piperidine-3-carboxamide	37	—
(2R,3S)-2-(4-(cyclopentyl(1,7-naphthyridin-8-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	168	—
cis-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-2-(2-oxaspiro[4.5]decan-8-yl)piperidine-3-carboxamide	203	++
cis-3-(4-aminophenyl)-4-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)morpholine-2-carboxamide	187	+++
cis-4-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-2,3,4,6,11,11a-hexahydro-1H-pyrido[1,2-b]isoquinoline-3-carboxamide	43	—
(3S,4R)-4-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-1,2,3,4,6,11,12,12a-octahydrobenzo[c]pyrido[1,2-a]azepine-3-carboxamide	44	++++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	193	+++
(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	47	++++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	118	++++

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(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	119	++++
cis-4-(4-(cyclopentylamino)phenyl)-7-fluoro-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-1,2,3,4,6,11,12,12a-octahydrobenzo[e]pyrido[1,2-a]azepine-3-carboxamide	41	+++
(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazol-4-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	54	+++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	77	—
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(pyridin-3-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	57	+++
cis-N-(3-cyano-4-methylphenyl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	62	+++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	147	+++
(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	49	++++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	66	++++
(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	50	++++
cis-N-(benzo[d]oxazol-6-yl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	67	+++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	46	+++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(3-(methylsulfonyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	70	++
cis-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(tetrahydro-2H-pyran-4-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	111	+++

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cis-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(oxazole-4-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	110	+++
cis-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(thiazole-4-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	114	+++
cis-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrimidine-5-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	115	+++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	78	++++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-5-hydroxy-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	204	+++
cis-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	88	++++
cis-2-(4-(cyclopentyl(methyl)amino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-6-methyl-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide	144	+++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(quinolin-7-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	73	+++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(oxetan-3-yl)-1H-indazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	59	+++
cis-1-(2-fluoro-6-methylbenzoyl)-N-(quinolin-7-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	90	+++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	121	+++
(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	126	++++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	189	+++
cis-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide.	158	++++

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(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	89	++++
cis-2-(4-((3,3-dimethylmorpholino)methyl)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	141	++
(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-N-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	51	++++
(2R,3S,4aR,7aR)-N-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	94	++++
(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-N-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	124	+++
(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	96	+++
(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	98	++++
(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	138	++
(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	139	+++
cis-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-(((R)-2-(trifluoromethyl)pyrrolidin-1-yl)methyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	205	++++
((2R,3S)-3-(5-(tert-butyl)benzo[d]oxazol-2-yl)-2-(4-(cyclopentylamino)phenyl)piperidin-1-yl)(2-fluoro-6-methylphenyl)methanone	181	—
((2R,3S)-3-(6-(tert-butyl)-1H-benzo[d]imidazol-2-yl)-2-(4-(cyclopentylamino)phenyl)piperidin-1-yl)(2-fluoro-6-methylphenyl)methanone	180	++++

—: IC₅₀ > 5000nM in migration assay; or IC₅₀ > 10000nM in Ca²⁺ flux assay

+: 5000 nM ≥ IC₅₀ ≥ 2000 nM in migration assay (compound shows weak activity at 2000nM and the % inhibition is less than 50%) or 10000 nM ≥ IC₅₀ ≥ 2000 nM

++: 500 nM ≤ IC₅₀ < 2000 nM;

+++; 50 nM ≤ IC₅₀ < 500 nM;

++++: IC₅₀ < 50 nM.

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Example B3: Calcium mobilization

[0453] U937/C5aR cells or HEK293/C5aR cells were washed by PBS and suspended in growth media at the density of 1×10^6 cells/ml. Seed 20 μ l cell suspension to the 384-well plate and culture for overnight. Transfer 250nl compound solution to the cell plate using Echo, incubate for 60min. Cells were added with Fluo-4 Direct TM dye and incubate for 50min at 37 °C 5% CO₂ and 10 min at room temperature. Place the cell plate into FLIPRTETRA (Molecular Devices). Transfer 10 μ l of 5-fold EC80 concentrations of agonist human C5a to the cell plates. Read fluorescence signal, data was calculated by GraphPad Prism and shown in Table B3.

Table B3

Compound Name	Compound No.	IC ₅₀ (nM)
(2R,3R)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrimidin-4-yl)piperidine-3-carboxamide	3	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrimidin-4-yl)piperidine-3-carboxamide	4	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2,6-dimethylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	11	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(3,5-dimethylisoxazole-4-carbonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	190	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(quinazolin-4-yl)piperidine-3-carboxamide	5	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(quinoline-8-carbonyl)piperidine-3-carboxamide	188	+++
(2R,3S)-1-(2-chloropyrimidin-4-yl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	2	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrido[3,2-d]pyrimidin-4-yl)piperidine-3-carboxamide	161	+
(2R,3R)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrido[3,2-d]pyrimidin-4-yl)piperidine-3-carboxamide	7	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrido[3,4-d]pyrimidin-4-yl)piperidine-3-carboxamide	162	+

benzyl cyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(pyrido[3,2-d]pyrimidin-4-yl)piperidin-2-yl)phenyl)carbamate	166	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(1,7-naphthyridin-8-yl)piperidine-3-carboxamide	6	+
benzyl cyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(1,7-naphthyridin-8-yl)piperidin-2-yl)phenyl)carbamate	164	+
benzylcyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(pyrido[3,4-b]pyrazin-5-yl)piperidin-2-yl)phenyl)carbamate	165	+
benzyl cyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(quinazolin-4-yl)piperidin-2-yl)phenyl)carbamate	163	+
benzyl cyclopentyl(4-((2R,3S)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)-1-(pyrido[3,4-d]pyrimidin-4-yl)piperidin-2-yl)phenyl)carbamate	167	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2,4-dimethylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	9	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2,5-dimethylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	10	—
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((3,5-dimethylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	12	—
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(mesitylsulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	13	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((4-fluoro-2-methylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	15	+
(2R,3S)-1-((3-chloro-2-methylphenyl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	16	—
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((5-fluoro-2-methylphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	17	+
(2R,3S)-1-((3-fluoro-2-methylphenyl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	18	—
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2,6-difluorophenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	19	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2,6-dichlorophenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	20	—

methyl 2-(((2R,3S)-2-(4-(cyclopentylamino)phenyl)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)piperidin-1-yl)sulfonyl)-3-methylbenzoate	21	—
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(o-tolylsulfonyl)piperidine-3-carboxamide	22	—
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2-methoxyphenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	23	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((2-(trifluoromethoxy)phenyl)sulfonyl)piperidine-3-carboxamide	24	—
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((2-fluorophenyl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	25	—
(2R,3S)-1-((2-chlorophenyl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	26	—
(2R,3S)-1-((2-bromophenyl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	27	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((2-(trifluoromethyl)phenyl)sulfonyl)piperidine-3-carboxamide	28	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((2-(methylsulfonyl)phenyl)sulfonyl)piperidine-3-carboxamide	29	+
(2R,3S)-1-((2-cyanophenyl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	30	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((2-nitrophenyl)sulfonyl)piperidine-3-carboxamide	14	+
Methyl 2-(((2R,3S)-2-(4-(cyclopentylamino)phenyl)-3-((4-methyl-3-(trifluoromethyl)phenyl)carbamoyl)piperidin-1-yl)sulfonyl)benzoate	31	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(naphthalen-2-ylsulfonyl)piperidine-3-carboxamide	32	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(naphthalen-1-ylsulfonyl)piperidine-3-carboxamide	33	+

(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(phenylsulfonyl)piperidine-3-carboxamide	34	—
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyridin-3-ylsulfonyl)piperidine-3-carboxamide	35	—
(2R,3S)-1-((2-chloropyridin-3-yl)sulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	36	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((perfluorophenyl)sulfonyl)piperidine-3-carboxamide	37	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-((1,3,5-trimethyl-1H-pyrazol-4-yl)sulfonyl)piperidine-3-carboxamide	38	—
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-((3,5-dimethylisoxazol-4-yl)sulfonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	8	+
(2R,3S)-1-(benzylsulfonyl)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	40	+
(2R,3S)-2-(4-(cyclopentyl(1,7-naphthyridin-8-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	168	+
(2R,3R)-2-(4-(cyclopentyl(1,7-naphthyridin-8-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	171	+
(2R,3S)-2-(4-(cyclopentyl(thieno[2,3-c]pyridin-7-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	173	+
(2R,3S)-2-(4-(cyclopentyl(isoquinolin-1-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	175	+
(2R,3S)-2-(4-(cyclopentyl(quinazolin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	177	+
(2R,3S)-2-(4-(cyclopentyl(phthalazin-1-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	179	+
(2R,3S)-2-(4-(cyclopentyl(thiazolo[4,5-c]pyridin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	169	+
(2R,3S)-2-(4-(cyclopentyl(pyrido[3,4-b]pyrazin-5-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	172	+
(2R,3S)-2-(4-(cyclopentyl(pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	176	+

(2R,3R)-2-(4-(cyclopentyl(pyrido[3,2-d]pyrimidin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	174	+
(2R,3S)-2-(4-(cyclopentyl(pyrido[3,4-d]pyrimidin-4-yl)amino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	178	+
cis-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-2-(2-oxaspiro[4.5]decan-8-yl)piperidine-3-carboxamide	203	+
(2R,3S)-2-(4-(N-cyclopentyl-2-fluoro-6-methylbenzamido)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	188	+
cis-3-(4-aminophenyl)-4-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)morpholine-2-carboxamide	187	+
cis-4-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-2,3,4,6,11,11a-hexahydro-1H-pyrido[1,2-b]isoquinoline-3-carboxamide	43	+
(3S,4R)-4-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-1,2,3,4,6,11,12,12a-octahydrobenzo[e]pyrido[1,2-a]azepine-3-carboxamide	44	++
(3R,4S)-4-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-1,2,3,4,6,11,12,12a-octahydrobenzo[e]pyrido[1,2-a]azepine-3-carboxamide	45	+
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	193	++++
(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	47	++++
(2S,3R,4aS,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	48	+
(2R,3S)-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	200	+
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	118	+++
(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	119	+++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-	206	+

6-(2,2,2-trifluoroethyl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide		
cis-4-(4-(cyclopentylamino)phenyl)-7-fluoro-N-(4-methyl-3-(trifluoromethyl)phenyl)-6-oxo-1,2,3,4,6,11,12,12a-octahydrobenzo[e]pyrido[1,2-a]azepine-3-carboxamide	41	+
(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(tetrahydro-2H-pyran-4-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	52	+
(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methylpiperidin-4-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	53	+
(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazol-4-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	54	+
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(2-(trifluoromethyl)pyridin-4-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	79	+
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	77	+
(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)benzyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	185	+
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(3-fluorophenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	56	+++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(pyridin-3-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	57	+
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(2-methylpyrimidin-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	58	+++
cis-N-(4-chloro-3-(trifluoromethyl)phenyl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	60	+++
cis-2-(4-(cyclopentylamino)phenyl)-N-(4-fluoro-3-(trifluoromethyl)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	61	+
cis-N-(3-cyano-4-methylphenyl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	62	+++

cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(6-methylpyridin-3-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	63	++
cis-2-(4-(cyclopentylamino)phenyl)-N-(3,4-dichlorophenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	64	+
cis-2-(4-(cyclopentylamino)phenyl)-N-(3,4-difluorophenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	65	+++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	147	+++
(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	49	++++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	66	++++
(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	50	++
cis-N-(benzo[d]oxazol-6-yl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	67	+++
cis-N-(benzo[d]thiazol-6-yl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	69	+
cis-2-(4-(cyclopentylamino)phenyl)-N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	71	+
cis-3-(6-chloro-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-2-(4-(cyclopentyl amino)phenyl)octahydro-1H-cyclopenta[b]pyridin-1-yl(2-fluoro-6-methylphenyl)methanone	72	+
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	46	+++
cis-N-(3-chlorophenyl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	55	++
cis-2-(4-(cyclopentyl(methyl)amino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(2-methyl-1,2,3,4-tetrahydroisoquinolin-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	201	+
tert-butyl 6-cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-	202	+

cyclopenta[b]pyridine-3-carboxamido)-3,4-dihydroisoquinoline-2(1H)-carboxylate		
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1,2,3,4-tetrahydroisoquinolin-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	184	+
cis-2-(4-(cyclopentylamino)phenyl)-N-(3-(dimethylphosphoryl)-4-methylphenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	76	+
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(3-(methylsulfonyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	70	+
cis-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(tetrahydro-2H-pyran-4-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	111	+
cis-2-(4-(cyclopentylamino)phenyl)-1-(1-methyl-1H-pyrazole-4-carbonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	112	—
cis-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(oxazole-4-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	110	—
cis-2-(4-(cyclopentylamino)phenyl)-1-(1-methyl-1H-imidazole-4-carbonyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	113	—
cis-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(thiazole-4-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	114	—
cis-2-(4-(cyclopentylamino)phenyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-1-(pyrimidine-5-carbonyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	115	—
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-formamido-3-hydroxyphenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	68	++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	78	++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-5-hydroxy-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	204	+
cis-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	88	++++

cis-N-(5-chloro-6-(2H-1,2,3-triazol-2-yl)pyridin-3-yl)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	75	—
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-benzo[d]imidazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	74	—
cis-2-(4-(cyclopentyl(methyl)amino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-6-methyl-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-pyrrolo[3,4-b]pyridine-3-carboxamide	144	+
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(quinolin-7-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	73	+++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-(oxetan-3-yl)-1H-indazol-6-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	59	++
cis-1-(2-fluoro-6-methylbenzoyl)-N-(quinolin-7-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	90	+++
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	121	+++
(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	126	+
cis-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazolo[4,3-b]pyridin-6-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	189	+
cis-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	158	+++
(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	89	++
cis-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	135	++
cis-N-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	136	+
cis-2-(4-((3,3-dimethylmorpholino)methyl)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	141	+

(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-N-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	51	++
(2R,3S,4aR,7aR)-N-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide.	94	+
cis-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((1-methylpiperidin-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	117	+
cis-1-(2-fluoro-6-methylbenzoyl)-N-phenyl-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	129	+
cis-1-(2-fluoro-6-methylbenzoyl)-N-(pyridin-3-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	128	+
cis-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-pyrazol-4-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	127	+
(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-N-(4-(dimethylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)octahydrofuro[3,4-b]pyridine-3-carboxamide	124	+
(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	96	+
(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide	98	++
(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1H-indazol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	138	+
(2R,3S,4aR,7aS)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indol-5-yl)octahydrofuro[3,4-b]pyridine-3-carboxamide	139	+
((2R,3S)-3-(5-(tert-butyl)benzo[d]oxazol-2-yl)-2-(4-(cyclopentylamino)phenyl)piperidin-1-yl)(2-fluoro-6-methylphenyl)methanone	181	+
((2R,3S)-3-(6-(tert-butyl)-1H-benzo[d]imidazol-2-yl)-2-(4-(cyclopentylamino)phenyl)piperidin-1-yl)(2-fluoro-6-methylphenyl)methanone	180	+

(2R,3S)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)piperidine-3-carboxamide	159	+
((2R,3R)-2-(4-(cyclopentylamino)phenyl)-3-(((4-methyl-3-(trifluoromethyl)phenyl)amino)methyl)piperidin-1-yl)(2-fluoro-6-methylphenyl)methanone	160	+

–: $IC_{50} > 5000$ nM in migration assay; or $IC_{50} > 10000$ nM in Ca^{2+} flux assay
 +: $5000 \text{ nM} \geq IC_{50} \geq 2000 \text{ nM}$ in migration assay (compound shows weak activity at 2000 nM and the % inhibition is less than 50%) or $10000 \text{ nM} \geq IC_{50} \geq 2000 \text{ nM}$
 ++: $500 \text{ nM} \leq IC_{50} < 2000 \text{ nM}$;
 +++: $50 \text{ nM} \leq IC_{50} < 500 \text{ nM}$;
 ++++: $IC_{50} < 50 \text{ nM}$.

Example B4: *In vivo* characterization of selected compounds

[0454] Compound Nos. 47, 49, and 89 were used for *in vivo* characterization of their activities. The names of the compounds are shown in Table B4.

Table B4

Compound No.	Compound name
47	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(4-methyl-3-(trifluoromethyl)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
49	(2R,3S,4aR,7aR)-2-(4-(cyclopentylamino)phenyl)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide
89	(2R,3S,4aR,7aR)-1-(2-fluoro-6-methylbenzoyl)-N-(1-methyl-1H-indazol-5-yl)-2-(4-((tetrahydro-2H-pyran-4-yl)amino)phenyl)octahydro-1H-cyclopenta[b]pyridine-3-carboxamide

C5a induced neutropenia in a Cynomolgus model

[0455] To study the efficacy of compounds in a non-human primate model, human C5a (hC5a) induced neutropenia is studied in a cynomolgus model. Intravenous injection of hC5a induced upregulation of adhesion molecules on blood vessel walls, leading to decreased neutrophils in the blood stream and attached to the vascular walls. Monkeys were pre-dosed with vehicle or specific compound, and 4 hours later, hC5a (10 µg/kg, ACROBiosystems) was administered and 1 minute later neutrophils are quantified in peripheral blood. The experimental design is shown in FIG. 1A.

[0456] FIG. 1B shows that compound Nos. 47 and 49 effectively rescued the neutropenia induced by human C5a in cynomolgus monkey compared to vehicle as the negative control. The percent change in the number of neutrophils in the blood collected after C5a injection (241min) was calculated relative to the sample collected prior to C5a injection (239min). The plasma concentration of each compound was calculated as the average concentration prior to C5a injection of 2 individual monkeys.

C5a induced neutropenia in human C5aR knock-in mice model

[0457] To study the efficacy of compounds in an animal model, human C5aR knock-in mice were created by replacing the coding region of mouse C5aR with human C5aR coding sequence. Intravenous injection of hC5a induced upregulation of adhesion molecules on blood vessel walls, leading to decreased neutrophils in the blood stream and attached to the vascular walls. Human C5aR knock-in mice were pre-dosed with vehicle or specific compound, and 2 hours later, human C5a (20µg/kg, ACROBiosystems) was administered and 1 minute later neutrophils are quantified in peripheral blood. The experimental design is shown in FIG. 2A.

[0458] FIG. 2B shows that compound #49 effectively rescued the neutropenia induced by human C5a in human C5aR knock-in mice at 0.3 mg/kg and 3 mg/kg. The percent change in the number of neutrophils in the blood collected after C5a injection (121min), relative to the sample collected prior to C5a injection (119min). The plasma concentration of each compound is the average concentration prior to C5a injection of 3 individual mice.

Neutrophil CD11b FACS assay

[0459] Peripheral blood samples were collected from Cynomolgus monkey/huC5aR knock-in mice at indicated timepoints. 100µl aliquots were mixed with a range of C5a concentrations and incubated at 37°C for 30min. Blood was cooled down on wet ice for at least 3min, anti-CD11b monoclonal antibody (BD Biosciences) was added and incubated at 4°C for 60min. Red blood cells were lysed by adding erythrocyte lysis buffer (Solarbio) and incubated on ice for 10min, white blood cells were washed by pre-cold PBS twice and suspended by 2% PFA/PBS buffer. Neutrophils were classified with flow cytometry by their forward/side-scatter properties and mean fluorescence intensity of anti-CD11b staining on cells was read by FACS (Beckman).

[0460] FIG. 3 shows that C5a induced CD11b upregulation on granulocytes ex-vivo in cyno monkey whole blood was blocked by orally pre-dosing compound Nos. 47 and 49 at

10mg/kg. The EC50 values of compound No. 47 and 49 were comparable at 2.759×10^{-7} M and 2.559×10^{-7} M, respectively. The percent of CD11b signal was calculated by the formula $\% = (\text{MFI}[\text{C5a conc.}] - \text{MFI}[\text{C5a=0}]) / (\text{MFI}[\text{max}] - \text{MFI}[\text{C5a=0}]) \times 100\%$. Each data point was the average of 2 individual monkeys. The plasma concentration of each compound is the average concentration prior to C5a injection of 2 individual monkeys.

[0461] FIG. 4 shows that CD11b upregulation on neutrophil was blocked by orally pre-dosing compound No. 49 in mice whole blood at 0.3 mg/kg and 3mg/kg, at 2 hours and 12 hours post-dosing. Whole blood was collected at indicated timepoints (2 hours or 12 hours after dosing compound) and further stimulated with human C5a in vitro. CD11b FACS antibody was added and incubate for 60min at 4C before red blood cells were lysed. The percent of CD11b signal was calculated by the formula $\% = (\text{MFI}[\text{C5a conc.}] - \text{MFI}[\text{C5a=0}]) / (\text{MFI}[\text{max}] - \text{MFI}[\text{C5a=0}]) \times 100\%$. Each data point was the average $\pm$ SD of 3 individual mice.

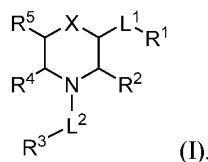
[0462] FIG. 5 shows that CD11b upregulation on neutrophil was blocked by orally pre-dosing compound Nos. 47 and 89 in mice whole blood at 0.3 mg/kg and 3 mg/kg at 2 hours after dosing. Whole blood was collected at 2hrs after dosing compound and further stimulated with human C5a in vitro. CD11b FACS antibody was added and incubate for 60min at 4C before red blood cells were lysed. The percent of CD11b signal was calculated by the formula $\% = (\text{MFI}[\text{C5a conc.}] - \text{MFI}[\text{C5a=0}]) / (\text{MFI}[\text{max}] - \text{MFI}[\text{C5a=0}]) \times 100\%$. Each data point was the average of 2 individual mice.

[0463] FIG. 6 shows that CD11b upregulation on neutrophil was blocked by orally pre-dosing compound Nos. 47 and 49 in mice whole blood at 0.3 mg/kg and 3 mg/kg at 2 hours after dosing. Whole blood was collected at 2hrs after dosing compound and further stimulated with human C5a in vitro. CD11b FACS antibody was added and incubate for 60min at 4C before red blood cells were lysed. The percent of CD11b signal was calculated by the formula $\% = (\text{MFI}[\text{C5a conc.}] - \text{MFI}[\text{C5a=0}]) / (\text{MFI}[\text{max}] - \text{MFI}[\text{C5a=0}]) \times 100\%$. Each data point was the average $\pm$ SD of 2 individual mice.

[0464] All publications, including patents, patent applications, and scientific articles, mentioned in this specification are herein incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, including patent, patent application, or scientific article, were specifically and individually indicated to be incorporated by reference.

CLAIMS

1. A compound of formula (I),



or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

X is -O- or -CHR⁶-,

provided that when X is -O-, then L¹ is *-C(O)NH-* and L² is -C(O)-;

R¹ is C₃₋₁₂ cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, or C₆₋₁₄ aryl, each of which is independently optionally substituted with one or more R¹¹,

wherein each R¹¹ is independently oxo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, -CN, -OR^{1a}, -SR^{1a}, -NR^{1a}R^{1b}, -NO₂, -C(O)R^{1a}, -OC(O)R^{1a}, -C(O)OR^{1a}, -C(O)NR^{1a}R^{1b}, -OC(O)NR^{1a}R^{1b}, -NR^{1a}C(O)R^{1b}, -NR^{1a}C(O)OR^{1b}, -S(O)R^{1a}, -S(O)₂R^{1a}, -NR^{1a}S(O)R^{1b}, -C(O)NR^{1a}S(O)R^{1b}, -NR^{1a}S(O)₂R^{1b}, -C(O)NR^{1a}S(O)₂R^{1b}, -S(O)NR^{1a}R^{1b}, -S(O)₂NR^{1a}R^{1b}, -P(O)R^{1a}R^{1b}, C₃₋₆ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C₆₋₁₄ aryl, -(C₁₋₆ alkylene) NR^{1a}R^{1b}, -(C₁₋₆ alkylene) C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene) 3- to 12-membered heterocyclyl, -(C₁₋₆ alkylene) 5- to 12-membered heteroaryl, or -(C₁₋₆ alkylene) C₆₋₁₄ aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, hydroxyl, C₁₋₆ alkoxy, and -CN,

wherein R^{1a} and R^{1b} are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C₆₋₁₄ aryl, or

R^{1a} and R^{1b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, hydroxyl, C₁₋₆ alkoxy, and -CN;

R^2 is C_{3-12} cycloalkyl, 3- to 12- membered heterocyclyl, or C_{6-14} aryl, each of which is independently optionally substituted with one or more $-Q-W$, wherein:

Q is C_{1-6} alkylene, $-(N-L^3-R^Q)-$ or $-O-$,

wherein R^Q is H, C_{1-6} alkyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, and

L^3 is $-C(O)-$, $^*-C(O)O-CH_2-^{**}$, or a bond, wherein $*$ indicates the point of attachment to N and ** indicates the point of attachment to R^Q , W is H, C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, each of which is independently optionally substituted with one or more R^7 ;

R^3 is H, C_{3-12} cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, wherein the C_{3-12} cycloalkyl, 3- to 12- membered heterocyclyl, 5- to 12-membered heteroaryl, and C_{6-14} aryl are each independently optionally substituted with one or more R^{31} ,

wherein each R^{31} is independently oxo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, $-CN$, $-OR^{3a}$, $-SR^{3a}$, $-NR^{3a}R^{3b}$, $-NO_2$, $-C(O)R^{3a}$, $-OC(O)R^{3a}$, $-C(O)OR^{3a}$, $-C(O)NR^{3a}R^{3b}$, $-OC(O)NR^{3a}R^{3b}$, $-NR^{3a}C(O)R^{3b}$, $-NR^{3a}C(O)OR^{3b}$, $-S(O)R^{3a}$, $-S(O)_2R^{3a}$, $-NR^{3a}S(O)R^{3b}$, $-C(O)NR^{3a}S(O)R^{3b}$, $-NR^{3a}S(O)_2R^{3b}$, $-C(O)NR^{3a}S(O)_2R^{3b}$, $-S(O)NR^{3a}R^{3b}$, $-S(O)_2NR^{3a}R^{3b}$, $-P(O)R^{3a}R^{3b}$, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C_{6-14} aryl, $-(C_{1-6}$ alkylene) $NR^{3a}R^{3b}$, $-(C_{1-6}$ alkylene) C_{3-6} cycloalkyl, $-(C_{1-6}$ alkylene) 3- to 12-membered heterocyclyl, $-(C_{1-6}$ alkylene) 5- to 12-membered heteroaryl, or $-(C_{1-6}$ alkylene) C_{6-14} aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and $-CN$,

wherein R^{3a} and R^{3b} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, or

R^{3a} and R^{3b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and $-CN$; and

R^4 , R^5 , and R^6 are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, $-CN$, hydroxyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered

heteroaryl, or C₆₋₁₄ aryl, wherein the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, and C₆₋₁₄ aryl are each independently optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, hydroxyl, C₁₋₆ alkoxy, and -CN, and wherein,

R⁴ and R⁵ or R⁵ and R⁶ may be taken together with the carbon atoms to which they are attached to form a ring B which is independently optionally substituted with one or more R⁸, wherein ring B is C₃₋₁₂ cycloalkyl or 3- to 12- membered heterocyclyl, and

R⁴ may be taken with the carbon atom to which it is attached, the nitrogen atom adjacent to the carbon atom, L², and part of R³ to form a 6- to 8- membered heterocyclyl; each R⁷ is independently oxo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, -CN, -OR^{7a}, -SR^{7a}, -NR^{7a}R^{7b}, -NO₂, -C(O)R^{7a}, -OC(O)R^{7a}, -C(O)OR^{7a}, -C(O)NR^{7a}R^{7b}, -OC(O)NR^{7a}R^{7b}, -NR^{7a}C(O)R^{7b}, -NR^{7a}C(O)OR^{7b}, -S(O)R^{7a}, -S(O)₂R^{7a}, -NR^{7a}S(O)R^{7b}, -C(O)NR^{7a}S(O)R^{7b}, -NR^{7a}S(O)₂R^{7b}, -C(O)NR^{7a}S(O)₂R^{7b}, -S(O)NR^{7a}R^{7b}, -S(O)₂NR^{7a}R^{7b}, -P(O)R^{7a}R^{7b}, C₃₋₆ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C₆₋₁₄ aryl, -(C₁₋₆ alkylene) NR^{7a}R^{7b}, -(C₁₋₆ alkylene)C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene) 3- to 12-membered heterocyclyl, -(C₁₋₆ alkylene) 5- to 12-membered heteroaryl, or -(C₁₋₆ alkylene) C₆₋₁₄ aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, hydroxyl, C₁₋₆ alkoxy, and -CN, wherein

R^{7a} and R^{7b} are each independently H, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C₆₋₁₄ aryl, or

R^{7a} and R^{7b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, hydroxyl, C₁₋₆ alkoxy, and -CN;

each R⁸ is independently oxo, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, halogen, -CN, -OR^{8a}, -SR^{8a}, -NR^{8a}R^{8b}, -NO₂, -C(O)R^{8a}, -OC(O)R^{8a}, -C(O)OR^{8a}, -C(O)NR^{8a}R^{8b}, -OC(O)NR^{8a}R^{8b}, -NR^{8a}C(O)R^{8b}, -NR^{8a}C(O)OR^{8b}, -S(O)R^{8a}, -S(O)₂R^{8a}, -NR^{8a}S(O)R^{8b}, -C(O)NR^{8a}S(O)R^{8b}, -NR^{8a}S(O)₂R^{8b}, -C(O)NR^{8a}S(O)₂R^{8b}, -S(O)NR^{8a}R^{8b}, -S(O)₂NR^{8a}R^{8b}, -P(O)R^{8a}R^{8b}, C₃₋₆ cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, C₆₋₁₄ aryl, -(C₁₋₆ alkylene) NR^{8a}R^{8b}, -(C₁₋₆ alkylene)C₃₋₆ cycloalkyl, -(C₁₋₆ alkylene) 3- to 12-

membered heterocyclyl, $-(C_{1-6} \text{ alkylene})$ 5- to 12-membered heteroaryl, or $-(C_{1-6} \text{ alkylene})$ C_{6-14} aryl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and $-CN$, wherein

R^{8a} and R^{8b} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} cycloalkyl, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, or C_{6-14} aryl, or

R^{8a} and R^{8b} are taken together with the nitrogen atom to which they attach to form a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and $-CN$;

L^1 is $^*-C(O)NH-^{**}$, a bond, $-C(O)-$, $^*-CH_2-NH-^{**}$, or $^*-C(O)NH-CH_2-^{**}$, wherein $*$ indicates the point of attachment to the carbon atom of the piperidine and ** indicates the point of attachment to R^1 ;

L^2 is $-C(O)-$, a bond, $-CH_2-$, $-S(O)_2-$, or $\#-S(O)_2-CH_2-##$, wherein $\#$ indicates the point of attachment to the nitrogen atom and $##$ indicates the point of attachment to R^3 ,

provided that when X is $-CHR^6-$ and R^4 , R^5 , and R^6 are all H, then at least one of the following conditions apply:

(1) L^1 is a bond, $-C(O)-$, $^*-CH_2-NH-^{**}$, or $^*-C(O)NH-CH_2-^{**}$,

(2) L^2 is a bond, $-CH_2-$, $-S(O)_2-$, or $\#-S(O)_2-CH_2-##$, and

(3) R^2 is phenyl substituted with one or more $-Q-W$, wherein Q is $-(N-L^3-R^Q)-$ and R^Q is 5- to 12-membered heteroaryl or C_{6-14} aryl.

2. The compound claim 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^4 and R^5 are taken together with the carbon atoms to which they are attached to form a ring B, which is optionally substituted with one or more R^8 .

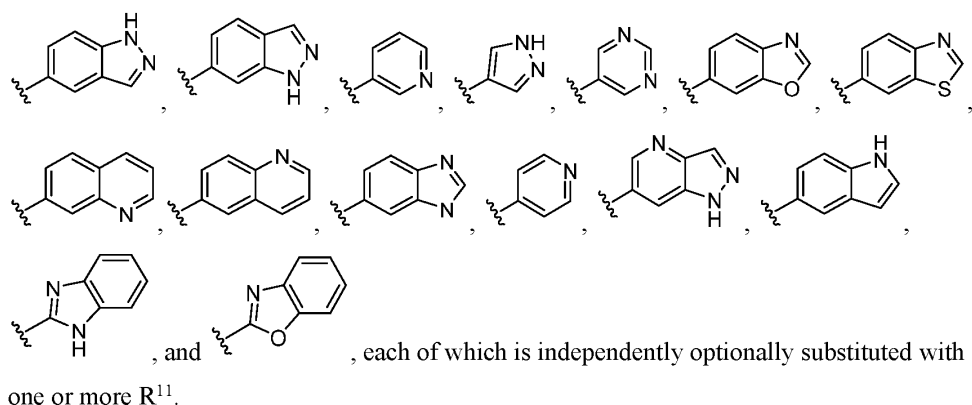
3. The compound of claim 1 or 2, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein ring B is a C_{3-12} cycloalkyl, which is optionally substituted with one or more R^8 .

4. The compound of claim 3, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein ring B is cyclopentyl, which is optionally substituted with one or more R^8 .

5. The compound of claim 1 or 2, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein ring B is a 3- to 12- membered heterocyclyl, which is optionally substituted with one or more R⁸.
6. The compound of claim 5, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein the ring B is tetrahydrofuranyl, which is optionally substituted with one or more R⁸.
7. The compound of claim 5, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein B is pyrrolidinyl, which is optionally substituted with one or more R⁸.
8. The compound of any one of claims 1-7, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R⁸ is independently C₁₋₆ alkyl, C₃₋₆ cycloalkyl, 3- to 12-membered heterocyclyl, or -C(O)R^{8a}, each of which is independently optionally substituted with one or more halogen.
9. The compound of claim 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R⁴ is H.
10. The compound of claim 1 or 9, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R⁵ is H or hydroxyl.
11. The compound of claims 1-10, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein X is -CHR⁶-, wherein R⁶ is H.
12. The compound of claim 1, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R⁴ is taken with the carbon atom to which it is attached, the nitrogen atom adjacent to the carbon atom, L², and part of R³ to form a 6- to 8- membered heterocyclyl.
13. The compound of any one of claims 1-12, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R¹ is C₆₋₁₄ aryl, which is optionally substituted with one or more R¹¹.
14. The compound of claim 13, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R¹ is phenyl, which is optionally substituted with one or more R¹¹.

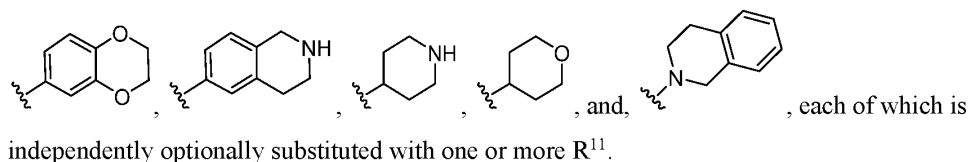
15. The compound of any one of claims 1-12, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is 5- to 12-membered heteroaryl, which is optionally substituted with one or more R^{11} .

16. The compound of claim 15, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is selected from the group consisting of:



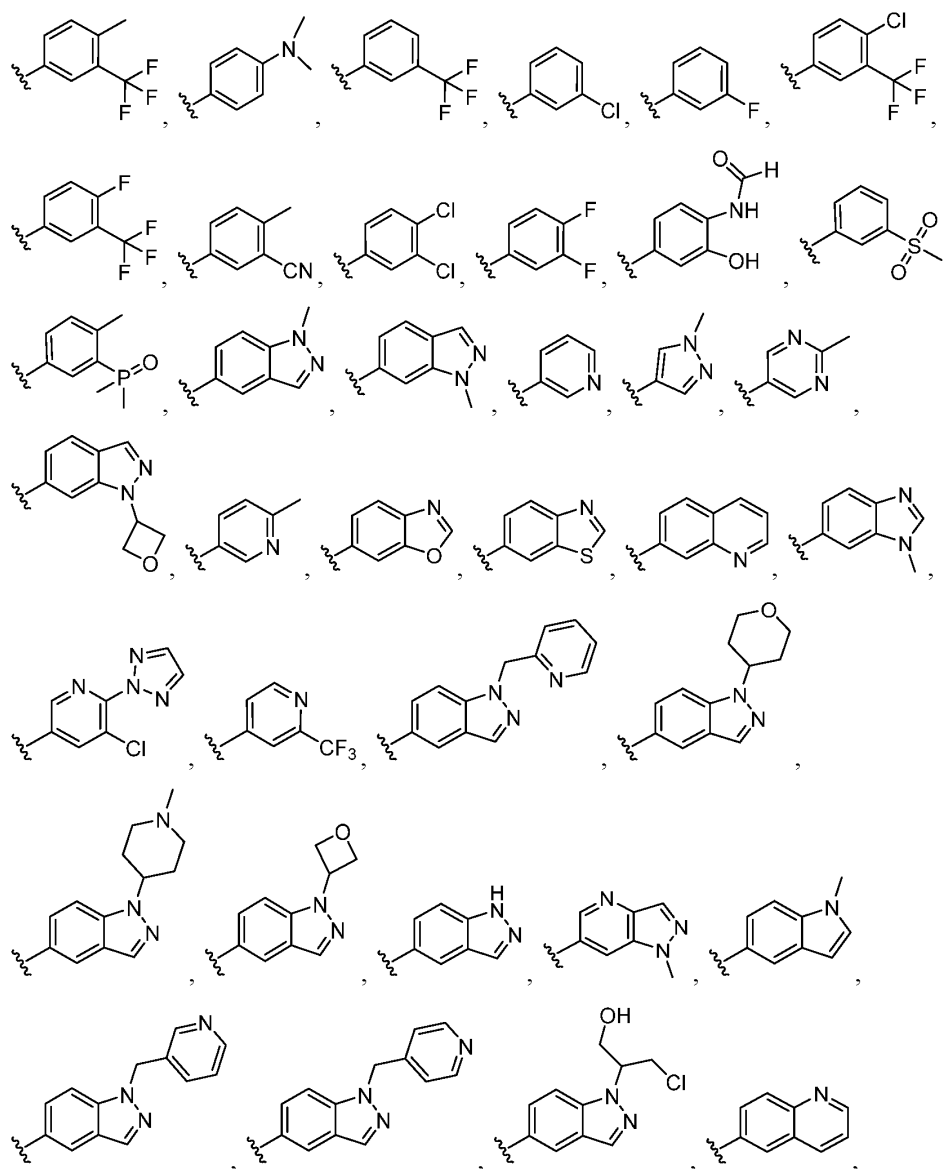
17. The compound of any one of claims 1-12, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is 3- to 12-membered heterocyclyl optionally substituted with one or more R^{11} .

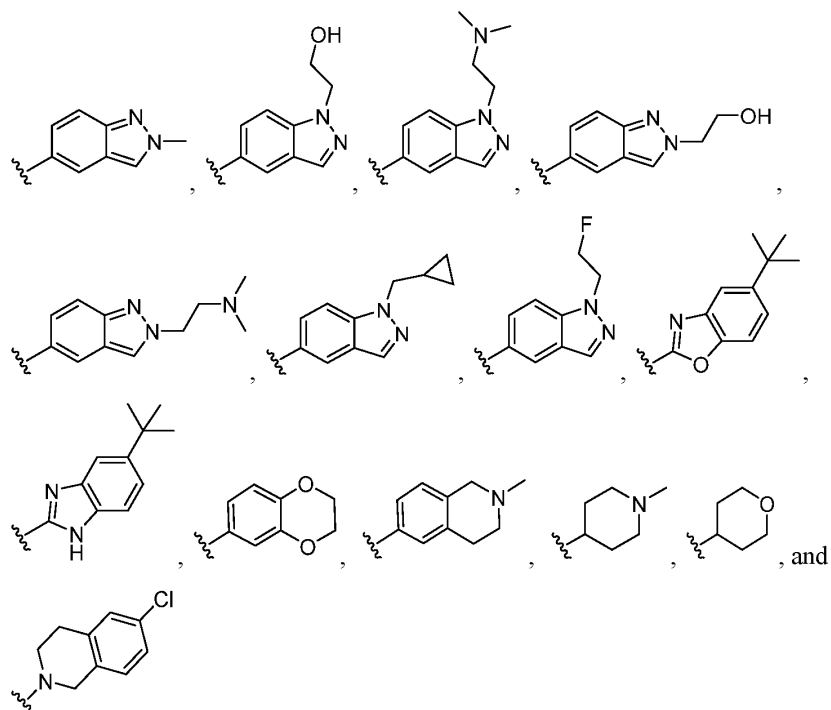
18. The compound of claim 17, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is selected from the group consisting of:



19. The compound of any one of claims 1-18, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^{11} is independently C_{1-6} alkyl, $-NR^{1a}R^{1b}$, halogen, $-CN$, $-OR^{1a}$, $-NR^{1a}C(O)R^{1b}$, $-S(O)_2R^{1a}$, $-P(O)R^{1a}R^{1b}$, 3- to 12-membered heterocyclyl, 5- to 12-membered heteroaryl, $-(C_{1-6} \text{ alkylene})$ 5- to 12-membered heteroaryl, $-(C_{1-6} \text{ alkylene}) NR^{1a}R^{1b}$, or $-(C_{1-6} \text{ alkylene}) C_{3-6}$ cycloalkyl, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and $-CN$.

20. The compound of any one of claims 1-12, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is selected from the group consisting of:

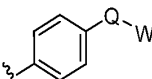




21. The compound of any one of claims 1-20, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{6-14} aryl optionally substituted with one or more $-Q-W$.

22. The compound of claim 21, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is phenyl optionally substituted with one or more $-Q-W$.

23. The compound of claim 22, or a stereoisomer, tautomer, or a pharmaceutically

acceptable salt of any of the foregoing, wherein R^2 is .

24. The compound of any one of claims 1-23, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q is C_{1-6} alkylene.

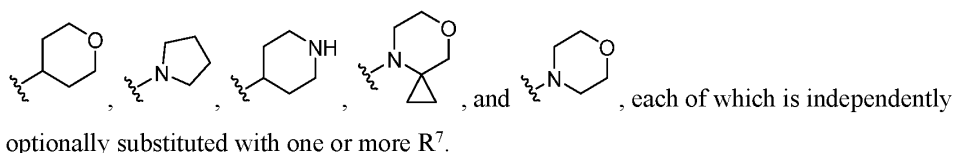
25. The compound of claim 24, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q is $-CH_2-$.

26. The compound of any one of claims 1-23, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q is $-O-$.

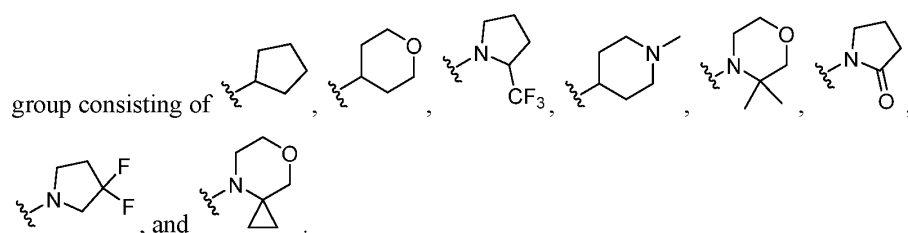
27. The compound of any one of claims 1-23, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q is $-(N-L^3-R^Q)-$.
28. The compound of claim 27, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^Q is H.
29. The compound of claim 27, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^Q is 5- to 12-membered heteroaryl or C_{6-14} aryl.
30. The compound of any one of claims 1-29, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein W is C_{3-12} cycloalkyl, which is optionally substituted with one or more R^7 .

31. The compound of claim 30, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein W is , which is optionally substituted with one or more R^7 .

32. The compound of any one of claims 1-29, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein W is 3- to 12- membered heterocyclyl, which is optionally substituted with one or more R^7 .
33. The compound of claim 32, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein W is selected from the group consisting of:



34. The compound of any one of claims 1-33, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^7 is independently oxo, C_{1-6} alkyl, or halogen, wherein the C_{1-6} alkyl is optionally substituted with one or more halogen.
35. The compound of any one of claims 1-29, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein W is selected from the

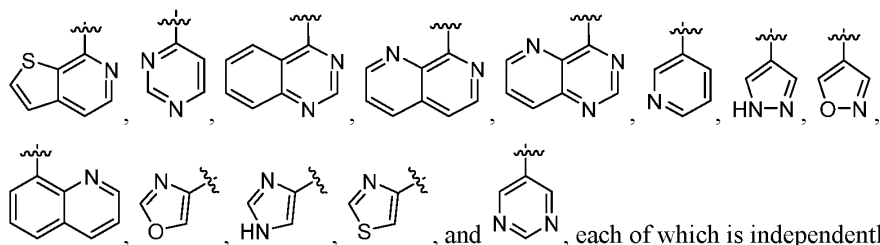


36. The compound of any one of claims 1-35, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R³ is C₆₋₁₄ aryl, which is independently optionally substituted with one or more R³¹.

37. The compound of claim 36, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R³ is phenyl, which is optionally substituted with one or more R³¹.

38. The compound of any one of claims 1-35, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R³ is 5- to 12-membered heteroaryl, which is independently optionally substituted with one or more R³¹.

39. The compound of claim 38, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R³ is selected from the group consisting of:

optionally substituted with one or more R³¹.

40. The compound of any one of claims 1-35, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R³ is 3- to 12- membered heterocyclyl, which is independently optionally substituted with one or more R³¹.

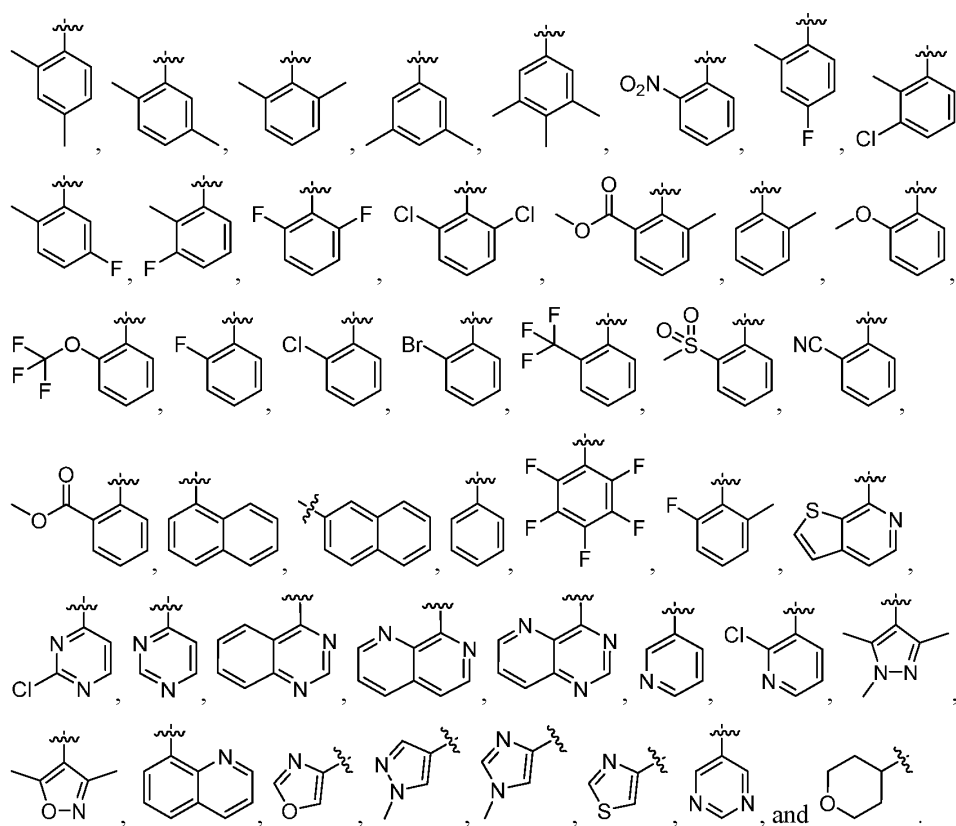
41. The compound of claim 40, or a stereoisomer, tautomer, or a pharmaceutically



acceptable salt of any of the foregoing, wherein R³ is , which is independently optionally substituted with one or more R³¹.

42. The compound of any one of claims 1-41, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein each R^{31} is independently C_{1-6} alkyl, $-CN$, $-NO_2$, halogen, $-OR^{3a}$, $-C(O)OR^{3a}$, or $-S(O)_2R^{3a}$, each of which is independently optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, hydroxyl, C_{1-6} alkoxy, and $-CN$.

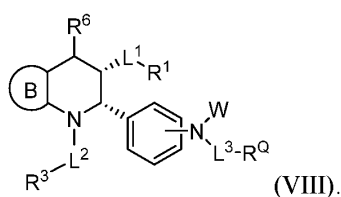
43. The compound of any one of claims 1-35, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^3 is selected from the group consisting of:



44. The compound of any one of claims 1-43, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^1 is $^*-C(O)NH-^{**}$.

45. The compound of any one of claims 1-43, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^1 is a bond.

46. The compound of any one of claims 1-43, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^1 is $-C(O)-$.
47. The compound of any one of claims 1-43, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^1 is $*-C(O)NH-CH_2-^{**}$.
48. The compound of any one of claims 1-43, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^1 is $*-C(O)NH-CH_2-^{**}$.
49. The compound of any one of claims 1-48, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^2 is $-C(O)-$.
50. The compound of any one of claims 1-48, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^2 is a bond.
51. The compound of any one of claims 1-48, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^2 is $-S(O)_2-$.
52. The compound of any one of claims 1-48, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^2 is $\#-S(O)_2-CH_2-^{\#}$.
53. The compound of claim 1, where the compound is of formula (VIII),



54. A compound selected from the group consisting of the compounds in Table 1, or a pharmaceutically acceptable salt of any of the foregoing.
55. A pharmaceutical composition comprising the compound of any one of claims 1-54, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing, and a pharmaceutically acceptable carrier or excipient.
56. A kit comprising the compound of any one of claims 1-54, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing.
57. A method of inhibiting C5a receptor, comprising contacting C5a receptor with a compound of any one of claims 1-54, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing.

58. A method of treating a disorder mediated by the complement pathways in a subject, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-54, or a stereoisomer, tautomer, or a pharmaceutically acceptable salt of any of the foregoing.

59. The method of claim 58, wherein the disorder is an inflammatory disease, a cardiovascular or cerebrovascular disease, or an autoimmune disease.

60. The method of claim 59, wherein the disorder is an autoimmune disease.

61. The method of any one of claims 58-60, wherein the disease or disorder is at least selected from the group consisting of: macular degeneration (MD), age-related macular degeneration (AMD), ischemia reperfusion injury, arthritis, rheumatoid arthritis, lupus, ulcerative colitis, stroke, post-surgery systemic inflammatory syndrome, asthma, allergic asthma, chronic obstructive pulmonary disease (COPD), paroxysmal nocturnal hemoglobinuria (PNH) syndrome, autoimmune hemolytic anemia (AIHA), Gaucher disease, myasthenia gravis, neuromyelitis optica, (NMO), multiple sclerosis, delayed graft function, antibody-mediated rejection, atypical hemolytic uremic syndrome (aHUS), central retinal vein occlusion (CRVO), central retinal artery occlusion (CRAO), epidermolysis bullosa, sepsis, septic shock, organ transplantation, inflammation (including, but not limited to, inflammation associated with cardiopulmonary bypass surgery and kidney dialysis), C3 glomerulopathy, membranous nephropathy, IgA nephropathy, glomerulonephritis (including, but not limited to, anti-neutrophil cytoplasmic antibody (ANCA)-mediated glomerulonephritis, lupus nephritis, and combinations thereof), ANCA-mediated vasculitis, Shiga toxin induced HUS, and antiphospholipid antibody-induced pregnancy loss, graft versus host disease (GVHD), bullous pemphigoid, hidradenitis suppurativa, dermatitis herpetiformis, sweets syndrome, pyoderma gangrenosum, palmo-plantar pustulosis & pustular psoriasis, rheumatoid neutrophilic dermatoses, subcorneal pustular dermatosis, bowel-associated dermatosis-arthritis syndrome, neutrophilic eccrine hidradenitis, linear IgA disease, or any combinations thereof.