AZA-TETRACYCLIC OXAZEPINE COMPOUNDS AND USES THEREOF

BACKGROUND

[0001] Ras is a small GTP-binding protein that functions as a nucleotide-dependent switch for central growth signaling pathways. In response to extracellular signals, Ras is converted from a GDP-bound (Ras^{GDP}) to a GTP-bound (Ras^{GTP}) state, as catalyzed by guanine nucleotide exchange factors (GEFs), notably the SOS1 protein. Active Ras^{GTP} mediates its diverse growth-stimulating functions through its direct interactions with effectors including Raf, PI3K, and Ral guanine nucleotide dissociation stimulator. The intrinsic GTPase activity of Ras then hydrolyzes GTP to GDP to terminate Ras signaling. The Ras GTPase activity can be further accelerated by its interactions with GTPase-activating proteins (GAPs), including the neurofibromin 1 tumor suppressor.

[0002] Mutant Ras has a reduced GTPase activity, which prolongs its activated state, thereby promoting Ras-dependent signaling and cancer cell survival or growth. Mutation in Ras that affects its ability to interact with GAP or to convert GTP back to GDP will result in a prolonged activation of the protein and consequently a prolonged signal to the cell telling it to continue to grow and divide. Because these signals result in cell growth and division, overactive RAS signaling may ultimately lead to cancer. Mutations in any one of the three main isoforms of RAS (HRas, NRas, or KRas) genes are common events in human tumorigenesis. Among the three Ras isoforms (K, N, and H), KRas is most frequently mutated.

[0003] The most common KRas mutations are found at residue G12 and G13 in the P-loop and at residue Q61. G12D is a frequent mutation of KRas gene (glycine-12 to aspartate). Mutations of Ras in cancer are associated with poor prognosis. Inactivation of oncogenic Ras in mice results in tumor shrinkage. Thus, Ras is widely considered an oncology target of exceptional importance.

[0004] Accordingly, there is a pressing need for therapies for G12D mutant KRas mediated cancers.

BRIEF SUMMARY

[0005] Provided herein are solutions to the problems above and other problems in the art.

[0006] In a first aspect provided herein is a compound of formula (I) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein.

[0007] In a second aspect provided herein is a compound of formula (IId) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein.

[0008] In another aspect provided herein is a compound or pharmaceutically acceptable salt thereof as set forth in Table 1.

[0009] In another aspect provided herein is a pharmaceutical composition comprising a compound, stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein.

[0010] In another aspect provided herein is a method of treating a cancer comprising a KRas mutation, the method comprising administering to a patient having such cancer, a compound, stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein.

[0011] In another aspect provided herein is a method for regulating activity of a KRas mutant protein, the method comprising reacting the mutant protein with a compound, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein.

[0012] In another aspect provided herein is a method for inhibiting proliferation of a cell population, the method comprising contacting the cell population with a compound, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein.

[0013] In another aspect provided herein is a method for inhibiting tumor metastasis comprising administering to an individual in need thereof a therapeutically effective amount of the compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein or a pharmaceutical composition as described herein to a subject in need thereof.

In another aspect provided herein is method for preparing a labeled KRas G12D mutant protein, the method comprising reacting a KRas G12D mutant protein with a labeled compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, as described here to result in the labeled KRas G12D mutant protein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figure 1 shows the pharmacokinetic profile of compounds 6, 7, 81, and 194, and comparator compound.

DETAILED DESCRIPTION

Definitions

[0015] Disclosed herein are 6-aza tetracyclic oxazepine compounds as described herein or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof and pharmaceutical compositions thereof that, in certain embodiments, are inhibitors or modulators of mutant KRas. In certain instances, such compounds and compositions are inhibitors or modulators of mutant G12D KRas as provided herein. The compounds and compositions

described herein are useful in treating diseases and disorders mediated by mutant KRas, including $KRas^{G12D}$ mutations.

[0016] While the disclosure herein provides enumerated embodiments, it is understood that they are not intended to limit the compounds and methods described herein to those embodiments. On the contrary, the disclosure is intended to cover all alternatives, modifications, and equivalents that can be included within the scope of the present disclosure as defined by the claims.

[0017] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. The nomenclature used in this Application is based on IUPAC systematic nomenclature, unless indicated otherwise.

[0018] The following definitions are provided to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure. All references referred to herein are incorporated by reference in their entirety.

[0019] The terms “halogen” and “halo” are used interchangeably and refer to F, Cl, Br or I. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl, polyhaloalkyl, and perhaloalkyl.

[0020] The term "alkyl" refers to a saturated linear or branched-chain monovalent hydrocarbon radical. In one example, the alkyl radical is one to eighteen carbon atoms (C_{1-18}). In other examples, the alkyl radical is C_{1-12}, C_{1-10}, C_{1-8}, C_{1-6}, C_{1-5}, C_{1-4}, or C_{1-3}. Examples of alkyl groups include methyl (Me, $–CH_3$), ethyl (Et, $–CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $–CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $–CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $–CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $–CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $–CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $–C(CH_3)_3$), 1-pentyl (n-pentyl, $–CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($–CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($–CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($–CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($–CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($–CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($–CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($–CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($–CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($–C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($–CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($–CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($–C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($–CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($–C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($–CH(CH_3)C(CH_3)_3$, 1-heptyl and 1-octyl.

[0021] The term “oxo” refers to =O.

[0022] The term "alkoxy" refers to –O–alkyl.

[0023] The terms “cyano” or “nitrile” refers to –C≡N or –CN.

[0024] The term "haloalkoxy" refers to –O–haloalkyl.

[0025] The terms "hydroxy" and “hydroxyl” refer to –OH.

[0026] The term “alkylidene” refers to linear or branched-chain monovalent hydrocarbon radical having formula =CR’R", where R’ and R" can be the same or different. In one example, an alkylidene radical is 1 to 6 carbons (C_{1-6}). In another example, the alkylidene radical is C_{1-3}, C_{1-2}, or C_1. Exemplary alkylidenes include, but are not limited to, methylidene (=CH_2), ethylidene (=$CHCH_3$), and propylidene (=CH-CH_2-CH_3).

[0027] The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical with at least one carbon-carbon double bond and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. In one example, the alkenyl radical is two to eighteen carbon atoms (C_{2-18}). In other examples, the alkenyl radical is C_{2-12}, C_{2-10}, C_{2-8}, C_{2-6}, or C_{2-3}. Examples include, but are not limited to, ethenyl or vinyl (–CH=CH_2), prop-1-enyl (–CH=$CHCH_3$), prop-2-enyl (–CH_2CH=CH_2), 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, and hexa-1,3-dienyl.

[0028] The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical with at least one carbon-carbon, triple bond. In one example, the alkynyl radical is two to eighteen carbon atoms (C_{2-18}). In other examples, the alkynyl radical is C_{2-12}, C_{2-10}, C_{2-8}, C_{2-6}, or C_{2-3}. Examples include, but are not limited to, ethynyl (–C°CH), prop-1-ynyl (–C°CCH_3), prop-2-ynyl (propargyl, –CH_2C°CH), but-1-ynyl, but-2-ynyl, and but-3-ynyl.

[0029] The term "alkylene” refers to a saturated, branched, or straight chain hydrocarbon group having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. In one example, the divalent alkylene group is one to eighteen carbon atoms (C_{1-18}). In other examples, the divalent alkylene group is C_{1-12}, C_{1-10}, C_{1-8}, C_{1-6}, C_{1-5}, C_{1-4}, or C_{1-3}. Example alkylene groups include methylene (–CH_2–), 1,1-ethyl (–CH(CH_3)–), (1,2-ethyl (–CH_2CH_2–), 1,1-propyl (–CH(CH_2CH_3)–), 2,2-propyl (–$C(CH_3)_2$–), 1,2-propyl (–CH(CH_3)CH_2–), 1,3-propyl (–$CH_2CH_2CH_2$–), 1,1-dimethyleth-1,2-yl (–$C(CH_3)_2CH_2$–), 1,4-butyl (–$CH_2CH_2CH_2CH_2$–), and the like.

[0030] The term “cycloalkyl” refers to a saturated hydrocarbon ring group. Cycloalkyl encompasses mono-, bi-, tricyclic, spiro and bridged, saturated ring systems. In one example, the cycloalkyl group is 3 to 12 carbon atoms (C_{3-12}). In other examples, cycloalkyl is C_{3-4}, C_{3-5}, C_{3-7}, C_{3-8}, C_{3-10}, or C_{5-10}. In other examples, the cycloalkyl group, as a monocycle, is C_{3-4}, C_{3-8}, C_{3-6}, or C_{5-6}. In another example, the cycloalkyl group, as a bicycle, is C_7-C_{12}. In another example, the cycloalkyl group, as a spiro system, is C_{5-12}. Examples of monocyclic cycloalkyl include

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl and cyclododecyl. Exemplary arrangements of bicyclic cycloalkyls having 7 to 12 ring atoms include, but are not limited to, [4,4], [4,5], [5,5], [5,6] or [6,6] ring systems. Exemplary bridged bicyclic cycloalkyls include, but are not limited to, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. Examples of spirocycloalkyl include, spiro[2.2]pentane, spiro[2.3]hexane, spiro[2.4]heptane, spiro[2.5]octane and spiro[4.5]decane.

[0031] The terms "heterocyclic group", "heterocyclic", "heterocycle", "heterocyclyl", or "heterocyclo" are used interchangeably and refer to any mono-, bi-, tricyclic, spiro or bridged, saturated, partially saturated or unsaturated, non-aromatic ring system, having 3 to 20 ring atoms, where the ring atoms are carbon, and at least one atom in the ring or ring system is a heteroatom selected from nitrogen, sulfur or oxygen. If any ring atom of a cyclic system is a heteroatom, that system is a heterocycle, regardless of the point of attachment of the cyclic system to the rest of the molecule. In one example, heterocyclyl includes 3-10 ring atoms ("members") and includes monocycles, bicycles, tricycles, spiro, and bridged ring systems, wherein the ring atoms are carbon, where at least one atom in the ring or ring system is a heteroatom selected from nitrogen, sulfur or oxygen. In other examples, heterocyclyl includes 4-10 or 5-10 ring atoms. In one example, heterocyclyl includes 1 to 4 heteroatoms. In one example, heterocyclyl includes 1 to 3 heteroatoms. In another example, heterocyclyl includes 3- to 7-membered monocycles having 1-2, 1-3 or 1-4 heteroatoms selected from nitrogen, sulfur or oxygen. In another example, heterocyclyl includes 4- to 6-membered monocycles having 1-2, 1-3 or 1-4 heteroatoms selected from nitrogen, sulfur or oxygen. In another example, heterocyclyl includes 3-membered monocycles. In another example, heterocyclyl includes 4-membered monocycles. In another example, heterocyclyl includes 5-6 membered monocycles. In some embodiments, a heterocycloalkyl includes at least one nitrogen. In one example, the heterocyclyl group includes 0 to 3 double bonds. Any nitrogen or sulfur heteroatom may optionally be oxidized (e.g., NO, SO, SO_2), and any nitrogen heteroatom may optionally be quaternized (e.g., $[NR_4]^+Cl^-$, $[NR_4]^+OH^-$). Example heterocycles are oxiranyl, aziridinyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, pyrrolidinyl, dihydro-1H-pyrrolyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothienyl, tetrahydrothienyl, imidazolidinyl, piperidinyl, piperazinyl, isoquinolinyl, tetrahydroisoquinolinyl, morpholinyl, thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, dihydropyranyl, tetrahydropyranyl, hexahydrothiopyranyl, hexahydropyrimidinyl, oxazinanyl, thiazinanyl, thioxanyl, homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, oxazepinyl, oxazepanyl, diazepanyl, 1,4-diazepanyl, diazepinyl, thiazepinyl, thiazepanyl, tetrahydrothiopyranyl, oxazolidinyl, thiazolidinyl, isothiazolidinyl, 1,1-dioxoisothiazolidinonyl,

1,1-dioxoisothiazolyl, oxazolidinonyl, imidazolidinonyl, 4,5,6,7-tetrahydro[2H]indazolyl, tetrahydrobenzoimidazolyl, 4,5,6,7-tetrahydrobenzo[d]imidazolyl, thiazinyl, oxazinyl, thiadiazinyl, oxadiazinyl, dithiazinyl, dioxazinyl, oxathiazinyl, thiatriazinyl, oxatriazinyl, dithiadiazinyl, imidazolinyl, dihydropyrimidyl, tetrahydropyrimidyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, thiapyranyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrimidinonyl, pyrimidindionyl, pyrimidin-2,4-dionyl, piperazinonyl, piperazindionyl, pyrazolidinylimidazolinyl, 3-azabicyclo[3.1.0]hexanyl, 3,6-diazabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptanyl, azabicyclo[2.2.2]hexanyl, 2-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 2-azabicyclo[2.2.2]octanyl, 8-azabicyclo[2.2.2]octanyl, 7-oxabicyclo[2.2.1]heptane, azaspiro[3.5]nonanyl, azaspiro[2.5]octanyl, azaspiro[4.5]decanyl, 1-azaspiro[4.5]decan-2-onyl, azaspiro[5.5]undecanyl, tetrahydroindolyl, octahydroindolyl, tetrahydroisoindolyl, tetrahydroindazolyl, 1,1-dioxohexahydrothiopyranyl.

[0032] In particular embodiments, a heterocyclylgroup or a heteroaryl group is attached at a carbon atom of the heterocyclyl group or the heteroaryl group. By way of example, carbon bonded heterocyclyl groups include bonding arrangements at position 2, 3, 4, 5, or 6 of a pyridine ring, position 3, 4, 5, or 6 of a pyridazine ring, position 2, 4, 5, or 6 of a pyrimidine ring, position 2, 3, 5, or 6 of a pyrazine ring, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole ring, position 2, 4, or 5 of an oxazole, imidazole or thiazole ring, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole ring, position 2 or 3 of an aziridine ring, position 2, 3, or 4 of an azetidine ring, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline ring or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline ring.

[0033] In certain embodiments, the heterocyclyl group or heteroaryl group is N-attached. By way of example, nitrogen bonded heterocyclyl or heteroaryl groups include bonding arrangements at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline.

[0034] "Fused" refers to any ring structure described herein that shares one or more atoms (e.g., carbon or nitrogen atoms) with an existing ring structure in the compounds described herein.

[0035] The term "acyl" refers to a carbonyl containing substituent represented by the formula –C(=O)-R in which R is a substituent such as hydrogen, alkyl, cycloalkyl, aryl or heterocyclyl, wherein the alkyl, cycloalkyl, aryl and heterocyclyl are as defined herein. Acyl groups include alkanoyl (e.g., acetyl), aroyl (e.g., benzoyl), and heteroaroyl (e.g., pyridinoyl).

[0036] The term "haloalkyl" refers to an alkyl chain in which one or more hydrogen has been replaced by a halogen. Examples of haloalkyls are trifluoromethyl, difluoromethyl, and fluoromethyl. A substituted haloalkyl refers to a haloalkyl having a moiety other than a halogen. An unsubstituted haloalkyl refers to a haloalkyl substituted with no moiety other than hydrogen or halogen as described herein.

[0037] As used herein a wavy line "〰" that intersects a bond in a chemical structure indicate the point of attachment of the atom to which the wavy bond is connected in the chemical structure to the remainder of a molecule, or to the remainder of a fragment of a molecule.

[0038] In certain embodiments, divalent groups are described generically without specific bonding configurations. It is understood that the generic description is meant to include both bonding configurations, unless specified otherwise. For example, in the group R^1–R^2–R^3, if the group R^2 is described as –$CH_2C(O)$–, then it is understood that this group can be bonded both as R^1–$CH_2C(O)$–R^3, and as R^1–$C(O)CH_2$–R^3, unless specified otherwise.

[0039] The term "pharmaceutically acceptable" refers to molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, such as, for example, a human, as appropriate.

[0040] Compounds described herein may be in the form of a salt, such as a pharmaceutically acceptable salt. "Pharmaceutically acceptable salts" include both acid and base addition salts. "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid and the like, and organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

[0041] The term "pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particular base addition salts are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine,

ethanolamine, 2-diethylaminoethanol, tromethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particular organic non-toxic bases include isopropylamine, diethylamine, ethanolamine, tromethamine, dicyclohexylamine, choline, and caffeine.

[0042] In some embodiments, a salt is selected from a hydrochloride, hydrobromide, trifluoroacetate, sulfate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulfonate, p-toluenesulfonate, bisulfate, benzenesulfonate, ethanesulfonate, malonate, xinafoate, ascorbate, oleate, nicotinate, saccharinate, adipate, formate, glycolate, palmitate, L-lactate, D-lactate, aspartate, malate, L-tartrate, D-tartrate, stearate, furoate (e.g., 2-furoate or 3-furoate), napadisylate (naphthalene-1,5-disulfonate or naphthalene-1-(sulfonic acid)-5-sulfonate), edisylate (ethane-1,2-disulfonate or ethane-1-(sulfonic acid)-2-sulfonate), isothionate (2-hydroxyethylsulfonate), 2-mesitylenesulfonate, 2-naphthalenesulfonate, 2,5-dichlorobenzenesulfonate, D-mandelate, L-mandelate, cinnamate, benzoate, adipate, esylate, malonate, mesitylate (2-mesitylenesulfonate), napsylate (2-naphthalenesulfonate), camsylate (camphor-10-sulfonate, for example (1S)-(+)-10-camphorsulfonic acid salt), glutamate, glutarate, hippurate (2-(benzoylamino)acetate), orotate, xylate (p-xylene-2-sulfonate), and pamoic (2,2'-dihydroxy-1,1'-dinaphthylmethane-3,3'-dicarboxylate).

[0043] A “sterile” formulation is aseptic or free from all living microorganisms and their spores.

[0044] The term “stereoisomers” refer to compounds that have identical chemical constitution but differ with regard to the arrangement of the atoms or groups in space. Stereoisomers include diastereomers, enantiomers, atropisomers, conformers and the like.

[0045] The term “chiral” refers to molecules that have the property of non-superimposability of the mirror image partner, while the term “achiral” refers to molecules which are superimposable on their mirror image partner.

[0046] The term “diastereomer” refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g., melting points, boiling points, spectral properties or biological activities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography such as HPLC.

[0047] The term “enantiomers” refers to two stereoisomers of a compound that are non-superimposable mirror images of one another.

[0048] The term "atropisomers" refers to two conformers resulting from hindered rotation about a single bond where the steric strain barrier to rotation can be high enough to allow for the isolation of each conformer.

[0049] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S,* are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

[0050] The term "tautomer" or "tautomeric form" refers to structural isomers of different energies that are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

[0051] Certain compounds described herein can exist in unsolvated forms as well as solvated forms, including hydrated forms. A "solvate" refers to an association or complex of one or more solvent molecules and a compound described herein. Examples of solvents that form solvates include water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, and ethanolamine. Certain compounds described herein can exist in multiple crystalline or amorphous forms. In general, all physical forms are contemplated herein. The term "hydrate" refers to the complex where the solvent molecule is water.

[0052] The compounds and pharmaceutically acceptable salts thereof described herein also embrace isotopically-labeled compounds that are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. All isotopes of any particular atom or element as specified are contemplated herein, and their uses. Exemplary isotopes that can be

incorporated into compounds and pharmaceutically acceptable salts thereof described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I. Certain isotopically-labeled compounds or pharmaceutical acceptable salts thereof described herein (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (^{3}H) and carbon-14 (^{14}C) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds or pharmaceutical acceptable salts thereof described herein can generally be prepared by following procedures analogous to those disclosed in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0053] Compounds and pharmaceutically acceptable salts thereof described herein may contain one or more asymmetric carbon atoms. Accordingly, the compounds may exist as diastereomers, enantiomers or mixtures thereof. The syntheses of the compounds may employ racemates, diastereomers or enantiomers as starting materials or as intermediates. Mixtures of particular diastereomeric compounds may be separated, or enriched in one or more particular diastereomers, by chromatographic or crystallization methods. Similarly, enantiomeric mixtures may be separated, or enantiomerically enriched, using the same techniques or others known in the art. Each of the asymmetric carbon or nitrogen atoms may be in the R or S configuration and both of these configurations are contemplated herein.

[0054] In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined. Unless otherwise specified, if solid wedges or dashed lines are used, relative stereochemistry is intended.

[0055] A “subject,” “individual,” or “patient” is a vertebrate and are used interchangeably herein. In certain embodiments, the vertebrate is a mammal. Mammals include, but are not limited to, farm animals (such as cows), sport animals, pets (such as guinea pigs, cats, dogs, rabbits and horses), primates, mice and rats. In certain embodiments, a mammal is a human. In embodiments comprising administration of a compound of to a patient, the patient is typically in need thereof.

[0056] The terms "inhibiting" and "reducing," or any variation of these terms, includes any measurable decrease or complete inhibition to achieve a desired result. For example, there may be a decrease of about, at most about, or at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more, or any range derivable therein, reduction of activity compared to normal.

[0057] The term "treatment" refers to clinical intervention designed to alter the natural course of the patient or cell being treated during the course of clinical pathology. Desirable effects of treatment include decreasing the rate of disease progression, ameliorating or palliating the disease state, and remission or improved prognosis. For example, a patient is successfully "treated" if one or more symptoms associated with a cancer described herein are mitigated or eliminated, including, but are not limited to, reducing the proliferation of (or destroying) cancerous cells, decreasing symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, and/or prolonging survival of patients.

[0058] The term "delaying progression" of a disease refers to deferring, hindering, slowing, retarding, stabilizing, and/or postponing development of a cancer described herein. This delay can be of varying lengths of time, depending on the history of the cancer and/or patient being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the patient does not develop cancer or relapse.

[0059] A "mutant KRas mediated disease" and the like refer to a disease described herein (e.g., a cancer described herein) having symptoms or requiring treatment as set forth herein that is/are wholly or partly associated with, a result of, a function of, or otherwise correlated to mutant KRas activity as described herein. In one such embodiment, the mutant KRas is $KRas^{G12D}$.

[0060] An "effective amount" or "therapeutically effective amount" is at least the minimum amount required to effect a measurable improvement or prevention of a cancer described herein. An effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the patient, and the ability of the agent to elicit a desired response in the patient. An effective amount is also one in which any toxic or detrimental effects of the treatment are outweighed by the therapeutically beneficial effects. Beneficial or desired results include results such as eliminating or reducing the risk, lessening the severity, delaying the onset of the disease (including biochemical, histological and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease), decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of

the disease, and/or prolonging survival. In some embodiments, an effective amount of the drug may have the effect in reducing the number of cancer cells; reducing the tumor size; inhibiting (i.e., slow or stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow or stop) tumor metastasis; inhibiting (i.e., slow or stop) tumor growth; and/or relieving one or more of the symptoms associated with the disorder. An effective amount can be administered in one or more administrations.

[0061] The term "co-administration," "administered in combination with," and their grammatical equivalents, as used herein, encompass administration of two or more agents to an animal, including humans, so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times (i.e., sequential administration) in separate compositions, or administration in a composition in which both agents are present.

[0062] The term “package insert” is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

[0063] The terms "antagonist" and "inhibitor" are used interchangeably, and they refer to a compound having the ability to inhibit a biological function of a target protein, whether by inhibiting the activity or expression of the protein, such as a mutant form of KRas. Accordingly, the terms "antagonist" and "inhibitors" are defined in the context of the biological role of the target protein. While preferred antagonists herein specifically interact with (e.g., bind to) the target, compounds that inhibit a biological activity of the target protein by interacting with other members of the signal transduction pathway of which the target protein is a member are also specifically included within this definition. A preferred biological activity inhibited by an antagonist is associated with the development, growth, or spread of a tumor.

[0064] The term "agonist" as used herein refers to a compound having the ability to initiate or enhance a biological function of a target protein, whether by inhibiting the activity or expression of the target protein. Accordingly, the term "agonist" is defined in the context of the biological role of the target polypeptide. While preferred agonists herein specifically interact with (e.g., bind to) the target, compounds that initiate or enhance a biological activity of the target polypeptide by interacting with other members of the signal transduction pathway of which the target polypeptide is a member are also specifically included within this definition.

[0065] The terms “cancer” and “cancerous”, “neoplasm”, and “tumor” and related terms are used interchangeably herein and refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. A “tumor” comprises one or more

cancerous cells. Examples of cancer include carcinoma, blastoma, sarcoma, seminoma, glioblastoma, melanoma, leukemia, and myeloid or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (e.g., epithelial squamous cell cancer) and lung cancer including small-cell lung cancer, non-small cell lung cancer ("NSCLC"), adenocarcinoma of the lung and squamous carcinoma of the lung. Other cancers include skin, keratoacanthoma, follicular carcinoma, hairy cell leukemia, buccal cavity, pharynx (oral), lip, tongue, mouth, salivary gland, esophageal, larynx, hepatocellular, gastric, stomach, gastrointestinal, small intestine, large intestine, pancreatic, cervical, ovarian, liver, bladder, hepatoma, breast, colon, rectal, colorectal, genitourinary, biliary passage, thyroid, papillary, hepatic, endometrial, uterine, salivary gland, kidney or renal, prostate, testis, vulval, peritoneum, anal, penile, bone, multiple myeloma, B-cell lymphoma, diffuse large B-Cell lymphoma (DLBCL), central nervous system, brain, head and neck, Hodgkin's, and associated metastases. Other examples of neoplastic disorders include myeloproliferative disorders, such as polycythemia vera, essential thrombocytosis, myelofibrosis, such as primary myelofibrosis, and chronic myelogenous leukemia (CML).

[0066] A "chemotherapeutic agent" is an agent useful in the treatment of a given disorder, for example, cancer or inflammatory disorders. Examples of chemotherapeutic agents are well-known in the art. Additionally, chemotherapeutic agents include pharmaceutically acceptable salts, acids or derivatives of any of chemotherapeutic agents, as well as combinations of two or more of them.

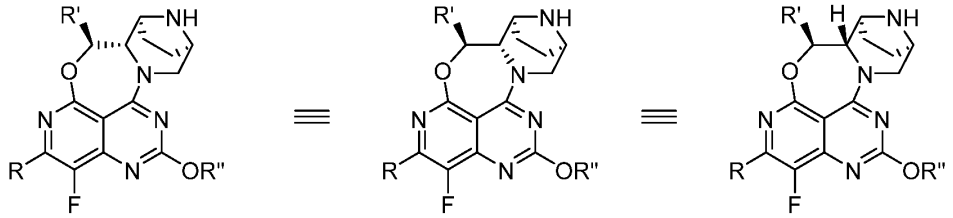
[0067] Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into compounds and pharmaceutically acceptable salts thereof described herein, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{32}P, ^{33}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Isotopically-labeled compounds (e.g., those labeled with ^{3}H and ^{14}C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes can be useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, in compounds and pharmaceutically acceptable salts thereof described herein, one or more carbon atoms are replaced by ^{13}C- or ^{14}C-enriched carbon. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds can generally be prepared by following procedures

analogous to those disclosed in the Schemes or in the Examples herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0068] It is specifically contemplated that any limitation discussed with respect to one embodiment provided herein may apply to any other embodiment provided herein. Furthermore, any compound and pharmaceutically acceptable salts thereof described herein or composition described herein may be used in any method provided herein, and any method provided herein may be used to produce or to utilize any compound and pharmaceutically acceptable salts thereof described herein or composition described herein.

[0069] Throughout this application, the term "about" is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value.

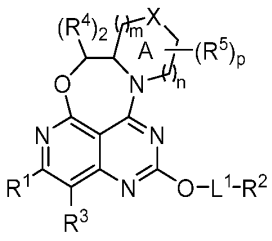
[0070] Compounds described herein may have stereochemistry depicted as follows:



It is understood that all three stereochemical depictions above are equivalent as set forth herein.

Compounds

[0071] Provided herein are compounds having the formula: A compound of formula (I):



(I),

wherein

X is O or NR^6

m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is R^7-substituted or unsubstituted naphthyl, R^7-substituted or unsubstituted isoquinolinyl, R^7-substituted or unsubstituted indazolyl, R^7-substituted or unsubstituted indanyl, R^7-substituted or unsubstituted benzothiazolyl, R^{7A}-substituted phenyl, or R^{7A}-substituted pyridinyl;

each R^7 is independently halogen, OH, NH_2, $N(Me)_2$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} alkynyl, unsubstituted C_{1-3} alkoxy, or unsubstituted C_{1-3} haloalkyl

each R^{7A} is independently halogen, CN, NH_2, $N(Me)_2$, R^{7B}-substituted or unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or unsubstituted cyclopropyl

R^{7B} is CN, oxo, or C_{1-3} alkyl;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl, or;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0072] Still further provided herein, in one embodiment, is a compound of formula (I) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

X is O or NR^6;

m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is R^{7A}-substituted phenyl or R^{7A}-substituted pyridinyl;

each R^{7A} is independently halogen, NH_2, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

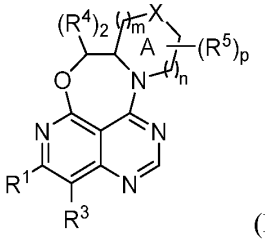
R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0073] In another embodiment, is a compound of formula (I-1):



(I-1),

wherein R^1, R^3, R^4, R^5, X, m, and n are as described herein.

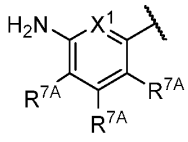
[0074] In one embodiment, each R^4 is hydrogen. In another embodiment, one R^4 is hydrogen and one R^4 is methyl. In another embodiment, one R^4 is hydrogen and one R^4 is CF_3.

[0075] In one embodiment, R^1 is R^7-substituted or unsubstituted naphthyl, R^7-substituted or unsubstituted isoquinolinyl, R^7-substituted or unsubstituted indazolyl, R^7-substituted or unsubstituted indanyl, or R^7-substituted or unsubstituted benzothiazolyl. In one embodiment, R^1 is R^7-substituted or unsubstituted naphthyl, R^7-substituted or unsubstituted isoquinolinyl, or R^7-substituted or unsubstituted indazolyl. In another embodiment, R^1 is R^7-substituted or unsubstituted naphthyl. In another embodiment, R^1 is R^7-substituted or unsubstituted isoquinolinyl. In another embodiment, R^1 is R^{7A}-substituted phenyl or R^{7A}-substituted pyridinyl. In one embodiment, R^1 is R^7-substituted naphthyl. In one such embodiment, R^1 is R^7-substituted isoquinolinyl and each R^4 is hydrogen. In another embodiment, R^1 is R^7-substituted naphthyl, R^7-substituted isoquinolinyl, R^7-substituted indazolyl, R^7-substituted indanyl, R^7-substituted benzothiazolyl, or R^{7A}-substituted phenyl. In such embodiments, each R^4 is hydrogen or one R^4 is hydrogen and one R^4 is methyl.

[0076] In one embodiment, each R^{7A} is independently halogen, CN, NH_2, $N(Me)_2$, R^{7B}-substituted or unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or unsubstituted cyclopropyl. In another embodiment, each R^{7A} is independently halogen, NH_2, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl. In still another embodiment, at least one R^{7A} is NH_2. In one such embodiment, where at least one R^{7A} is NH2, at least one other R^{7A} is unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or halogen.

[0077] In one embodiment, each R^7 is independently halogen, OH, NH_2, $N(Me)_2$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} alkynyl, unsubstituted C_{1-3} alkoxy, or unsubstituted C_{1-3} haloalkyl. In one embodiment, each R^7 is independently halogen, OH, NH_2, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} alkynyl. In still another embodiment, at least one R^7 is NH_2. In another embodiment, at least one R^7 is OH.

[0078] In one embodiment, R^1 is:



(E)

wherein X^1 is N or CR^{7C}.

[0079] In one such embodiment, X^1 is N or CF and each R^{7A} is independently hydrogen, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl. In one such embodiment, each R^{7A} is independently hydrogen, Cl, methyl, ethyl, or CF_3, where no more than one R^{7A} is hydrogen. In one embodiment, at least one R^{7A} is NH_2. In one embodiment, each R^{7A} is independently halogen, NH_2, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl. In one embodiment, one R^{7A} is cyclopropyl. In one such embodiment, one R^{7A} is cyclopropyl and is *para* to the amino group. In another such embodiment, one R^{7A} is cyclopropyl and is *meta* to the amino group. In one embodiment, X^1 is N. In one embodiment, X^1 is CR^{7C}. In one such embodiment, R^{7C} is hydrogen or halogen.

[0080] In another embodiment provided herein is a compound of formula (I) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

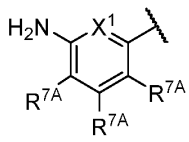
X is O or NR^6;

m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is formula  (E), wherein X^1 is N or CR^{7C} and R^{7C} is hydrogen or halogen;

each R^{7A} is independently halogen, CN, NH_2, $N(Me)_2$, R^{7B}-substituted or unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or unsubstituted cyclopropyl;

R^{7B} is CN, oxo, or C_{1-3} alkyl;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

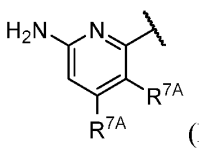
R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0081] In one such embodiment, X^1 is N and R^{7A} is hydrogen, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl. In another such embodiment, at least one R^{7A} is unsubstituted C_{1-3} haloalkyl (e.g. CF_3). Where X^1 is N, in some embodiments, R^1 comprises the moiety of formula (E1);



(E1)

[0082] In another embodiment is a compound of formula (I) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

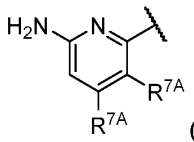
X is O or NR^6;

m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is of formula  (E1);

each R^{7A} is independently halogen, CN, NH_2, $N(Me)_2$, R^{7B}-substituted or unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or unsubstituted cyclopropyl;

R^{7B} is CN, oxo, or C_{1-3} alkyl;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

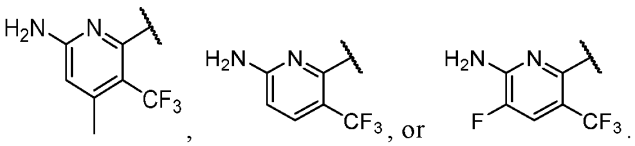
R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

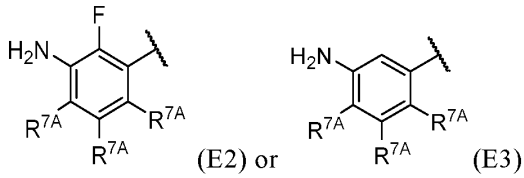
R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0083] In one embodiment, where R^1 comprises the moiety of formula E1, each R^{7A} is independently hydrogen, Cl, methyl, or CF_3. In another such embodiment, each R^{7A} is independently hydrogen, methyl, or CF_3.

[0084] In one embodiment, where R^1 is a moiety of formula (E) and X^1 is N, R^1 is:



[0085] In another embodiment, R^1 comprises the moiety of formula (E2);



wherein each R^{7A} is independently hydrogen, halogen, unsubstituted C_{1-3} alkyl or unsubstituted C_{1-3} haloalkyl. In one such embodiment, no more than one R^{7A} is hydrogen. In another such embodiment, R^{7A} is not hydrogen. In one embodiment of the moieties (E2) and (3), at least one R^{7A} is halogen. In one embodiment of the moieties (E2) and (E3), at least one R^{7A} is unsubstituted C1-3 haloalkyl (e.g., CF_3, CHF_2, CF_2CF_3, $CHCF_3$, or CH_2CF_3).

[0086] In another embodiment is a compound of formula (I) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

X is O or NR^6;

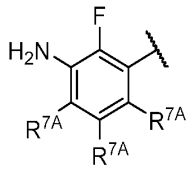
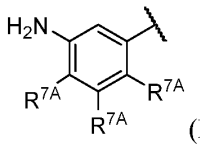
m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is (E2) or (E3)


(E2) or  (E3);

each R^{7A} is independently hydrogen, halogen, unsubstituted C_{1-3} alkyl or unsubstituted C_{1-3} haloalkyl;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

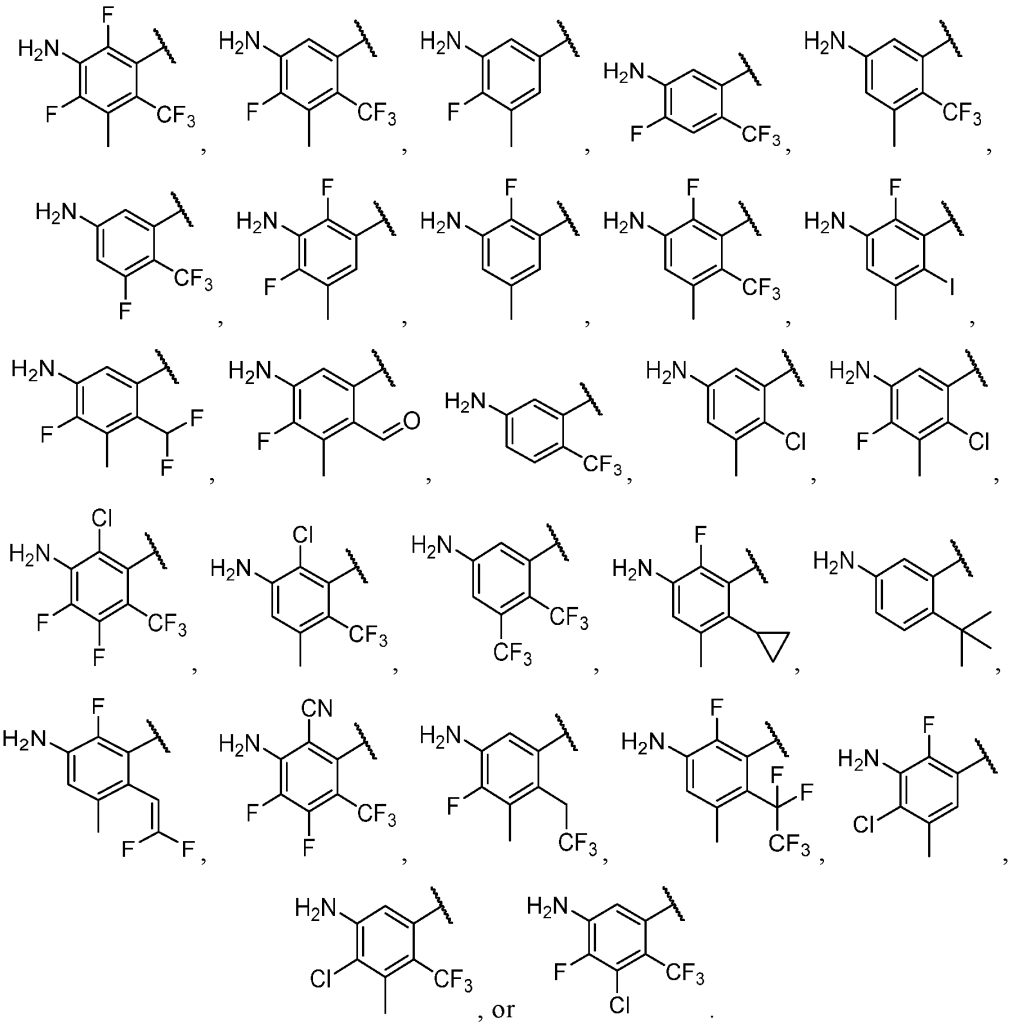
R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0087] In one embodiment, R^1 is:



[0088] In another embodiment is a compound of formula (I), or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

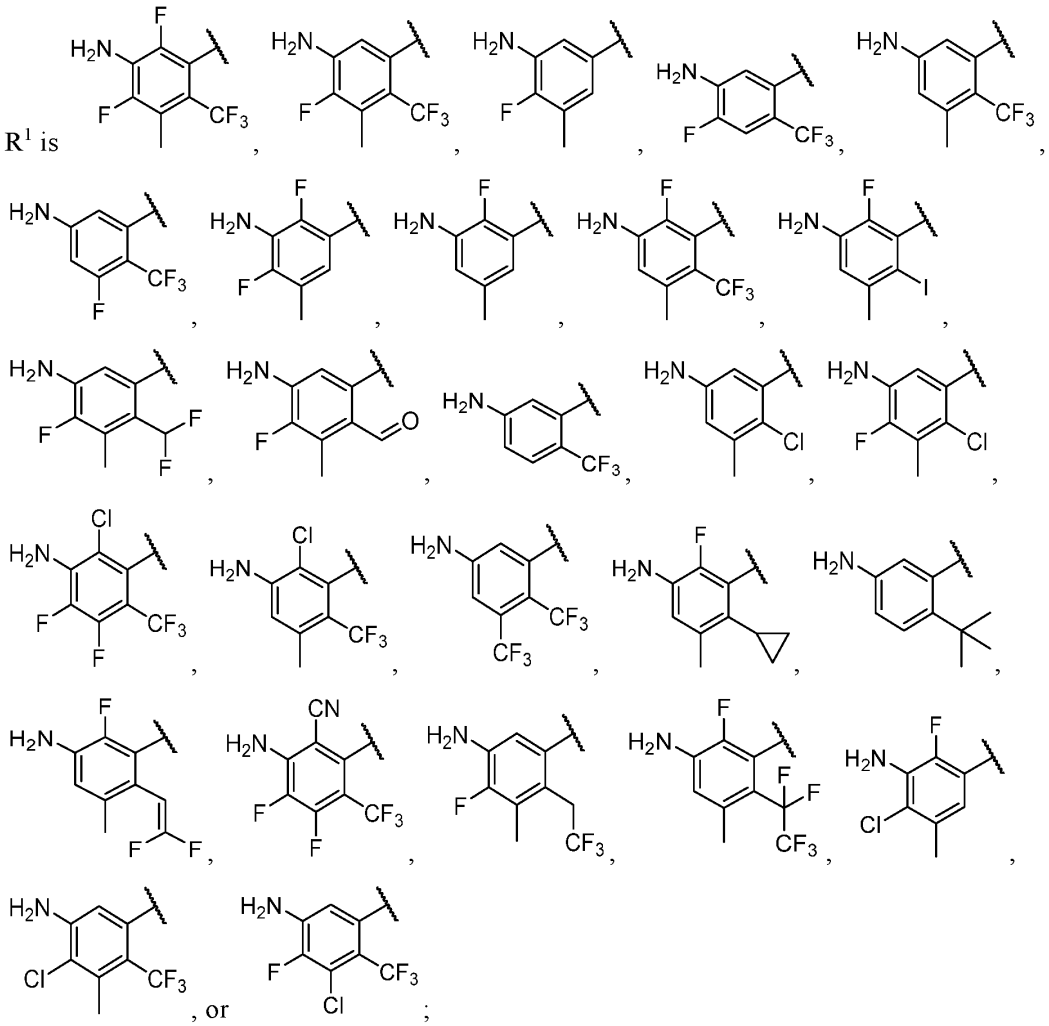
X is O or NR^6;

m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is  , or ;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

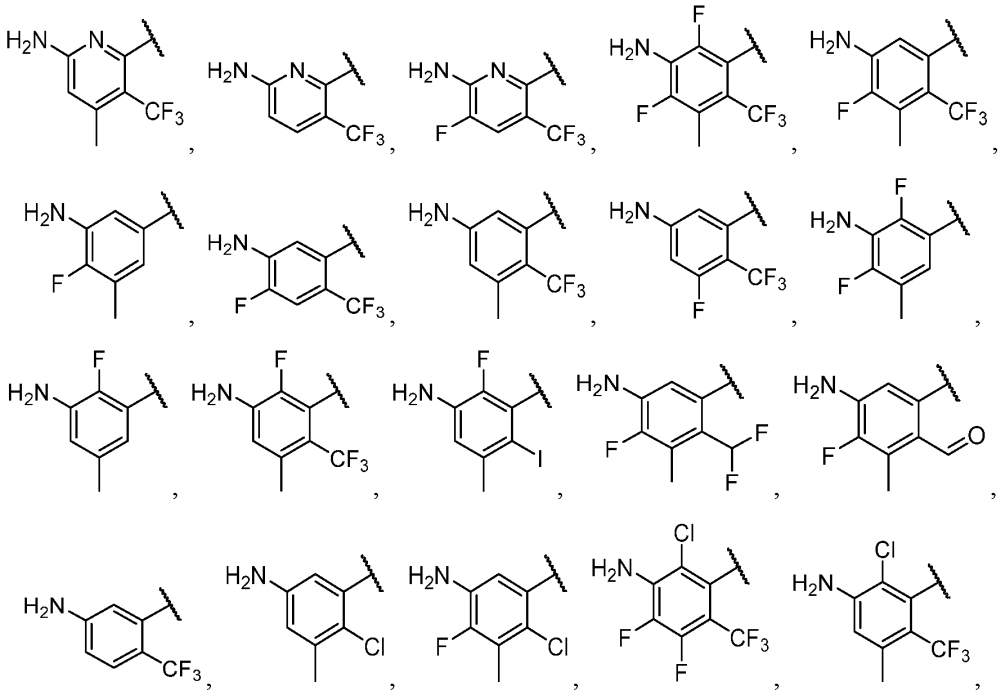
R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

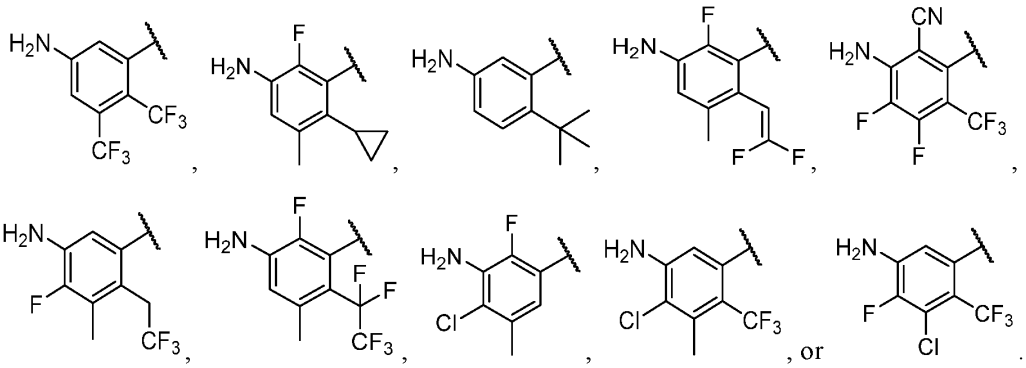
R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

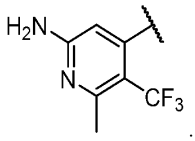
R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0089] In one embodiment, R^1 is:





[0090] In another embodiment, R^1 is:



[0091] In another embodiment is a compound of formula (I) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

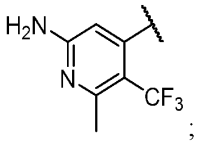
X is O or NR^6;

m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is  ;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein

two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

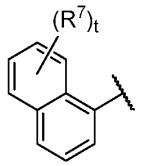
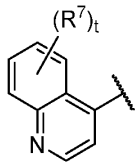
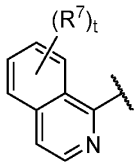
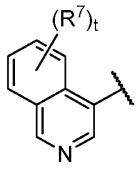
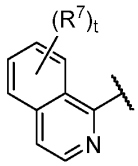
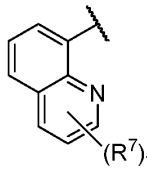
R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

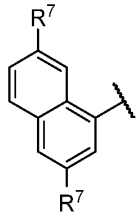
R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0092] In another embodiment, R^1 is:


(F),

(F1),

(F2),

(F3),

(F4), or

(F5), or a stereoisomer thereof, wherein t is 0, 1, 2, or 3. In one embodiment, t is 1 or 2. In another embodiment, t is 3. In one embodiment of the compounds described herein, R^1 is not a formula of F, F1, F2, F3, F4, or F5 and is a monocylic ring.

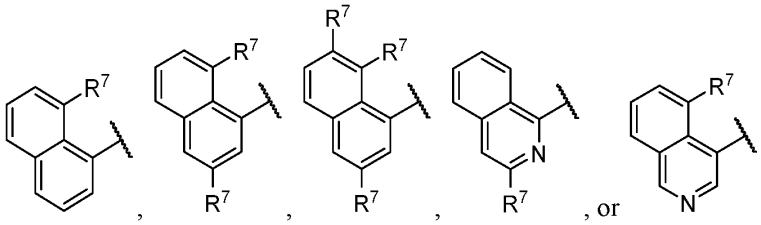
[0093] In another embodiment, R^1 is a moiety of formula (F), (F1), (F2), or (F3), wherein t is 0, 1, 2, or 3. In one embodiment, t is 1 or 2. In another embodiment, t is 3.

[0094] In one embodiment, R^1 is:



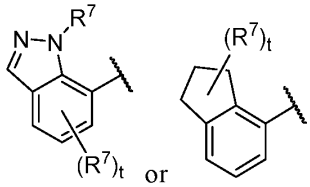
or a stereoisomer thereof, wherein R^7 is as described herein.

[0095] In another embodiment, R^1 is:



, or a stereoisomer thereof.

[0096] In another embodiment, R^1 is:



, or a stereoisomer thereof,

wherein t is 0, 1, 2, or 3. In one embodiment, t is 1 or 2. In one embodiment, R^7 is halogen, NH_2, OH, C_{1-3}alkyl, or C_{2-3}alkynyl.

[0097] In one embodiment of the compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein, R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N or O. In another embodiment of the compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein, R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more nitrogen heteroatoms. In another embodiment, R^2 is R^9-substituted or unsubstituted 5-8 membered heterocycle comprising at least one nitrogen heteroatom.

[0098] In one embodiment, each R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle. In one embodiment, each R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, or OCH_2F. In another such embodiment, each R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F,R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl,

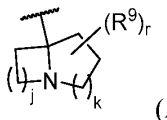
unsubstituted C_{1-3} alkoxy, or R^{10}-substituted or unsubstituted C_{1-3} alkylidene. In still another embodiment, each R^9 is independently R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, or R^{10}-substituted or unsubstituted C_{1-3} alkylidene. In another embodiment, each R^9 is independently halogen, R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle.

[0099] In another embodiment, two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms. In one such embodiment, two R^9 together form an unsubstituted cyclopropyl moiety. In another embodiment, two R^9 together form an unsubstituted oxetanyl or azetidinyl.

[0100] In another embodiment, two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons. In one such embodiment, the bridge comprises one carbon atom. In another such embodiment, the bridge comprises 2 carbon atoms.

[0101] In one embodiment, R^9 is halogen or R^{10}-substituted or unsubstituted C_{1-3} alkylidene.

[0102] In one embodiment, R^2 is



(A),

or a stereoisomer thereof, wherein,

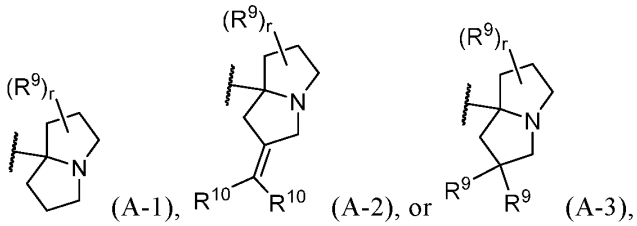
R^9 is halogen or R^{10}-substituted or unsubstituted C_{1-3} alkylidene

r is an integer of 0-12;

j is 1, 2, or 3; and

k is 1 or 2.

[0103] In one embodiment, R^2 is a moiety of formula:



(A-1), (A-2), or (A-3),

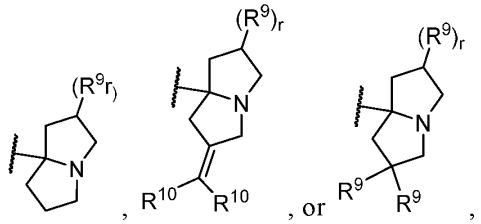
or a stereoisomer thereof, wherein

R^9 is independently halogen or R^{10}-substituted or unsubstituted C_{1-3} alkylidene;

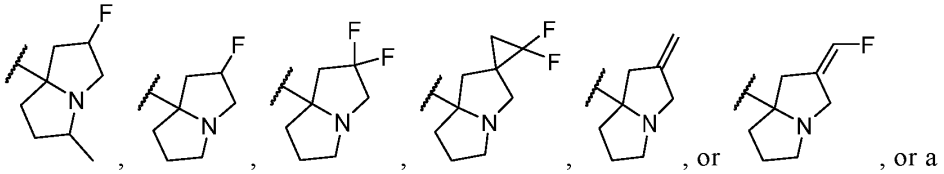
each R^{10} is independently hydrogen or halogen; and

r is 1 or 2.

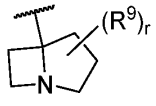
[0104] In one embodiment, R^2 is a moiety of formula:


, or a stereoisomer thereof.

[0105] In one embodiment, R^2 is a moiety of formula:

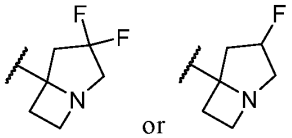

, or a stereoisomer thereof.

[0106] In one embodiment, R^2 is a moiety of formula:

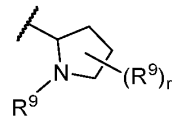

(A-4),

or a stereoisomer thereof, wherein R^9 and r are as described herein. In one such embodiment, r is 1 or 2. In one embodiment, each R^9 is independently halogen or R^{10}-substituted or unsubstituted $C_{1\text{-}3}$alkyl.

[0107] In one embodiment, R^2 is a moiety of formula:


, or a stereoisomer thereof.

[0108] In another embodiment, R^2 is

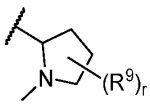

(B),

or a stereoisomer thereof, wherein

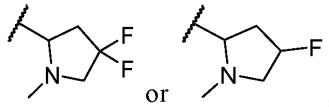
R^9 is independently halogen, oxo, or unsubstituted $C_{1\text{-}3}$ alkyl; and

r is 1 or 2.

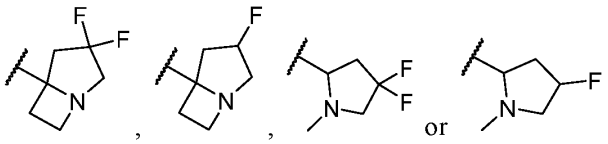
[0109] In another embodiment, R^2 is


, or a stereoisomer thereof.

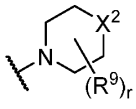
[0110] In another embodiment, R^2 is

 or , or a stereoisomer thereof.

[0111] In still another embodiment, R^2 is

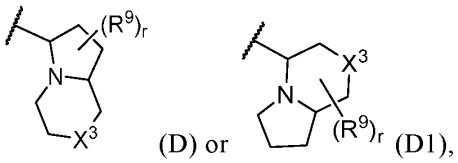
 or , or a stereoisomer thereof.

[0112] In another embodiment, R^2 is

 (C),

or a stereoisomer thereof, herein X^2 is CR^9 or O. In one embodiment, X^2 is O. In one such embodiment, X^2 is O and r is 0.

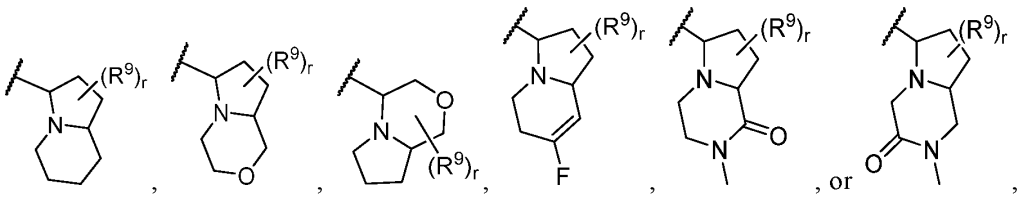
[0113] In another embodiment, R^2 is

 (D) or (D1),

or a stereoisomer thereof, wherein X^3 is CR^9 , NR^9, or O.

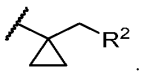
[0114] In one embodiment, R^2 is a moiety of formula (D), where X^3 is CR^9, wherein R^9 is as described herein. In one such embodiment, X^3 is CH_2 or CF_2. In another such embodiment, R^2 is a moiety of formula (D) or (D1) and X^3 is O. In one embodiment, R^2 is a moiety of formula (D), X^3 is O and R^9 is unsubstituted $C_{1\text{-}3}$alkyl or halogen. In another embodiment, R^2 is a moiety of formula (D) X^3 is NR^9, and R^9 is oxo or unsubstituted $C_{1\text{-}3}$alkyl.

[0115] In one embodiment, R^2 is

 or ,

or a stereoisomer thereof. In one embodiment, r is 0 or 1.

[0116] In one embodiment, L^1 is methylene. In one embodiment, R^2 is as described herein and L^1 is methylene. In another embodiment, L^1 is R^{L1}-substituted or unsubstituted $C_{2\text{-}3}$ alkylene. In one such embodiment, L^1 is unsubstituted $C_{2\text{-}3}$ alkylene. In another such embodiment, L^1 is R^{L1}-substituted $C_{2\text{-}3}$ alkylene, where two R^{L1} together form an unsubstituted $C_{3\text{-}4}$ cycloalkyl. In one such embodiment, L^1 has the formula:



[0117] In one embodiment of the compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein, R^3 is halogen. In another embodiment, R^3 is -CN.

[0118] In one embodiment of the compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein, each R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl. In one such embodiment, each R^5 is independently unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl. In some embodiments, p is 0 or 1.

[0119] In another embodiment, two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N. In one such embodiment, two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons. In one such embodiment, the bridge comprises 1 or 2 carbon atoms. In another such embodiment, the bridge comprises 1 carbon atom. In another such embodiment, the bridge comprises 2 carbon atoms.

[0120] In one embodiment, two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11}. In one embodiment, the bridge comprises an O heteroatom. In another embodiment, the bridge comprises NR^{11} where R^{11} is hydrogen or methyl.

[0121] In some embodiments, Ring A is a 6 membered ring (i.e., where m and n are both 1). In one embodiment, Ring A is a 7-membered ring where m is 2 and n is 1. In another embodiment, Ring A is a 7-membered ring where m is 1 and n is 2. In one embodiment, X is NR^6, where R^6 is as described herein.

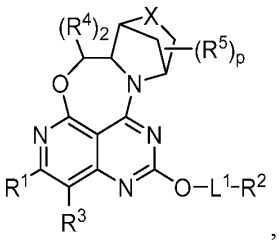
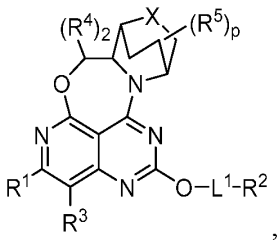
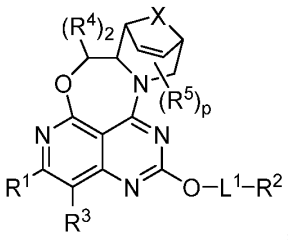
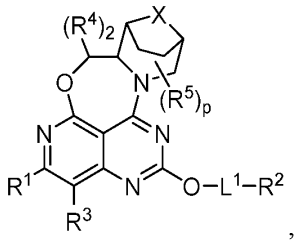
[0122] In one embodiment, R^6 is hydrogen or R^{6A}-substituted or unsubstituted C_{1-3} alkyl. In one embodiment, R^6 is R^{6A}-substituted or unsubstituted C_{1-3} alkyl. In one embodiment, R^6 is hydrogen. In one embodiment, R^6 is methyl.

[0123] In some embodiments, R^6 is R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl.

[0124] In such embodiments, R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle. In another such embodiment, R^{6A} is halogen, CN, OH, OMe, OEt, OCF_3, SO_2Me, unsubstituted C_{1-3} alkyl, or 4-membered heterocycle.

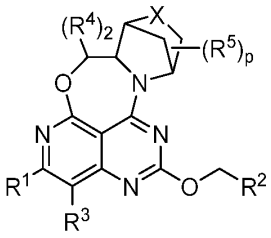
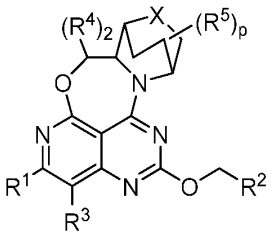
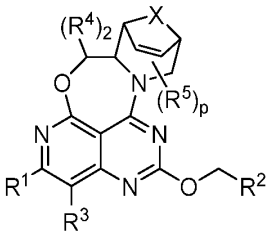
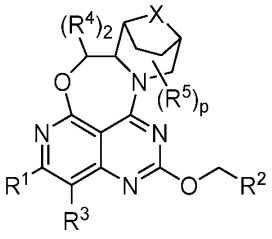
[0125] In one embodiment, each R^{6B} is independently C_{1-3} alkyl or C_{1-3} haloalkyl. In one such embodiment, R^{6B} is independently C_{1-3} alkyl.

[0126] Further provided herein are compounds of formula (I) as described herein having formula:


,

,

, or

,

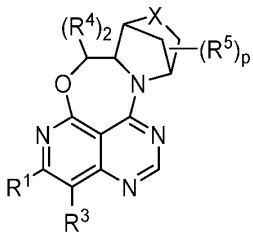
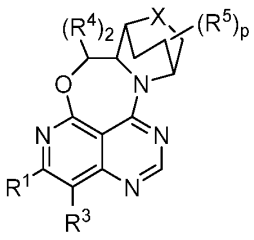
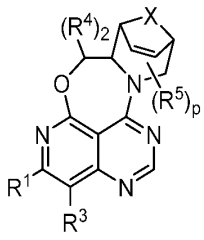
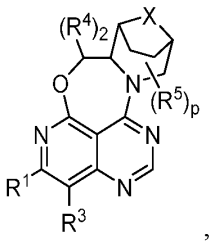
or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, X, L^1, and p are as described herein.

[0127] Further provided herein are compounds of formula (I) as described herein having formula:


(IIa),

(IIb),

(IIc), or

(IId),

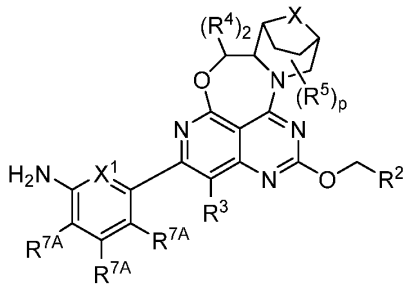
or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, X, and p are as described herein.

[0128] Further provided herein are compounds of formula (I) as described herein having formula:

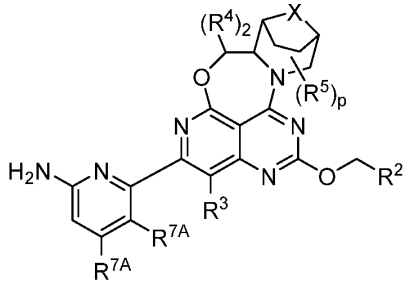
or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1, R^3, R^4, R^5, X, and p are as described herein.

[0129] In one embodiment, the compound of formula (IId) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, comprises formula (IId-1),



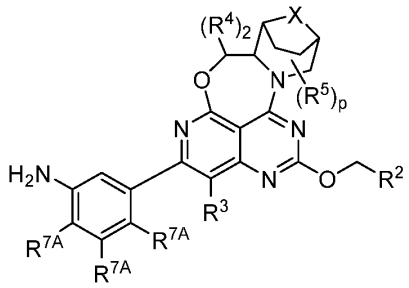
wherein R^2, R^3, R^4, R^5, R^{7A}, X, X^1, and p are as described herein.

[0130] In one embodiment, the compound of formula (IId) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, comprises formula (IId-2),



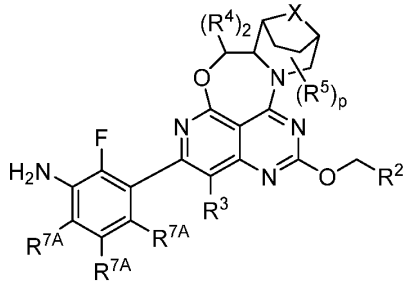
wherein R^2, R^3, R^4, R^5, R^{7A}, X, and p are as described herein.

[0131] In one embodiment, the compound of formula (IId) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, comprises formula (IId-3),



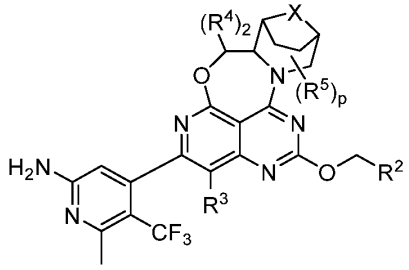
wherein R^2, R^3, R^4, R^5, R^{7A}, X, and p are as described herein.

[0132] In one embodiment, the compound of formula (IId) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, comprises formula (IId-4),



wherein R^2, R^3, R^4, R^5, R^{7A}, X, and p are as described herein.

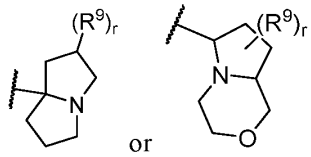
[0133] In one embodiment, the compound of formula (IId) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, comprises formula (IId-5),



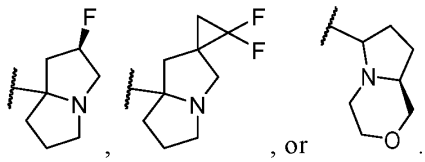
wherein R^2, R^3, R^4, R^5, X, and p are as described herein

[0134] In one embodiment, X is NH or $N(CH_3)$. In one embodiment, R^1 is a moiety of formula for (E), (E1), (E2), (E3), (F), (F1), (F2), (F3), (F4), or (F5) as described herein. In one embodiment, R^2 is a moiety of formula (A), (A-1), (A-2), (A-3), (A-4), (B), (C), (D), or (D1) as described herein.

[0135] In one embodiment of the compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein of formula (IIa), (IIb), (IIc), or (IId), R^2 comprises a moiety of formula:

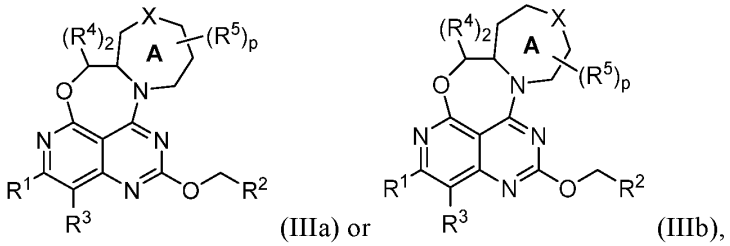

or , or a stereoisomer thereof. In one such embodiment, the compound, stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein comprises formula (IId) as described herein. In another such embodiment, the compound, stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein comprises formula (IId-1), (IId-2), (IId-3), (IId-4), or (IId-5), as described herein.

[0136] In one such embodiment, the compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein of formula (IIa), (IIb), (IIc), or (IId), R^2 comprises a moiety of formula:


, , or .

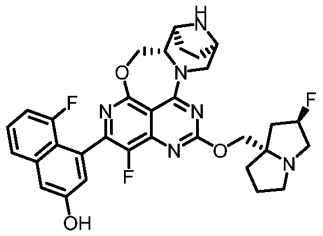
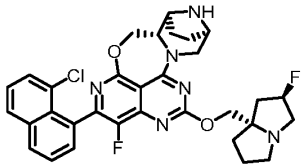
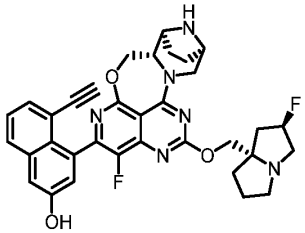
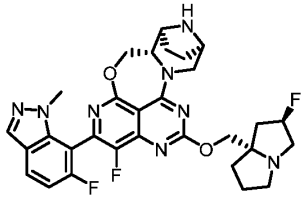
[0137] In one such embodiment, the compound, stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein comprises formula (IId) as described herein. In another such embodiment, the compound, stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein comprises formula (IId-1), (IId-2), (IId-3), (IId-4), or (IId-5), as described herein.

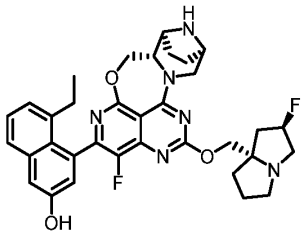
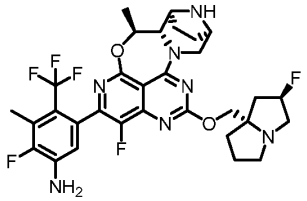
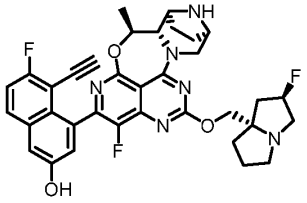
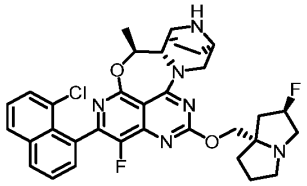
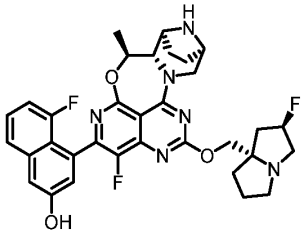
[0138] In another embodiment, the compound of formula (I) as described herein has formula:

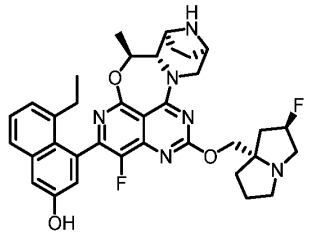
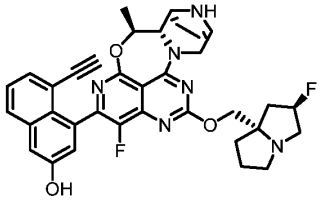
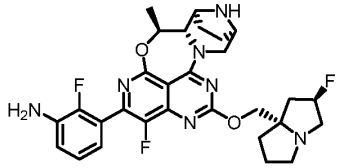
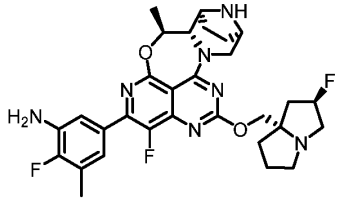
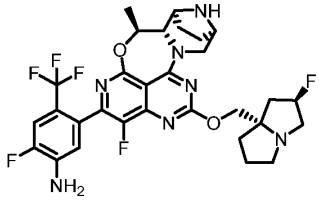

(IIIa) or (IIIb),

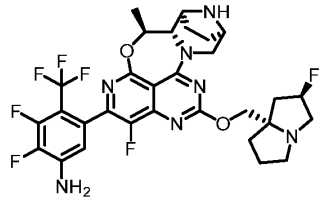
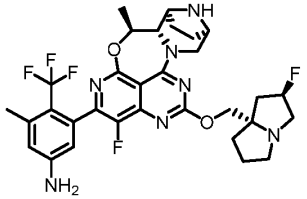
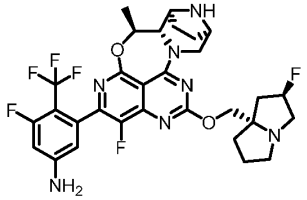
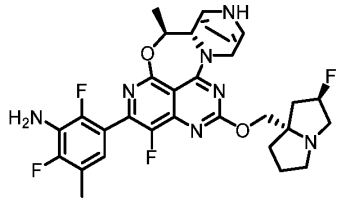
or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, X, and p are as described herein. In one such embodiment, X is N R^6, where R^6 is hydrogen or R^{6A}-substituted or unsubstituted C_{1-3} alkyl.

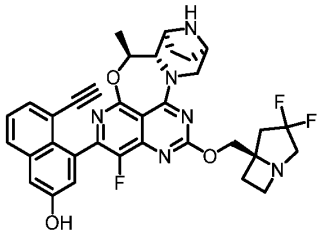
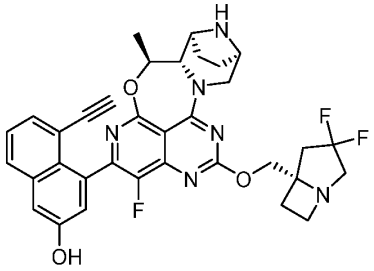
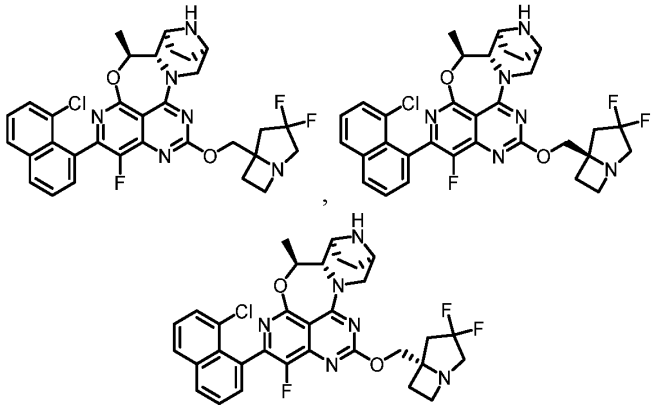
[0139] Table 1:

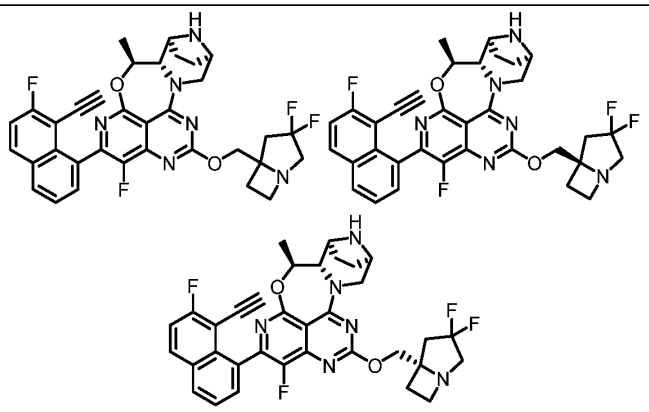
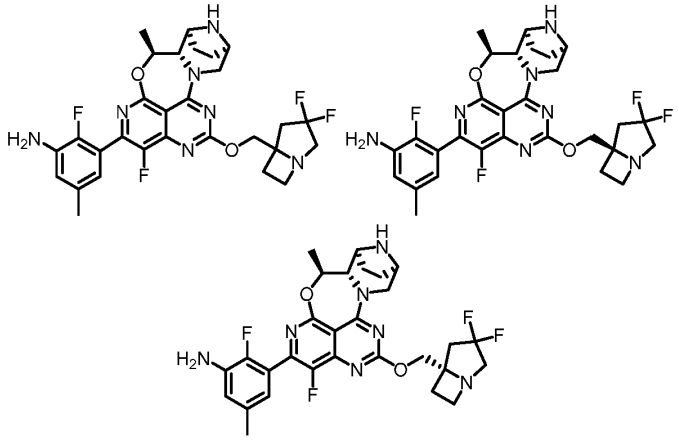
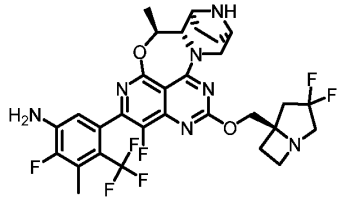
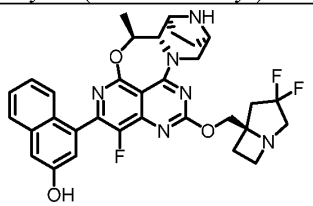
Cmpd. No.	Chemical Structure
1	 5-fluoro-4-((5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol
2	 (5aS,6S,9R)-2-(8-chloronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene
3	 5-ethynyl-4-((5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol
4	 (5aS,6S,9R)-1-fluoro-2-(6-fluoro-1-methyl-1H-indazol-7-yl)-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene

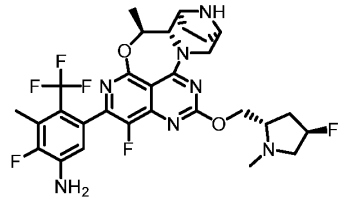
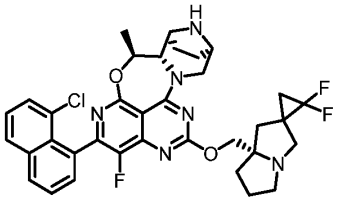
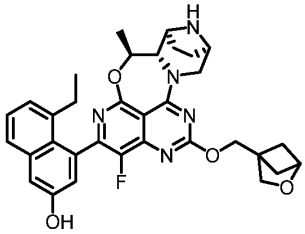
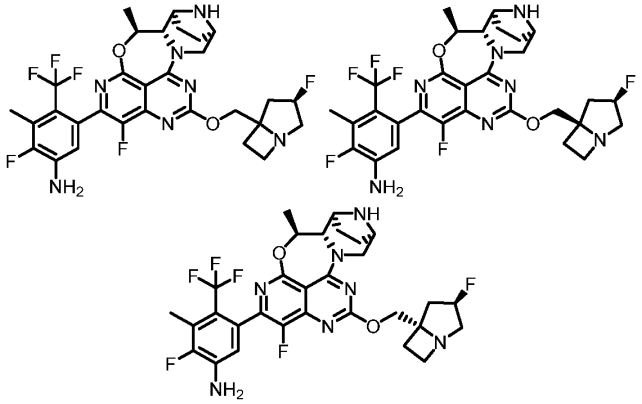
5	 5-ethyl-4-((5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol
6	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
7	 5-Ethynyl-6-fluoro-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol
8	 (5S,5aS,6S,9R)-2-(8-chloronaphthalen-1-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene
9	 5-fluoro-4-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-

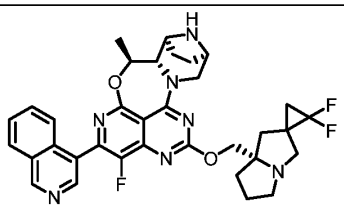
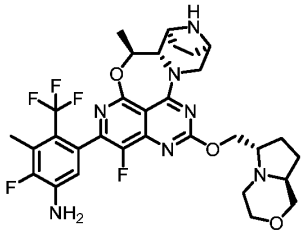
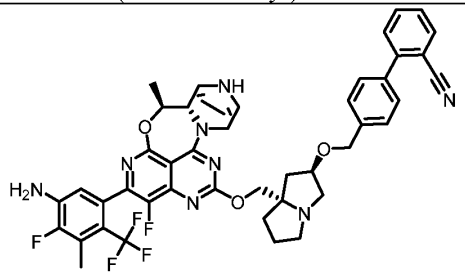
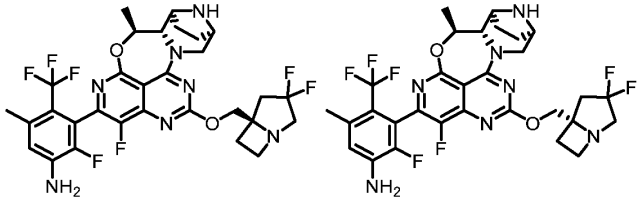
	3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol
10	 5-ethyl-4-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol
11	 5-ethynyl-4-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol
12	 2-fluoro-3-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)aniline
13	 2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methylaniline
14	 2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-

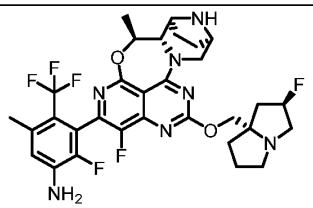
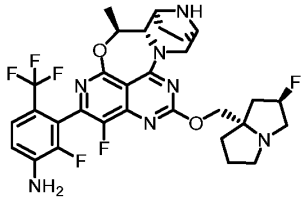
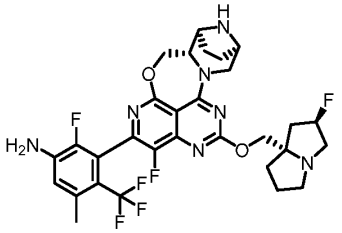
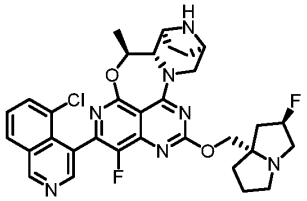
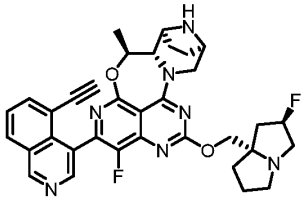
	3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline
15	 2,3-difluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline
16	 3-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline
17	 3-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline
18	 2,6-difluoro-3-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-methylaniline

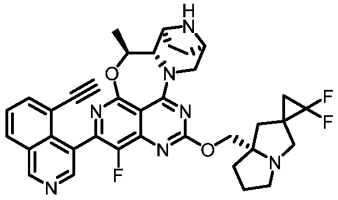
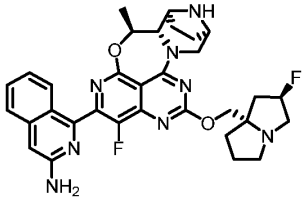
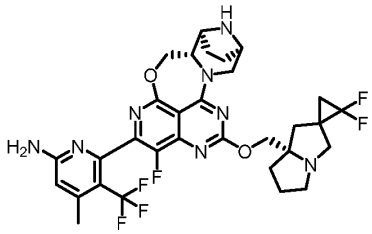
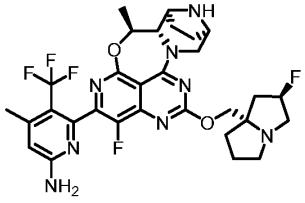
19	 4-((5*S*,5a*S*,6*S*,9*R*)-12-((3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-ethynylnaphthalen-2-ol
20	 4-((5*S*,5a*S*,6*S*,9*R*)-12-((3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-ethynylnaphthalen-2-ol
21	 (5S,5aS,6S,9R)-2-(8-chloronaphthalen-1-yl)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene

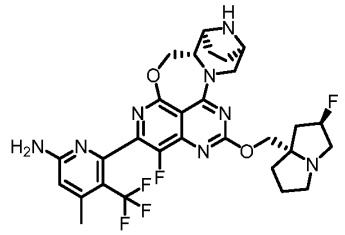
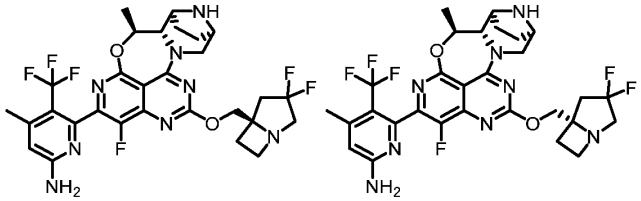
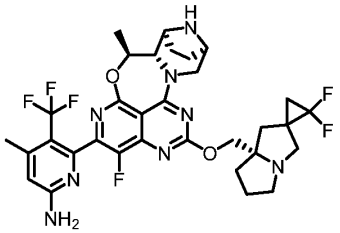
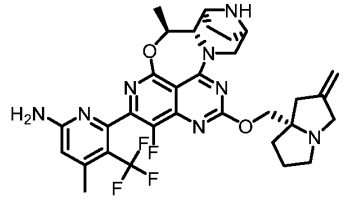
22	 (5S,5aS,6S,9R)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene
23	 3-((5S,5aS,6S,9R)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-5-methylaniline
24	 5-((5S,5aS,6S,9R)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline
25	 4-((5S,5aS,6S,9R)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-

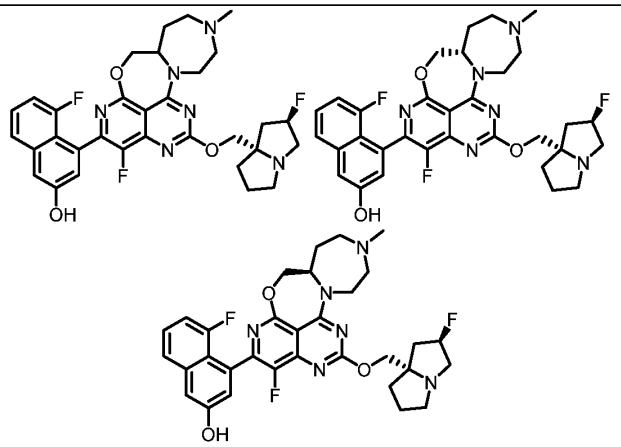
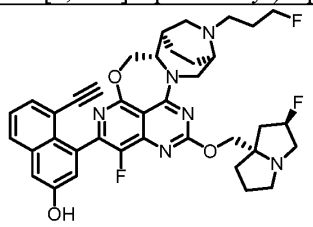
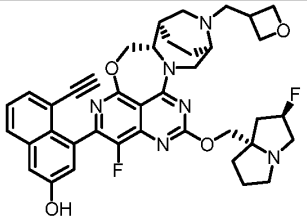
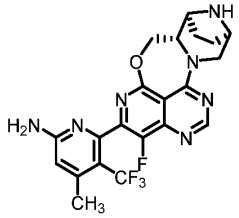
	yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol
26	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
27	 (5S,5aS,6S,9R)-2-(8-chloronaphthalen-1-yl)-12-(((7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene
28	 4-((5S,5aS,6S,9R)-12-((2-oxabicyclo[2.1.1]hexan-4-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-ethylnaphthalen-2-ol
29	 2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((3R)-3-fluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline

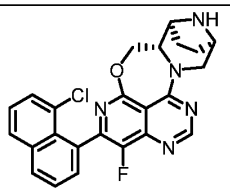
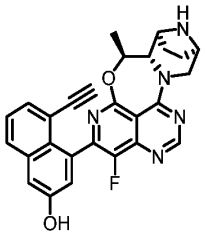
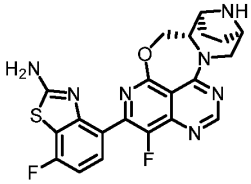
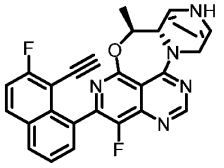
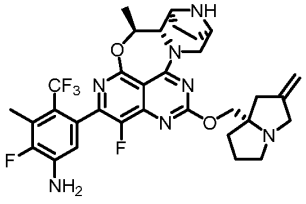
30	 (5S,5aS,6S,9R)-12-(((7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-2-(isoquinolin-4-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene
31	 2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
32	 4'-((((2R,7aS)-7a-((((5S,5aS,6S,9R)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-12-yl)oxy)methyl)hexahydro-1H-pyrrolizin-2-yl)oxy)methyl)-[1,1'-biphenyl]-2-carbonitrile
33	 3-((5*S*,5a*S*,6*S*,9*R*)-12-((3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-5-methyl-4-(trifluoromethyl)aniline

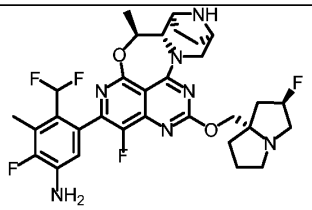
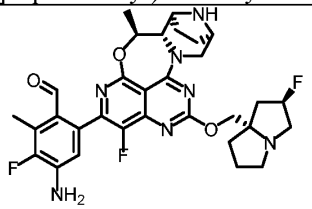
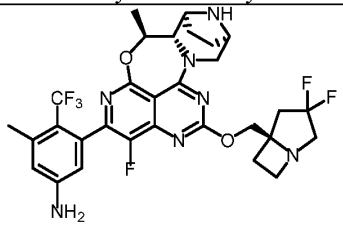
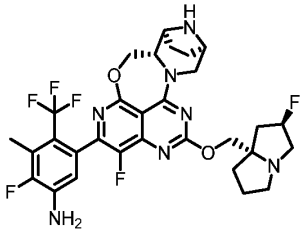
34	 2-Fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-mthyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline
35	 2-fluoro-3-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline
36	 2-fluoro-3-((5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline
38	 (5*S*,5a*S*,6*S*,9*R*)-2-(5-Chloroisoquinolin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene
39	 (5*S*,5a*S*,6*S*,9*R*)-2-(5-Ethynylisoquinolin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-

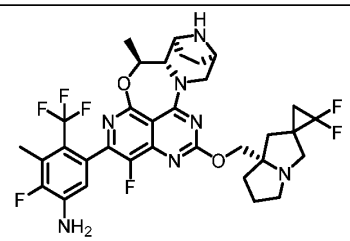
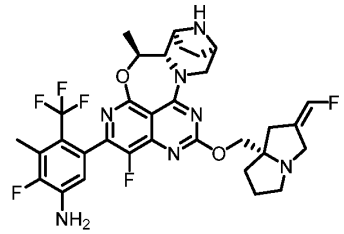
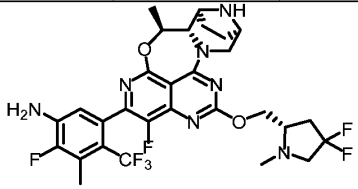
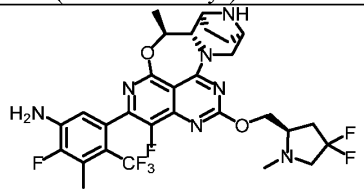
	hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene
40	 (5S,5aS,6S,9R)-12-(((7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-2-(5-ethynylisoquinolin-4-yl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene
41	 1-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)isoquinolin-3-amine
42	 6-((5a*S*,6*S*,9*R*)-12-(((7a'*S*)-2,2-Difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine
43	 6-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

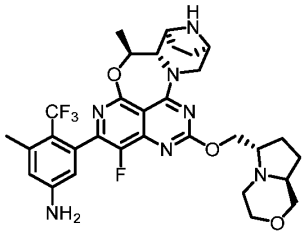
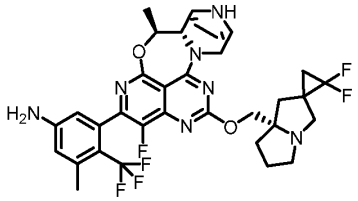
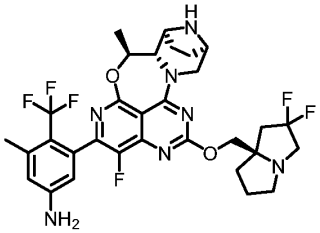
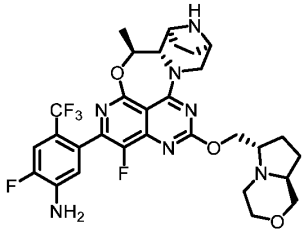
44	 6-((5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine
45	 6-((5S,5aS,6S,9R)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine
47	 6-((5S,5aS,6S,9R)-12-(((7a'S)-2,2-difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalen-2-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine
48	 6-((5S,5aS,6S,9R)-1-fluoro-5-methyl-12-(((S)-2-methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

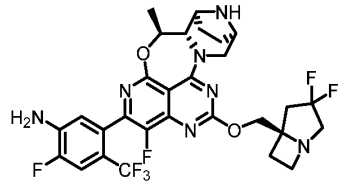
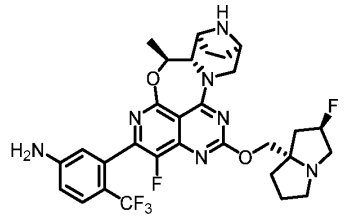
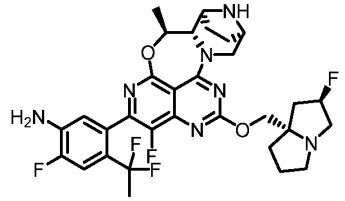
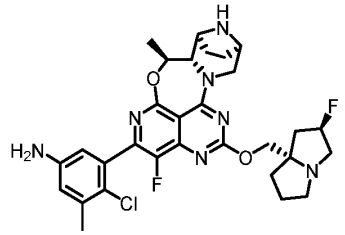
49	 5-Fluoro-4-(1-fluoro-12-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-8-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,8,10a,11,13-pentaazanaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol
50	 5-Ethynyl-4-((5a*S*,6*R*,9*R*)-1-fluoro-14-(3-fluoropropyl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol
51	 5-ethynyl-4-((5aS,6R,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-14-(oxetan-3-ylmethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol
52	 6-((5a*S*,6*S*,9*R*)-1-Fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

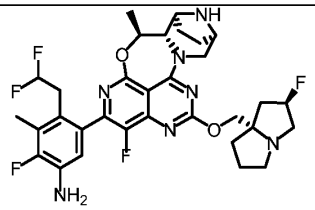
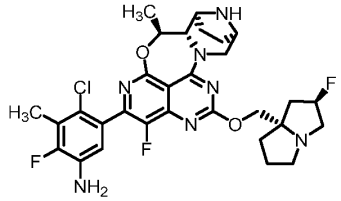
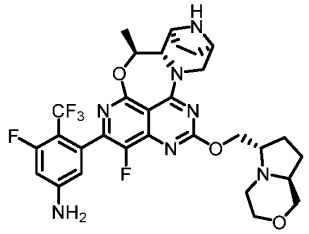
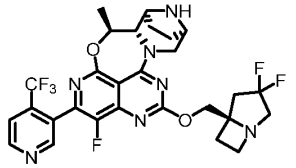
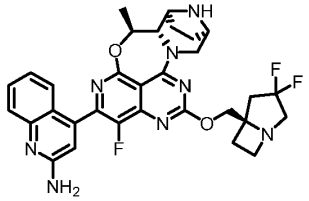
53	 (5a*S*,6*S*,9*R*)-2-(8-Chloronaphthalen-1-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene
54	 5-Ethynyl-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol
55	 7-fluoro-4-((5aS,6S,9R)-1-fluoro-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)benzo[d]thiazol-2-amine
56	 (5S,5aS,6S,9R)-2-(8-ethynyl-7-fluoronaphthalen-1-yl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene
57	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-(((*S*)-2-methylenetetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl) aniline

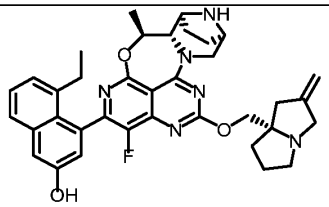
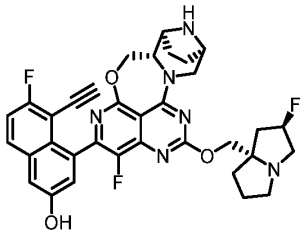
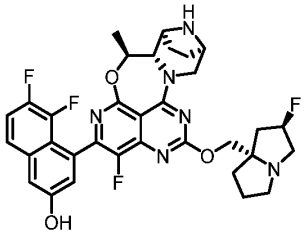
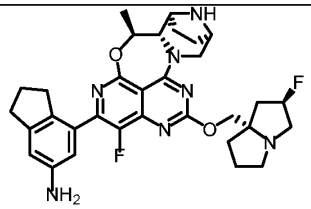
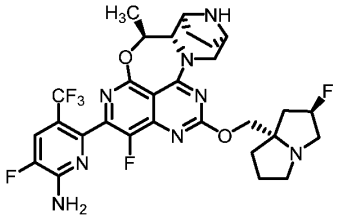
58	 4-(Difluoromethyl)-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methylaniline
59	 4-Amino-3-fluoro-6-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-methylbenzaldehyde
60	 3-((5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-petaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline
61	 2-Fluoro-5-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline

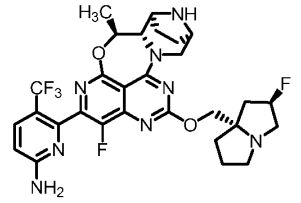
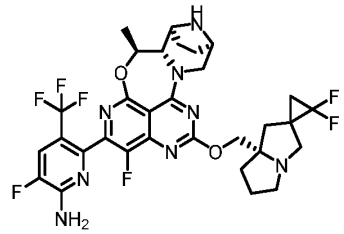
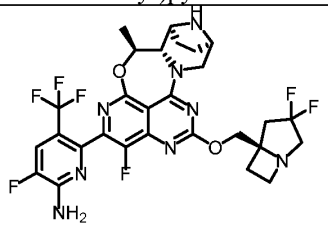
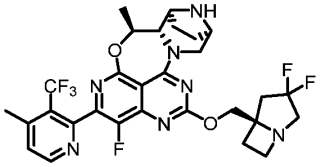
62	 5-((5*S*,5a*S*,6*S*,9*R*)-12-(((7a'*S*)-2,2-Difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline
64	 2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
65	 5-((5*S*,5a*S*,6*S*,9*R*)-12-(((*S*)-4,4-Difluoro-1-methylpyrrolidin-2-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline
66	 5-((5S,5aS,6S,9R)-12-(((R)-4,4-difluoro-1-methylpyrrolidin-2-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline

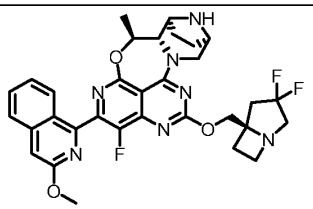
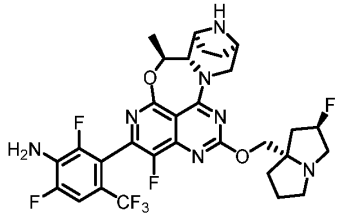
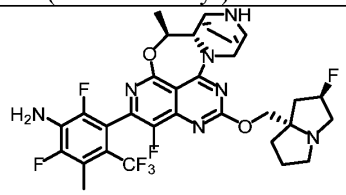
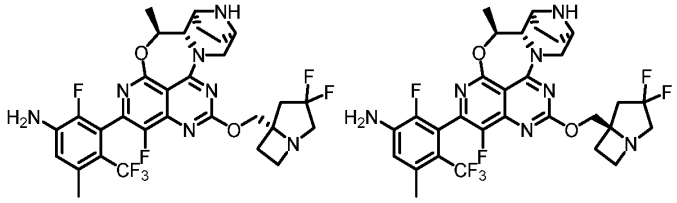
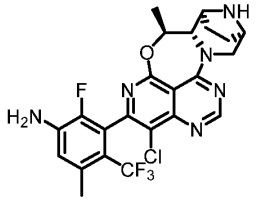
67	 3-((5*S*,5a*S*,6*S*,9*R*)-1-Fuoro-1-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline
68	 3-((5*S*,5a*S*,6*S*,9*R*)-12-(((7a'*S*)-2,2-Difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline
69	 3-((5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-2,2-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline
70	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-(trifluoromethyl)aniline

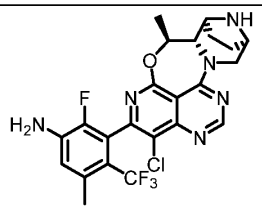
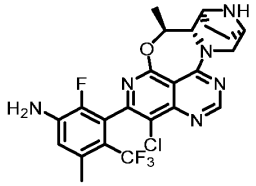
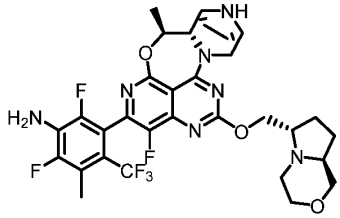
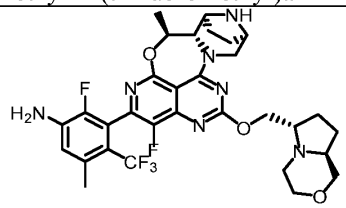
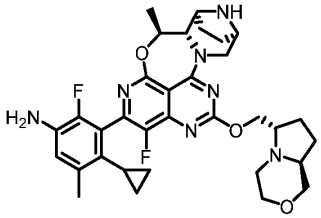
71	 5-((5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-4-(trifluoromethyl)aniline
72	 3-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-(trifluoromethyl)aniline
73	 4-(1,1-difluoroethyl)-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)aniline
74	 4-Chloro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methylaniline

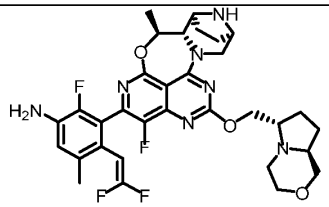
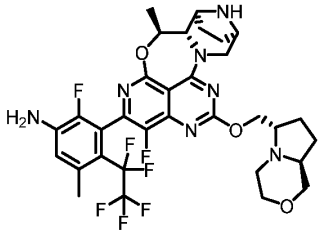
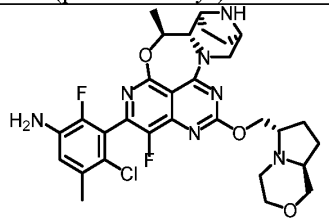
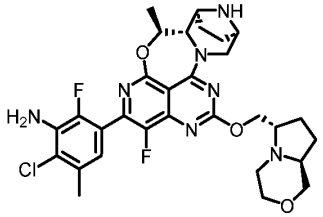
75	 4-(2,2-Difluoroethyl)-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methylaniline
76	 4-Chloro-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methylaniline
77	 3-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-(trifluoromethyl)aniline
78	 (5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-2-(4-(trifluoromethyl)pyridin-3-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene
79	 4-((5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)quinolin-2-amine

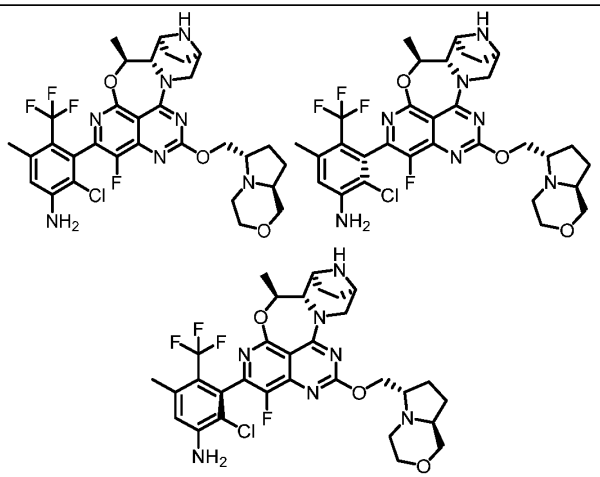
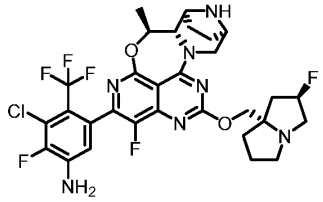
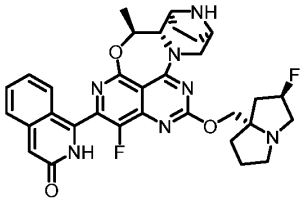
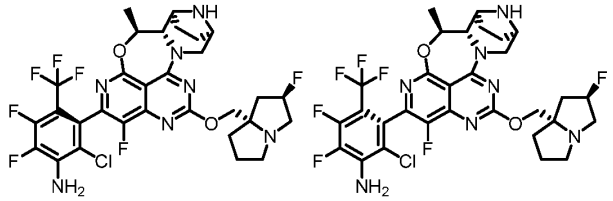
80	 5-Ethyl-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-(((*S*)-2-methylenetetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol
81	 5-Ethynyl-6-fluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol
82	 5,6-Difluoro-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol
83	 7-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2,3-dihydro-1*H*-inden-5-amine
84	 3-Fluoro-6-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-

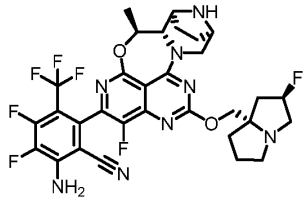
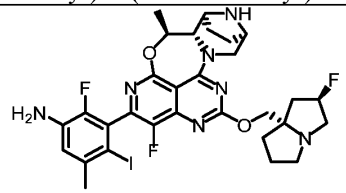
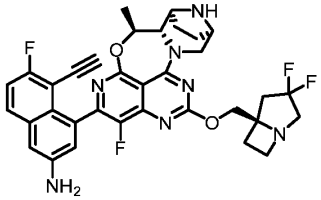
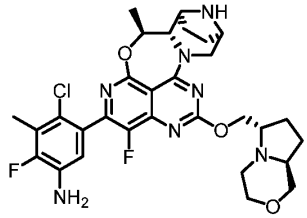
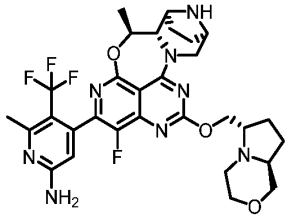
	pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-(trifluoromethyl)pyridin-2-amine
85	 6-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-(trifluoromethyl)pyridin-2-amine
86	 6-((5*S*,5a*S*,6*S*,9*R*)-12-(((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-fluoro-5-(trifluoromethyl)pyridin-2-amine
87	 6-((5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-fluoro-5-(trifluoromethyl)pyridin-2-amine
88	 (5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-2-(4-methyl-3-(trifluoromethyl)pyridin-2-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene

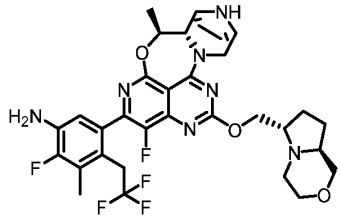
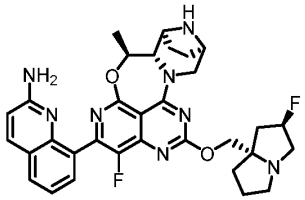
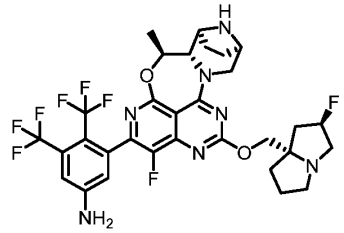
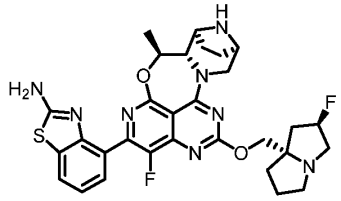
89	 (5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-2-(3-methoxyisoquinolin-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene
90	 2,6-Difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline
91	 2,6-Difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline
92	 3-((5*S*,5a*S*,6*S*,9*R*)-12-(((*S*)-3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-5-methyl-4-(trifluoromethyl)aniline
93	 3-((5*S*,5a*S*,6*S*,9*R*)-1-chloro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-5-methyl-4-(trifluoromethyl)aniline (**mixture of atropisomers**)

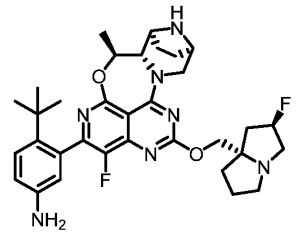
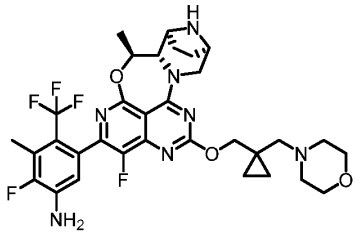
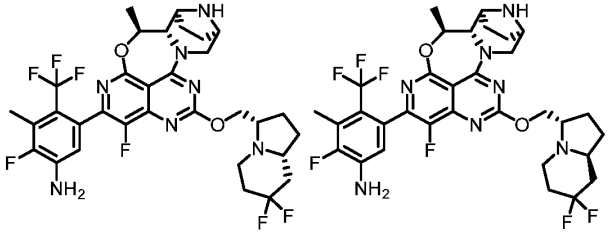
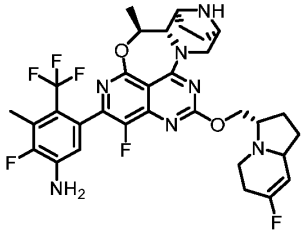
94	 3-((5*S*,5a*S*,6*S*,9*R*)-1-chloro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-5-methyl-4-(trifluoromethyl)aniline
95	 3-((5*S*,5a*S*,6*S*,9*R*)-1-chloro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-5-methyl-4-(trifluoromethyl)aniline
96	 2,6-difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline
97	 2-Fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline
98	 4-Cyclopropyl-2-fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methylaniline

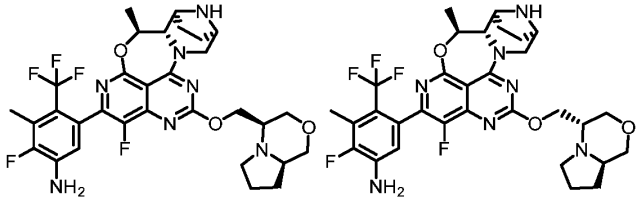
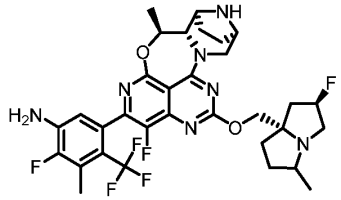
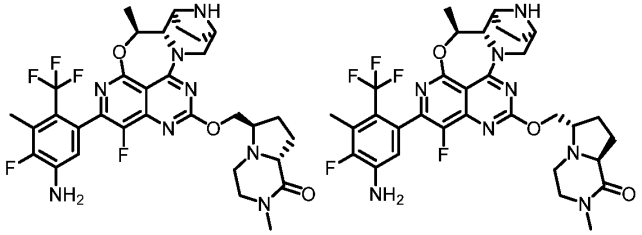
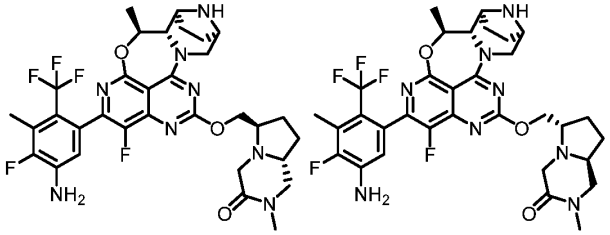
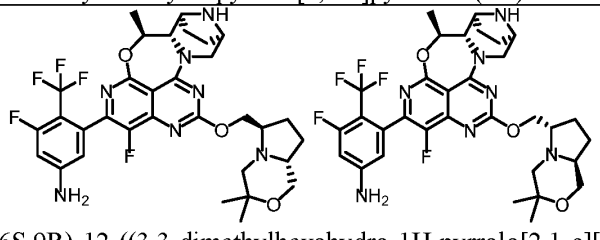
99	 4-(2,2-Difluorovinyl)-2-fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methylaniline
100	 2-Fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(perfluoroethyl)aniline
101	 4-Chloro-2-fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methylaniline
102	 2-Chloro-6-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methylaniline

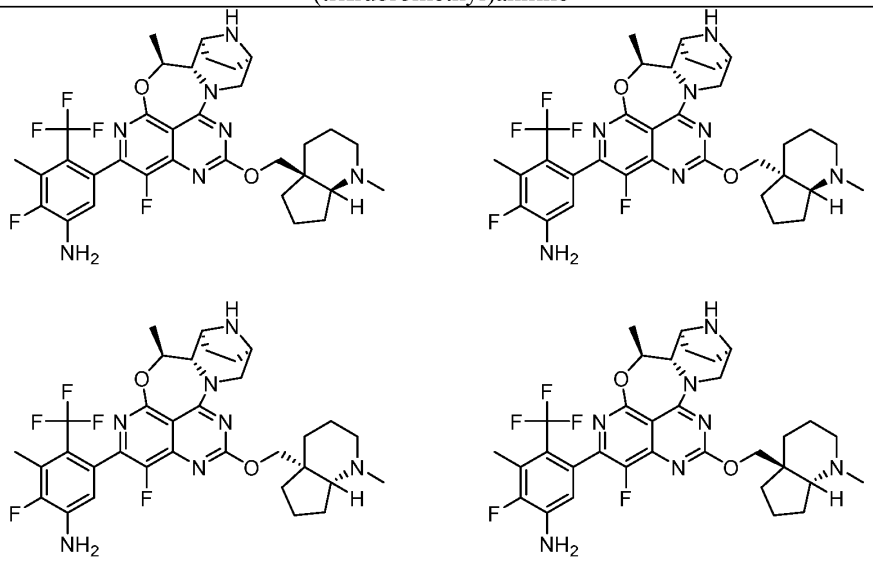
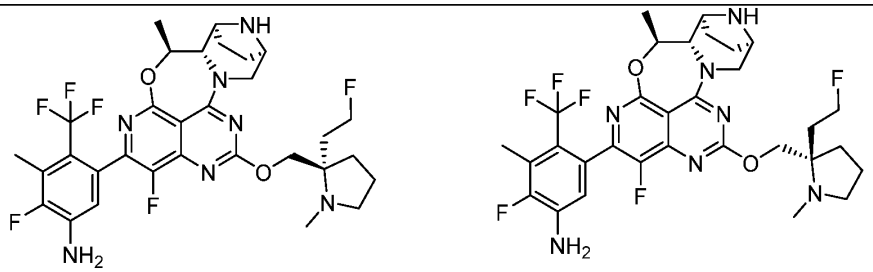
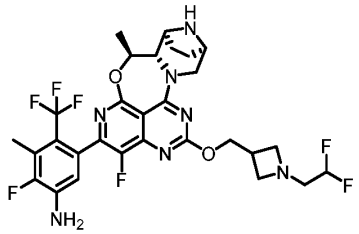
103	 2-Chloro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline and 2-Chloro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
104	 3-Chloro-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-(trifluoromethyl)aniline
105	 1-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)isoquinolin-3(2*H*)-one
106	 2-Chloro-5,6-difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-

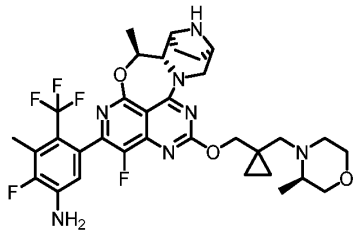
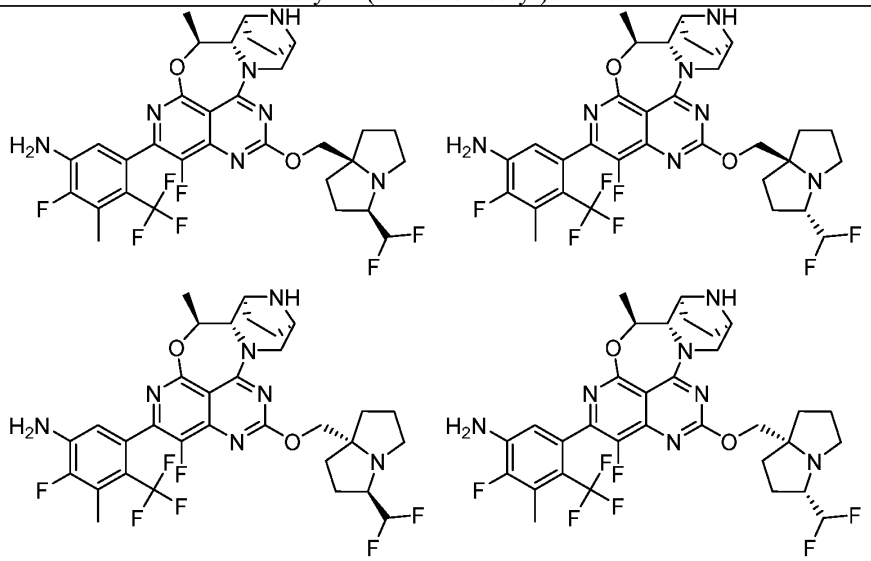
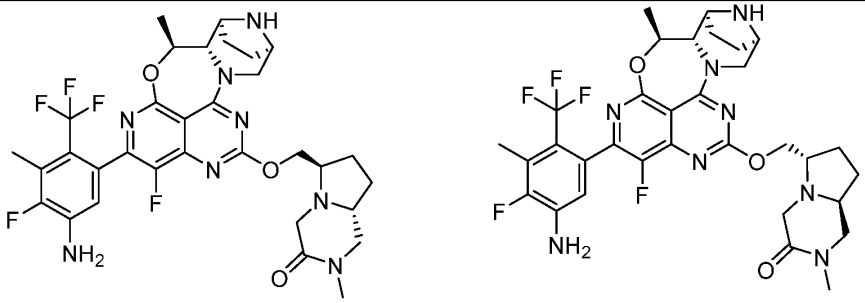
	hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-(trifluoromethyl)aniline (**two atropisomers**)
107	 2-Amino-3,4-difluoro-6-((5*S*,5a*S*,6*S*,9R)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-(trifluoromethyl)benzonitrile
108	 2-Fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-iodo-5-methylaniline
110	 4-((5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-amine
111	 4-Chloro-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methylaniline
112	 4-((5S,5aS,6S,9R)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-

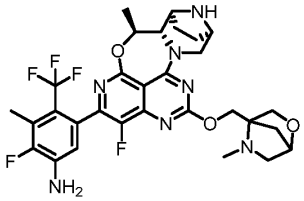
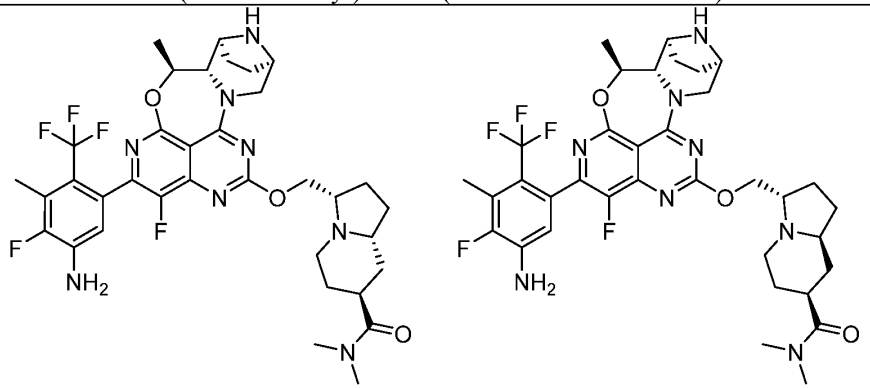
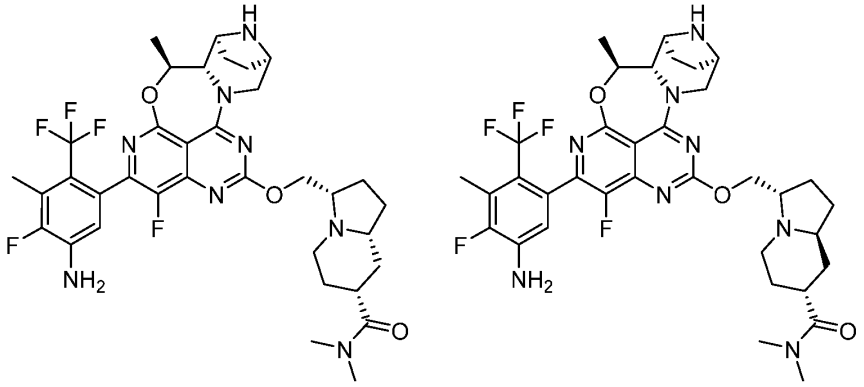
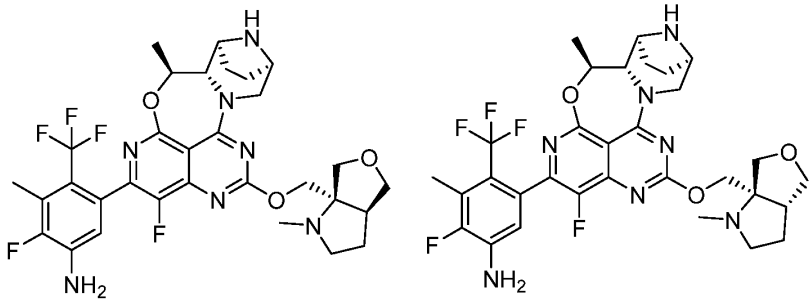
	c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
113	 2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(2,2,2-trifluoroethyl)aniline
114	 8-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)quinolin-2-amine
115	 3-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4,5-bis(trifluoromethyl)aniline
116	 4-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)benzo[d]thiazol-2-amine

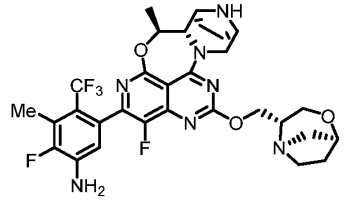
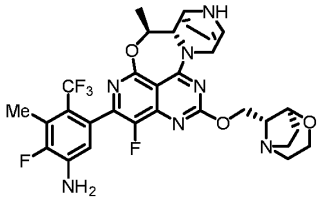
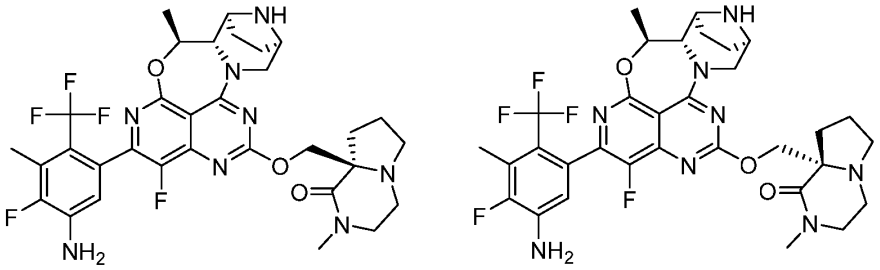
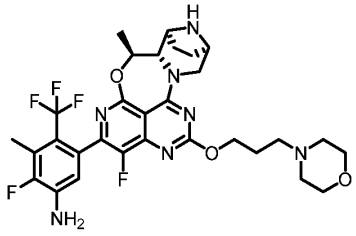
117	 4-(tert-butyl)-3-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)aniline
118	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
119	 5-((5S,5aS,6S,9R)-12-(((3S)-7,7-difluorooctahydroindolizin-3-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (**two isomers**)
120	 2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((3S)-7-fluoro-1,2,3,5,6,8a-hexahydroindolizin-3-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline

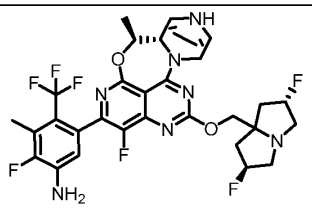
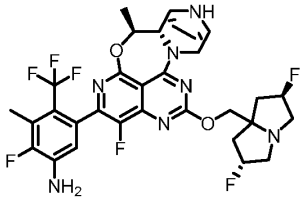
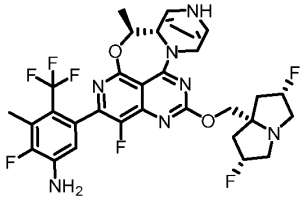
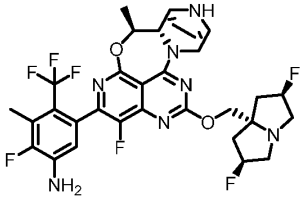
121	 2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((8aR)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-4-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (**two isomers**)
122	 2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluoro-5-methyltetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
123	 6-((((5*S*,5a*S*,6*S*,9*R*)-2-(5-Amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-12-yl)oxy)methyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one
124	 6-((((5*S*,5a*S*,6*S*,9*R*)-2-(5-Amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-12-yl)oxy)methyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one
125	 3-((5S,5aS,6S,9R)-12-((3,3-dimethylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-

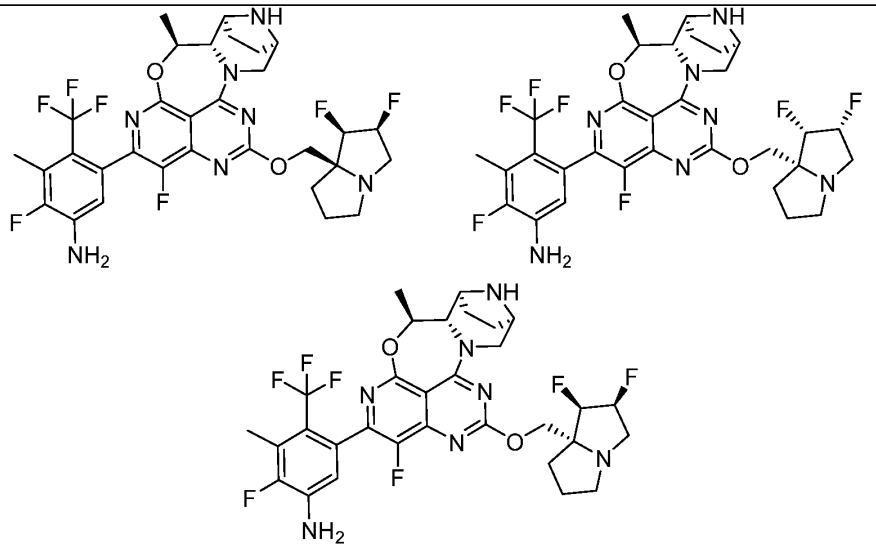
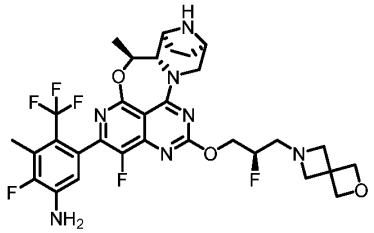
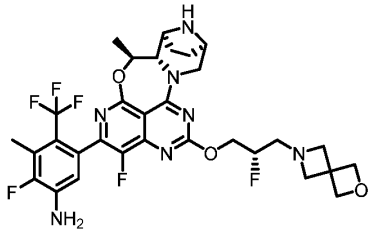
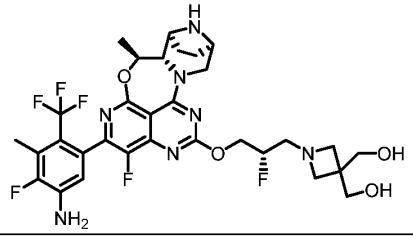
	6-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-fluoro-4-(trifluoromethyl)aniline
126	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-methyloctahydro-4a*H*-cyclopenta[*b*]pyridin-4a-*yl*)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (**four isomers**)
127	 2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-((2-(2-fluoroethyl)-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (**two isomers**)
128	 5-((5*S*,5a*S*,6*S*,9*R*)-12-((1-(2,2-Difluoroethyl)azetidin-3-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline

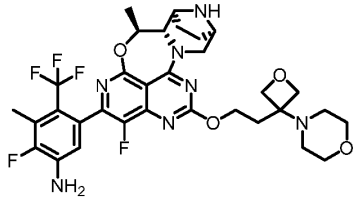
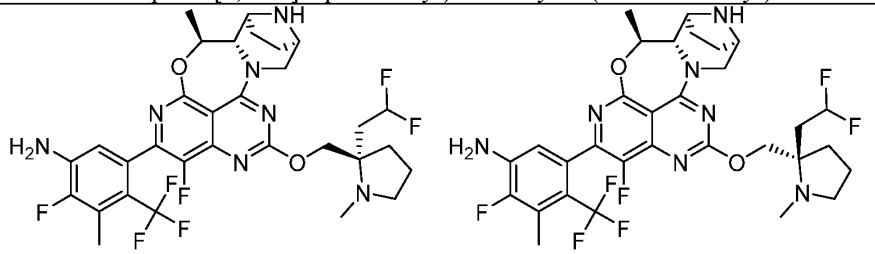
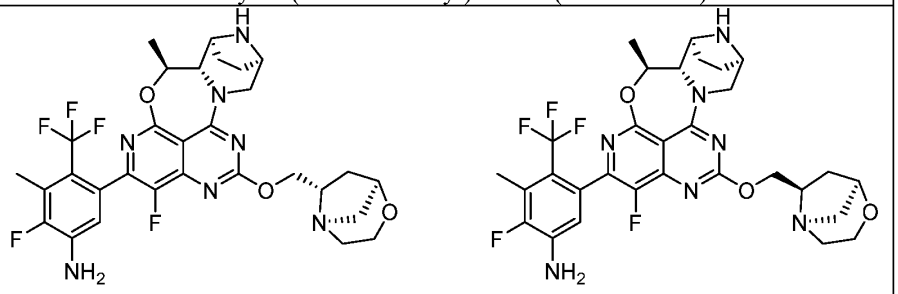
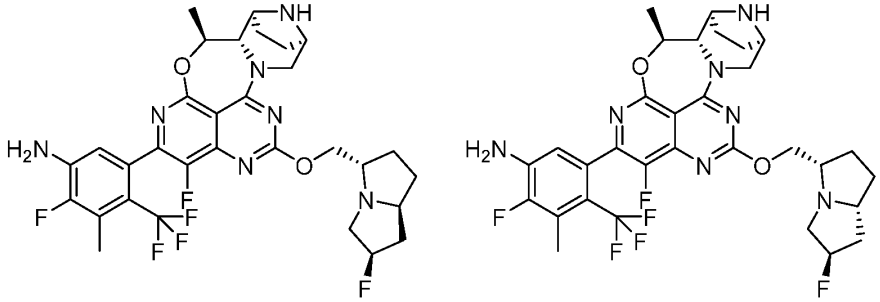
129	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-(((*R*)-3-methylmorpholino)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
130	 5-((5*S*,5a*S*,6*S*,9*R*)-12-((3-(Difluoromethyl)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (**two isomers**)
131	 6-((((5S,5aS,6S,9R)-2-(5-Amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-12-yl)oxy)methyl)-2-methylhexahydropyrrolo[1,2-a]pyrazin-3(4H)-one (**four isomers**)

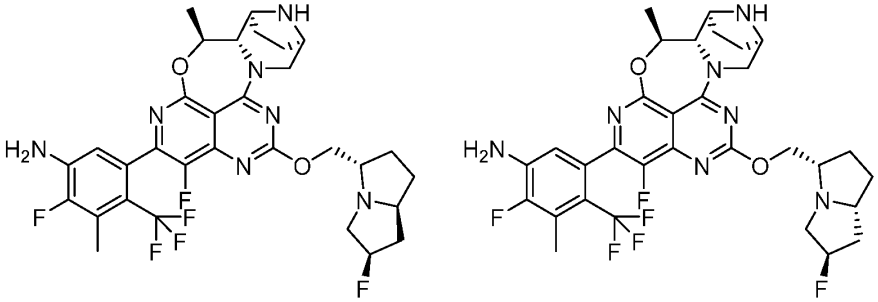
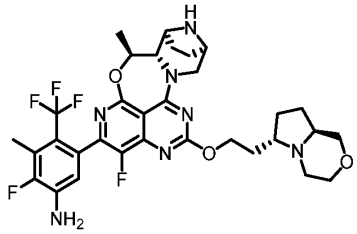
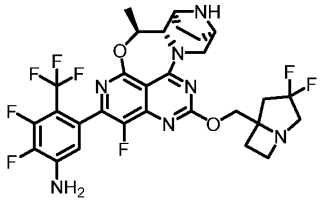
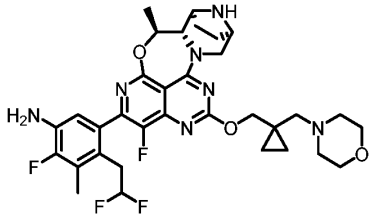
132	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-4-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (**mixture of two isomers**)
133	  (3*S*)-3-((((5*S*,5a*S*,6*S*,9*R*)-2-(5-Amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-12-yl)oxy)methyl)-*N*,*N*-dimethyloctahydroindolizine-7-carboxamide (**four isomers**)
134	

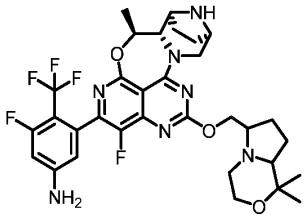
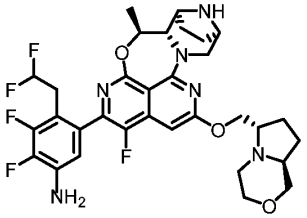
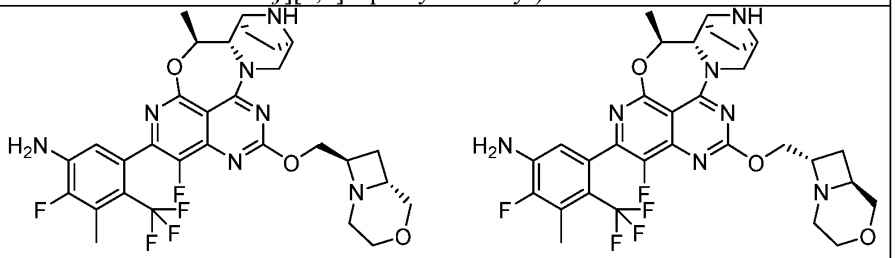
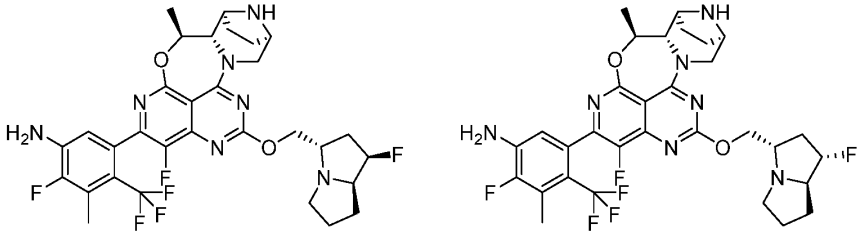
	2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-methyltetrahydro-1*H*-furo[3,4-*b*]pyrrol-6a(6*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (**two isomers**)
135	 5-((5*S*,5a*S*,6*S*,9*R*)-12-(((1*R*,2*S*,5*S*)-4-Oxa-1-azabicyclo[3.2.1]octan-2-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline
136	 5-((5*S*,5a*S*,6*S*,9*R*)-12-(((5*S*,8*R*)-4-Oxa-1-azabicyclo[3.2.1]octan-8-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline
137	 8a-((((5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-12-yl)oxy)methyl)-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2*H*)-one (**two isomers**)
138	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-(3-morpholinopropoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline

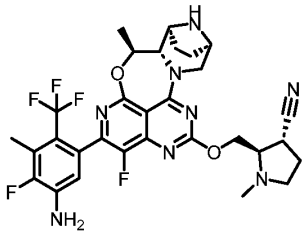
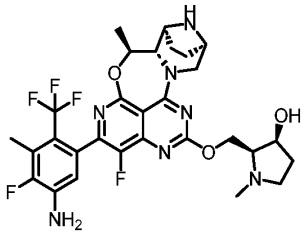
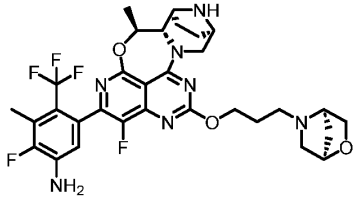
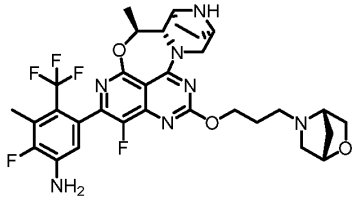
139	 5-((5*S*,5a*S*,6*S*,9*R*)-12-(((2*S*,6*S*)-2,6-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline
140	 5-((5*S*,5a*S*,6*S*,9*R*)-12-(((2*R*,6*R*)-2,6-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline
141	 5-((5*S*,5a*S*,6*S*,9*R*)-12-(((2*R*,6*S*,7*ar*)-2,6-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline
142	 5-((5*S*,5a*S*,6*S*,9*R*)-12-(((2*R*,6*S*,7as)-2,6-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline

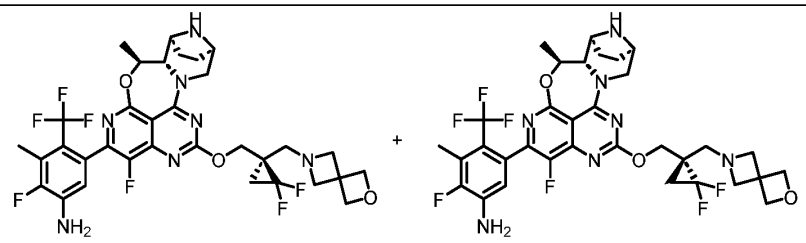
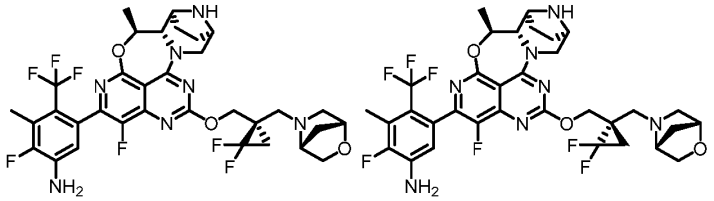
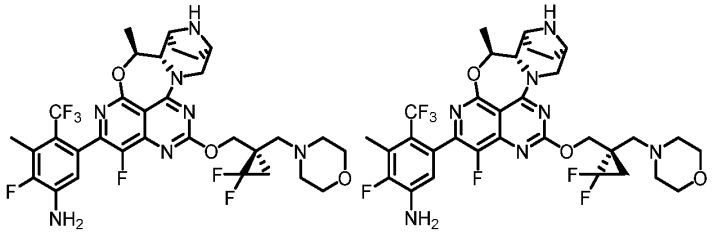
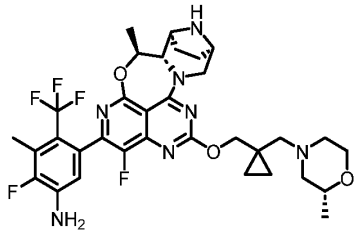
143	 5-((5*S*,5a*S*,6*S*,9*R*)-12-((1,2-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (**three isomers**)
144	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-((1-(((*S*)-2-(fluoromethyl)morpholino)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
145	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-((1-(((*R*)-2-(fluoromethyl)morpholino)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
146	

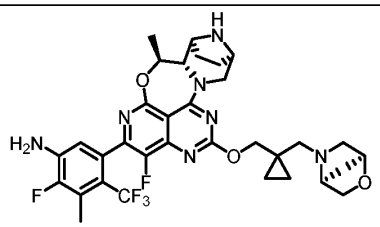
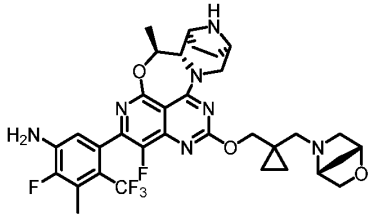
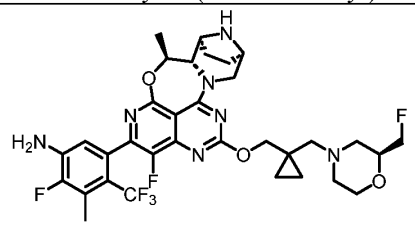
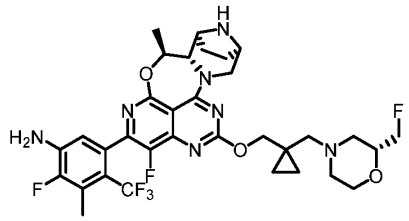
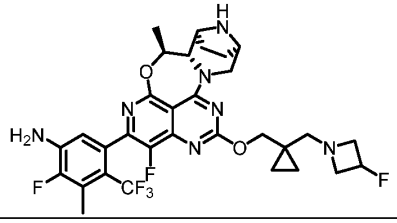
	2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-((1-(((*R*)-2-(fluoromethyl)morpholino)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
149	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-(2-(3-morpholinooxetan-3-yl)ethoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
150	 5-((5*S*,5a*S*,6*S*,9*R*)-12-((2-(2,2-Difluoroethyl)-1-methylpyrrolidin-2-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (**two isomers**)
151	 5-((5*S*,5a*S*,6*S*,9*R*)-12-(((1*R*,5*R*)-4-Oxa-1-azabicyclo[3.2.1]octan-7-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (**two isomers**)
152	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*R*)-6-fluorohexahydro-1*H*-pyrrolizin-3-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-

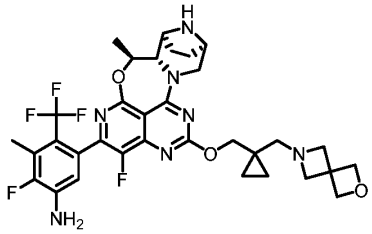
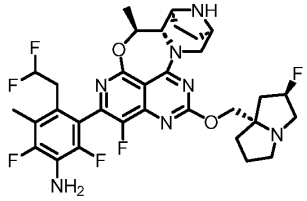
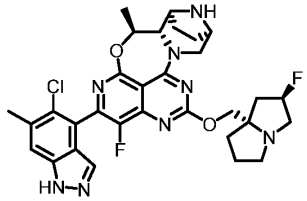
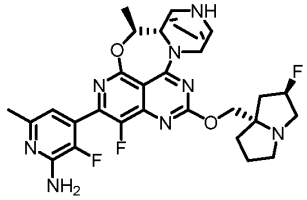
	3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (**two isomers**)
153	 5-((5*S*,5*aS*,6*S*,9*R*)-12-((6,6-Difluorohexahydro-1*H*-pyrrolizin-3-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (**three isomers**)
154	 2-Fluoro-5-((5*S*,5*aS*,6*S*,9*R*)-1-fluoro-12-(2-((6*S*,8*aS*)-hexahydro-1*H*-pyrrolo[2,1-c] [1,4]oxazin-6-yl)ethoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
155	 5-((5*S*,5a*S*,6*S*,9*R*)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2,3-difluoro-4-(trifluoromethyl)aniline
156	 4-(2,2-Difluoroethyl)-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methylaniline

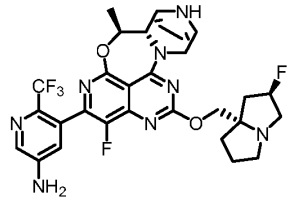
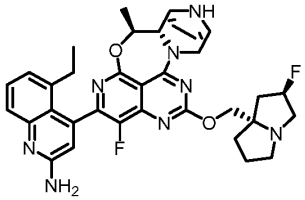
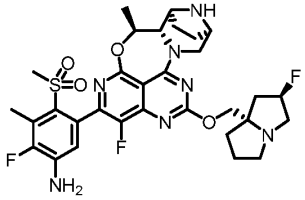
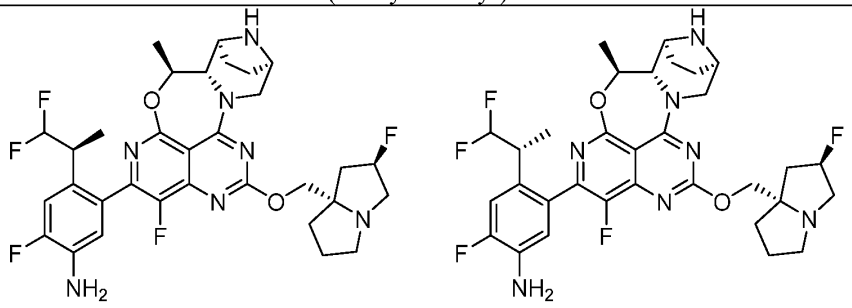
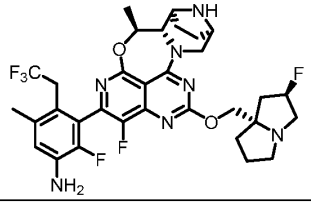
157	 3-((5*S*,5a*S*,6*S*,9*R*)-12-((1,1-Dimethylhexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-fluoro-4-(trifluoromethyl)aniline (**mixture of isomers**)
158	 4-(2,2-Difluoroethyl)-2,3-difluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-13-(((6*S*,8a*S*)-hexahydro-1H-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-6,9-epiminoazepino[2',1':3,4][1,4]oxazepino[5,6,7-*ij*][2,7]naphthyridin-2-yl)aniline
159	 5-((5*S*,5a*S*,6*S*,9*R*)-12-((4-Oxa-1-azabicyclo[4.2.0]octan-8-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (**two diastereomers**)
160	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-((1-fluorohexahydro-1*H*-pyrrolizin-3-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (**two diastereomers**)

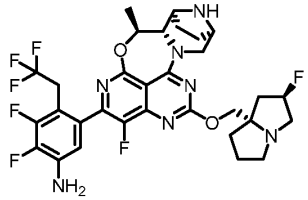
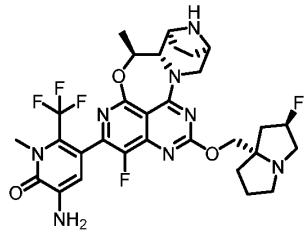
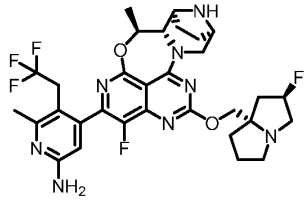
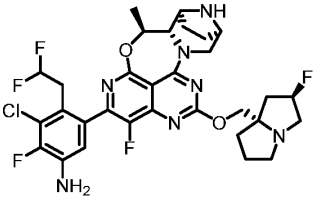
161	 (2*R*,3*R*)-2-((((5*S*,5a*S*,6*S*,9*R*)-2-(5-Amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-12-yl)oxy)methyl)-1-methylpyrrolidine-3-carbonitrile
162	 (2*S*,3*S*)-2-((((5*S*,5a*S*,6*S*,9*R*)-2-(5-Amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-12-yl)oxy)methyl)-1-methylpyrrolidin-3-ol
163	 5-((5*S*,5a*S*,6*S*,9*R*)-12-(3-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline
164	 5-((5*S*,5a*S*,6*S*,9*R*)-12-(3-((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline

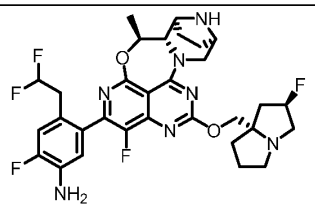
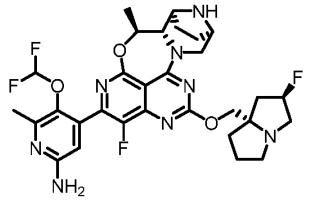
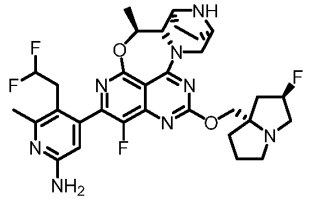
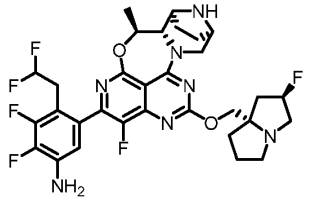
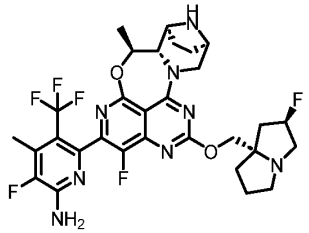
165	 5-((5*S*,5a*S*,6*S*,9*R*)-12-((1-((2-Oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-2,2-difluorocyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (**two diastereomers**)
166	 5-((5*S*,5a*S*,6*S*,9*R*)-12-((1-(((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)-2,2-difluorocyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (mixture of **two diastereomers**)
167	 5-((5*S*,5*aS*,6*S*,9*R*)-12-((2,2-Difluoro-1-(morpholinomethyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (**mixture of diastereomers**)
168	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-(((*R*)-2-methylmorpholino)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline

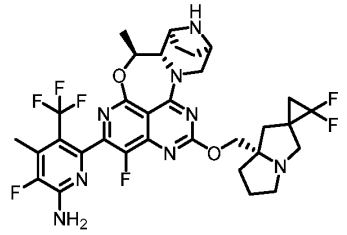
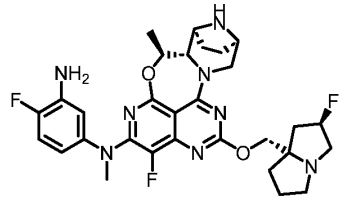
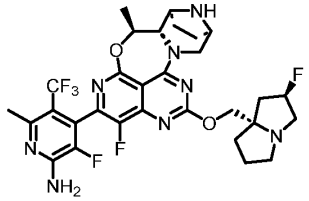
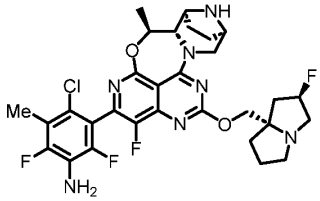
169	 5-((5*S*,5a*S*,6*S*,9*R*)-12-((1-(((1*S*,4*S*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline
170	 5-((5*S*,5a*S*,6*S*,9*R*)-12-((1-(((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline
171	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-((1-(((*S*)-2-(fluoromethyl)morpholino)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)aniline
172	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-((1-(((*R*)-2-(fluoromethyl)morpholino)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline
173	

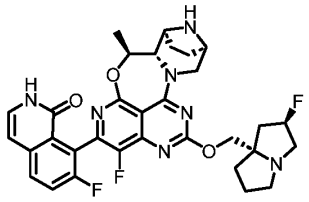
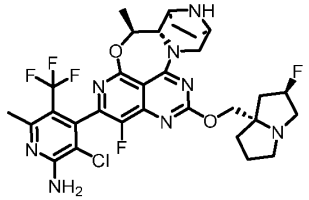
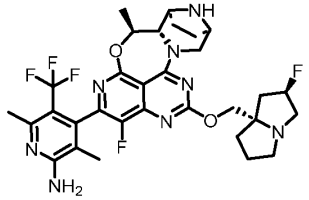
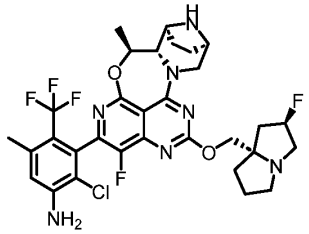
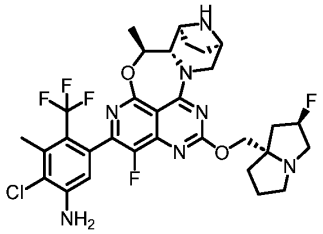
	2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-((1-((3-fluoroazetidin-1-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)aniline
174	 5-((5*S*,5a*S*,6*S*,9*R*)-12-((1-((2-Oxa-6-azaspiro[3.3]heptan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalene-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline
175	 4-(2,2-Difluoroethyl)-2,6-difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-5-methylaniline
176	 (5*S*,5a*S*,6*S*,9*R*)-2-(5-Chloro-6-methyl-1*H*-indazol-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene
177	 3-Fluoro-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7°(5*H*)-yl)methoxy)-5-methyl-5°,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10°,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-6-methylpyridin-2-amine

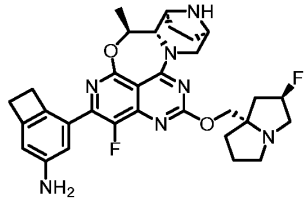
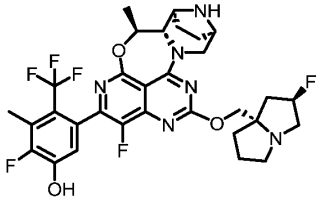
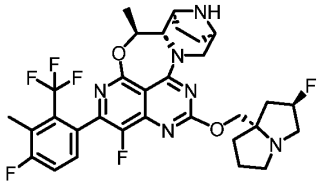
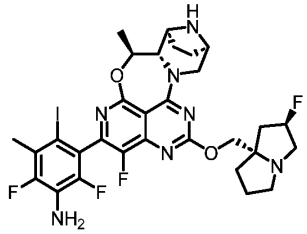
178	 5-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-(trifluoromethyl)pyridin-3-amine
179	 5-Ethyl-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)quinolin-2-amine
180	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-methyl-4-(methylsulfonyl)aniline
181	 4-(1,1-Difluoropropan-2-yl)-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)aniline (**two isomers**)
182	

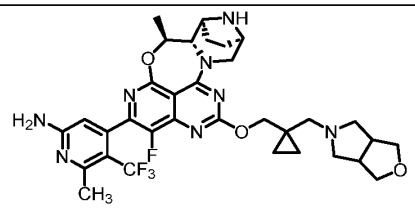
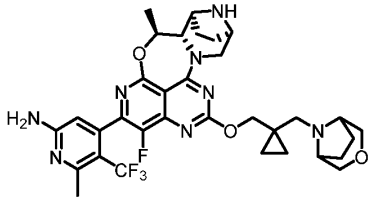
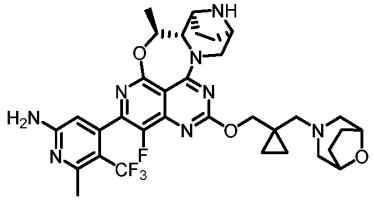
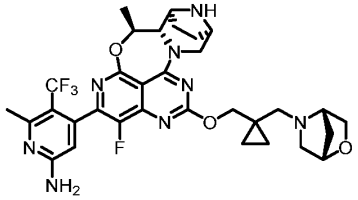
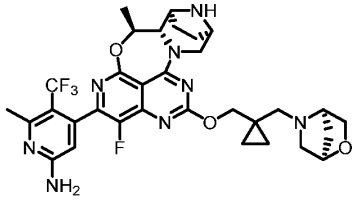
	2-Fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7°(5*H*)-yl)methoxy)-5-methyl-5°,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10°,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-methyl-4-(2,2,2-trifluoroethyl)aniline
183	 2,3-Difluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro -1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14 -pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-4-(2,2,2-trifluoroethyl) aniline
184	 3-Amino-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-1-methyl-6-(trifluoromethyl)pyridin-2(1*H*)-one
185	 4-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(2,2,2-trifluoroethyl)pyridin-2-amine
186	 3-Chloro-4-(2,2-difluoroethyl)-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)aniline

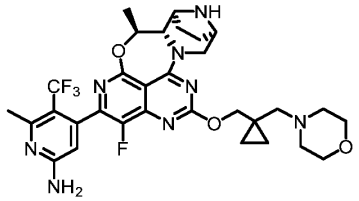
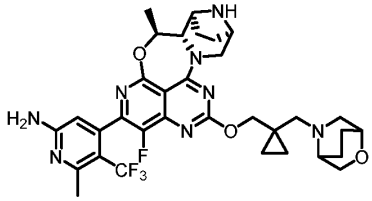
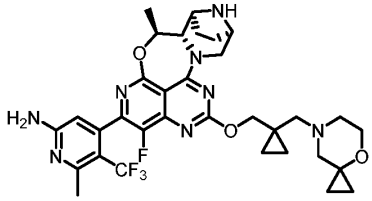
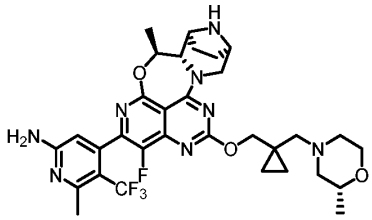
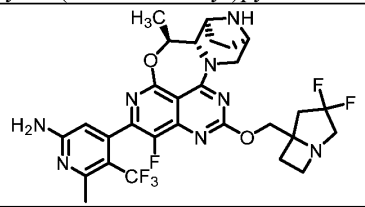
187	 4-(2,2-Difluoroethyl)-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)aniline (**byproduct of Example 186**)
188	 5-(Difluoromethoxy)-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methylpyridin-2-amine
189	 5-(2,2-Difluoroethyl)-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methylpyridin-2-amine
190	 4-(2,2-Difluoroethyl)-2,3-difluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)aniline
191	 3-Fluoro-6-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-

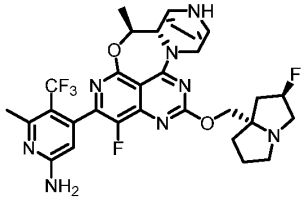
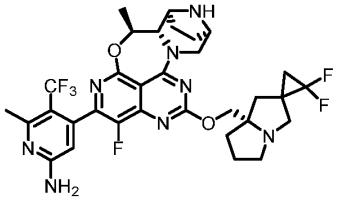
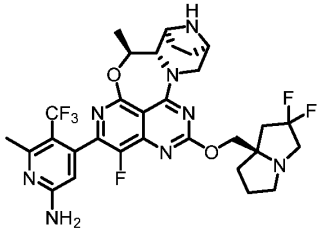
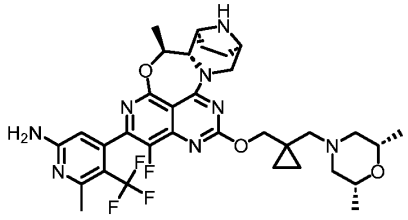
	3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine
192	 6-((5*S*,5a*S*,6*S*,9*R*)-12-(((7a'*S*)-2,2-Difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-fluoro-4-methyl-5-(trifluoromethyl)pyridin-2-amine
193	 4-Fluoro-N^1-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-N^1-methylbenzene-1,3-diamine
194	 3-Fluoro-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7°(5*H*)-yl)methoxy)-5-methyl-5°,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10°,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
195	 4-chloro-2,6-difluoro-3-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7°(5H)-yl)methoxy)-5-methyl-5°,6,7,8,9,10-hexahydro-5H-4-oxa-3,10°,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-methylaniline

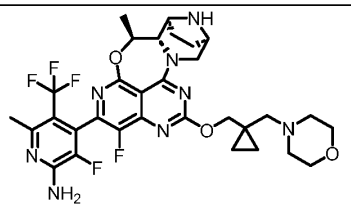
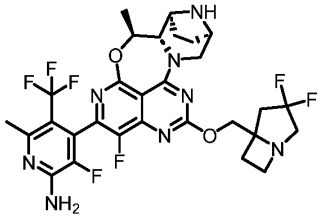
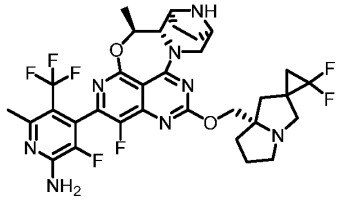
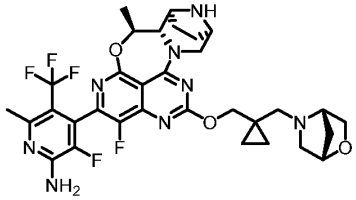
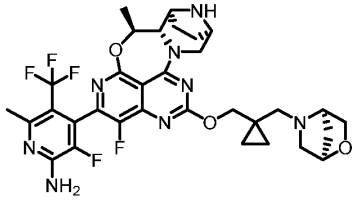
196	 7-Fluoro-8-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7°(5*H*)-yl)methoxy)-5-methyl-5°,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10°,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)isoquinolin-1(2*H*)-one
197	 3-chloro-4-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
198	 4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3,6-dimethyl-5-(trifluoromethyl)pyridin-2-amine
199	 2-Chloro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-5-methyl-4-(trifluoromethyl)aniline
200	 2-Chloro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-

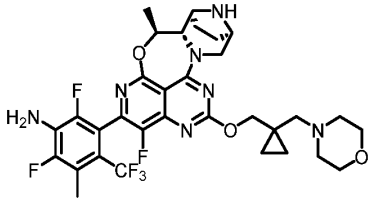
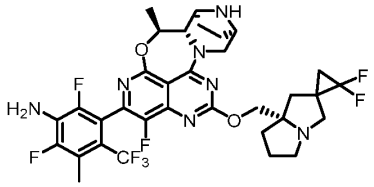
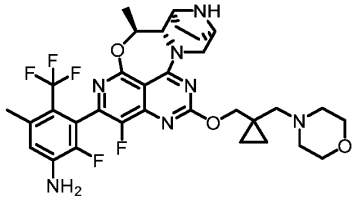
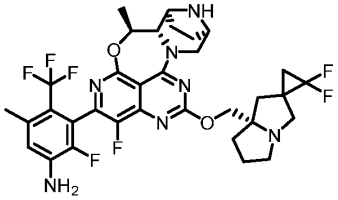
	pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)aniline
201	 5-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)bicyclo[4.2.0]octa-1(6),2,4-trien-3-amine
202	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)phenol
203	 (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene
204	 2,6-Difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-4-iodo-5-methylaniline

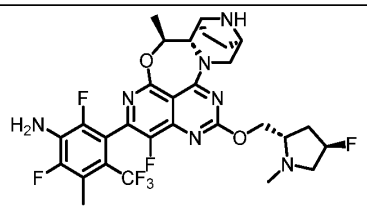
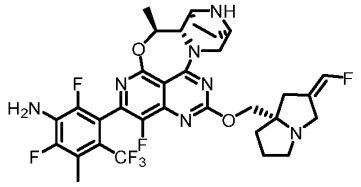
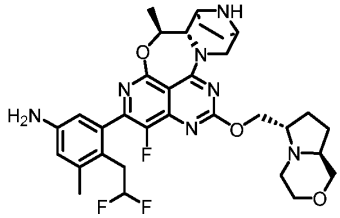
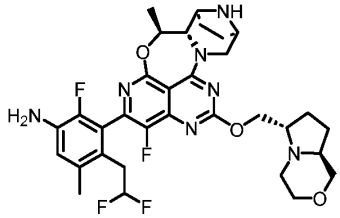
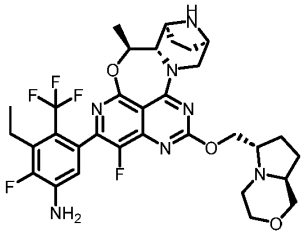
205	 4-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-5-methyl-12-((1-((tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5(3*H*)-yl)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
206	 4-((5*S*,5a*S*,6*S*,9*R*)-12-((1-((3-Oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
207	 4-((5S,5aS,6S,9R)-12-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
208	 4-((5*S*,5a*S*,6*S*,9*R*)-12-((1-(((1*S*,4*S*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
209	 4-((5*S*,5a*S*,6*S*,9*R*)-12-((1-(((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-

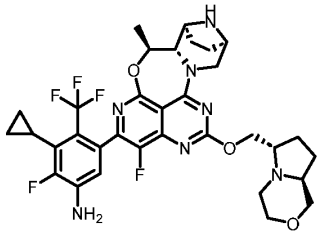
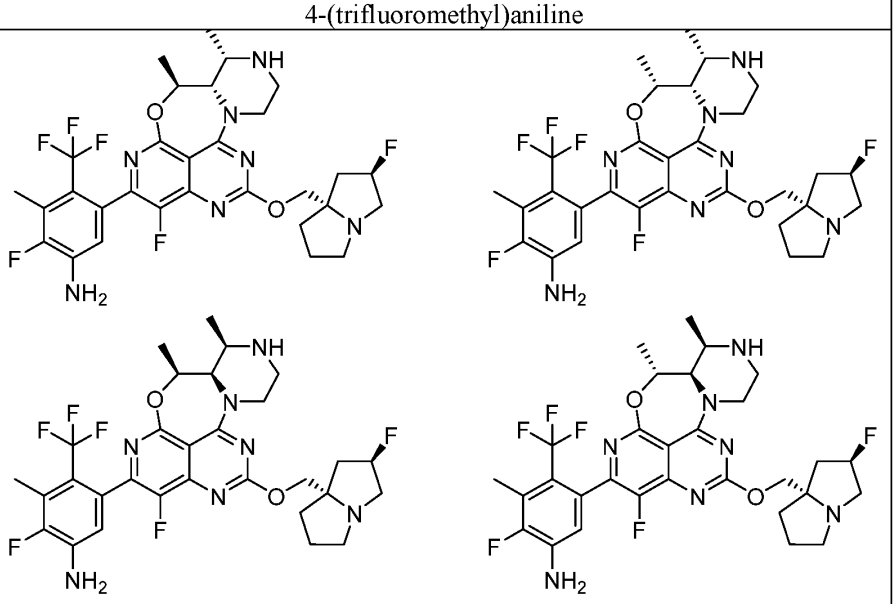
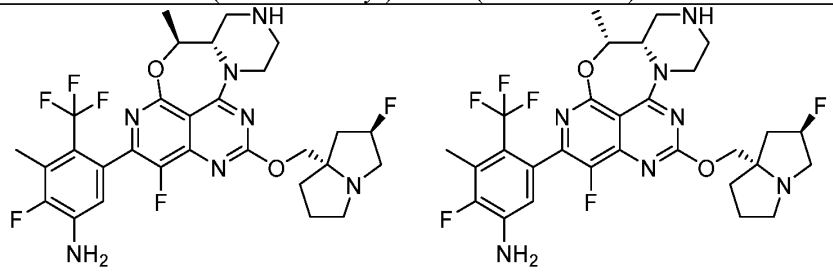
	5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
210	 4-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
211	 4-((5*S*,5a*S*,6*S*,9*R*)-12-((1-((2-Oxa-5-azabicyclo[2.2.2]octan-5-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5°,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10°,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
212	 4-((5*S*,5a*S*,6*S*,9*R*)-12-((1-((4-Oxa-7-azaspiro[2.5]octan-7-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
213	 4-((*5S,5aS,6S,9R*)-1-Fluoro-5-methyl-12-((1-(((*R*)-2-methylmorpholino)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
214	

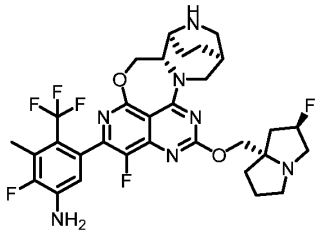
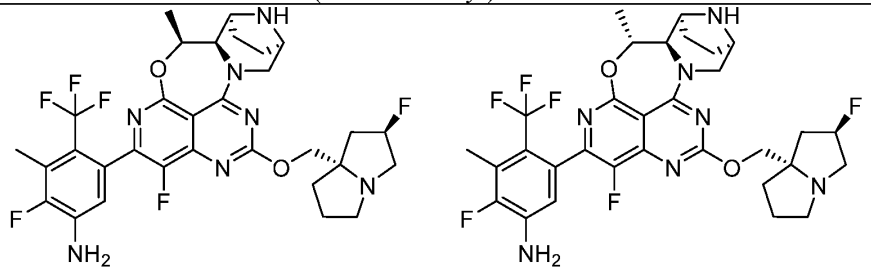
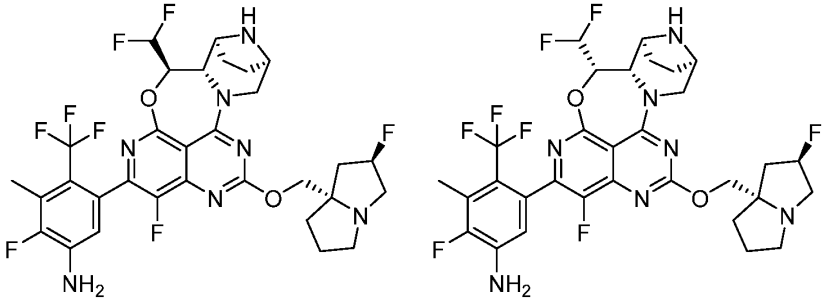
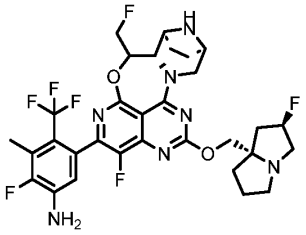
	4-((5*S*,5a*S*,6*S*,9*R*)-12-((3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5°,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10°,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
215	 4-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7°(5*H*)-yl)methoxy)-5-methyl-5°,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10°,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
216	 4-((5*S*,5a*S*,6*S*,9*R*)-12-(((7a'*S*)-2,2-Difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
217	 4-((5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-2,2-difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
218	 4-((5*S*,5a*S*,6*S*,9*R*)-12-((1-(((2*R*,6*S*)-2,6-Dimethylmorpholino)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

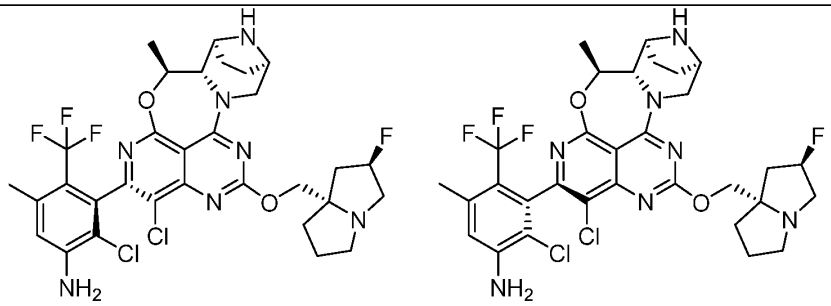
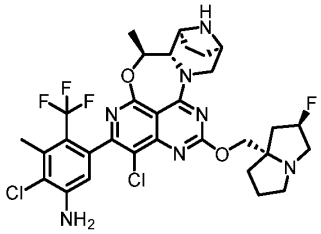
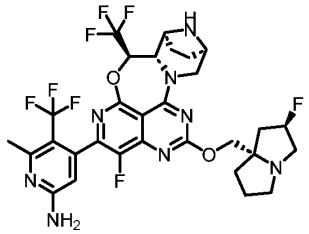
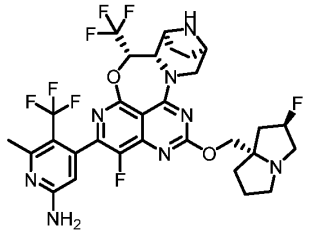
219	 3-Fluoro-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
220	 4-((5*S*,5a*S*,6*S*,9*R*)-12-((3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-2-amine
221	 4-((5*S*,5a*S*,6*S*,9*R*)-12-(((7a'S)-2,2-Difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-2-amine
222	 4-((5*S*,5a*S*,6*S*,9*R*)-12-((1-(((1*S*,4*S*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-2-amine
223	

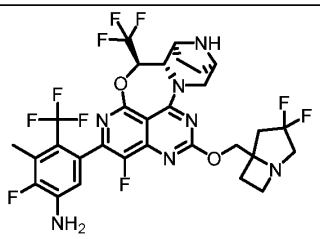
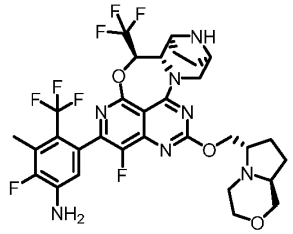
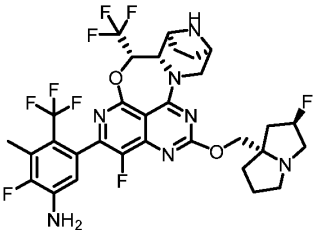
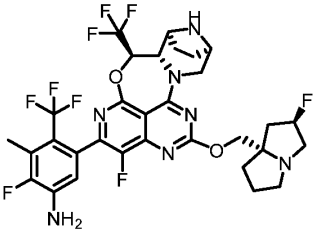
	4-((5*S*,5a*S*,6*S*,9*R*)-12-((1-(((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-2-amine
224	 2,6-Difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-5-methyl-4-(trifluoromethyl)aniline
225	 3-((5*S*,5a*S*,6*S*,9*R*)-12-(((7a'*S*)-2,2-Difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalene-2-yl)-2,6-difluoro-5-methyl-4-(trifluoromethyl)aniline
226	 2-Fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-5-methyl-4-(trifluoromethyl)aniline
227	 3-((5*S*,5a*S*,6*S*,9*R*)-12-(((7a'*S*)-2,2-Difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalene-2-yl)-2-fluoro-5-methyl-4-(trifluoromethyl)aniline

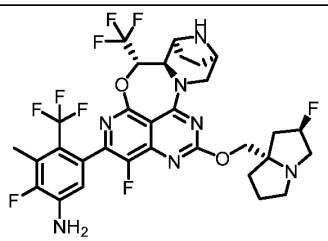
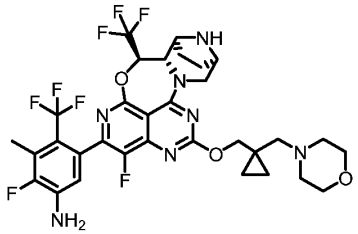
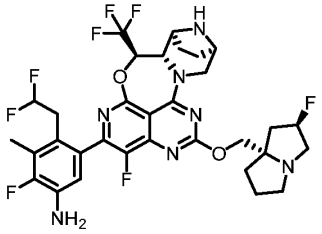
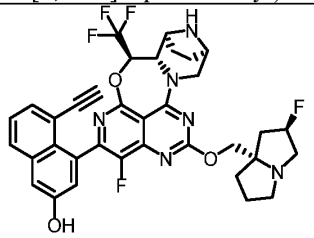
228	 2,6-Difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-5-methyl-4-(trifluoromethyl)aniline
229	 2,6-Difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((*S*,*Z*)-2-(fluoromethylene)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-5-methyl-4-(trifluoromethyl)aniline
230	 *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-2-(2,2-difluoroethyl)-3-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate
231	 4-(2,2-Difluoroethyl)-2-fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-5-methylaniline
232	 3-Ethyl-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-

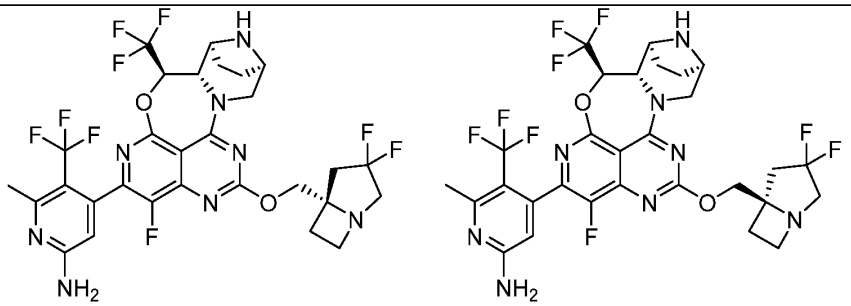
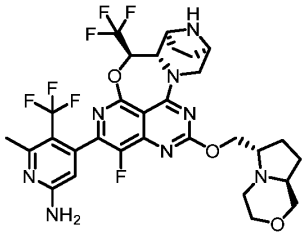
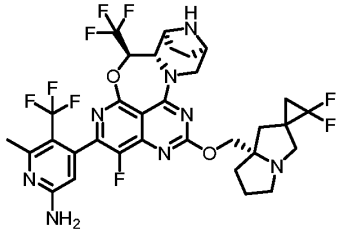
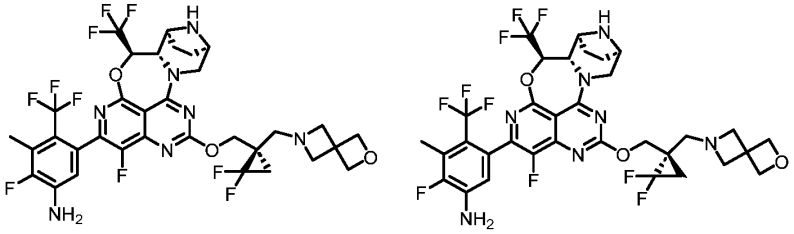
	4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-4-(trifluoromethyl)aniline
233	 3-Cyclopropyl-2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-4-(trifluoromethyl)aniline
234	 2-Fluoro-5-(1-fluoro-11-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6-dimethyl-5,5a,6,7,8,9-hexahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-*de*]naphthalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (**four isomers**)
235	 2-Fluoro-5-((5a*S*)-1-fluoro-11-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5,5a,6,7,8,9-hexahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-*de*]naphthalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (**two isomers**)

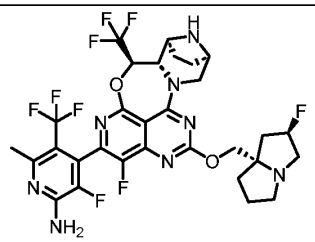
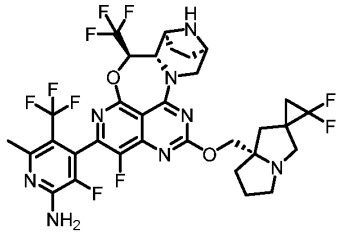
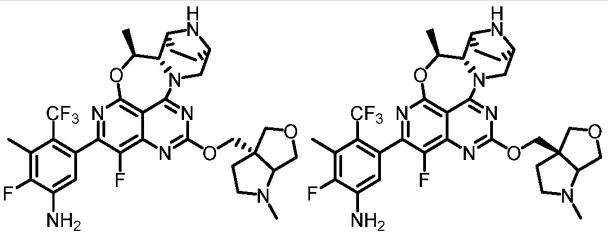
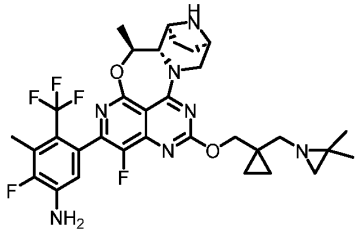
236	 2-Fluoro-5-((5a*S*,6*S*,9*S*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,15-pentaaza-6,9-ethanonaphtho[1,8-*ab*]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)aniline
237	 2-Fluoro-5-((5a*R*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)aniline (**two isomers**)
238	 5-((6*S*,9*R*)-5-(Difluoromethyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (**two isomers**)
239	 2-Fluoro-5-((5a*S*,6*S*,9*R*)-1-fluoro-5-(fluoromethyl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)aniline

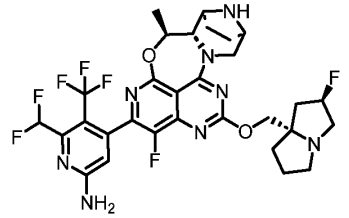
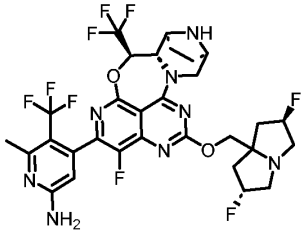
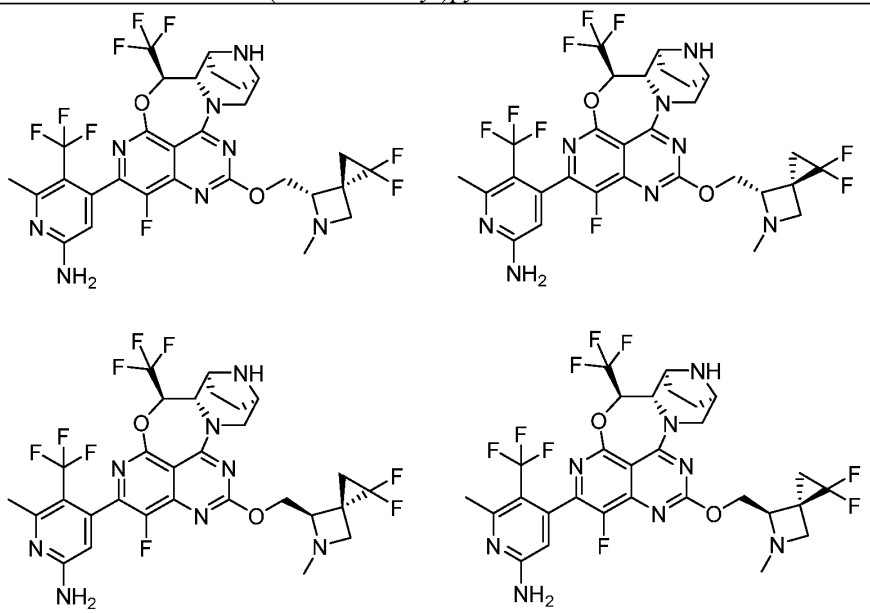
240	 2-Chloro-3-((5S,5aS,6S,9R)-1-chloro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-5-methyl-4-(trifluoromethyl)aniline (**two atropisomers**)
241	 2-Chloro-5-((5S,5aS,6S,9R)-1-chloro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)aniline
242	 4-((5*R*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]pyridine-2-yl)-6-methyl-5-(trifluoromethyl)pyridine-2-amine
243	 4-((6R,9S)-1-fluoro-12-(((2S,7aR)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

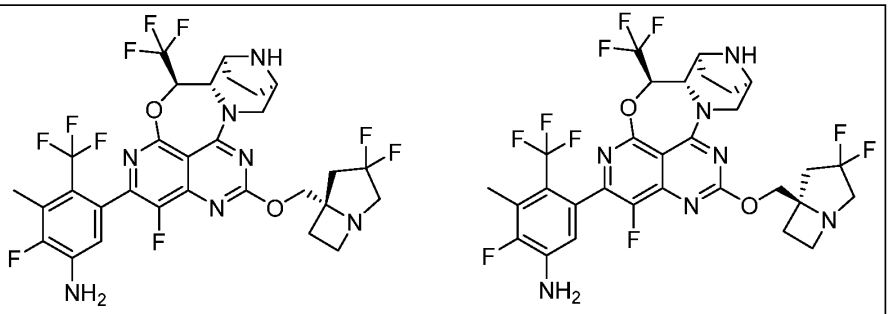
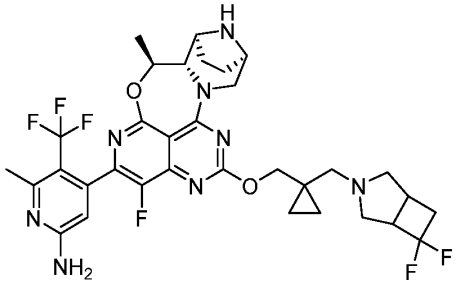
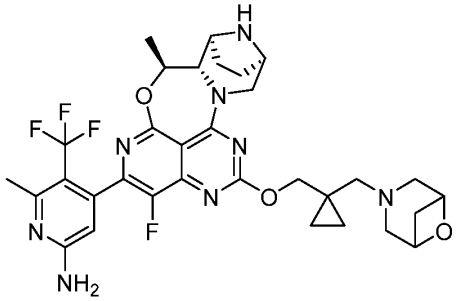
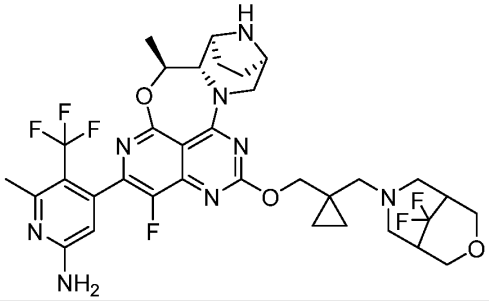
244	 5-((5*R*,5a*S*,6*S*,9*R*)-12-((3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (**mixture of two diastereomers**)
245	 2-Fluoro-5-((5*R*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)aniline
246	 2-Fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)aniline
247	 2-Fluoro-5-((5R,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)aniline

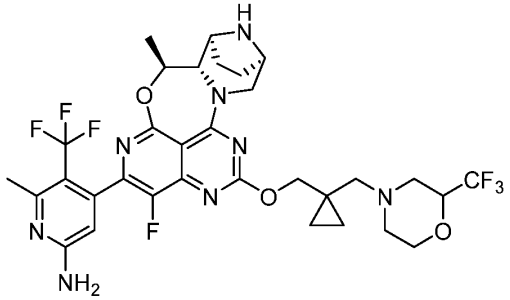
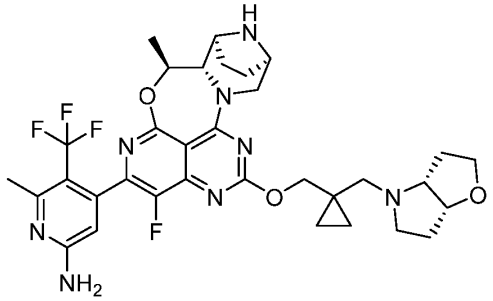
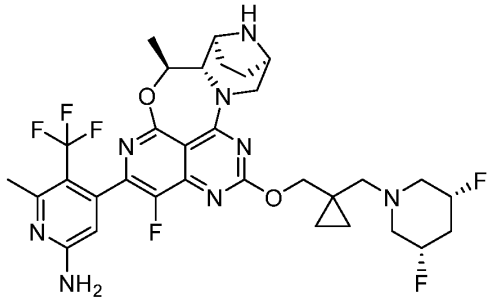
248	 2-Fluoro-5-((5*S*, 5a*R*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)aniline
249	 2-Fluoro-5-((5*R*,5a*S*,6*S*,9*R*)-1-fluoro-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)aniline
250	 4-(2,2-Difluoroethyl)-2-fluoro-5-((5*R*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-methylaniline
251	 5-Ethynyl-4-((5*R*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)naphthalen-2-ol

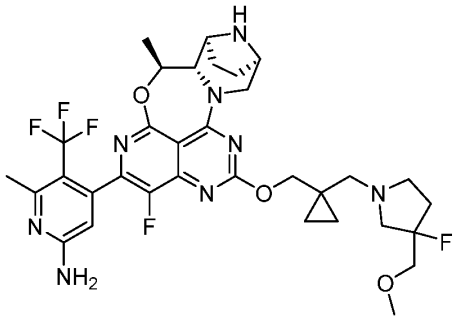
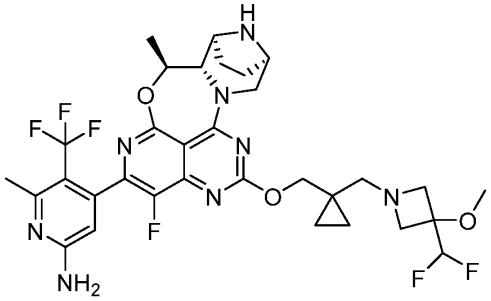
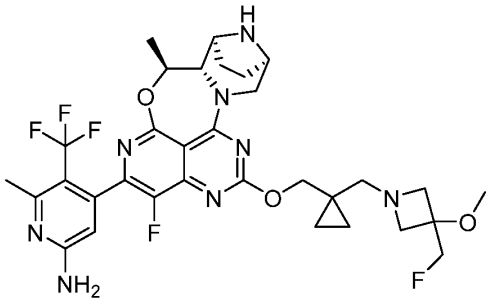
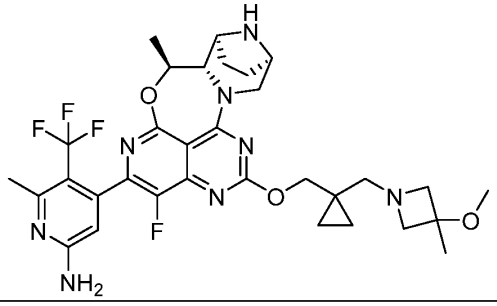
252	 4-((5*R*,5a*S*,6*S*,9*R*)-12-((3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (**two isomers**)
253	 4-((5*R*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
254	 4-((5*R*,5a*S*,6*S*,9*R*)-12-(((7a'*S*)-2,2-Difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
255	 5-((5R,5aS,6S,9R)-12-(((R)-1-((2-oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-2,2-difluorocyclopropyl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (**mixture and two separate diastereomers**)

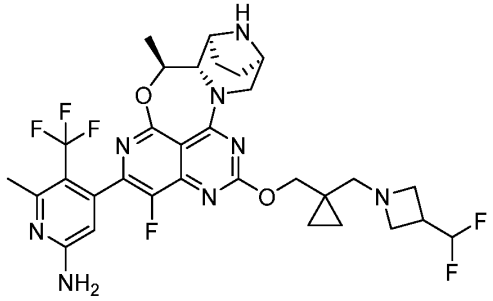
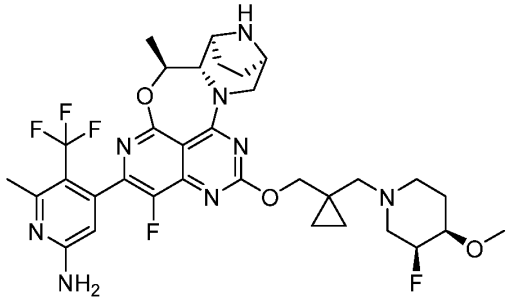
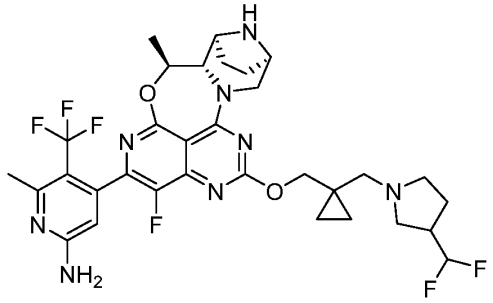
256	 3-Fluoro-4-((5R,5aS,6S,9R)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
257	 4-((5*R*,5a*S*,6*S*,9*R*)-12-(((7a'*S*)-2,2-Difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-2-amine
258	 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-methyltetrahydro-1*H*-furo[3,4-*b*]pyrrol-3a(4*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-3-methyl-4-(trifluoromethyl)aniline (**two isomers**)
259	 5-((5*S*,5a*S*,6*S*,9*R*)-12-((1-((2,2-Dimethylaziridin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline

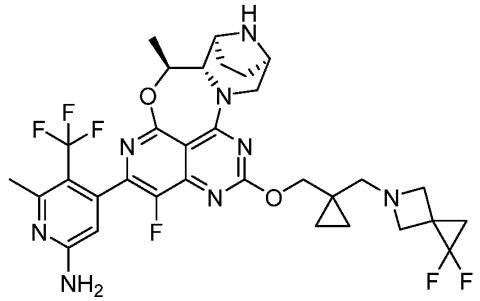
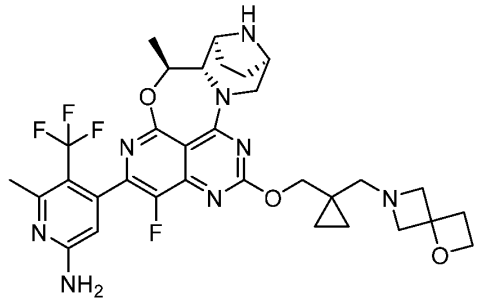
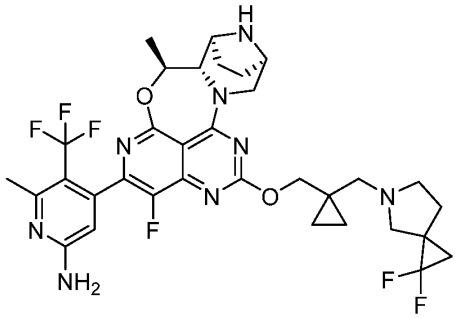
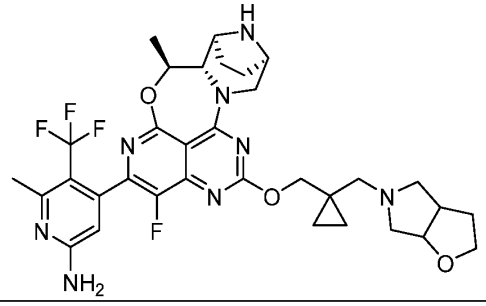
260	 6-(Difluoromethyl)-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-5-(trifluoromethyl)pyridin-2-amine
261	 4-((5*R*,5a*S*,6*S*,9*R*)-12-(((2*R*,6*R*)-2,6-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
262	 4-((5*R*,5a*S*,6*S*,9*R*)-12-((1,1-Difluoro-5-methyl-5-azaspiro[2.3]hexan-4-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (**four isomers**)

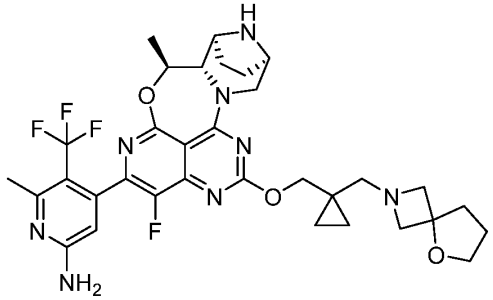
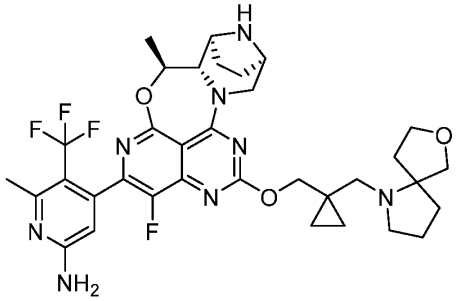
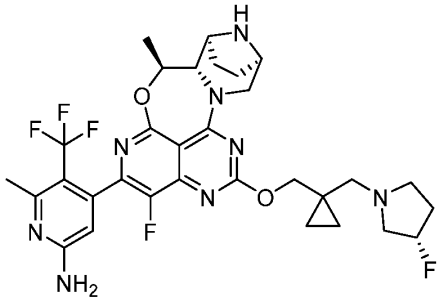
263	 5-((5*R*,5a*S*,6*S*,9*R*)-12-((3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (**two diastereoimers**)
264	 4-((5S,5aS,6S,9R)-12-((1-((6,6-difluoro-3-azabicyclo[3.2.0]heptan-3-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (**mixture of diastereomers**)
265	 4-((5S,5aS,6S,9R)-12-((1-((6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
266	

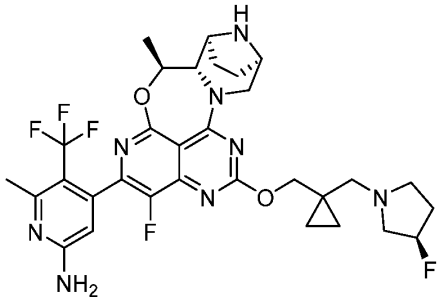
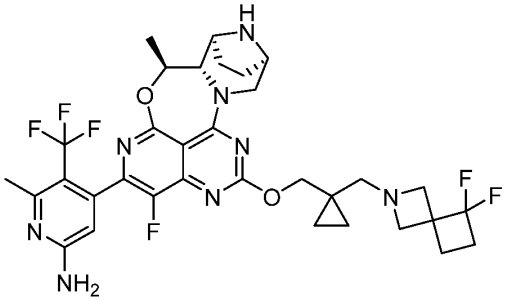
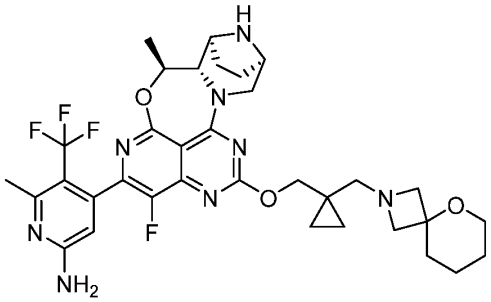
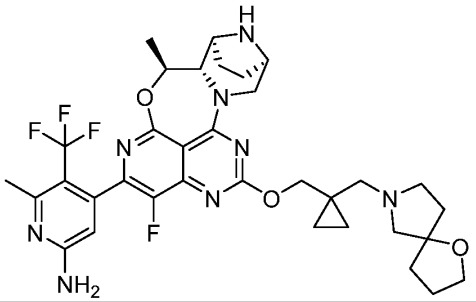
	4-((5S,5aS,6S,9R)-12-((1-((9,9-difluoro-3-oxa-7-azabicyclo[3.3.1]nonan-7-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
267	 4-((5S,5aS,6S,9R)-1-fluoro-5-methyl-12-((1-((2-(trifluoromethyl)morpholino)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridn-2-amine (**mixture of diastereomers**)
268	 4-((5S,5aS,6S,9R)-1-fluoro-12-((1-(((3aR,6aR)-hexahydro-4H-furo[3,2-b]pyrrol-4-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
269	 4-((5S,5aS,6S,9R)-12-((1-(((3S,5R)-3,5-difluoropiperidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

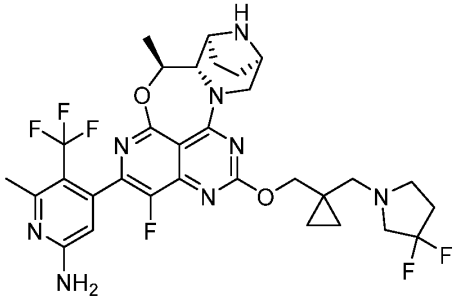
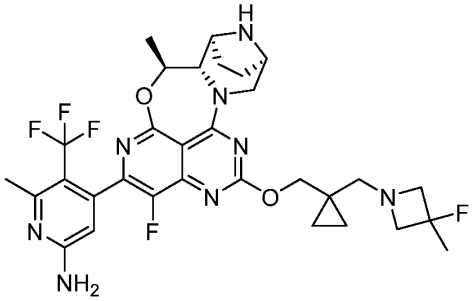
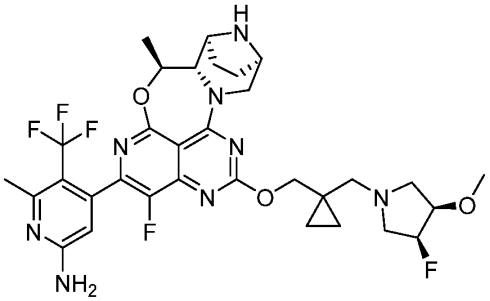
270	 4-((5S,5aS,6S,9R)-1-fluoro-12-((1-((3-fluoro-3-(methoxymethyl)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (**mixture of diastereomers**)
271	 4-((5S,5aS,6S,9R)-12-((1-((3-(difluoromethyl)-3-methoxyazetidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
272	 4-((5S,5aS,6S,9R)-1-fluoro-12-((1-((3-(fluoromethyl)-3-methoxyazetidin-1-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
273	

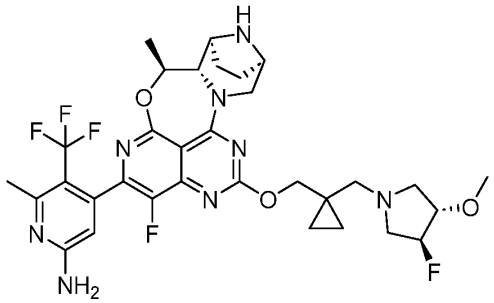
	4-((5S,5aS,6S,9R)-1-fluoro-12-((1-((3-methoxy-3-methylazetidin-1-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
274	 4-((5S,5aS,6S,9R)-12-((1-((3-(difluoromethyl)101eptalene-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
275	 4-((5S,5aS,6S,9R)-1-fluoro-12-((1-(((3S,4R)-3-fluoro-4-methoxypiperidin-1-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
276	 4-((5S,5aS,6S,9R)-12-((1-((3-(difluoromethyl)pyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (**mixture of diastereomers**)

277	 4-((5S,5aS,6S,9R)-12-((1-((1,1-difluoro-5-azaspiro[2.3]hexan-5-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
278	 4-((5S,5aS,6S,9R)-12-((1-((1-oxa-6-azaspiro[3.3]heptan-6-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
279	 4-((5S,5aS,6S,9R)-12-((1-((1,1-difluoro-5-azaspiro[2.4]heptan-5-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (**mixture of diastereomers**)
280	

	4-((5S,5aS,6S,9R)-1-fluoro-12-((1-((hexahydro-5H-furo[2,3-c]pyrrol-5-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (**mixture of diastereomers**)
281	 4-((5S,5aS,6S,9R)-12-((1-((5-oxa-2-azaspiro[3.4]octan-2-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
282	 4-((5S,5aS,6S,9R)-12-((1-((7-oxa-1-azaspiro[4.4]nonan-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (**mixture of diastereomers**)
283	 4-((5S,5aS,6S,9R)-1-fluoro-12-((1-(((S)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

284	 4-((5S,5aS,6S,9R)-1-fluoro-12-((1-(((R)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
285	 4-((5S,5aS,6S,9R)-12-((1-((5,5-difluoro-2-azaspiro[3.3]heptan-2-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
286	 4-((5S,5aS,6S,9R)-12-((1-((5-oxa-2-azaspiro[3.5]nonan-2-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
287	

	4-((5S,5aS,6S,9R)-12-((1-((1-oxa-7-azaspiro[4.4]nonan-7-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (**mixture of diastereomers**)
288	 4-((5S,5aS,6S,9R)-12-((1-((3,3-difluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
289	 4-((5S,5aS,6S,9R)-1-fluoro-12-((1-((3-fluoro-3-methylazetidin-1-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine
290	 4-((5S,5aS,6S,9R)-1-fluoro-12-((1-(((3S,4R)-3-fluoro-4-methoxypyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

291	 4-((5S,5aS,6S,9R)-1-fluoro-12-((1-(((3S,4S)-3-fluoro-4-methoxypyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[0140] In one embodiment is a compound selected from compounds 1-36, 38-45, 47-62, 64-108, 110-146, and 149-291 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0141] In one embodiment is a compound selected from compounds 1-36, 38-45, 47-62, 64-108, and 110-125 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0142] In one embodiment is a compound selected from compounds 126-146 and 149-291 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0143] In one embodiment is a compound selected from compounds 6, 15, 24, 26, 29, 31-32, 57-59, 61-62, 64-66, 75-76, 91, 96, 104, 106, 111, 113, 118-124, 126-146, 149-156, 158-175, 181, 183, 186, 190-192, 195, 200, 204, 224-225, 228-229, 232-239, 241, 244-250, 255, 258-259, and 263 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0144] In one embodiment is a compound selected from compounds 6, 12-18, 23-24, 26, 29, 31-36, 57-58, 60-62, 64-77, 90-97, 100-102, 104, 108, 111, 113, 115, 118-146, 149-175, 181-183, 186-187, 190, 195, 200, 204, 224-232, 234-239, 241, 244-250, 255, 258-259, and 263 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0145] In one embodiment is a compound selected from compounds 6, 13-14, 16-18, 23-24, 26, 29, 31-34, 36, 57-62, 64-72, 74, 76, 91-104, 106-108, 111, 113, 115, 117-146, 149-154, 157, 159-174, 199, 200, 224-229, 234-241, 244-249, 255, 258-259, and 263 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0146] In one embodiment is a compound selected from compounds 6, 12-18, 23-24, 26, 29, 31-36, 42-45, 47-48, 52, 57-58, 60-78, 84-88, 90-97, 100-104, 106, 108, 111-113, 115, 118-146, 149-175, 177-178, 181-183, 185-187, 189-192, 194-195, 197-200, 203-232, 234-250, and 252-

291 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0147] In one embodiment is a compound selected from compounds 6, 13-14, 16-18, 23-24, 26, 29, 31-34, 36, 42-45, 47-48, 52, 57-62, 64-72, 74, 76, 84-88, 91-104, 106-108, 111, 113, 115, 117-146, 149-154, 157, 159-174, 199, 200, 224-229, 234-241, 244-249, 255, 258-259, and 263 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0148] In one embodiment is a compound selected from compounds 42-45, 47-48, and 52 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0149] In one embodiment is a compound selected from compounds 112, 205-218, 242-243, 252-254, 261-262, and 264-291 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

Synthesis of Compounds

[0150] Compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein of the present disclosure can be made by a variety of methods depicted in the illustrative synthetic reaction schemes shown and described below. The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's *Reagents for Organic Synthesis*; Wiley & Sons: New York, vol. 1-21; R. C. LaRock, *Comprehensive Organic Transformations*, 2nd edition Wiley-VCH, New York 1999; *Comprehensive Organic Synthesis*, B. Trost and I. Fleming (Eds.) vol. 1-9 Pergamon, Oxford, 1991; *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky and C. W. Rees (Eds.) Pergamon, Oxford 1984, vol. 1-9; *Comprehensive Heterocyclic Chemistry II*, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1996, vol. 1-11; and *Organic Reactions*, Wiley & Sons: New York, 1991, vol. 1-40. The following synthetic reaction schemes are merely illustrative of some methods by which the compounds or pharmaceutical acceptable salts thereof described herein can be synthesized, and various modifications to these synthetic reaction schemes can be made and will be suggested to one skilled in the art having referred to the disclosure contained herein.

[0151] Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing compounds described herein and necessary reagents and intermediates include, for example, those described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley and Sons (1999); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995) and subsequent editions thereof.

[0152] Compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein described herein can be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, or 10 to 100 compounds. Libraries of compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein of the formulae described herein can be prepared by a combinatorial split and mix approach or by multiple parallel syntheses using, for example, either solution phase or solid phase chemistry. Thus, according to a further aspect provided herein is a compound library comprising at least 2 compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein.

[0153] The Examples provide exemplary methods for preparing compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein. Those skilled in the art will appreciate that other synthetic routes can be used to synthesize the compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein described herein. Although specific starting materials and reagents are depicted and discussed in the Examples, other starting materials and reagents can be substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the exemplary compounds prepared by the described methods can be further modified in light of this disclosure using conventional chemistry.

[0154] In preparing compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein protection of remote functionality (e.g., primary or secondary amine) of intermediates can be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection can be readily determined. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

[0155] In the methods of preparing compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein, it can be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps are separated and/or purified to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium and low pressure liquid

chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

[0156] Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like. Selection of appropriate methods of separation depends on the nature of the materials involved, such as, boiling point and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like.

[0157] Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein described herein can be atropisomers (e.g., substituted biaryls). Enantiomers can also be separated by use of a chiral HPLC column.

[0158] A single stereoisomer, e.g., an enantiomer, substantially free of its stereoisomer can be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Eliel, E. and Wilen, S. "Stereochemistry of Organic Compounds," John Wiley & Sons, Inc., New York, 1994; Lochmuller, C. H., (1975) J. Chromatogr., 113(3):283-302). Racemic mixtures of chiral compounds or pharmaceutically acceptable salts thereof described herein can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: "Drug Stereochemistry, Analytical Methods and Pharmacology," Irving W. Wainer, Ed., Marcel Dekker, Inc., New York (1993).

[0159] Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, a-methyl-b-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts can be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

[0160] Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (E. and Wilen, S. "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g., (-) menthyl chloroformate in the presence of base, or Mosher ester, a-methoxy-a-(trifluoromethyl)phenyl acetate (Jacob III. J. Org. Chem. (1982) 47:4165), of the racemic mixture, and analyzing the ^{1}H NMR spectrum for the presence of the two atropisomeric enantiomers or diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed., Chapman and Hall, New York; Okamoto, J. Chromatogr., (1990) 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

[0161] The chemical reactions described herein may be readily adapted to prepare other compounds and pharmaceutically acceptable salts thereof described herein. For example, the synthesis of non-exemplified compounds and pharmaceutically acceptable salts thereof described herein may 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. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds and pharmaceutically acceptable salts thereof described herein.

Pharmaceutical Formulations

[0162] Also provided herein are pharmaceutical compositions comprising compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein and one or more pharmaceutically acceptable excipients.

[0163] Compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein as described herein can be formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Thus, further provided herein is a pharmaceutical composition comprising a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein as described herein and one or more pharmaceutically acceptable excipients.

[0164] A typical formulation is prepared by mixing a compound or pharmaceutically acceptable salt thereof as described herein and an excipient. Suitable carriers, diluents and excipients include, but are not limited to, materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water and the like. The particular excipient used will depend upon the means and purpose for which the compound or pharmaceutically acceptable salt thereof as described herein is being applied. Solvents are generally selected based on solvents recognized as safe (GRAS) to be administered to a mammal. In general, safe solvents are non-toxic aqueous solvents such as water and other non-toxic solvents that are soluble or miscible in water. Suitable aqueous solvents include water, ethanol, propylene glycol, polyethylene glycols (e.g., PEG 400, PEG 300), etc. and mixtures thereof. The formulations can also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents and other known additives to provide an elegant presentation of the drug (i.e., a compound described herein or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

[0165] The formulations can be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound or pharmaceutically acceptable salt thereof as described herein or stabilized form thereof (e.g., complex with a cyclodextrin derivative or other known complexation agent) is dissolved in a suitable solvent in the presence of one or more of the excipients described above. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein as described herein is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to enable patient compliance with the prescribed regimen.

[0166] The pharmaceutical composition (or formulation) for application can be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article

for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container can also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label can also include appropriate warnings.

[0167] Pharmaceutical formulations of the compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein can be prepared for various routes and types of administration. For example, a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof having the desired degree of purity can optionally be mixed with one or more pharmaceutically acceptable excipients (Remington's Pharmaceutical Sciences (1980) 16th edition, Osol, A. Ed.), in the form of a lyophilized formulation, milled powder, or an aqueous solution. Formulation can be conducted by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed. The pH of the formulation depends mainly on the particular use and the concentration of compound, but can range from about 3 to about 8. For example, formulation in an acetate buffer at pH 5 can be a suitable embodiment.

[0168] The pharmaceutical composition ordinarily can be stored as a solid composition, a lyophilized formulation or as an aqueous solution.

[0169] The pharmaceutical compositions described herein can be formulated, dosed and administered in a fashion, i.e., amounts, concentrations, schedules, course, vehicles and route of administration, consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The effective amount of the compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof to be administered will be governed by such considerations, and is the minimum amount necessary to ameliorate, or treat the hyperproliferative disorder.

[0170] As a general proposition, the initial pharmaceutically effective amount of the compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof administered parenterally per dose will be in the range of about 0.01-100 mg/kg, namely about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. In another embodiment, a pharmaceutical composition described

herein comprises an effective amount of a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein in an amount of about: 1mg-10mg; 10mg-25mg; 20mg-50mg; 50mg-75mg; 70mg-100mg;100mg-150mg; 100mg-200mg; 100mg-500mg; 200mg-500mg; 250mg-500mg; 500mg-1000mg; or 750mg-1000mg.

[0171] Acceptable pharmaceutically acceptable excipients are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEENÔ, PLURONICSÔ or polyethylene glycol (PEG). The active pharmaceutical ingredients can also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

[0172] Sustained-release preparations of compounds or pharmaceutically acceptable salts thereof as described herein may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing a compound or pharmaceutically acceptable salt thereof as described herein , which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinyl alcohol)), polylactides (US 3773919), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOTÔ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate) and poly-D-(-)-3-hydroxybutyric acid.

[0173] The formulations include those suitable for the administration routes detailed herein. The formulations can conveniently be presented in unit dosage form and can be prepared by any

methods. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0174] Formulations of a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein suitable for oral administration can be prepared as discrete units such as pills, capsules, cachets or tablets each containing a predetermined amount of such compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets can optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom. Tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, e.g., gelatin capsules, syrups or elixirs can be prepared for oral use. Formulations of compounds or pharmaceutically acceptable salts thereof as described herein intended for oral use can be prepared according to any method for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients can be, for example, inert diluents, such as calcium or sodium carbonate, lactose, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets can be uncoated or can be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax can be employed.

[0175] For treatment of the eye or other external tissues, e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% W/W. When formulated in an ointment, the active

ingredients can be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients can be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base can include a polyhydric alcohol, i.e., an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations can desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulfoxide and related analogs. The oily phase of the emulsions of compositions provided herein can be constituted from known ingredients in a known manner. While the phase can comprise merely an emulsifier, it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of described herein include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

[0176] Aqueous suspensions comprising a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein can contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, croscarmellose, povidone, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

[0177] The pharmaceutical compositions of a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein can be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated using suitable dispersing or wetting agents and suspending agents

which have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butanediol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables.

[0178] The amount of active ingredient that can be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans can contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which can vary from about 5 to about 95% of the total compositions (weight:weight(w/w)). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion can contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

[0179] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which can contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which can include suspending agents and thickening agents.

[0180] Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of about 0.5 to 20% w/w, for example about 0.5 to 10% w/w, for example about 1.5%w/w.

[0181] Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0182] Formulations for rectal administration can be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0183] Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1

and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration can be prepared according to conventional methods and can be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis disorders as described below.

[0184] Formulations suitable for vaginal administration can be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers considered to be appropriate.

[0185] The formulations can be packaged in unit-dose or multi-dose containers, for example sealed ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water, for injection immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

[0186] In one embodiment, the compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof are formulated as a prodrug. The term prodrug as used herein refers to a derivative of a compound that can be hydrolyzed, oxidized, or cleaved under biological conditions to provide the compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof. A prodrug as defined herein includes derivatives comprising one or more moieties that modulate or improve one or more physical, physiological or pharmaceutical property such as, but not limited to, solubility, permeability, uptake, biodistribution, metabolic stability, onset of action or some other druglike property, and is transformed to the bioactive or more biologically active substance as provided herein. In one embodiment, a prodrug herein has no biological activity until release of the compound or pharmaceutically acceptable salt thereof.

Methods of Administration

[0187] Compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein can be administered by any route appropriate to the condition to be treated. Suitable routes include oral, parenteral (including subcutaneous, intramuscular, intravenous (IV), intraarterial, intradermal, intrathecal and epidural), transdermal, rectal, nasal, topical (including buccal and sublingual), vaginal, intraperitoneal, intrapulmonary and intranasal. In one embodiment, a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein is administered orally or by IV. For local

immunosuppressive treatment, the compounds can be administered by intralesional administration, including perfusing or otherwise contacting the graft with the inhibitor before transplantation. It will be appreciated that the preferred route can vary with for example the condition of the recipient. Where the compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof is administered orally, it can be formulated as a pill, capsule, tablet, etc. with a pharmaceutically acceptable carrier or excipient. Where the compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof is administered parenterally, it can be formulated with a pharmaceutically acceptable parenteral vehicle and in a unit dosage injectable form, as detailed below.

[0188] Thus, in one aspect provided herein is a pharmaceutical composition comprising a compound or pharmaceutically acceptable salt thereof as described herein and one or more pharmaceutically acceptable excipients. In one embodiment, compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein are administered as pharmaceutical compositions capable of being administered to a subject orally or parenterally. The compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein can be formulated for topical or parenteral use where the compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof is dissolved or otherwise suspended in a solution suitable for injections, suspensions, syrups, creams, ointments, gels, sprays, solutions and emulsions.

[0189] Oral administration can promote patient compliance in taking the compound (e.g., formulated as a pharmaceutical composition), thereby increasing compliance and efficacy. Oral pharmaceutical compositions comprising a compound described herein include, but are not limited to, tablets (e.g., coated, non-coated and chewable) and capsules (e.g., hard gelatin capsules, soft gelatin capsules, enteric coated capsules, and sustained release capsules). Tablets can be prepared by direct compression, by wet granulation, or by dry granulation. Oral pharmaceutical compositions comprising a compound described herein can be formulated for delayed or prolonged release.

[0190] A dose to treat human patients can range from about 10 mg to about 1000 mg of a compound described herein. A typical dose can be about 100 mg to about 300 mg of the compound. A dose can be administered once a day (QID), twice per day (BID), or more frequently, depending on the pharmacokinetic and pharmacodynamic properties, including absorption, distribution, metabolism, and excretion of the particular compound. Administration as used herein refers to the frequency of dosing and not, for example, the number of individual units a patient described herein must take for a dose. Thus, in some embodiments, a patient may take two or more dosage units (e.g., two or more pills/tablets/capsules) QD. In addition, toxicity

factors can influence the dosage and administration regimen. When administered orally, the pill, capsule, or tablet can be ingested daily or less frequently for a specified period of time. The regimen can be repeated for a number of cycles of therapy.

Methods of Treating and Uses

[0191] The compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein are useful as Ras inhibitors. In one aspect, the compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein are useful as KRas inhibitors. In another aspect, the compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein are useful as NRas inhibitors. In another aspect, the compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein are useful as HRas inhibitors. In one embodiment, the compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein are useful as G12D Ras inhibitors, and as G12D KRas inhibitors.

[0192] Provided herein are methods of contacting a cell, such as an *ex vivo* cell, with a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein, to inhibit Ras activity (e.g., KRas activity) in the cell. In another embodiment, the activity is mutant G12D KRas activity.

[0193] Further provided herein are methods of treating a cancer comprising a KRas mutation, the method comprising administering to a patient having such cancer, an effective amount of a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof or a pharmaceutical composition as described herein. In one embodiment, the KRas mutation is a $KRas^{G12D}$ mutation.

[0194] In one embodiment, the methods further comprise testing a sample (e.g., as set forth herein) from the patient before administration of a compound of pharmaceutically acceptable salt thereof described herein for the absence or presence of a $KRas^{G12D}$ mutation. In one such embodiment, a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof or pharmaceutical composition described herein is administered to the patient after the patient sample is determined to be positive for (e.g., the presence of) a $KRas^{G12D}$ mutation.

[0195] The methods of treating a cancer described herein relate to the treatment of cancer such as acute myeloid leukemia, cancer in adolescents, childhood adrenocortical carcinoma, AIDS-related cancers (e.g. lymphoma and Kaposi's sarcoma), anal cancer, appendix cancer, astrocytomas, atypical teratoid rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumors, Burkitt lymphoma, carcinoid tumor, embryonal tumors, germ cell tumor, primary lymphoma, cervical

cancer, childhood cancers, chordoma, cardiac tumors, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, extrahepatic ductal carcinoma in situ (DCIS), embryonal tumors, CNS cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, eye cancer, fibrous histiocytoma of bone, gall bladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, kidney cancer, laryngeal cancer, lip and oral cavity cancer, lobular carcinoma in situ (LCIS), lung cancer, lymphoma, metastatic squamous neck cancer with occult primary, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, multiple myeloma, Merkel cell carcinoma, malignant mesothelioma, malignant fibrous histiocytoma of bone and osteosarcoma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), oral cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, parathyroid cancer, penile cancer, pharyngeal cancer, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, unusual cancers of childhood, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or viral-induced cancer.

[0196] In some embodiments, the cancer is a hematological cancer, pancreatic cancer, MYH associated polyposis, colorectal cancer or lung cancer. In one embodiment, the cancer is lung cancer, colorectal cancer, appendiceal cancer, or pancreatic cancer. In one embodiment, the cancer is pancreatic cancer, lung cancer, or colon cancer. The lung cancer can be adenocarcinoma, non-small cell lung cancer (NSCLC), or small cell lung cancer (SCLC). In one embodiment, the cancer is colorectal cancer. In another embodiment, the cancer is pancreatic cancer. In one embodiment, the cancer is lung adenocarcinoma.

[0197] The methods provided herein can also comprise testing a sample from the patient before administration of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein for the absence or presence of a $KRas^{G12D}$ mutation. In

one embodiment, a compound, stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof or pharmaceutical composition is administered to the patient after the patient sample shows the presence of a $KRas^{G12D}$ mutation. In one embodiment, a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein is not administered unless a patient sample comprises a $KRas^{G12D}$ mutation.

[0198] In one embodiment, the cancer is pancreatic cancer, lung cancer, or colorectal cancer. In another embodiment, the cancer is tissue agnostic (comprises a $KRas^{G12D}$ mutation). In one such embodiment, the pancreatic cancer, lung cancer, or colorectal cancer comprises a $KRas^{G12D}$ mutation.

[0199] Further provided herein are methods of treating lung cancer comprising a $KRas^{G12D}$ mutation in a patient having such a lung cancer. In one such embodiment, is a method (M1) of treating lung cancer comprising a $KRas^{G12D}$ mutation in a patient having such a lung cancer, the method comprising administering to the patient an effective amount of a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof (or a pharmaceutical composition comprising the same) described herein. In one embodiment, the lung cancer is non-small cell lung carcinoma (NSCLC). In one embodiment, lung cancer is adenocarcinoma, NSCLC, squamous-cell lung carcinoma (SCLC) or large-cell lung carcinoma. In one embodiment, lung cancer is adenocarcinoma, NSCLC, or SCLC. In another embodiment, the lung cancer is small cell lung carcinoma. In still another embodiment, the lung cancer is glandular tumors, carcinoid tumors or undifferentiated carcinomas. The lung cancer can be stage I or II lung cancer. In one embodiment, the lung cancer is stage III or IV lung cancer. The methods provided herein include administration of the compound as a 1L therapy.

[0200] Still further provided herein are methods of treating pancreatic cancer comprising a $KRas^{G12D}$ mutation in a patient having such pancreatic cancer. In one such embodiment, is a method (M2) of pancreatic lung cancer comprising a $KRas^{G12D}$ mutation in a patient having pancreatic cancer, the method comprising administering to the patient an effective amount of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein. In one embodiment, the patient has been previously treated with radiation and one or more chemotherapy agents. In one embodiment, the pancreatic cancer is stage 0, I, or II. In another embodiment, the pancreatic cancer is stage III or stage IV.

[0201] Still further provided herein are methods of treating colon cancer comprising a $KRas^{G12D}$ mutation in a patient having such colon cancer. In one such embodiment, is a method (M3) of treating colon cancer comprising a $KRas^{G12D}$ mutation in a patient having, the method comprising administering to the patient an effective amount of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein to the patient.

In one embodiment, the colon cancer is stage I or II. In another embodiment, the colon cancer is stage III or stage IV.

[0202] In one embodiment of the methods M1, M2, and M3 as described herein, the method further comprises:

(a) determining the absence or presence of a $KRas^{G12D}$ mutation in a sample taken from a patient with a suspected diagnosed cancer; and

(b) administering to the patient an effective amount of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein.

[0203] Further provided herein are methods of treating tissue agnostic cancer comprising a $KRas^{G12D}$ mutation. In one embodiment of such methods, the method comprises:

(a) determining the absence or presence of a $KRas^{G12D}$ mutation in a sample taken from a patient with a suspected diagnosed cancer; and

(b) administering to the patient an effective amount of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein.

[0204] In one embodiment of such methods, the patient is diagnosed with a cancer described herein. In another embodiment of such methods, the sample is a tumor sample taken from the subject. In one such embodiment, the sample is taken before administration of any therapy. In another such embodiment, the sample is taken before administration of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein and after administration of another chemotherapeutic agent. In another embodiment of such methods, the compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein is administered as provided herein (e.g. orally or IV).

[0205] Also provided herein is a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof for use as a therapeutically active substance. In one such embodiment, the compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof can be for the therapeutic treatment of a cancer comprising a $Kras^{G12D}$ mutation.

[0206] Further provided herein is a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof for the therapeutic and/or prophylactic treatment of a cancer comprising a $KRas^{G12D}$ mutation. In one embodiment, the compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof is used in the preparation of a medicament for the therapeutic treatment of a cancer comprising a $KRas^{G12D}$ mutation. Still further provided herein are uses of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof as described herein in the manufacture of a medicament for inhibiting tumor metastasis.

[0207] Further provided herein are methods for inhibiting tumor metastasis, the method comprising administering to a patient having a tumor a therapeutically effective amount of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein. In one embodiment, the inhibition is of a tumor comprising a $KRas^{G12D}$ mutation. In another embodiment, inhibiting tumor metastasis in a patient described herein results in reduction of tumor size. In another embodiment, inhibiting tumor metastasis in a patient described herein results in stabilizing (e.g. no further growth) of tumor size. In another embodiment, inhibiting tumor metastasis in a patient described herein results in remission of the cancer and/or its symptoms.

[0208] Further provided herein are methods for inhibiting proliferation of a cell population, the method comprising contacting the cell population with a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein. In one embodiment, the cell population is in a human patient. In another embodiment, the cell population comprises a $KRas^{G12D}$ mutation.

[0209] Further provided herein are methods of inhibiting KRas in a patient in need of therapy, comprising administering to the patient a therapeutically effective amount of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein. In one embodiment, the KRas inhibited is $KRas^{G12D}$. In another embodiment, inhibiting KRas results in decreased tumor size. In another embodiment, inhibiting KRas results in remission of the cancer and/or its symptoms.

[0210] Further provided herein are methods for regulating activity of a KRas mutant protein, the method comprising reacting the mutant protein with a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein. In one embodiment, the mutant protein comprises a $KRas^{G12D}$ mutation. In one embodiment, the activity of KRas is decreased after contacting with a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein. In another embodiment, the downregulation of activity of the KRas mutant protein treats a cancer described herein in a patient described herein. In another embodiment, the downregulation of activity of the KRas mutant protein results in decreased tumor size. In another embodiment, the downregulation of activity of the KRas mutant protein results in remission of a cancer described herein and/or its symptoms.

[0211] In some embodiments, the methods provided herein comprise inhibiting $Kras^{G12D}$ activity in a cell by contacting said cell with an amount of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein sufficient to inhibit the activity of $KRas^{G12D}$ in said cell. In some embodiments, the methods provided herein comprise inhibiting $KRas^{G12D}$ activity in a tissue by contacting said tissue with an amount of a

compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein sufficient to inhibit the activity of $KRas^{G12D}$ in said tissue. In some embodiments, the methods provided herein comprise inhibiting $KRas^{G12D}$ activity in a patient described herein by contacting said patient with an amount of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein sufficient to inhibit the activity of $KRas^{G12D}$ in said patient.

[0212] Further provided herein are methods for preparing a labeled $KRas^{G12D}$ mutant protein, the method comprising reacting a $KRas^{G12D}$ mutant protein with a labeled compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein to result in the labeled $KRas^{G12D}$ mutant protein. In one embodiment, the label is an imaging agent. In one embodiment, the labeled $KRas^{G12D}$ can be used to detect the absence or presence of G12D mutant KRas in a patient sample, thereby detecting the presence or absence of a cancer mediated by mutant KRas.

[0213] Still further provided herein are methods of inhibiting Ras-mediated cell signaling. In one embodiment, the methods comprise contacting a cell with an effective amount of one or more compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof disclosed herein thereof. Inhibition of Ras-mediated signal transduction can be assessed and demonstrated by a wide variety of ways known in the art. Non-limiting examples include a showing of (a) a decrease in GTPase activity of Ras; (b) a decrease in GTP binding affinity or an increase in GDP binding affinity; (c) an increase in K off of GTP or a decrease in K off of GDP; (d) a decrease in the levels of signaling transduction molecules downstream in the Ras pathway, such as a decrease in pMEK level; and/or (e) a decrease in binding of Ras complex to downstream signaling molecules including but not limited to Raf. Kits and commercially available assays can be utilized for determining one or more of the above.

[0214] KRas mutations, including G12D mutants, have also been identified in hematological malignancies (e.g., cancers that affect blood, bone marrow, and/or lymph nodes). Accordingly, certain embodiments are directed to administration of a disclosed compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof (e.g., in the form of a pharmaceutical composition) as described herein to a patient in need of treatment of a hematological malignancy. Such malignancies include but are not limited to leukemias and lymphomas. For example, the presently disclosed compounds can be used for treatment of diseases such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), chronic myelogenous leukemia (CML), acute monocytic leukemia (AMoL) and/ or other leukemias. In other embodiments, the compounds or a pharmaceutically acceptable salt thereof described herein are

useful for treatment of lymphomas such as all subtypes of Hodgkin's lymphoma or non-Hodgkin's lymphoma.

[0215] Determining whether a tumor or cancer comprises a $KRas^{G12D}$ mutation can be undertaken by assessing the nucleotide sequence encoding the KRas protein, by assessing the amino acid sequence of the KRas protein, or by assessing the characteristics of a putative KRas mutant protein. The sequence of wild-type human KRas (e.g., Accession No. NP203524) is known in the art.

[0216] Methods for detecting a mutation in a KRas nucleotide sequence are known by those of skill in the art. These methods include, but are not limited to, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays, polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) assays, real-time PCR assays, PCR sequencing, mutant allele-specific PCR amplification (MASA) assays, direct sequencing, primer extension reactions, electrophoresis, oligonucleotide ligation assays, hybridization assays, TaqMan assays, SNP genotyping assays, high resolution melting assays and microarray analyses. In some embodiments, samples are evaluated for G12d KRas mutations by real-time PCR. In real-time PCR, fluorescent probes specific for the KRas G12D mutation are used. When a mutation is present, the probe binds and fluorescence is detected. In some embodiments, the KRas G12D mutation is identified using a direct sequencing method of specific regions (e.g., exon 2 and/or exon 3) in the KRas gene. This technique will identify all possible mutations in the region sequenced.

[0217] Methods for determining whether a tumor or cancer comprises a $KRas^{G12D}$ mutation can use a variety of samples. In some embodiments, the sample is taken from a subject having a tumor or cancer. In some embodiments, the sample is a fresh tumor/cancer sample. In some embodiments, the sample is a frozen tumor/cancer sample. In some embodiments, the sample is a formalin-fixed paraffin-embedded sample. In some embodiments, the sample is processed to a cell lysate. In some embodiments, the sample is processed to DNA or RNA.

[0218] Further provided herein are uses of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein, in the manufacture of a medicament for treating cancer. In some embodiments, the medicament is formulated for oral administration. In some embodiments, the medicament is formulated for injection (e.g. IV administration). In some embodiments, the cancer is comprises a $KRas^{G12D}$ mutation. In some embodiments, the cancer is a hematological cancer, pancreatic cancer, MYH associated polyposis, colorectal cancer or lung cancer. In one embodiment, the cancer is lung cancer, colorectal cancer, or pancreatic cancer. In one embodiment, the cancer is colorectal cancer. In another embodiment, the cancer is pancreatic cancer. In some embodiments, the cancer is lung

adenocarcinoma. In some embodiments, are uses of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein, in the manufacture of a medicament for inhibiting tumor metastasis.

Combination Therapies

[0219] The compounds or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein may be employed alone or in combination with other therapeutic agents for the treatment of a disease or disorder described herein. The second compound of the pharmaceutical combination formulation or dosing regimen preferably has complementary activities to the compound or a pharmaceutically acceptable salt thereof described herein such that they do not adversely affect each other. The combination therapy may provide "synergy" and prove "synergistic", *i.e.*, the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately.

[0220] The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. The combined administration includes co-administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities.

[0221] Combination therapies herein comprise the administration of a compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein, and the use of at least one other treatment method. The amounts of the compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

[0222] In various embodiments of the method, the additional therapeutic agent is an epidermal growth factor receptor (EGFR) inhibitor, phosphatidylinositol kinase (PI3K) inhibitor, insulin-like growth factor receptor (IGF1R) inhibitor, a Janus kinase (JAK) inhibitor, a Met kinase inhibitor, a SRC family kinase inhibitor, a mitogen-activated protein kinase (MEK) inhibitor, an extracellular-signal-regulated kinase (ERK) inhibitor, a topoisomerase inhibitor (such as irinotecan, or such as etoposide, or such as doxorubicin), a taxane (such as anti-microtubule agents including paclitaxel and docetaxel), an anti-metabolite agent (such as 5-FU or such as gemcitabine), or an alkylating agent (such as cisplatin or such as cyclophosphamide), or a taxane.

[0223] In some embodiments, the additional therapeutic agent is an epidermal growth factor receptor (EGFR) inhibitor, such as Erlotinib or such as Afatinib. In some embodiments the additional therapeutic agent is gefitinib, osimertinib, or dacomitinib. In some embodiments the

additional therapeutic agent is a monoclonal antibody such as cetuximab (Erbitux) or panitumumab (Vectibix). In some embodiments the GFR inhibitor is a dual or pan- HER inhibitor. In other embodiments, the additional therapeutic agent is a phosphatidylinositol-3-kinase (PI3K) inhibitor, such as GDC-0077, GDC-0941, MLN1117, BYL719 (Alpelisib) or BKM120 (Buparlisib). GDC-0941 refers to 2-(1H-indazol-4-yl)-6-(4- methanesulfonyl-piperazin-1- ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine or a salt thereof (e.g., bismesylate salt).

[0224] In still other embodiments, the additional therapeutic agent is an insulin-like growth factor receptor (IGF1R) inhibitor. For example, in some embodiments the insulin-like growth factor receptor (IGF1R) inhibitor is NVP-AEW541. In other embodiments, the additional therapeutic agent is IGOSI-906 (Linsitinib), BMS-754807, or in other embodiments the additional therapeutic agent is a neutralizing monoclonal antibody specific to IGF1R such as AMG-479 (ganitumab), CP-751,871 (figitumumab), IMC-A12 (cixutumumab), MK-0646 (dalotuzumab), or R-1507 (robatumumab).

[0225] In some other embodiments, the additional therapeutic agent is a Janus kinase (JAK) inhibitor. In some embodiments, the additional therapeutic agent is CYT387, GLPG0634, Baricitinib, Lestaurtinib, momelotinib, Pacritinib, Ruxolitinib, or TG101348.

[0226] In some other embodiments, the additional therapeutic agent is an anti-glypican 3 antibody. In some embodiments, the anti-glypican 3 antibody is codrituzumab.

[0227] In some other embodiments, the additional therapeutic agent is an antibody drug conjugate (ADC). In some embodiments, the ADC is polatuzumab vedotin, RG7986, RG7882, RG6109, or RO7172369.

[0228] In some other embodiments, the additional therapeutic agent is an MDM2 antagonist. In some embodiments, the MDM2 antagonist is idasanutlin.

[0229] In some other embodiments, the additional therapeutic agent is an agonistic antibody against CD40. In some embodiments, the agonistic antibody against CD40 is selicrelumab (RG7876).

[0230] In some other embodiments, the additional therapeutic agent is a bispecific antibody. In some embodiments, the bispecific antibody is RG7828 (BTCT4465A), RG7802, RG7386 (FAP-DR5), RG6160, RG6026, ERY974, or anti-HER2/CD3.

[0231] In some other embodiments, the additional therapeutic agent is a targeted immunocytokine. In some embodiments, the targeted immunocytokine is RG7813 or RG7461.

[0232] In some other embodiments, the additional therapeutic agent is an antibody targeting colony stimulating factor-1 receptor (CSF-1R). In some embodiments, the CSF-1R antibody is emactuzumab.

[0233] In some other embodiments, the additional therapeutic agent is a personalized cancer vaccine. In some embodiments, the personalized cancer vaccine is RG6180.

[0234] In some other embodiments, the additional therapeutic agent is an inhibitor of BET (bromodomain and extraterminal family) proteins (BRD2/3/4/T). In some embodiments, the BET inhibitor is RG6146.

[0235] In some other embodiments, the additional therapeutic agent is an antibody designed to bind to TIGIT. In some embodiments, the anti-TIGIT antibody is RG6058 (MTIG7192A).

[0236] In some other embodiments, the additional therapeutic agent is a selective estrogen receptor degrader (SERD). In some other embodiments, the SERD is RG6047 (GDC-0927) or RG6171 (GDC-9545, giredestrant).

[0237] In some other embodiments the additional therapeutic agent is an MET kinase inhibitor, such as Crizotinib, tivantinib, AMG337, cabozantinib, or foretinib. In other embodiments the additional therapeutic agent is a neutralizing monoclonal antibody to MET such as onartuzumab.

[0238] In more embodiments, the additional therapeutic agent is a SRC family non-receptor tyrosine kinase inhibitor. For example, in some embodiments the additional therapeutic agent is an inhibitor of the subfamily of SRC family non-receptor tyrosine kinases. Exemplary inhibitors in this respect include Dasatinib. Other examples in this regard include Ponatinib, saracatinib, and bosutinib.

[0239] In yet other embodiments, the additional therapeutic agent is a mitogen-activated protein kinase (MEK) inhibitor. In some of these embodiments, the mitogen-activated protein kinase (MEK) inhibitor is trametinib, selumetinib, COTELLIC® (cobimetinib), PD0325901, or RO5126766. In other embodiments the MEK inhibitor is GSK-1120212, also known as trametinib.

[0240] In yet other embodiments, the additional therapeutic agent is an extracellular-signal-regulated kinase (ERK) inhibitor. In some of these embodiments, the mitogen-activated protein kinase (MEK) inhibitor is SCH722984 or GDC-0994.

[0241] In other embodiments the protein kinase inhibitor is taselisib, ipatasertib, GDC-0575, GDC-5573 (HM95573), RG6114 (GDC-0077), CKI27, Afatinib, Axitinib, Atezolizumab, Bevacizumab, Bostutinib, Cetuximab, Crizotinib, Dasatinib, Erlotinib, Fostamatinib, Gefitinib, Imatinib, Lapatinib, Lenvatinib, Ibrutinib, Nilotinib, Panitumumab, Pazopanib, Pegaptanib, Ranibizumab, Ruxolitinib, Sorafenib, Sunitinib, SU6656, Trastuzumab, Tofacitinib, Vandetanib, or Vemurafenib. In still more embodiments, the additional therapeutic agent is a topoisomerase inhibitor. In some of these embodiments, the topoisomerase inhibitor is Irinotecan. In some more

embodiments, the additional therapeutic agent is a taxane. Exemplary taxanes include Taxol and Docetaxel.

[0242] In addition to the above additional therapeutic agent, other chemotherapeutics are presently known in the art and can be used in combination with the compounds and pharmaceutically acceptable salts thereof described herein. In some embodiments, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, angiogenesis inhibitors, and anti-androgens.

[0243] Non-limiting examples are chemotherapeutic agents, cytotoxic agents, and non-peptide small molecules such as Gleevec® (Imatinib Mesylate), Velcade® (bortezomib), Casodex (bicalutamide), Iressa® (gefitinib), and Adriamycin as well as a host of chemotherapeutic agents. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (CYTOXAN™); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methyl melamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphaoramide and trimethylol melamine; nitrogen mustards such as chlorambucil, chlornaphazine, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, Casodex™, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo- L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone;

mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; polysaccharide K; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel (TAXOL™, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (TAXOTERE™, Rhone-Poulenc Rorer, Antony, France); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included as suitable chemotherapeutic cell conditioners are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, (Nolvadex™), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; Xeloda®; ibandronate; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS 2000; and difluoromethylornithine (DMFO). Where desired, the compounds or pharmaceutical acceptable salts thereof or pharmaceutical composition as described herein can be used in combination with commonly prescribed anti-cancer drugs such as Herceptin®, Avastin®, Gazyva®, Tecentriq®, Alecensa®, Perjeta®, Venclexta™, Erbitux®, Rituxan®, Taxol®, Arimidex®, Taxotere®, ABVD, AVICINE, Abagovomab, Acridine carboxamide, Adecatumumab, 17-N-Allylamino-17-demethoxygeldanamycin, Alpharadin, Alvocidib, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone, Amonafide, Anthracenedione, Anti-CD22 immunotoxins, Antineoplastic, Antitumorigenic herbs, Apaziquone, Atiprimod, Azathioprine, Belotecan, Bendamustine, BIBW 2992, Biricodar, Brostallicin, Bryostatin, Buthionine sulfoximine, CBV (chemotherapy), Calyculin, cell-cycle nonspecific antineoplastic agents, Dichloroacetic acid, Discodermolide, Elsamitrucin, Enocitabine, Epothilone, Eribulin, Everolimus, Exatecan, Exisulind, Ferruginol, Forodesine, Fosfestrol, ICE chemotherapy regimen, IT-101, Imexon, Imiquimod, Indolocarbazole, Irofulven, Laniquidar, Larotaxel, Lenalidomide, Lucanthone, Lurtotecan, Mafosfamide, Mitozolomide, Nafoxidine, Nedaplatin, Olaparib, Ortataxel, PAC-1, Pawpaw, Pixantrone, Proteasome inhibitor, Rebeccamycin, Resiquimod, Rubitecan, SN-38, Salinosporamide A, Sapacitabine, Stanford V, Swainsonine, Talaporfin, Tariquidar, Tegafur-uracil, Temodar, Tesetaxel, Triplatin tetranitrate, Tris(2-chloroethyl)amine, Troxacitabine, Uramustine, Vadimezan, Vinflunine, ZD6126 or Zosuquidar.

[0244] The exact method for administering the compound and the additional therapeutic agent will be apparent to one of ordinary skill in the art. In some exemplary embodiments the compound and the additional therapeutic agent are co-administered. In other embodiments, the compound and the additional therapeutic agent are separately administered.

[0245] In some embodiments, the compound and the additional therapeutic agent are administered with the second agent simultaneously or separately. This administration in combination can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. That is, the compound and any of the additional therapeutic agents described herein can be formulated together in the same dosage form and administered simultaneously. Alternatively, the compound and any of the additional therapeutic agents described herein can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, the compound can be administered just followed by any of the additional therapeutic agents described herein, or vice versa. In some embodiments of the separate administration protocol, the compound and any of the additional therapeutic agents described herein are administered a few minutes apart, or a few hours apart, or a few days apart.

Articles of Manufacture

[0246] Also provided herein are articles of manufacture, or "kit", containing materials useful for the treatment of a cancer provided herein. In one embodiment, the kit comprises a container comprising compound or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof described herein. The kit may further comprise a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, blister pack, etc. The container may be formed from a variety of materials such as glass or plastic. The container may hold a compound or a pharmaceutically acceptable salt thereof described herein or a formulation thereof which is effective for treating the condition and may have a sterile access port (for example, the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a compound or a pharmaceutically acceptable salt thereof described herein. Alternatively, or additionally, the article of manufacture may further comprise a second container comprising a pharmaceutical diluent, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution or dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0247] In another embodiment, the kits are suitable for the delivery of solid oral forms of a compound or a pharmaceutically acceptable salt thereof described herein, such as tablets or

capsules. Such a kit can include a number of unit dosages. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms.

Embodiments

[0248] Provided below are exemplary embodiments of the invention.

[0249] Embodiment 0. A compound of formula (I) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

X is O or NR^6

m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is R^7-substituted or unsubstituted naphthyl, R^7-substituted or unsubstituted isoquinolinyl, R^7-substituted or unsubstituted indazolyl, R^7-substituted or unsubstituted indanyl, R^7-substituted or unsubstituted benzothiazolyl, R^{7A}-substituted phenyl, or R^{7A}-substituted pyridinyl;

each R^7 is independently halogen, OH, NH_2, $N(Me)_2$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} alkynyl, unsubstituted C_{1-3} alkoxy, or unsubstituted C_{1-3} haloalkyl

each R^{7A} is independently halogen, CN, NH_2, $N(Me)_2$, R^{7B}-substituted or unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or unsubstituted cyclopropyl

R^{7B} is CN, oxo, or C_{1-3} alkyl;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;
each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;
R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein
two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or
two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};
R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;
R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle
R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle and
R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0250] Embodiment 1. A compound of formula (I) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein
X is O or NR^6;
m is 1 or 2;
n is 1 or 2;
wherein n and m together make a 6- or 7-membered ring Ring A;
p is 0, 1, or 2;
R^1 is formula (E), wherein X^1 is N or CR^{7C} and R^{7C} is hydrogen or halogen;
each R^{7A} is independently halogen, CN, NH_2, $N(Me)_2$, R^{7B}-substituted or unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or unsubstituted cyclopropyl;
R^{7B} is CN, oxo, or C_{1-3} alkyl;
L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;
R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;
R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;
R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or
R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein

two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein
two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;
each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;
R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;
each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;
R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein
two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or
two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};
R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;
R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;
R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and
R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0251] Embodiment 2. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of embodiment 1, wherein X^1 is CR^{7C} and R^{7C} is hydrogen or halogen.

[0252] Embodiment 3. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of embodiment 1, wherein X^1 is N.

[0253] Embodiment 4. A compound of formula (I) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein
X is O or NR^6;
m is 1 or 2;
n is 1 or 2;
wherein n and m together make a 6- or 7-membered ring Ring A;
p is 0, 1, or 2;
R^1 is a moiety of formula (E2) or (E3)

each R^{7A} is independently hydrogen, halogen, unsubstituted C_{1-3} alkyl or unsubstituted C_{1-3} haloalkyl;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein

two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein

two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0254] Embodiment 5. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of embodiment 4, wherein no more than one R^{7A} is hydrogen.

[0255] Embodiment 6. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of embodiment 4, wherein R^{7A} is not hydrogen.

[0256] Embodiment 7. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of embodiment 4, wherein at least one R^{7A} is halogen.

[0257] Embodiment 8. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of embodiment 4, wherein at least one R^{7A} is unsubstituted C_{1-3} haloalkyl.

[0258] Embodiment 9. A compound of formula (I): or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

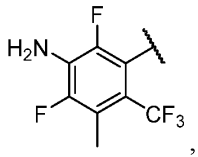
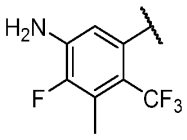
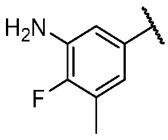
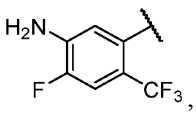
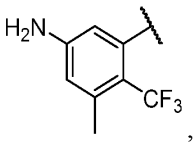
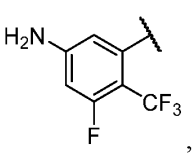
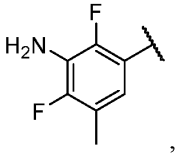
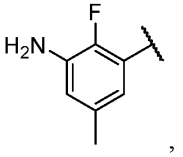
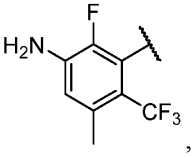
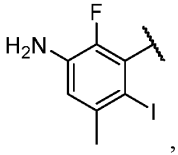
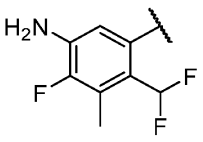
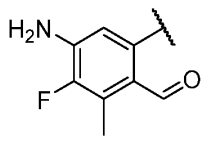
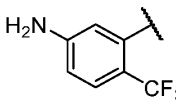
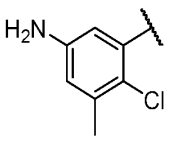
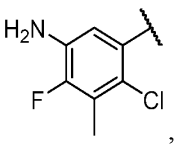
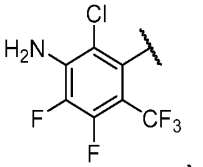
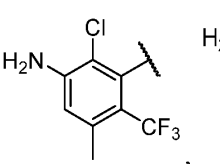
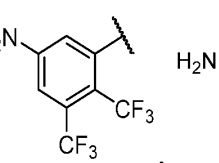
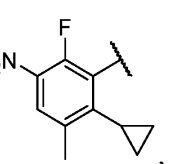
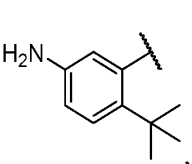
X is O or NR^6;

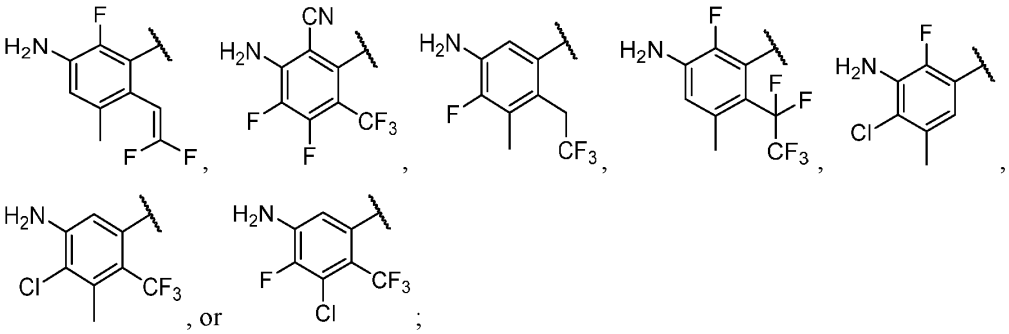
m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , , .



L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein

two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein

two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0259] Embodiment 10. A compound of formula (I) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

X is O or NR^6;

m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is R^{7A}-substituted phenyl or R^{7A}-substituted pyridinyl;

each R^{7A} is independently halogen, NH_2, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein

two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein

two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0260] Embodiment 11. A compound of formula (I) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

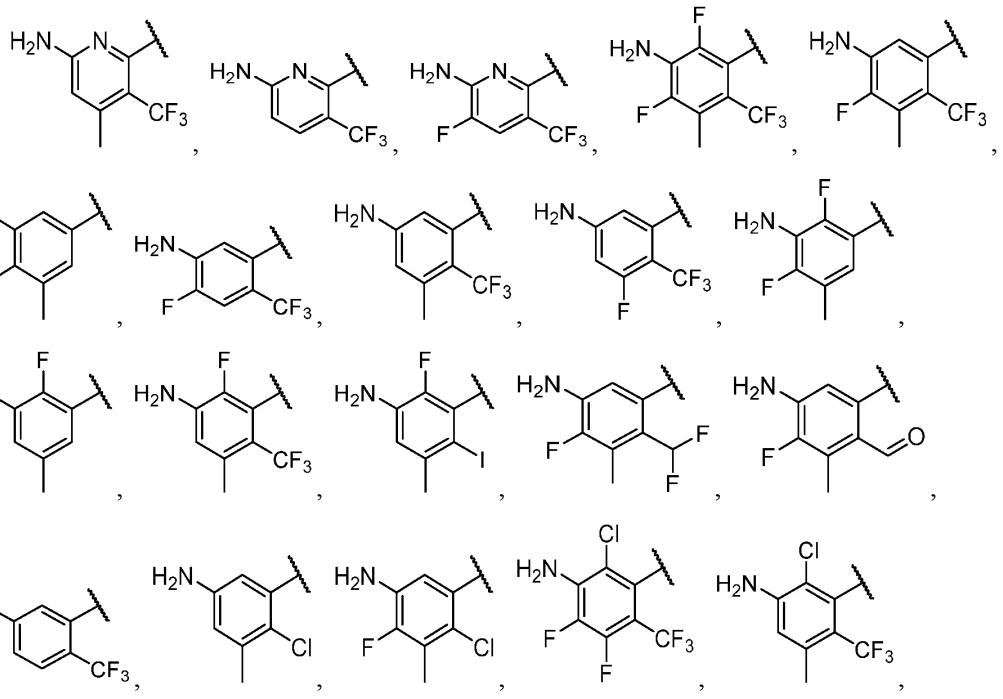
X is O or NR^6;

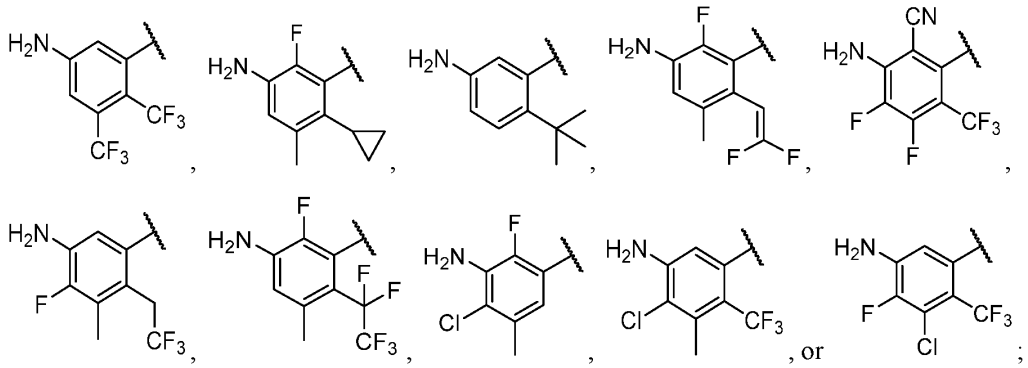
m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is 



L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein

two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein

two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0261] Embodiment 12. A compound of formula (I) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

X is O or NR^6;

m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is of formula (E1);

each R^{7A} is independently halogen, CN, NH_2, $N(Me)_2$, R^{7B}-substituted or unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or unsubstituted cyclopropyl;

R^{7B} is CN, oxo, or C_{1-3} alkyl;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein

two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein

two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0262] Embodiment 13. A compound of formula (I) or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

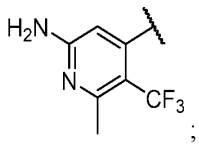
X is O or NR^6;

m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is  ;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein

two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein

two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

[0263] Embodiment 14. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-13, wherein each R^4 is hydrogen.

[0264] Embodiment 15. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-13, wherein one R^4 is hydrogen and one R^4 is methyl.

[0265] Embodiment 16. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-13, wherein R^4 is hydrogen and one R^4 is $-CF_3$.

[0266] Embodiment 17. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-3 and 12, wherein each R^{7A} is independently halogen, NH_2, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl.

[0267] Embodiment 18. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-3, 10, 12, and 14-17, wherein at least one R^{7A} is NH_2.

[0268] Embodiment 19. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-18, wherein L^1 is methylene.

[0269] Embodiment 20. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-18, wherein L^1 is R^{L1}-substituted or unsubstituted C_{2-3} alkylene.

[0270] Embodiment 21. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-20, wherein R^2 is a moiety of formula (A), or a stereoisomer thereof, wherein,

R^9 is halogen or R^{10}-substituted or unsubstituted C_{1-3} alkylidene

r is an integer of 0-12;

j is 1, 2, or 3; and

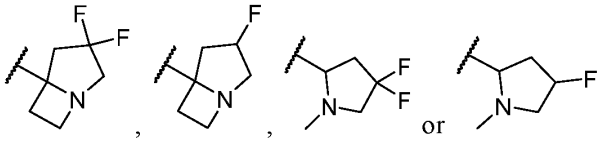
k is 1 or 2.

[0271] Embodiment 22. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-20, wherein R^2 is a moiety of formula (B), or a stereoisomer thereof, wherein

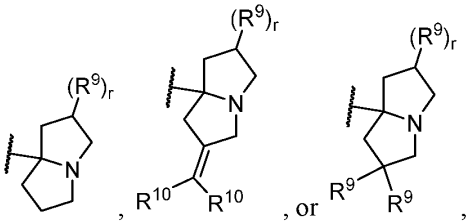
R^9 is independently halogen or unsubstituted C_{1-3} alkyl; and

r is 1 or 2.

[0272] Embodiment 23. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-20, wherein R^2 is:


, or a stereoisomer thereof.

[0273] Embodiment 24. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-20, wherein R^2 is:

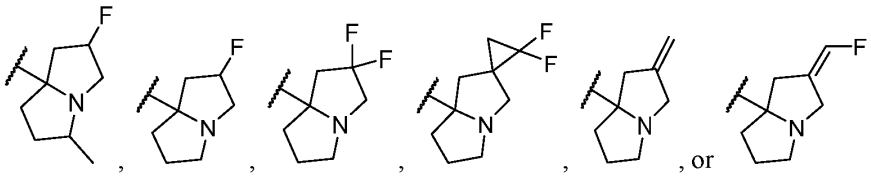

, or a stereoisomer thereof, wherein

R^9 is independently halogen or R^{10}-substituted or unsubstituted C_{1-3} alkylidene;

each R^{10} is independently hydrogen or halogen; and

r is 1 or 2.

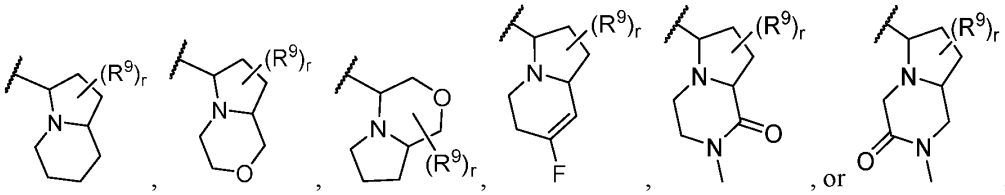
[0274] Embodiment 25. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-20, wherein R^2 is:


, or a stereoisomer thereof.

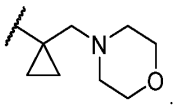
[0275] Embodiment 26. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-20, wherein R^2 is a moiety of formula (C) or a stereoisomer thereof, wherein X^2 is CR^9 or O.

[0276] Embodiment 27. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-20, wherein R^2 is a moiety of formula (D) or (D1) or a stereoisomer thereof, wherein X^3 is CR^9 , NR^9, or O.

[0277] Embodiment 28. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-20, wherein R^2 is:


, or a stereoisomer thereof.

[0278] Embodiment 29. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-20, wherein R^2 is:



[0279] Embodiment 30. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-29, wherein R^3 is halogen.

[0280] Embodiment 31. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-30, wherein two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons.

[0281] Embodiment 32. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of embodiment 31, wherein the bridge comprises 2 carbon atoms.

[0282] Embodiment 33. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of embodiment 31, the bridge comprises 1 carbon atom.

[0283] Embodiment 34. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-33, wherein X is NR^6.

[0284] Embodiment 35. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of embodiment 34, wherein R^6 is hydrogen or R^{6A}-substituted or unsubstituted C_{1-3} alkyl.

[0285] Embodiment 36. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of embodiment 34, wherein R^6 is R^{6A}-substituted or unsubstituted C_{1-3} alkyl.

[0286] Embodiment 37. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 34-36, wherein R^{6A} is halogen, CN, OH, OMe, OEt, OCF_3, SO_2Me, unsubstituted C_{1-3} alkyl, or 4-membered heterocycle.

[0287] Embodiment 38. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of embodiment 34, wherein R^6 is hydrogen.

[0288] Embodiment 39. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-38, wherein R^2 is azetidinyl, oxetanyl, or thietanedioxide.

[0289] Embodiment 40. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-13, wherein the compound of formula (I) comprises formula (IIa), (IIb), (IIc), or (IId), or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0290] Embodiment 41. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-13, wherein the compound of formula (I) comprises formula (IIIa) or (IIIb), or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0291] Embodiment 42. A compound selected from compounds 1-36, 38-45, 47-62, 64-108, 110-146, and 149-291 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0292] Embodiment 43. A compound selected from compounds 1-36, 38-45, 47-62, 64-108, and 110-125 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0293] Embodiment 44. A compound selected from compounds 126-146 and 149-291 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0294] Embodiment 45. A compound selected from compounds 6, 15, 24, 26, 29, 31-32, 57-59, 61-62, 64-66, 75-76, 91, 96, 104, 106, 111, 113, 118-124, 126-146, 149-156, 158-175, 181, 183, 186, 190-192, 195, 200, 204, 224-225, 228-229, 232-239, 241, 244-250, 255, 258-259, and 263 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0295] Embodiment 46. A compound selected from compounds 6, 12-18, 23-24, 26, 29, 31-36, 57-58, 60-62, 64-77, 90-97, 100-102, 104, 108, 111, 113, 115, 118-146, 149-175, 181-183,

186-187, 190, 195, 200, 204, 224-232, 234-239, 241, 244-250, 255, 258-259, and 263 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0296] Embodiment 47. A compound selected from compounds 6, 13-14, 16-18, 23-24, 26, 29, 31-34, 36, 57-62, 64-72, 74, 76, 91-104, 106-108, 111, 113, 115, 117-146, 149-154, 157, 159-174, 199, 200, 224-229, 234-241, 244-249, 255, 258-259, and 263 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0297] Embodiment 48. A compound selected from compounds 6, 12-18, 23-24, 26, 29, 31-36, 42-45, 47-48, 52, 57-58, 60-78, 84-88, 90-97, 100-104, 106, 108, 111-113, 115, 118-146, 149-175, 177-178, 181-183, 185-187, 189-192, 194-195, 197-200, 203-232, 234-250, and 252-291 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0298] Embodiment 49. A compound selected from compounds 6, 13-14, 16-18, 23-24, 26, 29, 31-34, 36, 42-45, 47-48, 52, 57-62, 64-72, 74, 76, 84-88, 91-104, 106-108, 111, 113, 115, 117-146, 149-154, 157, 159-174, 199, 200, 224-229, 234-241, 244-249, 255, 258-259, and 263 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0299] Embodiment 50. A compound selected from compounds 42-45, 47-48, and 52 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0300] Embodiment 51. A compound selected from compounds 112, 205-218, 242-243, 252-254, 261-262, and 264-291 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0301] Embodiment 52. A pharmaceutical composition comprising a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-51, and one or more pharmaceutically acceptable excipients.

[0302] Embodiment 53. A method of treating cancer, the method comprising administering an effective amount of a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of embodiments 1-51, or a pharmaceutical composition of embodiment 52.

[0303] Embodiment 54. The method of embodiment 53, wherein the cancer is characterized as comprising a KRas mutation.

[0304] Embodiment 55. The method of embodiment 54, wherein the KRas mutation corresponds to a $KRas^{G12D}$ mutation.

[0305] Embodiment 56. The method of any one of embodiments 53-55, further comprising testing a sample from the patient before administration for the absence or presence of a $KRas^{G12D}$ mutation.

[0306] Embodiment 57. The method of embodiment 56, wherein the compound, stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof or pharmaceutical composition is administered to the patient after the patient sample shows the presence of a $KRas^{G12D}$ mutation.

[0307] Embodiment 58. The method of any one of embodiments 53-57, wherein the cancer is tissue agnostic.

[0308] Embodiment 59. The method of any one of embodiments 53-57, wherein the cancer is pancreatic cancer, lung cancer, or colorectal cancer.

[0309] Embodiment 60. The method of embodiment 59, wherein the lung cancer is lung adenocarcinoma, NSCLC, or SCLC.

[0310] Embodiment 61. The method of embodiment 59, wherein the cancer is pancreatic cancer.

[0311] Embodiment 62. The method of embodiment 59, wherein the cancer is colorectal cancer.

[0312] Embodiment 63. The method of any one of embodiments 53-62, further comprising administering at least one additional therapeutic agent.

[0313] Embodiment 64. The method of embodiment 63, wherein the additional therapeutic agent comprises an epidermal growth factor receptor (EGFR) inhibitor, phosphatidylinositol kinase (PI3K) inhibitor, insulin-like growth factor receptor (IGF1R) inhibitor, a Janus kinase (JAK) inhibitor, a Met kinase inhibitor, a SRC family kinase inhibitor, a mitogen-activated protein kinase (MEK) inhibitor, an extracellular-signal-regulated kinase (ERK) inhibitor, a topoisomerase inhibitor, a taxane, an anti-metabolite agent, or an alkylating agent.

[0314] Embodiment 65. A compound according to any one of embodiments 1-51, or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, for use as a therapeutically active substance.

[0315] Embodiment 66. Use of a compound of any one of embodiments 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, for the therapeutic treatment of a cancer comprising a $KRas^{G12D}$ mutation.

[0316] Embodiment 67. Use of a compound according to any one of embodiments 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically salt thereof, in the manufacture of a medicament for inhibiting tumor metastasis.

[0317] Embodiment 68. Use of a compound of any one of embodiments 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, for the preparation of a medicament for the therapeutic treatment of a cancer comprising a $KRas^{G12D}$ mutation.

[0318] Embodiment 69. A compound according to any one of embodiments 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically salt thereof, for the therapeutic and/or prophylactic treatment of a cancer comprising a $KRas^{G12D}$ mutation.

[0319] Embodiment 70. A method for regulating activity of a KRas mutant protein, the method comprising reacting the mutant protein with a compound of any one of embodiments 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0320] Embodiment 71. A method for inhibiting proliferation of a cell population, the method comprising contacting the cell population with the compound of any one of embodiments 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

[0321] Embodiment 72. A method of embodiment 71, wherein the inhibition of proliferation is measured as a decrease in cell viability of the cell population.

[0322] Embodiment 73. A method for inhibiting tumor metastasis comprising administering to an individual in need thereof a therapeutically effective amount of the compound of any one of embodiments 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof to a subject in need thereof.

[0323] Embodiment 74. A compound of any one of embodiments 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in regulating activity of a KRas mutant protein.

[0324] Embodiment 75. A compound of any one of embodiments 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in inhibiting proliferation of a cell population.

[0325] Embodiment 76. The compound, stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt for use of embodiment 75, wherein the inhibition of proliferation is measured as a decrease in cell viability of the cell population.

[0326] Embodiment 77. A compound of any one of embodiments 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in inhibiting tumor metastasis.

[0327] Embodiment 78. Use of a compound of any one of embodiments 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for regulating activity of a KRas mutant protein.

[0328] Embodiment 79. Use of a compound of any one of embodiments 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting proliferation of a cell population.

[0329] Embodiment 80. The use of embodiment 79, wherein the inhibition of proliferation is measured as a decrease in cell viability of the cell population.

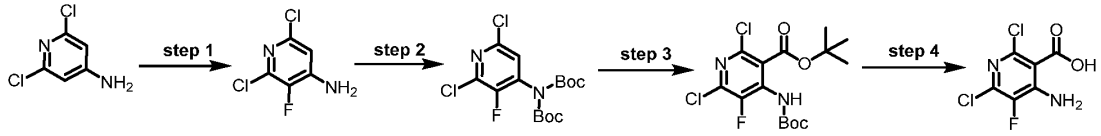
[0330] Embodiment 81. Use of a compound of any one of embodiments 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting tumor metastasis.

Examples

[0331] The following Examples are presented by way of illustration, not limitation.

[0332] INTERMEDIATES

[0333] **Intermediate 1:** 4-Amino-2,6-dichloro-5-fluoronicotinic acid



[0334] Step 1: 2,6-Dichloro-3-fluoropyridin-4-amine

[0335] Under nitrogen, a solution of 2,6-dichloropyridin-4-amine (9.01 g, 55.3 mmol) and SelectFlour (23.6 g, 66.6 mmol) in DMF (90 mL) and acetonitrile (90 mL) was stirred for 30 min at 80°C. The mixture was concentrated under vacuum. The crude product was purified by reverse phase chromatography (gradient: 0–40 % acetonitrile in water (0.1% formic acid)) to afford the title compound (4.62 g, 46.2% yield) as a light brown solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 181. ^{1}H NMR (300 MHz, DMSO- *d6, ppm*) δ 6.99 (s, 2H), 6.70 (d, J = 5.4 Hz, 1H).

[0336] Step 2: *tert*-Butyl *N*-*tert*-butoxycarbonyl-*N*-(2,6-dichloro-3-fluoro-4-pyridyl)carbamate

[0337] Under nitrogen, to a solution of 2,6-dichloro-3-fluoropyridin-4-amine (4.82 g, 26.6 mmol) in THF (100mL) was added NaHMDS (53.1 mL, 2M in THF) at 0°C. The resulting solution was stirred for 30 min at 0°C. Then Boc_2O (29.0 g, 133 mmol) in THF (450 mL) was added at 0°C and stirred at room temperature overnight. The reaction was quenched with aqueous NH_4Cl. A majority of THF was removed under vacuum and the resulting solution was extracted with EtOAc. The combined organic layers were concentrated under vacuum to afford the title compound (9.11 g, crude) as a white solid which was used without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 381. ^{1}H NMR (300 MHz, DMSO- *d6, ppm*) δ 6.13 (s, 1H), 1.42 (s, 9H), 1.38 (d, J = 2.4 Hz, 9H).

[0338] Step 3: *tert*-Butyl 4-((*tert*-butoxycarbonyl)amino)-2,6-dichloro-5-fluoronicotinate

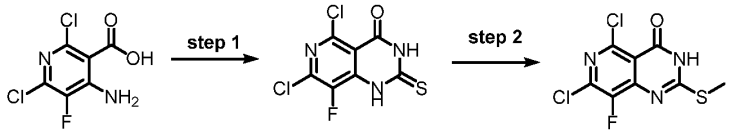
[0339] Under nitrogen, to a solution of *tert*-butyl *N*-*tert*-butoxycarbonyl-*N*-(2,6-dichloro-3-fluoro-4-pyridyl)carbamate (9.11 g, 23.9 mmol) in THF (180mL) was added LDA (41.9 mL, 1M in THF) at -78°C. The resulting solution was stirred for 0.5 h at -78°C. The reaction was quenched with aq. NH_4Cl and extracted with EtOAc (300 mL*2). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0-10%) to afford the title

compound (4.18 g, 45.9 % yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 381. ^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 10.07 (s, 1H), 1.54 (s, 9H), 1.45 (s, 9H).

[0340] Step 4: 4-Amino-2,6-dichloro-5-fluoronicotinic acid

[0341] A solution of tert-butyl 4-((tert-butoxycarbonyl)amino)-2,6-dichloro-5-fluoronicotinate (4.18 g, 11.0 mmol) in TFA (15mL) and DCM (15mL) was stirred at 40 °C for 3 hours. The solvent was concentrated under vacuum to afford the title compound (2.86 g, crude) as a brown solid which was used without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 225.

[0342] **Intermediate 2:** 5,7-Dichloro-8-fluoro-2-(methylthio)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one



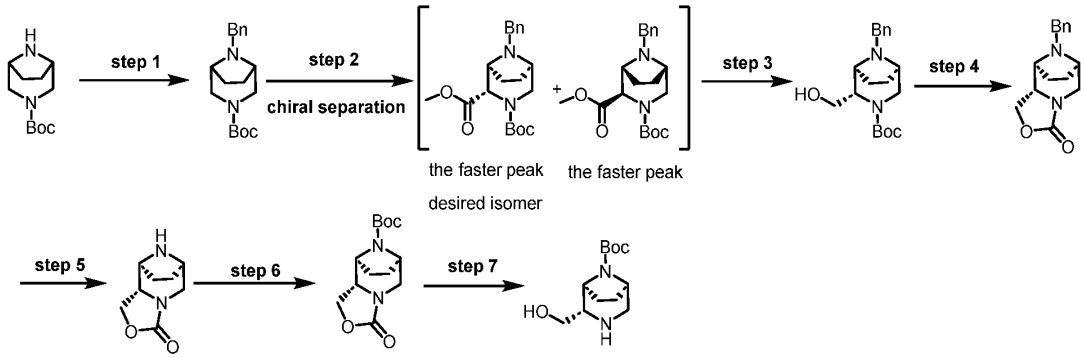
[0343] Step 1: 5,7-Dichloro-8-fluoro-2-thioxo-2,3-dihydropyrido[4,3-*d*]pyrimidin-4(1*H*)-one

[0344] To a solution of 4-amino-2,6-dichloro-5-fluoronicotinic acid (2.01 g, 8.92 mmol, **intermediate 1**) in MeCN (60 mL)/pyridine (20 mL) was added ethoxycarbonyl isothiocyanate (4.20 mL, 35.6 mmol). The resulting solution was stirred at room temperature for 2 hours and concentrated under vacuum. The residue was purified by reverse phase chromatography (gradient: 0–40% acetonitrile in water (0.1% formic acid)) to afford the title compound 1.58 g (46.6% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 264. ^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 13.30 (s, 1H), 12.86 (s, 1H).

[0345] Step 2: 5,7-Dichloro-8-fluoro-2-(methylthio)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one

[0346] Under nitrogen, to a solution of 5,7-dichloro-8-fluoro-2-thioxo-2,3-dihydropyrido[4,3-*d*]pyrimidin-4(1*H*)-one (1.58 g, 5.93 mmol) in DMF (20 mL) was added Ch_3ONa (320 mg, 5.93 mmol) at 0°C. The resulting solution was stirred for 10 min at room temperature. Then CH_3I (842 mg, 5.93 mmol) was added slowly at room temperature. Stirred overnight at room temperature. The reaction solution was added slowly with stirring to cold water. The solid was collected by filtration and dried in an oven to afford the title compound (2.07 g, crude) as a yellow solid which was used for the next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 280. ^{1}H NMR (300 MHz, DMSO- *d6, ppm*) δ 13.35 (br, 1H), 2.61 (s, 3H).

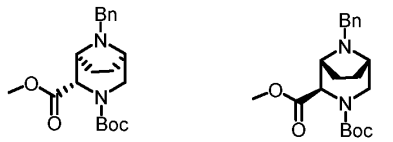
[0347] **Intermediate 3:** *tert*-Butyl (1*R*,2*S*,5*S*)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0348] Step 1: tert-Butyl (1*R*,5*S*)-8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

[0349] To a solution of tert-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (50.0 g, 236 mmol) in DMF (800 mL) was added K_2CO_3 (65.1 g, 472 mmol) and BnBr (60.1g, 353.53 mmol). Stirred at rt for 2 hours. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with water (500 mL×3), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0~10%) to afford the title compound (69 g, 96.9% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 303$.

[0350] Step 2: 3-(*tert*-Butyl) 2-methyl (1*R*,2*S*,5*S*)-8-benzyl-3,8-diazabicyclo[3.2.1]octane-2,3-dicarboxylate and 3-(*tert*-Butyl) 2-methyl (1*R*,2*R*,5*S*)-8-benzyl-3,8-diazabicyclo[3.2.1]octane-2,3-dicarboxylate



the faster peak
desired isomer

the faster peak

[0351] Under N_2, to a solution of tert-butyl 8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (23.0 g, 76.06 mmol) and TMEDA (17.7 g, 152.59 mmol) in diethyl ether (500 mL) was added dropwise s-BuLi (117 mL, 1.3 M in hexane) at -78°C, and the mixture was stirred at -78°C for 1.5 hours. Then methyl carbonochloridate (17.9 g, 189 mmol) in 40 mL Et_2O was added dropwise at -78°C. The reaction was warmed to room temperature gradually and stirred an additional 16 hours. The reaction was quenched with saturated $NaHCO_3$ (aq), diluted with water and extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0~10%) to afford 16 g of racemic mixtures (mixture of cis) as yellow oil. The mixture was separated by chiral-SFC (Column: Lux® 5μm Cellulose-2,

5×25cm, 5um; Mobile Phase A: CO_2, Mobile Phase B: MeOH (0.1% 2M NH_3-MeOH); Flow rate:180 mL/min; Gradient:18% B; 220 nm; RT_1:5.07; RT_2: 5.57) to afford 5.9 g the faster peak and 5.6 g of the slower peak as yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 361$.

[0352] Step 3: *tert*-Butyl (1*R*,2*S*,5*S*)-8-benzyl-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

[0353] Under nitrogen, to a solution of 3-(tert-butyl) 2-methyl (1R,2S,5S)-8-benzyl-3,8-diazabicyclo[3.2.1]octane-2,3-dicarboxylate (20.0g, 55.5mmol, faster peak of previous operation) in THF (300 mL) was added $LiAlH_4$ (4.20g, 111mmol) at 0°C. The resulting solution was stirred for 30 mins at 0°C and quenched with $Na_2SO_4.10H_2O$. The solid was filtered off and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0~20%) to afford the title compound (14.3 g, 77.5% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 333$.

[0354] Step 4: (6*S*,9*R*,9*aS*)-10-Benzylhexahydro-1*H*,3*H*-6,9-epiminooxazolo[3,4-a]azepin-3-one

[0355] Under nitrogen, to a solution of tert-butyl 8-benzyl-4-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (5.1 g, 15.34 mmol) in THF (100 mL) was added NaH (1.35 g, 33.75 mmol, 60% in mineral oil) at 0°C. The resulting solution was stirred for 3 hours at room temperature, quenched with NH_4Cl (aq) and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0~40%) to afford the title compound (3.5 g, 88.3% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 259$.

[0356] Step 5: (6*S*,9*R*,9*aS*)-Hexahydro-1H,3H-6,9-epiminooxazolo[3,4-a]azepin-3-one

[0357] A mixture of (6*S*,9*R*,9*aS*)-10-Benzylhexahydro-1*H*,3*H*-6,9-epiminooxazolo[3,4-a]azepin-3-one (10.0 g, 38.7 mmol) and Pd/C (3.0 g, 10% dry) in methyl alcohol (200 mL) was stirred under an atmosphere of hydrogen at room temperature for 2 hours at room temperature. The catalyst was filtered off. The filtrate was concentrated under reduced pressure to afford 6g crude product which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 169$.

[0358] Step 6: *tert*-Butyl (6*S*,9*R*,9*aS*)-3-oxohexahydro-1*H*,3*H*-6,9-epiminooxazolo[3,4-a]azepine-10-carboxylate

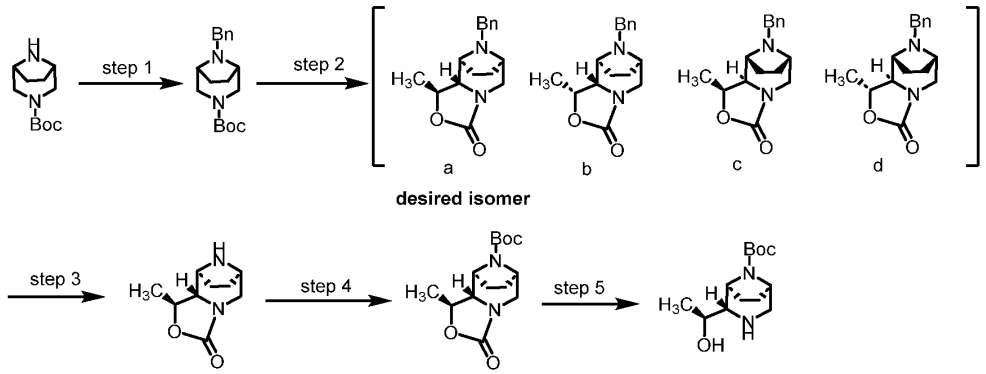
[0359] A solution of (6*S*,9*R*,9*aS*)-Hexahydro-1H,3H-6,9-epiminooxazolo[3,4-a]azepin-3-one (6.00 g, 35.7 mmol), $(Boc)_2O$ (12.6g, 57.8mmol) and DIPEA (10.0 g, 77.5 mmol) in dichloromethane (100 mL) was stirred at rt for 2 hours. The reaction mixture was washed with saturated sodium chloride solution. The organic phase was dried over anhydrous Na_2SO_4 and

concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0~40%) to afford the title compound 7.50 g (78.4% yield) as white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 269$.

[0360] Step 7: *tert*-Butyl (1*R*,2*S*,5*S*)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[0361] A solution of *tert*-Butyl (6*S*,9*R*,9*aS*)-3-oxohexahydro-1*H*,3*H*-6,9-epiminooxazolo[3,4-a]azepine-10-carboxylate (7.50 g, 28.0 mmol) and NaOH (16.8 g, 420 mmol) in ethanol (200 mL) and water (70 mL) was stirred at 80°C for 16 hours. A majority of EtOH was stripped off under reduced pressure. The residual solution was adjusted to pH=8 with aqueous HCl (1M) and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with DCM/MeOH (5/1) to afford the title compound (5 g, 73.8% yield) as an off white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 243$. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 4.72 - 4.57 (m, 1H), 4.02 - 3.90 (m, 2H), 3.25 - 3.15 (m, 2H), 2.82 - 2.68 (m, 2H), 2.64 - 2.53 (m, 1H), 1.85 - 1.61 (m, 3H), 1.61 - 1.47 (m, 1H), 1.41 (s, 9H).

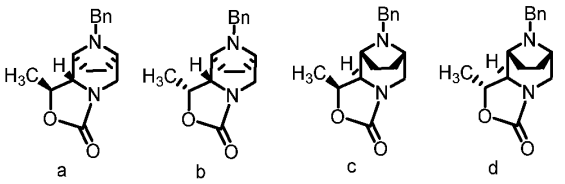
[0362] **Intermediate 4:** *tert*-Butyl (1*R*,2*S*,5*S*)-2-((*S*)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[0363] Step 1: *tert*-Butyl 8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

[0364] Under nitrogen, to a solution of *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (5.00 g, 23.5 mmol) in N,N-dimethylformamide (50 mL) was added K_2CO_3 (6.51 g, 47.1 mmol) and (bromomethyl)benzene (6.01 g, 35.1 mmol) at 0°C. Stirred for 1 h at room temperature. The reaction mixture was poured into ice water, extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc/ petroleum ether) to yield 7 g (98.3% yield) the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 303$.

[0365] Step 2: (1*S*,6*S*,9*R*,9a*S*)-10-Benzyl-1-methylhexahydro-1*H*,3*H*-6,9-epiminooxazolo[3,4-a]azepin-3-one



desired isomer

[0366] Under nitrogen, to a solution of *tert*-butyl 8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (7.0 g, 23.1mmol) and TMEDA (5.38 g, 46.3mmol) in diethyl ether (70 mL) was added s-BuLi (35.6 mL, 46.3mmol, 1.3 M in hexane) dropwise at -78°C. The resulting solution was stirred for 1.5 h at -78°C. Then acetaldehyde (2.55 g, 57.8mmol) was added at -78°C. The reaction was allowed to warm to room temperature gradually and stirred overnight. The mixture was quenched with NH_4Cl (aq.) and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (0-50% EtOAc in petroleum ether) to yield 5.1 g mixture of 4 diastereoisomers. The mixture was separated by Prep-SFC (Column: CHIRALPAK IH, 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: IPA(0.5% 2M NH_3-MeOH); Flow rate: 70 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 6.31; RT2(min): 8.33; Sample Solvent: MeOH-----Preparative; Injection Volume: 1.9 mL; Number Of Runs: 50) to yield the compound a (1.39 g, 22% yield) (the first peak) and compound d (1.47 g, 23.3% yield) (the third peak) and mixture of compound b and c (the second peak). The mixture of compound b and c was re-separated by Prep-SFC (Column: CHIRALPAK IH, 5*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: IPA(0.5% 2M NH_3-MeOH); Flow rate: 200 mL/min; Gradient: isocratic 50% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.73; RT2(min): 8.44; Sample Solvent: MeOH-----Preparative; Injection Volume: 10 mL; Number Of Runs: 6) to yield compound b (0.500 g, 7.9% yield) (the faster peak) and compound c (0.430 g, 6.8% yield) (the slower peak) as yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 273$.

[0367] Step 3: (1*S*,6*S*,9*R*,9a*S*)-1-Methylhexahydro-1*H*,3*H*-6,9-epiminooxazolo[3,4-a]azepin-3-one

[0368] A solution of (1*S*,6*S*,9*R*,9a*S*)-10-Benzyl-1-methylhexahydro-1*H*,3*H*-6,9-epiminooxazolo[3,4-a]azepin-3-one (1.00 g, 3.67 mmol) (the compound a of previous step) and Pd/C (500 mg, 10%) in methyl alcohol (15 mL) was stirred for 1 h at room temperature under an atmosphere of hydrogen gas. The catalyst was filtered off. The filtrate was concentrated under vacuum to yield 658 mg (crude) the title compound as a yellow oil which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 183$.

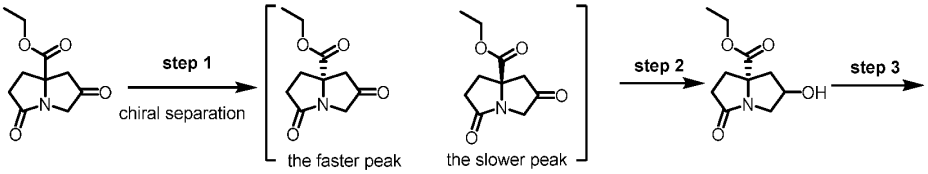
[0369] Step 4: *tert*-Butyl (1*S*,6*S*,9R,9a*S*)-1-methyl-3-oxohexahydro-1H,3H-6,9-epiminooxazolo[3,4-a]azepine-10-carboxylate

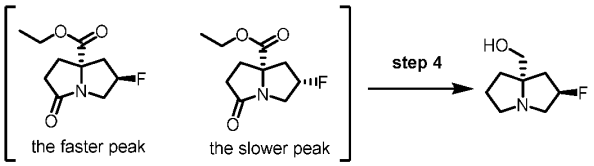
[0370] A solution of (1*S*,6*S*,9*R*,9a*S*)-1-methylhexahydro-1*H*,3*H*-6,9-epiminooxazolo[3,4-a]azepin-3-one (658 mg, 3.61 mmol), $(Boc)_2O$ (1.18 g, 5.41 mmol) and DIPEA (1.4 g, 10.8 mmol) in dichloromethane (10 mL) was stirred for 30 min at room temperature. The reaction system was quenched with water, extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-100% EtOAc / petroleum ether) to yield the title compound (920 mg, 90.2% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 283.

[0371] Step 5: *tert*-Butyl (1*R*,2*S*,5*S*)-2-((*S*)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

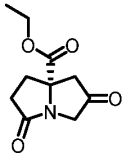
[0372] A solution of *tert*-butyl (1*S*,6*S*,9R,9a*S*)-1-methyl-3-oxohexahydro-1H,3H-6,9-epiminooxazolo[3,4-a]azepine-10-carboxylate (900 mg, 3.19 mmol) and NaOH (1.28 g, 32.0 mmol) in ethanol (12 mL) and water (4 mL) was stirred for 1 h at 80°C. The reaction solution was cooled to room temperature and diluted with water, extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield 815 mg (crude) as an oil which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 257. ^1H NMR (300 MHz, DMSO-d_6) δ 4.54 (s, 1H), 3.94 (d, *J* = 5.1 Hz, 1H), 3.82 (s, 1H), 2.73 (d, *J* = 11.3 Hz, 1H), 2.60 (d, *J* = 11.5 Hz, 1H), 2.41 (d, *J* = 8.1 Hz, 1H), 2.15 (s, 1H), 179 – 1.67 (m, 3H), 1.56 (s, 1H), 1.40 (s, 9H), 1.04 (d, *J* = 6.3 Hz, 3H).

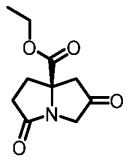
[0373] **Intermediate 5:** ((2*R*,7a*S*)-2-Fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol





[0374] Step 1: Ethyl (*S*)-2,5-dioxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate and Ethyl (*R*)-2,5-dioxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate


the faster peak

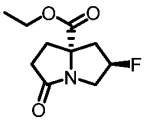

the slower peak

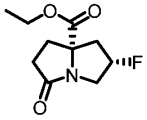
[0375] 20.0 g ethyl 2,5-dioxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (20.0 g, 94.6 mmol) was separated by SFC (Column: AD 2.12*25cm,5um; Mobile Phase A: CO_2, Mobile Phase B: EtOH:ACN=1:1; Flow rate:200 mL/min; Gradient:50% B; 220 nm; RT1: 2.44; RT2: 3.58; Injection Volumn:10 ml; Number Of Runs:15) to afford ethyl (*S*)-2,5-dioxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (8.21 g, the faster peak) as a yellow oil and ethyl (*R*)-2,5-dioxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (7.92 g, the slower peak) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 212$. ^1H NMR (400 MHz, Chloroform-*d*) δ 4.22 (q, J = 7.2 Hz, 2H), 4.14 – 4.05 (m, 1H), 3.54 (d, *J* = 18.6 Hz, 1H), 3.02 – 2.91 (m, 2H), 2.87-2.72 (m, 1H), 2.60 – 2.38 (m, 2H), 2.23-2.11 (m, 1H), 1.28 (t, *J* = 7.1 Hz,3H).

[0376] Step 2: Ethyl (7a*S*)-2-hydroxy-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate

[0377] Under nitrogen, to a solution of ethyl (*S*)-2,5-dioxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (1.22 g, 5.68 mmol) in tetrahydrofuran (100 mL) was added $NaBH_4$ (70.3 mg, 1.85 mmol) at 0 °C. The mixture was stirred for 30 mins at 0 °C. The reaction was quenched with water and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-6% MeOH/ DCM) to afford the title compound (0.631 g, 62% yield) as a light yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 214$.

[0378] Step 3: Ethyl (2*R*,7a*S*)-2-fluoro-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate and Ethyl (2*S*,7a*S*)-2-fluoro-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate


the faster peak


the slower peak

[0379] Under nitrogen, to a solution of ethyl (7a*S*)-2-hydroxy-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (809 mg, 3.80 mmol) was added DAST (923 mg, 5.74 mmol, dissolved in 20 mL DCM) at -15 °C. The mixture was stirred for 3 hours at room temperature. The mixture was quenched with EtOH. The solvent was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-100% EtOAc/ petroleum) to afford 425 mg (52% yield) of ethyl (2*R*,7a*S*)-2-fluoro-5-oxotetrahydro-1*H*-pyrrolizine-7a(5H)-carboxylate as a colorless oil and 219 mg (26.9% yield) of ethyl (2*S*,7a*S*)-2-

fluoro-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate as white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 216$.

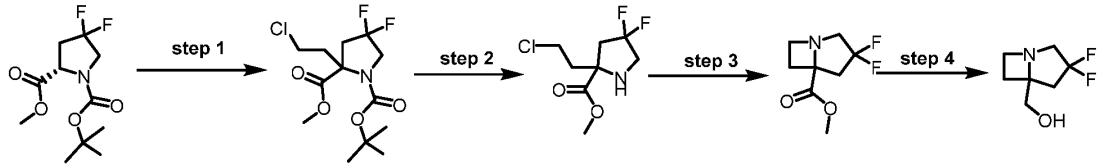
[0380] Ethyl (2*R*,7a*S*)-2-fluoro-5-oxotetrahydro-1H-pyrrolizine-7a(5*H*)-carboxylate **(the faster peak)**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.32 (d, *J* = 19.2 Hz, 1H), 4.26 – 4.11 (m, 3H), 3.25 – 3.12 (m, 1H), 2.85 – 2.59 (m, 3H), 2.48 – 2.39 (m, 1H), 2.37 – 2.07 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H).

[0381] Ethyl (2*S*,7a*S*)-2-fluoro-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate **(the slower peak)**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.47 – 5.32 (m, 1H), 4.29 – 4.24 (m, 2H), 4.08 – 3.96 (m, 1H), 3.46 – 3.35 (m, 1H), 2.98 – 2.78 (m, 2H), 2.53 – 2.42 (m, 2H), 2.20 – 2.12 (m, 1H), 1.91 – 1.76 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H).

[0382] Step 4: ((2*R*,7a*S*)-2-Fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol

[0383] Under nitrogen, to a solution of ethyl (2*R*,7a*S*)-2-fluoro-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (310 mg, 1.44 mmol) in tetrahydrofuran (7 mL) was added $LiAlH_4$ (3.1 mL, 1M in THF) at 0 °C. The mixture was stirred for 0.5 h at 70 °C. The mixture was quenched with $Na_2SO_4.10H_2O$ and filtered. The solvent was removed by blowing N_2 and afford the title compound 124 mg (crude) as yellow oil which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 160$.

[0384] **Intermediate 6:** (3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methanol



[0385] Step 1. 1-(*tert*-Butyl) 2-methyl 2-(2-chloroethyl)-4,4-difluoropyrrolidine-1,2-dicarboxylate

[0386] Under nitrogen, to a solution of 1-tert-butyl 2-methyl (2S)-4,4-difluoropyrrolidine-1,2-dicarboxylate (2.0g, 7.54mmol) in tetrahydrofuran (30mL) was added LiHMDS (10.mL, 10mmol) at -78°C and stirred at -78°C for 0.5 hours. Then 1-chloro-2-iodoethane (2.87g, 15.1mmol) was added and stirred at room temperature for 1 hour. The reaction was quenched with NH_4Cl (aq.), extracted with EtOAc. The combined organic layers were dried over $NaSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0~60%) to afford the title compound 900 mg (36.4% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 328$

[0387] Step 2. Methyl 2-(2-chloroethyl)-4,4-difluoropyrrolidine-2-carboxylate

[0388] Under nitrogen, to a solution of 1-(tert-butyl) 2-methyl 2-(2-chloroethyl)-4,4-difluoropyrrolidine-1,2-dicarboxylatee (470mg, 1.43mmol) in dichloromethane (5mL) was added

TFA (1mL) at room temperature. The resulting solution was stirred at room temperature for 1 hour. The solvent was concentrated under vacuum to afford the title compound 300mg (crude) as a yellow oil which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 228$

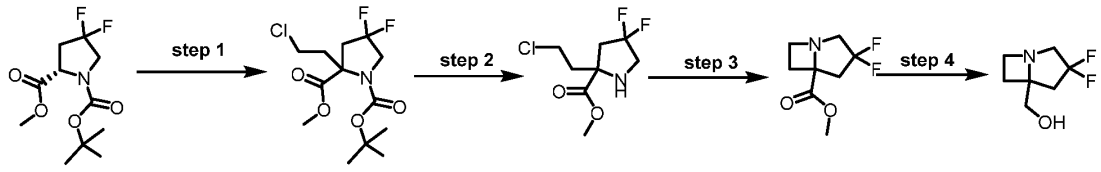
[0389] Step 3. Methyl 3,3-difluoro-1-azabicyclo[3.2.0]heptane-5-carboxylate

[0390] Under nitrogen, to a solution of methyl 2-(2-chloroethyl)-4,4-difluoro-pyrrolidine-2-carboxylate (300mg, 1.32mmol) in acetonitrile (5mL) was added Et_3N (1 mL) at room temperature and stirred at 85°C for 12 hours. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with DCM/MeOH (0~6%) to afford the title compound 150 mg (59.5% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 192$

[0391] Step 4. (3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methanol

[0392] Under nitrogen, to a solution of methyl 3,3-difluoro-1-azabicyclo[3.2.0]heptane-5-carboxylate (150 mg, 0.780 mmol) in tetrahydrofuran (3mL) was added $LiAlH_4$ (2.4mL, 2.4mmol, 1M in THF) at 0°C. The solution was stirred at 0°C for 0.5 hours. The solvent was removed by blowing nitrogen to afford 110 mg (crude) the title compound as a yellow oil which was used for next reaction without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 164$. purification.

[0393] **Intermediate 6A:** (3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methanol



[0394] Step 1. 1-(*tert*-Butyl) 2-methyl 2-(2-chloroethyl)-4,4-difluoropyrrolidine-1,2-dicarboxylate

[0395] Under nitrogen, to a solution of 1-tert-butyl 2-methyl (2S)-4,4-difluoropyrrolidine-1,2-dicarboxylate (2.0 g, 7.54 mmol) in tetrahydrofuran (30 mL) was added LiHMDS (10 mL, 10 mmol) at -78°C and the mixture was stirred at -78°C for 0.5 hours. Then 1-chloro-2-iodoethane (2.87 g, 15.1 mmol) was added and the mixture was stirred at room temperature for 1 hour. The reaction was quenched with NH_4Cl (aq.) and then extracted with EtOAc. The combined organic layers were dried over $NaSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0~60%) to afford the title compound 900 mg (36.4% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 328$

[0396] Step 2. Methyl 2-(2-chloroethyl)-4,4-difluoropyrrolidine-2-carboxylate

[0397] Under nitrogen, to a solution of 1-(tert-butyl) 2-methyl 2-(2-chloroethyl)-4,4-difluoropyrrolidine-1,2-dicarboxylatee (470 mg, 1.43 mmol) in dichloromethane (5 mL) was added TFA (1 mL) at room temperature. The resulting solution was stirred at room temperature for 1 hour. The solvent was concentrated under vacuum to afford the title compound 300 mg (crude) as a yellow oil which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 228$

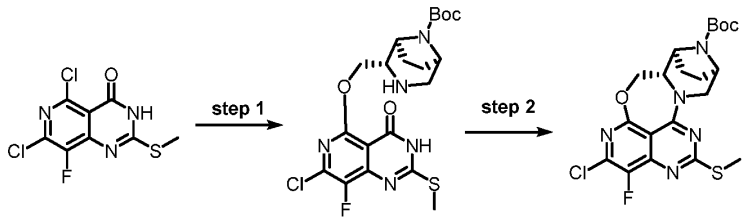
[0398] Step 3. Methyl 3,3-difluoro-1-azabicyclo[3.2.0]heptane-5-carboxylate

[0399] Under nitrogen, to a solution of methyl 2-(2-chloroethyl)-4,4-difluoro-pyrrolidine-2-carboxylate (300 mg, 1.32 mmol) in acetonitrile (5 mL) was added Et_3N (1 mL) at room temperature and the mixture was stirred at 85°C for 12 hours. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with DCM/MeOH (0~6%) to afford the title compound 150 mg (59.5 % yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 192$

[0400] Step 4. (3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methanol

[0401] Under nitrogen, to a solution of methyl 3,3-difluoro-1-azabicyclo[3.2.0]heptane-5-carboxylate (150 mg, 0.780 mmol) in tetrahydrofuran (3 mL) was added $LiAlH_4$ (2.4 mL, 2.4 mmol, 1 M in THF) at 0°C. The solution was stirred at 0°C for 0.5 hours. The solvent was removed by blowing nitrogen through it to afford 110 mg of the crude title compound as a yellow oil which was used for next reaction without further purification. LC-MS: (ESI, m/z): $[M+H]^+ =$ 164. purification.

[0402] **Intermediate 7:** *tert*-Butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



[0403] Step 1: *tert* -Butyl (1*S*,2*S*,5*R*)-2-(((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

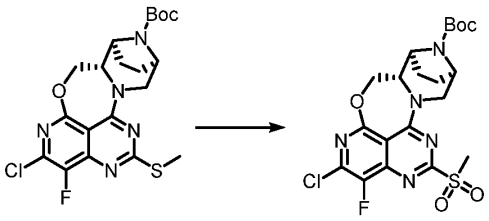
[0404] Under nitrogen, to a solution of *tert* -butyl (1*S*,2*S*,5*R*)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (289 mg, 1.19 mmol, **intermediate 3**) in THF (20 mL) was added NaH (191 mg, 4.78 mmol, 60% in mineral oil) at 0°C. The resulting solution was stirred for 0.5 h at room temperature. Then 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (803 mg, 1.43 mmol, **intermediate 2**) was added at 0°C, and the mixture

was stirred for 1 hour at room temperature. The reaction was quenched aqueous NH_4Cl, diluted with water and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound (1.05 g crude) as a white solid which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 486$.

[0405] Step 2: *tert* -Butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[0406] To a solution of *tert* -butyl (1*S*,2*S*,5*R*)-2-(((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.05 g, 2.15 mmol) in DCM (10 mL) was added DIPEA (4.16 g, 32.3 mmol) and BOPCl (2.20 g, 8.61 mmol). The resulting solution was stirred at room temperature for 2 hours, diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0%-40%) to afford the title compound (381 mg, 37.8% yield) as a light yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 469$

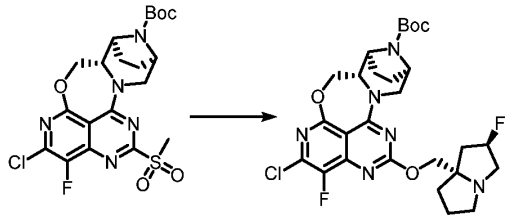
[0407] **Intermediate 8:** *tert* -Butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



[0408] To a solution of *tert* -butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (381 mg, 0.816 mmol, **intermediate 7**) in EtOAc (5 mL) was added mCPBA (423 mg, 2.45 mmol) at 0°C. The solution was stirred at room temperature for 1 hour, diluted with saturated $NaHCO_3$ solution (20 mL) and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0-60%) to afford the title compound 372 mg (91.3% yield) as white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 500$. ^1H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 4.99 (d, J = 13.5 Hz, 1H), 4.77 (dd, J = 13.5, 1.9 Hz, 1H), 4.59 (dd, J = 13.5, 7.4 Hz, 1H), 4.38 (d, J = 8.3 Hz, 2H), 4.20 (d, J = 7.1 Hz,

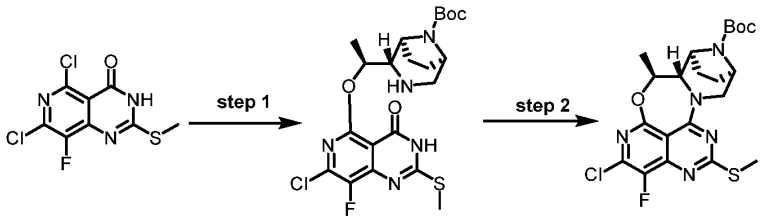
1H), 3.42 (s, 3H), 3.22 (d, J = 13.6 Hz, 1H), 1.93 (d, J = 6.7 Hz, 1H), 1.86 – 1.64 (m, 3H), 1.45 (s, 9H).

[0409] **Intermediate 9:** *tert* -Butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



[0410] Under nitrogen, to a mixture of *tert* -butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (201 mg, 0.401 mmol, **intermediate 8**) and ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (128 mg, 0.802 mmol, **intermediate 5**) in toluene (2 mL) was added t-BuONa (77.1 mg, 0.802 mmol) at 0°C. The solution was stirred at room temperature for 1 hour, diluted with water (20 mL) and extracted with EtOAc (50 mL*2). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The resulting residue was purified by flash chromatography on silica gel eluting with CH_3OH/DCM (0-10%) to afford the title compound (151 mg, 64.8% yield) as light yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 579. ^1H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 5.29 (d, J = 54.2 Hz, 1H), 4.89 (d, J = 13.4 Hz, 1H), 4.72 – 4.62 (m, 1H), 4.48 (dd, J = 13.3, 7.3 Hz, 1H), 4.40 – 4.25 (m, 2H), 4.19 – 3.95 (m, 3H), 3.15 – 2.97 (m, 4H), 2.89 – 2.76 (m, 1H), 2.17 – 2.11 (m, 1H), 2.07 – 2.02 (m, 1H), 1.94 – 1.62 (m, 8H), 1.45 (s, 9H).

[0411] **Intermediate 10:** *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0412] Step 1: *tert*-Butyl (1*S*,2*S*,5*R*)-2-((*S*)-1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

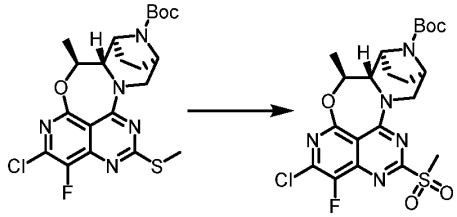
[0413] Under nitrogen, to a solution of *tert*-butyl (1*S*,2*S*,5*R*)-2-((*S*)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (769 mg, 3.00 mmol, **intermediate 4**) in THF (10 mL)

was added NaH (480 mg, 12.0 mmol, 60% in mineral oil) at 0°C. The resulting solution was stirred for 0.5 h at room temperature. Then 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (1.01 g, 3.60 mmol, **intermediate 2**) was added at 0°C, and the mixture was stirred for 2 hours at room temperature. The reaction was quenched with aqueous NH_4Cl, diluted with water and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound (1.61 g crude) as a white solid, which was used in the next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 500$.

[0414] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[0415] To a solution of *tert*-butyl (1*S*,2*S*,5*R*)-2-((*S*)-1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.61g, 3.21mmol) in DCM (15 mL) was added DIPEA (6.22 g, 48.2 mmol) and BOPCl (3.28 g, 12.9 mmol). The reaction mixture was stirred at room temperature for 2 hours and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0%-55%) to afford the title compound (1.21 g, 77.9% yield) as a light yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 482$.

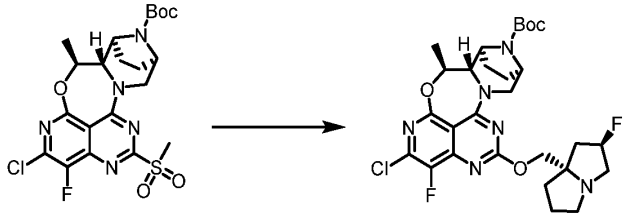
[0416] **Intermediate 11:** *tert*-Butyl (5*S*,5*aS*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0417] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (1.21g, 2.5mmol, **intermediate 10**) in EtOAc (20 mL) was added mCPBA (1.30 g, 7.52 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, diluted with $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0-60%) to afford the title compound (931 mg, 72.4% yield) as white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 514$. ^1H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 5.32 – 5.16 (m, 1H), 4.74 (t, J = 7.7 Hz, 1H), 4.35 (d, J = 5.2 Hz,

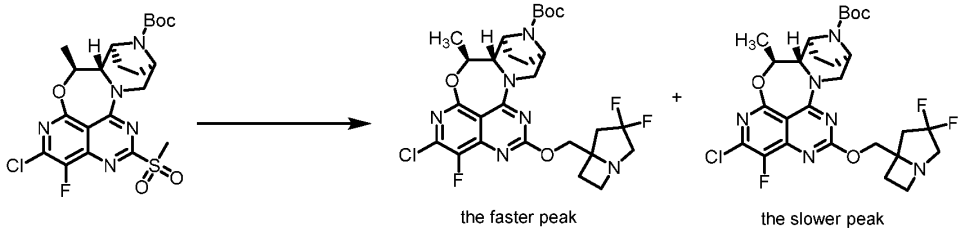
1H), 4.30 – 4.10 (m, 2H), 3.42 (s, 3H), 3.20 (d, J = 13.4 Hz, 1H), 1.93 – 1.70 (m, 4H), 1.53 (d, J = 6.3 Hz, 3H), 1.47 (s, 9H).

[0418] **Intermediate 12:** *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0419] Under nitrogen, to a solution of ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (37.5 mg, 0.240 mmol, **intermediate 5**) and *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (60.6 mg, 0.120 mmol, **intermediate 11**) in toluene (1.5 mL) was added t-BuONa (22.6 mg, 0.240 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, quenched with water, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with CH_3OH/DCM (0-10%) to afford the title compound (40.6 mg, 58.1% yield) as light yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 593.

[0420] **Intermediate 13:** *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chlro-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



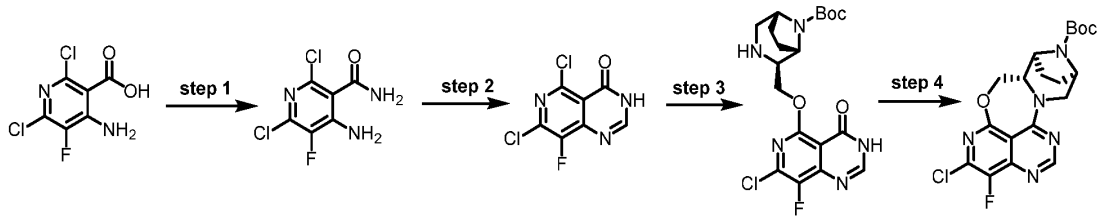
[0421] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (3.50 g, 6.81 mmol, **intermediate 11**) and (3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methanol (1.30 g, 7.97 mmol, **intermediate 6**) in toluene (35 mL) was added t-BuONa (1.30 g, 13.5 mmol) at 0°C. The resulting solution was stirred at room temperature for 1h, quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under

vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-6% MeOH/DCM) to afford 2.06 g (50.7% yield) of a mixture of two diastereoisomers as a white solid. The diastereoisomers were separated by Chiral-Prep-HPLC (Column: CHIRALPAK IE-3, 4.6*50 mm, 3 um; Mobile Phase A: Hex(0.1%DEA): EtOH=50: 50; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford yield 643 mg of the faster peak and 676 mg of the slower peak as white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 597.

[0422] The faster peak (desired isomer): ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 5.18 (d, *J* = 13.2 Hz, 1H), 4.64 (t, *J* = 7.6 Hz, 1H), 4.44 – 4.29 (m, 3H), 4.16 (s, 1H), 3.99 (d, *J* = 9.0 Hz, 1H), 3.54 (dd, *J* = 9.0, 4.7 Hz, 1H), 3.33 – 3.15 (m, 1H), 3.15 (d, *J* = 4.4 Hz, 1H), 3.13 – 2.98 (m, 2H), 2.75 – 2.52 (m, 1H), 2.50 – 2.38 (m, 1H), 2.41 – 2.25 (m, 1H), 1.87 (s, 3H), 1.73 (s, 1H), 1.50 (d, *J* = 6.3 Hz, 3H), 1.47 (s, 9H).

[0423] The slower peak: ^{1}H NMR (300 MHz, DMSO-d_6, ppm): ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 5.18 (d, *J* = 13.2 Hz, 1H), 4.64 (t, *J* = 7.6 Hz, 1H), 4.44 – 4.29 (m, 3H), 4.16 (s, 1H), 3.99 (d, *J* = 9.0 Hz, 1H), 3.54 (dd, *J* = 9.0, 4.7 Hz, 1H), 3.33 – 3.15 (m, 1H), 3.15 (d, *J* = 4.4 Hz, 1H), 3.13 – 2.98 (m, 2H), 2.75 – 2.52 (m, 1H), 2.50 – 2.38 (m, 1H), 2.41 – 2.25 (m, 1H), 1.87 (s, 3H), 1.73 (s, 1H), 1.50 (d, *J* = 6.3 Hz, 3H), 1.47 (s, 9H).

[0424] **Intermediate 14:** *tert*-Butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



[0425] Step 1: 4-Amino-2,6-dichloro-5-fluoronicotinamide

[0426] A solution of 4-amino-2,6-dichloro-5-fluoronicotinic acid (2.86 g, 12.7 mmol), NH_4Cl (3.38 g, 63.8 mmol), HATU (7.25 g, 19.1 mmol) and DIPEA (16.5 g, 127 mmol) in DMA (28 mL) was stirred at room temperature for 0.5 hour. The resulting solution was diluted with EtOAc (80 mL) and washed with water (60mL*4). The organic layer was concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with CH_3OH/DCM (0-5%) to afford the title compound (1.61 g, 56.5% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 224. ^{1}H NMR (400 MHz, DMSO-*d6*, *ppm*) δ 8.06 (s, 1H), 7.81 (s, 1H), 6.87 (s, 2H).

[0427] Step 2: 5,7-Dichloro-8-fluoropyrido[4,3-d]pyrimidin-4(3*H*)-one

[0428] A solution of 4-amino-2,6-dichloro-5-fluoronicotinamide (1.51 g, 6.74 mmol) in triethoxymethane (30 mL) was stirred at 150°C for 3 hours. Then the mixture was concentrated under vacuum. The residue was triturated with EtOAc/petroleum ether (1:1, 10 mL). The solid

was collected by filtration to afford the title compound (1.04 g, crude) as a yellow solid which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 234. ^{1}H NMR (400 MHz, DMSO-*d6*, *ppm*) δ 13.02 (br s, 1H), 8.41 (s, 1H).

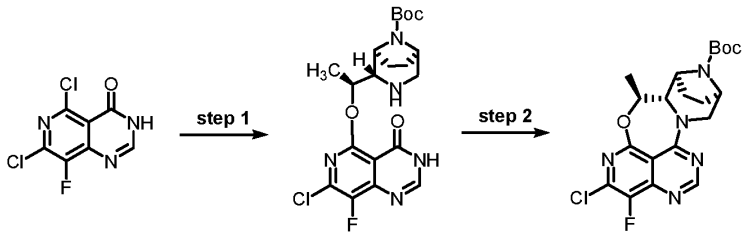
[0429] Step 3: *tert*-Butyl (1*S*,2*S*,5*R*)-2-(((7-chloro-8-fluoro-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[0430] Under nitrogen, to a solution of *tert*-butyl (1*S*,2*S*,5*R*)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (624 mg, 2.58 mmol, intermediate 3) in DMF (6 mL) was added NaH (134 mg, 3.35 mmol, 60% in mineral oil) at 0°C. The resulting solution was stirred for 30 min at rt. Then 5,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4(3*H*)-one (601 mg, 2.57 mmol) was added and stirred at 80°C for 1 hour. The reaction mixture was cooled to room temperature and quenched with aq. NH_4Cl. The reaction mixture was diluted with EtOAc (50 mL) and washed with brine (50 mL*4). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with CH_3OH/DCM (0-10%) to afford the title compound (452 mg, 40% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 440. ^{1}H NMR (400 MHz, *d6*, *ppm*) δ 8.32 (s, 1H), 4.25 – 4.05 (m, 3H), 3.98 (d, J = 6.4 Hz, 1H), 3.20 -3.11 (m, 1H), 2.80 (d, J = 11.5 Hz, 1H), 2.60 (s, 1H), 2.03 -1.92 (m, 1H), 1.82 – 1.57 (m, 3H), 1.37 (t, J = 9.6 Hz, 9H).

[0431] Step 4: *tert*-Butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[0432] Under nitrogen, a solution of *tert*-butyl (1*S*,2*S*,5*R*)-2-(((7-chloro-8-fluoro-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (452 mg, 1.03 mmol), BOP-Cl (1.05 g, 4.12 mmol) and DIPEA (1.99 g, 15.5 mmol) in DCM (10mL) was stirred for 2 h at room temperature. Then the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0-40%) to afford the title compound (315 mg, 72.6% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 422.

[0433] **Intermediate 15:** *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



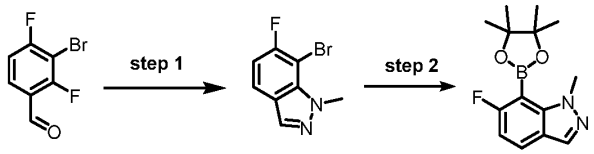
[0434] Step 1: tert-Butyl (1*R*,2*S*,5*S*)-2-((*S*)-1-((7-chloro-8-fluoro-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[0435] Under nitrogen, to a solution of tert-butyl (1R,2S,5S)-2-((S)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (229 mg, 0.890 mmol, **intermediate 4**) in DMF (6 mL) was added NaH (71.6 mg, 1.79 mmol, 60% in mineral oil) at 0°C. The resulting solution was stirred for 30 min at rt. Then 5,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4(3*H*)-one (251 mg, 1.07 mmol, **intermediate 14, step 2**) was added and stirred at 80°C for 1 hour. The reaction mixture was quenched with aq. NH_4Cl, diluted with EtOAc (20 mL) and washed with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound (476 mg, crude) as a white solid which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 454$.

[0436] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[0437] To a solution of *tert*-butyl (1*R*,2*R*,5*S*)-2-((*S*)-1-((7-chloro-8-fluoro-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (476 mg, 1.05 mmol) in DCM (20mL) was added DIPEA (2.03 g, 15.71 mmol) and BOPCl (1.07 g, 4.19 mmol). The solution was stirred at rt for 2 hours, then concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0 %-50 %) to afford the title compound (221 mg, 48.3% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 436$.

[0438] **Intermediate 16:** 6-Fluoro-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole



[0439] Step 1: 7-Bromo-6-fluoro-1-methyl-1*H*-indazole

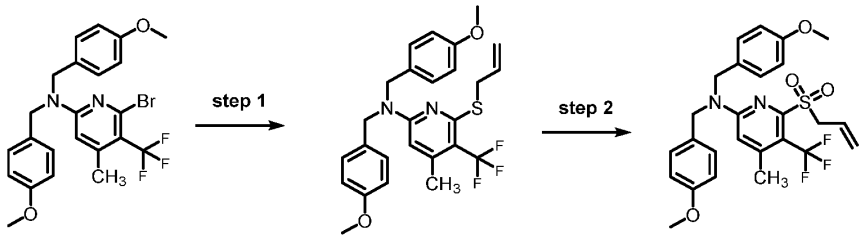
[0440] Under nitrogen, a solution of 3-bromo-2,4-difluoro-benzaldehyde (500 mg, 2.26 mmol), 1-methylhydrazine sulfuric acid salt (1.63 g, 11.3 mmol) and K_2CO_3 (3.12 g, 22.6 mmol) in NMP (15mL) was stirred at 200°C for 2h under microwave irradiation. The reaction system was cooled to room temperature, diluted with water (100 mL) and extracted with EtOAc (100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0~10%) to afford 7-bromo-6-fluoro-1-methyl-indazole (333.2 mg, 64.3% yield) as a white

solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 229/231; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.80 (dd, J = 8.7, 5.0 Hz, 1H), 7.15 (t, J = 8.9 Hz, 1H), 4.31 (s, 3H).

[0441] Step 2: 6-Fluoro-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indazole

[0442] Under nitrogen, a solution of 7 7-bromo-6-fluoro-1-methyl-1*H*-indazole (150 mg, 0.660 mmol), Pin_2B_2 (836 mg, 3.29 mmol), Pd(dppf)Cl (48.2 mg, 0.0700 mmol) and KOAc (258 mg, 2.63 mmol) in DMF (5 mL) was stirred for overnight at 80°C. The resulting solution was purified by reverse phase chromatography (gradient: 0–60 % acetonitrile in water (0.05% NH_4HCO_3)) to afford the title compound (49.9 mg, 27.5% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 277. ^{1}H-NMR (300 MHz, DMSO- *d6, ppm*): δ 8.07 (s, 1H), 7.88 (dd, J = 8.8, 5.6 Hz, 1H), 6.98 (dd, J = 9.5, 8.8 Hz, 1H), 4.05 (s, 3H), 1.38 (s, 12H)

[0443] **Intermediate 17 :** 6-(Allylsulfonyl)-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine



[0444] Step 1: 6-(Allylthio)-*N,N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

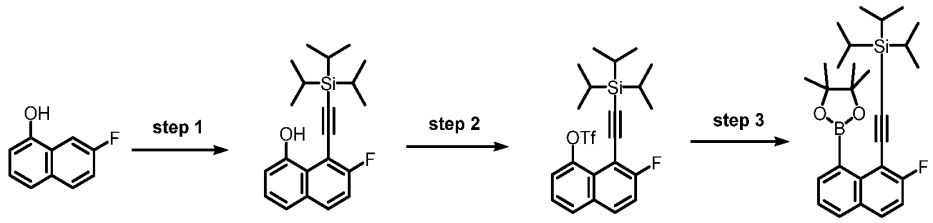
[0445] Under nitrogen, to a solution of allyl mercaptan (3.74 g, 50.5 mmol) and K_2CO_3 (2.79 g, 20.2 mmol) in DMF (20 mL) was added 6-bromo-*N,N*-bis[(4-methoxyphenyl)methyl]-4-methyl-5-(trifluoromethyl)pyridin-2-amine (5.01 g, 10.1 mmol). The solution was stirred at room temperature overnight and diluted with acetonitrile (20 ml). The solid was filtered off. The filtrate was concentrated under reduced pressure to afford 5.05 g (crude) of the title compound as dark red oil which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 489.

[0446] Step 2 :6-(Allylsulfonyl)-*N*, *N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2 amine

[0447] To a solution of 6-allylsulfanyl-*N,N*-bis[(4-methoxyphenyl)methyl]-4-methyl-5-(trifluoromethyl)pyridin-2-amine (5.05 g, 10.3 mmol) in DCM (150 mL) was added *m*CPBA (14.3 g, 82.7 mmol). The reaction mixture was stirred at room temperature overnight, quenched with saturated $NaHCO_3$ aqueous solution (100 mL) and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The

residue was purified by silica gel (gradient: 0%-65% ethyl acetate/petroleum ether) to afford 1.70 g (31.6 % yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 521. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 7.16 (d, J = 8.6 Hz, 4H), 7.01 (s, 1H), 6.90 (d, J = 8.7 Hz, 4H), 5.61 (ddt, J = 18.8, 9.4, 7.1 Hz, 1H), 5.30 (s, 1H), 5.27 (dd, J = 6.0, 1.7 Hz, 1H), 4.76 (s, 4H), 4.15 (d, J = 7.2 Hz, 2H), 3.72 (s, 6H), 2.38 (s, 3H).

[0448] **Intermediate 18:** ((2-Fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane



[0449] Step 1: 7-Fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol

[0450] Under nitrogen, to a solution of 7-fluoronaphthalen-1-ol (2.50 g, 15.4 mmol) and (bromoethynyl)triisopropylsilane (4.82 g, 18.4 mmol) in DCE (24 mL) were added dichloro(p-cymene)ruthenium(II) dimer (1.42 g, 2.31 mmol), K_2CO_3 (2.13 g, 15.4 mmol) and NaOAc (253 mg, 3.09 mmol). The mixture was stirred at 40°C overnight and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0-15%) to afford 5.01 g (94.7% yield) of the title compound as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$, *ppm*) δ 9.00 (s, 1H), 7.68 (dd, J = 9.1, 5.8 Hz, 1H), 7.30 – 7.21 (m, 2H), 7.18 – 7.06 (m, 1H), 6.96 – 6.88 (m, 1H), 1.13 – 1.06 (m, 21H).

[0451] Step 2: 7-Fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate

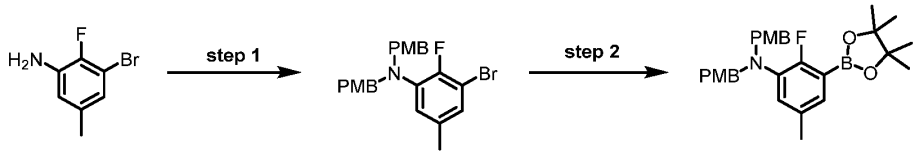
[0452] Under nitrogen, to a solution of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (8.95 g, 26.1 mmol) and DIPEA (6.75 g, 52.3 mmol) in DCM (90 mL) was added trifluoromethanesulfonic anhydride (11.1 g, 39.2 mmol) dropwise at -40°C for 15 min. The solution was stirred at -40°C for 1 h and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0-15%) to afford 10.4 g (83.5% yield) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$, *ppm*) δ 7.90 – 7.81 (m, 2H), 7.58 (d, J = 7.8 Hz, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.43 – 7.35 (m, 1H), 1.33 – 1.15 (m, 21H).

[0453] Step 3: ((2-Fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane

[0454] Under nitrogen, a solution of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (3.01 g, 6.32 mmol), Pin_2B_2 (3.22 g, 12.7 mmol), $Pd(dppf)Cl_2$ (486 mg, 0.630 mmol) and KOAc (1.24 g, 12.7 mmol) in 1,4-Dioxane (12 mL) was stirred at 110°C

overnight. The resulting reaction mixture was diluted with EtOAc (100 mL), washed with water (50 mL) and brine (100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0-13%) to afford 1.61 g (55.9% yield) of the title compound as a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$, *ppm*) δ 7.87 – 7.71 (m, 3H), 7.48 – 7.37 (m, 1H), 7.32 – 7.18 (m, 1H), 1.44 (s, 12H), 1.26 – 1.07 (m, 21H).

[0455] **Intermediate 19:** 2-Fluoro-*N*,*N*-*bis*(4-methoxybenzyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



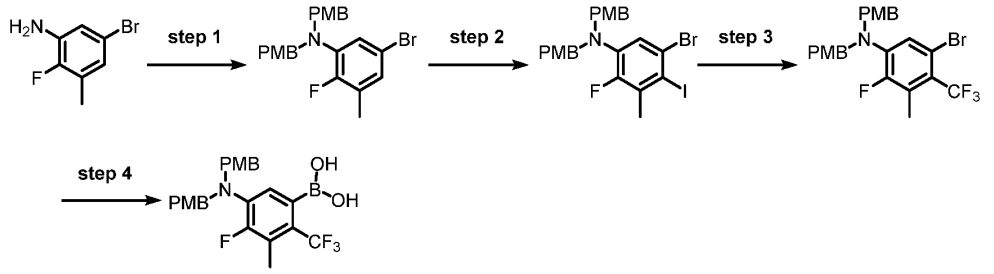
[0456] Step 1: 3-Bromo-2-fluoro-*N*,*N*-*bis*(4-methoxybenzyl)-5-methylaniline

[0457] Under nitrogen, to a solution of 3-bromo-2-fluoro-5-methylaniline (10.3 g, 50.4 mmol) in THF (90 mL) was added NaH (6.06 g, 151 mmol, 60% in mineral oil) at 0°C. The resulting solution was stirred for 20 min at room temperature. Then PMBCl (19.7 g, 125 mmol) was added at 0 °C and stirred at room temperature for 1.5 hours. The reaction was quenched with aq. NH_4Cl and extracted with EtOAc (100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-9% EtOAc /DCM) to afford 20.4 g (90.9% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 443.

[0458] Step 2: 2-Fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0459] Under nitrogen, a solution of 3-bromo-2-fluoro-*N*,*N*-*bis*(4-methoxybenzyl)-5-methylaniline (5.01 g, 11.2 mmol), Pin_2B_2 (5.72 g, 22.5 mmol), $Pd(dppf)Cl_2$ (1.73 g, 2.25 mmol) and KOAc (3.31 g, 33.7 mmol) in 1,4-dioxane (55 mL) was stirred for 5 h at 120°C. The resulting solution was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% EtOAc /petroleum ether) to afford 4.81 g (79.2% yield) of the title compound as a yellow syrup. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 492. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 7.28 (s, 6H), 7.24-7.10 (m, 4H), 6.80 (d, J = 30.0 Hz, 4H), 3.78 (s, 6H), 2.12 (s, 3H), 1.40 (s, 12H).

[0460] **Intermediate 20:** (5-(Bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid



[0461] Step 1: 5-Bromo-2-fluoro-*N,N*-bis(4-methoxybenzyl)-3-methylaniline

[0462] Under nitrogen, to a solution of 5-bromo-2-fluoro-3-methylaniline (4.81 g, 23.5 mmol) in DMF (40 mL) was added NaH (2.82 g, 70.5 mmol, 60% in mineral oil) at 0°C. The resulting solution was stirred for 20 min at room temperature. Then PMBCl (7.42 g, 47.3 mmol) was added. Stirred at room temperature for 1 hour and quenched with aq. NH_4Cl. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (2*80 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was slurried with ethanol to yield 6.50 g (crude) of the title compound as an off-white solid which was used for next step without further purification. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 444

[0463] Step 2: 5-Bromo-2-fluoro-4-iodo-*N,N*-bis(4-methoxybenzyl)-3-methylaniline

[0464] Under nitrogen, to a solution of 5-bromo-2-fluoro-*N,N*-bis(4-methoxybenzyl)-3-methylaniline (5.70 g, 12.8 mmol) in acetic acid (50 mL) was added NIS (3.20 g, 14.2 mmol) at room temperature. The solution was stirred for 20 min at room temperature. The reaction was quenched with aq. $Na_2S_2O_3$ and diluted with EtOAc (150 mL). Phases were separated. The organic layer was washed with water (4*100 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/ petroleum ether (0-30%) to yield 7.21 g (98.5% yield) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 570.

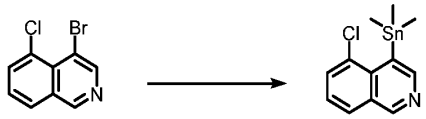
[0465] Step 3: 5-Bromo-2-fluoro-*N,N*-bis(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)aniline

[0466] Under nitrogen, to a solution of 5-bromo-2-fluoro-4-iodo-*N,N*-bis(4-methoxybenzyl)-3-methylaniline (7.08 g, 12.4 mmol) in DMF (80 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (15.2 mL, 119 mmol) and CuI (23.4 g, 123 mmol) at room temperature. The reaction mixture was stirred for 6 hours at 75°C, diluted with H_2O (40 mL) and extracted with EtOAc (70 mL* 2). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/ petroleum ether (0-50%) to yield 3.47 g (54.5% yield) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 512.

[0467] Step 4: (5-(Bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid

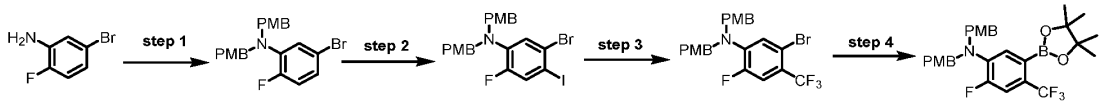
[0468] Under nitrogen, to a solution of 5-bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)aniline (2.40 g, 4.68 mmol) and triisopropyl borate (1.60 mL, 6.91mmol) in THF (35 mL) was added n-BuLi (2.2 mL, 2.5 M in THF) at -78°C. The resulting solution was stirred for 1h at -78°C. The reaction was quenched with aq. NH_4Cl, diluted with H_2O (20 mL) and extracted with EtOAc (50 mL*2). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc(0.1% TEA)/ petroleum ether (10% DCM) (0-30%) to yield 1.22 g (54.4% yield) of the title compound as a yellow syrup. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 477.

[0469] **Intermediate 21:** 5-Chloro-4-(trimethylstannyl)isoquinoline



[0470] Under nitrogen, a solution of 4-bromo-5-chloroisoquinoline (450 mg, 1.86 mmol), Sn_2Me_6 (2.00 g, 6.10 mmol) and $Pd(PPh_3)_4$ (215 mg, 0.190 mmol) in toluene (5 mL) was stirred at 100°C for 48 h. The reaction system was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organic layers were washed with water, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase chromatography (gradient: 0-78% acetonitrile/ water (0.1%FA)) to afford 341 mg (56.3% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 328. ^1H NMR (400 MHz, Chloroform-*d*, *ppm*) δ 9.22 (s, 1H), 8.71 (s, 1H), 7.95 – 7.88 (m, 1H), 7.85 – 7.78 (m, 1H), 7.58 – 7.50 (m, 1H), 0.47 (s, 9H).

[0471] **Intermediate 22:** 2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline e



[0472] Step 1: 5-Bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)aniline

[0473] Under nitrogen, to a solution of 5-bromo-2-fluoro-aniline (10.1 g, 53.2 mmol) in DMF (70 mL) was added NaH (6.40 g, 160 mmol, 60% in mineral oil) at 0°C. Stirred for 30 min at room temperature. Then PMBCl (18.2 g, 117 mmol) was added at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction was quenched with aq. NH_4Cl (20 mL), diluted with EtOAc (250 mL) and washed with water (200 mL*4). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash

chromatography on silica gel (gradient: 0%-17% EtOAc / petroleum ether) to yield 24.1 g of the title compound as a yellow syrup. LC-MS: (ESI, *m/z*): $[M+H]^+$= 430.

[0474] Step 2: 5-Bromo-2-fluoro-4-iodo-*N*, *N*-bis(4-methoxybenzyl)aniline

[0475] Under nitrogen, a solution of 5-bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)aniline (23.9 g, 55.5 mmol) and NIS (14.9 g, 66.5 mmol) in acetic acid (150 mL) was stirred at room temperature for 1.5 hours. The reaction was quenched with aq. $Na_2S_2O_3$ (15 mL), diluted with EtOAc (300 mL) and washed with water (250 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-22% EtOAc / petroleum ether) to yield 16.7 g (54.0 % yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 556.

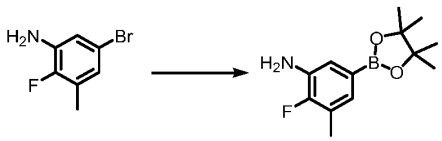
[0476] Step 3: 5-Bromo-2-fluoro-*N*, *N*-bis(4-methoxybenzyl)-4-(trifluoromethyl)aniline

[0477] Under nitrogen, a solution of 5-bromo-2-fluoro-4-iodo-*N*, *N*-bis(4-methoxybenzyl)aniline (1.01 g, 1.82 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (3.46 g, 18.0 mmol) and CuI (3.42 g, 18.0 mmol) in DMF (10 mL) was stirred at 90°C for 24 hours. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (35 mL* 4). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-85% ACN in water (0.05% NH_4HCO_3)) to afford 460 mg (51.3% yield) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$= 498.

[0478] Step 4: 2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline

[0479] Under nitrogen, a solution of 5-bromo-2-fluoro-*N*, *N*-bis[(4-methoxyphenyl)methyl]-4-(trifluoromethyl)aniline (321 mg, 0.640 mmol), Pin_2B_2 (327 mg, 1.29 mmol), $Pd(dppf)Cl_2$ (99.1 mg, 0.131 mmol) and KOAc (189 mg, 1.93 mmol) in 1,4-dioxane (2 mL) was stirred for 1 h at 110°C. Then the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-12% EtOAc / petroleum ether) to afford 160 mg (45.5% yield) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$= 546.

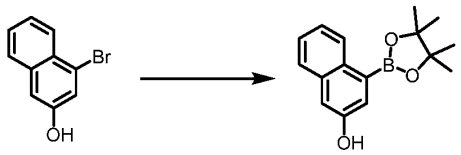
[0480] **Intermediate 23:** 2-Fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[0481] Under nitrogen, a solution of 5-bromo-2-fluoro-3-methyl-aniline (101 mg, 0.493 mmol), Pin_2B_2 (253 mg, 0.996 mmol), KOAc (145 mg, 1.48 mmol) and $Pd(dppf)Cl_2$ (38.4 mg, 0.0500 mmol) in 1,4-dioxane (3 mL) was stirred for 3 hours at 110°C. The reaction mixture was

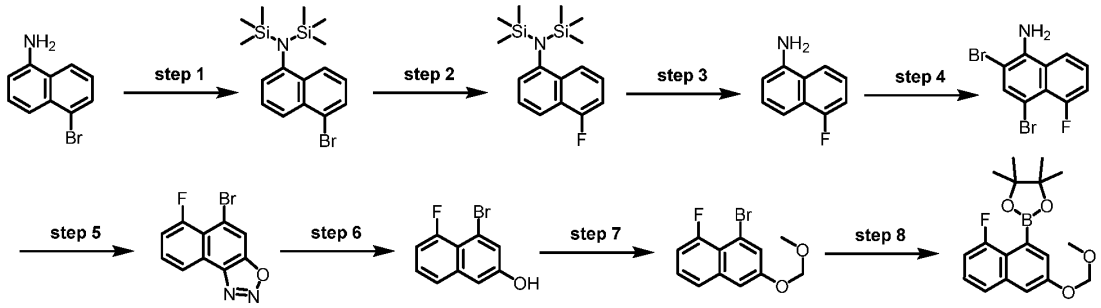
diluted with H_2O (20 mL), extracted with EtOAc (2 *10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0-8%) to yield 184 mg (crude, contain some Pin_2B_2) of the title compound as a yellow oil which was used for next step without further purification. LC-MS: (ESI, *m/z*): $[M+H]^+$= 251.

[0482] **Intermediate 24:** 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol



[0483] Under nitrogen, a solution of 4-bromonaphthalen-2-ol (400 mg, 1.79 mmol), Pin_2B_2 (911 mg, 3.59 mmol), $Pd(dppf)Cl_2$ (275 mg, 0.360 mmol) and KOAc (527 mg, 5.38 mmol) in 1,4-dioxane (2 mL) was stirred for 2 h at 110°C. Then the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-15% EtOAc/petroleum ether) to afford 335 mg (92% yield) of the title compound as white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 271. ^1H NMR (300 MHz, DMSO-d_6, ppm): δ 9.66 (s, 1H), 8.49 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 9 Hz, 1H), 7.5 (d, J = 3 Hz, 1H), 7.42-7.24 (m, 3H), 1.38 (s, 12H).

[0484] **Intermediate 25:** 2-(8-Fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0485] Step 1: *N*-(5-Bromonaphthalen-1-yl)-1,1,1-trimethyl-*N*-(trimethylsilyl)silanamine

[0486] Under nitrogen, to a solution of 5-bromonaphthalen-1-amine (45.3 g, 204 mmol) in THF (500 mL) was added LiHMDS (451 mL, 1M in THF) at -78°C and stirred at 20°C for 3 h. Then the solution cooled back to -78°C. TMSCl (48.7 g, 448 mmol) was added at -78°C. The mixture was warmed naturally to 20°C and stirred at 20°C for 3 h. Then the mixture was concentrated under vacuum. The residue was treated with hexane. The solid was filtered off. The filtrate was concentrated under vacuum to afford 87.1 g (crude) of the title compound as a red oil which was used for next step without further purification. LC-MS: (ESI, m/z): [M+H]+ = 443. ^1H-NMR (300 MHz, $CDCl_3$, ppm) δ 8.21 – 8.16 (m, 1H), 7.97 – 7.84 (m, 2H), 7.63 – 7.55 (m, 1H), 7.49 – 7.41 (m, 1H), 7.22 – 7.17 (m, 1H), 0.04 (s, 21H).

[0487] Step 2: *N*-(5-Fluoronaphthalen-1-yl)-1,1,1-trimethyl-*N*-(trimethylsilyl)silanamine

[0488] Under nitrogen, to a solution of *N*-(5-bromonaphthalen-1-yl)-1,1,1-trimethyl-*N*-(trimethylsilyl)silanamine (87.2 g, 238 mmol) in THF (800 mL) was added n-BuLi (148 mL, 2.5 M in n-hexane) at -78 °C and stirred for 20 min at -78 °C. Then *N*-Fluoro-*N*-(phenylsulfonyl) benzenesulfonamide (121 g, 382 mmol) was added at this temperature. The reaction mixture was warmed naturally to room temperature and stirred at this temperature for 1 h. The reaction mixture was diluted with water (300 mL) and extracted with EtOAc (500 mL*3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 100% petroleum ether) to afford 45.1 g (62.1%) of the title compound as a light red syrup. LC-MS: (ESI, m/z): $[M+H]^+$ = 203.

[0489] Step 3: 5-Fluoronaphthalen-1-amine

[0490] To a solution of *N*-(5-Fluoronaphthalen-1-yl)-1,1,1-trimethyl-*N*-(trimethylsilyl)silanamine (45.1 g, 148 mmol) in MeOH (300 mL) was added aqueous HCl (40 mL, 1 M) and stirred at room temperature for 10 min. Then the mixture was concentrated under vacuum. The resulting residue was purified by reverse phase chromatography (gradient: 0–65 % acetonitrile in water (0.1% TFA)) to afford 23.4 g (98.4% yield) of the title compound as a brown solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 162. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 7.69 – 7.55 (m, 2H), 7.47 – 7.26 (m, 2H), 7.20 – 7.11 (m, 1H), 6.88 – 6.83 (m, 1H), 4.20 (s, 2H).

[0491] Step 4: 2,4-Dibromo-5-fluoronaphthalen-1-amine

[0492] To a solution of 5-fluoronaphthalen-1-amine (10.0 g, 62.0 mmol) in HOAc (100 mL) was added a solution of bromine (21.4 g, 134 mmol) in HOAc (100 mL) at 0°C. Then the mixture was stirred at 70°C for 3 h. Cooled to room temperature. The solid was collected by fltration and washed with HOAc (300 mL). Then the solid was suspended in aqueous NaOH (15%, 200 mL) and stirred for 20 min. The solid was collected by filtration and washed with water (200 mL), dried under vacuum to afford 20.1 g (crude) of the title compound as a black solid which was used for next step without furhter purificaiton.. LC-MS: (ESI, m/z): $[M+H]^+$ = 318. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 7.85 (s, 1H), 7.65 – 7.59 (m, 1H), 7.51 – 7.39 (m, 1H), 7.32 – 7.22 (m, 1H), 4.67 (br s, 2H).

[0493] Step 5: 5-Bromo-6-fluoronaphtho[1,2-*d*][1,2,3]oxadiazole

[0494] To a solution of 2,4-dibromo-5-fluoronaphthalen-1-amine (18.0 g, 56.4 mmol) in propionic acid (45.0 mL, 603 mmol) and HOAc (360 mL) was added $NaNO_2$ (5.84 g, 84.6 mmol) at 0°C. Then the mixture was stirred at 0°C for 50 min, warmed to 20 °C and stirred for 1.5 h. The solid was collected by filtration, washed with water (200 mL) and dried under vacuum to afford 10.9 g (crude) of the title compound as a brown solid which was used for next step without

furhter purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 269. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 7.59 – 7.50 (m, 1H), 7.20 (s, 1H), 7.14 – 6.99 (m, 2H).

[0495] Step 6: 4-Bromo-5-fluoronaphthalen-2-ol

[0496] To a solution of 5-bromo-6-fluoronaphtho[1,2-*d*][1,2,3]oxadiazole (10.9 g, 40.8 mmol) in EtOH (150 mL) and THF (75 mL) was added $NaBH_4$ (3.15 g, 82.9 mmol) at 0°C. Then the mixture was stirred at room temperature for 1.5 h and quenched with $NaHSO_4$ (125 mL, 10% in water). A majority of EtOH was stripped off under vacuum. The residual reaction mixture was extracted with EtOAc (3*150 mL). The combined organic phases were washed with water (150 mL), brine (150 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0–55% EtOAc /petroleum ether) to afford 5.10 g (51.8% yield) of the title compound as a brown solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 241. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 7.56 – 7.43 (m, 2H), 7.42 – 7.33 (m, 1H), 7.22 – 7.02 (m, 2H).

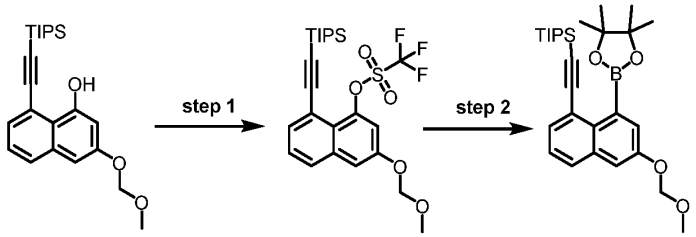
[0497] Step 7: 1-Bromo-8-fluoro-3-(methoxymethoxy)naphthalene

[0498] To a solution of 4-bromo-5-fluoronaphthalen-2-ol (4.11 g, 17.0mmol) in DCM (42.0 mL) was added MOMBr (3.82 g, 30.6 mmol) and DIPEA (5.52 g, 42.7 mmol) at 0°C. Stirred at 0°C for 0.5 h. The reaction mixture was diluted with water (50 mL) and extracted with DCM (3*50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0–15% EtOAc /petroleum ether) to afford 4.12 g (84.4% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 299. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 7.64 – 7.50 (m, 2H), 7.45 – 7.34 (m, 2H), 7.15 – 7.05 (m, 1H), 5.29 (s, 2H), 3.54 (s, 3H).

[0499] Step 8: 2-(8-Fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[0500] Under nitrogen, a solution of 1-bromo-8-fluoro-3-(methoxymethoxy)naphthalene (5.1 g, 17.9 mmol), Pin_2B_2 (11.4 g, 44.9 mmol), $Pd(dppf)Cl_2$ (1.38 g, 1.80 mmol) and KOAc (5.28 g, 53.8 mmol) in 1,4-dioxane (100 mL) was stired at 110°C for 4 h. Cooled to room temperature. The resulting reaction mixture was partitioned between water and EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0–25% EtOAc /petroleum ether) to afford 7.60 g (contain 45% Pin_2B_2) of the title compound as a white solid which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 333. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 7.54 – 7.49 (m, 1H), 7.45 – 7.24 (m, 3H), 7.07 – 6.99 (m, 1H), 5.31 (s, 2H), 3.52 (s, 3H), 1.46 (s, 12H).

[0501] **Intermediate 26:** Triisopropyl((6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane



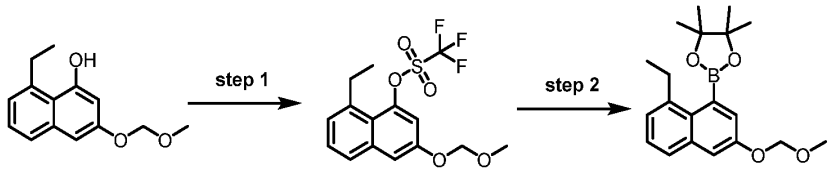
[0502] Step 1: 3-(Methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate

[0503] To a solution of 3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (1.00 g, 2.60 mmol) and *N*-(4-chlorophenyl)-1,1,1-trifluoro-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (1.23 g, 3.13 mmol) in THF (10 mL) was added NaH (114.6 mg, 2.86 mmol, 60% in oil) at 0°C. The reaction mixture was stirred at room temperature for 1 h. The resulting reaction mixture was diluted with water (30 mL) and extracted with EtOAc (150 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-15% EtOAc/ petroleum ether) to afford the title compound (1.41 g, 92.7% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 580. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 7.81 – 7.70 (m, 2H), 7.51 – 7.39 (m, 2H), 7.35 – 7.31 (m, 1H), 5.31 (s, 2H), 3.54 (s, 3H), 1.27 – 1.13 (m, 21H).

[0504] Step 2: Triisopropyl((6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane

[0505] Under nitrogen, a solution of 3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (1.12 g, 2.17mmol), Pin_2B_2 (1.65 g, 6.50 mmol), $Pd(dppf)Cl_2$ (166.7 mg, 0.22 mmol) and KOAc (745 mg, 7.59 mmol) in toluene (11 mL) was stirred at 110°C overnight. The mixture was partitioned between EtOAc and water. The organic phase was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% EtOAc/ petroleum ether) to afford 833 mg (77.7% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 558. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 7.76 – 7.66 (m, 2H), 7.49 (d, J = 2.6 Hz, 1H), 7.42 – 7.32 (m, 2H), 5.30 (s, 2H), 3.52 (s, 3H), 1.45 (s, 12H), 1.23 – 1.15 (m, 21H).

[0506] **Intermediate 27:** 2-(8-Ethyl-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



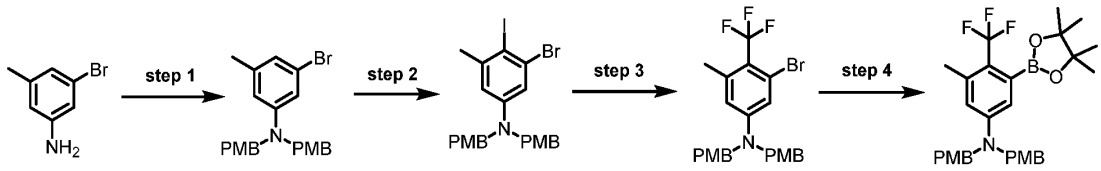
[0507] Step 1: 8-Ethyl-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate

[0508] Under nitrogen, to a solution of 8-ethyl-3-(methoxymethoxy)naphthalen-1-ol (1.00 g, 4.31 mmol) in DCM (15 mL) was added DIPEA (2.22 g, 17.2 mmol) and Tf_2O (1.82 g, 6.45 mmol) at -40°C. The resulting solutinon was stirred at -40°C for 1 h and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-15% EtOAc /petroleum ether) to afford 1.41 g (89.3% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): [M+H]+ = 365. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 7.69 –7.63 (m, 1H), 7.50 – 7.39 (m, 2H), 7.37 – 7.25 (m, 2H), 5.32 (s, 2H), 3.55 (s, 3H), 3.32 – 3.22 (m, 2H), 1.35 – 1.28 (m, 3H).

[0509] Step 2: 2-(8-Ethyl-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[0510] Under nitrogen, a solution of 8-ethyl-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (1.41 g, 3.87mmol), Pin_2B_2 (2.95 g, 11.6 mmol), $Pd(dppf)Cl_2$ (298 mg, 0.390 mmol) and KOAc (949 mg, 9.67 mmol) in 1,4-dioxane (15mL) was stirred at 110 °C overnight. The mixture was partitioned between EtOAc and water. The organic phase was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-15% EtOAc /petroleum ether) to afford 872 mg (65.8% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): [M+H]+ = 343. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 7.65 – 7.58 (m, 1H), 7.46 – 7.34 (m, 3H), 7.30 – 7.25 (m, 1H), 5.31 (s, 2H), 3.53 (s, 3H), 3.26 – 3.16 (m, 2H), 1.46 (s, 12H), 1.42 – 1.34 (m, 3H).

[0511] **Intermediate 28:** *N*,*N*-bis(4-Methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline



[0512] Step 1: 3-Bromo-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline

[0513] Under nitrogen, to a solution of 3-bromo-5-methyl-aniline (500 mg, 2.69 mmol) in DMF (5 mL) was added NaH (324 mg, 8.10 mmol, 60% in mineral oil) at 0°C. Stirred for 0.5 hours. Then PMBCl (1.05g, 6.69 mmol) was added and stirred at room temperature for 12 hours. The reaction was quenched with NH_4Cl solution and extracted with EtOAc. The combined

organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% ethyl acetate/petroleum ether) to afford the title compound (441 mg, 87.8% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 426/428.

[0514] Step 2: 3-Bromo-4-iodo-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline

[0515] To a solution of 3-bromo-N,N-bis[(4-methoxyphenyl)methyl]-5-methyl-aniline (2.00 g, 4.69 mmol) in DMF (20 mL) was added NIS (1.58 g, 7.03 mmol) and TsOH (96.0 mg, 0.560 mmol) in portions at room temperature. The resulting solution was stirred at room temperature for 20 min and then quenched with $Na_2S_2O_3$ aqueous solution. The solution was extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-18% ethyl acetate/petroleum ether) to afford the title compound (1.58 g, 50.6% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 552/554.

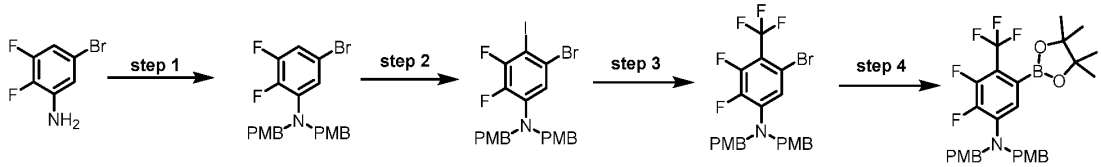
[0516] Step 3: 3-Bromo-*N*,*N*-bis(4-methoxybenzyl)-5-methyl-4-(trifluoromethyl)aniline

[0517] Under nitrogen, a solution of 3-bromo-4-iodo-N,N-bis[(4-methoxyphenyl)methyl]-5-methyl-aniline (1.58 g, 2.86 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (1.82 mL, 14.3 mmol) and CuI (547 mg, 2.86 mmol) in DMF (15 mL) was stirred at 90°C for 1 hour. The reaction mixture was partitioned between EtOAc and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% ethyl acetate/petroleum ether) to afford the title compound (695 mg, 43.2% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 494/496.

[0518] Step 4: *N*,*N*-Bis(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl) aniline

[0519] Under nitrogen, a solution of 3-bromo-N,N-bis[(4-methoxyphenyl)methyl]-5-methyl-4-(trifluoromethyl)aniline (100 mg, 0.2mmol), Pin_2B_2 (153.6 mg, 0.600 mmol), $PdCl_2$(dppf) (15.0 mg, 0.0200 mmol) and KOAc (59.3 mg, 0.610 mmol) in 1,4-dioxane (10 mL) was stirred at 100°C for 3 hours. Then the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% ethyl acetate/petroleum ether) to afford the title compound (33.0 mg, 22.7% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 542.

[0520] **Intermediate 29:** 2,3-Difluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline



[0521] Step 1: 5-Bromo-2,3-difluoro-*N,N*-bis(4-methoxybenzyl)aniline

[0522] Under nitrogen, to a solution of 5-bromo-2,3-difluoro-aniline (500 mg, 2.40 mmol) in DMF (10 mL) was added NaH (384 mg, 9.6 mmol, 60% in mineral oil) at 0°C, and the mixture was stirred at room temperature for 1 hour. Then PMBCl (1.13g, 7.21 mmol) was added and stirred at room temperature for 4 hours. The reaction was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-5% ethyl acetate/petroleum ether) to afford the title compound (900 mg, 84.6% yield) as an oil. LC-MS: (ESI, m/z): $[M+H]^+ = 448$.

[0523] Step 2: 5-Bromo-2,3-difluoro-4-iodo-*N,N*-bis(4-methoxybenzyl)aniline

[0524] A solution of 5-bromo-2,3-difluoro-N,N-bis[(4-methoxyphenyl)methyl]aniline (900 mg, 2.01 mmol) and NIS (676 mg, 3.02 mmol) in acetic acid (10 mL) was stirred at room temperature for 2 hours. Then the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-5% ethyl acetate/petroleum ether) to afford the title compound (800 mg, 69.4% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 574$.

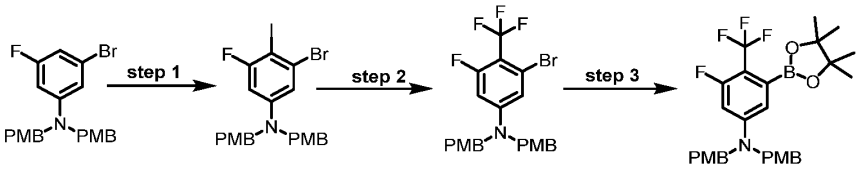
[0525] Step 3: 5-Bromo-2,3-difluoro-*N,N*-bis(4-methoxybenzyl)-4-(trifluoromethyl)aniline

[0526] Under nitrogen, to a solution of 5-bromo-2,3-difluoro-4-iodo-N,N-bis[(4-methoxyphenyl)methyl]aniline (900 mg, 1.57 mmol) and methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (1.50 g, 7.85 mmol) in DMA (9 mL) was added CuI (300 mg, 1.57 mmol) at room temperature. The reaction was stirred at 90°C for 4 hours. The reaction mixture was partitioned between water and EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% ethyl acetate/petroleum ether) to afford the title compound (600 mg, 74.1% yield) as brown oil. LC-MS: (ESI, m/z): $[M+H]^+ = 516$.

[0527] Step 4: 2,3-Difluoro-*N,N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline

[0528] Under nitrogen, a solution of 5-bromo-2,3-difluoro-N,N-bis[(4-methoxyphenyl)methyl]-4-(trifluoromethyl)aniline (500 mg, 0.970 mmol), Pin_2B_2 (739 mg, 2.91 mmol), $PdCl_2$(dppf) (71.0 mg, 0.100 mmol) and KOAc (285 mg, 2.91 mmol) in 1,4-dioxane (5 mL) was stirred at 100°C for 4 hours. The reaction was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% ethyl acetate/petroleum ether) to afford the title compound (260 mg, 47.7% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 564$.

[0529] **Intermediate 30:** 3-Fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline



[0530] Step 1: 3-Bromo-5-fluoro-4-iodo-*N*,*N*-bis(4-methoxybenzyl)aniline

[0531] To a solution of 3-bromo-5-fluoro-N,N-bis[(4-methoxyphenyl)methyl]aniline (600 mg, 1.39 mmol) and NIS (484 mg, 2.16 mmol) in DMF (5 mL) was added TsOH (29.0 mg, 0.170 mmol). The resulting mixture was stirred for 1 hour at room temperature. The reaction was quenched with $Na_2S_2O_3$ aqueous solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-25% ethyl acetate / petroleum ether) to yield 200 mg (25.5% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 556$.

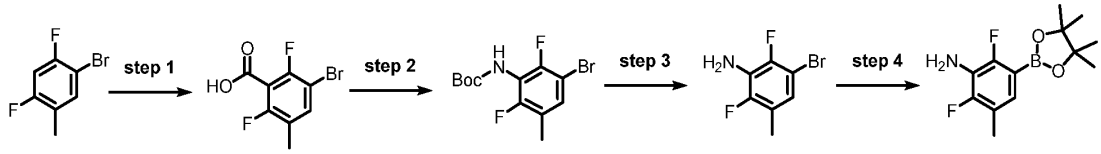
[0532] Step 2: 3-Bromo-5-fluoro-*N*,*N*-bis(4-methoxybenzyl)-4-(trifluoromethyl)aniline

[0533] Under nitrogen, to a solution of 3-bromo-5-fluoro-4-iodo-N,N-bis[(4-methoxyphenyl) methyl] aniline (100 mg, 0.180 mmol) and CuI (46.0 mg, 0.240 mmol) in DMF (1 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.16 mL, 1.19 mmol) at room temperature. The resulting solution was stirred at 90°C for 2 hours. The reaction mixture was diluted with EtOAc and washed with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-25% ethyl acetate / petroleum ether) to yield 125 mg (crude) of the title compound as a light yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 498$.

[0534] Step 3: 3-Fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline

[0535] Under nitrogen, a solution of 3-bromo-5-fluoro-N,N-bis[(4-methoxyphenyl)methyl]-4-(trifluoromethyl)aniline (129 mg, 0.260 mmol), $PdCl_2$(dppf) (19.0 mg, 0.0300 mmol), KOAc (76.0 mg, 0.780 mmol) and Pin_2B_2 (198 mg, 0.780 mmol) in 1,4-dioxane (2 mL) was stirred at 110°C overnight. The resulting solution was diluted with EtOAc and washed with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase chromatography (solvent gradient: 0-60% ACN in water (0.05% NH_4HCO_3)) to yield 50 mg (35.4% yield) of the title compound as a colorless oil. LC-MS: (ESI, m/z): $[M+H]^+ = 546$.

[0536] **Intermediate 31:** 2,6-Difluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[0537] Step 1: 3-Bromo-2,6-difluoro-5-methylbenzoic acid

[0538] Under nitrogen, to a stirred solution of 1-bromo-2,4-difluoro-5-methylbenzene (1.00 g, 4.83 mmol) in THF (25 mL) was added LDA (3.14 mL, 6.28 mmol, 2 mol/L in THF) at -85°C. The solution was stirred for 2 h at -85°C. Then the reaction mixture was poured into a solution of dry ice (250 g) in THF (25 mL). The resulting solution was stirred at room temperature for 1 h. The reaction was quenched with NH_4Cl solution (100 mL). THF was stripped off under reduced pressure and the residual solution was acidified to pH=1 with 1 mol/L HCl solution. The solids were collected by filtration and washed with H_2O to afford the titled compound (980 mg, 80.8% yield) as a yellow solid. ^1H NMR (300 MHz, DMSO-d_6) δ 14.14 (s, 1H), 7.90 – 7.77 (m, 1H), 2.23 (s, 3H).

[0539] Step 2: *tert*-Butyl (3-bromo-2,6-difluoro-5-methylphenyl)carbamate

[0540] A solution of 3-bromo-2,6-difluoro-5-methyl-benzoic acid (2.00 g, 7.97 mmol), diphenyl azidophosphate (3.28 g, 11.9 mmol) and triethylamine (1.62 g, 16.0 mmol) in 2-methyl-2-propanol (50 mL) was stirred overnight at 90°C, then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-10% EtOAc / petroleum ether) to afford (2.00 g, 77.9% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M-H]^+ = 320$.

[0541] Step 3: 3-Bromo-2,6-difluoro-5-methylaniline

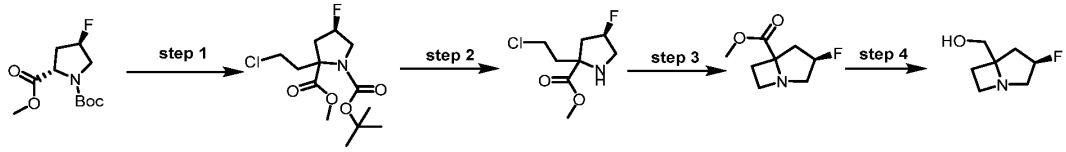
[0542] A solution of *tert*-butyl N-(3-bromo-2,6-difluoro-5-methyl-phenyl) carbamate (2.00 g, 6.21 mmol) and HCl (30 mL, 4 mol/L in dioxane) in dichloromethane (30 mL) was stirred for 5 h at room temperature. Then the mixture was concentrated under reduced pressure. The residue was partitioned between saturated $NaHCO_3$ (aq.) and EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc / petroleum ether) to afford (1 g, 77.9% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+1+MeCN]^+ = 263$.

[0543] Step 4: 2,6-Difluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0544] Under nitrogen, to a stirred solution of 3-bromo-2,6-difluoro-5-methyl-aniline (300 mg, 1.35 mmol) in 1,2-dimethoxyethane (DME) (10 mL) was added Pin_2B_2 (515 mg, 2.03 mmol), $Pd(dppf)Cl_2$ (98.9 mg, 0.140 mmol) and KOAc (265 mg, 2.70 mmol) at room

temperature. The resulting solution was stirred overnight at 90°C. Then the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc / petroleum ether) to afford (310 mg, 85.3% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+1+MeCN]^+ = 311$.

[0545] **Intermediate 32:** ((3*S*)-3-Fluoro-1-azabicyclo[3.2.0]heptan-5-yl)methanol



[0546] Step 1: 1-(*tert*-Butyl) 2-methyl (4*R*)-2-(2-chloroethyl)-4-fluoropyrrolidine-1,2-dicarboxylate

[0547] Under nitrogen, to a solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-fluoropyrrolidine-1,2-dicarboxylate (5.00 g, 20.2 mmol) and HMPA (10.9 g, 60.9 mmol) in tetrahydrofuran (70 mL) was added LiHMDS in THF (60.7 mL, 60.7 mmol, 1 M) at -78 °C. The resulting solution was stirred at -78 °C for 1 h. Then 1-bromo-2-chloroethane (8.36 mL, 100 mmol) was added. The resulting solution was stirred at room temperature for 1 h. The mixture was quenched with NH_4Cl (aq.), extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residual was purified by flash chromatography on silica gel (gradient: 0%-100% EtOAc/petroleum ether) to yield 1.26 g (20.1% yield) of the title compound as a colorless oil. LC-MS: (ESI, m/z): $[M+H]^+ = 310$.

[0548] Step 2: Methyl (4*R*)-2-(2-chloroethyl)-4-fluoropyrrolidine-2-carboxylate

[0549] To a solution of 1-(*tert*-Butyl) 2-methyl (4*R*)-2-(2-chloroethyl)-4-fluoropyrrolidine-1,2-dicarboxylate (1.26 g, 3.87 mmol) in dichloromethane (10 mL) was added TFA (5 mL). The resulting solution was stirred at room temperature for 30 min. Solvent was evaporated under vacuum to yield 2 g (crude) of the title compound as a yellow oil which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 210$.

[0550] Step 3: Methyl (3*S*)-3-fluoro-1-azabicyclo[3.2.0]heptane-5-carboxylate

[0551] A solution of methyl (4*R*)-2-(2-chloroethyl)-4-fluoropyrrolidine-2-carboxylate (2.00 g, 3.82 mmol) and K_2CO_3 (1.60 g, 11.6 mmol) in acetonitrile (30 mL) was stirred at 85 °C for 1 h. The solids were filtered off. The filtrate was concentrated under vacuum to yield 2.9 g (crude) of the title compound as a yellow oil which was used for next step without further purification. LC-MS: (ESI, *m/z*): $[M+H]^+ = 174$.

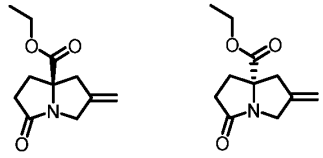
[0552] Step 4 : ((3*S*)-3-Fluoro-1-azabicyclo[3.2.0]heptan-5-yl)methanol

[0553] Under nitrogen, to a solution of methyl (3*S*)-3-fluoro-1-azabicyclo[3.2.0]heptane-5-carboxylate (2.90 g, 16.7 mmol) in tetrahydrofuran (20 mL) was added $LiAlH_4$ in THF (16.7 mL,

16.7 mmol, 1 M) at 0 °C. The resulting solution was stirred at 0 °C for 30 min. The mixture was quenched with $Na_2SO_4.10H_2O$ and filtrated. The solvent was removed by blowing N_2 (volatile) to yield 2 g (crude) as a yellow oil which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 146.

[0554] **Intermediate 33:** ((7a'S)-2,2-Difluorodihydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methanol.

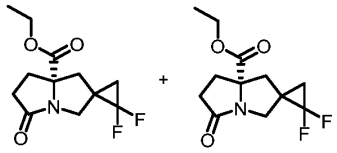
[0555] Step 1: Ethyl (*R*)-2-methylene-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate & Ethyl (*S*)-2-methylene-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate



the faster peak the slower peak

[0556] Ethyl 2-methylene-5-oxotetrahydro-1*H*-pyrrolizine-7a(5H)-carboxylate (19.9 g, was separated by Chiral SFC (Column: CHIRALPAK IH, 50*250 mm; Mobile Phase A: CO2, Mobile Phase B: EtOH; Flow rate: 150 mL/min; Gradient:26% B; 220 nm; RT1:4.8; RT2:6.43; Injection Volumn:1.8 ml; Number Of Runs: 122) to afford ethyl (*R*)-2-methylene-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (7.61 g, the faster peak) and ethyl (*S*)-2-methylene-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (7.29 g, the slower peak). LC-MS: (ESI, m/z): $[M+H]^+$ = 210. ^1H NMR (400 MHz, Chloroform-*d*) δ5.12 – 5.00 (m, 2H), 4.32-4.28 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.73 (d, *J* = 15.7 Hz, 1H), 3.06 (d, *J* = 15.7 Hz, 1H), 2.85-2.72 (m, 1H), 2.66-2.57 (m, 1H), 2.53 – 2.41 (m, 2H), 2.19-2.08 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). The HNMR of two isomers are the same.

[0557] Step 2: Ethyl (7*a*'*S*)-2,2-difluoro-5'-oxodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizine]-7a'(5'*H*)-carboxylate



the faster peak
desired isomer

the slower peak

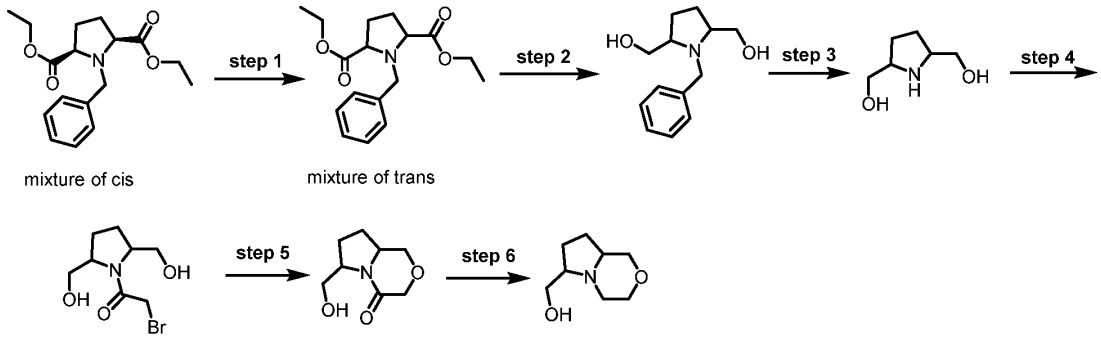
[0558] Under nitrogen, a solution of ethyl (*S*)-2-methylene-5-oxotetrahydro-1*H*-pyrrolizine-7*a*(5*H*)-carboxylate (200 mg, 0.960 mmol) and NaI (71.7 mg, 0.480 mmol) in THF (5 mL) was added $TMSCF_3$ (476 mg, 3.35 mmol) at room temperature. The resulting solution was stirred for 2.5 h at 65 °C. The solution was diluted with DCM, washed with sodium thiosulfate solution and dried over with Na_2SO_4. The organic layer was concentrated under vacuum. The residue was

purified by flash chromatography on silica gel (gradient: 0%-35% ethyl acetate/petroleum ether) to afford the faster peak 95.0 mg (38.3% yield) and (gradient: 35%-90% ethyl acetate /petroleum ether) to afford the slower peak 108 mg (43.6% yield) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 260.The faster peak: ^{1}H NMR (300 MHz, DMSO-d_6, *ppm*) δ 4.25-4.19 (m, 2H), 3.80 – 3.70 (m, 1H), 3.04 (d, J = 12.1, 3.5 Hz, 1H), 2.62-2.58 (m, 1H), 2.51 – 2.12 (m, 5H) , 1.60 (t, J = 9.3 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H). The slower peak: ^{1}H NMR (300 MHz, DMSO-d_6, *ppm*) δ 4.24 – 4.08 (m, 2H), 3.61 (d, J = 11.7, 2.7 Hz, 1H), 3.11 (d, J = 11.6 Hz, 1H), 2.72 – 2.54 (m, 1H), 2.44 – 2.13 (m, 5H), 1.79-1.58 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H).

[0559] Step 2: ((7*a'S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7*a*'(5'*H*)-yl)methanol

[0560] Under nitrogen, to a solution of ethyl (7*a'S*)-2,2-difluoro-5'-oxodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizine]-7a'(5'*H*)-carboxylate (95.0 mg, 0.370 mmol, the faster peak of previous step) in THF (2.5 mL) was added $LiAlH_4$ (1.1 mL, 1 M in THF). The solution was stirred at 65 °C for 1 hour. The reaction was cooled to room temperature and quenched with Na_2SO_4•$10H_2O$. After filtration, the filtrate was concentrated under reduced pressure to afford 42.0 mg (56.4% yield) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 204.

[0561] **Intermediate 34**: (Hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)methanol (mixture of trans)



[0562] Step 1: Diethyl 1-benzylpyrrolidine-2,5-dicarboxylate (mixture of trans)

[0563] To a solution of diethyl *cis*-1-benzylpyrrolidine-2,5-dicarboxylate (8.60 g, 28.2 mmol) in tetrahydrofuran (120 mL) was added LiHMDS (43.4 mL, 56.4 mmol) at -35 °C. After 1 h, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0–15% ethyl acetate / petroleum ether) to afford 1.27 g (14% yield) of the title compound as a light yellow oil. The *cis*-isomer was recovered (6.3 g). LC-MS: (ESI, m/z):

$[M+H]^+$ = 306.2. ^{1}H NMR (300 MHz, DMSO-d_6, *ppm*) δ 7.32 – 7.20 (m, 5H), 4.13 – 3.87 (m, 6H), 3.75 – 3.60 (m, 3H), 2.25 – 2.11 (m, 2H), 1.91 – 1.75 (m, 2H), 1.25 – 1.06 (m, 3H).

[0564] Step 2: (1-Benzylpyrrolidine-2,5-diyl)dimethanol (mixture of trans)

[0565] To an ice-cooled solution of diethyl *trans*-1-benzylpyrrolidine-2,5-dicarboxylate (2.30 g, 7.53 mmol) in tetrahydrofuran (30 mL) under nitrogen was added $LiAlH_4$ (716 mg, 18.8 mmol) in several portions. The reaction was warmed to room temperature. After 2 h, the mixture was quenched with Na_2SO_4•$10H_2O$. The solid was filtered, and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0–10% MeOH / DCM) to yield 1.65 g (99% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 222.1. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 7.38 – 7.15 (m, 5H), 4.34 (s, 2H), 3.95 – 3.82 (m, 2H), 3.46 – 3.36 (m, 2H), 3.28 – 3.20 (m, 2H), 3.01 – 2.90 (m, 2H), 1.90 – 1.75 (m, 2H), 1.71 – 1.58 (m, 2H).

[0566] Step 3: Pyrrolidine-2,5-diyldimethanol (mixture of trans)

[0567] Under hydrogen (1 atm), a solution of (1-benzylpyrrolidine-2,5-diyl)dimethanol (0.60 g, 2.7 mmol) and Pd / C (180 mg, 10% w/w) in methyl alcohol (10 mL) was stirred at room temperature for 2 h. The catalyst was filtered, and the filtrate was concentrated to afford 405 mg (crude) of the title compound as a light yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 132.1. The crude product was used without further purification.

[0568] Step 4: 1-(2,5-Bis(hydroxymethyl)pyrrolidin-1-yl)-2-bromoethan-1-one (mixture of trans)

[0569] To an ice-cooled solution of pyrrolidine-2,5-diyldimethanol (355 mg, 2.71 mmol) and *N*-methyl morpholine (410 mg, 4.06 mmol) in tetrahydrofuran (10 mL) was added 2-bromoacetyl bromide (539 mg, 2.67 mmol). After 1 h, the reaction was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0–10% MeOH/DCM) to yield 130 mg (19% yield) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 252.1. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 5.03 (s, 1H), 4.71 (s, 1H), 4.24 (d, J = 11.4 Hz, 1H), 4.09 – 3.99 (m, 1H), 3.92 – 3.87 (m, 2H), 3.69 (s, 2H), 3.17 (s, 2H), 2.04 – 1.72 (m, 4H).

[0570] Step 5 : 6-(Hydroxymethyl)tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-4(3*H*)-one (mixture of trans)

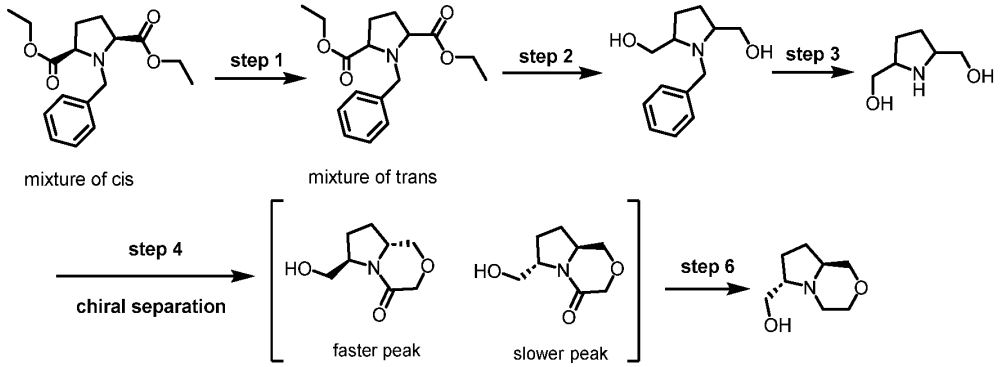
[0571] To an ice-cooled suspension of NaH (65.0 mg, 1.63 mmol, 60% in mineral oil) in tetrahydrofuran (5 mL) was added 1-(2,5-bis(hydroxymethyl)pyrrolidin-1-yl)-2-bromoethan-1-one (130 mg, 0.517 mmol) in 1 mL THF. After 1 h, the resulting solution was warmed to room temperature for 3 h. The reaction was diluted with water and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0–10% MeOH / DCM) to yield the title compound as an oil (37.0 mg, 42% yield). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 172.2. ^{1}H

NMR (400 MHz, DMSO-d_6, *ppm*) δ 4.88 – 4.82 (m, 1H), 4.14 – 3.97 (m, 3H), 3.84 (d, J = 16 Hz, 1H), 3.71 – 3.61 (m, 1H), 3.59 – 3.48 (m, 2H), 3.23 – 3.15 (m, 1H), 2.03 – 1.87 (m, 2H), 1.82 – 1.66 (m, 1H), 1.39 – 1.19 (m, 1H).

[0572] Step 6 : (Hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methanol (mixture of trans)

[0573] To an ice-cooled suspension of $LiAlH_4$ (27.3 mg, 0.720 mmol) in tetrahydrofuran (5 mL) under nitrogen was added 6-(hydroxymethyl)tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-4(3*H*)-one (60.0 mg, 0.350 mmol) in 0.5 mL THF. The resulting solution warmed to 60 °C for 2 h. The reaction was cooled to room temperature and quenched with Na_2SO_4•$10H_2O$. The solid was filtered, and the filtrate was concentrated to yield the title compound as a light yellow oil (60 mg, crude). LC-MS: (ESI, *m/z*): $[M+H]^+$= 158.1. The crude product was used for next step without further purification.

[0574] **Intermediate 34A**: ((6*S*,8a*S*)-Hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methanol



[0575] Step 1: Diethyl 1-benzylpyrrolidine-2,5-dicarboxylate (mixture of trans)

[0576] To a solution of diethyl *cis*-1-benzylpyrrolidine-2,5-dicarboxylate (8.60 g, 28.2 mmol) in tetrahydrofuran (120 mL) was added LiHMDS (43.4 mL, 56.4 mmol) at -35 °C. After 1 h, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0–15% ethyl acetate / petroleum ether) to afford 1.27 g (14% yield) of the title compound as a light yellow oil. The *cis*-isomer was recovered (6.3 g). LC-MS: (ESI, m/z): $[M+H]^+$ = 306.2. ^{1}H NMR (300 MHz, DMSO-d_6, *ppm*) δ 7.32 – 7.20 (m, 5H), 4.13 – 3.87 (m, 6H), 3.75 – 3.60 (m, 3H), 2.25 – 2.11 (m, 2H), 1.91 – 1.75 (m, 2H), 1.25 – 1.06 (m, 3H).

[0577] Step 2: (1-Benzylpyrrolidine-2,5-diyl)dimethanol (mixture of trans)

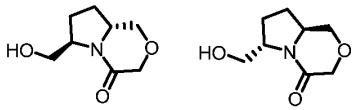
[0578] To an ice-cooled solution of diethyl *trans*-1-benzylpyrrolidine-2,5-dicarboxylate (2.30 g, 7.53 mmol) in tetrahydrofuran (30 mL) under nitrogen was added $LiAlH_4$ (716 mg, 18.8 mmol) in several portions. The reaction was warmed to room temperature. After 2 h, the mixture was quenched with Na_2SO_4•$10H_2O$. The solid was filtered, and the filtrate was concentrated under

vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0–10% MeOH / DCM) to yield 1.65 g (99% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 222.1. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 7.38 – 7.15 (m, 5H), 4.34 (s, 2H), 3.95 – 3.82 (m, 2H), 3.46 – 3.36 (m, 2H), 3.28 – 3.20 (m, 2H), 3.01 – 2.90 (m, 2H), 1.90 – 1.75 (m, 2H), 1.71 – 1.58 (m, 2H).

[0579] Step 3: Pyrrolidine-2,5-diyldimethanol (mixture of trans)

[0580] Under hydrogen (1 atm), a solution of (1-benzylpyrrolidine-2,5-diyl)dimethanol (0.60 g, 2.7 mmol) and Pd / C (180 mg, 10% w/w) in methanol (10 mL) was stirred at room temperature for 2 h. The catalyst was filtered, and the filtrate was concentrated to afford 405 mg (crude) of the title compound as a light yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 132.1. The crude product was used without further purification.

[0581] Step 4: (6*R*,8a*R*)-6-(Hydroxymethyl)tetrahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-4(3*H*)-one & (6*S*,8a*S*)-6-(hydroxymethyl)tetrahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-4(3*H*)-one



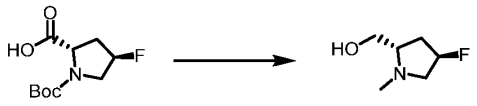
[0582] To a solution of pyrrolidine-2,5-diyldimethanol (7.9 g, 60.305 mmol) in IPA (300.0 mL) was added potassium trimethylsilanolate (16.98 g, 132.671 mmol) at 0 °C. Then 2-bromoacetyl bromide (13.27 g, 66.336 mmol) was added. The solution was stirred for 1 min at 0 °C. The reaction was quenched with MeOH (20 mL). The solids were filtered out and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% MeOH/dichloromethane) to yield 3.9 g (mixture of trans) of the title compound as a yellow oil. The enantiomers were separated by chiral SFC with the following conditions (Column, CHIRAL ART Amylose-SA, 3*25cm,5um; mobile phase, CO_2 (70%) and MeOH(0.1% 2 M NH_3-MeOH)(30%)) to afford the faster peak 1.98 g and the slower peak 1.9 g (desired isomer) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 172. H-NMR-PH-GNE-VINT-073-0: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.85 (t, J = 5.7 Hz, 1H), 4.14 - 3.99 (m, 3H), 3.84 (d, J = 16.5 Hz, 1H), 3.67 - 3.56 (m, 1H), 3.67 - 3.51 (m, 2H), 3.23 - 3.16 (m, 1H), 2.00 - 1.89 (m, 2H), 1.80 - 1.69 (m, 1H), 1.34 - 1.25 (m, 1H).

[0583] Step 5 : ((6*S*,8a*S*)-Hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methanol

[0584] To an ice-cooled suspension of $LiAlH_4$ (27.3 mg, 0.720 mmol) in tetrahydrofuran (5 mL) under nitrogen was added (6*S*,8a*S*)-6-(hydroxymethyl)tetrahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-4(3*H*)-one (60.0 mg, 0.350 mmol) in 0.5 mL THF. The resulting solution warmed to 60 °C for 2 h. The reaction was cooled to room temperature and quenched with

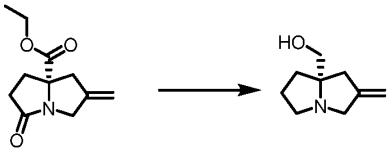
Na_2SO_4•$10H_2O$. The solid was filtered, and the filtrate was concentrated to yield the title compound as a light yellow oil (60 mg, crude). LC-MS: (ESI, *m/z*): $[M+H]^+$= 158.1. The crude product was used for next step without further purification.

[0585] **Intermediate 35:** ((2*S*,4*R*)-4-Fluoro-1-methylpyrrolidin-2-yl)methanol



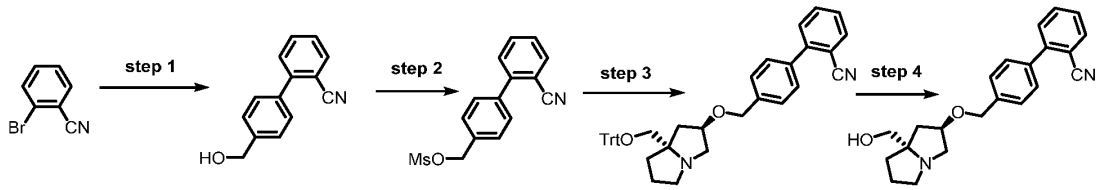
[0586] Under nitrogen, to a solution (2*S*,4*R*)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (60.0 g, 257 mmol) in tetrahydrofuran (1000 mL) was added $LiAlH_4$ (19.6 g, 515 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, and then stirred at 60 °C for 2 h. The reaction mixture was cooled over ice bath and water (20 mL) was slowly added to quench the reaction, followed 20% aqueous NaOH solution (20 mL) and 20 mL water. The solids were filtered off and filtrate was concentrated under vacuum. The residue was redissolved in DCM, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-15% MeOH in DCM (0.1% TEA)) to yield 12.4 g (36% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 134. ^1H NMR (300 MHz, DMSO-d_6, *ppm*) δ 5.25 – 4.97 (m, 1H), 4.44 (dd, *J* = 6.0, 5.0 Hz, 1H), 3.50 – 3.22 (m, 3H), 2.57-2.50 (m, 1H), 2.46 – 2.31 (m, 1H), 2.30 (s, 3H), 2.07-1.87 (m, 1H), 1.87-1.60 (m, 1H).

[0587] **Intermediate 36:** (*R*)-(2-Methylenetetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methanol and (*S*)-(2-Methylenetetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



[0588] Under nitrogen, to a solution of ethyl (*S*)-2-methylene-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (110 mg, 0.510 mmol, **intermediate 33, step 1**) in tetrahydrofuran (5 mL) was added $LiAlH_4$ (1.1 mL, 1M in THF) at 0 °C. The mixture was stirred for 0.5 hours at 70 °C. The mixture was quenched with $Na_2SO_4.10H_2O$ and filtered. The solvent was removed by blowing nitrogen (low boiling point for the product) to afford the title compound (62.8 mg, crude) which was used for the next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 154.

[0589] **Intermediate 37:** 4'-((((2*R*,7a*S*)-7a-(Hydroxymethyl) hexahydro-1*H*-pyrrolizin-2-yl)oxy)methyl)-[1,1'-biphenyl]-2-carbonitrile



[0590] Step 1: 4'-(Hydroxymethyl)-[1,1'-biphenyl]-2-carbonitrile

[0591] Under nitrogen, a solution of 2-bromobenzonitrile (1.25 g, 6.87 mmol), $Pd(PPh_3)_4$ (793 mg, 0.690 mmol), 4-(hydroxymethyl) phenylboronic acid (1.15 g, 7.55 mmol), K_2CO_3 (1.90 g, 13.8 mmol) and water (5 mL) in 1,2-dimethoxyethane (50 mL) was stirred for 12 hours at 100°C. The reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc / petroleum ether) to afford the title compound (1.26 g, 87.7% yield) as a yellow solid. ^1H NMR (300 MHz, DMSO-d_6) δ 8.00 – 7.90 (m, 1H), 7.85 – 7.75 (m, 1H), 7.69 – 7.51 (m, 6H), 5.75 (s, 1H), 4.69 (s, 2H).

[0592] Step 2: (2'-Cyano-[1,1'-biphenyl]-4-yl)methyl methanesulfonate

[0593] To a solution of 2-[4-(hydroxymethyl)phenyl]benzonitrile (235 mg, 1.12 mmol)] and *N*,*N*-diisopropylethylamine (0.58 mL, 3.36 mmol) in dichloromethane (10 mL) was added methanesulfonicanhydride (254 mg, 1.46 mmol) at 0°C under nitrogen. The resulting solution was stirred for 2 h at room temperature, diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound (320 mg, crude) as a yellow oil which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+Na]^+ = 310$.

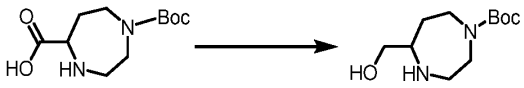
[0594] Step 3: 4'-((((2*R*,7a*S*)-7a-((Trityloxy)methyl)hexahydro-1*H*-pyrrolizin-2-yl)oxy)methyl)-[1,1'-biphenyl]-2-carbonitrile

[0595] Under nitrogen, to a solution of (2*R*,8*S*)-8-(trityloxymethyl)-1,2,3,5,6,7-hexahydropyrrolizin-2-ol (448 mg, 1.12 mmol) in tetrahydrofuran (4 mL) was added NaH (269 mg, 6.73 mmol, 60% in mineral oil) at 0°C. The resulting solution was stirred for 0.5 h at room temperature. Then [4-(2-cyanophenyl)phenyl]methyl methanesulfonate (322 mg, 1.12 mmol) in tetrahydrofuran (4 mL) was added at room temperature and stirred at 50°C for 12 hours. The reaction was quenched with saturated NH_4Cl solution (20 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc / petroleum ether) to afford (440 mg, 66.5% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 591$.

[0596] Step 4: 4'-((((2*R*,7a*S*)-7a-(Hydroxymethyl)hexahydro-1*H*-pyrrolizin-2-yl)oxy)methyl)-[1,1'-biphenyl]-2-carbonitrile

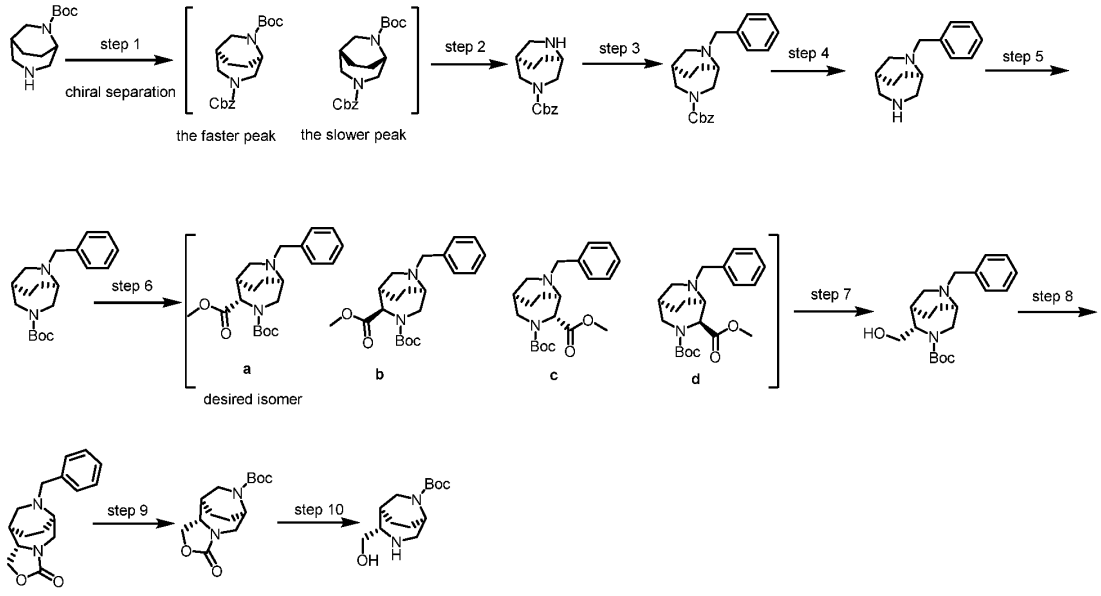
[0597] A solution of 4'-((((2*R*,7a*S*)-7a-((trityloxy)methyl)hexahydro-1*H*-pyrrolizin-2-yl)oxy)methyl)-[1,1'-biphenyl]-2-carbonitrile (440 mg, 0.740 mmol) in 2,2,2-trifluoroacetic acid (5 mL) was stirred for 1 h at room temperature, then concentrated under vacuum. The crude product was purified by reverse phase chromatography (gradient: 0-60 % acetonitrile in water (0.05% TFA)) to afford the title compound (220 mg, 84.8% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 349.

[0598] **Intermediate 38:** *tert*-Butyl 5-(hydroxymethyl)-1,4-diazepane-1-carboxylate



[0599] A solution of 1-tert-butoxycarbonyl-1,4-diazepane-5-carboxylic acid (200mg, 0.820mmol) and BH_3·THF (4.91 mL, 4.91mmol, 1 M in THF) in THF (5mL) was stirred at 40°C for 18 hours. The reaction system was quenched with MeOH and concentrated under vacuum to afford the title compound 130 mg (crude) as a yellow oil which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 231.

[0600] **Intermediate 39:** *tert*-Butyl (1*R*,2*S*,5*R*)-2-(hydroxymethyl)-3,6-diazabicyclo[3.2.2]nonane-6-carboxylate



[0601] Step 1: 3-Benzyl 6-(*tert*-butyl) (1*S*,5*R*)-3,6-diazabicyclo[3.2.2]nonane-3,6-dicarboxylate

[0602] Under nitrogen, a solution of *tert*-butyl 3,6-diazabicyclo[3.2.2]nonane-6-carboxylate (500 mg, 2.21 mmol), CbzCl (492 mg, 2.88 mmol) and DIPEA (1.42 g, 11.1 mmol) in

dichloromethane (10 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with DCM, washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-100% EtOAc/petroleum ether) to afford 800 mg of the title compound as a colorless oil. The two enantiomers were separated by Prep-SFC with the following conditions: (Column: CHIRALPAK IG, 3*25cm, 5μm ; Mobile Phase A:CO_2, Mobile Phase B:IPA(0.5% 2M NH_3-MeOH); Flow rate:70 mL/min; Gradient:30% B; Column Temperature: 35 °C; Back Pressure: 100 bar; 215 nm; RT1:6.86; RT2:7.89; Injection Volumn:1.5 ml; Number Of Runs:20) to yield 330 mg of faster peak and 340 mg slower peak as a white oil. The faster peak is the desired isomer. LC-MS: (ESI, m/z): $[M+H]^+$ = 361.

[0603] Step 2: Benzyl (1*R*,5*R*)-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate

[0604] A solution of 3-benzyl 6-(*tert*-butyl) (1*S*,5*R*)-3,6-diazabicyclo[3.2.2]nonane-3,6-dicarboxylate (10.0 g, 27.7 mmol) in dichloromethane (60mL) and 4 M HCl/dioxane (20 mL) was stirred at room temperature for 2 h. Then the mixture was concentrated under vacuum to yield 11.2 g (crude) of the title compound as a yellow solid which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ =261.

[0605] Step 3: Benzyl (1*R*,5*R*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate

[0606] A solution of benzyl (1*R*,5*R*)-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate (11.4 g, 43.7 mmol), benzyl bromide (8.99 g, 52.5 mmol) and DIPEA (11.3 g, 87.5 mmol) in *N*,*N*-dimethylformamide (50 mL) was stirred at 80°C for 3 hours. The reaction mixture was partitioned between EtOAc and water. The organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-40% EtOAc in petroleum ether) to afford 8.30 g of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 351

[0607] Step 4: (1*S*,5*R*)-6-Benzyl-3,6-diazabicyclo[3.2.2]nonane (2,2,2-trifluoroacetic acid salt)

[0608] A solution of benzyl (1*R*,5*R*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate (8.30 g, 23.6 mmol) in TFA (60 mL) was stirred at 70°C for 2 hours, then concentrated under vacuum to afford 5.80 g (crude) of the title compound as a yellow oil which was used for the next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 217.

[0609] Step 5: *tert*-Butyl (1*R*,5*R*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate

[0610] A solution of (1*S*,5*R*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane (2,2,2-trifluoroacetic acid salt) (5.80 g, crude), Boc_2O (8.60 g, 39.4 mmol) and DIPEA (10.3 g, 79.8 mmol) in dichloromethane (120 mL) was stirred at room temperature for 2 h, then concentrated under vacuum. The residue was purified by reverse phase chromatography (gradient: 0-100%

acetonitrile in water (0.05% NH_4HCO_3)) to afford 6.30 g of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 317$.

[0611] Step 6: 3-(*tert*-Butyl) 2-methyl (1*R*,2*S*,5*R*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-2,3-dicarboxylate

[0612] Under nitrogen, to a solution of *tert*-butyl (1*R*,5*R*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate (6.09 g, 19.2mmol) and TMEDA (2.72 g, 23.4mmol) in diethyl ether (46 mL) was added s-BuLi (18.8 mL, 1.3 M in hexanes) at -78°C. The resulting solution was stirred at -78°C for 1.5 h. Then methyl chloroformate (1.77 mL, 22.8mmol) in diethyl ether (4.5 mL) was added and stirred at room temperature for 2 hours. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc in petroleum ether) to yield two fractions: faster peak: 2.6 g (undesired regioisomer) and slower peak: 1.50 g (desired isomer, containing trace of endo isomers). LC-MS: (ESI, m/z): $[M+H]^+ = 375$.

[0613] Step 7: *tert*-Butyl (1*R*,2*S*,5*R*)-6-benzyl-2-(hydroxymethyl)-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate

[0614] Under nitrogen, to a solution of 3-(*tert*-butyl) 2-methyl (1*R*,2*S*,5*R*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-2,3-dicarboxylate (580 mg, 1.54 mmol, slower peak in the previous step) was added $LiAlH_4$ (3.2 mL, 1 M in THF) at 0°C. The resulting solution was stirred at 0°C for 2 h and quenched with $Na_2SO_4.10H_2O$. The solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-100% EtOAc in petroleum ether) to yield 520 mg of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 347$. ^1H NMR (400 MHz, DMSO-d_6) δ 7.37 – 7.16 (m, 5H), 4.59 (d, J = 42.8 Hz, 1H), 4.39 – 4.19 (m, 2H), 3.74 – 3.56 (m, 2H), 3.46 (dt, J = 28.9, 10.3 Hz, 2H), 2.84 (s, 1H), 2.78 – 2.61 (m, 3H), 2.21 (s, 1H), 1.89 (dq, J = 29.0, 15.0, 13.0 Hz, 2H), 1.46 (s, 11H).

[0615] Step 8: (6*R*,9*R*,9a*S*)-11-Benzylhexahydro-1*H*,3*H*-6,9-(epiminomethano)oxazolo[3,4-a]azepin-3-one

[0616] Under nitrogen, to a solution of *tert*-butyl (1*R*,2*S*,5*R*)-6-benzyl-2-(hydroxymethyl)-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate (480 mg, 1.39 mmol) in tetrahydrofuran (15 mL) was added NaH (112 mg, 2.82 mmol, 60% in mineral oil) at 0°C. The reaction was stirred at room temperature for 12 h. Aqueous NH_4Cl was added to quench the reaction. Then the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-60% EtOAc in petroleum ether) to yield 360 mg of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 273$.

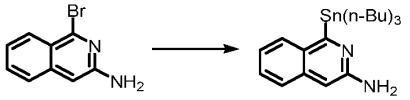
[0617] Step 9: *tert*-Butyl (6*R*,9*R*,9a*S*)-3-oxohexahydro-1H,3H-6,9-(epiminomethano)oxazolo[3,4-a]azepine-11-carboxylate

[0618] Under H_2 (3atm), a mixture of (6*R*,9*R*,9a*S*)-11-benzylhexahydro-1*H*,3*H*-6,9-(epiminomethano)oxazolo[3,4-a]azepin-3-one (330 mg, 1.20 mmol), 10% Pd/C (99.0 mg, dry) and Boc_2O (530 mg, 2.45 mmol) in methyl alcohol (70 mL) was stirred at room temperature for 1 hour. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (gradient: 0-100% EtOAc in petroleum ether) to yield 350 mg of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 283.

[0619] Step 10: *tert*-Butyl (1*R*,2*S*,5*R*)-2-(hydroxymethyl)-3,6-diazabicyclo[3.2.2]nonane-6-carboxylate

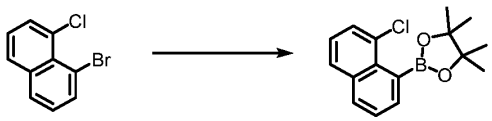
[0620] A solution of *tert*-butyl (6*R*,9*R*,9a*S*)-3-oxohexahydro-1*H*,3*H*-6,9-(epiminomethano)oxazolo[3,4-a]azepine-11-carboxylate (275 mg, 0.972 mmol) and NaOH (585 mg, 14.6 mmol) in ethanol (9 mL) and water (3 mL) was stirred at 80°C for 12 hours. Then the mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on pre-packed C18 column (gradient: 0-100% CH_3CN in water (0.05% NH_4HCO_3)) to yield 250 mg of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 257. ^1H NMR (300 MHz, DMSO-d_6) δ 4.60 (br, 1H), 3.91-4.08 (m, 1H), 3.40-3.01 (m, 4H), 3.00 – 2.90 (m, 1H), 2.60-2.45 (m, 2H), 2.00 (br, 1H), 1.95-1.85 (m, 1H), 1.80-1.55 (m, 3H), 1.35(s, 9H), 1.30-1.20 (m, 1H).

[0621] **Intermediate 40:** 1-(Tributylstannyl)isoquinolin-3-amine



[0622] Under nitrogen, a solution of 1-bromoisoquinolin-3-amine (100 mg, 0.450 mmol), $Sn_2(n\text{-}Bu)_6$ (286 mg, 0.500 mmol), $Pd_2(dba)_3$ (41.2 mg, 0.0500 mmol), PCy_3 (25.3 mg, 0.0900 mmol) and LiCl (94.6 mg, 2.25 mmol) in 1,4-dioxane (1.5 mL) was stirred at 115°C for 2 hours. Then the mixture was concentrated under vacuum. The residue was purified by flash chromatography on neutral alumina with EtOAc/petroleum ether (0-15%) to afford the title compound (107 mg, 54.8% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 435.

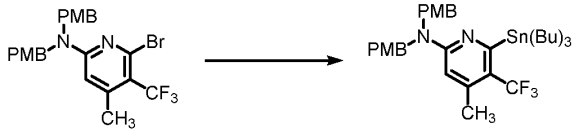
[0623] **Intermediate 41:** 2-(8-Chloronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0624] Under nitrogen, a solution of 1-bromo-8-chloronaphthalene (2.99 g, 12.4 mmol), Pin_2B_2 (4.71 g, 18.5 mmol), $PdCl_2$(dppf) (908 mg, 1.24 mmol) and KOAc (2.42 g, 24.7 mmol) in DMF (35 mL) was stirred at 80°C overnight. The reaction mixture was diluted with EtOAc (100

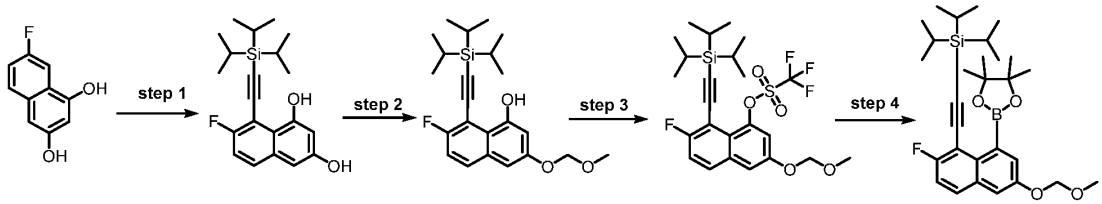
mL), washed with water (100 mL*4). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0 - 20 %) to the title compound (3.01 g, 84.2 % yield) as a yellow solid. ^{1}H-NMR (300 MHz, DMSO-d_6, *ppm*) δ 8.04 (dd, J = 7.5, 2.0 Hz, 1H), 7.96 (dd, J = 8.2, 1.3 Hz, 1H), 7.70 (dd, J = 7.5, 1.3 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.58 – 7.48 (m, 1H), 1.36 (s, 12H)

[0625] **Intermediate 42:** *N*,*N*-Bis(4-methoxybenzyl)-4-methyl-6-(tributylstannyl)-5-(trifluoromethyl)pyridin-2-amine

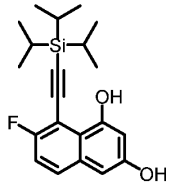


[0626] Under nitrogen, a solution of 6-bromo-*N*,*N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (1.51 g, 3.05 mmol), Sn_2(n-Bu)$_6$ (2.65 mg, 4.57 mmol), $Pd_2(dba)_3$ (279 mg, 0.300 mmol), PCy_3 (170 mg, 0.610 mmol) and LiCl (641 mg, 15.3 mmol) in 1,4-dioxane (15 mL) was stirred for 2 h at 110°C. The resulting reaction mixture was cooled to room temperature, diluted with water (35 mL) and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on neutral Al_2O_3 eluting with EtOAc/petroleum ether (0 - 8 %) to afford the title compound (1.01 g, 46.8% yield) as a colorless syrup. The product is not too stable. It is not suitable for long term storage. LC-MS: (ESI, m/z): $[M+H]^+$ = 707.

[0627] **Intermediate 43:** ((2-Fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane



[0628] Step 1: 7-Fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol



[0629] Under nitrogen, a solution of 7-fluoronaphthalene-1,3-diol (10.1 g, 56.7 mmol), 2-bromoethynyl(triisopropyl)silane (17.8 g, 68.1 mmol), dichloro(*p*-cymene)ruthenium (II) dimer (3.50 g, 5.72 mmol) and KOAc (11.2 g, 114 mmol) in 1,4-dioxane (110 mL) was stirred

overnight at 110°C, then concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc /petroleum ether (0-25%) to afford the title compound (16.1 g, 79.2% yield) as a dark brown solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 359.

[0630] Step 2: 7-Fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol

[0631] To a solution of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol (16.1 g, 44.9 mmol) and DIPEA (17.5 g, 136 mmol) in DCM (160 mL) was added MOMBr (6.70 g, 54.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc /petroleum ether (0-15%) to afford the title compound (9.90 g, 54.8% yield) as a yellow solid. LC-MS: (ESI, m/z): [M+H]+ = 403. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 9.01 (s, 1H), 7.55 (dd, *J* = 9.1, 5.7 Hz, 1H), 7.07 (t, *J* = 8.8 Hz, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 6.70 (dd, *J* = 2.5, 0.9 Hz, 1H), 5.14 (s, 2H), 3.40 (s, 3H), 1.18 – 0.98 (m, 21H).

[0632] Step 3: 7-Fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate

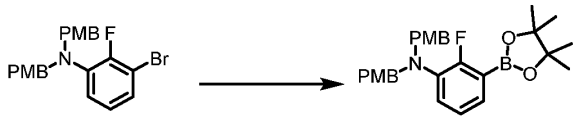
[0633] Under nitrogen, to a solution of 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (5.01 g, 12.4 mmol) and *N*-(4-chlorophenyl)-1,1,1-trifluoro-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (5.85 g, 14.9 mmol) in THF (50 mL) was added NaH (547 mg, 13.7 mmol, 60% in mineral oil) at 0°C. The resulting reaction mixture was stirred at room temperature for 1 h, diluted with water (30 mL) and extracted with EtOAc (150 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-8% EtOAc / petroleum ether) to afford 5.11 g (76.8% yield) of the title compound as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 7.81 – 7.65 (m, 1H), 7.49 – 7.30 (m, 3H), 5.30 (s, 2H), 3.54 (s, 3H), 1.35 – 1.01 (m, 21H).

[0634] Step 4: ((2-Fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane

[0635] Under nitrogen, a solution of 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (1.51 g, 2.81 mmol), Pin_2B_2 (1.43 g, 5.62 mmol), $Pd(dppf)Cl_2$ (216 mg, 0.280 mmol) and KOAc (826 mg, 8.43 mmol) in toluene (12 mL) was stirred overnight at 110°C. The resulting reaction mixture was cooled to room temperature and the solid was filtered off. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% EtOAc / petroleum ether) to afford 981 mg (68.2% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): [M+H]+ = 513. ^{1}H-NMR (300 MHz, $CDCl_3$, ppm) δ 7.66 (dd, J = 9.0, 5.6 Hz, 1H), 7.52 –

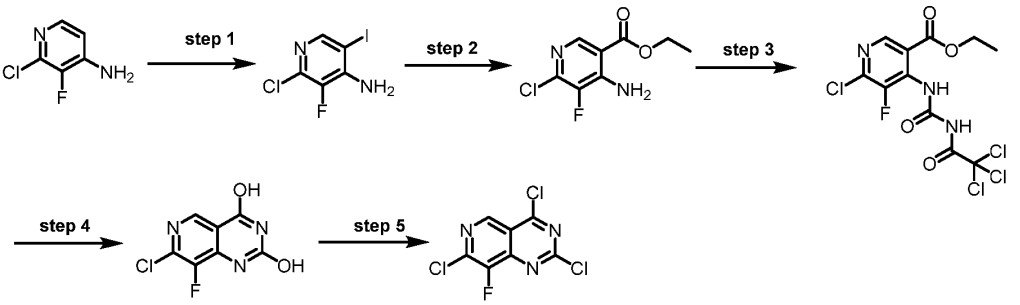
7.48 (m, 1H), 7.40 – 7.35 (m, 1H), 7.22 (t, J = 8.8 Hz, 1H), 5.27 (s, 2H), 3.50 (s, 3H), 1.43 (s, 12H), 1.19 – 1.12 (m, 21H).

[0636] **Intermediate 44:** 2-fluoro-N,N-bis(4-methoxybenzyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[0637] Under nitrogen, a solution of 3-bromo-2-fluoro-*N*, *N*-bis[(4-methoxyphenyl)methyl]aniline (12.6 g, 29.3 mmol), Pin_2B_2 (22.4 g, 88.1mmol), $PdCl_2(dppf)$ (2.15 g, 2.94 mmol) and KOAc (8.64 g, 88.1mmol) in 1,4-dioxane (20 mL) was stirred at 80°C for 2 hours. The resulting solution was diluted with water and extracted with petroleum ether. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% EtOAc / petroleum ether) to afford the title compound (10.4 g, 74.4% yield) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 478. Z

[0638] **Intermediate 45:** 2,4,7-Trichloro-8-fluoropyrido[4,3-*d*]pyrimidine



[0639] Step 1: 2-Chloro-3-fluoro-5-iodopyridin-4-amine

[0640] To a solution of 2-chloro-3-fluoropyridin-4-amine (20.0 g, 136 mmol) and NIS (37.0 g, 164 mmol) in CH_3CN (260 mL) was added *p*-toluene sulfonic acid monohydrate (1.30 g, 6.83 mmol). The solution was stirred at 70 °C for 16 hours. The solvent was evaporated under vacuum. The residue was diluted with EtOAc (600 mL), washed with saturated Na_2CO_3 solution (2 x 300 mL), saturated Na_2SO_3 solution (300 mL) and brine (300 mL). The organic layers were concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc /petroleum ether (0-35%) to afford 37.0 g (99.5% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): [M+H]+ =273. ^{1}H -NMR: (400 MHz, methanol-d_4, ppm) δ 8.08 (s, 1H).

[0641] Step 2: Ethyl 4-amino-6-chloro-5-fluoronicotinate

[0642] To a solution of 2-chloro-3-fluoro-5-iodopyridin-4-amine (15.0 g, 55.1 mmol) in EtOH (260 mL) was added $Pd(PPh_3)_2Cl_2$ (3.87 g, 5.51 mmol) and Et_3N (20.1 g, 199 mmol) at room temperature. The mixture was stirred under CO (2 atm) for 15 hours at 80 °C, then concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/DCM (0-36%) to afford 13.6 g (crude) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 219. ^{1}H -NMR: (400 MHz, DMSO-d_6, ppm) δ 8.37 (s, 1H), 7.59 (br, 2H), 4.32 (q, J=7.2 Hz, 2H), 1.32 (t, J=7.2 Hz, 3H).

[0643] Step 3: Ethyl 6-chloro-5-fluoro-4-(3-(2,2,2-trichloroacetyl)ureido)nicotinate

[0644] Under nitrogen, to a solution of ethyl 4-amino-6-chloro-5-fluoronicotinate (12.6 g, 57.5 mmol) in THF (150 mL) was added trichloroacetyl isocyanate (10.3 mL, 86.3 mmol) at 25 °C. The resulting solution was stirred for 20 min at 25 °C. The mixture was concentrated under vacuum. The residue was washed with MTBE (250 mL). The solid was collected and dried to afford 17.1g (crude) of the title compound as a pale pink solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 406.

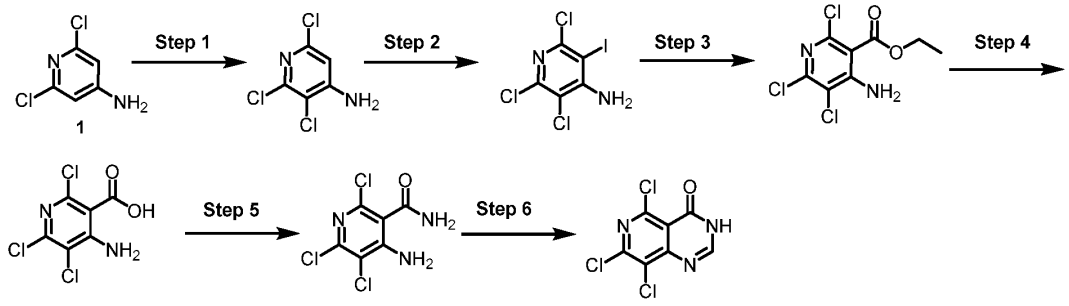
[0645] Step 4: 7-Chloro-8-fluoropyrido[4,3-*d*]pyrimidine-2,4-diol

[0646] To a solution of ethyl 6-chloro-5-fluoro-4-(3-(2,2,2-trichloroacetyl)ureido)nicotinate (16.1 g, 39.6 mmol) in MeOH (160 mL) was added ammonia MeOH solution (29 mL, 7 M). The solution was stirred at 25 °C for 1 hour, then concentrated under vacuum. The residue was washed with MTBE (200 mL) to afford 9.72 g (crude) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 216. ^{1}H -NMR: (400 MHz, DMSO-d_6, ppm):δ 8.33 (br, 1H).

[0647] Step 5: 2,4,7-Trichloro-8-fluoropyrido[4,3-*d*]pyrimidine

[0648] Under nitrogen, a solution of 7-chloro-8-fluoropyrido[4,3-*d*]pyrimidine-2,4-diol (7.01 g, 32.5 mmol) and DIPEA (21.0 g, 162.8 mmol) in $POCl_3$ (70 mL) was stirred for 2 h at 100 °C. The mixture was added slowly to ice water, maintaining the system at <10 °C. The solids were collected by filtration and washed with water (300 mL). The solid was dried under vacuum to afford 6.20 g (crude) of the title compound as a red brown solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 252. The crude was used for next step without further purification.

[0649] **Intermediate 46:** 5,7,8-Trichloropyrido[4,3-*d*]pyrimidin-4(3*H*)-one



[0650] Step 1: 2,3,6-Trichloropyridin-4-amine

[0651] A solution of 2,6-dichloropyridin-4-amine (20.0 g, 123 mmol) and NCS (16.4 g, 123 mmol) in tetrahydrofuran (500 mL) was stirred at 50 °C for 24 hours. The reaction system was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organic layers were evaporated under vacuum. The residual was slurried with petroleum ether: EtOAc = 10 :1 and filtered to afford 21g of the title compound (crude) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 197.

[0652] Step 2: 2,3,6-Trichloro-5-iodopyridin-4-amine

[0653] To a solution of 2,3,6-trichloropyridin-4-amine (22.0 g, 111 mmol) in ACN (200 mL) was added NIS (30 g, 134 mmol) and TsOH (2.18 g, 11 mmol) at room temperature. The solution was stirred for 2 h at 70 °C. The resulting mixture was concentrated under vacuum. The residual was diluted with aqueous Na_2HSO_3, extracted with EtOAc. The combined organic layers were washed with aqueous Na_2CO_3, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (gradient: 0%-30% EtOAc/petroleum ether) to afford 35 g (97.1% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ =323.

[0654] Step 3: Ethyl 4-amino-2,5,6-trichloronicotinate

[0655] Under carbon monoxide, a mixture of 2,3,6-trichloro-5-iodo-pyridin-4-amine (8.0 g, 24.7 mmol), $Pd(PPh_3)_2Cl_2$ (1.74 g, 2.47 mmol) and triethylamine (7.51 g, 74. 2 mmol) in ethanol (80 mL) was stirred for 48h at 80 °C. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% EtOAc/DCM) to yield 3.7 g (55.5% yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 269.

[0656] Step 4: 4-Amino-2,5,6-trichloronicotinic acid

[0657] To a solution of ethyl 4-amino-2,5,6-trichloro-pyridine-3-carboxylate (3.0g, 11.3mmol) in EtOH (20 mL) was added NaOH (890 mg, 22.3 mmol) and water (60 mL). The resulting mixture was stirred for 2h at room temperature. The resulting mixture was filtered. The filtrate was acidified to pH 3 with HCl. The precipitated solids were collected by filtration and dried in oven to afford 1.5g of the title compound (55.8% yield) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 241.

[0658] Step 5: 4-Amino-2,5,6-trichloronicotinamide

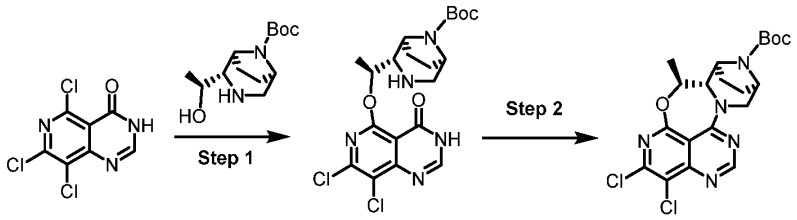
[0659] A solution of 4-amino-2,5,6-trichloro-pyridine-3-carboxylic acid (300 mg, 1.24 mmol), NH_4Cl (332 mg, 6.21 mmol), HATU (709 mg, 1.86 mmol) and DIPEA (1.6 g, 12.4 mmol) in *N*,*N*-dimethylacetamide (5 mL) was stirred at room temperature for 1 hour. The resulting solution was diluted with EtOAc (8 mL), washed with water. The separated organic layer was

concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-5% MeOH/DCM) to yield 200 mg (66.9% yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 240.

[0660] Step 6: 5,7,8-Trichloropyrido[4,3-d]pyrimidin-4(3*H*)-one

[0661] A solution of 4-amino-2,5,6-trichloro-pyridine-3-carboxamide (200 mg, 0.83 mmol) in triethoxymethane (3 mL) was stirred at 140 °C for 5 hours. The solvent was removed under vacuum. The residue was diluted with EtOAc/DCM (1/5, 3 mL). After filtration, the solids were collected and dried under vacuum to afford the title compound (120 mg, crude) as a white solid which was used for next reaction without further purification. LC-MS: (ESI, *m/z*): $[M+H]^+$= 250.

[0662] **Intermediate 47:** *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1,2-dichloro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0663] Step 1: *tert*-Butyl (1*S*,2*S*,5*R*)-2-((*S*)-1-((7,8-dichloro-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

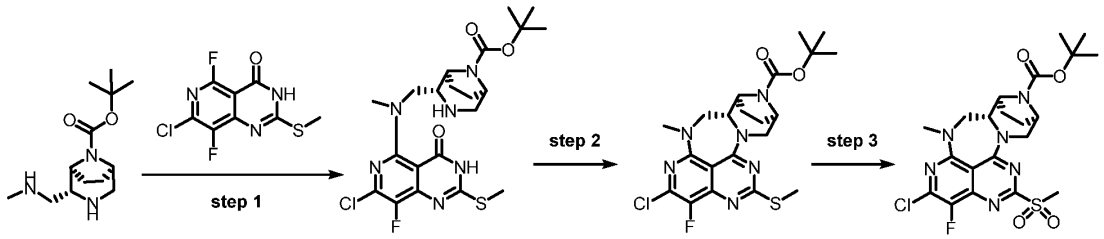
[0664] Under nitrogen, to a solution of tert-butyl rac-(1*S*,2*S*,5*R*)-2-[rac-(1S)-1-hydroxyethyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (112 mg, 0.44 mmol, Intermediate 4) in N,N-dimethylformamide (2 mL) was added NaH (69 mg, 1.74 mmol, 60% suspension in oil) at 0°C. The resulting solution was stirred at room temperature for 0.5 h. Then 5,7,8-trichloro-3H-pyrido[4,3-d]pyrimidin-4-one (120 mg, 0.480 mmol, intermediate 46) was added and the mixture was stirred at room temperature for 2h. The reaction was quenched with water, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% MeOH/DCM) to yield 155 mg (68.8 % yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$= 470.

[0665] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1,2-dichloro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[0666] Under nitrogen, a solution of tert-butyl rac-(1S,2S,5R)-2-[rac-(1S)-1-[(7,8-dichloro-4-oxo-3H-pyrido[4,3-d]pyrimidin-5-yl)oxy]ethyl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (20.0 mg, 0.04 mmol), BOPCl (32.5 mg, 0.130 mmol) and DIPEA (32.9 mg, 0.260 mmol) in dichloromethane (2 mL) was stirred for 2h at room temperature. The solvent was concentrated

under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% MeOH/DCM) to afford 15 mg (78% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$= 452.

[0667] **Intermediate 49:** *tert*-Butyl (5*aR*,6*S*,9*R*)-2-chloro-1-fluoro-4-methyl-12-(methylsulfonyl)-4,5,5a,6,7,8,9,10-octahydro-3,4,10a,11,13,14-hexaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[0668] Step 1: *tert*-Butyl (1*S*,2*R*,5*R*)-2-(((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)(methyl)amino)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[0669] To a solution of *tert*-butyl (1*R*,2*R*,5*S*)-2-((methylamino)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.25 g, 8.81 mmol, intermediate 48) and 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one (2.78 g, 9.93 mmol, intermediate 2) in N,N-dimethylacetamide (30 mL) was added DIPEA (1.71 g, 13.2 mmol) at room temperature. The solution was stirred for 1 hour at 80 °C. The reaction mixture was cooled to room temperature, diluted with EtOAc and washed with water and brine. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (2.16 g, 49.1% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 499. ^{1}H NMR (300 MHz, $CDCl_3$, *ppm*) δ 4.78 – 4.53 (m, 1H), 4.47 – 4.29 (m, 1H), 4.08 – 3.87 (m, 1H), 3.83 – 3.59 (m, 2H), 3.59 – 3.35 (m, 2H), 2.82 (s, 3H), 2.67 (s, 3H), 2.27 – 1.91 (m, 5H), 1.49 (d, J = 10.1 Hz, 9H).

[0670] Step 2: *tert*-Butyl (5a*R*,6*S*,9*R*)-2-chloro-1-fluoro-4-methyl-12-(methylthio)-4,5,5a,6,7,8,9,10-octahydro-3,4,10a,11,13,14-hexaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

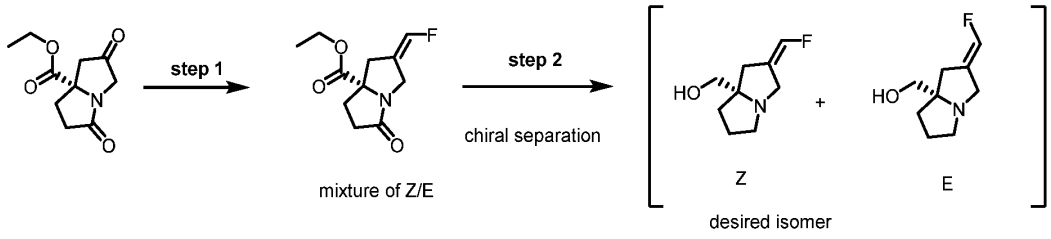
[0671] To a solution of *tert*-butyl (1*S*,2*R*,5*R*)-2-(((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)(methyl)amino)methyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.16 g, 4.33 mmol) in dichloromethane (20 mL) were added BOPCl (4.41 g, 17.3 mmol) and DIPEA (8.39 g, 64.9 mmol) at room temperature. The solution was stirred for 3 hours at room temperature. The reaction mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to

afford the title compound (1.70 g, 81.7% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 481. ^1H NMR (300 MHz, $CDCl_3$, *ppm*) δ 5.07 – 4.93 (m, 1H), 4.82 – 4.60 (m, 1H), 4.58 – 4.27 (m, 2H), 3.77 – 3.62 (m, 1H), 3.49 (d, J = 15.4 Hz, 1H), 3.29 (s, 3H), 3.28 – 3.11 (m, 1H), 2.61 (s, 3H), 2.15 – 1.93 (m, 2H), 1.78 – 1.58 (m, 2H), 1.55 (s, 9H).

[0672] Step 3: *tert*-Butyl (5a*R*,6*S*,9*R*)-2-chloro-1-fluoro-4-methyl-12-(methylsulfonyl)-4,5,5a,6,7,8,9,10-octahydro-3,4,10a,11,13,14-hexaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[0673] To a solution of *tert*-butyl (5a*R*,6*S*,9*R*)-2-chloro-1-fluoro-4-methyl-12-(methylthio)-4,5,5a,6,7,8,9,10-octahydro-3,4,10a,11,13,14-hexaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (1.70 g, 3.53 mmol) in EtOAc (20 mL) was added m-CPBA (1.83 g, 10.6 mmol) at 0 °C. The resulting solution was stirred for 3 hours at 0 °C. The reaction was quenched with aqueous $Na_2S_2O_3$. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-60% EtOAc in petroleum ether) to afford the title compound (937 mg, 51.7% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 513. ^1H NMR (300 MHz, $CDCl_3$, *ppm*) δ 5.07 – 4.93 (m, 1H), 4.82 – 4.60 (m, 1H), 4.58 – 4.27 (m, 2H), 3.77 – 3.62 (m, 1H), 3.49 (d, J = 15.4 Hz, 1H), 3.29 (s, 3H), 3.28 – 3.11 (m, 1H), 2.61 (s, 3H), 2.15 – 1.93 (m, 2H), 1.78 – 1.58 (m, 2H), 1.55 (s, 9H).

[0674] **Intermediate 50:** (*S,Z/E*)-(2-(Fluoromethylene)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (mixture of Z/E)



[0675] Step 1: Ethyl (S,Z/E)-2-(fluoromethylene)-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate

[0676] Under N_2, to a solution of 2-((fluoromethyl)sulfonyl) pyridine (177 mg, 1.01 mmol) in tetrahydrofuran (10 mL) was added KHMDS (1.2 mL, 1.20 mmol) at -78 °C. The reaction system was stirred 30 min at -78 °C, ethyl (*S*)-2,5-dioxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (200 mg, 0.950 mmol, Intermediate 5, step 1, the faster peak) in THF (5 mL) was added slowly at -78 °C. After stirred 3 hours at -78 °C, the reaction system was warm to room temperature and stirred another 1 hour at room temperature. The reaction was quenched with aqueous saturated ammonium chloride (1 mL), followed by 3 M HCl (2 mL). The resulting solution was stirred for 1 hour at room temperature. The solution was diluted with water, extracted with EtOAc. The

combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-30% ethyl acetate/petroleum ether) to yield 65.0 mg (30% yield) of the title compound as a yellow oil. LC-MS: (ES, m/z): $[M+1]^+ = 228.1$. ^1H NMR (400 MHz, Chloroform-d_1, *ppm*) δ 6.75 – 6.65 (m, 1H), 6.55 – 6.44 (m, 1H), 4.45 – 4.32 (m, 2H), 4.27 – 4.20 (m, 4H), 3.90 (d, J = 16 Hz, 1H), 3.73 (d, J = 16 Hz, 1H), 3.32 (d, J = 16 Hz, 1H), 3.04 (d, J = 16 Hz, 1H), 2.89 – 2.75 (m, 2H), 2.72 – 2.56 (m, 2H), 2.53 – 2.35 (m, 4H), 2.25 – 2.08 (m, 2H), 1.33 – 1.28 (m, 6H). (diploid H due to it is a mixture of Z/E)

[0677] Step 2: (*S,Z*)-(2-(Fluoromethylene)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol and (*S,E*)-(2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol

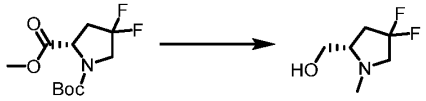
[0678] Under nitrogen, to a solution of ethyl (S,Z/E)-2-(fluoromethylene)-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (60.0 mg, 0.260 mmol) in tetrahydrofuran (5 mL) was added DIBAL-H (2.64 mL, 2.64 mmol) at 0 °C. The resulting solution was stirred for 1 hour at room temperature. The reaction was quenched with $Na_2SO_4.10H_2O$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% MeOH/DCM(0.1%Et_3N)) to yield 26.0 mg (mixture of Z/E, two peaks on normal phase column, but collected together) (57% yield) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 172.1$. ^1H NMR (300 MHz, Chloroform-d_1, *ppm*) δ 6.79 – 6.38 (m, 2H), 3.92 – 3.70 (m, 2H), 3.61 – 3.20 (m, 8H), 2.79 – 2.44 (m, 5H), 2.36 – 2.26 (m, 1H), 2.14 – 1.66 (m, 8H). (diploid H due to it is a mixture of Z/E).

[0679] The two isomers (Z/E) were separated by normal phase column with the same condition as described above. 2.20 g (*Z*, the desired isomer) and 2.70 g (*E*, the undesired isomer) were obtained from 9.7g ethyl (S,Z/E)-2-(fluoromethylene)-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate following the same procedure and purification method described above. Both are yellow oils.

[0680] *Z* isomer: LC-MS: (ESI, *m/z*): $[M+H]^+ = 172$. ^1H NMR (300 MHz, Chloroform-d_1, *ppm*) δ 6.64 – 6.29 (m, 1H), 3.79 – 3.65 (m, 1H), 3.48 – 3.37 (m, 1H), 3.35 – 3.23 (m, 2H), 3.14 – 3.03 (m, 1H), 2.69 – 2.58 (m, 1H), 2.46 – 2.35 (m, 1H), 2.30 – 2.17 (m, 1H), 2.03 – 1.59 (m, 4H).

[0681] *E isomer*: LC-MS: (ESI, *m/z*): $[M+H]^+ = 172$. ^1H NMR (300 MHz, Chloroform-d_1, *ppm*) δ 6.76 – 6.42 (m, 1H), 3.75 – 3.65 (m, 1H), 3.48 – 3.34 (m, 2H), 3.33 – 3.18 (m, 2H), 2.73 – 2.40 (m, 3H), 2.09 – 1.65 (m, 4H).

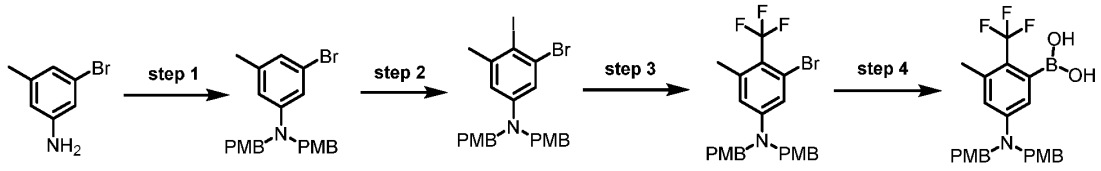
[0682] **Intermediate 51:** (*S*)-(4,4-Difluoro-1-methylpyrrolidin-2-yl)methanol



[0683] To a solution of 1-(*tert*-butyl) 2-methyl (*S*)-4,4-difluoropyrrolidine-1,2-dicarboxylate (300 mg, 1.13 mmol,) in tetrahydrofuran (5 mL) was added $LiAlH_4$ (107 mg, 2.82 mmol) at 0 °C and the mixture was stirred at 60 °C for 1 hour. The reaction was quenched with $Na_2SO_4.10H_2O$. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-14% EtOAc in petroleum ether) to afford the title compound (95.0 mg, 55.6% yield, **isomer 1**) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 152$.

[0684] Analogous to the method described as above, the other enantiomer (*R*)-(4,4-difluoro-1-methylpyrrolidin-2-yl)methanol (96.6 mg, 56.5% yield) was prepared from 1-(tert-butyl) 2-methyl (*R*)-4,4-difluoropyrrolidine-1,2-dicarboxylate (300 mg, 1.13 mmol). LC-MS: (ESI, m/z): $[M+H]^+ = 152$.

[0685] **Intermediate 52:** (5-(Bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)boronic acid



[0686] Step 1: 3-Bromo-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline

[0687] Under nitrogen, to a solution of 3-bromo-5-methyl-aniline (500 mg, 2.69 mmol) in DMF (5 mL) was added NaH (324 mg, 8.10 mmol, 60% in mineral oil) at 0°C, and the mixture was stirred for 0.5 hours. Then PMBCl (1.05g, 6.69 mmol) was added and the mixture was stirred at room temperature for 12 hours. The reaction was quenched with NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% ethyl acetate/petroleum ether) to afford the title compound (441 mg, 87.8% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 426/428$.

[0688] Step 2: 3-Bromo-4-iodo-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline

[0689] To a solution of 3-bromo-N,N-bis[(4-methoxyphenyl)methyl]-5-methyl-aniline (2.00 g, 4.69 mmol) in DMF (20 mL) was added NIS (1.58 g, 7.03 mmol) and TsOH (96.0 mg, 0.560 mmol) in portions at room temperature. The resulting solution was stirred at room temperature for 20 min and then quenched with $Na_2S_2O_3$ aqueous solution. The solution was extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-18%

ethyl acetate/petroleum ether) to afford the title compound (1.58 g, 50.6% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 552/554.

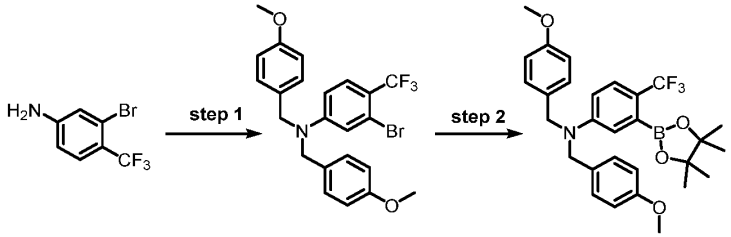
[0690] Step 3: 3-Bromo-*N*,*N*-bis(4-methoxybenzyl)-5-methyl-4-(trifluoromethyl)aniline

[0691] Under nitrogen, a solution of 3-bromo-4-iodo-N,N-bis[(4-methoxyphenyl)methyl]-5-methyl-aniline (1.58 g, 2.86 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (1.82 mL, 14.3 mmol) and CuI (547 mg, 2.86 mmol) in DMF (15 mL) was stirred at 90°C for 1 hour. The reaction mixture was partitioned between EtOAc and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% ethyl acetate/petroleum ether) to afford the title compound (695 mg, 43.2% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 494/496.

[0692] Step 4: (5-(Bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)boronic acid

[0693] Under nitrogen, to a solution of 3-bromo-*N*,*N*-bis(4-methoxybenzyl)-5-methyl-4-(trifluoromethyl)aniline (2.43 g, 4.92 mmol) and triisopropyl borate (1.39 g, 7.37 mmol) in tetrahydrofuran (25 mL) was added *n*-BuLi (3.69 mL, 5.90 mmol, 1.6 M in hexanes) at -65 °C. The reaction was stirred at -65 °C for 1 hour. Then the reaction was quenched with water, extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase chromatography (gradient: 0-70% acetonitrile in water (0.5% NH_4HCO_3)) to afford the title compound (1.16g, 51.2% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 460.

[0694] **Intermediate 53:** *N*,*N*-Bis(4-methoxybenzyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline



[0695] Step 1: 3-Bromo-*N*,*N*-bis(4-methoxybenzyl)-4-(trifluoromethyl)aniline

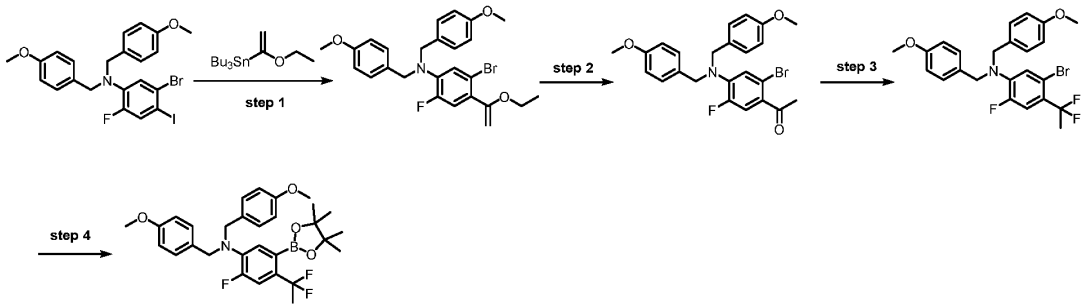
[0696] Under nitrogen, to a solution of 3-bromo-4-(trifluoromethyl)aniline (1.00 g, 2.52 mmol) in DMF (14 mL) was added NaH (0.500 g, 12.5 mmol, 60%) at 0°C. The resulting solution was stirred for 0.5 h at room temperature. Then PMB-Cl (1.60 g, 10.2 mmol) was added and the solution was stirred at room temperature overnight. The reaction was quenched with ice water, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified

by flash chromatography on silica gel (gradient: 0-5% ethyl acetate in petroleum ether) to afford the title compound 2.20 g (crude) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 480.

[0697] Step 2: *N,N*-Bis(4-methoxybenzyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline

[0698] Under nitrogen, to a solution of 3-bromo-*N,N*-bis(4-methoxybenzyl)-4-(trifluoromethyl)aniline (2.20 g, 4.58 mmol) and Pin_2B_2 (3.22 g, 12.7 mmol) in 1,4-dioxane (20 mL) was added KOAc (1.24 g, 12.7 mmol) and $Pd(dppf)Cl_2$ (0.620 g, 0.850 mmol) at room temperature. The resulting solution was stirred overnight at 110°C. After cooling to room temperature, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% ethyl acetate in petroleum ether) to afford 900 mg (37.3% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 528.

[0699] **Intermediate 54:** 4-(1,1-Difluoroethyl)-2-fluoro-*N,N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[0700] Step 1: 5-Bromo-4-(1-ethoxyvinyl)-2-fluoro-*N,N*-bis(4-methoxybenzyl)aniline

[0701] Under nitrogen, a solution of 5-bromo-2-fluoro-4-iodo-N,N-bis(4-methoxybenzyl)aniline (5.00 g, 8.99 mmol), tributyl(1-ethoxyvinyl)stannane (4.57 mL, 13.5 mmol) and $Pd(Ph_3)_2Cl_2$ (0.500 g, 0.710 mmol) in N,N-Dimethylformamide (20 mL) was stirred at 80°C for 16 hours. The reaction was cooled to room temperature, diluted with water and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford 7.0 g crude of the title compound as yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 500/502. The crude was used for next step without further purification.

[0702] Step 2: 1-(4-(Bis(4-methoxybenzyl)amino)-2-bromo-5-fluorophenyl)ethan-1-one

[0703] To a solution of 5-bromo-4-(1-ethoxyvinyl)-2-fluoro-*N,N*-bis(4-methoxybenzyl)aniline (7.0 g, crude) in DMF (10 mL) was added concentrated hydrochloric acid (2.0 mL, 36%) at room temperature. The solution was stirred at room temperature for 1 hour. The solution was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on

pre-packed C18 column (gradient: 0-60% CH_3CN in water (0.05% NH_4HCO_3)) to afford 3.0 g (45% yield) of the title compound as a light brown oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 472,474.

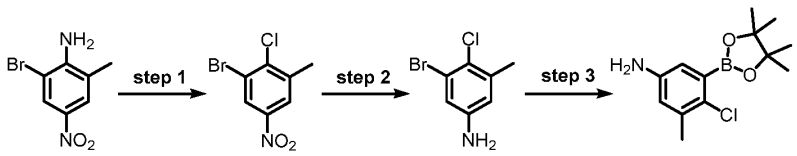
[0704] Step 3: 5-Bromo-4-(1,1-difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)aniline

[0705] Under nitrogen, a solution of 1-(4-(bis(4-methoxybenzyl)amino)-2-bromo-5-fluorophenyl)ethan-1-one (970 mg, 2.05 mmol) in BAST (5.0 mL) was stirred at 60°C for 16 hours. The reaction was cooled to room temperature, quenched with aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-3% EtOAc in petroleum ether) to afford 150 mg (24% yield) of the title compound as brown oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 494/496.

[0706] Step 4: 4-(1,1-Difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0707] Under nitrogen, a solution of 5-bromo-4-(1,1-difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)aniline (415 mg, 0.840 mmol), $PdCl_2$(dppf) (122 mg, 0.170 mmol), Pin_2B_2 (640 mg, 2.52 mmol) and KOAc (247 mg, 2.52 mmol) in 1,4-Dioxane (3 mL) was stirred for 16 hours at 110°C. The reaction was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-10% EtOAc in petroleum ether) to afford 120 mg (26% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 542.

[0708] **Intermediate 55:** 4-Chloro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[0709] Step 1: 1-Bromo-2-chloro-3-methyl-5-nitrobenzene

[0710] To a solution of 2-bromo-6-methyl-4-nitroaniline (500 mg, 2.16 mmol) and $CuCl_2$ (486 mg, 3.61 mmol) in acetonitrile (20 mL) was added *tert*-butyl nitrite (0.510 mL, 4.33 mmol). The resulting solution was stirred for 12 hours at 50°C. The reaction was quenched with aqueous sodium thiosulfate solution, diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% ethyl acetate in petroleum ether) to afford 530 mg (97.8% yield) of the title compound as a white solid. ^1H NMR

(300 MHz, DMSO-d_6, *ppm*) δ 6.82 (d, *J* = 2.4, 0.6 Hz, 1H), 6.68 (dd, *J* = 2.4, 0.8 Hz, 1H), 2.22 (s, 3H).

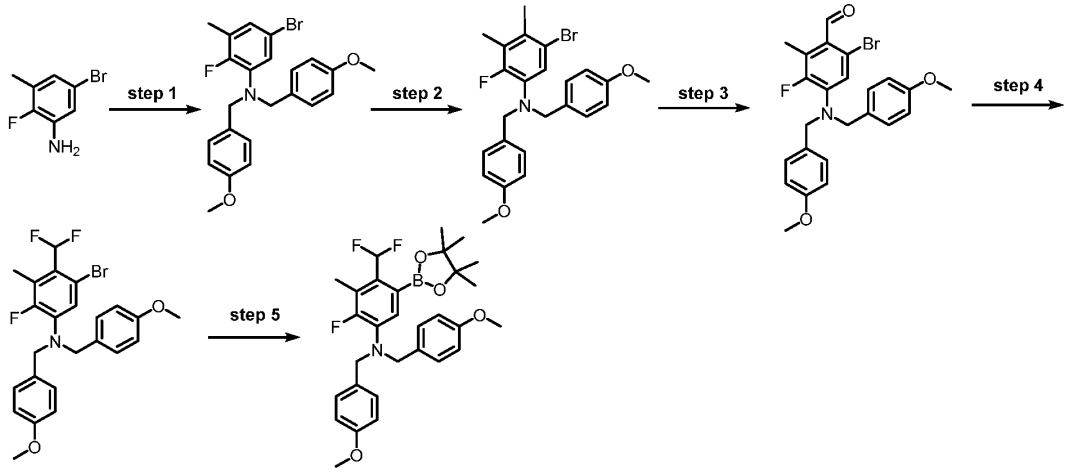
[0711] Step 2: 3-Bromo-4-chloro-5-methylaniline

[0712] To a mixture of 1-bromo-2-chloro-3-methyl-5-nitrobenzene (500 mg, 2.00 mmol) and iron powder (559 mg, 9.98 mmol) in ethanol (14 mL) and H_2O (6 mL) was added NH_4Cl (1.07 g, 20.0 mmol) at room temperature. The resulting solution was stirred for 2 h at 80°C under nitrogen. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% ethyl acetate in petroleum ether) to afford 338 mg (76.8% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 220.

[0713] Step 3: 4-Chloro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0714] Under nitrogen, to a solution of 3-bromo-4-chloro-5-methylaniline (600 mg, 2.72 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.07 g, 8.16 mmol) in 1,4-dioxane (10 mL) was added Pd(dppf)Cl_2 (199 mg, 0.270 mmol) and KOAc (800 mg, 8.16 mmol). The resulting mixture was stirred for 12 h at 100°C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-100% ethyl acetate in petroleum ether) to afford 556 mg (76.4% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 268.

[0715] **Intermediate 56:** 4-(Difluoromethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[0716] Step 1: 5-Bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline

[0717] Under nitrogen, to a solution of 5-bromo-2-fluoro-3-methylaniline (5.00 g, 24.5 mmol) in *N*,*N*-Dimethylformamide (60 mL) was added NaH (2.94 g, 73.5 mmol, 60% in mineral oil) at 0°C. The resulting solution was stirred at room temperature for 30 min. Then PMB-Cl (8.06 g, 51.5 mmol) was added at 0°C and the mixture was stirred at room temperature for 2 hours. The

reaction was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was added EtOH (30 mL). The solid was collected by filtration to afford 10.1 g (93% yield) of the title compound as off-white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 444,446. ^1H NMR (300 MHz, $CDCl_3$, *ppm*) δ 7.21 – 7.17 (m, 4H), 6.88 – 6.81 (m, 6H), 4.21 (s, 4H), 3.83 (s, 6H), 2.27 (s, 3H).

[0718] Step 2: 5-Bromo-2-fluoro-4-iodo-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline

[0719] To a solution of 5-bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline (7.00 g, 15.7 mmol) in acetic acid (70 mL) was added NIS (4.15 g, 18.4 mmol) at room temperature. The resulting solution was stirred at room temperature for 1h. The reaction was quenched with aqueous $Na_2S_2O_3$ solution. The resulting solution was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-10% EtOAc in petroleum ether) to afford 7.73 g (64% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 570,572. ^1H NMR (300 MHz, $CDCl_3$, *ppm*) δ 7.22 – 7.16 (m, 4H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.88 – 6.84 (m, 4H), 4.21 (s, 4H), 3.83 (s, 6H), 2.50 (s, 3H).

[0720] Step 3: 4-(Bis(4-methoxybenzyl)amino)-6-bromo-3-fluoro-2-methylbenzaldehyde

[0721] Under nitrogen, to a solution of 5-bromo-2-fluoro-4-iodo-N,N-bis(4-methoxybenzyl)-3-methylaniline (6.93 g, 12.2 mmol) in tetrahydrofuran (80 mL) was added i-PrMgCl (6.80 mL, 13.6 mmol, 2 M in THF) at -60°C. The solution was stirred at -60°C for 1 hour. Then DMF (8.89 g, 122 mmol) was added at -60°C. The solution was warmed to room temperature and stirred for 0.5 hour. Then the reaction was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-10% EtOAc in petroleum ether) to afford 2.12 g (37% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 472,474. ^1H NMR (300 MHz, $CDCl_3$, *ppm*) δ 10.30 (s, 1H), 7.19 – 7.17 (m, 4H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.91 – 6.87 (m, 4H), 4.46 (s, 4H), 3.82 (s, 6H), 2.55 (s, 3H).

[0722] Step 4: 5-Bromo-4-(difluoromethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline

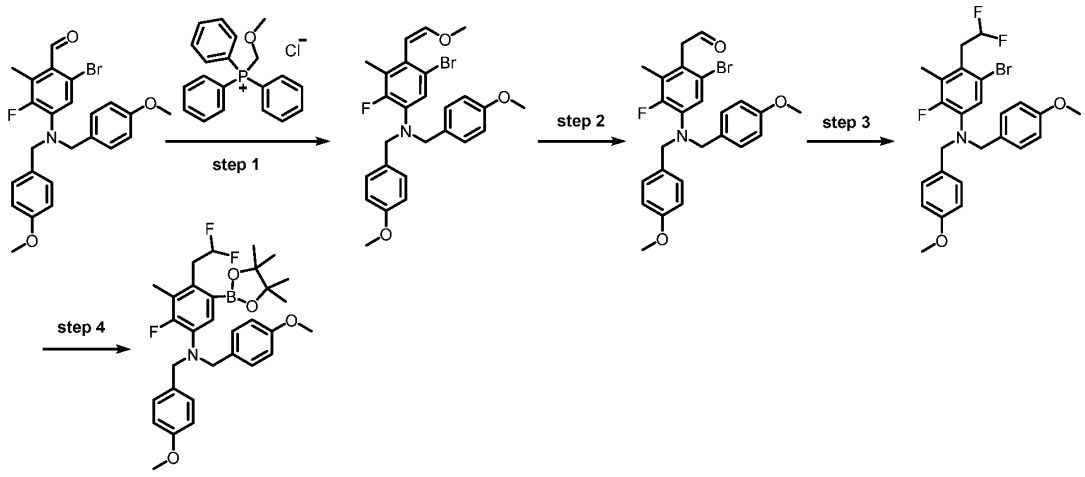
[0723] Under nitrogen, to a solution of 4-(bis(4-methoxybenzyl)amino)-6-bromo-3-fluoro-2-methylbenzaldehyde (700 mg, 1.48 mmol) in dichloromethane (20 mL) was added DAST (4.80 mL, 39.2 mmol) at -15°C. The solution was stirred at room temperature for 16 hours. The reaction was quenched with aqueous $NaHCO_3$ solution and extracted with DCM. The combined

organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-6% EtOAc in petroleum ether) to afford 647 mg (88% yield) of the title compound as yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 494,496. ^1H NMR (400 MHz, $CDCl_3$, *ppm*) δ 7.22 – 7.17 (m, 4H), 7.12 – 6.83 (m, 6H), 4.34 (s, 4H), 3.82 (s, 6H), 2.46 (s, 3H).

[0724] Step 5: 4-(Difluoromethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0725] Under nitrogen, a solution of 5-bromo-4-(difluoromethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline (647 mg, 1.31 mmol), $PdCl_2$(dppf) (180 mg, 0.230 mmol), Pin_2B_2 (998 mg, 3.93 mmol) and KOAc (385 mg, 3.92 mmol) in 1,4-dioxane (15 mL) was stirred at 90°C for 5 hours. The solid was filtered out. The filtrate was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-11% EtOAc in petroleum ether) to afford 412 mg (58% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 542. ^1H NMR (400 MHz, $CDCl_3$, *ppm*) δ 7.52 – 7.26 (m, 6H), 6.76 (d, *J* = 8.4 Hz, 4H), 4.59 - 4.55 (m, 4H), 3.74 (s, 6H), 2.39 (s, 3H), 1.29 (s, 12H).

[0726] **Intermediate 57:** 4-(2,2-Difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[0727] Step 1: 5-Bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-4-(2-methoxyvinyl)-3-methylaniline

[0728] Under nitrogen, to a solution of (methoxymethyl)triphenylphosphonium chloride (2.04 g, 5.95 mmol) in tetrahydrofuran (30 mL) was added t-BuOK (7.40 mL, 7.40 mmol, 1 M in THF) at 0°C. The solution was stirred at room temperature for 0.5 hour. Then 4-(bis(4-methoxybenzyl)amino)-6-bromo-3-fluoro-2-methylbenzaldehyde (1.41 g, 2.99 mmol, Intermediate 56, step 3) was added at 0°C. The solution was stirred at room temperature for 2

hours. Then the reaction was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-11% EtOAc in petroleum ether) to afford 1.44 g (96% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 500/502. ^1H NMR (400 MHz, $CDCl_3$, *ppm*) δ 7.26 – 7.22 (m, 4H), 6.82 (d, *J* = 8.8 Hz, 4H), 6.55 (d, *J* = 13.2 Hz, 1H), 6.14 (d, *J* = 6.8 Hz, 0.5H), 5.55 (d, *J* = 13.2 Hz, 1H), 5.18 (d, *J* = 6.8 Hz, 0.5H), 4.27 - 4.23 (m, 4H), 3.78 (s, 6H), 3.71 – 3.67 (m, 3H), 2.28 – 2.21 (m, 3H).

[0729] Step 2: 2-(4-(Bis(4-methoxybenzyl)amino)-6-bromo-3-fluoro-2-methylphenyl)acetaldehyde

[0730] To a solution of 5-bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-4-(2-methoxyvinyl)-3-methylaniline (1.29 g, 2.58 mmol) in tetrahydrofuran (15 mL) was added concentrated hydrochloric acid (1.5 mL, 36%) at -15°C. The solution was stirred at -15°C for 1 hour. Then the solution was stirred for 5 hours at room temperature. The reaction was quenched with aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-11% EtOAc in petroleum ether) to afford 890 mg (71% yield) of the title compound as an colorless oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 486/488.

[0731] Step 3: 5-Bromo-4-(2,2-difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline

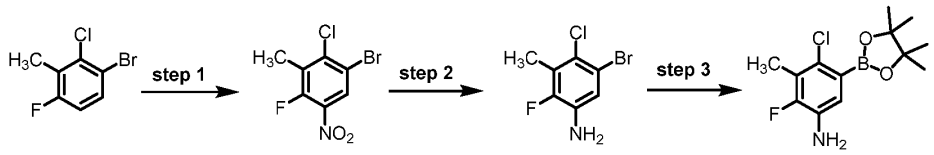
[0732] Under nitrogen, to a solution of 2-(4-(bis(4-methoxybenzyl)amino)-6-bromo-3-fluoro-2-methylphenyl)acetaldehyde (500 mg, 1.03 mmol) in dichloromethane (15 mL) was added DAST (3.20 mL, 26.2 mmol) at -10°C. The solution was stirred at room temperature for 3 hours. The reaction was quenched with aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-7% EtOAc in petroleum ether) to afford 518 mg (99% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 508/510.

[0733] Step 4: 4-(2,2-Difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0734] Under nitrogen, a solution of 5-bromo-4-(2,2-difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline (518 mg, 1.02 mmol), $PdCl_2$(dppf) (140 mg, 0.180 mmol), Pin_2B_2 (712 mg, 2.80 mmol) and KOAc (300 mg, 3.07 mmol) in 1,4-Dioxane (12 mL) was stirred at 85°C for 7 hours. The solid was filtered out. The filtrate was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash

chromatography on silica gel eluting (gradient: 0-5% EtOAc in petroleum ether) to afford 504 mg (89% yield) of the title compound as an colorless oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 556. ^1H NMR (400 MHz, $CDCl_3$, *ppm*) δ 7.44 – 7.29 (m, 4H), 6.81 – 6.76 (m, 4H), 6.01 – 5.72 (m, 2H), 4.47 - 4.26 (m, 4H), 3.77 (s, 6H), 3.50 – 3.43 (m, 2H), 2.25 (s, 3H), 1.27 – 2.26 (m, 12H).

[0735] **Intermediate 58:** 4-Chloro-2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



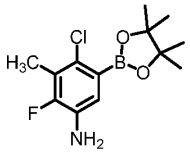
[0736] Step 1: 1-Bromo-2-chloro-4-fluoro-3-methyl-5-nitrobenzene

[0737] To a solution of 1-bromo-2-chloro-4-fluoro-3-methylbenzene (500 mg, 2.24 mmol) in H_2SO_4 (3.8 mL) was added HNO_3 (0.200 mL, 2.68 mmol) at 0 °C. The solution was stirred at room temperature for 2 h. The reaction was quenched with ice water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by TLC (petroleum ether: EtOAc=5:1) to afford 450 mg (74.8% yield) of the title compound as a yellow oil. ^1H NMR (300 MHz, DMSO-d_6, *ppm*) δ 8.45 (d, J = 7.5 Hz, 1H), 2.43 (d, J = 2.9 Hz, 3H).

[0738] Step 2: 5-Bromo-4-chloro-2-fluoro-3-methylaniline

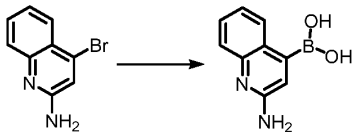
[0739] To a solution of 1-bromo-2-chloro-4-fluoro-3-methyl-5-nitrobenzene (450 mg, 1.68 mmol) and iron powder (472 mg, 8.45 mmol) in ethanol (4.8 mL) and water (0.8 mL) was added NH_4Cl (467 mg, 8.80 mmol) at room temperature. The solution was heated to 80 °C for 2 h. The reaction system was cooled to room temperature. The solid was filtered off. EtOH was evaporated under vacuum. The residual was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc in petroleum ether) to afford 277 mg (69.3% yield) of the title compound as a yellow solid. ^1H NMR (300 MHz, DMSO-d_6, *ppm*) δ 6.96 (dd, J = 13.8, 7.8 Hz, 1H), 5.47 (d, J = 30.8 Hz, 2H), 2.24 (t, J = 2.8 Hz, 3H).

[0740] Step 3: 4-Chloro-2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) aniline



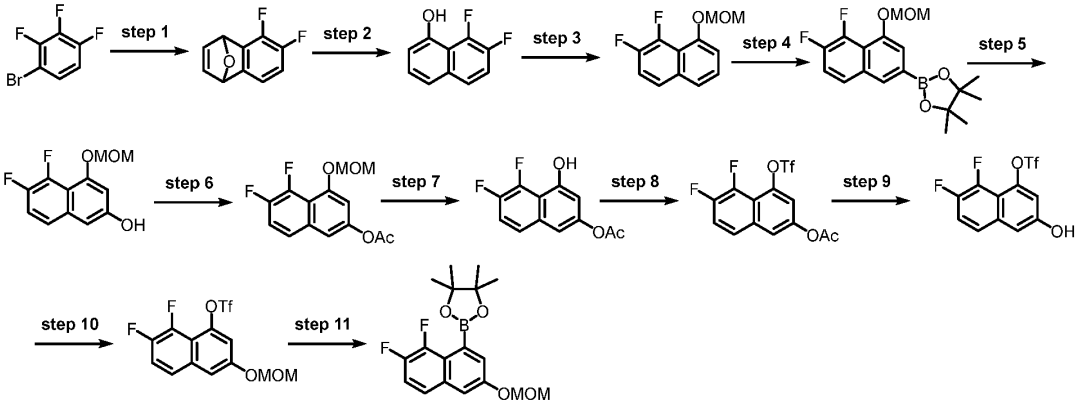
[0741] Under nitrogen, a solution of 5-bromo-4-chloro-2-fluoro-3-methylaniline (277 mg, 1.16 mmol), Pin_2B_2 (594 mg, 2.34 mmol), KOAc (229 mg, 2.34 mmol) and $PdCl_2$(dppf) (85.4 mg, 0.120 mmol) in 1,4-dioxane (5 mL) was stirred at 110 °C for 2 h. The reaction system was cooled to room temperature. The solid was filtered off and washed with EtOAc. The combined filtrates were concentrated under reduced pressure The residue was purified by flash chromatography on silica gel (gradient: 0-10% EtOAc in petroleum ether) to yield 120 mg (36.2% yield) of the title compound as a yellow solid. LCMS: (ESI): $[M+H]^+$ = 286. ^{1}H NMR (300 MHz, DMSO-d_6, *ppm*) δ 6.96 (d, *J* = 10.3 Hz, 1H), 5.21 (s, 2H), 2.18 (d, *J* = 2.6 Hz, 3H), 1.29 (s, 12H).

[0742] **Intermediate 59:** (2-Aminoquinolin-4-yl)boronic acid



[0743] Under nitrogen, a solution of 4-bromoquinolin-2-amine (100 mg, 0.450 mmol), KOAc (132 mg, 1.34 mmol), Pd(dppf)Cl_2 (32.7 mg, 0.0400 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (342 mg, 1.34 mmol) in 1,4-dioxane (5 mL) was stirred for 2 hours at 100°C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on pre-packed C18 column (gradient: 0-30% CH_3CN in water (0.05% TFA) to afford 29.5 mg (24.4% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 189.

[0744] **Intermediate 60:** 2-(7,8-Difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0745] Step 1: 5,6-Difluoro-1,4-dihydro-1,4-epoxynaphthalene

[0746] Under nitrogen, to a solution of 1-bromo-2,3,4-trifluorobenzene (24.0 g, 113 mmol) and furan (19.9 g, 293 mmol) in toluene (240 mL) was added n-BuLi (54.8 mL, 2.5 M in hexane)

at -15 °C. The mixture was stirred at room temperature overnight. The reaction mixture was quenched with water and filtered. The filtrate was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The resulting residue was purified by reverse phase chromatography (gradient: 0–100 % ACN in water (0.1% FA)) to yield 6.1g (29.8% yield) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.16 - 7.02 (m, 2H), 6.94 (dd, J = 7.7, 3.4 Hz, 1H), 6.84 - 6.64 (m, 1H), 6.00 (s, 1H), 5.74 (s, 1H).

[0747] Step 2: 7,8-Difluoronaphthalen-1-ol

[0748] A solution of 5,6-difluoro-1,4-dihydro-1,4-epoxynaphthalene (6.01 g, 33.3 mmol) and HCl (38.8 mL, 12 M) in EtOH (60 mL) was stirred at 80 °C for 3 h. The EtOH was concentrated under vacuum. The residue was adjusted pH to 7 with NaOH solid and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was slurried with petroleum ether at room temperature for 1 h. The solid was collected by filtration to afford 4.50 g (75% yield) of the title compound as a pink solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 – 7.54 (m, 1H), 7.43 – 7.36 (m, 2H), 7.33 – 7.28 (m, 1H), 7.07 – 6.96 (m, 1H), 6.67 (d, 1H).

[0749] Step 3: 1,2-Difluoro-8-(methoxymethoxy)naphthalene

[0750] To a solution of 7,8-difluoronaphthalen-1-ol (4.41 g, 24.4 mmol) in DCM (45 mL) was added DIPEA (9.46 g, 73.4 mmol) and MOMBr (6.11 g, 48.9 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The mixture was diluted with water and extracted with DCM. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% EtOAc/ petroleum ether) to yield 4.51g (82.3% yield) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.51 (m, 1H), 7.49 – 7.43 (m, 1H), 7.39 – 7.30 (m, 2H), 7.20 – 7.13 (m, 1H), 5.36 (s, 2H), 3.59 (s, 3H).

[0751] Step 4: 2-(5,6-Difluoro-4-(methoxymethoxy)naphthalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[0752] Under nitrogen, to a solution of 1,2-difluoro-8-(methoxymethoxy)naphthalene (1.01 g, 4.46 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.43 g, 11.2 mmol) in THF (12 mL) was added $(Ir(OMe)(cod))_2$ (292 mg, 0.450 mmol) and dtbbpy (144 mg, 0.540 mmol). The mixture was stirred at 70 °C for 2 h. The solution was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-40% EtOAc /petroleum ether) to yield 1.20 g (crude) of the title compound as a yellow oil.

[0753] Step 5: 5,6-Difluoro-4-(methoxymethoxy)naphthalen-2-ol

[0754] To a solution of 2-(5,6-difluoro-4-(methoxymethoxy)naphthalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (8.41 g, 9.60 mmol) in THF (85 mL) was added HOAc (95 mL) and H_2O_2 (8.8 mL, 30% in H_2O) at 0 °C. The mixture was stirred at room temperature for 1 h. The reaction solution was diluted with saturated $NaHSO_3$ aqueous and extracted with EtOAc. The organic layer was dried by anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-30% EtOAc /petroleum ether) to yield 493 mg (21.4% yield) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.30 (m, 2H), 7.16 – 7.09 (m, 1H), 7.07 – 6.99 (m, 1H), 5.37 (s, 2H), 3.63 (s, 3H).

[0755] Step 6: 5,6-Difluoro-4-(methoxymethoxy)naphthalen-2-yl acetate

[0756] To a solution of 5,6-difluoro-4-(methoxymethoxy)naphthalen-2-ol (494 mg, 2.06 mmol), Et_3N (415 mg, 4.11 mmol) and DMAP (25.1 mg, 0.210 mmol) in DCM (6.5 mL) was added acetyl chloride (320 mg, 4.08 mmol) at 0 °C. The solution was stirred at room temperature for 1 h. The solution was diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% EtOAc /petroleum ether) to yield 543 mg (93.6% yield) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.34 (m, 3H), 7.21 – 7.11 (m, 1H), 5.38 (s, 2H), 3.59 (s, 3H), 2.42 (s, 3H).

[0757] Step 7: 5,6-Difluoro-4-hydroxynaphthalen-2-yl acetate

[0758] To a solution of 5,6-difluoro-4-(methoxymethoxy)naphthalen-2-yl acetate (523 mg, 1.85 mmol) in EtOAc (6 mL) was added HCl (2 mL, 4 M in 1,4-dioxane) and the mixture was stirred at -40 °C for 0.5 h. Then the solution was stirred at 0 °C for 0.5 h. The solution diluted with saturated water $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-50% EtOAc/ petroleum ether) to yield 302 mg (51.9% yield) of the title compound as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 – 7.30 (m, 3H), 7.00 (m, 1H), 6.52 (d, J = 21.1 Hz, 1H), 2.41 (s, 3H).

[0759] Step 8: 5,6-Difluoro-4-(((trifluoromethyl)sulfonyl)oxy)naphthalen-2-yl acetate

[0760] To a solution of 5,6-difluoro-4-hydroxynaphthalen-2-yl acetate (250 mg, 1.05 mmol) in DCM (3 mL) was added DIPEA (407 mg, 3.15 mmol) and Tf_2O (356 mg, 1.26 mmol) at -78 °C. The solution was stirred at -78 °C for 1 h. The solution was warmed to room temperature, diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0%-25% EtOAc/ petroleum ether) to yield 115

mg (29.6% yield) of the title compound as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 – 7.77 (m, 1H), 7.62 – 7.47 (m, 3H), 2.44 (s, 3H).

[0761] Step 9: 7,8-Difluoro-3-hydroxynaphthalen-1-yl trifluoromethanesulfonate

[0762] To a solution of 5,6-difluoro-4-(((trifluoromethyl)sulfonyl)oxy)naphthalen-2-yl acetate (120 mg, 0.320 mmol) in THF (1.5 mL) and H_2O (0.5 mL) was added LiOH (9.4 mg, 0.390 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The solution was adjusted pH to 6 with AcOH. The solution was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum to yield 112 mg (crude) of the title compound as a yellow oil. The crude was used for next step without further purification.

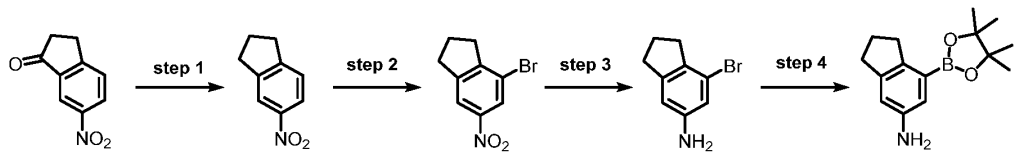
[0763] Step 10: 7,8-Difluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate

[0764] To a solution of 7,8-difluoro-3-hydroxynaphthalen-1-yl trifluoromethanesulfonate (105 mg, 0.320 mmol) in DCM (1.5 mL) was added DIPEA (124 mg, 0.960 mmol) and MOMBr (80.1 mg, 0.640 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. The solution was diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum The residue was purified by flash chromatography on silica gel (gradient: 0%-10% EtOAc/ petroleum ether) to yield 96.6 mg (81.0% yield) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 – 7.73 (m, 1H), 7.52 – 7.34 (m, 3H), 5.40 (s, 2H), 3.59 (s, 3H).

[0765] Step 11: 2-(7,8-Difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[0766] Under nitrogen, a solution of 7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (90.1 mg, 0.240 mmol), Pin_2B_2 (122.9 mg, 0.4800 mmol), $Pd(dppf)Cl_2$ (18.6 mg, 0.0200 mmol) and KOAc (119 mg, 1.21 mmol) in DMF (1.5 mL) was stirred at 80 °C overnight. The solution was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum The residue was purified by flash chromatography on silica gel (gradient: 0%-15% EtOAc/ petroleum ether) to yield 59.6 mg (70.3% yield) of the title compound as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 – 7.71 (m, 1H), 7.65 – 7.58 (m, 1H), 7.52 – 7.41 (m, 1H), 7.37 – 7.31 (m, 1H), 5.37 (s, 2H), 3.58 (s, 3H), 1.46 (s, 12H).

[0767] **Intermediate 61:** 7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-inden-5-amine



[0768] Step 1: 5-Nitro-2,3-dihydro-1*H*-indene

[0769] To a solution of 6-nitro-2,3-dihydro-1*H*-inden-1-one (3.00 g, 16.9 mmol) in Et_3SiH (8 mL) was added TFA (16 mL) at 0 °C. The solution was stirred at room temperature for 2 hours. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-7% EtOAc in petroleum ether) to afford the title compound (1.37 g, 49.1% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 164.

[0770] Step 2: 4-Bromo-6-nitro-2,3-dihydro-1*H*-indene

[0771] To a solution of 5-nitro-2,3-dihydro-1*H*-indene (300 mg, 1.84 mmol) in sulfuric acid (3 mL) and water (3 mL) was added NBS (327 mg, 1.84 mmol) at room temperature. The solution was stirred at room temperature for 1 hour. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford 350 mg of the title compound (crude) as brown solid. The crude product was used for next step without purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 243.

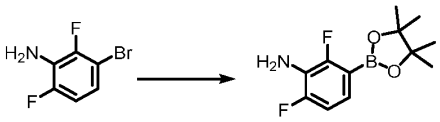
[0772] Step 3: 7-Bromo-2,3-dihydro-1*H*-inden-5-amine

[0773] A mixture of 4-bromo-6-nitro-2,3-dihydro-1*H*-indene (350 mg, 1.45 mmol), NH_4Cl (781 mg, 14.6 mmol) and iron powder (409 mg, 7.30 mmol) in water (1.5 mL) and EtOAc (3.5 mL) was stirred at 80 °C for 2 hours. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-6% EtOAc in petroleum ether) to afford the title compound (300 mg, 63.6% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 222.

[0774] Step 4: 7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1*H*-inden-5-amine

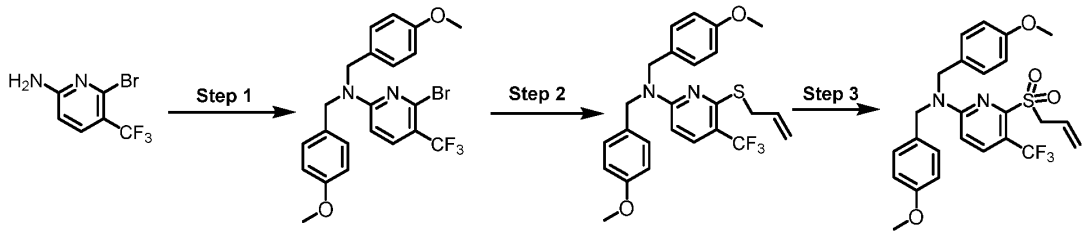
[0775] Under nitrogen, a solution of 7-bromo-2,3-dihydro-1*H*-inden-5-amine (250 mg, 1.18 mmol), Pin_2B_2 (902 mg, 3.55 mmol), $PdCl_2$(dppf) (86.7 mg, 0.120 mmol) and KOAc (348 mg, 3.55 mmol) in 1,4-dioxane (3 mL) was stirred at 100 °C for 3 hours. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-94% dichloromethane in petroleum ether) to afford the title compound (150 mg, 43.7% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 260.

[0776] **Intermediate 62:** 2,6-Difluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[0777] Under nitrogen, a solution of 3-bromo-2,6-difluoroaniline (1.00 g, 4.81 mmol), B_2Pin_2 (1.83 g, 7.21 mmol), Pd(dppf)Cl_2 (703 mg, 0.960 mmol) and KOAc (942 mg, 9.62 mmol) in 1,4-dioxane (15 mL) was stirred at 80 °C overnight. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc in petroleum ether) to afford the title compound (497 mg, 40.5% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 256.

[0778] **Intermediate 63**: 6-(Allylsulfonyl)-*N*,*N*-bis(4-methoxybenzyl)-5-(trifluoromethyl)pyridin-2-amine



[0779] Step 1: 6-Bromo-*N*,*N*-bis(4-methoxybenzyl)-5-(trifluoromethyl)pyridin-2-amine

[0780] Under nitrogen, to a solution of 6-bromo-5-(trifluoromethyl)pyridin-2-amine (1.81 g, 7.49 mmol) in N,N-dimethylformamide (18 mL) was added NaH (902 mg, 22.6 mmol, 60% suspension in oil) at 0 °C. The resulting solution was stirred for 30 min at room temperature. Then PMB-Cl (2932.1 mg, 18.8 mmol) was added at 0 °C and the mixture was stirred at room temperature for 1 hour. The reaction was quenched with aq. NH_4Cl, extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0-15%) to afford the title compound (3.56 g, 98.7% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 481.

[0781] Step 2: 6-(Allylthio)-*N*,*N*-bis(4-methoxybenzyl)-5-(trifluoromethyl)pyridin-2-amine

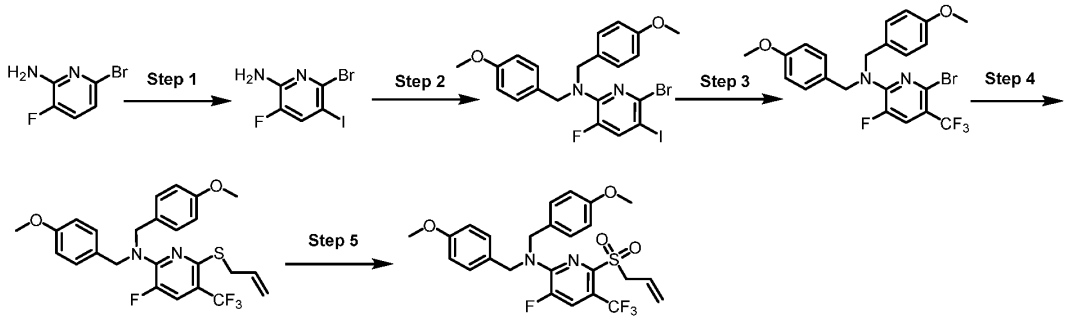
[0782] To a solution of 6-bromo-*N*,*N*-bis[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)pyridin-2-amine (500 mg, 1.04 mmol), K_2CO_3 (287 mg, 2.08 mmol) in DMF (10 mL) was added prop-2-ene-1-thiol (0.41 mL, 5.19 mmol). The resulting mixture was stirred for overnight at 50 °C. The resulting mixture was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced

pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% EtOAc/ petroleum ether) to yield 350 mg (70.4% yield) the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$= 475.

[0783] Step 3: 6-(Allylsulfonyl)-*N,N*-bis(4-methoxybenzyl)-5-(trifluoromethyl)pyridin-2-amine

[0784] Under nitrogen, to a solution of 6-allylsulfanyl-N,N-bis[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)pyridin-2-amine (165 mg, 0.35 mmol) in dichloromethane (5 mL) was added m-CPBA (240 mg, 1.39 mmol) at 0 °C. The solution was stirred at 25°C for 18 hours. The reaction mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, water and brine, dried over MgSO4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-50% EtOAc / petroleum ether) to yield 60 mg (34.1 % yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ =507.

[0785] **Intermediate 64:** 6-(Allylsulfonyl)-3-fluoro-*N,N*-bis(4-methoxybenzyl)-5-(trifluoromethyl)pyridin-2-amine



[0786] Step 1: 6-Bromo-3-fluoro-5-iodopyridin-2-amine

[0787] A solution of 6-bromo-3-fluoro-pyridin-2-amine (200 mg, 1.05 mmol) and NIS (282 mg, 1.26 mmol) in AcOH (10 mL) was stirred at 25 °C for 1 hour. The resulting mixture was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% EtOAc/petroleum ether) to yield the title compound (270 mg, 81.4 % yield) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 317/319.

[0788] Step 2: 6-Bromo-3-fluoro-5-iodo-*N,N*-bis(4-methoxybenzyl)pyridin-2-amine

[0789] Under nitrogen, to a solution of 6-bromo-3-fluoro-5-iodo-pyridin-2-amine (100 mg, 0.320 mmol) in N,N-dimethylformamide (2 mL) was added NaH (50.5 mg, 1.26 mmol, 60% suspension in oil) at 0 °C. The resulting solution was stirred at room temperature for 30 min. Then PMBCl (98.8 mg, 0.63 mmol) was added. The solution was stirred at 25°C for 1 hour. The resulting mixture was quenched with NH_4Cl, diluted with water and extracted with EtOAc. The

combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% EtOAc/petroleum ether) to yield the title compound (145 mg, 82.5% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ =557.

[0790] Step 3: 6-((2*R*,5a*S*,6*R*,9*R*)-3-Chloro-1-fluoro-13-(((*S*,*Z*)-2-(fluoromethylene)tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-15-(3-fluoropropyl)-5a,6,7,8,9,10-hexahydro-5H-9,6-(epiminomethano)azepino[2',1':3,4][1,4]oxazepino[5,6,7-de]quinazolin-2-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

[0791] Under nitrogen, to a solution of 6-bromo-3-fluoro-5-iodo-N,N-bis[(4-methoxyphenyl)methyl]pyridin-2-amine (2.0 g, 3.59 mmol) in N,N-dimethylformamide (20 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (4.57 mL, 35.9 mmol) and CuI (6.82 g, 35.9 mmol) at 25°C. The resulting solution was stirred at room temperature for 3h. The resulting mixture was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% EtOAc/petroleum ether) to yield the title compound (1.7 g, 94.9 % yield) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 499.

[0792] Step 4: 6-(Allylthio)-3-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(trifluoromethyl)pyridin-2-amine

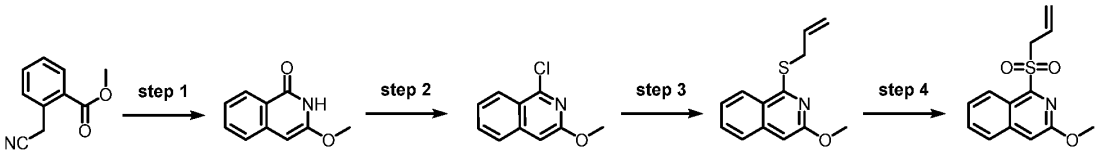
[0793] To a solution of the 6-bromo-3-fluoro-*N*,*N*-bis[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)pyridin-2-amine (500 mg, 1.00 mmol) in tetrahydrofuran (5 mL) was added isopropylmagnesium chloride lithium chloride (1 mL, 1.3 mmol) and allyl disulfide (146 mg, 1.00 mmol) at 0 °C. The solution was allowed to warm to room temperature and stirred overnight. The reaction was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by reverse phase chromatography (gradient: 0–95 % acetonitrile in water (0.1% NH_4HCO_3)) to afford the title compound 350 mg (71% yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 493.

[0794] Step 5: 6-(Allylsulfonyl)-3-fluoro-N,N-bis(4-methoxybenzyl)-5-(trifluoromethyl)pyridin-2-amine

[0795] Under nitrogen, to a solution of 6-allylsulfanyl-3-fluoro-N,N-bis[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)pyridin-2-amine (50.0 mg, 0.10 mmol) in dichloromethane (2 mL) was added m-CPBA (52.6 mg, 0.30 mmol) at 0 °C. The solution was stirred at 25°C for 18 hours. The reaction mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by

flash chromatography on silica gel (gradient: 0%-50% EtOAc / petroleum ether) to yield 20 mg (37.6 % yield) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$= 525.

[0796] **Intermediate 65:** 1-(Allylsulfonyl)-3-methoxyisoquinoline



[0797] Step 1: 3-Methoxyisoquinolin-1(2*H*)-one

[0798] Under nitrogen, to a stirred solution of methyl 2-(cyanomethyl)benzoate (2.00 g, 11.4 mmol) in methanol (30 mL) was added NaOMe (1.23 g, 22.8 mmol) at 0°C. The resulting solution was stirred at 70°C for 3 h. After the reaction system was cooled to room temperature, the mixture was acidified with 1 mol/L HCl till the solution turn to yellow from green, then cool to 0°C till the white solid was precipitated. The solid was collected by filtration, washed with water and dry in oven to afford the title compound 600 mg (30.0% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 176.

[0799] Step 2: 1-Chloro-3-methoxyisoquinoline

[0800] Under nitrogen, to a stirred solution of 3-methoxyisoquinolin-1(2*H*)-one (450 mg, 2.57 mmol) in acetonitrile (20 mL) was added $POCl_3$ (1.97 mg, 12.8 mmol). The resulting solution was stirred at 80°C for 3 h. The mixture was concentrated under vacuum. The residue was neutralized by saturated $NaHCO_3$ solution and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford 240 mg (48.3% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 194.

[0801] Step 3: 1-(Allylthio)-3-methoxyisoquinoline

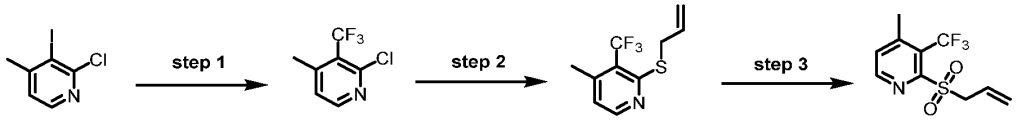
[0802] To a stirred solution of 1-chloro-3-methoxy-isoquinoline (200 mg, 1.03 mmol) and K_2CO_3 (286 mg, 2.07 mmol) in DMF (2.5 mL) was added prop-2-ene-1-thiol (0.39 mL, 4.85 mmol). The resulting solution was stirred at 25°C overnight. The crude product was purified by reverse phase chromatography (gradient: 0-100 % acetonitrile in water (0.05% TFA) to afford 180 mg (75.6% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 232.

[0803] Step 4: 1-(Allylsulfonyl)-3-methoxyisoquinoline

[0804] To a stirred solution of 1-(allylthio)-3-methoxyisoquinoline (211 mg, 0.912 mmol) in DCM (5 mL) was added *m*-CPBA (472 mg, 2.74 mmol) at 0°C. The resulting solution was stirred at room temperature for 3 h. The reaction was quenched with aqueous $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous sodium sulfate and

concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc in petroleum ether) to afford 200 mg (83.2% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 264.

[0805] **Intermediate 66:** 2-(Allylsulfonyl)-4-methyl-3-(trifluoromethyl)pyridine



[0806] Step 1: 2-Chloro-4-methyl-3-(trifluoromethyl)pyridine

[0807] Under nitrogen, to a solution of 2-chloro-3-iodo-4-methylpyridine (1.00 g, 3.95 mmol) and CuI (755 mg, 3.95 mmol) in N, N-dimethylacetamide (10 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (2.51 mL, 19.8 mmol) at 0 °C. The mixture was stirred at 90 °C for 1 h. The solution was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% EtOAc in petroleum ether) to afford 300 mg (38.8% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 196.

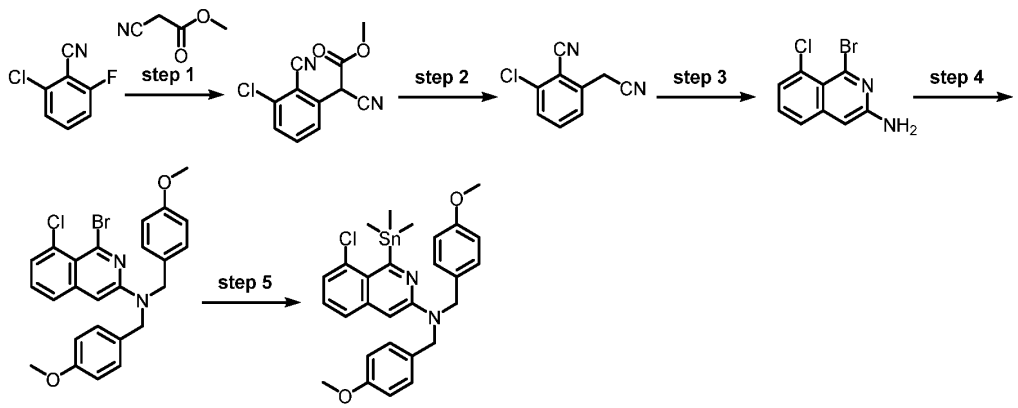
[0808] Step 2: 2-(Allylthio)-4-methyl-3-(trifluoromethyl)pyridine

[0809] A solution of prop-2-ene-1-thiol (1.95 mL, 24.5 mmol), K_2CO_3 (1.35 g, 9.81 mmol) and 2-chloro-4-methyl-3-(trifluoromethyl)pyridine (956 mg, 4.89 mmol) in N,N-dimethylformamide (10 mL) was stirred at room temperature overnight. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-5% ethyl acetate in petroleum ether) to afford (1.02 g, 88.5% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 234.

[0810] Step 3: 2-(Allylsulfonyl)-4-methyl-3-(trifluoromethyl)pyridine

[0811] To a solution of 2-(allylthio)-4-methyl-3-(trifluoromethyl)pyridine (700 mg, 3.00 mmol) in dichloromethane (10 mL) was added m-CPBA (1.56 g, 9.01 mmol) at 0 °C. The resulting solution stirred at room temperature overnight. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-40% EtOAc in petroleum ether) to afford (370 mg, 43.7% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 266.

[0812] **Intermediate 67:** 8-Chloro-*N*,*N*-bis(4-methoxybenzyl)-1-(trimethylstannyl)isoquinolin-3-amine



[0813] Step 1: Methyl 2-(3-chloro-2-cyanophenyl)-2-cyanoacetate

[0814] A solution of 2-chloro-6-fluorobenzonitrile (5.00 g, 32.1 mmol), K_2CO_3 (8.87 g, 64.3 mmol) and methyl 2-cyanoacetate (3.69 mL, 41.8 mmol) in dimethyl sulfoxide (50 mL) was stirred at 50 °C for 6 hours. The solution was cooled to room temperature, diluted with EtOAc and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. To the crude product was slurried by EtOAc/DCM (1:30) and the solids were collected by filtration to afford the title compound (3.30 g, 43.8% yield) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 7.66 – 7.57 (m, 1H), 7.21 (dd, J = 8.4, 7.7 Hz, 1H), 6.88 (dd, J = 7.8, 1.0 Hz, 1H), 3.45 (s, 3H).

[0815] Step 2: 2-Chloro-6-(cyanomethyl)benzonitrile

[0816] To a solution of methyl 2-(3-chloro-2-cyanophenyl)-2-cyanoacetate (3.00 g, 12.8 mmol) in dimethyl sulfoxide (24 mL) was added HCl (6.0 mL, 36.0 mmol, 6 M in water). The reaction system was stirred at 70 °C overnight. The solution was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was slurried by DCM/petroleum ether (1:30) to afford the title compound (1.64 g, 50.3 % yield) as a green solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 7.84 – 7.70 (m, 2H), 7.70 – 7.58 (m, 1H), 4.33 (s, 2H).

[0817] Step 3: 1-Bromo-8-chloroisoquinolin-3-amine

[0818] A solution of 2-chloro-6-(cyanomethyl)benzonitrile (1.54 g, 8.72 mmol) in 40% HBr/HOAc was stirred at 0 °C for 1.5 hours. The reaction mixture was adjusted pH to 8 with saturated Na_2CO_3 solution. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-80% DCM in petroleum ether) to afford the title compound (714 mg, 31.6 % yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 257.

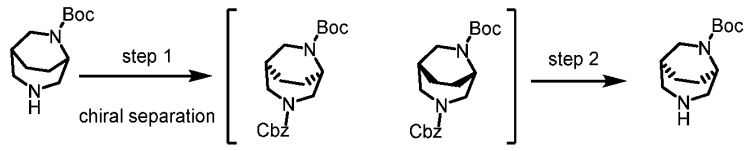
[0819] Step 4: 1-Bromo-8-chloro-*N*,*N*-bis(4-methoxybenzyl)isoquinolin-3-amine

[0820] To a solution of 1-bromo-8-chloroisoquinolin-3-amine (600 mg, 2.33 mmol) in *N*,*N*-dimethylacetamide (8 mL) was added NaH (223 mg, 5.83 mmol, 60% suspension in oil) at 0 °C. The mixture was stirred for 30 min. PMBCl (804 mg, 5.13 mmol) was added and the mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was quenched with water. The filtrate was concentrated under reduced pressure. The residual was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (388 mg, 32.7% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 497.

[0821] Step 5: 8-Chloro-*N*,*N*-bis(4-methoxybenzyl)-1-(trimethylstannyl)isoquinolin-3-amine

[0822] Under nitrogen, a solution of 1-bromo-8-chloro-*N*,*N*-bis(4-methoxybenzyl)isoquinolin-3-amine (60.0 mg, 0.120 mmol), Sn_2Me_6 (128 mg, 0.390 mmol) and $Pd(PPh_3)_4$ (13.9 mg, 0.0100 mmol) in toluene (1 mL) was stirred at 100 °C overnight. The solution was cooled to room temperature, diluted with water and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to afford 139 mg of the crude product as a green oil which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 583.

[0823] **Intermediate 68:** *tert*-Butyl (1*S*,5*R*)-3,6-diazabicyclo[3.2.2]nonane-6-carboxylate



the faster peak the slower peak

[0824] Step 1: 3-Benzyl 6-(*tert*-butyl) (1*S*,5*R*)-3,6-diazabicyclo[3.2.2]nonane-3,6-dicarboxylate

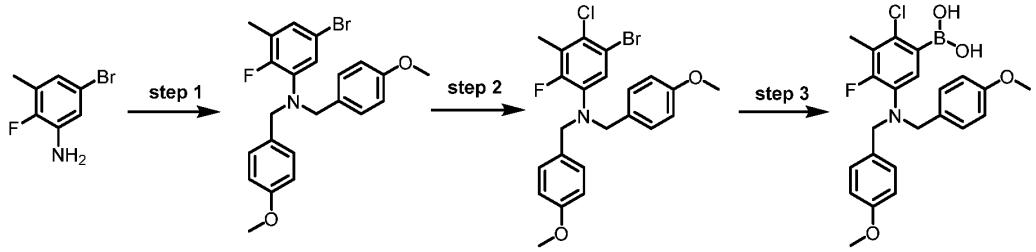
[0825] Under nitrogen, a solution of *tert*-butyl 3,6-diazabicyclo[3.2.2]nonane-6-carboxylate (500 mg, 2.21 mmol), CbzCl (492 mg, 2.88 mmol) and DIPEA (1.42 g, 11.1 mmol) in dichloromethane (10 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with DCM and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-100% EtOAc/petroleum ether) to afford 800 mg of the title compound as a colorless oil. The two enantiomers were separated by Prep-SFC with the following conditions: (Column: CHIRALPAK IG, 3*25cm, 5μm ; Mobile Phase A:CO_2, Mobile Phase B:IPA(0.5% 2 M NH_3-MeOH); Flow rate:70 mL/min; Gradient:30% B; Column Temperature: 35 °C; Back Pressure: 100 bar; 215 nm; RT1:6.86; RT2:7.89; Injection Volumn:1.5 ml; Number Of Runs:20)

to yield 330 mg of faster peak and 340 mg slower peak as a white oil. The faster peak is the desired isomer. LC-MS: (ESI, m/z): $[M+H]^+ = 361$.

[0826] Step 2: *tert*-Butyl (1*S*,5*R*)-3,6-diazabicyclo[3.2.2]nonane-6-carboxylate

[0827] Under hydrogen, a solution of 3-benzyl 6-(*tert*-butyl) (1*S*,5*R*)-3,6-diazabicyclo[3.2.2]nonane-3,6-dicarboxylate (500 mg, 1.39 mmol) and Pd/C (150.0 mg, 10%. wet) in methanol (20 mL) was stirred at 25°C overnight. After filtration, the filtrate was concentrated under vacuum to yield 300 mg (crude) of the title compound as a colorless oil which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 227$.

[0828] **Intermediate 69:** (5-(Bis(4-methoxybenzyl)amino)-2-chloro-4-fluoro-3-methylphenyl)boronic acid



[0829] Step 1: 5-Bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline

[0830] Under nitrogen, to a solution of 5-bromo-2-fluoro-3-methyl-aniline (1.00 g, 4.90 mmol) in N,N-dimethylformamide (10 mL) was added NaH (788 mg, 19.7 mmol, 60% oil suspension) at 0 °C. The solution was stirred at 0 °C for 30 min. Then PMBCl (1.92 g, 12.3mmol) was added at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (2.15 g, 98.7% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 444$.

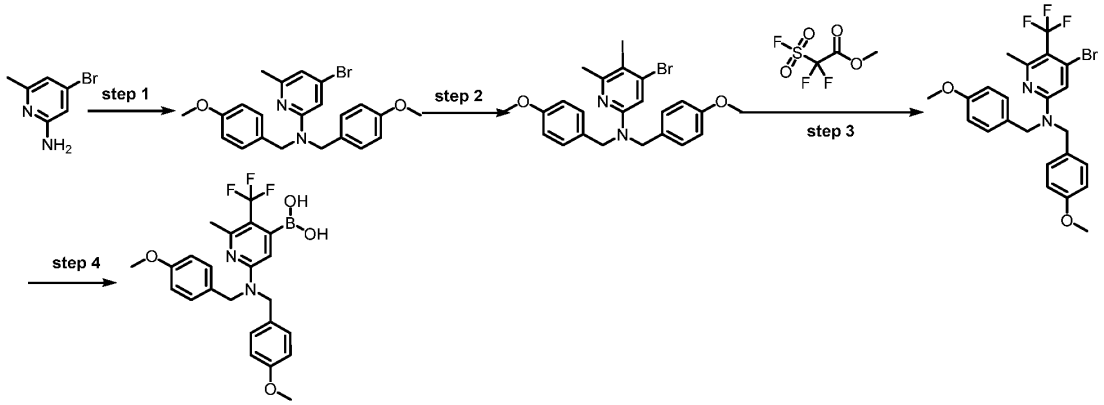
[0831] Step 2: 5-Bromo-4-chloro-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline

[0832] A solution of 5-bromo-2-fluoro-*N*,*N*-bis[(4-methoxyphenyl)methyl]-3-methyl-aniline (1.00 g, 2.25 mmol) and NCS (300 mg, 2.26 mmol) in 1-methyl-2-pyrrolidinone (10 mL) was stirred at 60 °C for 1 h. EtOAc was added to dilute the reaction mixture, which was then washed with water and brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (1.01 g, 93.7% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 478$.

[0833] Step 3: (5-(Bis(4-methoxybenzyl)amino)-2-chloro-4-fluoro-3-methylphenyl)boronic acid

[0834] Under nitrogen, to a solution of 5-bromo-4-chloro-2-fluoro-*N*,*N*-bis[(4-methoxyphenyl)methyl]-3-methyl-aniline (500 mg, 1.04 mmol) and triisopropyl borate (985 mg, 5.24 mmol) in tetrahydrofuran (10 mL) was added n-BuLi (2.5 M in Hex) (0.63 mL, 1.58 mmol) at -78 °C. The resulting solution was stirred at -78 °C for 1 h. MeOH was added at -78 °C to quench the reaction. Solvent was evaporated under vacuum. The residue was purified by flash chromatography on silica gel (gradient:0-30% EtOAC (0.01% Et_3N) in petroleum ether (10% DCM)) to afford the title compound (244 mg, 52.7% yield) as a colorless oil. LC-MS: (ESI, m/z): [M+H]+ = 444.

[0835] **Intermediate 70:** (6-(Bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)boronic acid



[0836] Step 1: 4-Bromo-*N*,*N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine

[0837] Under nitrogen, to a solution of 4-bromo-6-methylpyridin-2-amine (1.0 g, 5.35 mmol) was added NaH (535 mg, 13.4 mmol, 60% oil suspension) at 0 °C. The mixture was stirred for 20 min. PMBCl (1.85 g, 11.8 mmol) was added, and the mixture was allowed to warm to room temperature and stirred for 1 additional hour. The reaction was quenched with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (2.20 g, 94.7 % yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 427.

[0838] Step 2: 4-Bromo-5-iodo-*N*,*N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine

[0839] A solution of 4-bromo-*N*,*N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (2.10 g, 4.91 mmol) and NIS (1.11 g, 4.91 mmol) in acetic acid (20mL) was stirred at room temperature for 30 min. The reaction was quenched with water. The resulting mixture was extracted with

EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (2.60 g, 88.9 % yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 553.

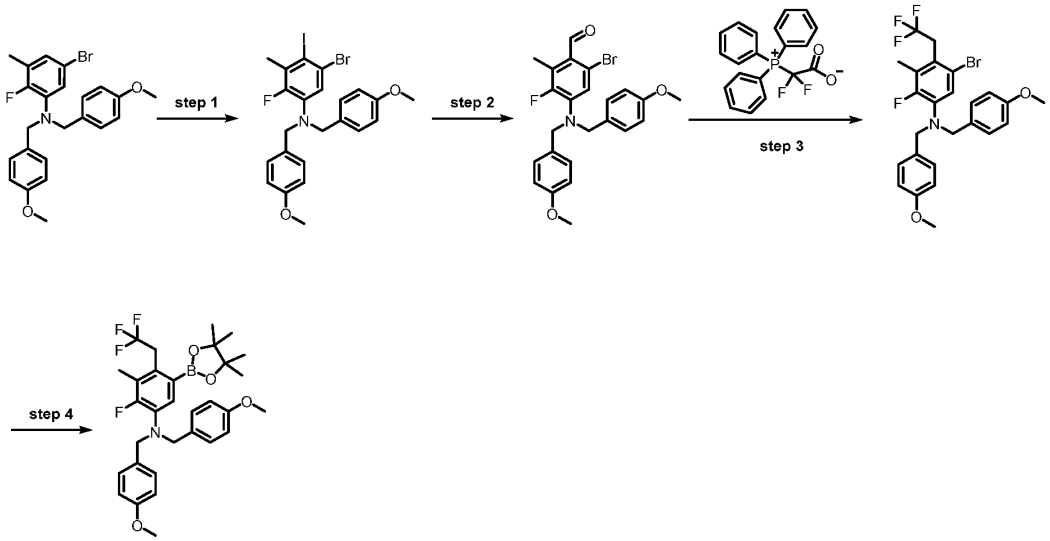
[0840] Step 3: 4-Bromo-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[0841] Under nitrogen, a solution of 4-bromo-5-iodo-*N*,*N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (2.58 g, 4.66 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (5.94 mL, 46.6 mmol) and CuI (8.86 g, 46.6 mmol) in *N*,*N*-Dimethylacetamide (25 mL) was stirred at 90 °C for 1 hour. The solution was cooled to room temperature. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was diluted with EtOAc, then washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (1.92 g, 70.5 % yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 495.

[0842] Step 4: (6-(Bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)boronic acid

[0843] Under nitrogen, to a solution of 4-bromo-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (1.83 g, 3.69 mmol) and triisopropyl borate (1.28 mL, 5.54 mmol) in tetrahydrofuran (20 mL) was added a solution of *n*-BuLi (2.77 mL, 1.6 M in hexane) at -78 °C, and the mixture was stirred at -78 °C for 1 hour. The reaction was quenched with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-40% EtOAc in petroleum ether) to afford the title compound (562 mg, 31.3 % yield) as a white oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 461.

[0844] **Intermediate 71:** 2-Fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(2,2,2-trifluoroethyl)aniline



[0845] Step 1: 5-Bromo-2-fluoro-4-iodo-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline

[0846] A solution of 5-bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline (4.11 g, 9.25 mmol, intermediate 69, step 1) and NIS (2.71 g, 12.0 mmol) in acetic acid (40 mL) was stirred at room temperature for 1 hour. Then the reaction was quenched with aqueous $Na_2S_2O_3$ solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-8% EtOAc in petroleum ether) to afford 4.22 g (80% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 570,572.

[0847] Step 2: 4-(Bis(4-methoxybenzyl)amino)-6-bromo-3-fluoro-2-methylbenzaldehyde

[0848] Under nitrogen, to a solution of 5-bromo-2-fluoro-4-iodo-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline (4.17 g, 7.31 mmol) in tetrahydrofuran (45 mL) was added i-PrMgCl (4.10 mL, 2M in THF) at -60°C. The solution was stirred at -60°C for 1 hour. Then DMF (5.34 g, 73.2 mmol) was added at -60°C. The solution was warmed to room temperature and stirred for 0.5 hour. Then the reaction was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% EtOAc in petroleum ether) to afford 1.72 g (50% yield) of the title compound as yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 472,474.

[0849] Step 3: 5-Bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-4-(2,2,2-trifluoroethyl)aniline

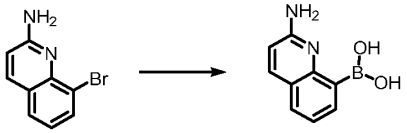
[0850] A solution of 4-(bis(4-methoxybenzyl)amino)-6-bromo-3-fluoro-2-methylbenzaldehyde (660 mg, 1.40 mmol) and 2,2-difluoro-2-(triphenylphosphonio)acetate (998 mg, 2.80 mmol) in N,N-Dimethylformamide (16 mL) was stirred at 60°C for 2.5 hours. To the

reaction solution was added TBAF (12.0 mL, 1M in THF), and the mixture was stirred at 60°C for 3 hours. The reaction was cooled to room temperature, quenched with brine and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-5% EtOAc in petroleum ether) to afford 424 mg (58% yield) of the title compound as colorless oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 526/528. ^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 7.21 (d, *J* = 8.7 Hz, 4H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 4H), 4.25 (s, 4H), 3.81 – 3.75 (m, 2H), 3.72 (s, 6H), 2.27 (s, 3H).

[0851] Step 4: 2-Fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(2,2,2-trifluoroethyl)aniline

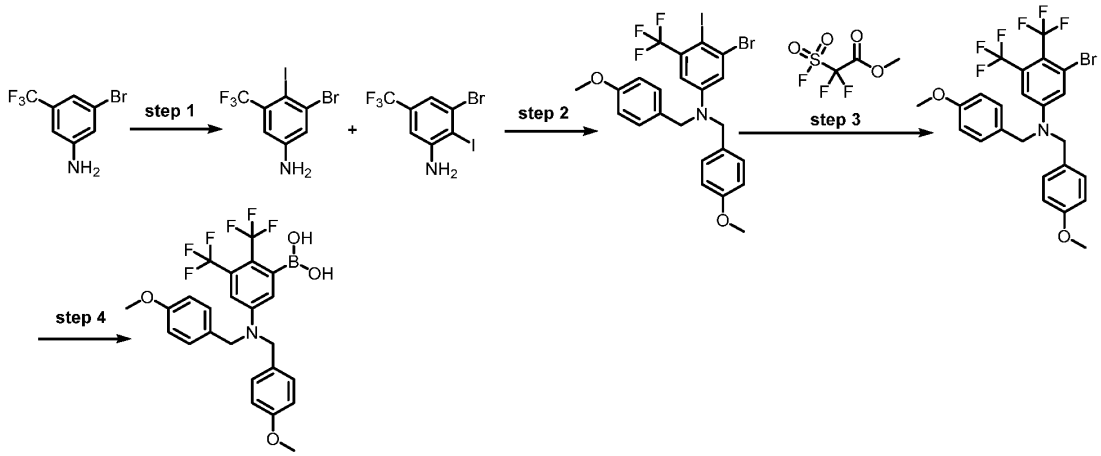
[0852] Under nitrogen, a solution of 5-bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-4-(2,2,2-trifluoroethyl)aniline (510 mg, 0.970 mmol), $PdCl_2$(dppf) (149 mg, 0.190 mmol), Pin_2B_2 (738 mg, 2.91 mmol) and KOAc (286 mg, 2.91 mmol) in 1,4-dioxane (15 mL) was stirred at 110°C for 4 hours. The reaction system was cooled to room temperature, diluted with brine and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-7% EtOAc in petroleum ether) to afford 330 mg (59% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 574. ^{1}H NMR (300 MHz, $CDCl_3$, *ppm*) δ 7.33 – 7.23 (m, 5H), 6.84 – 6.81 (m, 4H), 4.24 (s, 4H), 3.93 – 3.86 (m, 2H), 3.80 (s, 6H), 2.27 (s, 3H), 1.30 (s, 12H).

[0853] **Intermediate 72:** (2-Aminoquinolin-8-yl)boronic acid



[0854] Under nitrogen, a mixture of 8-bromoquinolin-2-amine (100 mg, 0.450 mmol), Pin_2B_2 (342 mg, 1.34 mmol), Pd(dppf)Cl_2 (32.7 mg, 0.0400 mmol) and KOAc (132 mg, 1.34 mmol) in 1,4-dioxane (5 mL) was stirred at 100°C for 3 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-30% CH_3CN in water (0.05% TFA) to afford 55.0 mg (45.4 % yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 189.

[0855] **Intermediate 73:** (5-(Bis(4-methoxybenzyl)amino)-2,3-bis(trifluoromethyl)phenyl)boronic acid



[0856] Step 1: 3-Bromo-4-iodo-5-(trifluoromethyl)aniline and 3-bromo-2-iodo-5-(trifluoromethyl)aniline

[0857] A solution of 3-bromo-5-(trifluoromethyl)aniline (1.00 g, 4.17 mmol) and NIS (937 mg, 4.17 mmol) in acetic acid (10 mL) was stirred at room temperature for 1 hour. The reaction was quenched with water, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound **1** (185 mg, 12.0 % yield) as a yellow solid, together with by-product **2** (980 mg, 63.1 % yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 366.

[0858] Step 2: 3-Bromo-4-iodo-*N*,*N*-bis(4-methoxybenzyl)-5-(trifluoromethyl)aniline

[0859] To a solution of 3-bromo-4-iodo-5-(trifluoromethyl)aniline (165 mg, 0.450 mmol) was added NaH (45.1 mg, 1.13 mmol) at 0 °C. The mixture was stirred for 20 min. PMBCl (156 mg, 0.990 mmol) was added, and the mixture was allowed to warm to room temperature and stirred for 1 additional hour. The reaction was quenched with water, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc in petroleum ether) to afford the title compound (238 mg, 81.0 % yield) as a light yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 606.

[0860] Step 3: 3-Bromo-*N*,*N*-bis(4-methoxybenzyl)-4,5-bis(trifluoromethyl)aniline

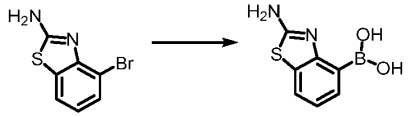
[0861] Under nitrogen, a solution of 3-bromo-4-iodo-*N*,*N*-bis(4-methoxybenzyl)-5-(trifluoromethyl)aniline (200 mg, 0.330 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.42 mL, 3.30 mmol) and CuI (627 mg, 3.30 mmol) in *N*,*N*-dimethylacetamide (3mL) was stirred at 80 °C for 1 hour. The solution was cooled to room temperature. The resulting mixture was diluted with EtOAc and washed with water. The separated organic layer was concentrated

under reduce pressure. The residual was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (108 mg, 57.9 % yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 548.

[0862] Step 4: (5-(Bis(4-methoxybenzyl)amino)-2,3-bis(trifluoromethyl)phenyl)boronic acid

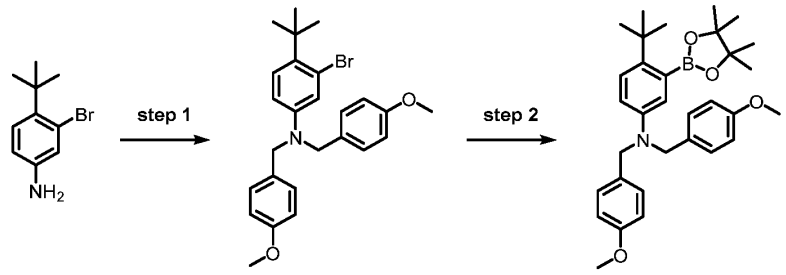
[0863] Under nitrogen, to a solution of 3-bromo-*N*,*N*-bis(4-methoxybenzyl)-4,5-bis(trifluoromethyl)aniline (95.0 mg, 0.170 mmol) and triisopropyl borate (0.06 mL, 0.260 mmol) in tetrahydrofuran (2mL) was added a solution of *n*-BuLi (0.13 mL, 1.6 M in hexane) at -78 °C. The reaction was stirred at -78 °C for 1 hour. The reaction was quenched with water, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (25.0 mg, 28.1 % yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 514.

[0864] **Intermediate 74:** (2-Aminobenzo[*d*]thiazol-4-yl)boronic acid



[0865] Under nitrogen, a mixture of 4-bromobenzo[*d*]thiazol-2-amine (200 mg, 0.873 mmol), Pin_2B_2 (665 mg, 2.62 mmol), $Pd(dppf)Cl_2$ (63.8 mg, 0.0873 mmol) and KOAc (257 mg, 2.62 mmol) in 1,4-dioxane (6 mL) was stirred at 100°C for 2 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-30% CH_3CN in water (0.05% NH_4HCO_3) to afford 90.0 mg (53.1% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 195.

[0866] **Intermediate 75:** 4-(*tert*-Butyl)-*N*,*N*-bis(4-methoxybenzyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[0867] Step 1: 3-Bromo-4-(*tert*-butyl)-*N*,*N*-bis(4-methoxybenzyl)aniline

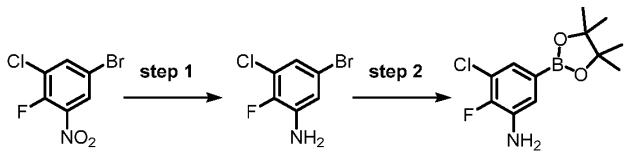
[0868] Under nitrogen, to a solution of 3-bromo-4-(*tert*-butyl)aniline (190 mg, 0.833 mmol) in *N*,*N*-dimethylformamide (3 mL) was added NaH (200 mg, 8.33 mmol) at 0 °C, and the mixture

was stirred at room temperature for 30 minutes. Then PMBCl (325 mg, 2.08 mmol) was added, and the mixture stirred at room temperature for 12 hours. The reaction was quenched with saturated NH_4Cl aqueous solution, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-12% ethyl acetate/petroleum ether) to afford the title compound (290 mg, 74.4% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 470$.

[0869] Step 2: 4-(*tert*-Butyl)-*N*,*N*-bis(4-methoxybenzyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0870] Under nitrogen, a mixture of 3-bromo-4-(*tert*-butyl)-*N*,*N*-*bis*(4-methoxybenzyl)aniline (280 mg, 0.598 mmol), Pin_2B_2 (228 mg, 0.898 mmol), $Pd(dppf)Cl_2$ (44.0 mg, 0.0600 mmol) and KOAc (117 mg, 1.19 mmol) in 1,4-dioxane (5 mL) was stirred at 90°C overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% ethyl acetate in petroleum ether) to afford the title compound (300 mg, 97% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 516$.

[0871] **Intermediate 76:** 3-Chloro-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[0872] Step 1: 5-Bromo-3-chloro-2-fluoroaniline

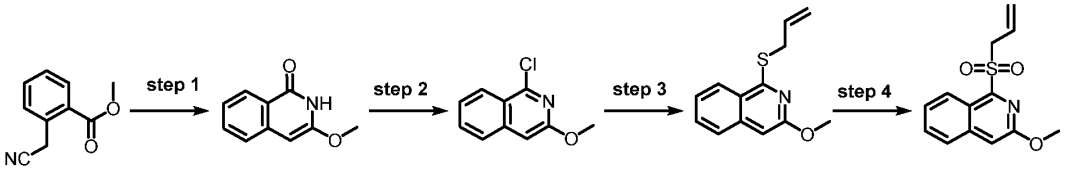
[0873] To a stirred solution of 5-bromo-1-chloro-2-fluoro-3-nitrobenzene (2.00 g, 7.86 mmol) in ethanol (70 mL) was added NH_4Cl (4.20 g, 78.6 mmol), Fe (2.19 g, 39.3 mmol) and H_2O (30 mL). The resulting solution was stirred at 80°C overnight. The reaction system was cooled to room temperature and extracted with EtOAc. The combined organic layers were washed with saturated NaCl solution, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford 1.5 g (85% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+MeCN]^+ = 265$.

[0874] Step 2: 3-Chloro-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[0875] Under nitrogen, a solution of 5-bromo-3-chloro-2-fluoroaniline (200 mg, 0.890 mmol), Pin_2B_2 (339 mg, 1.34 mmol), $Pd(dppf)Cl_2$ (65.2 mg, 0.0900 mmol) and KOAc (175 mg, 1.78

mmol) in 1,2-dimethoxyethane (8 mL) was stirred at 100°C overnight. The mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford 230 mg (95.1% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 272.

[0876] **Intermediate 77:** 1-(Allylsulfonyl)-3-methoxyisoquinoline



[0877] Step 1: 3-Methoxyisoquinolin-1(2*H*)-one

[0878] Under nitrogen, to a stirred solution of methyl 2-(cyanomethyl)benzoate (2.00 g, 11.4 mmol) in methanol (30 mL) was added NaOMe (1.23 g, 22.8 mmol) at 0°C. The result solution was stirred for 3 h at 70°C. The mixture was cooled to room temperature and acidified with 1 mol/L HCl until the solution turned from green to yellow. Then the solution was cooled to 0°C, and the white solid was precipitated. The solid was collected by filtration and dry under vacuum to afford the title compound 600 mg (30.0% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 176.

[0879] Step 2: 1-Chloro-3-methoxyisoquinoline

[0880] Under nitrogen, to a stirred solution of 3-methoxyisoquinolin-1(2*H*)-one (500 mg, 2.85 mmol) in acetonitrile (50 mL) was added $POCl_3$ (1.31 g, 8.56 mmol). The resulting solution was stirred at 80°C for 3 h. The mixture was concentrated under vacuum. The residue was dissolved by CH_2Cl_2 (50 mL), the pH was adjusted to pH=7 with saturated $NaHCO_3$ solution, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-40% EtOAc in petroleum ether) to afford 240 mg (43.4% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 194.

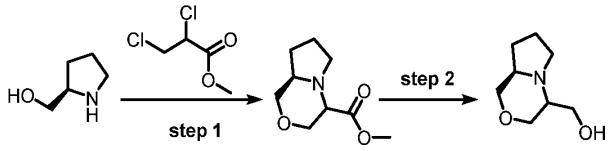
[0881] Step 3: 1-(Allylthio)-3-methoxyisoquinoline

[0882] Under nitrogen, to a stirred solution of 1-chloro-3-methoxyisoquinoline (200 mg, 1.03 mmol) in *N,N*-dimethylformamide (3 mL) were added K_2CO_3 (285 mg, 2.07 mmol) and allyl mercaptan (0.39 mL, 4.85 mmol). The resulting solution was stirred at 25°C overnight. The residue was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-100% CH_3CN in water (0.05% TFA)) to yield 200 mg (83.7% yield) the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 232.

[0883] Step 4: 1-(Allylsulfonyl)-3-methoxyisoquinoline

[0884] To a stirred solution of 1-(allylthio)-3-methoxyisoquinoline (211 mg, 0.910 mmol) in dichloromethane (5 mL) was added *m*-CPBA (472 mg, 2.74 mmol) in batches during 1 h at 0°C. The resulting solution was stirred at 25°C for 3 h. The reaction mixture was quenched with aqueous $Na_2S_2O_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-60% EtOAc in petroleum ether) to afford 200 mg (83.3% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 264$.

[0885] **Intermediate 78:** ((8a*R*)-Hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-4-yl)methanol



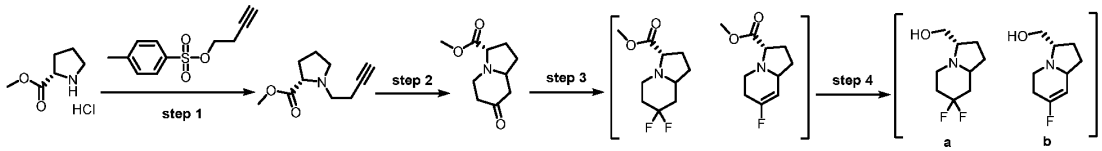
[0886] Step 1: Methyl (8a*R*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazine-4-carboxylate

[0887] Under nitrogen, to a solution of (*R*)-pyrrolidin-2-ylmethanol (1.01 g, 9.99 mmol) in *N*,*N*-dimethylformamide (20 mL) was added methyl 2,3-dichloropropanoate (1.56 g, 9.94 mmol) at 0°C. The resulting solution was stirred at 0°C for 2 hours and at room temperature for 1 hour. The solution was cooled to 0°C and NaH (1.04 g, 26.0 mmol, 60% in mineral oil) was added. The solution was stirred at 40°C for 5 hours. Then the reaction was quenched with aqueous NH_4Cl solution, and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-70% EtOAc in petroleum ether) to afford 871 mg (47% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 186$.

[0888] Step 2: ((8a*R*)-Hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-4-yl)methanol

[0889] Under nitrogen, to a solution of methyl (8a*R*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazine-4-carboxylate (125 mg, 0.680 mmol) in tetrahydrofuran (8 mL) was added $LiAlH_4$ (1.30 mL, 1.30 mmol, 1 M in THF) at 0°C. The solution was stirred at room temperature for 2 hours. The reaction was quenched with Na_2SO_4-$10H_2O$. The solid was filtered out. The solvent of filtrate was removed by nitrogen blowing to afford 90 mg (crude) of the title compound as colorless oil. The crude product was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 158$.

[0890] **Intermediate 79:** ((3*S*)-7,7-Difluorooctahydroindolizin-3-yl)methanol and ((3*S*)-7-Fluoro-1,2,3,5,6,8a-hexahydroindolizin-3-yl)methanol **and** ((3S)-7-fluoro-1,2,3,5,6,8a-hexahydroindolizin-3-yl)methanol



[0891] Step 1: Methyl but-3-yn-1-yl-*L*-prolinate

[0892] To a solution of methyl *L*-prolinate hydrochloride (3.99 g, 24.1 mmol) in acetonitrile (500 mL) were added but-3-yn-1-yl 4-methylbenzenesulfonate (13.6 g, 60.7 mmol), NaI (1.80 g, 12.0 mmol) and Cs_2CO_3 (54.9 g, 168 mmol). The solution was stirred at 80°C for 6 hours. The system was cooled to room temperature and the solid was filtered out. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford 3.41 g (78% yield) of the title compound as a brown oil. LC-MS: (ESI, m/z): $[M+H]^+ = 182$.

[0893] Step 2: Methyl (3*S*)-7-oxooctahydroindolizine-3-carboxylate

[0894] Under nitrogen, to a solution of methyl but-3-yn-1-yl-*L*-prolinate (3.41 g, 18.8 mmol) and 4 Å MS (10 g) in dichloromethane (100 mL) was added m-CPBA (4.35 g, 21.4 mmol) at 0°C. The solution was stirred at 0°C for 2 hours. Then the resulting solution was cooled to -78°C and added triphenylphosphine gold(I) bis(trifluoromethanesulfonyl)imidate (616 mg, 0.830 mmol). The solution was stirred at -78°C for 5 hours. The solution was diluted with DCM, washed with aqueous Na_2CO_3 solution and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-60% EtOAc in petroleum ether) to afford 1.73 g (47% yield) of the title compound as a brown oil. LC-MS: (ESI, m/z): $[M+H]^+ = 198$. ^1H NMR (300 MHz, $CDCl_3$, *ppm*) δ 3.93 – 3.88 (m, 1H), 3.72 (s, 3H), 3.39 – 3.23 (m, 2H), 2.99 – 2.88 (m, 1H), 2.62 – 2.44 (m, 2H), 2.40 – 2.148 (m, 4H), 2.09 – 1.97 (m, 1H),1.65 – 1.52 (m, 1H).

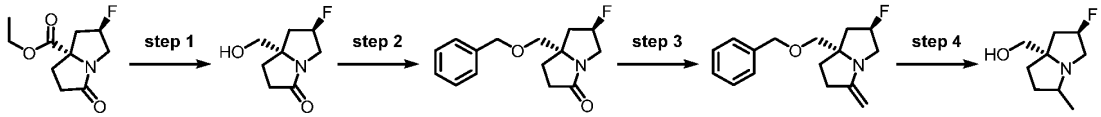
[0895] Step 3: ((3*S*)-7,7-Difluorooctahydroindolizin-3-yl)methanol and ((3*S*)-7-Fluoro-1,2,3,5,6,8a-hexahydroindolizin-3-yl)methanol **&** ((3S)-7-fluoro-1,2,3,5,6,8a-hexahydroindolizin-3-yl)methanol

[0896] Under nitrogen, to a solution of methyl (3*S*)-7-oxooctahydroindolizine-3-carboxylate (1.73 g, 8.77 mmol) in dichloromethane (30 mL) was added DAST (3.0 mL, 24.4 mmol) at -5°C. The solution was stirred at room temperature for 2 hours. The reaction was quenched with aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-26% EtOAc in petroleum ether) to afford 90 mg (5% yield) of the mixture of two title compounds as a brown oil. LC-MS: (ESI, m/z): $[M+H]^+ = 220$ and 200.

[0897] Step 4: ((3*S*)-7,7-Difluorooctahydroindolizin-3-yl)methanol and ((3*S*)-7-Fluoro-1,2,3,5,6,8a-hexahydroindolizin-3-yl)methanol

[0898] Under nitrogen, to a solution of the mixture of methyl (3*S*)-7,7-difluorooctahydroindolizine-3-carboxylate and methyl (3*S*)-7-fluoro-1,2,3,5,6,8a-hexahydroindolizine-3-carboxylate (90.2 mg, 0.410 mmol) in tetrahydrofuran (5 mL) was added $LiAlH_4$ (0.84 mL, 0.84 mmol, 1 M in THF) at 0°C. The solution was stirred at room temperature for 2 hours. Then the reaction was quenched with $Na_2SO_4.10H_2O$. The solid was filtered out. The filtrate was concentrated by nitrogen blowing to afford 80 mg mixture of the title compounds as a crude brown oil. The crude mixture was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 192 and 172.

[0899] **Intermediate 80:** ((2*R*,7a*S*)-2-Fluoro-5-methyltetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (single unknown stereoisomer)



[0900] Step 1: (6*R*,7a*S*)-6-Fluoro-7a-(hydroxymethyl)hexahydro-3*H*-pyrrolizin-3-one

[0901] To a solution of ethyl (2*R*,7a*S*)-2-fluoro-5-oxotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (1.08 g, 5.02 mmol) in methanol (10mL) was added $NaBH_4$ (284 mg, 7.50 mmol) at 0°C. The solution was stirred at room temperature for 1 hour. The reaction was quenched with saturated NH_4Cl aqueous solution. The solvent was concentrated under vacuum. The residue was re-dissolved in dichloromethane, dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound (636 mg, 73.2 % yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 174.

[0902] Step 2: (6*R*,7a*S*)-7a-((Benzyloxy)methyl)-6-fluorohexahydro-3*H*-pyrrolizin-3-one

[0903] To a solution of (6*R*,7a*S*)-6-fluoro-7a-(hydroxymethyl)hexahydro-3*H*-pyrrolizin-3-one in tetrahydrofuran (10mL) was added NaH (60% dispersion in mineral oil, 340 mg, 8.50 mmol) at 0°C. Then a solution of benzyl bromide (1.16 g, 6.80 mmol) in tetrahydrofuran (10mL) was added at 0°C, and the mixture was stirred at room temperature for 6 hours. The reaction was quenched with saturated NH_4Cl aqueous solution. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-60% ethyl acetate in petroleum ether) to afford the title compound (696 mg, 77.3 % yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 264. ^1H NMR (300 MHz, $CDCl_3$, *ppm*) δ 7.43 – 7.29 (m, 5H), 5.44 – 5.16 (m, 1H), 4.63 – 4.48 (m, 2H), 4.23 –

4.02 (m, 1H), 3.41 (d, J = 614.8 Hz, 2H), 3.28 – 3.06 (m, 1H), 2.88 – 2.70 (m, 1H), 2.49 – 2.34 (m, 1H), 2.33 – 2.14 (m, 1H), 2.12 – 1.94 (m, 2H), 1.60 (s, 1H).

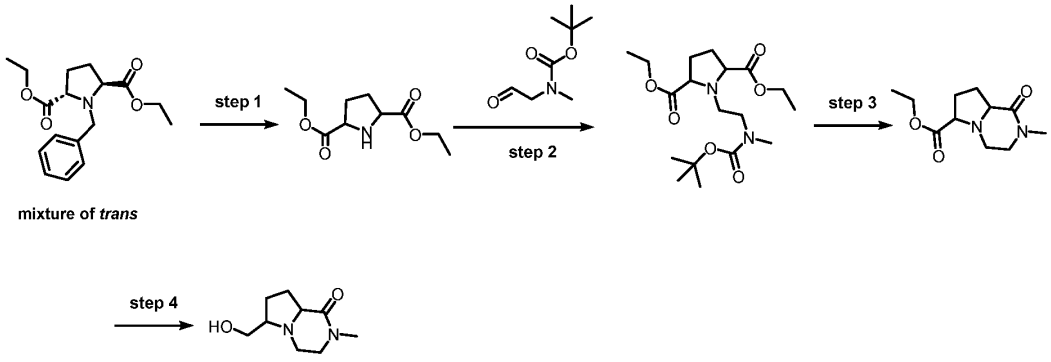
[0904] Step 3: (2*R*,7a*S*)-7a-((Benzyloxy)methyl)-2-fluoro-5-methylenehexahydro-1*H*-pyrrolizine

[0905] Under nitrogen, to a solution of (6*R*,7a*S*)-7a-((benzyloxy)methyl)-6-fluorohexahydro-3*H*-pyrrolizin-3-one (298 mg, 1.13 mmol) in tetrahydrofuran (10mL) was added Tebbe reagent (0.5M solution in toluene, 6.60 mL, 3.30 mmol) dropwise over a period of 30 minutes at -40°C. The temperature was warmed to room temperature, and the mixture was stirred for 2 hours. The reaction was quenched with saturated $NaHCO_3$ aqueous at 0°C until effervescence ceased. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound (1.06 g, crude) as a yellow oil. The crude product was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 262$.

[0906] Step 4: ((2*R*,7a*S*)-2-Fluoro-5-methyltetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (single unknown stereoisomer)

[0907] Under hydrogen, to a solution of (2*R*,7a*S*)-7a-((benzyloxy)methyl)-2-fluoro-5-methylenehexahydro-1*H*-pyrrolizine (261 mg, 1.00 mmol) in methanol (10mL) were added 10%Pd/C (106 mg, wet) and 20%$Pd(OH)_2$/C (140 mg) at room temperature. The solution was stirred at 50°C for 2 hours. The resulting mixture was filtered. the filter cake was washed with methanol. The combined filtrate was concentrated under vacuum to afford the title compound (single unknown stereoisomer, 140mg, crude) as an orange oil. The crude product was used for the next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 174$.

[0908] **Intermediate 81:** 6-(Hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (mixture of *trans* isomers)



[0909] Step 1: Diethyl pyrrolidine-2,5-dicarboxylate (mixture of *trans* isomers)

[0910] Under hydrogen, to a solution of diethyl 1-benzylpyrrolidine-2,5-dicarboxylate (mixture of *trans* isomers, 730 mg, 2.39 mmol) in methanol (10mL) were added 10%Pd/C (255

mg) and 20%$Pd(OH)_2/C$ (440 mg) at room temperature. The resulting mixture was stirred at room temperature for 2 hours. The resulting mixture was filtered. The filter cake was washed with methanol. The combined filtrate was concentrated under vacuum to afford the title compound (mixture of *trans* isomers, 507 mg, 98.4 % yield) as a light yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 216$. ^1H NMR (300 MHz, $CDCl_3$, *ppm*) δ 4.21 (q, J = 7.1 Hz, 4H), 4.06 – 3.93 (m, 2H), 2.31 – 2.10 (m, 2H), 2.04 – 1.88 (m, 2H), 1.30 (t, J = 7.1 Hz, 6H).

[0911] Step 2: Diethyl 1-(2-((*tert*-butoxycarbonyl)(methyl)amino)ethyl)pyrrolidine-2,5-dicarboxylate (mixture of *trans* isomers)

[0912] To a solution of diethyl pyrrolidine-2,5-dicarboxylate (mixture of *trans* isomers, 300mg, 1.39mmol) in dichloromethane (10mL) was added a solution of *tert*-butyl methyl(2-oxoethyl)carbamate (1.21g, 6.99mmol) in dichloromethane (2mL) at 0°C, and the mixture was stirred for 30 minutes. Then $NaBH(OAc)_3$ (1.48g, 6.98mmol) was added at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction was quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% ethyl acetate in petroleum ether) to afford the title compound (mixture of *trans* isomers, 488 mg, 94.0% yield) as a light yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 373$. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 4.19 (q, J = 7.1 Hz, 4H), 3.97 – 3.89 (m, 2H), 3.48 – 3.20 (m, 2H), 3.04 – 2.93 (m, 2H), 2.87 (s, 3H), 2.43 – 2.21 (m, 2H), 2.03 – 1.86 (m, 2H), 1.47 (s, 9H), 1.30 (t, J = 7.1 Hz, 6H).

[0913] Step 3: Ethyl 2-methyl-1-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (mixture of *trans* isomers)

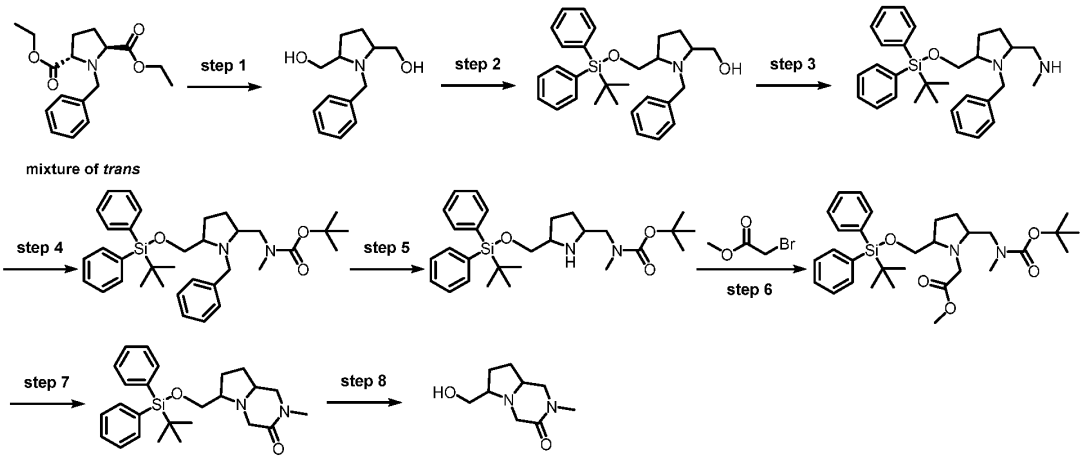
[0914] To a solution of diethyl 1-(2-((tert-butoxycarbonyl)(methyl)amino)ethyl)pyrrolidine-2,5-dicarboxylate (mixture of *trans* isomers, 438 mg, 1.18 mmol) in ethyl acetate (5mL) was added hydrogen chloride (4M solution in ethyl acetate, 6mL) at 0°C, and the mixture was stirred at room temperature for 2 hours. The solvent was concentrated under vacuum. The residue was dissolved in methanol, and DIPEA (2mL) was added. The resulting mixture was stirred at room temperature overnight. The solvent was concentrated under vacuum and the residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (mixture of *trans* isomers, 157mg, 58.8% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 227$.

[0915] Step 4: 6-(Hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (mixture of *trans* isomers)

[0916] Under nitrogen, to a mixture of ethyl 2-methyl-1-oxooctahydropyrrolo[1,2-*a*]pyrazine-6-carboxylate (mixture of *trans* isomers, 134 mg, 0.592 mmol) in tetrahydrofuran (10mL) was

added $LiBH_4$ (64.5mg, 2.96mmol) at room temperature. The solution was stirred at 60°C for 6 hours. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (mixture of *trans* isomers, 84.9 mg, crude) as a colorless solid. The crude product was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 185$.

[0917] **Intermediate 82:** 6-(hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (mixture of *trans* isomers)



[0918] Step 1: (1-Benzylpyrrolidine-2,5-diyl)dimethanol (mixture of *trans* isomers)

[0919] Under nitrogen, to a solution of diethyl 1-benzylpyrrolidine-2,5-dicarboxylate (mixture of *trans* isomers, 1.00 g, 3.28 mmol) in tetrahydrofuran (8mL) was added $LiALH_4$ (311 mg, 8.2 mmol) at 0°C. The solution was stirred at room temperature for 2 hours. The reaction was quenched with $Na_2SO_4.10H_2O$. After filtration, the filtrate was collected and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-7% ethyl acetate in petroleum ether) to afford the title compound (mixture of *trans* isomers,700 mg, 96.6% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 222$.

[0920] Step 2: (1-Benzyl-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)pyrrolidin-2-yl)methanol (mixture of *trans* isomers)

[0921] To a solution of (1-benzylpyrrolidine-2,5-diyl)dimethanol (mixture of *trans* isomers, 720mg, 2.36mmol) and DMAP (40.0 mg, 0.330 mmol) in *N*,*N*-dimethylformamide (8mL) were added TBDMSCl (896 mg, 3.26 mmol) and DIPEA (841 mg, 6.52 mmol). The solution was stirred at room temperature for 5 hours. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-13% EtOAc in petroleum ether) to afford the title compound (mixture of *trans* isomers, 370 mg, 56.7 % yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 460$.

[0922] Step 3: 1-(1-Benzyl-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)pyrrolidin-2-yl)-*N*-methylmethanamine (mixture of *trans* isomers)

[0923] Under nitrogen, to a solution of (1-benzyl-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)pyrrolidin-2-yl)methanol (mixture of *trans* isomers, 370 mg, 0.806 mmol) and DIPEA (208 mg, 1.61 mmol) in dichloromethane (3 mL) was added trifluoromethanesulfonic anhydride (364 mg, 1.29 mmol) at -78°C. The resulting solution was stirred for 15 minutes at -78 °C. Then CH_3NH_2 (1 mL, 2 M solution in THF) was added at -78°C. The solution was stirred at room temperature for 1 hour. The reaction mixture concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% ethyl acetate in petroleum ether) to afford the title compound (mixture of *trans* isomers, 300 mg, 78.9 % yield) as a light yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 473.

[0924] Step 4: *tert*-Butyl ((1-benzyl-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)pyrrolidin-2-yl)methyl)(methyl)carbamate (mixture of *trans* isomers)

[0925] To a solution of 1-(1-benzyl-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)pyrrolidin-2-yl)-N-methylmethanamine (mixture of *trans* isomers, 612 mg, 1.30 mmol) and DIPEA (201 mg, 1.56 mmol) in dichloromethane (5mL) was added Boc_2O (311mg, 1.43mmol) at 0°C. The solution was stirred at room temperature for 2 hours. The solvent was concentrated under vacuum and the residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (mixture of *trans* isomers, 270 mg, 36.5 % yield) as a light yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 573.

[0926] Step 5: *tert*-Butyl ((5-(((*tert*-butyldiphenylsilyl)oxy)methyl)pyrrolidin-2-yl)methyl)(methyl)carbamate (mixture of *trans* isomers)

[0927] Under hydrogen, to a solution of *tert*-butyl ((1-benzyl-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)pyrrolidin-2-yl)methyl)(methyl)carbamate(mixture of *trans* isomers, 290 mg, 0.507 mmol) in methanol (10mL) were added 10%Pd/C (54.0 mg) and 20%$Pd(OH)_2$/C (71.0mg) at room temperature. The resulting mixture was stirred at room temperature for 2 hours and then filtered. The filter cake was washed with methanol. The combined filtrate was concentrated under vacuum to afford the title compound (mixture of *trans* isomers, 210 mg, crude) as a light yellow oil. The crude product was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 483.

[0928] Step 6: Methyl 2-(2-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)pyrrolidin-1-yl)acetate (mixture of *trans* isomers)

[0929] To a mixture of *tert*-butyl ((5-(((*tert*-butyldiphenylsilyl)oxy)methyl)pyrrolidin-2-yl)methyl)(methyl)carbamate (mixture of *trans* isomers, 200 mg, 0.415 mmol) and K_2CO_3 (170 mg, 1.23 mmol) in acetonitrile (10mL) was added methyl 2-bromoacetate (100 mg, 0.654 mmol) at room temperature. The solution was stirred at 50°C for 5 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over

anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-18% ethyl acetate in petroleum ether) to afford the title compound (mixture of *trans* isomers, 215 mg, 93.5 % yield) as a light yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 555.

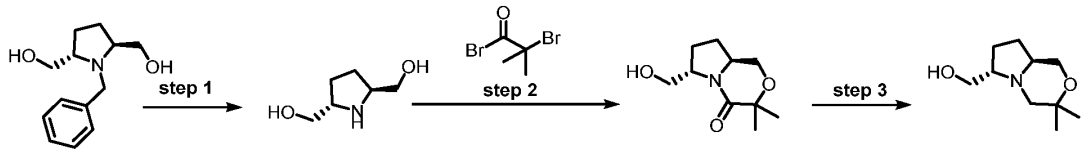
[0930] Step 7: 6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (mixture of *trans* isomers)

[0931] To a solution of methyl 2-(2-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)-5-(((tert-butyldiphenylsilyl)oxy)methyl)pyrrolidin-1-yl)acetate (mixture of *trans* isomers, 185 mg, 0.334 mmol) in ethyl acetate (5 mL) was added hydrogen chloride (6 mL, 4 M solution in ethyl acetate) at 0°C. The solution was stirred at room temperature for 2 hours. The solvent was concentrated under vacuum. The residue was dissolved in methanol and added DIPEA (1 mL, 6.00 mmol). The resulting mixture was stirred at room temperature overnight. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (mixture of *trans* isomers, 130 mg, 92.2 % yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 423.

[0932] Step 8: 6-(hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (mixture of *trans* isomers)

[0933] A solution of 6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methylhexahydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-one (mixture of *trans* isomers, 100 mg, 0.237 mmol) and hydrogen chloride (1 mL, 4 M solution in methanol) in methanol (10 mL) was stirred at 60°C for 2 hours. The solvent was concentrated under vacuum to afford the title compound (mixture of *trans* isomers, 35.0 mg, crude) as a colorless solid. The crude product was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 185.

[0934] **Intermediate 83:** ((6*S*,8a*S*)-3,3-Dimethylhexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)methanol



mixture of trans

[0935] Step 1: ((2*S*,5*S*)-Pyrrolidine-2,5-diyl)dimethanol

[0936] Under hydrogen, to a solution of ((2*S*,5*S*)-1-benzylpyrrolidine-2,5-diyl)dimethanol (305 mg, 1.38mmol) in methanol (5mL) was added 10% Pd/C (200 mg) at room temperature. The resulting solution was stirred at room temperature for 3 hours. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure to afford 194 mg (crude) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 132.

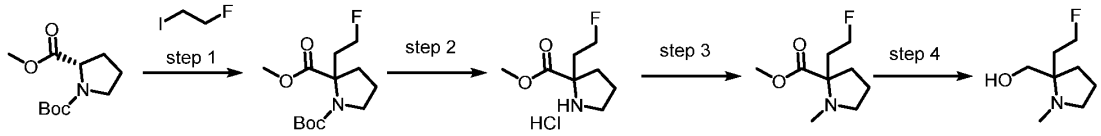
[0937] Step 2: (6*S*,8a*S*)-6-(Hydroxymethyl)-3,3-dimethyltetrahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-4(3*H*)-one

[0938] Under nitrogen, to a solution of ((2*S*,5*S*)-pyrrolidine-2,5-diyl)dimethanol (180 mg, 1.37 mmol) and TMSOK (351 mg, 2.74 mmol) in IPA (5 mL) was added 2-bromo-2-methylpropanoyl bromide (0. 2mL, 1.65 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 0.5 hour. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH in DCM) to afford the title compound (67 mg, 24.5 % yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 200.

[0939] Step 3: ((6*S*,8a*S*)-3,3-Dimethylhexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)methanol

[0940] Under nitrogen, to a solution of (6*S*,8a*S*)-6-(hydroxymethyl)-3,3-dimethyltetrahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-4(3*H*)-one (57.0 mg, 0.290 mmol) in tetrahydrofuran (1mL) was added a solution of $LiAlH_4$ in THF (0.29 mL, 2.5 M in THF) at 0 °C. The resulting solution was stirred at 70 °C for 0.5 hour. Then $Na_2SO_4 \cdot 10H_2O$ was added at 0°C. The solids were filtered and washed with tetrahydrofuran. The filtrate was concentrated under reduced pressure to afford 65 mg (crude) of the title compound as a white oil. The crude product was used for next step without further purification LC-MS: (ESI, m/z): $[M+H]^+$ = 186.

[0941] **Intermediate 84:** (2-(2-Fluoroethyl)-1-methylpyrrolidin-2-yl)methanol



[0942] Step 1: 1-(*tert*-Butyl) 2-methyl 2-(2-fluoroethyl) pyrrolidine-1,2-dicarboxylate

[0943] Under nitrogen, to a solution of 1-(*tert*-butyl) 2-methyl (*S*)-pyrrolidine-1,2-dicarboxylate (1.0 g, 4.36 mmol) in tetrahydrofuran (40 mL) was added LiHMDS (1 M in THF, 9 mL) at -15°C. The solution was stirred at -15°C for 1 hour. Then 1-fluoro-2-iodoethane (1.89 g, 10.9 mmol) was added and the solution was stirred additional 0.5 hour at -15°C. Then the mixture was warmed to room temperature and stirred for 2 hours. The reaction was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% EtOAc / petroleum ether) to afford 1.01 g of the title compound as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 276.

[0944] Step 2: Methyl 2-(2-fluoroethyl) pyrrolidine-2-carboxylate HCl salt

[0945] To a solution of 1-(*tert*-butyl) 2-methyl 2-(2-fluoroethyl) pyrrolidine-1,2-dicarboxylate (750 mg, 2.72 mmol) in dichloromethane (4 mL) was added HCl (4 M in 1,4-dioxane, 6 mL). The solution and was stirred at room temperature for 1 hour. Then the solution was concentrated

under vacuum to afford 561 mg (crude) of the title compound as white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 176.

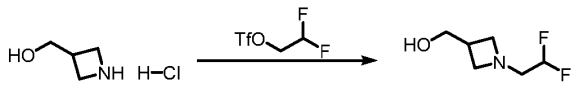
[0946] Step 3: Methyl 2-(2-fluoroethyl)-1-methylpyrrolidine-2-carboxylate

[0947] A solution of methyl 2-(2-fluoroethyl) pyrrolidine-2-carboxylate HCl salt (560 mg, 2.65 mmol), (HCHO)n (676 mg, 22.5 mmol) and NaOAc (440 mg, 5.37 mmol) in dichloromethane (10 mL) and methanol (5 mL) was stirred at room temperature for 2 hours. Then $NaBH(OAc)_3$ (1.13 g, 5.33 mmol) was added. The solution was stirred at room temperature for 16 hours. The solution was concentrated under vacuum. The residue was diluted with brine and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-35% EtOAc / petroleum ether) to afford 421 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 190.

[0948] Step 4: (2-(2-Fluoroethyl)-1-methylpyrrolidin-2-yl)methanol

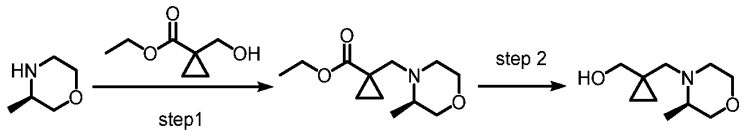
[0949] Under nitrogen, to a solution of methyl 2-(2-fluoroethyl)-1-methylpyrrolidine-2-carboxylate (470 mg, 2.48 mmol) in tetrahydrofuran (15 mL) was added $LiAlH_4$ (1 M in THF, 5 mL) at 0°C. The solution was stirred at room temperature for 1 hour. The reaction was quenched by $Na_2SO_4.10H_2O$. The solid was filtered out. The filtrate was concentrated under vacuum to afford 390 mg (crude) of the title compound as colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 162. The crude was used for next step without further purification.

[0950] **Intermediate 85:** (1-(2,2-Difluoroethyl) azetidin-3-yl)methanol



[0951] To a solution of azetidin-3-ylmethanol hydrochloride (500 mg, 4.05 mmol) in dichloromethane (5 mL) was added DIPEA (1.57 g, 12.2 mmol) at room temperature, and the mixture was stirred for 30 minutes. Then 2,2-difluoroethyl trifluoromethanesulfonate (870 mg, 4.06 mmol) was added, and the mixture was stirred for 2 hours at room temperature. The solvent was concentrated under vacuum to afford the title compound (2.00 g, crude) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 152. The crude was used for next step without further purification.

[0952] **Intermediate 86:** (*R*)-(1-((3-Methylmorpholino) methyl) cyclopropyl) methanol



[0953] Step 1: Ethyl (*R*)-1-((3-methylmorpholino) methyl) cyclopropane-1-carboxylate

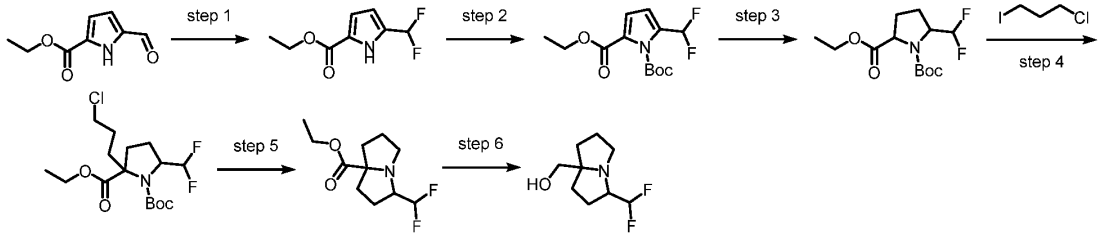
[0954] Under nitrogen, to a solution of ethyl 1-(hydroxymethyl) cyclopropane-1-carboxylate (500 mg, 3.47 mmol) and DIPEA (1.84 mL, 10.4 mmol) in dichloromethane (5 mL) was added

Tf_2O (1.2 mL, 7.1 mmol) dropwise at -10 °C and the solution was stirred for 5 minutes. Then a solution of (*R*)-3-methylmorpholine (351 mg, 3.47 mmol) in dichloromethane (1 mL) was added at -10 °C , and the mixture was stirred for 1 hour at room temperature. The solvent was concentrated under vacuum to afford the title compound (1.80 g, crude) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 228.

[0955] Step 2: (*R*)-(1-((3-Methylmorpholino) methyl) cyclopropyl) methanol

[0956] Under nitrogen, to a solution of ethyl (*R*)-1-((3-methylmorpholino) methyl) cyclopropane-1-carboxylate (1.80 g, crude) in THF (20 mL) was added $LiAlH_4$ (600 mg, 15.8 mmol) in portions at 0 °C , and the mixture was stirred for 1 hour at room temperature. The reaction was quenched with $Na_2SO_4.10H_2O$ and filtrated. The filtrate was concentrated under reduced pressure to afford the title compound (714 mg, crude) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 186. The crude was used for next step without further purification.

[0957] **Intermediate 87:** (3-(Difluoromethyl) tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methanol



[0958] Step 1: Ethyl 5-(difluoromethyl)-1*H*-pyrrole-2-carboxylate

[0959] Under nitrogen, a solution of ethyl 5-formyl-1*H*-pyrrole-2-carboxylate (5.00 g, 29.9 mmol) and BAST (19.9 g, 89.7 mmol) in 1,2-dichlorobenzene (300 mL) was stirred for 2 hours at 80 °C. The reaction was quenched with saturated $NaHCO_3$ aqueous solution. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% ethyl acetate in petroleum ether) to afford the title compound (5.00 g) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 190.

[0960] Step 2: 1-(*tert*-Butyl) 2-ethyl 5-(difluoromethyl)-1*H*-pyrrole-1,2-dicarboxylate

[0961] To a solution of ethyl 5-(difluoromethyl)-1*H*-pyrrole-2-carboxylate (5.00 g, 26.3 mmol), DMAP (650 mg, 5.30 mmol) and DIPEA (10.2 g, 79.0 mmol) in dichloromethane (300 mL) was added a solution of $(Boc)_2O$ (46.2 g, 212 mmol) in dichloromethane (200 mL) dropwise at 0 °C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was

purified by flash chromatography on silica gel (gradient: 0-10% ethyl acetate in petroleum ether) to afford the title compound (5.40 g) as a yellow solid. LC-MS: (ESI, *m/z*): $[M-56+H]^+$ = 234.

[0962] Step 3: 1-(*tert*-Butyl) 2-ethyl 5-(difluoromethyl) pyrrolidine-1,2-dicarboxylate

[0963] Under hydrogen (1 atm), a solution of 1-(*tert*-butyl) 2-ethyl 5-(difluoromethyl)-1*H*-pyrrole-1,2-dicarboxylate (5.40 g, 18.7 mmol) and 10%Pd/C (2.45 g) in ethanol (100 mL) was stirred for 1 hour at room temperature. The resulting mixture was filtered. The filter cake was washed with ethanol. The combined filtrate was concentrated under vacuum to afford the title compound (4.6 g, crude) as a yellow solid. LC-MS: (ESI, *m/z*): $[M-100+H]^+$ = 194.

[0964] Step 4: 1-(*tert*-Butyl) 2-ethyl 2-(3-chloropropyl)-5-(difluoromethyl) pyrrolidine-1,2-dicarboxylate

[0965] Under nitrogen, to a solution of 1-(*tert*-butyl) 2-ethyl 5-(difluoromethyl) pyrrolidine-1,2-dicarboxylate (3.80 g, 13.0 mmol) in tetrahydrofuran (100 mL) was added LDA (2M solution in tetrahydrofuran, 32.5 mL) dropwise at -78 °C, and the mixture was stirred for 1 h at -78 °C. Then a solution of 1-chloro-3-iodopropane (18.6 g, 91.0 mmol) in tetrahydrofuran (100 mL) was added dropwise at -78 °C and the solution was warmed to room temperature and stirred an additional 1 hour. The reaction was quenched with saturated NH_4Cl aqueous solution. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% ethyl acetate in petroleum ether) to afford the title compound (2.54 g) as a yellow oil. LC-MS: (ESI, *m/z*): $[M-100+H]^+$ = 270.

[0966] Step 5: Ethyl 3-(difluoromethyl) tetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate

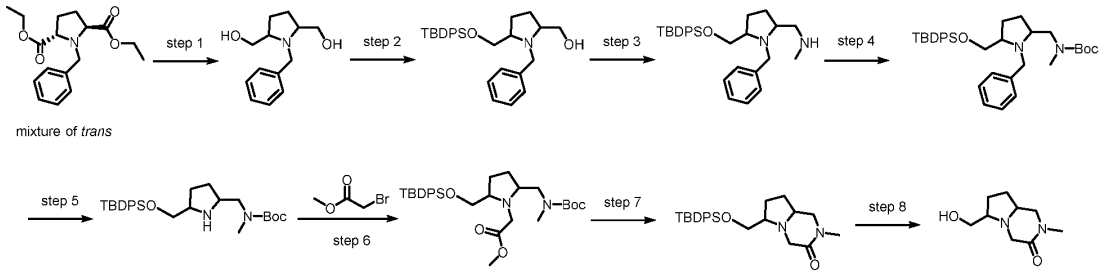
[0967] To a solution of 1-(*tert*-butyl) 2-ethyl 2-(3-chloropropyl)-5-(difluoromethyl) pyrrolidine-1,2-dicarboxylate (2.54 g, 6.88 mmol) in HFIP (100 mL) was added 2,2,2-trifluoroacetic acid (5 mL) at room temperature, and the mixture was stirred for 3 hours. The solvent was concentrated under vacuum. The residue was re-dissolved in ethanol (100 mL) and treated with K_2CO_3 (2.85 g, 20.6 mmol) and KI (114 mg, 0.688 mmol). The resulting mixture was stirred for 1 hour at 40 °C. After filtration, the filtrate was collected and concentrated under vacuum to afford the title compound (3.20 g, crude) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 234.

[0968] Step 6: (3-(Difluoromethyl) tetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methanol

[0969] Under nitrogen, to a solution of ethyl 3-(difluoromethyl) tetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (3.20 g, crude) in tetrahydrofuran (40 mL) was added $LiAlH_4$ (779 mg, 20.5 mmol) in portions at 0 °C, and the mixture was stirred for 1 hour at room temperature. The reaction was quenched with $Na_2SO_4.10H_2O$. After filtration, the filtrate was collected and

concentrated under vacuum to afford the title compound (600 mg, crude) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 192. The crude was used for next step without further purification.

[0970] **Intermediate 88:** 6-(Hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*] pyrazin-3(4*H*)-one (mixture of *trans* isomers)



[0971] Step 1: (1-Benzylpyrrolidine-2,5-diyl) dimethanol (mixture of *trans* isomers)

[0972] Under nitrogen, to a solution of diethyl 1-benzylpyrrolidine-2,5-dicarboxylate (mixture of *trans* isomers, 1.00 g, 3.28 mmol) in tetrahydrofuran (10 mL) was added $LiAlH_4$ (311 mg, 8.18 mmol) slowly at 0 °C and stirred for 2 hours at room temperature. The reaction was quenched with $Na_2SO_4.10H_2O$. After filtration, the filtrate was collected and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% ethyl acetate in petroleum ether) to afford the title compound (700 mg, mixture of *trans* isomers) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 222.

[0973] Step 2: (1-Benzyl-5-(((*tert*-butyldiphenylsilyl) oxy) methyl) pyrrolidin-2-yl) methanol (mixture of *trans* isomers)

[0974] To a solution of (1-benzylpyrrolidine-2,5-diyl) dimethanol (700 mg, 3.17 mmol), DIPEA (818 mg, 6.34 mmol) and DMAP (38.7 mg, 0.317 mmol) in *N*, *N*-dimethylformamide (10 mL) was added TBDPSCl (959 mg, 3.49 mmol) at room temperature. The solution was stirred for 5 hours at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (370 mg) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 460.

[0975] Step 3: 1-(1-Benzyl-5-(((*tert*-butyldiphenylsilyl) oxy) methyl) pyrrolidin-2-yl)-*N*-methylmethanamine (mixture of *trans* isomers)

[0976] Under nitrogen, to a solution of (1-benzyl-5-(((*tert*-butyldiphenylsilyl) oxy) methyl) pyrrolidin-2-yl) methanol (370 mg, 0.806 mmol) and DIPEA (208 mg,1.61 mmol) in dichloromethane (3 mL) was added trifluoromethanesulfonic anhydride (364 mg, 1.29 mmol) at -78 °C, and the mixture was stirred for 15 minutes. Then CH_3NH_2 (2M solution in THF, 1 mL) was added at -78 °C, and the mixture was stirred for 1 hour at room temperature. The reaction

mixture concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% ethyl acetate in petroleum ether) to afford the title compound (300 mg) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 473.

[0977] Step 4: *tert*-Butyl ((1-benzyl-5-(((*tert*-butyldiphenylsilyl) oxy) methyl) pyrrolidin-2-yl) methyl) (methyl)carbamate (mixture of *trans* isomers)

[0978] To a solution of 1-(1-benzyl-5-(((*tert*-butyldiphenylsilyl) oxy) methyl) pyrrolidin-2-yl)-*N*-methylmethanamine (300 mg, 0.634 mmol) and DIPEA (98.2 mg, 0.761 mmol) in dichloromethane (5 mL) was added $(Boc)_2O$ (152 mg, 0.697 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (270 mg) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 573.

[0979] Step 5: *tert*-Butyl ((5-(((*tert*-butyldiphenylsilyl) oxy) methyl) pyrrolidin-2-yl) methyl) (methyl) carbamate (mixture of *trans* isomers)

[0980] Under hydrogen (1atm), to a solution of *tert*-butyl ((1-benzyl-5-(((*tert*-butyldiphenylsilyl) oxy) methyl) pyrrolidin-2-yl) methyl) (methyl) carbamate (270 mg, 0.471 mmol) in methanol (10 mL) was added 10%Pd/C (49.9 mg) and 20%$Pd(OH)_2$/C (contain 61.7% water, 87.9 mg) at room temperature. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was filtered. The filter cake was washed with methanol. The combined filtrate was concentrated under vacuum to afford the title compound (210 mg, crude) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 483.

[0981] Step 6: Methyl 2-(2-(((*tert*-butoxycarbonyl) (methyl) amino) methyl)-5-(((*tert*-butyldiphenylsilyl) oxy) methyl) pyrrolidin-1-yl) acetate (mixture of *trans* isomers)

[0982] A mixture of *tert*-butyl ((5-(((*tert*-butyldiphenylsilyl) oxy) methyl) pyrrolidin-2-yl)-methyl) (methyl)carbamate (200 mg, 0.414 mmol), methyl 2-bromoacetate (95.2 mg, 0.623 mmol) and K_2CO_3 (172 mg, 1.23 mmol) in acetonitrile (10 mL) was stirred for 5 hours at 50°C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% ethyl acetate in petroleum ether) to afford the title compound (215 mg) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 555.

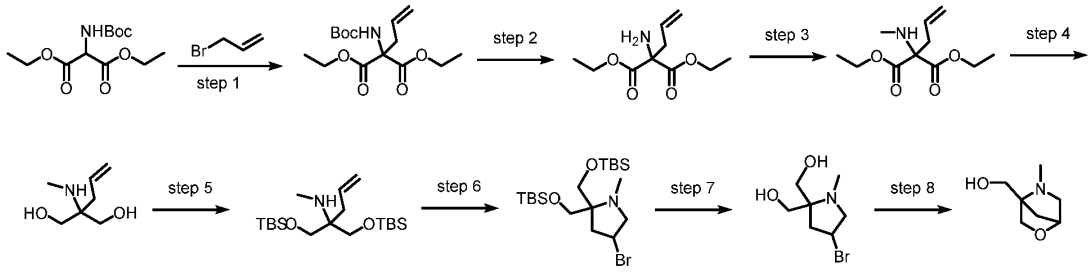
[0983] Step 7: 6-(((*tert*-Butyldiphenylsilyl) oxy) methyl)-2-methylhexahydropyrrolo[1,2-*a*] pyrazin-3(4*H*)-one (mixture of *trans* isomers)

[0984] To a solution of methyl 2-(2-(((*tert*-butoxycarbonyl) (methyl) amino) methyl)-5-(((tert-butyldiphenylsilyl) oxy) methyl) pyrrolidin-1-yl) acetate (185 mg, 0.334 mmol) in dioxane (5 mL) was added hydrogen chloride (4M solution in ethyl acetate, 6 mL) at 0 °C, and the mixture was stirred for 2 hours at room temperature. The solvent was concentrated under vacuum. The residue was re-dissolved in methanol and treated with DIPEA (1 mL). The resulting mixture was stirred at room temperature overnight. The solvent was concentrated under vacuum and the residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (130 mg) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 423$.

[0985] Step 8: 6-(Hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*] pyrazin-3(4*H*)-one (mixture of *trans* isomers)

[0986] Under nitrogen, to a solution of 6-(((*tert*-butyldiphenylsilyl) oxy) methyl)-2-methylhexahydropyrrolo[1,2-*a*] pyrazin-3(4*H*)-one (100 mg, 0.237 mmol) in methanol (10 mL) was added hydrogen chloride (4M solution in methanol, 1 mL, 4.00 mmol) at room temperature, and the mixture was stirred for 2 hours at 60 °C. The solvent was concentrated under vacuum to afford the title compound (65.0 mg, crude) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 185$. The crude was used for next step without further purification.

[0987] **Intermediate 89:** (5-Methyl-2-oxa-5-azabicyclo [2.2.1] heptan-4-yl)methanol



[0988] Step 1: Diethyl 2-allyl-2-((*tert*-butoxycarbonyl) amino) malonate

[0989] Under nitrogen, to a solution of diethyl 2-((*tert*-butoxycarbonyl) amino) malonate (10.0 g, 36.3 mmol) in tetrahydrofuran (100 mL) was added NaH (2.90 g, 72.5 mmol, 60% in mineral oil) and 3-bromoprop-1-ene (5.18 g, 43.2 mmol) at 0 °C. The resulting solution was stirred for 2 h at 80 °C. Then cooled to room temperature, quenched with NH_4Cl aqueous and extracted with EtOAc. The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc / petroleum ether) to afford 5.18 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 316$.

[0990] Step 2: Diethyl 2-allyl-2-aminomalonate

[0991] To a solution of diethyl 2-allyl-2-((*tert*-butoxycarbonyl) amino) malonate (4.68 g, 14.8 mmol) in dichloromethane (27.9 mL) was added TFA (9.30 mL). The resulting solution was stirred for 1 h at room temperature. Solvent was evaporated under vacuum to afford 6.5 g (crude) of the title compound (TFA salt) as yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 216$.

[0992] Step 3: Diethyl 2-allyl-2-(methylamino)malonate

[0993] A solution of crude diethyl 2-allyl-2-aminomalonate (6.5 g) from step 2, formaldehyde (1.11 g, 14.8 mmol, 40% in water) and NaOAc (2.44 g, 29.8 mmol) in dichloromethane (50 mL) was stirred for 2 h at room temperature. Then $NaBH(OAc)_3$ (6.30 g, 29.7 mmol) was added at room temperature, and the mixture was stirred for 1 h. Water was added to quench the reaction, extracted with DCM The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc / petroleum ether) to afford 1.09 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 230$.

[0994] Step 4: 2-Allyl-2-(methylamino) propane-1,3-diol

[0995] Under nitrogen, to a solution of diethyl 2-allyl-2-(methylamino) propanedioate (990 mg, 4.32 mmol) in tetrahydrofuran (10 mL) was added $LiAlH_4$ (3.46 mL, 2.5 M in THF) at 0 °C. The resulting solution was stirred for 30 min at room temperature The reaction was quenched by $Na_2SO_4.10H_2O$ and filtrated. The solvent was evaporated under vacuum to afford 491mg (crude) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 146$.

[0996] Step 5: 6-Allyl-*N*,2,2,3,3,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecan-6-amine

[0997] To a solution of 2-allyl-2-(methylamino) propane-1,3-diol (491 mg, 3.38 mmol) and triethylamine (1.71 g, 16.9 mmol) in dichloromethane (10 mL) was added *tert*-butylchlorodimethylsilane (1.52 g, 10.1 mmol) at 0 °C. The resulting solution was stirred for 2 h at room temperature. The reaction was quenched with NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc / petroleum ether) to afford 960 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 374$.

[0998] Step 6: 4-Bromo-2,2-bis(((*tert*-butyldimethylsilyl) oxy) methyl)-1-methylpyrrolidine

[0999] To a solution of 6-allyl-*N*,2,2,3,3,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecan-6-amine (760 mg, 2.03 mmol) in acetonitrile (10.0 mL) was added 1-bromopyrrolidine-2,5-dione (361 mg, 2.04 mmol) at room temperature. The resulting solution was stirred for 15 min at room temperature. Solvent was evaporated under vacuum to afford 240 mg (crude) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 452$.

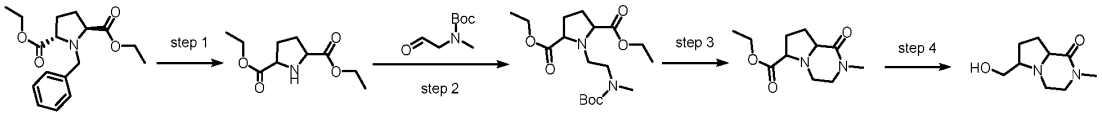
[1000] Step 7: (4-Bromo-1-methylpyrrolidine-2,2-diyl) dimethanol

[1001] To a mixture of 4-bromo-2,2-bis(((*tert*-butyldimethylsilyl) oxy) methyl)-1-methylpyrrolidine (240 mg, 0.530 mmol) in methanol methyl alcohol (2.00 mL) and tetrahydrofuran (2.00 mL) was added HCl (6.00 mL, 4 M in water). The resulting solution was stirred for overnight at room temperature. Solvent was evaporated under vacuum to afford 200 mg (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 224.

[1002] Step 8: (5-Methyl-2-oxa-5-azabicyclo [2.2.1] heptan-4-yl) methanol

[1003] Under nitrogen, to a solution of (4-bromo-1-methylpyrrolidine-2,2-diyl) dimethanol (200 mg, 0.890 mmol) in *N*,*N*-dimethylformamide (5 mL) was added NaH (71.4 mg, 1.79 mmol, 60% in mineral oil) at 0 °C. The resulting solution was stirred at room temperature for 2 h. The reaction was quenched with sat. NH_4Cl aqueous. Solvent was evaporated under vacuum. The residue was washed by DCM and filtrated. The solvent was evaporated under vacuum to afford 90 mg as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 144.

[1004] **Intermediate 90:** 6-(Hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*] pyrazin-1(2*H*)-one (mixture of *trans* isomers)



mixture of *trans*

[1005] Step 1: Diethyl pyrrolidine-2,5-dicarboxylate (mixture of *trans* isomers)

[1006] Under nitrogen, to a solution of diethyl 1-benzylpyrrolidine-2,5-dicarboxylate (mixture of *trans* isomers, 730 mg, 2.39 mmol) in ethanol (10 mL) was added 10% Pd/C (255 mg) and 20% $Pd(OH)_2/C$ (contained 61.7% water, 440 mg) at room temperature. The flask was evacuated and back fed with hydrogen three times. The resulting mixture was stirred under hydrogen (1atm) for 2 hours at room temperature. The resulting mixture was filtered over celite and the filter cake was washed with ethanol. The combined filtrate was concentrated under vacuum to afford the title compound (507 mg, crude) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 216. ^1H NMR (300 MHz, $CDCl_3$, *ppm*) δ 4.21 (q, J = 7.1 Hz, 4H), 4.06 – 3.93 (m, 2H), 2.31 – 2.10 (m, 2H), 2.04 – 1.88 (m, 2H), 1.30 (t, J = 7.1 Hz, 6H).

[1007] Step 2: Diethyl 1-(2-((*tert*-butoxycarbonyl) (methyl)amino) ethyl) pyrrolidine-2,5-dicarboxylate (mixture of *trans* isomers)

[1008] To a solution of diethyl pyrrolidine-2,5-dicarboxylate (300 mg, 1.39 mmol) in dichloromethane (10 mL) was added a solution of *tert*-butyl methyl(2-oxoethyl)carbamate (1.21 g, 6.99 mmol) in dichloromethane (2 mL) at 0°C, and the mixture was stirred for 30 minutes. Then $NaBH(OAc)_3$ (1.48 g, 6.98 mmol) was added at 0°C, and the mixture was stirred for 3 hours at room temperature. The reaction was quenched with water and extracted with

dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% ethyl acetate in petroleum ether) to afford the title compound (488 mg) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 373. ^1H NMR (300 MHz, $CDCl_3$, *ppm*) δ 4.19 (q, J = 7.1 Hz, 4H), 3.97 – 3.89 (m, 2H), 3.48 – 3.20 (m, 2H), 3.04 – 2.93 (m, 2H), 2.87 (s, 3H), 2.43 – 2.21 (m, 2H), 2.03 – 1.86 (m, 2H), 1.47 (s, 9H), 1.30 (t, J = 7.1 Hz, 6H).

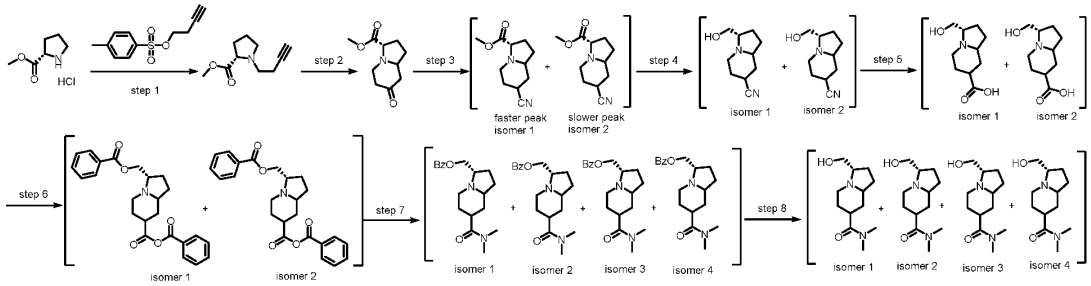
[1009] Step 3: Ethyl 2-methyl-1-oxooctahydropyrrolo[1,2-*a*] pyrazine-6-carboxylate (mixture of *trans* isomers)

[1010] To a solution of diethyl 1-(2-((*tert*-butoxycarbonyl) (methyl) amino) ethyl) pyrrolidine-2,5-dicarboxylate (438 mg, 1.18 mmol) in ethyl acetate (5 mL) was added hydrogen chloride (4M solution in ethyl acetate, 6 mL) at 0 °C, and the mixture was stirred for 2 hours at room temperature. The solvent was concentrated under vacuum. The residue was re-dissolved in ethanol (20 mL) and treated with DIPEA (2 mL, 12.0 mmol). The resulting mixture was stirred at room temperature overnight. The solvent was concentrated under vacuum and the residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (157 mg) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 227.

[1011] Step 4: 6-(Hydroxymethyl)-2-methylhexahydropyrrolo[1,2-*a*] pyrazin-1(2*H*)-one (mixture of *trans* isomers)

[1012] To a mixture of ethyl 2-methyl-1-oxooctahydropyrrolo[1,2-*a*] pyrazine-6-carboxylate (134 mg, 0.592 mmol) in tetrahydrofuran (10 mL) was added $LiBH_4$ (64.5 mg, 2.96 mmol) at room temperature, and the mixture was stirred for 6 hours at 60 °C. The reaction was quenched with $Na_2SO_4.10H_2O$. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (84.9 mg, crude) as a colorless solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 185. The crude was used for next step without further purification.

[1013] **Intermediate 91:** (3*S*)-3-(Hydroxymethyl)-*N*, *N*-dimethyloctahydroindolizine-7-carboxamide (four isomers)



[1014] Step 1: Methyl but-3-yn-1-yl-*L*-prolinate

[1015] A solution of methyl *L*-prolinate hydrochloride salt (10.1 g, 60.7 mmol), but-3-yn-1-yl 4-methylbenzenesulfonate (32.4 g, 145 mmol), NaI (4.58 g, 30.5 mmol) and $NaHCO_3$ (20.5 g, 243 mmol) in acetonitrile (500 mL) was stirred at 80°C for 16 hours. The solid was filtered out. The filtrate was concentrated under vacuum. The residue was diluted with DCM, washed with aqueous NaOH solution (5%), water and brine. The organic phase was concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-20% EtOAc / petroleum ether) to afford 11.1 g (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 182$.

[1016] Step 2: Methyl (3*S*)-7-oxooctahydroindolizine-3-carboxylate

[1017] Under nitrogen, to a solution of methyl but-3-yn-1-yl-*L*-prolinate (9.48 g, 52.3 mmol) and 4 Å MS (10 g) in dichloromethane (300 mL) was added m-CPBA (12.9 g, 63.3 mmol) at 0°C. The solution was stirred at 0°C for 2 hours. Then the solution was cooled to -78°C, a solution of PPh_3AuNTf_2 (1.95 g, 2.64 mmol) in DCM was added at -78°C. The solution was stirred at -78°C for 5 hours. The solution was diluted with DCM and the molecular sieves were filtered out. The filtrate was washed with aqueous $NaHCO_3$ solution and brine, dried over with anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-60% EtOAc / petroleum ether) to afford 5.58 g of the title compound as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 198$.

[1018] Step 3: Methyl (3*S*)-7-cyanooctahydroindolizine-3-carboxylate (two isomers)

[1019] Under nitrogen, to a solution of methyl (3*S*)-7-oxooctahydroindolizine-3-carboxylate (2.01 g, 10.2 mmol) and 1-((isocyanomethyl)sulfonyl)-4-methylbenzene (3.3 g, 16.9 mmol) in 1,2-dimethoxyethane (100 mL) and methanol (0.4 mL) was added t-BuOK (1 M in THF, 25 mL) at 0°C. The solution was stirred at room temperature for 3 hours. The solid was filtered out. The filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-60% EtOAc / petroleum ether) to afford 361 mg of the faster peak (isomer 1) and 362 mg of the slower peak (isomer 2) as brown oils. LC-MS: (ESI, *m/z*): $[M+H]^+ = 209$.

[1020] Step 4: (3*S*)-3-(Hydroxymethyl) octahydroindolizine-7-carbonitrile (two isomers)

[1021] Under nitrogen, to a solution of methyl (3*S*)-7-cyanooctahydroindolizine-3-carboxylate (500 mg, 2.4 mmol) (isomer 1of last step) in tetrahydrofuran (14 mL) was added $LiBH_4$ (2 M in THF, 2.5 mL) at 0°C. The solution was stirred at room temperature for 16 hours. The reaction was quenched by EtOAc. The solution was purified by ion exchange resin (Si-Propysulfonic acid) and concentrated under vacuum to afford 433 mg (crude) of the title compound (isomer 1) as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 181$.

[1022] Analogous to method described as above, the other isomer (isomer 2) 441 mg (crude) was prepared from methyl (3*S*)-7-cyanooctahydroindolizine-3-carboxylate (800 mg, 3.84 mmol) (isomer 2 of last step) as a crude brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 181.

[1023] Step 5: (3*S*)-3-(Hydroxymethyl) octahydroindolizine-7-carboxylic acid (two isomers)

[1024] A solution of (3*S*)-3-(hydroxymethyl) octahydroindolizine-7-carbonitrile (181 mg, 1 mmol) (isomer 1 of last step) in hydrochloric acid (6 mL, 12M) was stirred at 80°C for 2 hours. The solution was concentrated under vacuum to afford 270 mg (crude) of the title compound (isomer 1) as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 200.

[1025] Analogous to method described as above, the other isomer (isomer 2) 1.03 g (crude) was prepared from (3*S*)-3-(hydroxymethyl) octahydroindolizine-7-carbonitrile (440 mg, 2.44 mmol) (isomer 2 of last step) as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 200.

[1026] Step 6: Benzoic (3*S*)-3-((benzoyloxy)methyl) octahydroindolizine-7-carboxylic anhydride (two isomers)

[1027] To a solution of (3*S*)-3-(hydroxymethyl) octahydroindolizine-7-carboxylic acid (271 mg, crude) (isomer 1 of last step) in dichloromethane (8 mL) were added DIPEA (1.19 g, 9.22 mmol) and benzoyl chloride (585 mg, 4.16 mmol) at 0°C. The solution was stirred at room temperature for 16 hours. The solution was quenched by water, extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford 810 mg (crude) of the title compound (isomer 1) as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 408.

[1028] Analogous to method described as above, the other isomer (isomer 2) 4.31 g (crude) was prepared from (3*S*)-3-(hydroxymethyl) octahydroindolizine-7-carboxylic acid (1.03 g, crude) (isomer 2 of last step) as a crude brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 408.

[1029] Step 7: ((3*S*)-7-(Dimethylcarbamoyl) octahydroindolizin-3-yl)methyl benzoate (four isomers)

[1030] A mixture of benzoic (3*S*)-3-((benzoyloxy)methyl) octahydroindolizine-7-carboxylic anhydride (810 mg, crude) (isomer 1 of last step) and dimethylamine (2 M in THF, 12 mL) was stirred at room temperature for 4 hours. The solution was concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-40% ACN in water (0.05% NH_4HCO_3)) to afford 95 mg of the faster peak (isomer 1) and 67 mg of the slower peak (isomer 2) as brown oils. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 331.

[1031] Analogous to method described as above, the other isomers (the mixture of isomer 3 and isomer 4) 277 mg was prepared from (3*S*)-3-((benzoyloxy)methyl) octahydroindolizine-7-carboxylic anhydride (4.31 g, crude, 2.44 mmol) (isomer 2 of last step) as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 331.

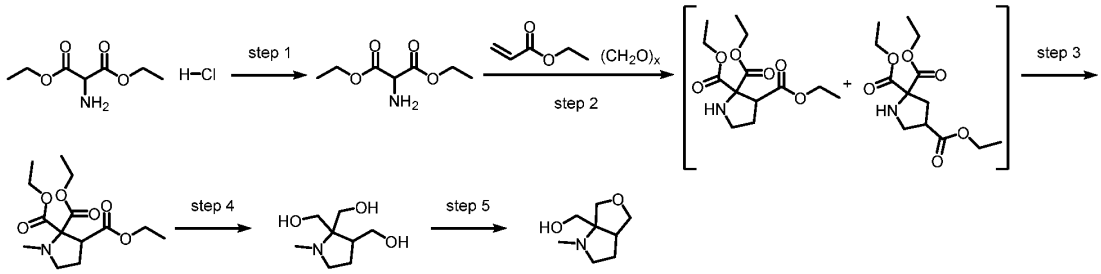
[1032] Step 8: (3*S*)-3-(Hydroxymethyl)-*N*,*N*-dimethyloctahydroindolizine-7-carboxamide (four isomers)

[1033] To a solution of ((3*S*)-7-(dimethylcarbamoyl) octahydroindolizin-3-yl)methyl benzoate (65.1 mg, 0.200 mmol) (isomer 1 of last step) in ethanol (1.5 mL) was added a solution of NaOH (24.8 mg, 0.620 mmol) in water (0.5 mL). The solution was stirred at room temperature for 2 hours. The reaction solution was adjusted to pH=7 with 2N HCl aqueous. Then the solution was purified by ion exchange resin (Si-Propysulfonic acid) and concentrated under vacuum to afford 43 mg (crude) of the title compound (isomer 1) as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 227. The crude was used for next step without further purification.

[1034] Analogous to method described as above, the other isomer (isomer 2) 46 mg (crude) was prepared from ((3*S*)-7-(dimethylcarbamoyl) octahydroindolizin-3-yl)methyl benzoate (66.5 mg, 0.200 mmol) (isomer 2 of last step) as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 227.

[1035] Analogous to method described as above, the other isomers (the mixture of isomer 3 and isomer 4) 145 mg (crude) was prepared from ((3*S*)-7-(dimethylcarbamoyl) octahydroindolizin-3-yl) methyl benzoate (277 mg, 0.840 mmol) (the mixture of isomer 3 and isomer 4) as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 227. These two isomers were separated at the target compound.

[1036] **Intermediate 92:** (1-Methyltetrahydro-1*H*-furo[3,4-*b*] pyrrol-6a(6*H*)-yl) methanol



[1037] Step 1: Diethyl 2-aminomalonate

[1038] To a solution of diethyl 2-aminomalonate hydrochloride (25.0 g, 118 mmol) in ethanol (10 mL) was added $NaHCO_3$ (19.8 g, 236 mmol) at room temperature in portions, and the mixture was stirred for 1 hour. The resulting mixture was filtered and the filtrate was concentrated under vacuum to afford the title compound (20.0 g, crude) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 176.

[1039] Step 2: Triethyl pyrrolidine-2,2,3-tricarboxylate & Triethyl pyrrolidine-2,2,4-tricarboxylate (~3:1 mixture)

[1040] A solution of diethyl 2-aminomalonate (20.0 g, 114 mmol), ethyl acrylate (11.4 g, 114 mmol) and polyformaldehyde (3.42 g, 38.0 mmol) in toluene (500 mL) was stirred overnight at 110 °C. The solvent was concentrated under vacuum. The residue was purified by flash

chromatography on silica gel (gradient: 0-50% ethyl acetate in petroleum ether) to afford the title compounds (25.0 g) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 288.

[1041] Step 3: Triethyl 1-methylpyrrolidine-2,2,3-tricarboxylate

[1042] To a solution of triethyl pyrrolidine-2,2,3-tricarboxylate and triethyl pyrrolidine-2,2,4-tricarboxylate (~3:1 mixture, 25.0 g, 87.1 mmol) and polyformaldehyde (13.1 g, 145 mmol) in dichloromethane (500 mL) was added $NaBH(OAc)_3$ (92.3 g, 436 mmol) at room temperature in portions, and the mixture was stirred overnight. The reaction was quenched with water at 0 °C and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc in petroleum ether) to afford the title compound (15.7 g) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 302. ^1H NMR (300 MHz, $CDCl_3$, *ppm*) δ 4.33 – 4.07 (m, 6H), 3.72 – 3.61 (m, 1H), 3.16 – 3.05 (m, 1H), 2.95 – 2.82 (m, 1H), 2.54 (s, 3H), 2.36 – 2.11 (m, 2H), 1.36 – 1.20 (m, 9H).

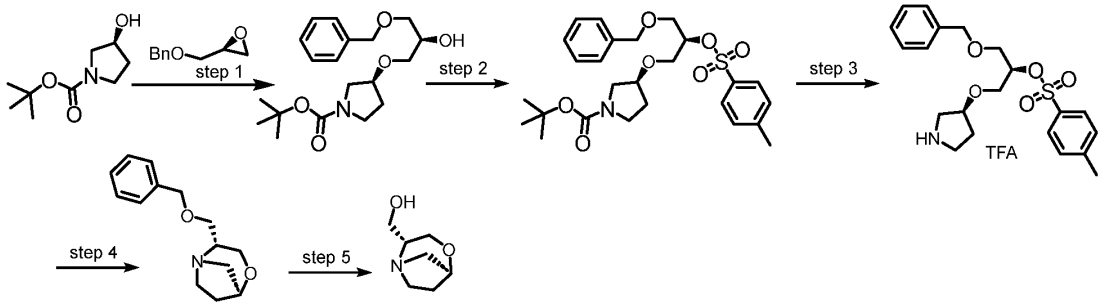
[1043] Step 4: (1-Methylpyrrolidine-2,2,3-triyl) trimethanol

[1044] Under nitrogen, to a solution of triethyl 1-methylpyrrolidine-2,2,3-tricarboxylate (9.00 g, 30.0 mmol) in tetrahydrofuran (200 mL) was added $LiAlH_4$ (2M solution in tetrahydrofuran, 30 mL) dropwise at 0 °C, and the mixture was stirred for 2 hours at room temperature. The reaction was quenched with $Na_2SO_4.10H_2O$. After filtration, the filtrate was collected and concentrated under vacuum to afford the title compound (5.10 g, crude) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 176.

[1045] Step 5: (1-Methyltetrahydro-1*H*-furo[3,4-*b*] pyrrol-6a(6*H*)-yl)methanol

[1046] Under nitrogen, to a solution of (1-methylpyrrolidine-2,2,3-triyl) trimethanol (175 mg, 1.00 mmol) and TEA (0.4 mL) in dichloromethane (4 mL) was added Tf_2O (0.3 mL, 1.78 mmol) dropwise at -10 °C, and the mixture was stirred for 30 minutes at room temperature. The solvent was concentrated under vacuum to afford the title compound (300 mg, crude) as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 158. The crude was used for next step without further purification.

[1047] **Intermediate 93:** ((2*R*,5*S*)-4-Oxa-1-azabicyclo [3.2.1] octan-2-yl) methanol



[1048] Step 1: *tert*-Butyl (*S*)-3-((*R*)-3-(benzyloxy)-2-hydroxypropoxy) pyrrolidine-1-carboxylate

[1049] Under nitrogen, to a solution of *tert*-butyl (*S*)-3-hydroxypyrrolidine-1-carboxylate (5.00 g, 26.7mmol) in THF (80mL) was added NaH (2.67g, 66.7mmol) at 0 °C. The resulting solution was stirred at 0 °C for 20 min. Then (*S*)-2-((benzyloxy) methyl) oxirane (4.38g, 26.7mmol) was added. The solution was stirred at 50 °C overnight. The reaction was quenched with water, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-60% ACN in water (0.05% NH_4HCO_3)) to afford the title compound (2.55g) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 352$.

[1050] Step 2: *tert*-Butyl (*S*)-3-((*R*)-3-(benzyloxy)-2-(tosyloxy) propoxy) pyrrolidine-1-carboxylate

[1051] To a solution of *tert*-butyl (*S*)-3-((*R*)-3-(benzyloxy)-2-hydroxypropoxy) pyrrolidine-1-carboxylate (2.65g, 7.54mmol) in dichloromethane (20mL) was added Et_3N (2.84g, 28.0 mmol), TsCl (1.75g, 9.18 mmol) and 4-DMAP (46.0 mg, 0.38 mmol) at 0 °C. The resulting solution was stirred at room temperature overnight. The reaction was quenched with water, washed with 0.1 M HCl and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-40% EtOAc / petroleum ether) to afford the title compound (2.57g) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 506$.

[1052] Step 3: (*R*)-1-(Benzyloxy)-3-(((*S*)-pyrrolidin-3-yl)oxy)propan-2-yl 4-methylbenzenesulfonate (TFA salt)

[1053] A solution of *tert*-butyl (*S*)-3-((*R*)-3-(benzyloxy)-2-(tosyloxy) propoxy) pyrrolidine-1-carboxylate (2.57g, 5.08mmol) in 2,2,2-trifluoroacetic acid (3mL) and dichloromethane (9mL) was stirred at room temperature for 1 hour. The mixture was concentrated under vacuum to afford crude product (3.30 g) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 406$.

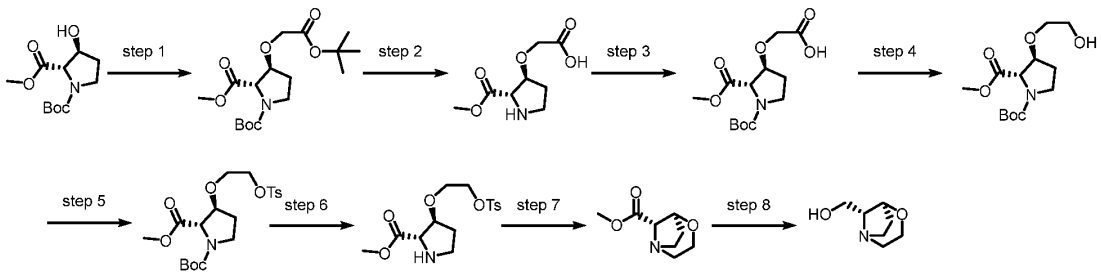
[1054] Step 4: (2*R*,5*S*)-2-((Benzyloxy)methyl)-4-oxa-1-azabicyclo [3.2.1] octane

[1055] A solution of (*R*)-1-(benzyloxy)-3-(((*S*)-pyrrolidin-3-yl) oxy) propan-2-yl 4-methylbenzenesulfonate (TFA salt) (3.30g, 6.35mmol) and K_2CO_3 (3.37g, 24.4mmol) in acetonitrile (30mL) was stirred at 70 °C overnight. The resulting mixture was concentrated under reduced pressure. The residue was purified by C18 column (solvent gradient: 0-100% ACN in water (0.05% NH_4HCO_3)) to afford the title compound (890mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 234$.

[1056] Step 5: ((2*R*,5*S*)-4-Oxa-1-azabicyclo [3.2.1] octan-2-yl) methanol

[1057] Under hydrogen (1atm), a solution of ((2*R*,5*S*)-2-((benzyloxy)methyl)-4-oxa-1-azabicyclo [3.2.1] octane (139mg, 0.600mmol) and 10% Pd/C (180mg) in methyl alcohol (4mL) was stirred at room temperature overnight. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure to afford the title compound (51mg crude) as a white oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 144. The crude was used for next step without further purification.

[1058] **Intermediate 94:** ((5*S*,8*R*)-4-Oxa-1-azabicyclo [3.2.1] octan-8-yl) methanol



[1059] Step 1: 1-(*tert*-Butyl) 2-methyl (2*S*,3*S*)-3-(2-(*tert*-butoxy)-2-oxoethoxy) pyrrolidine-1,2-dicarboxylate

[1060] Under nitrogen, to a solution of 1-(*tert*-butyl) 2-methyl (2*S*,3*S*)-3-hydroxypyrrolidine-1,2-dicarboxylate (1.01 g, 4.12 mmol) in THF (8 mL) was added NaH (247 mg, 6.18 mmol, 60% in mineral oil) at 0°C. The resulting solution was stirred for 0.5 hours at 0°C. Then *tert*-butyl 2-chloroacetate (1.22 mL, 8.25 mmol) was added, and the mixture was stirred at 0°C for 1 hour. The reaction was quenched with NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford 351 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 360.

[1061] Step 2: 2-(((2*S*,3*S*)-2-(Methoxycarbonyl) pyrrolidin-3-yl) oxy) acetic acid

[1062] To a solution of 1-(*tert*-butyl) 2-methyl (2*S*,3*S*)-3-(2-(*tert*-butoxy)-2-oxoethoxy) pyrrolidine-1,2-dicarboxylate (351 mg, 0.970 mmol) in acetonitrile (3 mL) was added HCl / 1,4-dioxane (1 mL, 4 mol/L), and the mixture was stirred at room temperature for 3 hours. The solvent was concentrated under vacuum to afford 298 mg (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 204.

[1063] Step 3: 2-(((2*S*,3*S*)-1-(*tert*-Butoxycarbonyl)-2-(methoxycarbonyl)pyrrolidin-3-yl)oxy)acetic acid

[1064] To a solution of 2-(((2*S*,3*S*)-2-(methoxycarbonyl) pyrrolidin-3-yl)oxy)acetic acid (261 mg, 1.28 mmol) in DCM (2 mL) was added DIPEA (1.30 g, 10.1 mmol) and $(Boc)_2O$ (837 mg, 3.84 mmol). The solution was stirred at room temperature for 1 hour. The resulting mixture was diluted with DCM and washed with water and brine. The organic layer was concentrated under

vacuum to afford 319 mg (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 304.

[1065] Step 4: 1-(*tert*-Butyl) 2-methyl (2*S*,3*S*)-3-(2-hydroxyethoxy) pyrrolidine-1,2-dicarboxylate

[1066] Under nitrogen, to a solution of 2-(((2*S*,3*S*)-1-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl) pyrrolidin-3-yl) oxy) acetic acid (262 mg, 0.860 mmol) in THF (3 mL) was added BH_3 (1.6 mL, 1M in THF) at 0°C. The resulting solution was stirred for 3 hours at 0°C. The reaction was quenched with MeOH. The reaction mixture concentrated under vacuum to afford 349 mg (crude) of the title compound as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 290.

[1067] Step 5: 1-(*tert*-Butyl) 2-methyl (2*S*,3*S*)-3-(2-(tosyloxy) ethoxy) pyrrolidine-1,2-dicarboxylate

[1068] Under nitrogen, to a solution of 1-(*tert*-butyl) 2-methyl (2*S*,3*S*)-3-(2-hydroxyethoxy) pyrrolidine-1,2-dicarboxylate (301 mg, 1.04 mmol), Et_3N (207 mg, 2.05 mmol) and 4-DMAP (12.7 mg, 0.100 mmol) in DCM (10 mL) was added TsCl (217 mg, 1.14 mmol) at room temperature. The solution was stirred for 8 hours at room temperature. The resulting mixture was diluted with EtOAc and washed with water and brine. The organic layer was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH / DCM) to afford 128 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 444.

[1069] Step 6: Methyl (2*S*,3*S*)-3-(2-(tosyloxy) ethoxy) pyrrolidine-2-carboxylate

[1070] To a solution of 1-(*tert*-butyl) 2-methyl (2*S*,3*S*)-3-(2-(tosyloxy) ethoxy) pyrrolidine-1,2-dicarboxylate (111 mg, 0.250 mmol) in acetonitrile (4.5 mL) was added HCl / 1,4-dioxane (1.5 mL, 4 mol/L), and the mixture was stirred at room temperature for 1 hour. The solvent was concentrated under vacuum to afford 103 mg (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 344.

[1071] Step 7: Methyl (5*S*,8*S*)-4-oxa-1-azabicyclo [3.2.1] octane-8-carboxylate

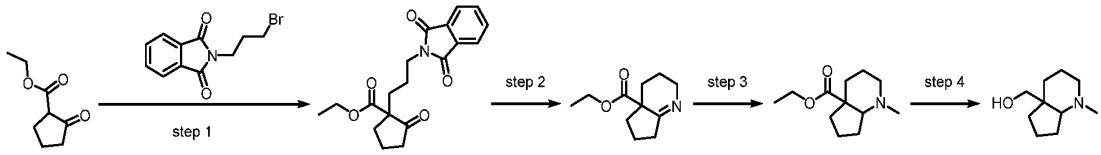
[1072] To a solution of methyl (2*S*,3*S*)-3-(2-(tosyloxy) ethoxy) pyrrolidine-2-carboxylate (103 mg, 0.300 mmol) in acetonitrile (5 mL) was added K_2CO_3 (227 mg, 1.64 mmol), and the mixture was stirred at 70°C for 3 hours. After filtration, the filtrate was concentrated under reduced pressure to afford 110 mg (crude) of the title compound as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 172.

[1073] Step 8: ((5*S*,8*R*)-4-Oxa-1-azabicyclo [3.2.1] octan-8-yl)methanol

[1074] Under nitrogen, to a solution of methyl (5*S*,8*S*)-4-oxa-1-azabicyclo [3.2.1] octane-8-carboxylate (110 mg, crude) in THF (3 mL) was added $LiAlH_4$ (1.3 mL, 1M in THF) at 0°C. The resulting solution was stirred for 1 hour at room temperature. The reaction was quenched by

$Na_2SO_4 \cdot 10H_2O$. After filtration, the filtrate was concentrated under reduced pressure to afford 63.1 mg (crude) of the title compound as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 144. The crude was used for next step without further purification.

[1075] **Intermediate 95:** (1-Methyloctahydro-4a*H*-cyclopenta[*b*]pyridin-4a-*yl*)methanol



[1076] Step 1: Ethyl 1-(3-(1,3-dioxoisoindolin-2-yl) propyl)-2-oxocyclopentane-1-carboxylate

[1077] To a solution of ethyl 2-oxocyclopentane-1-carboxylate (10.0 g, 64.1 mmol) in tetrahydrofuran (50 mL) and DMF (50 mL) was added NaH (60% dispersion in mineral oil, 3.08 g, 76.9 mmol) in 3 portions at 0 °C, and the mixture was stirred for 30 minutes. Then 2-(3-bromopropyl) isoindoline-1,3-dione (18.9 g, 70.5 mmol) in tetrahydrofuran (50 mL) was added at 0 °C, and the mixture was stirred overnight at 65 °C. The reaction was quenched with /saturated NH_4Cl aqueous solution. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (13.5 g) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 344. ^1H NMR (300 MHz, $CDCl_3$, *ppm*) δ 7.88 – 7.77 (m, 2H), 7.76 – 7.65 (m, 2H), 4.23 – 4.04 (m, 2H), 3.88 – 3.56 (m, 2H), 2.60 – 2.13 (m, 4H), 2.06 – 1.70 (m, 4H), 1.70 – 1.50 (m, 2H), 1.32 – 1.15 (m, 3H).

[1078] Step 2: Ethyl 2,3,4,5,6,7-hexahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate

[1079] To a solution of ethyl 1-(3-(1,3-dioxoisoindolin-2-yl) propyl)-2-oxocyclopentane-1-carboxylate (13.5 g, 39.2 mmol) in ethanol (200 mL) was added hydrazine hydrate (80%, 7.2 mL) at room temperature, and the mixture was stirred for 1 hour at 80 °C. The mixture was cooled to room temperature and the solid was filtered. The filtrate was concentrated under reduced pressure to afford the title compound (4.40 g, crude) as an off white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 196.

[1080] Step 3: Ethyl 1-methyloctahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate

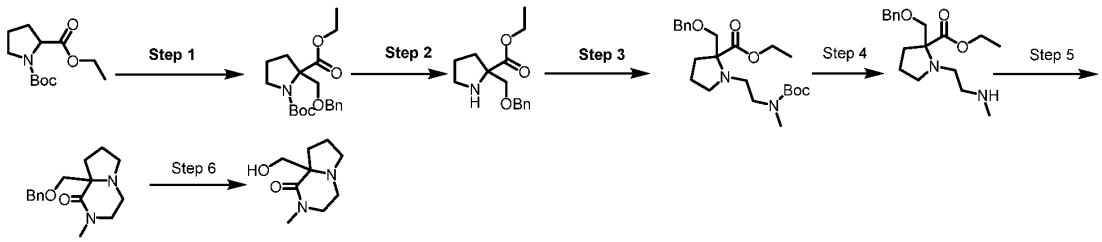
[1081] To a solution of ethyl 2,3,4,5,6,7-hexahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (4.40 g, 22.4 mmol) and polyformaldehyde (3.36 g, 37.3 mmol) in dichloromethane (300 mL) was added $NaBH(OAc)_3$ (23.7 g, 112 mmol) at room temperature in portions, and the mixture was stirred overnight. The reaction was quenched with water at 0 °C and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash

chromatography on silica gel (gradient: 0-40% EtOAc in petroleum ether) to afford the title compound (1.50 g) as a light colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 212.

[1082] Step 4: (1-Methyloctahydro-4aH-cyclopenta[b]pyridin-4a-yl) methanol

[1083] To a solution of ethyl 1-methyloctahydro-4a*H*-cyclopenta[*b*]pyridine-4a-carboxylate (1.50 g, 7.08 mmol) in tetrahydrofuran (20 mL) was added $LiAlH_4$ (2M solution in tetrahydrofuran, 7.1 mL) dropwise at 0 °C, and the mixture was stirred for 1 hour at room temperature. The reaction was quenched with $Na_2SO_4.10H_2O$. After filtration, the filtrate was collected and concentrated under vacuum to afford the title compound (600 mg crude) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 170. The crude was used for next step without further purification.

[1084] **Intermediate 96:** 8*a*-(Hydroxymethyl)-2-methylhexahydropyrrolo[1,2-a]pyrazin-1(2*H*)-one



[1085] Step 1: 1-(*tert*-Butyl) 2-ethyl 2-((benzyloxy)methyl) pyrrolidine-1,2-dicarboxylate

[1086] Under nitrogen, to a solution of 1-(tert-butyl) 2-ethyl pyrrolidine-1,2-dicarboxylate (10.0g, 41.1mmol) in tetrahydrofuran (100mL) was added LiHMDS (1M in THF, 100mL, 100mmol) at -40 °C. The resulting solution was stirred at -40 °C for 30 min. Then BOMCl (9.62g, 61.7mmol) was added at -40°C. The solution was stirred at 25°C for 1 hour. The reaction mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% EtOAc/petroleum ether) to afford 12g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 364.

[1087] Step 2: Ethyl 2-((benzyloxy) methyl) pyrrolidine-2-carboxylate

[1088] A solution of 1-(*tert*-butyl) 2-ethyl 2-(benzyloxymethyl) pyrrolidine-1,2-dicarboxylate (5.0g, 13.8mmol) in dichloromethane (50mL) and TFA (20mL) was stirred at room temperature for 2 hours. The resulting mixture was concentrated under reduced pressure. The residue was purified by C18 column (solvent gradient: 0-80% ACN in water (0.05% NH_4HCO_3)) to afford 3.4g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$= 264.

[1089] Step 3: Ethyl 2-((benzyloxy)methyl)-1-(2-((tert-butoxycarbonyl) (methyl)amino) ethyl) pyrrolidine-2-carboxylate

[1090] To a solution of ethyl 2-(benzyloxymethyl) pyrrolidine-2-carboxylate (2.5g, 9.49mmol) in dichloromethane (50mL) was added a solution of *tert*-butyl N-methyl-N-(2-oxoethyl)carbamate (8.2 g, 47.5 mmol) in dichloromethane (10mL) at 0°C, and the mixture was stirred for 30 minutes. Then $NaBH(OAc)_3$ (10g, 48 mmol) was added at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction was quenched with water and extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc/petroleum ether) to afford 3.9g as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ =421.

[1091] Step 4: Ethyl 2-((benzyloxy)methyl)-1-(2-(methylamino) ethyl) pyrrolidine-2-carboxylate

[1092] A solution of ethyl 2-(benzyloxymethyl)-1-[2-[*tert*-butoxycarbonyl(methyl) amino]ethyl]pyrrolidine-2-carboxylate (100mg, 0.24mmol) in aqueous HCl (1M) in EtOAc solution (1.5mL) and dichloromethane (3mL) was stirred at 25 °C for 4 hours. The resulting mixture was concentrated under reduced pressure to afford 50mg (crude) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 321. The crude was used for next step without further purification.

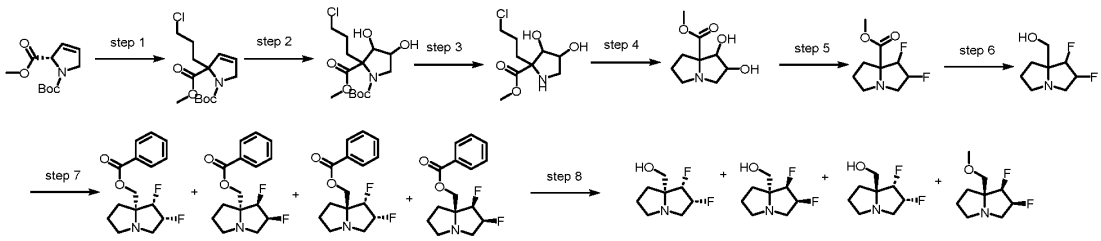
[1093] Step 5: 8*a*-((Benzyloxy)methyl)-2-methylhexahydropyrrolo[1,2-a] pyrazin-1(2*H*)-one

[1094] A solution of ethyl 2-(benzyloxymethyl)-1-[2-(methylamino)ethyl] pyrrolidine-2-carboxylate (1.0g, 3.12mmol) and DIPEA (4.02g, 31.2mmol) in MeOH was stirred at 25 °C for 72 hours. The resulting mixture was extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% MeOH/DCM) to afford 200 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$= 275.

[1095] Step 6: 8*a*-(Hydroxymethyl)-2-methylhexahydropyrrolo[1,2-a] pyrazin-1(2*H*)-one

[1096] Under nitrogen, to a solution of 8a-(benzyloxymethyl)-2-methyl-4,6,7,8-tetrahydro-3*H*-pyrrolo[1,2-a] pyrazin-1-one (300mg, 1.09mmol) in methyl alcohol (5mL) was added Pd/C (10%, 20.0 mg) at 25 °C. The resulting solution was stirred at room temperature for 18h. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound 250 mg crude. LC-MS: (ESI, *m/z*): $[M+H]^+$= 185. The crude product was used for next step without further purification.

[1097] **Intermediate 97:** (1,2-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methanol



[1098] Step 1: 1-(*tert*-Butyl) 2-methyl 2-(3-chloropropyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate

[1099] Under nitrogen, to a solution of 1-(*tert*-butyl) 2-methyl (*S*)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (10.8 g, 47.5 mmol) in THF (50 mL) was added LiHMDS (95.3 mL, 1 M in THF) dropwise at -30 °C, and the mixture was stirred for 1 hour at -30 °C. Then 1-bromo-3-chloropropane (22.4 g, 142 mmol) was added dropwise at -30 °C, and the mixture was stirred for 30 min. The mixture was warmed to room temperature and stirred for 1.5 h. The reaction was quenched with NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-40% EtOAc / petroleum ether) to afford 10.7 g of the title compound as a light yellow syrup. LC-MS: (ESI, *m/z*): $[M+H]^+ = 304$.

[1100] Step 2: 1-(*tert*-Butyl) 2-methyl 2-(3-chloropropyl)-3,4-dihydroxypyrrolidine-1,2-dicarboxylate

[1101] A solution of 1-(*tert*-butyl) 2-methyl 2-(3-chloropropyl)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (10.7 g, 35.2 mmol), NMMO (10.2 g, 88.3 mmol) and $K_2OsO_2(OH)_4$ (1.62 g, 4.40 mmol) in acetone (60 mL) and water (40 mL) was stirred at room temperature for 2 hours. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-4% MeOH / DCM) to afford 10.4 g of the title compound as a brown syrup. LC-MS: (ESI, *m/z*): $[M+H]^+ = 338$.

[1102] Step 3: Methyl 2-(3-chloropropyl)-3,4-dihydroxypyrrolidine-2-carboxylate

[1103] A solution of 1-(*tert*-butyl) 2-methyl 2-(3-chloropropyl)-3,4-dihydroxypyrrolidine-1,2-dicarboxylate (10.4 g, 30.7 mmol) and TFA (25 mL) in DCM (75 mL) was stirred at room temperature for 2 hours. The solvent was concentrated under vacuum to afford 8.26 g crude of the title compound as a brown syrup. LC-MS: (ESI, *m/z*): $[M+H]^+ = 238$.

[1104] Step 4: Methyl 1,2-dihydroxytetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate

[1105] A solution of methyl 2-(3-chloropropyl)-3,4-dihydroxypyrrolidine-2-carboxylate (8.26 g, 34.8 mmol) and K_2CO_3 (14.2 g, 103 mmol) in acetonitrile (60 mL) was stirred at room temperature for 1.5 hours. The solvent was concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-70% ACN in water (0.05% NH_4HCO_3)) to yield 13.0 g (crude) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 202$.

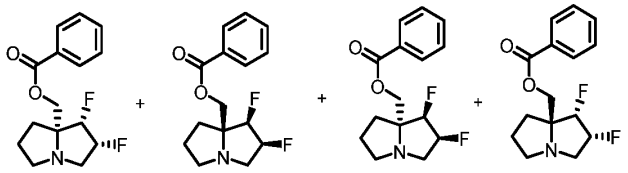
[1106] Step 5: Methyl 1,2-difluorotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate

[1107] Under nitrogen, a solution of methyl 1,2-dihydroxytetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (13.0g, 64.7 mmol) (crude) in DAST (65 mL) was stirred for 2 days at 40 °C, quenched by $NaHCO_3$ aqueous and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was dissolved with CH_3OH (30 mL). After filtration, the filtrate was concentrated under reduced pressure to afford 3.91 g crude of the title compound as a brown syrup. LC-MS: (ESI, *m/z*): $[M+H]^+ = 206$.

[1108] Step 6: (1,2-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methanol

[1109] Under nitrogen, a solution of methyl 1,2-difluorotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (2.65 g, crude) in THF (20 mL) was added $LiAlH_4$ (8.1 mL, 2.4 M in THF) at 0 °C. The resulting solution was stirred for 1 h at room temperature. The reaction was quenched with $Na_2SO_4.10H_2O$. After filtration, the filtrate was concentrated under reduced pressure to afford 1.19 g crude of the title compound as a brown syrup. LC-MS: (ESI, *m/z*): $[M+H]^+ = 178$.

[1110] Step 7: (1,2-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methyl benzoate



isomer 1 isomer 2 isomer 3 isomer 4

[1111] To a solution of (1,2-difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methanol (1.19 g, 6.72 mmol) and Et_3N (1.36 g, 13.5 mmol) in DCM (12mL) was added benzoyl chloride (1.42 g, 10.1 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-4% MeOH / DCM) to afford mixture product. The mixture was purified by C18 column (solvent gradient: 0-60% ACN in water (0.05% NH_4HCO_3)) to yield 633.3 mg of the mixture of isomer 1 and isomer 2 (faster peak) as a yellow syrup and 295.1 mg of the isomer 3 and isomer 4 (slower peak) as a yellow syrup. The isomer 1 and isomer 2 were separated by Chiral-Prep-HPLC (conditions: Column: CHIRAL ART Cellulose-SC, 2*25 cm,5um; Mobile Phase A: – (0.5 % 2 M NH_3-MeOH) -- –C, Mobile Phase B: IPA--HPLC; Flow rate:20 mL/min; Gradient:30 B to 30 B in 15 min; 220/254 nm; R_{T1}:8.505; R_{T2}:10.259) to afford 229 mg of **isomer 1** as a colorless syrup (single cis isomer, complete configuration not determined) and 223 mg of **isomer 2** as a colorless syrup (single cis isomer, complete configuration not determined). The **isomer 3** and **isomer 4** were separated by Chiral-Prep-HPLC (conditions: Column: LUX 5 um Cellulose-2, 2.12*25 cm; Mobile Phase A:–x (0.5% 2 M NH_3-MeOH) -- H–, Mobile Phase B: EtOH--HPLC; Flow rate:20 mL/min; Gradient:5 B to 5 B in 15 min; 220/254 nm; R_{T1}:9.533;

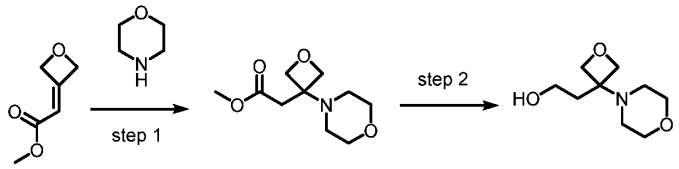
R_{T2}:13.438) to afford 117 mg of **isomer 3** as a colorless syrup (single trans isomer, the exact structure is not sure) and 108 mg of **isomer 4** as a colorless syrup (single trans isomer, the exact structure is not sure). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 282.

[1112] Step 8: (1,2-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methanol

[1113] A solution of (1,2-difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methyl benzoate (50.3 mg, 0.180 mmol) (isomer 1 from last step) and $LiOH.H_2O$ (45.3 mg, 1.08 mmol) in THF (1 mL) and water (0.25 mL) was stirred at room temperature overnight. The solution was diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum to afford 30.6 mg (crude) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 178.

[1114] Analogous to method described as above, another 3 isomers were prepared.

[1115] **Intermediate 100:** 2-(3-Morpholinooxetan-3-yl)ethan-1-ol



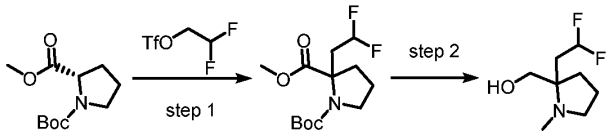
[1116] Step 1: Methyl 2-(3-morpholinooxetan-3-yl)acetate

[1117] A mixture of methyl 2-(oxetan-3-ylidene) acetate (1.01 g, 7.11 mmol) and morpholine (2.25 g, 25.8 mmol) was stirred at room temperature for 3 hours. The solution was diluted with EtOAc, washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-40% EtOAc / petroleum ether) to afford 1.01 g of the title compound as a light brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 216.

[1118] Step 2: 2-(3-Morpholinooxetan-3-yl)ethan-1-ol

[1119] Under nitrogen, to a solution of methyl 2-(3-morpholinooxetan-3-yl)acetate (600 mg, 2.79 mmol) in tetrahydrofuran (15 mL) was added $LiAlH_4$ (2 mL, 2.5 M in THF) at 0°C. The solution was stirred at room temperature for 2 hours. The reaction was quenched by $Na_2SO_4.10H_2O$, and the solid was filtered out. The filtrate was concentrated under vacuum to afford 487 mg (crude) of the title compound as an colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 188. The crude was used for next step without further purification.

[1120] **Intermediate 103:** (2-(2,2-Difluoroethyl)-1-methylpyrrolidin-2-yl)methanol



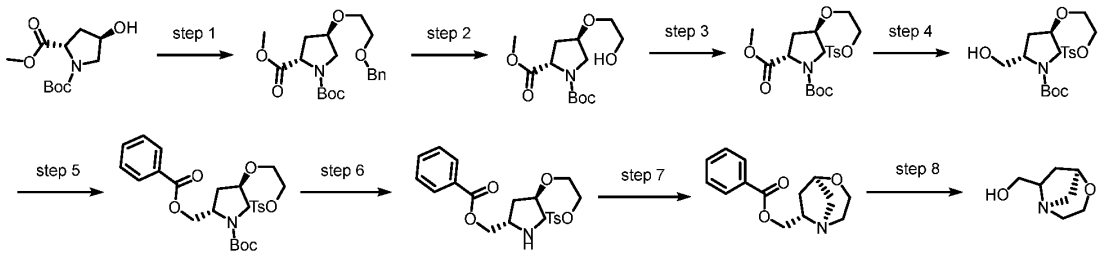
[1121] Step 1: 1-(*tert*-Butyl) 2-methyl 2-(2,2-difluoroethyl)pyrrolidine-1,2-dicarboxylate

[1122] To a solution of 1-(*tert*-butyl) 2-methyl (*S*)-pyrrolidine-1,2-dicarboxylate (2.50 g, 10.9 mmol) in tetrahydrofuran (50 mL) was added LiHMDS (1M in THF, 22 mL) dropwise at -40 °C, and the mixture was stirred for 1 hour. Then a solution of 2,2-difluoroethyl trifluoromethanesulfonate (3.50 g, 16.4 mmol) in tetrahydrofuran (50 mL) was added dropwise at -40 °C, and the mixture was stirred for additional 1 hour at room temperature. The reaction was quenched with saturated NH_4Cl. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% ethyl acetate in petroleum ether) to afford the title compound (1.50 g) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 294$.

[1123] Step 2: (2-(2,2-Difluoroethyl)-1-methylpyrrolidin-2-yl)methanol

[1124] To a solution of 1-(*tert*-butyl) 2-methyl 2-(2,2-difluoroethyl)pyrrolidine-1,2-dicarboxylate (1.50 g, 5.11 mmol) in tetrahydrofuran (15 mL) was added $LiAlH_4$ (389 mg, 10.3 mmol) in portions at 0 °C, and the mixture was stirred for 2 hours at 60 °C. The reaction was quenched with $Na_2SO_4.10H_2O$. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-15% ethyl acetate in petroleum ether) to afford the title compound (700 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 180$.

[1125] **Intermediate 104:** ((1*R*,5*R*)-4-Oxa-1-azabicyclo[3.2.1]octan-7-yl)methanol



[1126] Step 1: 1-(*tert*-Butyl) 2-methyl (2*S*,4*R*)-4-(2-(benzyloxy)ethoxy)pyrrolidine-1,2-dicarboxylate

[1127] Under nitrogen, to a solution of 1-(tert-butyl) 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (20.0 g, 81.6 mmol) in DMF (200 mL) was added NaI (1.22 g, 8.16 mmol) and NaH (3.92 g, 98.0 mmol, 60% dispersion in mineral oil) at 0 °C. The resulting solution was stirred at 0 °C for 20 min. Then ((2-bromoethoxy)methyl)benzene (19.2 g, 89.4 mmol) was added, and the mixture was stirred at room temperature for 1 h. The reaction was quenched by NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash

chromatography on silica gel (gradient: 0%-50% EtOAc / petroleum ether) to afford 12.8 g of the title compound as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 280.

[1128] Step 2: 1-(*tert*-Butyl) 2-methyl (2*S*,4*R*)-4-(2-hydroxyethoxy)pyrrolidine-1,2-dicarboxylate

[1129] Under hydrogen (1 atm), a suspension of Pd/C (1.68 g, 10%) and 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-(2-(benzyloxy)ethoxy)pyrrolidine-1,2-dicarboxylate (6.70 g, 17.7 mmol) in MeOH (700 mL) was stirred at room temperature for 2 days. The solution was filtered and the filtrate was concentrated under vacuum to afford 4.89 g (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M-100+H]^+$ = 190.

[1130] Step 3: 1-(*tert*-Butyl) 2-methyl (2*S*,4*R*)-4-(2-(tosyloxy)ethoxy)pyrrolidine-1,2-dicarboxylate

[1131] To a solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-(2-hydroxyethoxy)pyrrolidine-1,2-dicarboxylate (5.01 g, 17.3 mmol), DIPEA (2.46 g, 19.0 mmol) and 4-DMAP (211 mg, 1.73 mmol) in DCM (55 mL) was added TsCl (3.64 g, 19.0 mmol) at 0 °C. The solution was stirred at room temperature overnight. The resulting solution was partitioned between water and DCM. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-50% EtOAc / petroleum ether) to afford 4.76 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M-100+H]^+$ = 344.

[1132] Step 4: *tert*-Butyl (2*S*,4*R*)-2-(hydroxymethyl)-4-(2-(tosyloxy)ethoxy)pyrrolidine-1-carboxylate

[1133] Under nitrogen, a solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-(2-(tosyloxy)ethoxy)pyrrolidine-1,2-dicarboxylate (9.46 g, 21.3 mmol) in THF (100 mL) was added $LiAlH_4$ (8.54 mL, 2.5 M in THF) at 0 °C. The result solution was stirred at 0 °C for 30 min. The solution was quenched with $Na_2SO_4.10H_2O$ at 0 °C and filtrated. The solvent was concentrated under vacuum to afford 7.50 g (crude) of the title compound as a yellow crude oil. LC-MS: (ESI, *m/z*): $[M-100+H]^+$ = 316.

[1134] Step 5: *tert*-Butyl (2*S*,4*R*)-2-((benzoyloxy)methyl)-4-(2-(tosyloxy)ethoxy)pyrrolidine-1-carboxylate

[1135] To a solution of *tert*-butyl (2*S*,4*R*)-2-(hydroxymethyl)-4-(2-(tosyloxy)ethoxy)pyrrolidine-1-carboxylate (7.50 g, 18.1 mmol) and Et_3N (48 g, 54.2 mmol) in DCM (80 mL) was added benzoyl chloride (3.82 g, 27.2 mmol) at 0 °C. The result solution was stirred at room temperature for 3 h. The resulting solution was partitioned between water and EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-60%

EtOAc / petroleum ether) to afford 5.84 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M-100+H]^+ = 420$.

[1136] Step 6: ((2*S*,4*R*)-4-(2-(Tosyloxy)ethoxy)pyrrolidin-2-yl)methyl benzoate

[1137] A solution of *tert*-butyl (2*S*,4*R*)-2-((benzoyloxy)methyl)-4-(2-(tosyloxy)ethoxy)pyrrolidine-1-carboxylate (6.70 g, 12.9 mmol) in DCM (80 mL) and TFA (40 mL) was stirred at room temperature for 0.5 h. The solution was concentrated under vacuum to afford 9.40 g (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 420$.

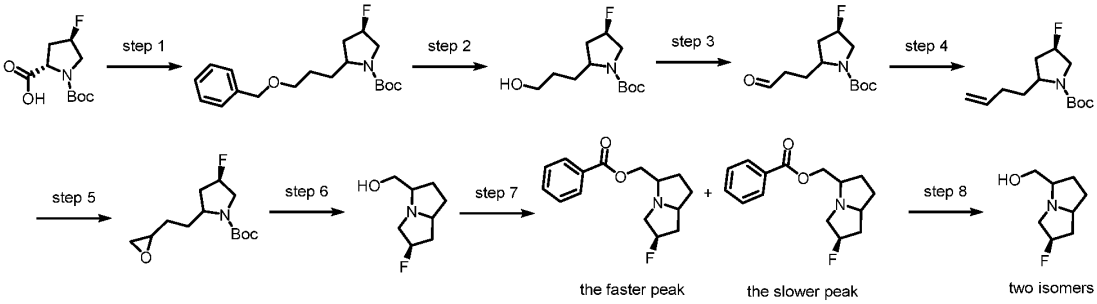
[1138] Step 7: ((1*R*,5*R*,7*S*)-4-Oxa-1-azabicyclo[3.2.1]octan-7-yl)methyl benzoate

[1139] To a solution of ((2*S*,4*R*)-4-(2-(tosyloxy)ethoxy)pyrrolidin-2-yl)methyl benzoate (9.40 g, 22.4 mmol) in DMA (285 mL) was added K_2CO_3 (21.7 g, 157 mmol). The solution was stirred at 40 °C for overnight. After filtrated, the solution was concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-50% ACN in water (0.05% NH_4HCO_3)) to afford 1.80 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 248$.

[1140] Step 8: ((1*R*,5*R*)-4-Oxa-1-azabicyclo[3.2.1]octan-7-yl)methanol

[1141] Under nitrogen, to a solution of ((1*R*,5*R*,7*S*)-4-Oxa-1-azabicyclo[3.2.1]octan-7-yl)methyl benzoate (500 mg, 2.02 mmol) in THF (5.5 mL) was added $LiAlH_4$ (3.04 mL, 1 M in THF) at 0 °C. The result solution was stirred at room temperature for 1 h. The solution was quenched with $Na_2SO_4.10H_2O$ at 0 °C and filtrated. The filtrate was concentrated under vacuum to afford 188 mg (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ =$ 144. The crude was used for next step without further purification.

[1142] **Intermediate 105:** ((6*R*)-6-Fluorohexahydro-1*H*-pyrrolizin-3-yl) methanol



[1143] Step 1: *tert*-Butyl (4*R*)-2-(3-(benzyloxy) propyl)-4-fluoropyrrolidine-1-carboxylate

[1144] Under nitrogen, to a solution of (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1.53 g, 6.56 mmol), (Ir[dF(CF3) ppy]2(dtbpy)) PF6 (89.0 mg, 0.0900mmol), 4,4-dOMe-bpy (94.0 mg, 0.430 mmol), $NiCl_2$-glyme (96.1 mg, 0.431 mmol) and K_2CO_3 (1.19 g, 8.70 mmol) in ACN (2.5 mL) was added ((3-bromopropoxy) methyl) benzene (1.00 g, 4.36 mmol) and H_2O (1.58 mL) at 0 °C. The resulting solution was stirred overnight at room temperature irradiation under blue LED light. After filtration, the filtrate was diluted with water,

extracted with EtOAc. The combined organic layers were concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-50% EtOAc / petroleum ether) to afford 525 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M-100+H]^+$ = 238.

[1145] Step 2: *tert*-Butyl (4*R*)-4-fluoro-2-(3-hydroxypropyl) pyrrolidine-1-carboxylate

[1146] Under nitrogen (1atm), to a solution of *tert*-butyl (4*R*)-2-(3-(benzyloxy) propyl)-4-fluoropyrrolidine-1-carboxylate (2.60 g, 7.71 mmol) in MeOH (25 mL) was added Pd / C (801 mg, 10 %) at room temperature. The resulting solution was stirred overnight at room temperature. After filtration, the filtrate was concentrated under vacuum to afford 2.01 g (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 248.

[1147] Step 3: *tert*-Butyl (4*R*)-4-fluoro-2-(3-oxopropyl)pyrrolidine-1-carboxylate

[1148] To a solution of *tert*-butyl (4*R*)-4-fluoro-2-(3-hydroxypropyl) pyrrolidine-1-carboxylate (400 mg, 1.62 mmol) in DCM (10 mL) was added Dess-Martin (1.03 g, 2.43 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 h. After filtration, the filtrate was partitioned between water and EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0% - 30% EtOAc / petroleum ether) to afford 132 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 246.

[1149] Step 4: *tert*- Butyl (4*R*)-2-(but-3-en-1-yl)-4-fluoropyrrolidine-1-carboxylate

[1150] Under nitrogen, to a solution of methyltriphenylphosphonium bromide (2.71 g, 7.60 mmol) in THF (15 mL) was added *t*-BuOK (9.53 mL, 1 M in THF) at 0 °C, and the mixture was stirred at room temperature for 30 min, then *tert*-butyl (4*R*)-4-fluoro-2-(3-oxopropyl) pyrrolidine-1-carboxylate (934 mg, 3.81 mmol) in THF (8 mL) was added at 0 °C. The mixture solution was stirred at room temperature for 2 h. The reaction was quenched with aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% EtOAc / petroleum ether) to afford 792 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 244.

[1151] Step 5: *tert*-Butyl (4*R*)-4-fluoro-2-(2-(oxiran-2-yl)ethyl)pyrrolidine-1-carboxylate

[1152] To a solution of *tert*- butyl (4*R*)-2-(but-3-en-1-yl)-4-fluoropyrrolidine-1-carboxylate (792 mg, 3.26 mmol) in DCM (9 mL) was added m-CPBA (959 mg, 5.54 mmol) at 0 °C. The mixture was stirred at room temperature overnight. The reaction was quenched with aqueous $Na_2S_2O_3$ and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash

chromatography on silica gel (gradient: 0%-50% EtOAc / petroleum ether) to afford 781 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M-56+H]^+ = 204$.

[1153] Step 6: ((6*R*)-6-Fluorohexahydro-1*H*-pyrrolizin-3-yl) methanol

[1154] A solution of *tert*-butyl (4*R*)-4-fluoro-2-(2-(oxiran-2-yl)ethyl)pyrrolidine-1-carboxylate (500 mg, 1.93 mmol) in TFA (1.5 mL) and DCM (6 mL) was stirred at room temperature overnight. The solvent was concentrated under vacuum to afford 568 mg (crude) of the title compound as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 160$.

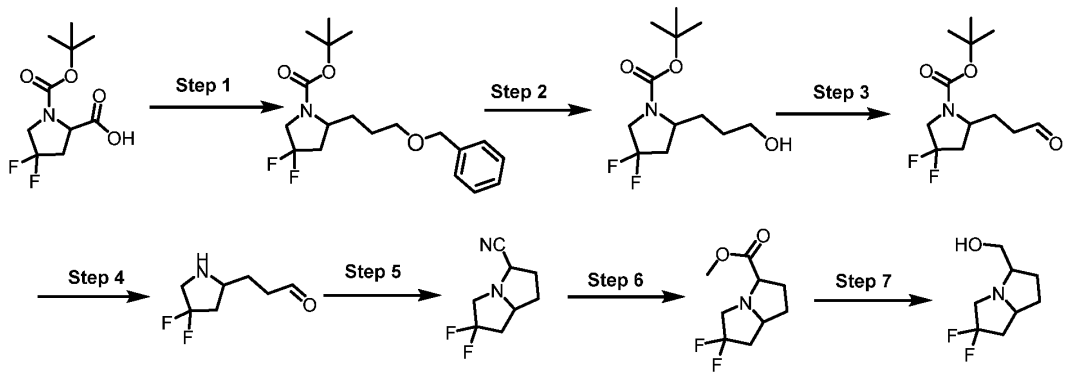
[1155] Step 7: ((6*R*)-6-Fluorohexahydro-1*H*-pyrrolizin-3-yl)methyl benzoate

[1156] To a solution of ((6*R*)-6-fluorohexahydro-1*H*-pyrrolizin-3-yl)methanol (200 mg, 1.26 mmol) and Et_3N (381 mg, 3.77 mmol) in DCM (3 mL) was added BzCl (213 mg, 1.51 mmol) at 0 °C. The solution was stirred at room temperature for 1.5 h. The solution was concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-50% ACN in water (0.05% NH_4HCO_3)) to afford 35.2 mg of the faster peak and 49.3 mg of the slower peak as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 264$.

[1157] Step 8: ((6*R*)-6-Fluorohexahydro-1*H*-pyrrolizin-3-yl)methanol

[1158] Under nitrogen, to a solution of ((6*R*)-6-fluorohexahydro-1*H*-pyrrolizin-3-yl)methyl benzoate (35.1 mg, 0.130 mmol) (the faster peak from last step) in THF (1.5 mL) was added $LiAlH_4$ (0.2 mL, 1 M in THF) at 0 °C. The solution was stirred at room temperature for 1 h. The mixture was quenched by $Na_2SO_4.10H_2O$ and filtrated. The solvent was removed by nitrogen blowing to afford 27.1 mg (crude) of the title compound as a yellow crude oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 160$. The crude was used for next step without further purification.

[1159] **Intermediate 106:** (6,6-Difluorohexahydro-1*H*-pyrrolizin-3-yl) methanol



[1160] Step 1: *tert*-Butyl 2-(3-(benzyloxy)propyl)-4,4-difluoropyrrolidine-1-carboxylate

[1161] Under nitrogen, a solution of (2S)-1-(tert-butoxycarbonyl)-4,4-difluoro-2-pyrrolidinecarboxylic acid (164mg, 0.65mmol), $NiCl_2$-glyme (9.59mg, 0.04mmol), 4,4-dOMe-bpy (9.44mg, 0.04mmol), ((3-bromopropoxy) methyl) benzene (0.08mL, 0.44mmol), (Ir[dF(CF3)ppy]2(dtbpy))PF6 (8.83mg, 0.01mmol), K_2CO_3 (120mg, 0.87mmol), water (0.16mL,

8.73mmol) and acetonitrile (5mL) was stirred for 48 h under irradiated with 34 W blue LEDs. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% EtOAc/petroleum ether) to yield 23 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 356.

[1162] Step 2: *tert*-Butyl 4,4-difluoro-2-(3-hydroxypropyl) pyrrolidine-1-carboxylate

[1163] Under hydrogen (1atm), to a solution of *tert*-butyl 2-(3-benzyloxypropyl)-4,4-difluoro-pyrrolidine-1-carboxylate (1.9g, 5.35mmol) in methanol (10mL) was added 10% Pd/C (200 mg) at 25 °C. The resulting solution was stirred at room temperature for 24 hours. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product 1.09g. LC-MS: (ESI, *m/z*): $[M+H]^+$=266.

[1164] Step 3: *tert*-Butyl 4,4-difluoro-2-(3-oxopropyl) pyrrolidine-1-carboxylate

[1165] To a solution of DMSO (2.12g, 27.2mmol) in dichloromethane (5mL) was added oxalyl chloride (2M in DCM, 11.3mL, 22.6mmol) at -78°C. After stirring for 10 min, the *tert*-butyl 4,4-difluoro-2-(3-hydroxypropyl) pyrrolidine-1-carboxylate (1.2g, 4.52mmol) dissolved in CH_2Cl_2 (5mL) was added, and the mixture was stirred at -78 °C for 45 min. Then Et_3N (4.58g, 45.2mmol) was added dropwise. The solution was stirred at -78 °C for 15 min and then allowed to warm up to room temperature over 30 min. The resulting mixture was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product 0.83g as yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ =264.

[1166] Step 4: 3-(4,4-Difluoropyrrolidin-2-yl)propanal

[1167] Under nitrogen, to a solution of *tert*-butyl 4,4-difluoro-2-(3-oxopropyl) pyrrolidine-1-carboxylate (100mg, 0.38mmol) in acetonitrile (2mL) was added TMSI (380mg, 1.9mmol) at 0 °C. The resulting solution was stirred at room temperature for 2 hours. The resulting mixture was concentrated under reduced pressure. The crude product 53mg was used for the next step without further purification. LC-MS: (ESI, *m/z*): $[M+H]^+$=164.

[1168] Step 5: 6,6-Difluorohexahydro-1*H*-pyrrolizine-3-carbonitrile

[1169] To a solution of 3-(4,4-difluoropyrrolidin-2-yl)propanal (100mg, 0.61mmol) in acetonitrile (2mL) was added TMSCN (303mg, 3.06mmol) at 0 °C. The resulting mixture was stirred for overnight at room temperature. The reaction was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the title compound 91mg (crude). LC-MS: (ESI, *m/z*): $[M+H]^+$=173. The crude was used for next step without further purification.

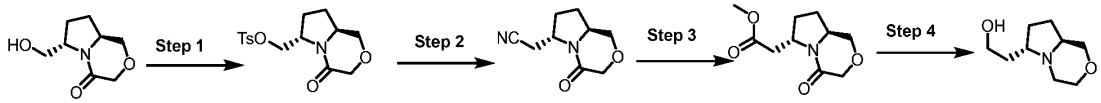
[1170] Step 6: Methyl 6,6-difluorohexahydro-1*H*-pyrrolizine-3-carboxylate

[1171] A solution of 6,6-difluorohexahydro-1*H*-pyrrolizine-3-carbonitrile (150mg, 0.87mmol) in hydrochloric acid solution (2mL) and methanol (2mL) was stirred at 40 °C for 18 hours. The resulting mixture was concentrated under reduced pressure to afford the crude product 129mg. LC-MS: (ESI, *m/z*): $[M+H]^+$= 206.

[1172] Step 7: (6,6-Difluorohexahydro-1*H*-pyrrolizin-3-yl) methanol

[1173] Under nitrogen, to a solution of methyl 6,6-difluorohexahydro-1*H*-pyrrolizine-3-carboxylate (50.0mg, 0.24mmol) in tetrahydrofuran (2mL) was added $LiAlH_4$ (0.32mL, 1.5 M in THF) at 0 °C. The resulting solution was stirred at room temperature for 2 hours. The resulting mixture was quenched with $Na_2SO_4.10H_2O$. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product 30mg as yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$= 178. The crude was used for next step without further purification.

[1174] **Intermediate 107:** 2-((6*S*,8*aS*)-Hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)ethan-1-ol



[1175] Step 1: ((6*S*,8*aS*)-4-Oxohexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)methyl 4-methylbenzenesulfonate

[1176] To a solution of *rac*-(6*S*,8*aS*)-6-(hydroxymethyl)-6,7,8,8a-tetrahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-4-one (500mg, 2.92mmol), Et_3N (886mg, 8.76mmol) in dichloromethane (10mL) was added TsCl (835mg, 4.38mmol) and DMAP (17.8mg, 0.15mmol) at 0 °C. The resulting mixture was stirred overnight at room temperature. The resulting mixture was diluted with water, extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% MeOH/DCM) to yield 650 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ =326.

[1177] Step 2: 2-((6*S*,8*aS*)-4-Oxohexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)acetonitrile

[1178] To a solution of [*rac*-(6S,8aS)-4-oxo-6,7,8,8a-tetrahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl]methyl 4-methylbenzenesulfonate (50.0mg, 0.15mmol), TBAF (161mg, 0.61mmol) in acetonitrile (3mL) was added TMSCN (91mg, 0.92mmol) at 0 °C. The resulting solution was stirred at 80 °C for 6h. The resulting mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% MeOH/DCM) to yield 20 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$=181.

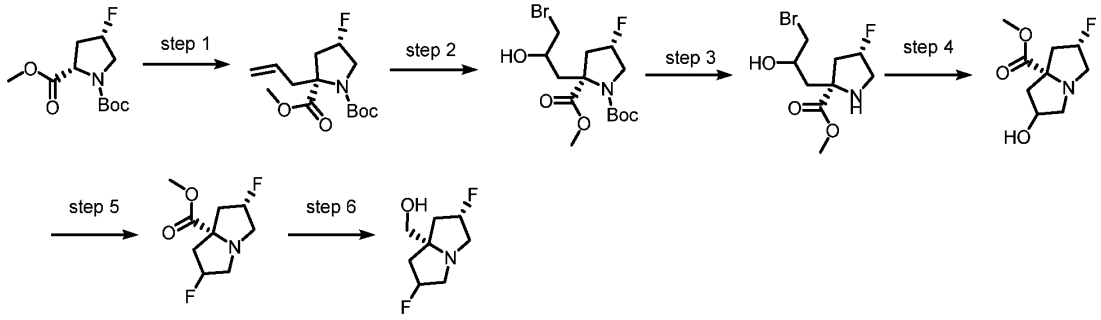
[1179] Step 3: Methyl 2-((6*S*,8*aS*)-4-oxohexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)acetate

[1180] A solution of 2-[rac-(6*S*,8*aS*)-4-Oxohexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl]acetonitrile (50mg, 0.3mmol) in methanol (1mL) and hydrochloric acid solution (1ml) was stirred at 40 degrees C for 72 hours. The resulting mixture was concentrated under reduced pressure to afford 40mg of the title compound as a yellow solid which was used without further purification. LC-MS: (ESI, *m/z*): $[M+H]^+$ =214.

[1181] Step 4: 2-((6*S*,*8aS*)-Hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)ethan-1-ol

[1182] Under nitrogen, to a solution of Methyl 2-[rac(6*S*,8*aS*)-4-oxohexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl]acetate (100mg, 0.47mmol) in tetrahydrofuran (2mL) was added $LiAlH_4$ (1.5M in THF, 0.46mL) at 0 °C. The resulting solution was stirred at 60 °C for 1h. The reaction was quenched with $Na_2SO_4.10H_2O$ and filtration. The filtrate was concentrated under reduced pressure to afford 60mg (crude) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$=172. The crude was used for next step without further purification.

[1183] **Intermediate 108:** ((2*S*)-2,6-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methanol



[1184] Step 1: 1-(*tert*-Butyl) 2-methyl (2*S*,4*S*)-2-allyl-4-fluoropyrrolidine-1,2-dicarboxylate

[1185] Under nitrogen, to a solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-4-fluoropyrrolidine-1,2-dicarboxylate (5.00 g, 20.2 mmol) in tetrahydrofuran (45.0 mL) was added LHMDS (40.5 mL, 1 M in THF) at -78 °C, and the mixture was stirred for 1 hour at -50 °C. Then allyl bromide (4.90 g, 40.5 mmol) was added, and the mixture was stirred at -50 °C. The mixture was wormed to 25 °C and stirred for 1 hour. The reaction was quenched by $Na_2S_2O_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-25% EtOAc / petroleum ether) to afford 5.30 g of the title compound as a yellow oil. LC-MS: (ESI, m/z): [M+H]+ = 288.

[1186] Step 2: 1-(*tert*-Butyl) 2-methyl (2*S*,4*S*)-2-(3-bromo-2-hydroxypropyl)-4-fluoropyrrolidine-1,2-dicarboxylate

[1187] To a solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-2-allyl-4-fluoropyrrolidine-1,2-dicarboxylate (4.07 g, 14.2 mmol) in DMSO (30 mL) and water (10mL) was added NBS (5.83 g,

32.9 mmol), and the mixture was stirred at room temperature for 1 hour. The solvent was concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-75 % ACN in water (0.1% TFA)) to afford 1.29 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ =384.

[1188] Step 3: Methyl (2*S*,4*S*)-2-(3-bromo-2-hydroxypropyl)-4-fluoropyrrolidine-2-carboxylate

[1189] A solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*S*)-2-(3-bromo-2-hydroxypropyl)-4-fluoropyrrolidine-1,2-dicarboxylate (730 mg, 1.90 mmol) in DCM (10 mL) and TFA (1 mL) was stirred at room temperature for 1 h. The solvent was concentrated under vacuum to afford 1.11 g (crude) of the title compound as a red oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 284.

[1190] Step 4: Methyl (2*S*,7a*S*)-2-fluoro-6-hydroxytetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate

[1191] To a solution of methyl (2*S*,4*S*)-2-(3-bromo-2-hydroxypropyl)-4-fluoropyrrolidine-2-carboxylate (1.11 g, 3.89 mmol)] in ACN (5 mL) was added K_2CO_3 (2.69 g, 19.5 mmol), and the mixture was stirred at room temperature for 1 h. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-8% MeOH / DCM) to afford 307 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 204.

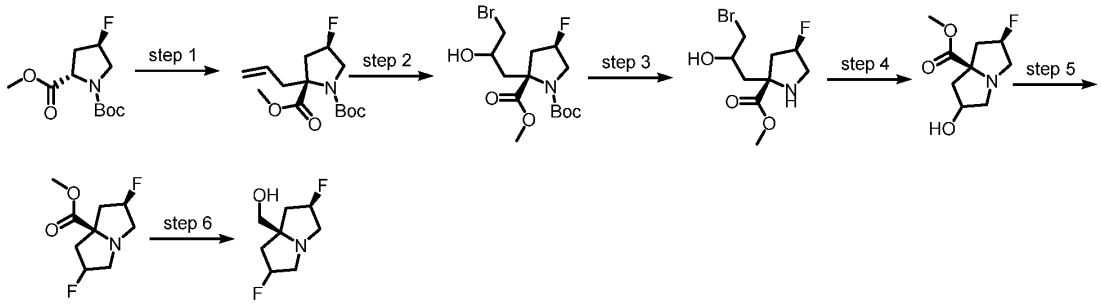
[1192] Step 5: Methyl (2*S*)-2,6-difluorotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate

[1193] Under nitrogen, to a solution of methyl (2*S*,7a*S*)-2-fluoro-6-hydroxytetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (307 mg, 1.51 mmol)] in DCM (6 mL) was added DAST (365 mg, 2.27 mmol) at -20°C. The solution was stirred at -20°C for 1 h. The reaction was quenched with $NaHCO_3$ aqueous, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% MeOH / DCM) to afford 165 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 206.

[1194] Step 6: ((2*S*)-2,6-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol

[1195] Under nitrogen, to a solution of methyl (2*S*)-2,6-difluorotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (165 mg, 0.800 mmol) in THF (5 mL) was added $LiAlH_4$ (0.32 mL, 2.5M in THF) 0 °C, and the mixture was stirred at room temperature for 0.5 h. The reaction was quenched with $Na_2SO_4.10H_2O$. After filtration, the filtrate was concentrated under reduced pressure to afford 70.1 mg (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 178. The crude was used for next step without further purification.

[1196] **Intermediate 109:** ((2*R*,7a*R*)-2,6-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methanol



[1197] Step 1: 1-(*tert*-Butyl) 2-methyl (2*R*,4*R*)-2-allyl-4-fluoropyrrolidine-1,2-dicarboxylate

[1198] Under nitrogen, to a solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-fluoropyrrolidine-1,2-dicarboxylate (10.0g, 40.4mmol) in tetrahydrofuran (20mL) was added LHMDS (80.8 mL, 1 M in THF) at -30 °C. The resulting solution was stirred for 1 hour at -30 °C. Then 3-bromoprop-1-ene (7.0 mL, 80.8 mmol) was added, and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-60% ACN in water (0.05% NH_4HCO_3)) to afford the title compound (5.27g) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 288.

[1199] Step 2: 1-(*tert*-Butyl) 2-methyl (2*R*,4*R*)-2-(3-bromo-2-hydroxypropyl)-4-fluoropyrrolidine-1,2-dicarboxylate

[1200] To a solution of 1-(*tert*-butyl) 2-methyl (2*R*,4*R*)-2-allyl-4-fluoropyrrolidine-1,2-dicarboxylate (5.27g, 18.3mmol) in dimethyl sulfoxide (21mL) and water (6mL) was added NBS (6.53g, 36.7mmol) at room temperature. The reaction was stirred at room temperature for 2 hours. The crude was purified by C18 column (solvent gradient: 0-50% ACN in water (0.05% NH_4HCO_3)) to afford the title compound (1.46g) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 384.

[1201] Step 3: Methyl (2*R*,4*R*)-2-(3-bromo-2-hydroxypropyl)-4-fluoropyrrolidine-2-carboxylate

[1202] A solution of 1-(*tert*-butyl) 2-methyl (2*R*,4*R*)-2-(3-bromo-2-hydroxypropyl)-4-fluoropyrrolidine-1,2-dicarboxylate (1.46g, 3.8mmol) in 2,2,2-trifluoroacetic acid (7.5mL) and dichloromethane (7.5mL) was stirred at room temperature for 0.5 hour. The solution was concentrated under vacuum to afford the title compound (1.88g, crude) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 284.

[1203] Step 4: Methyl (2*R*,7a*R*)-2-fluoro-6-hydroxytetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate

[1204] A solution of methyl (2*R*,4*R*)-2-(3-bromo-2-hydroxypropyl)-4-fluoropyrrolidine-2-carboxylate (1.88g, 6.62mmol) and K_2CO_3 (4.56g, 33.1mmol) in acetonitrile (15mL) was stirred at room temperature overnight. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was purified by C18 column (solvent gradient: 0-10% ACN in water (0.05% NH_4HCO_3)) to afford the title compound (673mg) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 204$.

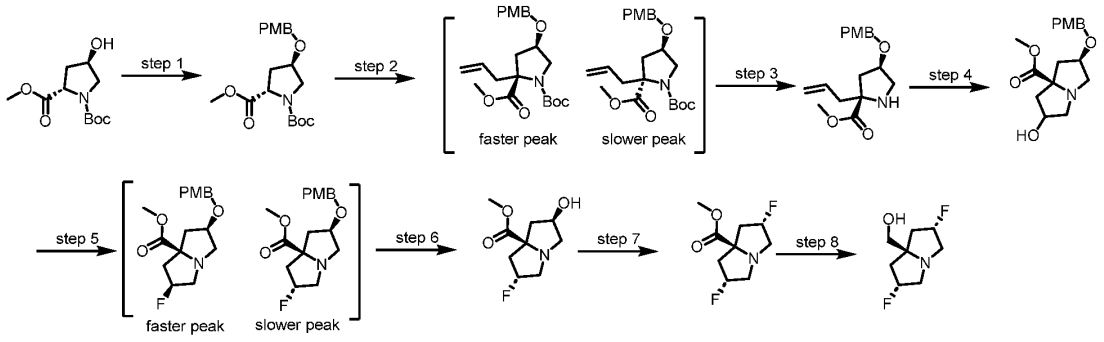
[1205] Step 5: Methyl (2*R*,7a*R*)-2,6-difluorotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate

[1206] To a solution of methyl (2*R*,7a*R*)-2-fluoro-6-hydroxytetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (600mg, 2.95mmol) in dichloromethane (6mL) was added DAST (950mg, 5.91mmol) at -20 °C and was stirred at room temperature overnight. The reaction was quenched by MeOH. The solution was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-2% MeOH in DCM (0.1% 7M NH_3/MeOH)) to afford the title compound (120mg) as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 206$.

[1207] Step 6: ((2*R*,7a*R*)-2,6-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol

[1208] Under nitrogen, to a solution of methyl (2*R*,7a*R*)-2,6-difluorotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (90.0mg, 0.440mmol) in tetrahydrofuran (2mL) was added $LiAlH_4$ (0.18mL, 2.5 M in THF) at 0 °C. The resulting solution was stirred at room temperature for 1 hour. Then 200 mg $Na_2SO_4.10H_2O$ was added, and the mixture was stirred at room temperature for 10 min. After filtration, the filtrate was concentrated under reduced pressure to afford the title compound (80mg, crude) as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 178$. The crude was used for next step without further purification.

[1209] **Intermediate 110:** ((2*R*,6*S*,7a*S*)-2,6-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methanol

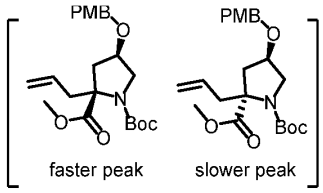


[1210] Step 1: 1-(*tert*-Butyl) 2-methyl (2*S*,4*R*)-4-((4-methoxybenzyl)oxy)pyrrolidine-1,2-dicarboxylate

[1211] To a solution of 1-(tert-butyl) 2-methyl (2S,4R)-4-hydroxypyrrolidine-1,2-dicarboxylate (20g, 81.6mmol) was added NaH (3.92g, 98.0mmol, 60% dispersion in mineral oil)

at 0 °C. The mixture was stirred for 30 min at 0°C. PMBCl (14.1g, 89.8mmol) was added and the mixture was allowed to warm to room temperature and stirred for 2 hours. The reaction was quenched with aqueous NH_4Cl solution. The resulting solution was extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-50% ACN in water (0.05% NH_4HCO_3)) to afford the title compound (11.0 g) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 366.

[1212] Step 2: 1-(*tert*-Butyl) 2-methyl (2*S*,4*R*)-2-allyl-4-((4-methoxybenzyl)oxy)pyrrolidine-1,2-dicarboxylate



[1213] Under nitrogen, to a solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-4-((4-methoxybenzyl) oxy) pyrrolidine-1,2-dicarboxylate (18g, 49.3mmol) in tetrahydrofuran (150mL) was added LHMDS (98.6mL, 1M in THF) at -78 °C. The resulting solution was stirred for 1 hour at -78 °C. Then 3-bromoprop-1-ene (11.8g, 98.6mmol) was added, and the mixture was stirred at -78 °C for 2 hours. The reaction was quenched with aqueous NH_4Cl solution. The organic solvent was removed under vacuum. The residual was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-15% EtOAc / petroleum ether) to afford 18.4g mixture of two isomers as a yellow oil. The isomers were separated by Prep Chiral-SFC with the following conditions:(Column: Mobile Phase A: CO_2, Mobile Phase B: IPA; Flow rate: 100 mL/min; Gradient: isocratic 10% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; R_{T1}(min): 4.37; R_{T2}(min): 5.73) to afford faster peak (12.6 g) and slower peak (6.06 g) as a yellow oil (LC-MS: (ESI, *m/z*): $[M+H]^+$ = 406).

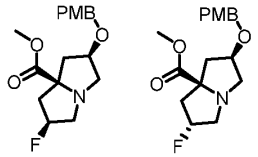
[1214] Step 3: Methyl (2*R*,4*R*)-2-allyl-4-((4-methoxybenzyl)oxy)pyrrolidine-2-carboxylate

[1215] Under nitrogen, to a solution of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*)-2-allyl-4-((4-methoxybenzyl) oxy) pyrrolidine-1,2-dicarboxylate (12.0g, 29.6mmol, the faster peak of last step) and 2,6-di-tert-butylpyridine (13.3mL, 59.3mmol) in dichloromethane (120mL) was added TMSOTf (13.2g, 59.3mmol) at room temperature. The resulting solution was stirred at room temperature overnight. The solvent was concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-60% ACN in water (0.05% NH_4HCO_3)) to afford the title compound (5.1 g) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 306.

[1216] Step 4: Methyl (6*R*,7a*R*)-2-hydroxy-6-((4-methoxybenzyl) oxy) tetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate

[1217] A solution of methyl (2*R*,4*R*)-2-allyl-4-((4-methoxybenzyl)oxy)pyrrolidine-2-carboxylate (3.5g, 11.5mmol), TFA (1.44g, 12.6mmol) and NBS (2.45mg, 13.7mmol) in acetone (28mL) and water (7mL) was stirred at room temperature for 2 hours. Then K_2CO_3 (1.58mg, 11.4mmol) was added, and the mixture was stirred at room temperature overnight. The solution was concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-25% ACN in water (0.05% NH_4HCO_3)) to afford the title compound (1.99g) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 322$.

[1218] Step 5: Methyl (2*R*,6*R*,7a*S*)-2-fluoro-6-((4-methoxybenzyl) oxy) tetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate



[1219] Under nitrogen, to a solution of methyl (6*R*,7a*R*)-2-hydroxy-6-((4-methoxybenzyl) oxy) tetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (1.99g, 6.19mmol) in dichloromethane (20mL) was added DAST (1.50g, 9.29mmol) at -40 °C. The resulting solution was stirred for 1 hour at room temperature. The reaction was quenched with MeOH. The solution was concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-25% ACN in water (0.05% NH_4HCO_3)) to afford faster peak (253mg) and slower peak (425mg) as a yellow oil (LC-MS: (ESI, *m/z*): $[M+H]^+ = 324$.

[1220] Step 6: Methyl (2*R*,6*R*,7a*S*)-2-fluoro-6-hydroxytetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate

[1221] A solution of methyl (2*R*,6*R*,7a*S*)-2-fluoro-6-((4-methoxybenzyl) oxy) tetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (420mg, 1.30mmol, the slower peak of last step) in dichloromethane (1mL) and 2,2,2-trifluoroacetic acid (1mL) was stirred at room temperature for 1 hour. The solution was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-4% MeOH in DCM(0.1% 7M NH_3/MeOH)) to afford the title compound (182 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 204$.

[1222] Step 7: Methyl (2*R*,6*S*,7a*s*)-2,6-difluorotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate

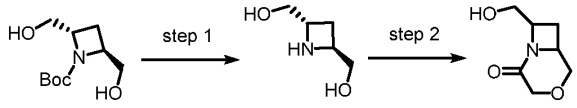
[1223] Under nitrogen, to a solution of methyl (2*R*,6*R*,7a*S*)-2-fluoro-6-hydroxytetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (182mg, 0.900mmol) in dichloromethane (2mL) was added DAST (288mg, 1.79mmol) at -30 °C. The resulting solution was stirred for 3 hours at room temperature. The reaction was quenched with MeOH. The solution was concentrated under

vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-2% MeOH in DCM(0.1% NH_3-MeOH)) to afford the title compound (61mg) as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 206.

[1224] Step 8:((2*R*,6*S*,7a*S*)-2,6-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol

[1225] Under nitrogen, to a solution of methyl (2*R*,6*S*,7a*s*)-2,6-difluorotetrahydro-1*H*-pyrrolizine-7a(5*H*)-carboxylate (60mg, 0.292 mmol) in tetrahydrofuran (2mL) was added $LiAlH_4$ (0.12mL, 2.4 M in THF) at 0 °C. The resulting solution was stirred at room temperature for 1 hour. Then $Na_2SO_4.10H_2O$ was added, and the mixture was stirred at room temperature for 5 min. After filtration, the filtrate was concentrated under vacuum to afford the title compound (65mg, crude) as a brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 178. The crude was used for next step without further purification.

[1226] **Intermediate 111:** 8-(Hydroxymethyl)-4-oxa-1-azabicyclo [4.2.0] octan-2-one (mixture trans)



mixture trans

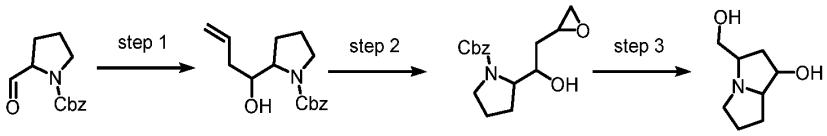
[1227] Step 1: ((2*S*,4*S*)-Azetidine-2,4-diyl) dimethanol

[1228] Under nitrogen, a solution of tert-butyl rac-(2*S*,4*S*)-2,4-bis(hydroxymethyl)azetidine-1-carboxylate (700 mg, 3.22 mmol) in DCM (3.2 mL) was added TFA (0.8 mL) at room temperature, and the mixture was stirred for 1h. The resulting solution was concentrated under vacuum to afford 1.20 g (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 118.

[1229] Step 2: 8-(Hydroxymethyl)-4-oxa-1-azabicyclo[4.2.0]octan-2-one

[1230] To a solution of ((2*S*,4*S*)-azetidine-2,4-diyl) dimethanol (1.20 g, 10.2 mmol) in i-PrOH (60 mL) was added TMSOK (9.81 g, 76.4 mmol) and chloroacetyl chloride (3.17mL, 39.84mmol) at 0 °C, and the mixture was stirred at room temperature for overnight. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% MeOH / DCM) to afford 210 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 158.

[1231] **Intermediate 112:** 3-(Hydroxymethyl) hexahydro-1*H*-pyrrolizin-1-ol



[1232] Step 1: Benzyl 2-(1-hydroxybut-3-en-1-yl) pyrrolidine-1-carboxylate

[1233] Under nitrogen, a solution of benzyl 2-formylpyrrolidine-1-carboxylate (6.50 g, 27.9 mmol) in THF (65 mL) was added allylmagnesium bromide (44.7 mL, 1 M in Et_2O) at 0 °C, and the mixture was stirred for 3 h at 0 °C. The reaction was quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-40% EtOAc / petroleum ether) to afford 4.20 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 276.

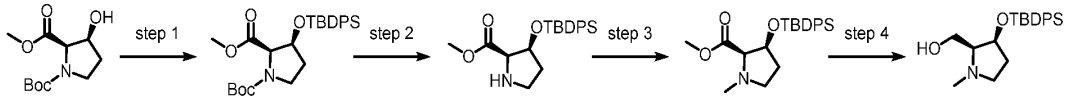
[1234] Step 2: Benzyl 2-(1-hydroxy-2-(oxiran-2-yl)ethyl)pyrrolidine-1-carboxylate

[1235] To a solution of benzyl 2-(1-hydroxybut-3-en-1-yl) pyrrolidine-1-carboxylate (4.11 g, 14.9 mmol) in DCM (50 mL) was added m-CPBA (4.4 g, 25.43 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated $NaHCO_3$ aqueous, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-35% EtOAc/petroleum ether) to afford 2.60 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 292.

[1236] Step 3: 3-(Hydroxymethyl) hexahydro-1*H*-pyrrolizin-1-ol

[1237] Under hydrogen (1 atm), to a solution of benzyl 2-(1-hydroxy-2-(oxiran-2-yl)ethyl)pyrrolidine-1-carboxylate (2.60 g, 8.92 mmol) in MeOH (25 mL) was added Pd / C (780 mg, 10%), and the mixture was stirred for 3 h at room temperature. After filtration, the filtrate was concentrated under vacuum to afford 1.41 g (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 158. The crude was used for next step without further purification.

[1238] **Intermediate 113:** ((2*S*,3*S*)-3-((*tert*-Butyldiphenylsilyl) oxy)-1-methylpyrrolidin-2-yl) methanol



[1239] Step 1: 1-(*tert*-Butyl) 2-methyl (2*R*,3*S*)-3-((*tert*-butyldiphenylsilyl)oxy)pyrrolidine-1,2-dicarboxylate

[1240] To a solution of 1-(*tert*-butyl) 2-methyl (2*R*,3*S*)-3-hydroxypyrrolidine-1,2-dicarboxylate (2.10 g, 8.56mmol) and imidazole (1.75g, 25.7mmol) in N, N-dimethylacetamide (20mL) was added TBDPSCl (4.71g, 17.1mmol) at room temperature. The resulting solution was stirred at room temperature overnight. Some starting material remained. Then additional imidazole (1.75g, 25.7mmol) and TBDPSCl (4.71g, 17.1mmol) was added, and the mixture was stirred at room temperature overnight. The resulting mixture was diluted with EtOAc, washed with brine and dried over anhydrous sodium sulfate. The solvent was concentrated under vacuum

and the residue was purified by flash chromatography on silica gel (gradient: 0-50% DCM/ petroleum ether) to afford the title compound (2.74g) as a pink oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 484.

[1241] Step 2: Methyl (2*R*,3*S*)-3-((tert-butyldiphenylsilyl) oxy) pyrrolidine-2-carboxylate

[1242] A solution of 1-(*tert*-butyl) 2-methyl (2*R*,3*S*)-3-((*tert*-butyldiphenylsilyl) oxy) pyrrolidine-1,2-dicarboxylate (2.74g, 5.67mmol) in dichloromethane (15mL) and 2,2,2-trifluoroacetic acid (5mL) was stirred at room temperature for 1 hour. The reaction mixture was adjusted pH to 8 with aqueous $NaHCO_3$ solution. The resulting solution was extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford the title compound (2.39g, crude) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 384.

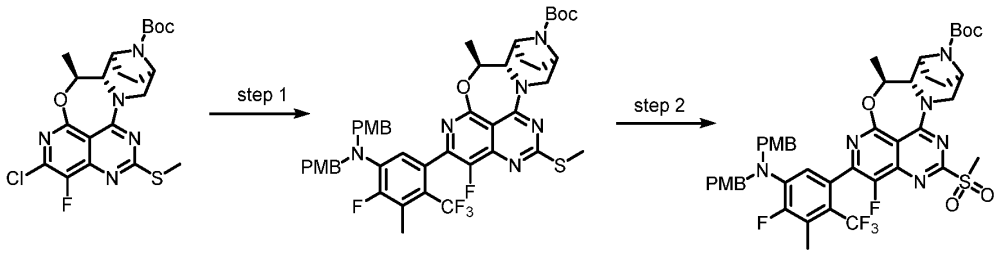
[1243] Step 3: Methyl (2*R*,3*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-1-methylpyrrolidine-2-carboxylate

[1244] A solution of methyl (2*R*,3*S*)-3-((tert-butyldiphenylsilyl)oxy)pyrrolidine-2-carboxylate (2.39g, 6.23mmol), paraformaldehyde (935mg, 31.2mmol) and AcOH (374mg, 6.23mmol) in methanol (21mL) was stirred at room temperature for 1 hour. Then $NaBH_3CN$ (1.57g, 24.9mmol) was added, and the mixture was stirred at room temperature overnight. The reaction was quenched with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound (2.71g, crude) as a white oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 398.

[1245] Step 4: ((2*S*,3*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methanol

[1246] A solution of methyl (2*R*,3*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-1-methylpyrrolidine-2-carboxylate (900mg, 2.26mmol), KBH_4 (733 mg, 13.5mmol) and $ZnCl_2$ (924mg, 6.79mmol) in 1,4-dioxane (10mL) was stirred at 100 °C for 2 hours. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was diluted with EtOAc and was washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by C18 column (solvent gradient: 0-50% ACN in water (0.05% TFA)) to afford the title compound (515 mg) as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 370.

[1247] **Intermediate 114:** *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



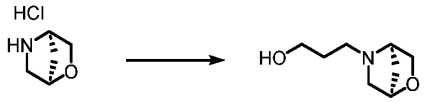
[1248] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1249] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho [1,8-*ab*]heptalene-14-carboxylate (701 mg, 1.45 mmol) and (5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (1.73 g, 3.63 mmol) in THF (9 mL) was added cataCXium A Pd G_3 (317 mg, 0.440 mmol) and K_3PO_4 (1.8 mL, 1.5 M in H_2O) at room temperature. The resulting solution was stirred for 3 h at 60°C. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on pre-packed C18 column (gradient: 0-100% CH_3CN in water (0.05% NH_4HCO_3)) to yield 941 mg of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 879$.

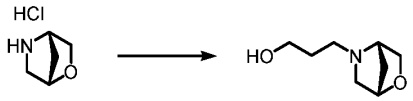
[1250] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1251] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (910 mg, 1.04 mmol) in DCM (10 mL) was added m-CPBA (537 mg, 3.11 mmol) at 0 °C. The resulting solution was stirred for 2 h at room temperature. The solution was diluted with $NaHCO_3$ solution and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-51% EtOAc in petroleum ether) to afford 378 mg of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 911$.

[1252] **Intermediates 115 and 116:** 3-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)propan-1-ol and (3-((1*S*,4*S*)-2-oxa-5-azabicyclo [2.2.1] heptan-5-yl) propan-1-ol)



intermediate 115

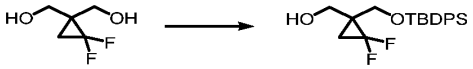


intermediate 116

[1253] Under nitrogen, a solution of (1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (100 mg, 0.740 mmol), 3-iodopropan-1-ol (276 mg, 1.48 mmol) and K_2CO_3 (287 mg, 2.08 mmol) in ACN (1.5 mL) was stirred at 80 °C for 2 h. The solution was cooled to room temperature, filtrated and concentrated under vacuum. The residue was purified by SCX-2 column (ion exchange resin) to afford 15 mg (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 158.

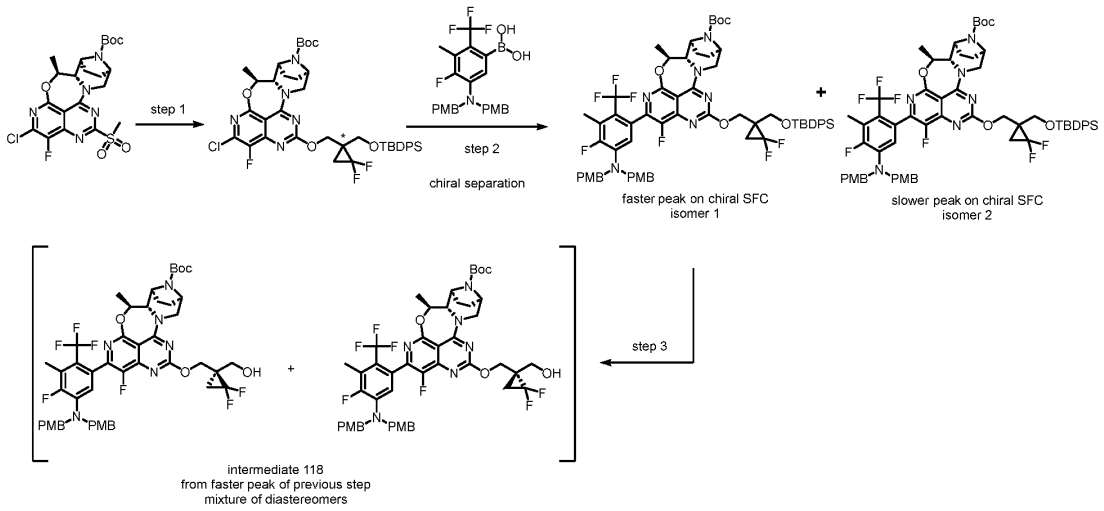
[1254] Analogous to method described as above, (3-((1*S*,4*S*)-2-oxa-5-azabicyclo [2.2.1] heptan-5-yl) propan-1-ol) was prepared.

[1255] **Intermediate 117:** (1-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methanol



[1256] To a solution of (2,2-difluorocyclopropane-1,1-diyl)dimethanol (200 mg, 1.45 mmol) and imidazole (197 mg, 2.90 mmol) in dichloromethane (10 mL) was added TBDPSCl (398 mg, 1.45 mmol) at 0 °C, and the mixture was stirred for 1 hour at room temperature. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-10% EtOAc in petroleum ether) to afford the title compound (320 mg) as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 377.

[1257] **Intermediate 118:** *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (two isomers)



[1258] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-((1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-2-chloro-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1259] To a solution of (1-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methanol (800 mg, 2.12 mmol, intermediate 117) in tetrahydrofuran (40 mL) was added NaH (60% dispersion in mineral oil, 424 mg, 10.6 mmol) at 0°C, and the mixture was stirred for 30 minutes at room temperature. Then *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (546 mg, 1.06 mmol) was added, and the mixture was stirred for 1 hour at room temperature. The reaction was quenched with saturated NH_4Cl aqueous solution. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (566 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 811$.

[1260] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((1-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (two isomers)

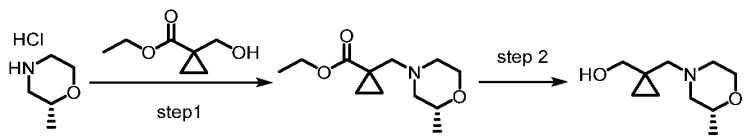
[1261] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-((1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-2-chloro-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (1.70 g, 2.10 mmol), (5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (3.01 g, 6.30 mmol), K_3PO_4 (1.5M aqueous

solution, 7 mL, 10.5 mmol) and cataCXium A Pd G3 (320 mg, 0.440 mmol) in tetrahydrofuran (35 mL) stirred for 3 hours at 60 °C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc in petroleum ether) to afford a mixture of isomers (2.40 g) as a yellow solid. The two diastereomers were separated by Chiral-Prep-SFC with the following conditions: (Column: (S, S)-Whelk-O 1 5μm Kromasil 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: IPA(0.1% 2M NH_3-MEOH); Flow rate: 100 mL/min; Gradient: isocratic 50% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 5.53; RT2(min): 6.6; Sample Solvent: ACN; Injection Volume: 1.9 mL; Number Of Runs: 7) to afford **isomer 1** (1.10 g, the faster peak) and **isomer 2** (1.04 g, the slower peak) as white solids. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1208.

[1262] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (two isomers)

[1263] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((1-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (1.10 g, 0.911 mmol, **isomer 1 of last step**) in tetrahydrofuran (30 mL) was added TBAF (1M solution in tetrahydrofuran, 3 mL, 3.00 mmol), and the mixture was stirred for 2 hours at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc in petroleum ether) to afford the title compound (810 mg, intermediate 118) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 969. It appears that isomerization took place in the TBDPS deprotection step to give a mixture of diastereomers of the title compound with respect to the stereogenic center of the difluorocyclopropyl moiety. This mixture was used as such in the following steps.

[1264] **Intermediate 119:** (*R*)-(1-((2-methylmorpholino)methyl)cyclopropyl)methanol



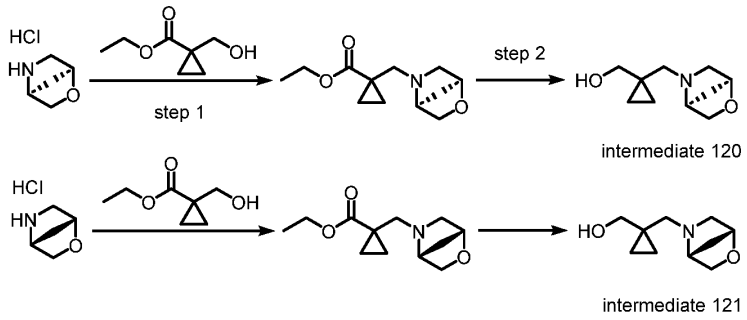
[1265] Step 1: Ethyl (*R*)-1-((2-methylmorpholino)methyl)cyclopropane-1-carboxylate

[1266] Under nitrogen, to a solution of ethyl 1-(hydroxymethyl)cyclopropane-1-carboxylate (500 mg, 3.47 mmol) and DIPEA (1.84 mL, 10.4 mmol) in dichloromethane (5 mL) was added Tf_2O (1.2 mL, 6.94 mmol) dropwise at -10 °C, and the mixture was stirred for 5 minutes. Then a solution of (*R*)-2-methylmorpholine in dichloromethane (5 mL) (pretreated (*R*)-2-methylmorpholine hydrochloride (477 mg, 3.47 mmol) with DIPEA (1.23 mL, 6.94 mmol)) was added at -10 °C, and the mixture was stirred for 1 hour at room temperature. The solvent was concentrated under vacuum to afford the title compound (1.90 g, crude) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 228$.

[1267] Step 2: (*R*)-(1-((2-methylmorpholino)methyl)cyclopropyl)methanol

[1268] To a solution of ethyl (*R*)-1-((2-methylmorpholino)methyl)cyclopropane-1-carboxylate (1.90 g, crude) in THF (20 mL) was added $LiAlH_4$ (600 mg, 15.8 mmol) in portions at 0 °C, and the mixture was stirred for 1 hour at room temperature. The reaction was quenched with $Na_2SO_4.10H_2O$ and filtrated. The filtrate was concentrated under reduced pressure to afford the title compound (1.00 g, crude) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 186$. The crude was used for next step without further purification.

[1269] **Intermediates 120 and 121:** (1-(((1*S*,4*S*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methanol and (1-(((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methanol



[1270] Step 1: Ethyl 1-(((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropane-1-carboxylate

[1271] Under nitrogen, to a solution of ethyl 1-(hydroxymethyl)cyclopropane-1-carboxylate (500 mg, 3.47 mmol) and DIPEA (1.84 mL, 10.4 mmol) in dichloromethane (10 mL) was added Tf_2O (1.2 mL, 6.94 mmol) dropwise at -10 °C, and the mixture was stirred for 5 minutes. Then a solution of (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptane in dichloromethane (5 mL) (pretreated (1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (490 mg, 3.47 mmol) with DIPEA (1.23 mL, 6.94 mmol)) was added at -10 °C, and the mixture was stirred for 1 hour at room temperature. The solvent was concentrated under vacuum to afford the title compound (1.50 g, crude) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 226$.

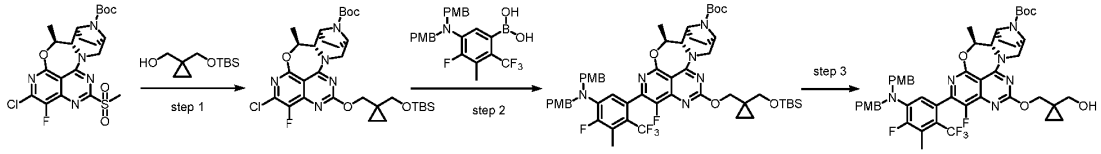
[1272] Analogous to method described as above, the enantiomer (1.30 g, crude) was prepared from (1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptane hydrochloride (490 mg, 3.47 mmol) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 226.

[1273] Step 2: (1-(((1*S*,4*S*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropyl)methanol

[1274] To a solution of ethyl 1-(((1*S*,4*S*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropane-1-carboxylate (1.50 g, crude) in THF (20 mL) was added $LiAlH_4$ (505 mg, 13.3 mmol) in portions at 0 °C, and the mixture was stirred for 1 hour at room temperature. The reaction was quenched with $Na_2SO_4.10H_2O$ and filtrated. The filtrate was concentrated under reduced pressure to afford the title compound (2.50 g, crude, intermediate 120) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 184.

[1275] Analogous to method described as above, the other isomer intermediate 121 (2.40 g, crude) was prepared from ethyl 1-(((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)methyl)cyclopropane-1-carboxylate (1.30 g, crude) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 184.

[1276] **Intermediate 122:** *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



[1277] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-((1-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)methoxy)-2-chloro-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1278] To a solution of (1-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)methanol (842 mg, 3.89 mmol) in tetrahydrofuran (10 mL) was added NaH (60% dispersion in mineral oil, 390 mg, 9.75 mmol) at 0 °C in 3 portions, and the mixture was stirred for 30 minutes at room temperature. Then *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (1.00 g, 1.95 mmol) was added, and the mixture was stirred for 2 hours at room temperature. The reaction was quenched with saturated NH_4Cl aqueous solution. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined

organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (800 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 650.

[1279] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

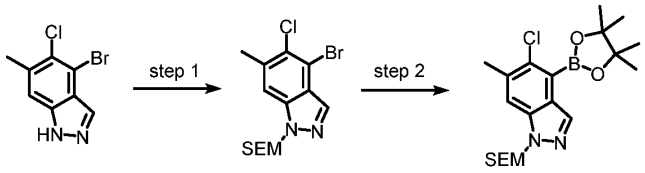
[1280] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-((1-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)methoxy)-2-chloro-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (800 mg, 1.23 mmol), (5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (1.17 g, 2.45 mmol), K_3PO_4 (1.5M in H_2O, 4 mL, 6.00 mmol) and cataCXium A Pd G3 (179 mg, 0.246 mmol) in tetrahydrofuran (20 mL) was stirred for 3 hours at 60 °C. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (1.20 g) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1047.

[1281] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1282] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (1.20 g, 1.15 mmol) in tetrahydrofuran (10 mL) was added TBAF (1M solution in tetrahydrofuran, 2.3 mL) at room temperature, and the mixture was stirred for 1 hour. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (1.00 g) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 933. ^1H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 7.16 (d, J = 8.0 Hz, 4H), 6.86 (d, J = 8.1 Hz, 4H), 6.78 – 6.46 (m, 1H), 5.15 (d, J = 13.1 Hz, 1H), 4.71 – 4.48 (m,

2H), 4.48 – 4.20 (m, 5H), 4.19 – 3.85 (m, 3H), 3.71 (s, 6H), 3.49 – 3.34 (m, 2H), 3.05 (d, J = 13.3 Hz, 1H), 2.35 (s, 3H), 1.96 – 1.61 (m, 4H), 1.54 – 1.39 (m, 12H), 0.62 – 0.40 (m, 4H).

[1283] **Intermediate 123:** 5-Chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole



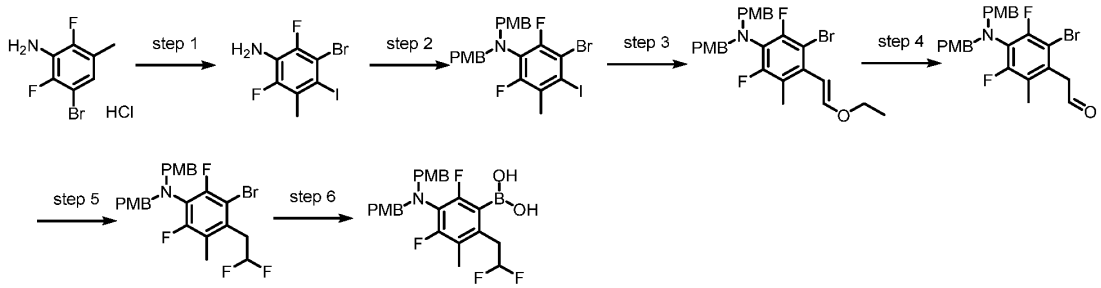
[1284] Step 1: 4-Bromo-5-chloro-6-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole

[1285] Under nitrogen, to a solution of 4-bromo-5-chloro-6-methyl-1*H*-indazole (300 mg, 1.22 mmol) in DMF (3.00 mL) was added NaH (59.0 mg, 1.48 mmol, 60% in mineral oil) at 0 °C. The resulting solution was stirred for 30 min at 0 °C. Then SEMCl (266 mg, 1.60 mmol) was added at 0 °C, and the mixture was stirred for 1 h at room temperature. The mixture was cooled to 0 °C, quenched with water and extracted with EtOAc. The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% EtOAc / petroleum ether) to afford 317 mg of the title compound as a white solid. LCMS: (ESI, *m/z*): $[M+H]^+$ = 375.

[1286] Step 2: 5-Chloro-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole

[1287] Under nitrogen, a solution of 4-bromo-5-chloro-6-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (267 mg, 0.714 mmol), Pd(dppf)Cl_2.DCM (58.3 mg, 0.0710 mmol), Pin_2B_2 (274 mg, 1.08 mmol) and KOAc (212 mg, 2.16 mmol) in 1,4-dioxane (3.00 mL) was stirred for 16 h at 100 °C. The reaction mixture was cooled to room temperature, filtered through a celite pad and washed with EtOAc. The filtrate was concentrated in vacuo. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% EtOAc / petroleum ether) to afford 166 mg of the title compound as a white solid. LCMS: (ESI, *m/z*): $[M+H]^+$ = 423.

[1288] **Intermediate 124:** (3-(bis(4-Methoxybenzyl) amino)-6-(2,2-difluoroethyl)-2,4-difluoro-5-methylphenyl) boronic acid



[1289] Step 1: 3-Bromo-2,6-difluoro-4-iodo-5-methylaniline

[1290] A solution of 3-bromo-2,6-difluoro-5-methyl-aniline (2.01 g, 9.02 mmol) and NIS (2.42 g, 10.8 mmol) in AcOH (10 mL) was stirred for 30 min at room temperature. The solution was quenched by $Na_2S_2O_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-6% EtOAc / petroleum ether) to afford 2.15 g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 348$.

[1291] Step 2: 3-Bromo-2,6-difluoro-4-iodo-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline

[1292] Under nitrogen, to a solution of 3-bromo-2,6-difluoro-4-iodo-5-methylaniline (2.13 g, 6.13 mmol) in DMF (20 mL) was added NaH (0.980 g, 24.5 mmol) at 0 °C. The resulting solution was stirred for 30 min at 0 °C. Then PMB-Cl (2.39 g, 15.3 mmol) was added, and the mixture was stirred at room temperature for 2 h. The solution was quenched with NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-8% EtOAc / petroleum ether) to afford 3.73g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 588$.

[1293] Step 3: (*E*)-3-Bromo-4-(2-ethoxyvinyl)-2,6-difluoro-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline

[1294] Under nitrogen, a solution of 3-bromo-2,6-difluoro-4-iodo-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline (3.77 g, 6.41 mmol), (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.40 g, 7.05 mmol), $Pd(dppf)Cl_2$ (0.980 g, 1.28 mmol) and K_2CO_3 (1.77 g, 12.8 mmol) in 1,4-dioxane (38 mL) and water (7.6 mL) was stirred for 5 h at 90 °C. The resulting reaction was cooled to room temperature and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% EtOAc / petroleum ether) to afford 1.62 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 532$.

[1295] Step 4: 2-(4-(bis(4-Methoxybenzyl)amino)-2-bromo-3,5-difluoro-6-methylphenyl)acetaldehyde

[1296] Under nitrogen, to a solution of (*E*)-3-bromo-4-(2-ethoxyvinyl)-2,6-difluoro-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline (1.61 g, 3.01 mmol) in THF (16 mL) was added HCl (3.2 mL, 36%) and stirred for 2 h at room temperature. The solution was quenched by $NaHCO_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford 1.51 g (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 504$.

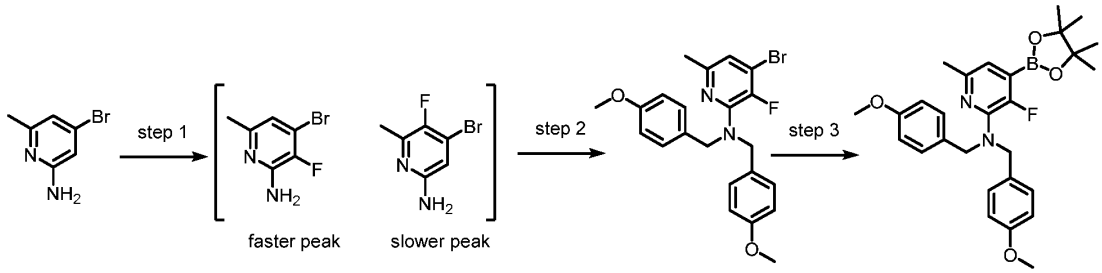
[1297] Step 5: 3-Bromo-4-(2,2-difluoroethyl)-2,6-difluoro-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline

[1298] Under nitrogen, to a solution of 2-(4-(bis(4-methoxybenzyl)amino)-2-bromo-3,5-difluoro-6-methylphenyl)acetaldehyde (1.51 g, 2.99 mmol) in DCM (16 mL) was added DAST (4.83 g, 29.9 mmol) at -10 °C, and the mixture was stirred for 2 h at room temperature. The solution was quenched with $NaHCO_3$ aqueous and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-9% EtOAc / petroleum ether) to afford 1.01 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 526$.

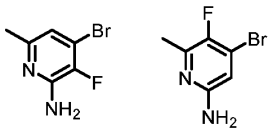
[1299] Step 6: (3-(bis(4-Methoxybenzyl)amino)-6-(2,2-difluoroethyl)-2,4-difluoro-5-methylphenyl) boronic acid

[1300] Under nitrogen, a solution of 3-bromo-4-(2,2-difluoroethyl)-2,6-difluoro-*N,N-bis*(4-methoxybenzyl)-5-methylaniline (500 mg, 0.950 mmol) and triisopropyl borate (893 mg, 4.75 mmol) in THF (5 mL) was added *n*-BuLi (1.9 mL, 2.5 M in THF) at -60 °C, and the mixture was stirred for 2 h at -60 °C. The solution was quenched by MeOH and the solution was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-29% EtOAc (0.1% TEA) / petroleum ether (10% DCM)) to afford 201 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 492$.

[1301] **Intermediate 125:** 3-Fluoro-*N,N*-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine



[1302] Step 1: 4-Bromo-3-fluoro-6-methylpyridin-2-amine



[1303] To a solution of 4-bromo-6-methylpyridin-2-amine (1.00g, 5.35mmol) in $CHCl_3$ (6mL) and water (6mL) was added SelectFluor (946mg, 2.67mmol) at room temperature. The reaction was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum. EtOAc was added and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on

silica gel (gradient: 0-100% EtOAc in petroleum ether) to afford **faster peak** (112 mg) and **slower peak** (215 mg) as yellow solids.

[1304] **Faster peak**: LC-MS: (ESI, m/z): $[M+H]^+ = 205$. ^1H NMR (300 MHz, DMSO-d_6) δ 6.64 (d, J = 3.7 Hz, 1H), 6.40 (s, 2H), 2.21 (d, J = 1.2 Hz, 3H).

[1305] **Slower peak**: LC-MS: (ESI, m/z): $[M+H]^+ = 205$. ^1H NMR (300 MHz, DMSO-d_6) δ 6.54 (d, J = 3.8 Hz, 1H), 5.99 (s, 2H), 2.25 (d, J = 3.2 Hz, 3H).

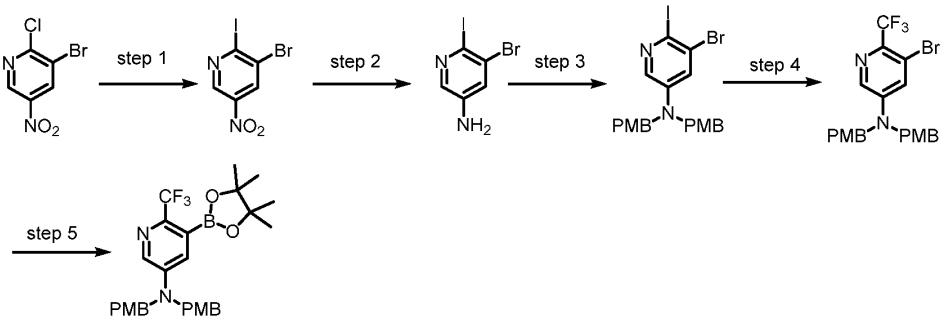
[1306] Step 2: 4-Bromo-3-fluoro-*N*,*N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine

[1307] To a solution of 4-bromo-3-fluoro-6-methylpyridin-2-amine (110mg, 0.540mmol, the faster peak of last step) in DMF (1 mL) was added NaH (53.6mg, 1.34mmol, 60% dispersion in mineral oil) at 0 °C. The mixture was stirred for 20 min at 0°C. PMBCl (185mg, 1.18mmol) was added and the mixture was allowed to warm to room temperature and stirred for 1 hour. The reaction was quenched by water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-40% EtOAc in petroleum ether) to afford the title compound (175mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 445$.

[1308] Step 3: 3-Fluoro-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine

[1309] Under nitrogen, a solution of 4-bromo-3-fluoro-*N*,*N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (150mg, 0.340mmol), B_2Pin_2 (128mg, 0.510mmol), $Pd(dppf)Cl_2$ (49.3 mg, 0.0700 mmol) and KOAc (66.0mg, 0.670mmol) in 1,4-dioxane (3mL) was stirred at 80 °C for 4 hours. The solution was cooled to room temperature. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-5% MeOH in DCM) to afford the title compound (150mg) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 411$ (Mass of the boronic acid). ^1H NMR (300 MHz, DMSO-d_6) δ 7.20 – 7.11 (m, 4H), 6.91 – 6.80 (m, 4H), 6.68 (d, J = 2.4 Hz, 1H), 4.50 (s, 4H), 3.70 (s, 6H), 2.27 (s, 3H), 1.26 (s, 12H).

[1310] **Intermediate 126:** *N*,*N*-Bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-(trifluoromethyl)pyridin-3-amine



[1311] Step 1: 3-Bromo-2-iodo-5-nitropyridine

[1312] A solution of 3-bromo-2-chloro-5-nitropyridine (2.0 g, 8.42 mmol) and NaI (12.9 g, 86 mmol) in 2,2,2-trifluoroacetic acid (20 mL) was stirred at room temperature for 24 hours. The reaction was quenched by aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% EtOAc / petroleum ether) to afford 990 mg of the title compound as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 329; 331.

[1313] Step 2: 5-Bromo-6-iodopyridin-3-amine

[1314] A solution of 3-bromo-2-iodo-5-nitropyridine (700 mg, 2.13 mmol), NH_4Cl (577 mg, 10.9 mmol) and ferrous powder (605 mg, 10.8 mmol) in ethanol (30 mL) and water (10 mL) was stirred at 80°C for 2.5 hours. The solution was concentrated under vacuum. The residue was diluted with brine, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-40% EtOAc / petroleum ether) to afford 570 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 299; 301.

[1315] Step 3: 5-Bromo-6-iodo-*N*,*N*-bis(4-methoxybenzyl)pyridin-3-amine

[1316] Under nitrogen, to a solution of 5-bromo-6-iodopyridin-3-amine (570 mg, 1.91 mmol) in *N*,*N*-dimethylformamide (18 mL) was added NaH (392 mg, 9.81 mmol, 60% dispersion in mineral oil) at 0°C. The solution was stirred at room temperature for 0.5 hour. Then PMB-Cl (906 mg, 5.78 mmol) was added. The solution was stirred at room temperature for 2 hours. The reaction was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc / petroleum ether) to afford 925 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 539; 541.

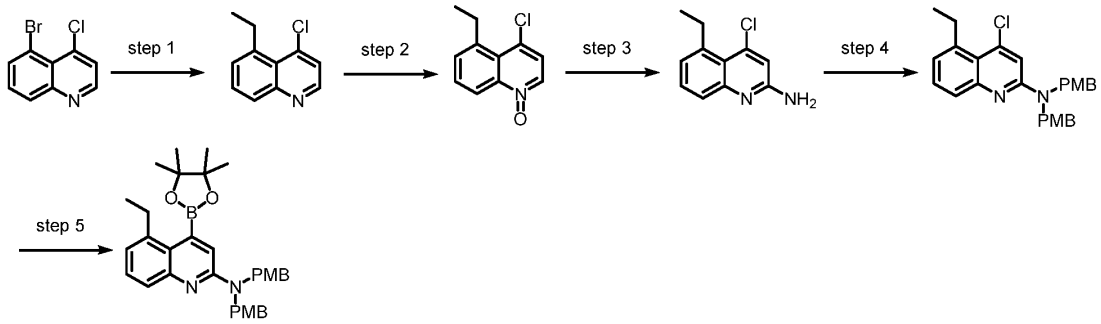
[1317] Step 4: 5-Bromo-*N*,*N*-bis(4-methoxybenzyl)-6-(trifluoromethyl)pyridin-3-amine

[1318] A solution of 5-bromo-6-iodo-*N*,*N*-bis(4-methoxybenzyl)pyridin-3-amine (1.05 g, 1.95 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (1.89 g, 9.84 mmol) and CuI (1.97 g, 10.4 mmol) in N,N-dimethylacetamide (14 mL) was stirred at 70°C for 7 hours. The solution diluted with brine, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-20% EtOAc / petroleum ether) to afford 802 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 481; 483.

[1319] Step 5: *N*,*N*-Bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridin-3-amine

[1320] Under nitrogen, a solution of 5-bromo-*N*,*N*-bis(4-methoxybenzyl)-6-(trifluoromethyl)pyridin-3-amine (800 mg, 1.66 mmol), Pin_2B_2 (1.28 g, 5.04 mmol), $PdCl_2(dppf)$ (263 mg, 0.359 mmol) and KOAc (498 mg, 5.08 mmol) in 1,4-Dioxane (25 mL) was stirred at 110°C for 6 hours. The solution was added brine and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc / petroleum ether) to afford 392 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 529.

[1321] **Intermediate 127:** 5-Ethyl-*N*,*N*-bis(4-methoxybenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-2-amine



[1322] Step 1: 4-Chloro-5-ethylquinoline

[1323] Under nitrogen, a solution of 5-bromo-4-chloro-quinoline (2.01 g, 8.29 mmol), ethylboronic acid (798 mg, 10.8 mmol), dichloro[9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene] palladium(II) (603 mg, 0.800 mmol) and Cs_2CO_3 (5.69 g, 17.5 mmol) in toluene (64 mL) and water (8 mL) was stirred at 100°C for 16 hours. The solution was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc / petroleum ether) to afford 1.12 g of the title compound as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 192.

[1324] Step 2: 4-Chloro-5-ethylquinoline 1-oxide

[1325] Under nitrogen, to a solution of 4-chloro-5-ethylquinoline (1.11 g, 5.79 mmol) in dichloromethane (35 mL) was added m-CPBA (2.12 g, 12.3 mmol) at 0°C. The solution was stirred at room temperature for 5 hours. The reaction was quenched with saturated NaS_2O_3 aqueous and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford 1.21 g (crude) of the title compound as a crude brown oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 208$.

[1326] Step 3: 4-Chloro-5-ethylquinolin-2-amine

[1327] A solution of 4-chloro-5-ethylquinoline 1-oxide (1.21 g, 5.83 mmol) and TsCl (1.86 g, 9.76 mmol) in dichloromethane (60 mL) was stirred at room temperature for 1 hour. Then the above solution was added to a solution of Et_3N (9.89 g, 97.9 mmol) and NH_4Cl (5.27 g, 98.5 mmol) in dichloromethane (60 mL). The solution was stirred at room temperature for 16 hours. The solid was filtered out and the filtrate was concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-45% ACN in water (0.05% NH_4HCO_3)) to afford 520 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 207$.

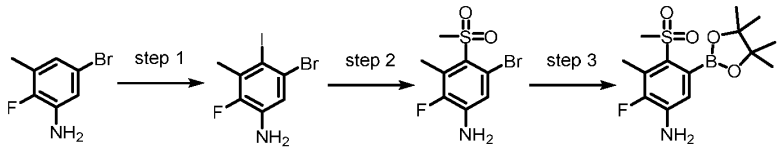
[1328] Step 4: 4-Chloro-5-ethyl-*N*,*N*-bis(4-methoxybenzyl)quinolin-2-amine

[1329] Under nitrogen, to a solution of 4-chloro-5-ethylquinolin-2-amine (520 mg, 2.52 mmol) in N,N-dimethylformamide (12 mL) was added NaH (401 mg, 10.0 mmol, 60% dispersion in mineral oil) at 0°C. The solution was stirred at room temperature for 0.5 hour. Then PMB-Cl (1.17 g, 7.45 mmol) was added and the solution was stirred at room temperature for 3 hours. The reaction was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-5% EtOAc / petroleum ether) to afford 993 mg of the title compound as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 447$.

[1330] Step 5: 5-Ethyl-*N*,*N*-bis(4-methoxybenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinolin-2-amine

[1331] Under nitrogen, a solution of 4-chloro-5-ethyl-*N*,*N*-bis(4-methoxybenzyl)quinolin-2-amine (990 mg, 2.22 mmol), Pin_2B_2 (1.72 g, 6.77 mmol), $PdCl_2$(dppf) (345 mg, 0.472 mmol) and KOAc (659 mg, 6.72 mmol) in 1,4-Dioxane (25 mL) was stirred at 110°C for 3 hours. The solution was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% EtOAc / petroleum ether) to afford 651 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 539$.

[1332] **Intermediate 128:** 2-Fluoro-3-methyl-4-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[1333] Step 1: 5-Bromo-2-fluoro-4-iodo-3-methylaniline

[1334] A solution of 5-bromo-2-fluoro-3-methylaniline (2.00 g, 9.80 mmol) and NIS (2.65 g, 11.8 mmol) in AcOH (50 mL) was stirred for 1 hour at room temperature. The solution was quenched with $Na_2S_2O_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (1.90 g) as an off-white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 330.

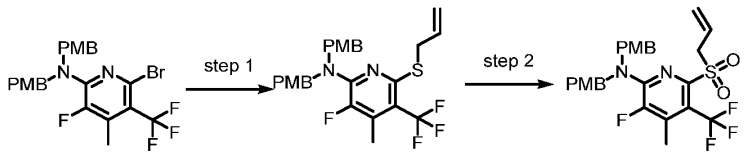
[1335] Step 2: 5-Bromo-2-fluoro-3-methyl-4-(methylsulfonyl)aniline

[1336] Under nitrogen, a mixture of 5-bromo-2-fluoro-4-iodo-3-methylaniline (1.90 g, 5.76 mmol), sodium methanesulfinate (705 mg, 6.91 mmol), L-proline sodium salt (158 mg, 1.15 mmol) and CuI (110 mg, 0.578 mmol) in DMSO (30 mL) was stirred overnight at 80 °C. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-40% EtOAc in petroleum ether) to afford the title compound (320 mg) as an off-white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 282.

[1337] Step 3: 2-Fluoro-3-methyl-4-(methylsulfonyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[1338] Under nitrogen, a solution of 5-bromo-2-fluoro-3-methyl-4-(methylsulfonyl)aniline (320 mg, 1.13 mmol), B_2Pin_2 (432 mg, 1.70 mmol), KOAc (334 mg, 3.40 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (277 mg, 0.342 mmol) in dioxane (3 mL) was stirred for 2 hours at 90 °C. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc in petroleum ether) to afford the title compound (140 mg) as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 330.

[1339] **Intermediate 129:** 6-(Allylsulfonyl)-3-fluoro-*N*,*N*-*bis*(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl) pyridin-2-amine



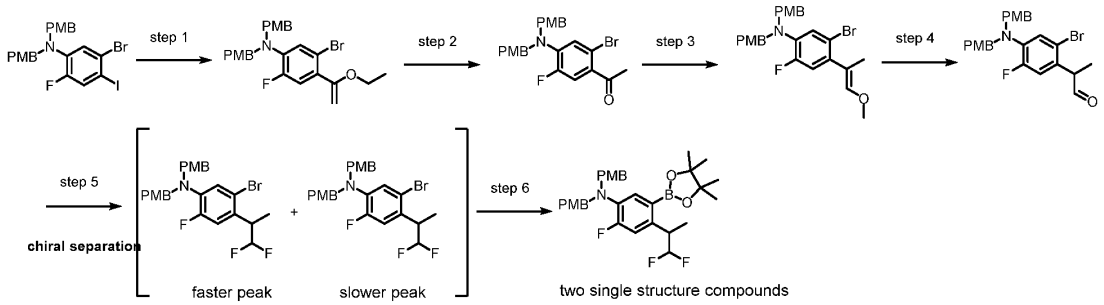
[1340] Step 1: 6-(Allylthio)-3-fluoro-*N*,*N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

[1341] To a solution of prop-2-ene-1-thiol (0.190 mL, 2.44 mmol) in DMF (2.5 mL) was added K_2CO_3 (134 mg, 0.970 mmol) and 6-bromo-3-fluoro-*N*,*N*-*bis*(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (250 mg, 0.490 mmol) at room temperature. The resulting solution was stirred overnight at room temperature. The resulting reaction was diluted with EtOAc, washed with water. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-16% EtOAc/petroleum ether) to afford 234 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 507$.

[1342] Step 2: 6-(Allylsulfonyl)-3-fluoro-*N*,*N*-*bis*(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl) pyridin-2-amine

[1343] Under nitrogen, a solution of 6-(allylthio)-3-fluoro-*N*, *N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl) pyridin-2-amine (234 mg, 0.460 mmol) and m-CPBA (240 mg, 1.39 mmol) in DCM (3 mL) was stirred overnight at room temperature. The reaction was quenched with $NaHCO_3$ aqueous and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-43% EtOAc / petroleum ether) to afford 99.7 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 539$.

[1344] **Intermediate 130:** 4-(1,1-Difluoropropan-2-yl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[1345] Step 1: 5-Bromo-4-(1-ethoxyvinyl)-2-fluoro-*N*, *N*-bis(4-methoxybenzyl) aniline

[1346] Under nitrogen, a solution of 5-bromo-2-fluoro-4-iodo-*N*, *N*-bis(4-methoxybenzyl) aniline (3.01 g, 5.41 mmol), tributyl(1-ethoxyvinyl) stannane (2.74 mL, 8.11 mmol) and $PdCl_2(PPh_3)_2$ (406 mg, 0.578 mmol) in DMF (15 mL) was stirred for 6 hours at 80°C. The resulting mixture was diluted with ethyl acetate and washed with water. The organic layer was concentrated under vacuum to afford 2.98 g (crude) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 500$.

[1347] Step 2: 1-(4-(Bis(4-methoxybenzyl) amino)-2-bromo-5-fluorophenyl) ethan-1-one

[1348] To a solution of 5-bromo-4-(1-ethoxyvinyl)-2-fluoro-*N*, *N*-bis(4-methoxybenzyl) aniline (2.98 g, 5.96 mmol) in DMF (15 mL) was added HCl (3 mL, 12 M), and the mixture was stirred at room temperature for 2 h. The resulting mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc / petroleum ether) to afford 1.71 g of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 472$.

[1349] Step 3: (*E*)-5-Bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-4-(1-methoxyprop-1-en-2-yl)aniline

[1350] Under nitrogen, to a solution of 1-(4-(bis(4-methoxybenzyl)amino)-2-bromo-5-fluorophenyl)ethan-1-one (1.69 g, 3.58 mmol) in THF (20 mL) was added *t*-BuOK (10.6 mL, 1M in THF) at 0°C. The resulting solution was stirred for 0.5 h at 0°C. Then (methoxymethyl)triphenylphosphonium chloride (4.01 g, 11.7 mmol) was added, and the mixture was stirred at 0°C for 1.5 h. The reaction was quenched with NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc / petroleum ether) to afford 1.31g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 500$.

[1351] Step 4: 2-(4-(Bis(4-methoxybenzyl)amino)-2-bromo-5-fluorophenylproopanal

[1352] A solution of (*E*)-5-bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-4-(1-methoxyprop-1-en-2-yl)aniline (1.31 g, 2.62 mmol) in THF (4 mL) was added HCl (1 mL, 12 M), and the mixture was stirred at room temperature for 2 h. The solvent was concentrated under vacuum. The resulting mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on –silica gel (gradient: 0 - 70% EtOAc / petroleum ether) to afford 763 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 486$.

[1353] Step 5: 5-Bromo-4-(1,1-difluoropropan-2-yl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)aniline

[1354] Under nitrogen, to a solution of 2-(4-(bis(4-methoxybenzyl)amino)-2-bromo-5-fluorophenyl)propanal (763 mg, 1.56 mmol) in DCM (10 mL) was added DAST (1.26 g, 7.83 mmol) at 0°C. The resulting solution was stirred for 2 h at room temperature. The reaction was quenched with NH_4Cl aqueous. The resulting mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc / petroleum ether) to afford 716 mg of the title compound as a yellow solid. The mixture product

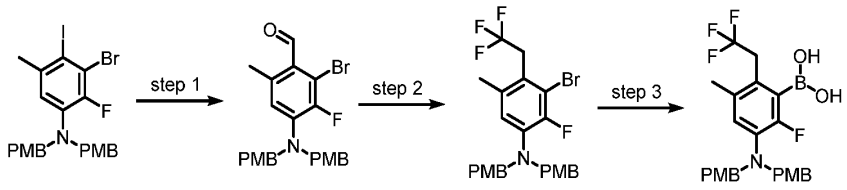
was purified by Chiral-Prep- HPLC (Column: Lux 5um Celluloes-3 5 x 25 cm, 5 μm; Mobile Phase– Hex(0.1% 2M NH_3-MeOH)--H–, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic; Wave Length: 220/254 nm; R_{T1}(min): 14.182; R_{T2}(min): 20–; Sample Solvent: EtOH--HPLC) afford 191mg of the faster peak and 175 mg of the slower peak as white solids. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 508.

[1355] Step 6: 4-(1,1-Difluoropropan-2-yl)-2-fluoro-*N,N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[1356] Under nitrogen, a solution of 5-bromo-4-(1,1-difluoropropan-2-yl)-2-fluoro-*N,N*-bis(4-methoxybenzyl)aniline (171 mg, 0.340 mmol, faster perk from last step), Pin_2B_2 (256 mg, 1.01 mmol), KOAc (99.2 mg, 1.01 mmol) and Pd(dppf)Cl_2 (49.6 mg, 0.0700 mmol) in 1,4-dioxane (10 mL) was stirred for 3 h at 100°C. The resulting mixture was diluted with ethyl acetate and washed with water. The separated organic layer was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc / petroleum ether) to afford 132 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 556.

[1357] Analogous to method described as above, the enantiomer 113 mg was prepared from 5-bromo-4-(1,1-difluoropropan-2-yl)-2-fluoro-*N,N*-bis(4-methoxybenzyl)aniline (slower perk from last step)

[1358] **Intermediate 131:** (3-(Bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(2,2,2-trifluoroethyl)phenyl)boronic acid.



[1359] Step 1: 4-(Bis(4-methoxybenzyl) amino)-2-bromo-3-fluoro-6-methylbenzaldehyde

[1360] Under nitrogen, to a solution of 3-bromo-2-fluoro-4-iodo-*N,N*-bis(4-methoxybenzyl)-5-methylaniline (500mg, 0.880mmol) in tetrahydrofuran (5mL) was added 2 M iPrMgCl in THF (1.32mL, 2.63mmol) at -20 °C. The resulting solution was stirred for 1 hour at -20 °C. Then DMF (640mg, 8.77mmol) was added, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with water, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (202 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 472.

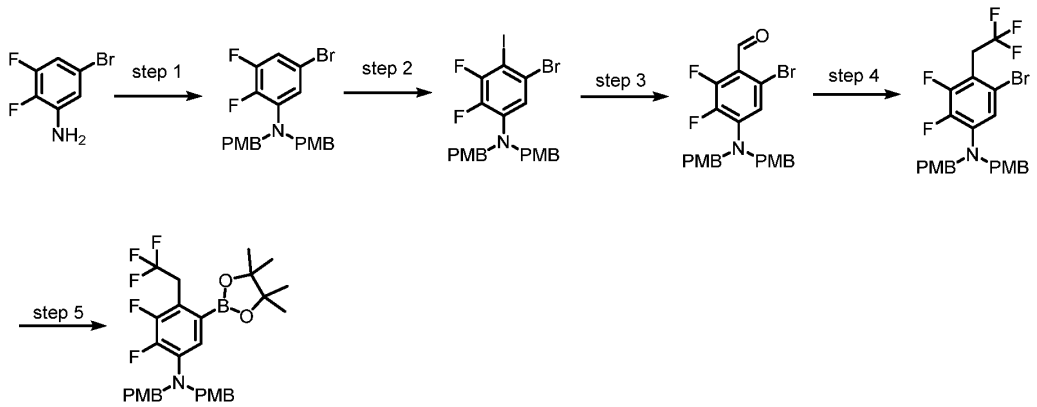
[1361] Step 2: 3-Bromo-2-fluoro-*N,N*-bis(4-methoxybenzyl)-5-methyl-4-(2,2,2-trifluoroethyl)aniline

[1362] Under nitrogen, to a solution of 4-(bis(4-methoxybenzyl)amino)-2-bromo-3-fluoro-6-methylbenzaldehyde (200mg, 0.420mmol) in N,N-dimethylacetamide (2mL) was added 2,2-difluoro-2-(triphenylphosphonio)acetate (301mg, 0.850mmol) at room temperature. The resulting solution was stirred at 60 °C overnight. Then TBAF (6.35 mL, 6.35 mmol) was added, and the mixture was stirred at 60 °C for 3 hours. The resulting solution was diluted with EtOAc and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% EtOAc in petroleum ether) to afford the title compound (85mg) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 526.

[1363] Step 3: (3-(Bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(2,2,2-trifluoroethyl) phenyl) boronic acid

[1364] Under nitrogen, to a solution of 3-bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-methyl-4-(2,2,2-trifluoroethyl)aniline (65.0mg, 0.123 mmol) and triisopropyl borate (0.04mL, 0.190mmol) in tetrahydrofuran (1mL) was added n-BuLi (1.6 M in hexane, 0.09 mL, 0.150 mmol) at -78 °C. The solution was stirred at -78 °C for 1 hour. The reaction was quenched by MeOH and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-25% EtOAc in petroleum ether) to afford the title compound (23mg) as a white oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 492.

[1365] **Intermediate 132:** 2,3-Difluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(2,2,2-trifluoroethyl)aniline



[1366] Step 1: 5-Bromo-2,3-difluoro-*N*,*N*-*bis*(4-methoxybenzyl)aniline

[1367] Under nitrogen, to a solution of 5-bromo-2,3-difluoroaniline (5.01 g, 24.1 mmol) in DMF (50 mL) was added NaH (3.69 g, 92.3 mmol, 60% dispersion in mineral oil) at 0 °C. The solution was stirred for 30 min at 0 °C. Then PMB-Cl (9.39 g, 60.2 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 1 hour. The solution was quenched by saturated NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over

anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-5% EtOAc / petroleum ether) to afford 9.70 g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 448.

[1368] Step 2: 5-Bromo-2,3-difluoro-4-iodo-*N*,*N*-*bis*(4-methoxybenzyl)aniline

[1369] To a solution of 5-bromo-2,3-difluoro-*N*,*N*-*bis*(4-methoxybenzyl)aniline (4.51 g, 10.1 mmol) in AcOH (45 mL) was added NIS (3.37 g, 15.1 mmol), and the mixture was stirred for 30 min at room temperature. The reaction was quenched by $Na_2S_2O_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-6% EtOAc / petroleum ether) to afford 4.74 g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 574.

[1370] Step 3: 4-(*bis*(4-Methoxybenzyl)amino)-6-bromo-2,3-difluorobenzaldehyde

[1371] Under nitrogen, to a solution of 5-bromo-2,3-difluoro-4-iodo-*N*,*N*-bis(4-methoxybenzyl) aniline (2.62 g, 4.56 mmol) in THF (26 mL) was added 2M iPr-MgCl (2.74 mL, 5.48 mmol) in THF at -60°C. The resulting solution was stirred for 1 h at -60 °C. Then DMF (3.33 g, 45.6 mmol) was added at -60 °C, and the mixture was stirred at room temperature for 30 min. The reaction was quenched by NH_4Cl aqueous, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% EtOAc / petroleum ether) to afford 1.11 g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 476;478.

[1372] Step 4: 5-Bromo-2,3-difluoro-*N*,*N*-bis(4-methoxybenzyl)-4-(2,2,2-trifluoroethyl)aniline

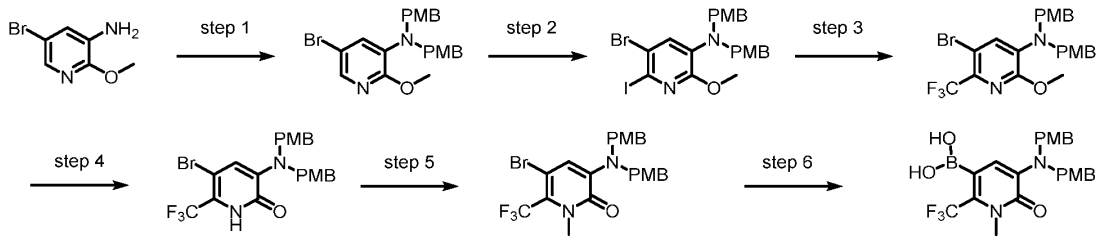
[1373] Under nitrogen, a solution of 4-(bis(4-methoxybenzyl)amino)-6-bromo-2,3-difluorobenzaldehyde (1.41 g, 2.95 mmol) and 2,2-difluoro-2-triphenylphosphaniumyl-acetate (2.10 g, 5.91 mmol) in DMF (18 mL) was stirred for 2.5 h at 60 °C. Then TBAF (26.6 mL, 1 M in THF) was added, and the mixture was stirred at 60 °C for 3 h. The resulting reaction was diluted with EtOAc, washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% EtOAc/petroleum ether) to afford 940 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 530.

[1374] Step 5: 2,3-Difluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(2,2,2-trifluoroethyl)aniline

[1375] Under nitrogen, a solution of 5-bromo-2,3-difluoro-*N*,*N*-*bis*(4-methoxybenzyl)-4-(2,2,2-trifluoroethyl) aniline (810 mg, 1.53 mmol), Pin_2B_2 (776 mg, 3.06 mmol), KOAc (449 mg,

4.58 mmol) and $Pd(dppf)Cl_2$ (234 mg, 0.310 mmol) in 1,4-dioxane (8 mL) was stirred for 8 hours at 90 °C. The solution was cooled to room temperature and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-40% EtOAc / petroleum ether) to afford 741 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 578.

[1376] **Intermediate 133:** (5-(Bis(4-methoxybenzyl)amino)-1-methyl-6-oxo-2-(trifluoromethyl)-1,6-dihydropyridin-3-yl)boronic acid



[1377] Step 1: 5-Bromo-2-methoxy-*N,N*-bis(4-methoxybenzyl)pyridin-3-amine

[1378] To a solution of 5-bromo-2-methoxypyridin-3-amine (2.01 g, 9.90 mmol) in DMF (25 mL) was added NaH (1.19 g, 29.7 mmol) at 0 °C under nitrogen. After 30 min, PMBCl (3.86 g, 24.7 mmol) was added, and the reaction mixture was warmed to room temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%-30% EtOAc / petroleum ether) afforded the title compound as a white solid (4.81 g). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 443.

[1379] Step 2: 5-Bromo-6-iodo-2-methoxy-*N,N*-bis(4-methoxybenzyl)pyridin-3-amine

[1380] To a solution of 5-bromo-2-methoxy-*N,N*-bis(4-methoxybenzyl)pyridin-3-amine (2.47 g, 5.57 mmol) in AcOH (15 mL) was added NIS (2.51 g, 11.1 mmol) at room temperature. After 1.5 h, the resulting mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (gradient: 0-20% EtOAc / petroleum ether) to afford 2.21 g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 569.

[1381] Step 3: 5-Bromo-2-methoxy-*N,N*-bis(4-methoxybenzyl)-6-(trifluoromethyl)pyridin-3-amine

[1382] Under nitrogen, to a mixture of 5-bromo-6-iodo-2-methoxy-*N,N*-bis(4-methoxybenzyl)pyridin-3-amine (2.01 g, 3.53 mmol), $Cu(O_2CCF_2SO_2F)_2$ (14.6 g, 35.0 mmol) and Cu powder (2.25 g, 35.2 mmol) was added DMF (20 mL) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. The reaction was diluted with ethyl acetate, and the resulting mixture was washed with water and brine. The organic layer was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (gradient: 0-20% EtOAc /

petroleum ether) to afford 1.35 g the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 511.

[1383] Step 4: 3-(Bis(4-methoxybenzyl)amino)-5-bromo-6-(trifluoromethyl)pyridin-2(1*H*)-one

[1384] A solution of 5-bromo-2-methoxy-*N*,*N*-bis(4-methoxybenzyl)-6-(trifluoromethyl)pyridin-3-amine (1.21 g, 2.35 mmol), LiCl (492 mg, 11.7 mmol) and PTSA (2.13 g, 12.4 mmol) in DMF (5 mL) was heated at 120 °C for 16 h. The reaction was diluted with ethyl acetate, and the resulting mixture was washed with water and brine. The organic layer was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (gradient: 0-20% EtOAc / petroleum ether) to afford 570 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 497.

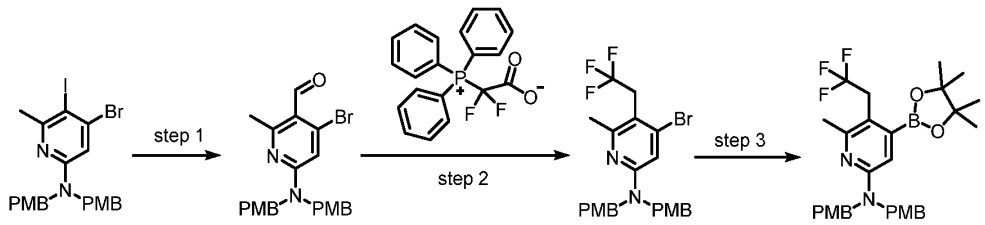
[1385] Step 5: 3-(Bis(4-methoxybenzyl)amino)-5-bromo-1-methyl-6-(trifluoromethyl)pyridin-2(1*H*)-one

[1386] A solution of 3-(bis(4-methoxybenzyl)amino)-5-bromo-6-(trifluoromethyl)pyridin-2(1*H*)-one (516 mg, 1.04 mmol), CH_3I (728 mg, 5.13 mmol) and K_2CO_3 (732 mg, 5.30 mmol) in MeOH (8 mL) was stirred at 65 °C for 2 h. The reaction was cooled to room temperature, and the solvent was concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-80% ACN in water (0.05% NH_4HCO_3)) to afford 136 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 511.

[1387] Step 6: (5-(Bis(4-methoxybenzyl)amino)-1-methyl-6-oxo-2-(trifluoromethyl)-1,6-dihydropyridin-3-yl)boronic acid

[1388] To a solution of 3-(bis(4-methoxybenzyl)amino)-5-bromo-1-methyl-6-(trifluoromethyl)pyridin-2(1*H*)-one (136 mg, 0.270 mmol) and triisopropyl borate (249 mg, 1.32 mmol) in THF (5 mL) was added *n*-BuLi (0.5 mL, 1.25 mmol) at –78 °C under nitrogen. The resulting solution was stirred for 1 h at –78 °C. The reaction was quenched with MeOH at –78 °C and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–30% EtOAc (0.1% Et_3N) / petroleum ether (10% DCM)) afforded the titled compound as a yellow oil (32.1 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 476.

[1389] **Intermediate 134:** *N*, *N*-Bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(2,2,2-trifluoroethyl)pyridin-2-amine



[1390] Step 1: 6-(Bis(4-methoxybenzyl)amino)-4-bromo-2-methylnicotinaldehyde

[1391] To a solution of 4-bromo-5-iodo-*N*, *N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (1.00 g, 1.80 mmol, intermediate 138, step 2) in THF (10.0 mL) at –15 °C was added *i*PrMgCl (2.72 mL, 2 M in THF) under nitrogen. After 1 h, DMF (2.00 mL) was added, and the reaction mixture was warmed to room temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–50% EtOAc in petroleum ether) afforded the titled compound as a yellow solid (576 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 509$.

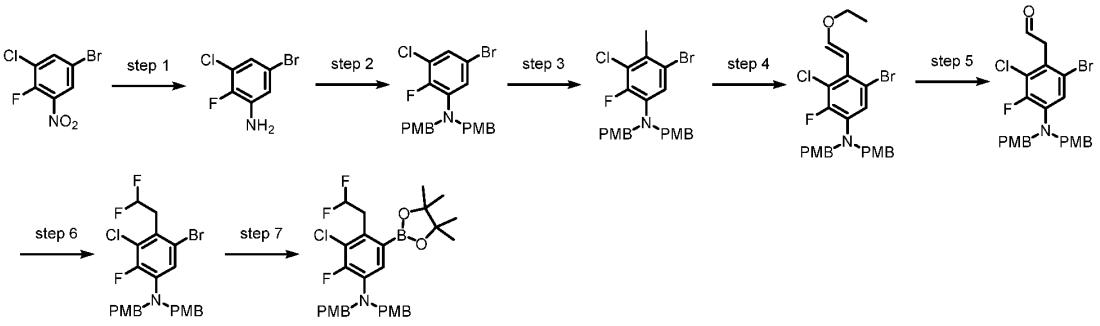
[1392] Step 2: 4-Bromo-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-5-(2,2,2-trifluoroethyl)pyridin-2-amine

[1393] A solution of 2,2-difluoro-2-(triphenylphosphonio)acetate (530 mg, 1.49 mmol) and 6-(bis(4-methoxybenzyl)amino)-4-bromo-2-methylnicotinaldehyde (339 mg, 0.740 mmol) in DMF (3.00 mL) was stirred under an atmosphere of nitrogen for 2.5 h at room temperature. TBAF (11.2 mL, 1 M in THF) was then added, and the resulting mixture was heated at 60 °C. After 12 h, the reaction was cooled to room temperature, and EtOAc was added. The resulting solution was washed with water. The organic was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–50% EtOAc in petroleum ether) afforded the titled compound as a white solid (506 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 509$.

[1394] Step 3: *N*,*N*-Bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(2,2,2-trifluoroethyl)pyridin-2-amine

[1395] A solution of 4-bromo-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-5-(2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.200 mmol), bis(pinacolato)diboron (149 mg, 0.590 mmol), $PdCl_2$(dppf) (28.5 mg, 0.0400 mmol) and KOAc (57.7 mg, 0.590 mmol) in 1,4-dioxane (1.00 mL) was heated at 90 °C under nitrogen. After 18 h, the reaction was concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–50% EtOAc in petroleum ether) afforded the titled compound as a colorless oil (97.8 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 557$.

[1396] **Intermediate 135:** 3-Chloro-4-(2,2-difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[1397] Step 1: 5-Bromo-3-chloro-2-fluoroaniline

[1398] A solution of 5-bromo-1-chloro-2-fluoro-3-nitrobenzene (10.1 g, 39.7 mmol), Fe (11.1 g, 198 mmol) and NH_4Cl (21.2 g, 399 mmol) in EtOH (70 mL) and water (30 mL) was heated at 80 °C for 2 h. The resulting solution was partitioned between water and EtOAc. The organic was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–20% EtOAc in petroleum ether) afforded the titled compound as a yellow solid (7.22 g). LC-MS: (ESI, *m/z*): $[M+H]^+ = 224$. ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 6.92 – 6.85 (m, 1H), 6.85 – 6.78 (m, 1H), 5.82 (s, 2H).

[1399] Step 2: 5-Bromo-3-chloro-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)aniline

[1400] To an ice-cooled solution of 5-bromo-3-chloro-2-fluoroaniline (7.81 g, 34.8 mmol) in DMF (80 mL) was added NaH (4.20 g, 105 mmol). After 30 min, PMBCl (11.5 g, 73.5 mmol) was added at 0 °C, and the mixture was warmed to room temperature for 2 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution, and the mixture was extracted with EtOAc. The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–10% EtOAc in petroleum ether) afforded the titled compound as a yellow solid (14.3 g). LC-MS: (ESI, *m/z*): $[M+H]^+ = 464$.

[1401] Step 3: 5-Bromo-3-chloro-2-fluoro-4-iodo-*N*,*N*-bis(4-methoxybenzyl)aniline

[1402] To a solution of 5-5-bromo-3-chloro-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)aniline (13.1 g, 28.1 mmol) in AcOH (150 mL) was added NIS (7.31 g, 32.5 mmol) at room temperature. After 2 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution and extracted with EtOAc. The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–10% EtOAc in petroleum ether) afforded the titled compound as a yellow oil (11.0 g). LC-MS: (ESI, *m/z*): $[M+H]^+ = 590$. ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 7.29 – 7.13 (m, 5H), 6.94 – 6.82 (m, 4H), 4.31 (s, 4H), 3.72 (s, 6H).

[1403] Step 4: (*E*)-5-Bromo-3-chloro-4-(2-ethoxyvinyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)aniline

[1404] A solution of 5-bromo-3-chloro-2-fluoro-4-iodo-*N*,*N*-bis(4-methoxybenzyl)aniline (4.01 g, 6.77 mmol), (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.69 g, 13.6 mmol), $Pd(dppf)Cl_2$ (1.04 g, 1.36 mmol) and K_2CO_3 (2.81 g, 20.4 mmol) in 1,4-dioxane (40 mL) and water (8 mL) was heated at 60 °C under nitrogen. After 48 h, the resulting solution was partitioned between water and EtOAc. The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–30% DCM in petroleum ether) afforded the titled compound as a yellow oil (976 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 534$.

[1405] Step 5: 2-(4-(Bis(4-methoxybenzyl)amino)-6-bromo-2-chloro-3-fluorophenyl)acetaldehyde

[1406] To a solution of (*E*)-5-bromo-3-chloro-4-(2-ethoxyvinyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)aniline (1.22 g, 2.28 mmol) in THF (15 mL) was added aqueous HCl (1.5 mL, 12 M) at room temperature. After 3 h, the solution was cooled to 0 °C, and the pH was adjusted to 7 with saturated aqueous $NaHCO_3$ solution. The resulting mixture was partitioned between water and EtOAc. The organic was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–10% EtOAc in petroleum ether) afforded the titled compound as a yellow oil (568 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 506$.

[1407] Step 6: 5-Bromo-3-chloro-4-(2,2-difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)aniline

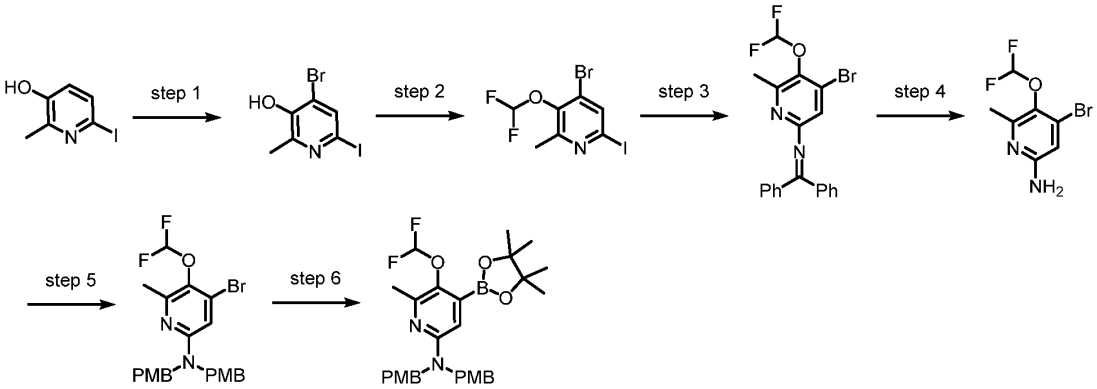
[1408] To a solution of 2-(4-(bis(4-methoxybenzyl)amino)-6-bromo-2-chloro-3-fluorophenyl)acetaldehyde (558 mg, 1.10 mmol) in DCM (8 mL) was added DAST (3.56 g, 22.1 mmol) at –10 °C. The reaction mixture was warmed to room temperature for 2.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution, and resulting mixture was extracted with DCM. The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–15% EtOAc in petroleum ether) afforded the titled compound as a yellow oil (542 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 528$.

[1409] Step 7: 3-Chloro-4-(2,2-difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[1410] A solution of 5-bromo-3-chloro-4-(2,2-difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)aniline (1.42 g, 3.19 mmol), bis(pinacolato)diboron (1.22 g, 4.8 mmol), $Pd(dppf)Cl_2$ (491 mg, 0.640 mmol) and KOAc (614 mg, 6.4 mmol) in 1,4-dioxane (14 mL) was heated at 80 °C under nitrogen overnight. The resulting solution was partitioned between water and EtOAc. The organic layer was dried over anhydrous sodium sulfate, filtered, and

concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–80% EtOAc in petroleum ether) afforded the titled compound as a yellow oil (1.73 g). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 576. ^1H NMR (400 MHz, $CDCl_3$, ppm): δ 7.29 – 7.11 (m, 5H), 6.96 – 6.78 (m, 4H), 6.35 – 5.85 (m, 1H), 4.24 (s, 4H), 3.71 (s, 6H), 3.65 – 3.44 (m, 2H), 1.26 (s, 12H).

[1411] **Intermediate 136:** 5-(Difluoromethoxy)-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-dioxaborolan-2-yl)pyridin-2-amine



[1412] Step 1: 4-Bromo-6-iodo-2-methylpyridin-3-ol

[1413] To a solution of 6-iodo-2-methylpyridin-3-ol (1.90 g, 8.09 mmol) in ACN (20 mL) was added NBS (2.16 g, 12.1 mmol) at room temperature. After 2h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$, and the mixture was extracted with EtOAc. The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–20% EtOAc in petroleum ether) provided the titled compound as a yellow solid (1.35 g). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 314.

[1414] Step 2: 4-Bromo-3-(difluoromethoxy)-6-iodo-2-methylpyridine

[1415] A solution of 4-bromo-6-iodo-2-methylpyridin-3-ol (600 mg, 1.91 mmol), sodium 2-chloro-2,2-difluoroacetate (728 mg, 4.78 mmol) and Cs_2CO_3 (1.56 g, 4.79 mmol) in DMF (8 mL) was heated at 100 °C under nitrogen for 2 h. The reaction was cooled to room temperature, diluted with EtOAc, and washed with water. The organic was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–10% EtOAc in petroleum ether) yielded a white solid (583 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 364.

[1416] Step 3: *N*-(4-Bromo-5-(difluoromethoxy)-6-methylpyridin-2-yl)-1,1-diphenylmethanimine

[1417] A solution of 4-bromo-3-(difluoromethoxy)-6-iodo-2-methylpyridine (500 mg, 1.37 mmol), diphenylmethanimine (274 mg, 1.51 mmol), Xantphos (160 mg, 0.280 mmol), $Pd_2(dba)_3$ (126 mg, 0.140 mmol) and Cs_2CO_3 (1.23 g, 3.76 mmol) in 1,4-dioxane (8 mL) was heated under

nitrogen at 80 °C overnight. The resulting solution was partitioned between water and EtOAc. The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–10% EtOAc in petroleum ether) provided a yellow oil (138 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 417.

[1418] Step 4: 4-Bromo-5-(difluoromethoxy)-6-methylpyridin-2-amine

[1419] To a solution of *N*-(4-Bromo-5-(difluoromethoxy)-6-methylpyridin-2-yl)-1,1-diphenylmethanimine (613 mg, 1.47 mmol) in DCM (6 mL) was added TFA (3 mL) at room temperature. After 1 h, the solution was concentrated under vacuum. The resulting mixture was cooled to 0 °C and added saturated aqueous $NaHCO_3$ solution until the measured pH was 7. The resulting solution was partitioned between water and DCM. The organic was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–50% EtOAc in petroleum ether) furnished a white solid (191 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 253.

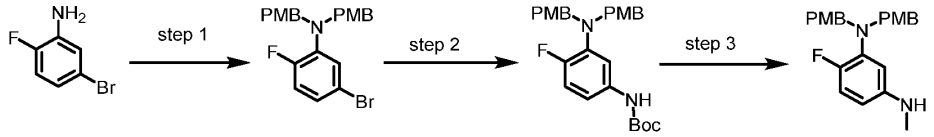
[1420] Step 5: 4-Bromo-5-(difluoromethoxy)-*N*,*N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine

[1421] To an ice-cooled solution of 4-bromo-5-(difluoromethoxy)-6-methylpyridin-2-amine (207 mg, 0.820 mmol) in DMF (3 mL) was added NaH (82.2 mg, 2.06 mmol) under nitrogen. After 30 min, PMBCl (219 mg, 1.40 mmol) was added at 0 °C, and the suspension was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–15% EtOAc in petroleum ether) provided a yellow solid (313 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 493.

[1422] Step 6: 5-(Difluoromethoxy)-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-dioxaborolan-2-yl)pyridin-2-amine

[1423] A solution of 4-bromo-5-(difluoromethoxy)-*N*,*N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (319 mg, 0.650 mmol), bis(pinacolato)diboron (823 mg, 3.24 mmol), $Pd(dppf)Cl_2$ (99.6 mg, 0.130 mmol) and KOAc (190 mg, 1.94 mmol) in 1,4-dioxane (5 mL) was heated at 100 °C under nitrogen overnight. The reaction was cooled to room temperature and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–25% EtOAc in petroleum ether) furnished a yellow solid (211 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 541. ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 7.23 – 6.44 (m, 10H), 4.63 (s, 4H), 3.70 (s, 6H), 2.30 (s, 3H), 1.22 (s, 12H).

[1424] **Intermediate 137:** 4-Fluoro-N^3,N^3-bis(4-methoxybenzyl)-N^1-methylbenzene-1,3-diamine



[1425] Step 1: 5-Bromo-2-fluoro-*N*,*N*-*bis*(4-methoxybenzyl)aniline

[1426] To an ice-cooled solution of 5-bromo-2-fluoroaniline (2.00 g, 10.5 mmol) in DMF (20 mL) was added NaH (2.11 g, 52.6 mmol, 60% dispersion in mineral oil) portion wise. The suspension was warmed to room temperature. After 30 min, PMBCl (4.11 g, 26.3 mmol) was added. After another hour, the reaction was quenched with saturated aqueous NH_4Cl solution and diluted with water. The mixture was extracted with ethyl acetate. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–20% ethyl acetate in petroleum ether) yielded a yellow oil (3.40 g). LC-MS: (ESI, *m/z*): $[M+H]^+ = 430$.

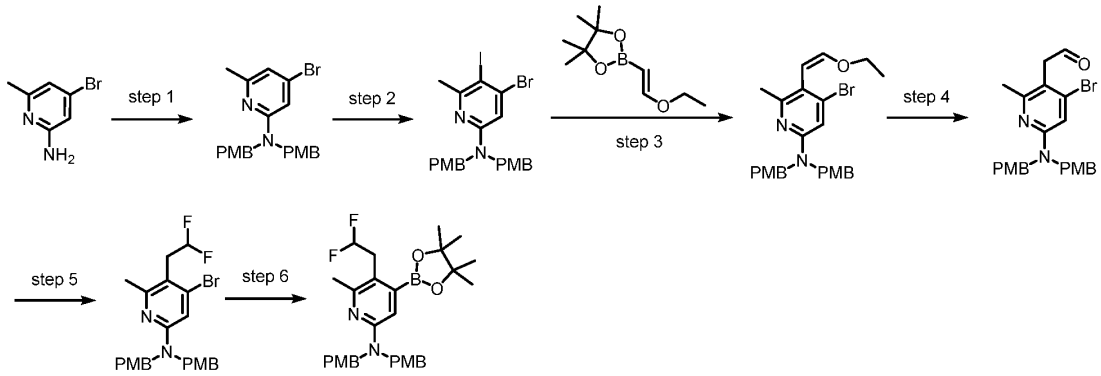
[1427] Step 2: *tert*-Butyl (3-(*bis*(4-methoxybenzyl)amino)-4-fluorophenyl)carbamate

[1428] Under nitrogen, a solution of 5-bromo-2-fluoro-*N*,*N*-*bis*(4-methoxybenzyl)aniline (1.00 g, 2.33 mmol), $BocNH_2$ (760 mg, 6.50 mmol), Cs_2CO_3 (3.04 g, 9.32 mmol), $Pd(OAc)_2$ (125 mg, 0.560 mmol) and Xantphos (269 mg, 0.466 mmol) in 1,4-dioxane (50 mL) was heated for 2 hours at 110 °C. The reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–20% ethyl acetate in petroleum ether) provided a yellow solid (570 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 467$.

[1429] Step 3: 4-Fluoro-N^3,N^3-bis(4-methoxybenzyl)-N^1-methylbenzene-1,3-diamine

[1430] To an ice-cooled solution of *tert*-butyl (3-(*bis*(4-methoxybenzyl)amino)-4-fluorophenyl)carbamate (0.550 g, 1.18 mmol) in tetrahydrofuran (30 mL) was added $LiAlH_4$ (112 mg, 2.95 mmol) portion wise. The suspension was heated to 60 °C for 1 h. The reaction was cooled to room temperature and quenched with $Na_2SO_4 \cdot 10H_2O$. After filtration, the filtrate was collected and concentrated under vacuum to afford the titled compound (490 mg,) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 381$. The crude material was used without further purification.

[1431] **Intermediate 138:** 5-(2,2-Difluoroethyl)-*N*, *N*-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-dioxaborolan-2-yl) pyridin-2-amine



[1432] Step 1: 4-Bromo-*N*,*N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine

[1433] To an ice-cooled solution of 4-bromo-6-methylpyridin-2-amine (4.00 g, 21.4 mmol) in DMF (40.0 mL) was added NaH (2.57 g, 64.1 mmol, 60% in mineral oil) under nitrogen. The resulting suspension was warmed to room temperature. After 30 min, 1-(chloromethyl)-4-methoxybenzene (7.03 g, 44.9 mmol) was added. After an additional 2 h, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–50% EtOAc in petroleum ether) afforded a white solid (8.00 g). LC-MS: (ESI, *m/z*): $[M+H]^+$= 427.

[1434] Step 2: 4-Bromo-5-iodo-*N*, *N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine

[1435] To a solution of 4-bromo-*N*, *N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (6.80 g, 15.9 mmol) in AcOH (68.0 mL) was added NIS (3.58 g, 15.9 mmol) at room temperature under nitrogen. After 30 min, the reaction was quenched with saturated aqueous sodium thiosulfate solution and extracted with EtOAc. The collected organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–50% EtOAc in petroleum ether) provided a white solid (7.20 g). LC-MS: (ESI, *m/z*): $[M+H]^+$= 553.

[1436] Step 3: (*Z*)-4-Bromo-5-(2-ethoxyvinyl)-*N*,*N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine

[1437] A solution of 4-bromo-5-iodo-*N*, *N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (1.30 g, 2.35 mmol), (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.470 g, 2.35 mmol), Cs_2CO_3 (1.53 g, 4.70 mmol) and $PdCl_2$(dppf) (170 mg, 0.23 mmol) in 1,4-dioxane (6 mL) and H_2O (0.6 mL) was heated at 72 °C for 4 h under nitrogen. The reaction was cooled to room temperature and extracted with EtOAc. The organic extracts were combined and dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–50% EtOAc in petroleum ether) afforded a colorless oil (408 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$= 497.

[1438] Step 4: 2-(6-(Bis(4-methoxybenzyl)amino)-4-bromo-2-methylpyridin-3-yl)acetaldehyde

[1439] To a solution of (*Z*)-4-bromo-5-(2-ethoxyvinyl)-*N*, *N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (0.400 g, 0.800 mmol) in THF (4 mL) was added aqueous HCl (1.00 mL, 12 M in water) at room temperature. After 3 h, the reaction was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic extracts were collected, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–50% EtOAc in petroleum ether) afforded a white solid (218 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$= 469.

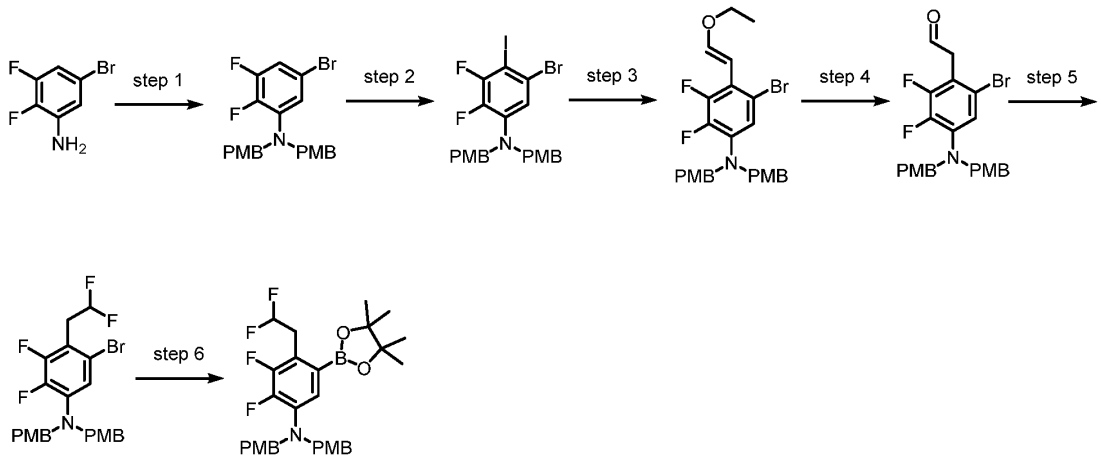
[1440] Step 5: 4-Bromo-5-(2,2-difluoroethyl)-*N*,*N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine

[1441] To a solution of 2-(6-(bis(4-methoxybenzyl)amino)-4-bromo-2-methylpyridin-3-yl)acetaldehyde (218 mg, 0.470 mmol) in DCM (10.0 mL) was added DAST (764 mg, 4.75 mmol) at room temperature. After 2 h, the reaction was quenched with EtOH and partitioned between water and EtOAc. The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–50% EtOAc in petroleum ether) afforded a white solid (215 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$= 491.

[1442] Step 6: 5-(2,2-Difluoroethyl)-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-dioxaborolan-2-yl) pyridin-2-amine

[1443] A solution of 4-bromo-5-(2,2-difluoroethyl)-*N*, *N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (215 mg, 0.440 mmol), bis(pinacolato)diboron (333 mg, 1.31 mmol), $PdCl_2$(dppf) (63.5 mg, 0.0900 mmol) and KOAc (128 mg, 1.31 mmol) in 1,4-dioxane (10.0 mL) was heated at 90 °C for 12 h under nitrogen. The resulting solution was cooled to room temperature and partitioned between water and EtOAc. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–50% EtOAc in petroleum ether) furnished a colorless oil (0.10 g). LC-MS: (ESI, *m/z*): $[M+H]^+$= 539.

[1444] **Intermediate 139:** 4-(2,2-Difluoroethyl)-2,3-difluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[1445] Step 1: 5-Bromo-2,3-difluoro-*N*,*N*-*bis*(4-methoxybenzyl)aniline

[1446] To an ice-cooled solution of 5-bromo-2,3-difluoroaniline (5.01 g, 24.1 mmol) in DMF (50 mL) was added NaH (3.69 g, 96.3 mmol). After 30 min, PMB-Cl (9.39 g, 60.2 mmol) was added, and the reaction was warmed to room temperature for 1 h. Excess sodium hydride was quenched by the slow addition of saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–5% EtOAc in petroleum ether) afforded a yellow solid (9.70 g). LC-MS: (ESI, *m/z*): $[M+H]^+ = 448$.

[1447] Step 2: 5-Bromo-2,3-difluoro-4-iodo-*N*,*N*-*bis*(4-methoxybenzyl)aniline

[1448] To a solution of 5-bromo-2,3-difluoro-*N*,*N*-*bis*(4-methoxybenzyl)aniline (4.51 g, 10.1 mmol) in AcOH (45 mL) was added NIS (3.37 g, 15.1 mmol) at room temperature. After 30 min, excess NIS was quenched by saturated aqueous $Na_2S_2O_3$ solution, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–6% EtOAc in petroleum ether) afforded a yellow solid (4.74 g). LC-MS: (ESI, *m/z*): $[M+H]^+ = 574$.

[1449] Step 3: (*E*)-5-Bromo-4-(2-ethoxyvinyl)-2,3-difluoro-*N*,*N*-bis(4-methoxybenzyl)aniline

[1450] A solution of 5-bromo-2,3-difluoro-4-iodo-*N*,*N*-bis(4-methoxybenzyl)aniline (2.01 g, 3.48 mmol), (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.38 g, 6.97 mmol), $Pd(dppf)Cl_2$ (535 mg, 0.700 mmol) and K_2CO_3 (961 mg, 6.97 mmol) in 1,4-dioxane (20 mL) and water (4 mL) was heated at 60 °C under nitrogen. After 4 h, the resulting solution cooled to room temperature and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–37% DCM in petroleum ether) afforded a yellow solid (1.23 g). LC-MS: (ESI, *m/z*): $[M+H]^+ = 518$.

[1451] Step 4: 2-(4-(bis(4-Methoxybenzyl) amino)-6-bromo-2,3-difluorophenyl) acetaldehyde

[1452] To a solution of (*E*)-5-bromo-4-(2-ethoxyvinyl)-2,3-difluoro-*N*,*N*-bis(4-methoxybenzyl)aniline (1.23 g, 2.55 mmol) in THF (12 mL) was added aqueous HCl (2.00 mL, 12M) at room temperature. After 2 h, the reaction was neutralized with saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–100% EtOAc in petroleum ether) afforded a yellow oil (0.20 g). LC-MS: (ESI, *m/z*): $[M+H]^+ = 490$.

[1453] Step 5: 5-Bromo-4-(2,2-difluoroethyl)-2,3-difluoro-*N*, *N*-bis(4-methoxybenzyl)aniline

[1454] To a solution of 2-(4-(*bis*(4-methoxybenzyl) amino)-6-bromo-2,3-difluorophenyl)acetaldehyde (190 mg, 0.390 mmol) in DCM (2 mL) was added DAST (1.25 g, 7.75 mmol) at –10 °C under nitrogen. The reaction was warmed to room temperature for 2 h. The reaction was diluted with saturated aqueous $NaHCO_3$ solution, and the resulting mixture was extracted with DCM. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–13% EtOAc in petroleum ether) afforded a yellow oil (130 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 512$.

[1455] Step 6: 4-(2,2-Difluoroethyl)-2,3-difluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[1456] A solution of 5-bromo-4-(2,2-difluoroethyl)-2,3-difluoro-*N*,*N*-bis(4-methoxybenzyl) aniline (110 mg, 0.21 mmol), bis(pinacolato)diboron (109 mg, 0.430 mmol), KOAc (63.2 mg, 0.640 mmol) and $Pd(dppf)Cl_2$ (33 mg, 0.040 mmol) in 1,4-dioxane (1.2 mL) was heated at 90 °C under nitrogen. After 2 h, the reaction was cooled to room temperature and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–18% EtOAc in petroleum ether) afforded a yellow oil (60.1 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 560$.

[1457] **Intermediate 140:** 7-Fluoro-1-methoxy-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) isoquinoline



[1458] Step 1: 8-Bromo-7-fluoroisoquinoline 2-oxide

[1459] A solution of 3-chloroperbenzoic acid (839 mg, 4.87 mmol) and 8-bromo-7-fluoroisoquinoline (1.00 g, 4.42 mmol) in dichloromethane (10 mL) was stirred at room temperature for 2 h. The reaction was diluted with DCM and washed with brine. The collected

organic was concentrated under vacuum to afford the titled compound (1.89 g, crude) as a light yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 242.

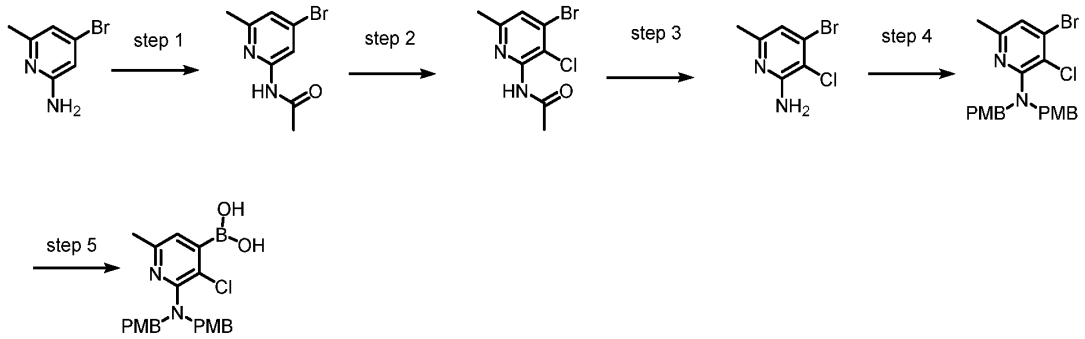
[1460] Step 2: 8-Bromo-7-fluoro-1-methoxyisoquinoline

[1461] To a solution of 8-bromo-7-fluoroisoquinoline 2-oxide (2.20 g, 9.09 mmol) and Et_3N (1.73 g, 17.1 mmol) in methanol (20 mL) was added methyl chloroformate (1.3 mL, 13.6 mmol) at room temperature. The resulting solution was stirred overnight at room temperature. The resulting mixture was diluted with EtOAc, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–20% EtOAc in petroleum ether) afforded a white solid (586 mg,). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 256.

[1462] Step 3: 7-Fluoro-1-methoxy-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline

[1463] A solution of 8-bromo-7-fluoro-1-methoxyisoquinoline (0.450 g, 1.76 mmol), bis(pinacolato)diboron (669 mg, 2.64 mmol), $Pd(dppf)Cl_2$ (257 mg, 0.350 mmol) and KOAc (344 mg, 3.51 mmol) in 1,4-dioxane (5mL) was heated at 80 °C under nitrogen. After 2 h, the mixture cooled to room temperature and filtered. The filtrate was concentrated *in vacuo*. The resulting residue was diluted with EtOAc and washed with water. The collected organic was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (gradient: 0–20% EtOAc in petroleum ether) afforded a white solid (270 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 304.

[1464] **Intermediate 141:** (2-(Bis(4-methoxybenzyl) amino)-3-chloro-6-methylpyridin-4-yl)boronic acid



[1465] Step 1: *N*-(4-Bromo-6-methylpyridin-2-yl)acetamide

[1466] A solution of 4-bromo-6-methylpyridin-2-amine (5.01 g, 26.9 mmol), acetic anhydride (7.50 mL, 72.7 mmol) and Et_3N (2.99 g, 29.6 mmol) in THF (30 mL) was heated at 65 °C. After 15 h, the mixture was cooled to room temperature. The precipitated solids were collected by

filtration and rinsed with petroleum ether to afford a white solid (5.41 g, crude). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 229.

[1467] Step 2: *N*-(4-Bromo-3-chloro-6-methylpyridin-2-yl) acetamide

[1468] Under nitrogen, a solution of *N*-(4-bromo-6-methylpyridin-2-yl) acetamide (2.08 g, 7.89 mmol), NaCl (1.01 g, 17.3 mmol) and oxone (6.91 g, 11.2 mmol) in H_2O (4.0 mL) and ACN (28 mL) was stirred at room temperature for 15 h. The resulting solution was partitioned between water and EtOAc. The collected organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0–80% ACN in water (0.05% formic acid)) to afford a white solid (502 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 263.

[1469] Step 3: 4-Bromo-3-chloro-6-methylpyridin-2-amine

[1470] A solution of *N*-(4-bromo-3-chloro-6-methylpyridin-2-yl) acetamide (0.800 g, 3.04 mmol) and NaOH (1.22 g, 30.5 mmol) in MeOH (10 mL) was heated at 60 °C under nitrogen. After 50 min, the solution was cooled to room temperature and concentrated *in vacuo*. The resulting residue was partitioned between water and EtOAc. The collected organic was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford a white solid (650 mg, crude). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 221.

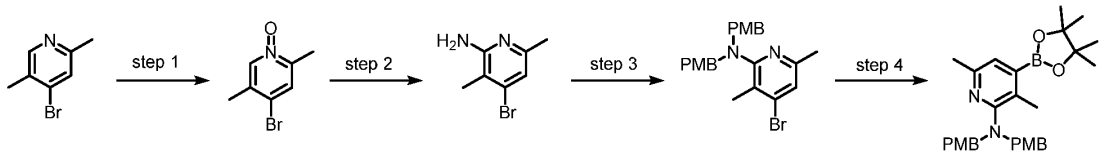
[1471] Step 4: 4-Bromo-3-chloro-*N,N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine

[1472] To an ice-cooled solution of 4-bromo-3-chloro-6-methylpyridin-2-amine (0.600 g, 2.71 mmol) in DMF (8 mL) was added NaH (273 mg, 6.82 mmol). The reaction was warmed to room temperature. After 0.5 h, the reaction was cooled to 0 °C before the addition of PMBCl (936 mg, 6.00 mmol). The reaction was warmed to room temperature again for 3 h. Excess NaH was quenched by the addition of saturated aqueous NH_4Cl solution, and the mixture was extracted with DCM. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification of the resulting residue by flash column chromatography on silica gel (gradient: 0–30% EtOAc in petroleum ether) afforded a white solid (1.21 g). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 461.

[1473] Step 5: (2-(Bis(4-methoxybenzyl) amino)-3-chloro-6-methylpyridin-4-yl)boronic acid

[1474] To a solution of 4-bromo-3-chloro-*N,N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (0.300 g, 0.650 mmol) and triisopropyl borate (613 mg, 3.31 mmol) in THF (5 mL) was added *n*-BuLi (1.1 mL, 2.5 M in THF) at –78 °C. After 1 h, the reaction was quenched with MeOH and concentrated under vacuum to afford a yellow oil (672 mg, crude). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 427. The crude product was used without further purification.

[1475] **Intermediate 142:** *N,N*-Bis(4-methoxybenzyl)-3,6-dimethyl-4-(4,4,5,5-tetramethyl-dioxaborolan-2-yl) pyridin-2-amine



[1476] Step 1: 4-Bromo-2,5-dimethylpyridine 1-oxide

[1477] To an ice-cooled solution of 4-bromo-2,5-dimethylpyridine (1.01 g, 5.43 mmol) in EtOAc (20 mL) was added 3-chloroperbenzoic acid (1.88 g, 10.8 mmol). The reaction was warmed to room temperature for 2 h. Excess 3-chloroperbenzoic acid was quenched with aqueous $Na_2S_2O_3$,and resulting mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification of the resulting residue by flash column chromatography on silica gel (gradient: 0–10% EtOAc in petroleum ether) afforded a yellow solid (932 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 202$.

[1478] Step 2: 4-Bromo-3,6-dimethylpyridin-2-amine

[1479] To a solution of 4-bromo-2,5-dimethylpyridine 1-oxide (491 mg, 2.43 mmol) and pyridine (962 mg, 12.2 mmol) in ACN (15 mL) was added TFAA (1.02 g, 4.86 mmol). The resulting solution was heated at 70 °C for 1.5 h. before the addition of NH_2-NH_2•H_2O (1.23 g, 24.6 mmol). After 2 h. the resulting mixture was cooled to room temperature, diluted with ethyl acetate, and washed with water. The collected organic was concentrated under vacuum to afford a yellow solid (359 mg, crude). LC-MS: (ESI, *m/z*): $[M+H]^+ = 201$.

[1480] Step 3: 4-Bromo-*N,N*-bis(4-methoxybenzyl)-3,6-dimethylpyridin-2-amine

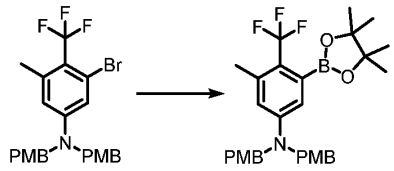
[1481] To an ice-cooled solution of 4-bromo-3,6-dimethylpyridin-2-amine (341 mg, 1.7 mmol) in DMF (10 mL) was added NaH (205 mg, 5.13 mmol, 60%). The suspension was warmed to room temperature for 0.5 h. PMBCl (559 mg, 3.58 mmol) was added to the reaction. After an additional 1.5 h, excess sodium hydride was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification of the residue by flash column chromatography on silica gel (gradient: 0–45% EtOAc in petroleum ether) afforded a yellow solid (507 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 441$.

[1482] Step 4: *N,N*-Bis(4-methoxybenzyl)-3,6-dimethyl-4-(4,4,5,5-tetramethyl-dioxaborolan-2-yl)pyridin-2-amine

[1483] Under nitrogen, a solution of 4-bromo-*N,N*-bis(4-methoxybenzyl)-3,6-dimethylpyridin-2-amine (507 mg, 1.15 mmol), bis(pinacolato)diboron (875 mg, 3.44 mmol), KOAc (338 mg, 3.45 mmol) and $Pd(dppf)Cl_2$ (168 mg, 0.230 mmol) in 1,4-dioxane (10 mL) was heated at 80 °C. After 4 h, the resulting mixture was cooled to room temperature, diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered, and

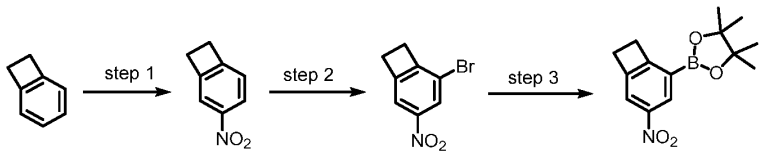
concentrated under vacuum. Purification of the residue by flash column chromatography on silica gel (gradient: 0–60% EtOAc in petroleum ether) afforded a yellow solid (417 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 489$.

[1484] **Intermediate 143:** *N,N-Bis*(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline



[1485] A solution of 3-bromo-*N,N-bis*(4-methoxybenzyl)-5-methyl-4-(trifluoromethyl)aniline (1.50 g, 3.03 mmol), bis(pinacolato)diboron (1.16 g, 4.56 mmol), KOAc (895 mg, 9.13 mmol) and $Pd(dppf)Cl_2•CH_2Cl_2$ (497 mg, 0.610 mmol) in 1,4-dioxane (50 mL) was heated at 110 °C under nitrogen. After 4 h, the reaction mixture was cooled to room temperature, diluted with water, and extracted with EtOAc. The collected organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (gradient: 0–20% dichloromethane in petroleum ether) to afford a yellow oil (0.50 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 542$.

[1486] **Intermediate 144:** 4,4,5,5-Tetramethyl-2-(4-nitrobicyclo[4.2.0]octa-1(6),2,4-trien-2-yl)-1,3,2-dioxaborolane



[1487] Step 1: 3-Nitrobicyclo[4.2.0]octa-1(6),2,4-triene

[1488] To a precooled mixture of H_2SO_4 (3.00 mL, 98.0%) and HNO_3 (3.78 mL, 68.0%) was added bicyclo[4.2.0]octa-1(6),2,4-triene (3.00 g, 28.8 mmol) at 5–10 °C. The mixture was stirred for 2 h at 10 °C. The solution was poured into ice-water and extracted with ether. The combined organic extracts were washed with 5% aqueous $NaHCO_3$ solution, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (gradient: 0%–50% EtOAc in petroleum ether) to afford a yellow oil (1.50 g).

[1489] Step 2: 2-Bromo-4-nitrobicyclo [4.2.0] octa-1(6),2,4-triene

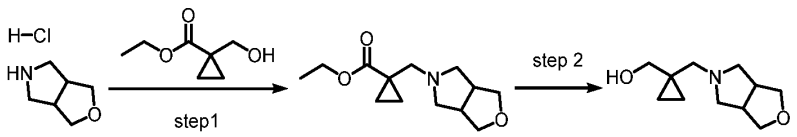
[1490] To a solution of 3-nitrobicyclo [4.2.0] octa-1(6),2,4-triene (1.00 g, 6.70 mmol) in H_2SO_4 (10 mL, 98%) and H_2O (10 mL) was added NBS (1.19 g, 6.70 mmol). The resulting solution was stirred for 12 h at room temperature. The reaction was diluted with water and

extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (gradient: 0%–50% EtOAc in petroleum ether) to afford a yellow oil (0.50 g).

[1491] Step 3: 4,4,5,5-Tetramethyl-2-(4-nitrobicyclo[4.2.0]octa-1(6),2,4-trien-2-yl)-1,3,2-dioxaborolane

[1492] A solution of 2-bromo-4-nitrobicyclo [4.2.0] octa-1(6),2,4-triene (0.500 g, 2.19 mmol), bis(pinacolato)diboron (835 mg, 3.28 mmol), $PdCl_2(dppf)$ (168 mg, 0.218 mmol) and KOAc (644 mg, 6.56 mmol) in 1,4-dioxane (5 mL) was heated at 100 °C under nitrogen. After 2 h, the reaction was cooled to room temperature, and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel (gradient: 0%–50% EtOAc in petroleum ether) to afford the titled compound as a yellow oil (87.5 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 276$.

[1493] **Intermediate 145:** (1-((Tetrahydro-1*H*-furo[3,4-*c*] pyrrol-5(3*H*)-yl)methyl)cyclopropyl)methanol



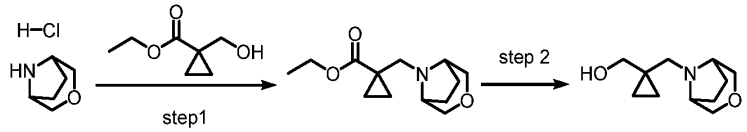
[1494] Step 1: Ethyl 1-((tetrahydro-1*H*-furo[3,4-*c*] pyrrol-5(3*H*)-yl) methyl) cyclopropane-1-carboxylate

[1495] To a solution of ethyl 1-(hydroxymethyl) cyclopropane-1-carboxylate (0.300 g, 2.08 mmol) and DIPEA (1.03 mL, 6.24 mmol) in dichloromethane (3 mL) under nitrogen was added Tf_2O (0.70 mL, 4.16 mmol) dropwise at –10 °C. After 5 min, a solution of hexahydro-1*H*-furo[3,4-*c*] pyrrole (311 mg, 2.08 mmol) and DIPEA (0.74 mL, 4.16 mmol) in dichloromethane (3 mL) was added at –10 °C, and the reaction was warmed to room temperature. After an hour, the solvent was concentrated under vacuum to afford the crude titled compound (1.00 g, crude) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 240$.

[1496] Step 2: (1-((Tetrahydro-1*H*-furo[3,4-*c*] pyrrol-5(3*H*)-yl)methyl)cyclopropyl)methanol

[1497] To an ice-cooked solution of ethyl 1-((tetrahydro-1*H*-furo[3,4-*c*] pyrrol-5(3*H*)-yl) methyl) cyclopropane-1-carboxylate (1.00 g, crude) in THF (40 mL) was added $LiAlH_4$ (336 g, 8.85 mmol) portion wise, and the reaction was warmed to room temperature. After an hour, $Na_2SO_4 \cdot 10H_2O$ was added, and the resulting suspension was filtered. The filtrate was concentrated under reduced pressure to afford the titled compound (1.50 g, crude) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 198$. The crude material was used without further purification.

[1498] **Intermediate 146:** (1-((3-Oxa-8-azabicyclo [3.2.1] octan-8-yl)methyl)cyclopropyl)methanol



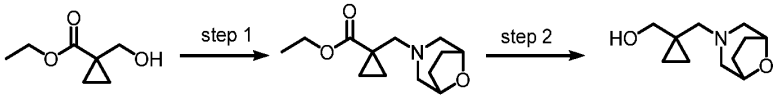
[1499] Step 1: Ethyl 1-((3-oxa-8-azabicyclo[3.2.1]octan-8-yl)methyl)cyclopropane-1-carboxylate

[1500] To a solution of ethyl 1-(hydroxymethyl) cyclopropane-1-carboxylate (0.500 g, 3.47 mmol) and DIPEA (1.84 mL, 10.4 mmol) in dichloromethane (5 mL) under nitrogen was added Tf_2O (1.2 mL, 6.94 mmol) dropwise at –10 °C . After 5 min, a solution of 3-oxa-8-azabicyclo[3.2.1]octane (518 mg, 3.47 mmol) and DIPEA (1.23 mL, 6.94 mmol) in dichloromethane (5 mL)) was added at –10 °C, and the reaction mixture was warmed to room temperature. After 1 h, the solvent was concentrated under vacuum to afford the titled compound (3 g, crude) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 240.

[1501] Step 2: (1-((3-Oxa-8-azabicyclo [3.2.1] octan-8-yl)methyl)cyclopropyl)methanol

[1502] To an ice-cooled solution of ethyl 1-((3-oxa-8-azabicyclo [3.2.1] octan-8-yl)methyl)cyclopropane-1-carboxylate (3.0 g, crude) in THF (40 mL) was added $LiAlH_4$ (1.00 g, 25.0 mmol) portion wise, and the reaction was warmed to room temperature. After 1 h, $Na_2SO_4•10H_2O$ was added, and the resulting suspension was filtered. The filtrate was concentrated under reduced pressure to afford the titled compound (2 g, crude) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 198. The crude was used without further purification.

[1503] **Intermediate 147:** (1-((8-Oxa-3-azabicyclo[3.2.1]octan-3-yl) methyl) cyclopropyl) methanol



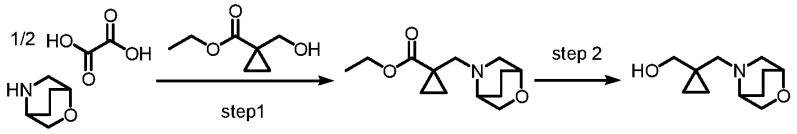
[1504] Step 1: Ethyl 1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl) methyl cyclopropane-1-carboxylate

[1505] To a solution of ethyl 1-(hydroxymethyl)cyclopropane-1-carboxylate (0.600 g, 4.16 mmol) and DIPEA (1.61 g, 12.5 mmol) in DCM (6.0 mL) under nitrogen was added Tf_2O (1.76 g, 6.24 mmol) at –78 °C. After 5 min, 8-oxa-3-azabicyclo[3.2.1]octane hydrogen chloride (621 mg, 4.15 mmol) was added at –78 °C. After 1 h, the reaction was warmed to room temperature and concentrated under vacuum to afford the titled compound as brown solid (4 g, crude). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 240.

[1506] Step 2: (1-((8-Oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methanol

[1507] To an ice-cooled solution of ethyl 1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropane-1-carboxylate (1.0 g, 4.2 mmol) in THF (10.0 mL) was added $LiAlH_4$ (1.67 mL, 2.5 M in THF), and the reaction was warmed to room temperature. After 1 h, $Na_2SO_4 \cdot 10H_2O$ was added, and the resulting suspension was filtered. The filtrate was concentrated under reduced pressure to afford the titled compound as colorless oil (0.9 g, crude) which was used without further purification. LC-MS: (ESI, *m/z*): $[M+H]^+ = 198$.

[1508] **Intermediate 148:** (1-((2-Oxa-5-azabicyclo[2.2.2]octan-5-yl)methyl)cyclopropyl)methanol



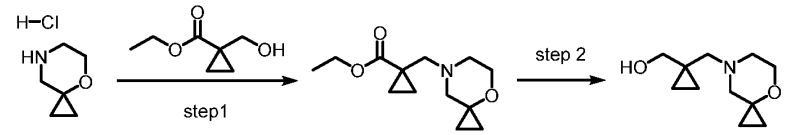
[1509] Step 1: Ethyl 1-((2-Oxa-5-azabicyclo[2.2.2]octan-5-yl)methyl)cyclopropane-1-carboxylate

[1510] To a solution of ethyl 1-(hydroxymethyl)cyclopropane-1-carboxylate (0.500 g, 3.47 mmol) and DIPEA (1.84 mL, 10.4 mmol) in dichloromethane (5 mL) under nitrogen was added Tf_2O (1.2 mL, 6.9 mmol) dropwise at –10 °C. After 5 min a solution of 2-oxa-5-azabicyclo[2.2.2]octane (393 mg, 3.47 mmol) in dichloromethane (5 mL) (pretreated 2-oxa-5-azabicyclo[2.2.2]octane hemioxalate with ion exchange resin column to remove oxalic acid) was added, and the reaction was warmed to room temperature. After 1 h, the reaction was concentrated under vacuum to afford the crude titled compound (2 g) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 240$.

[1511] Step 2: (1-((2-Oxa-5-azabicyclo[2.2.2]octan-5-yl)methyl)cyclopropyl)methanol

[1512] To an ice-cooled solution of ethyl 1-(2-oxa-5-azabicyclo[2.2.2]octan-5-ylmethyl)cyclopropanecarboxylate (2 g, crude) in THF (30 mL) was added $LiAlH_4$ (627 mg, 16.5 mmol) portion wise. The reaction was warmed to room temperature for 1 h. $Na_2SO_4 \cdot 10H_2O$ was added to the reaction, and the resulting suspension was filtered. The filtrate was concentrated under reduced pressure to afford the crude titled compound (580 mg) as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 198$. The crude product was used without further purification.

[1513] **Intermediate 149:** (1-((4-Oxa-7-azaspiro[2.5]octan-7-yl)methyl)cyclopropyl)methanol



[1514] Step 1: Ethyl 1-((4-oxa-7-azaspiro[2.5]octan-7-yl)methyl)cyclopropane-1-carboxylate

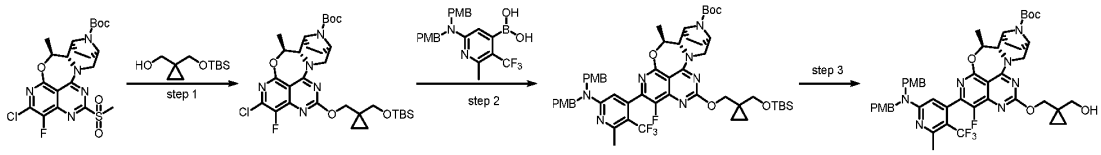
[1515] To a solution of ethyl 1-(hydroxymethyl)cyclopropane-1-carboxylate (300 mg, 2.08 mmol) and DIPEA (1.03 mL, 6.24 mmol) in dichloromethane (3 mL) under nitrogen was added

Tf_2O (0.70 mL, 4.16 mmol) dropwise at –10 °C. After 5 min, a solution of 4-oxa-7-azaspiro[2.5]octane hydrochloride (311 mg, 2.08 mmol) and DIPEA (0.74 mL, 4.16 mmol) in dichloromethane (3 mL) was added, and the reaction was warmed to room temperature. After 1 h, the solvent was concentrated under vacuum to afford the crude titled compound (1 g) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 240.

[1516] Step 2: (1-((4-Oxa-7-azaspiro[2.5]octan-7-yl)methyl)cyclopropyl)methanol

[1517] To an ice-cooled solution of ethyl 1-((4-oxa-7-azaspiro[2.5]octan-7-yl)methyl)cyclopropane-1-carboxylate (1 g, crude) in THF (40 mL) was added $LiAlH_4$ (316 g, 8.85 mmol) portion wise. The reaction mixture was warmed to room temperature for 1 h. $Na_2SO_4•10H_2O$ was added to the reaction, and the resulting suspension was filtered. The filtrate was concentrated under reduced pressure to afford the crude product as a yellow oil (1.4 g). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 198. The crude was used without further purification.

[1518] **Intermediate 150:** *tert*-Butyl (5S,5aS,6S,9R)-2-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[1519] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-((1-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)methoxy)-2-chloro-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1520] To an ice-cooled solution of (1-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)methanol (784 mg, 3.63 mmol) in tetrahydrofuran (12.5 mL) was added NaH (435 mg, 10.9 mmol, 60% in mineral oil). The resulting solution was warmed to room temperature. After 30 min, *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (931 mg, 1.81 mmol) was added.. After an additional hour, excess NaH was quenched with saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification of the residue by flash column chromatography on silica gel (gradient: 0%–20% EtOAc in petroleum ether) afforded product a white solid (826 mg). LCMS: (ESI, *m/z*): $[M+H]^+$ = 650.

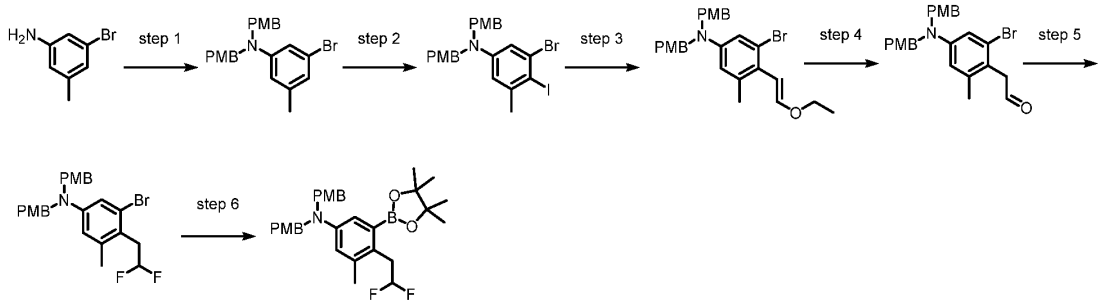
[1521] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-12-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1522] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-((1-(((tert-butyldimethylsilyl)oxy)methyl)cyclopropyl)methoxy)-2-chloro-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (826 mg, 1.27 mmol), (6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)boronic acid (1.56 g, 3.39 mmol), cataCXium A Pd G_3 (185 mg, 0.254 mmol) and K_3PO_4 (2.54 mL, 1.5 M in water) in tetrahydrofuran (12.7 mL) was heated at 60 °C under nitrogen. After 1 h, the reaction was cooled to room temperature, and the solution was partitioned between water and EtOAc. The collected organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification of the residue by flash column chromatography on silica gel (gradient: 0–20% MeOH in DCM) afforded product as a brown solid (1.30 g). LCMS: (ESI, *m/z*): $[M+H]^+ = 1030$.

[1523] Step 3: : *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1524] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-12-((1-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (1.30 g, 1.27 mmol) in tetrahydrofuran (12.0 mL) was added TBAF (2.60 mL, 1 M in THF) at room temperature. After 5 h, the reaction was concentrated *in vacuo*, and the resulting residue was purified by flash column chromatography on silica gel (gradient: 0%–55% EtOAc / petroleum ether) to afford product as a tawny solid (926 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 916$.

[1525] **Intermediate 151:** 4-(2,2-Difluoroethyl)-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[1526] Step 1: 3-Bromo-*N,N*-bis(4-methoxybenzyl)-5-methylaniline

[1527] To an ice-cooled solution of 3-bromo-5-methylaniline (3.51 g, 18.8 mmol) in DMF (30 mL) was added NaH (2.27 g, 56.7 mmol, 60% in mineral oil) under nitrogen. After 0.5 h, PMBCl (6.23 g, 39.6 mmol) was added, and the resulting mixture was warmed to room temperature for 3 h. Excess NaH was quenched with saturated aqueous NH_4Cl solution, and the mixture was extracted with EtOAc. The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (gradient: 0%–30% EtOAc / petroleum ether) to afford product as a yellow solid (3.81 g). LC-MS: (ESI, *m/z*): $[M+H]^+ = 426$.

[1528] Step 2: 3-Bromo-4-iodo-*N,N*-bis(4-methoxybenzyl)-5-methylaniline

[1529] A solution of 3-bromo-*N,N*-bis(4-methoxybenzyl)-5-methylaniline (3.81 g, 8.96 mmol) and NIS (2.11 g, 9.33 mmol) in AcOH (30 mL) was stirred at room temperature for 1 h. Excess NIS was quenched with saturated aqueous $Na_2S_2O_3$ solution, and the mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (gradient: 0%–30% EtOAc in petroleum ether) to yield product as a yellow solid (2.61 g). LC-MS: (ESI, *m/z*): $[M+H]^+ = 552$.

[1530] Step 3: (*E*)-3-Bromo-4-(2-ethoxyvinyl)-*N,N*-bis(4-methoxybenzyl)-5-methylaniline

[1531] A solution of (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.87 g, 9.44 mmol), K_2CO_3 (1.31 g, 9.49 mmol), $Pd(dppf)Cl_2$ (351 mg, 0.480 mmol) and 3-bromo-4-iodo-*N,N*-bis[(4-methoxyphenyl)methyl]-5-methyl-aniline (2.61 g, 4.71 mmol) in 1,4-dioxane (5 mL) and water (1 mL) was heated under nitrogen at 90 °C. After 2 h, the reaction was cooled to room temperature, diluted with EtOAc, and washed with water. The organic layer was concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–10% EtOAc in petroleum ether) afforded product as a yellow solid (893 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 496$.

[1532] Step 4: 2-(4-(Bis(4-methoxybenzyl)amino)-2-bromo-6-methylphenyl)acetaldehyde

[1533] To a solution of (*E*)-3-bromo-4-(2-ethoxyvinyl)-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline (891 mg, 1.79 mmol) in THF (5 mL) was added aqueous HCl (1.4 mL, 12 M) at room temperature. After 1 h, aqueous $NaHCO_3$ solution was added until the solution was neutral pH. The resulting mixture was extracted with EtOAc. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (gradient: 0–30% EtOAc in petroleum ether) to afford product as a yellow solid (311 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 468$.

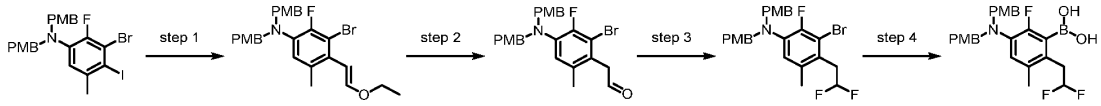
[1534] Step 5: 3-Bromo-4-(2,2-difluoroethyl)-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline

[1535] To an ice-cooled solution of 2-(4-(bis(4-methoxybenzyl)amino)-2-bromo-6-methylphenyl)acetaldehyde (450 mg, 0.960 mmol) in DCM (15 mL) was added DAST (1.24 g, 7.70 mmol). After 1 h at 0 °C, saturated aqueous $NaHCO_3$ solution was added, and the resulting mixture was extracted with EtOAc. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (gradient: 0–15% EtOAc in petroleum ether) to afford product as a yellow solid (215 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 490$.

[1536] Step 6: 4-(2,2-Difluoroethyl)-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

[1537] A solution of 3-bromo-4-(2,2-difluoroethyl)-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline (215 mg, 0.440 mmol), Pin_2B_2 (224 mg, 0.880 mmol), $Pd(dppf)Cl_2$ (32.3 mg, 0.0400 mmol) and K_2CO_3 (129 mg, 1.32 mmol) in 1,4-doxane (8 mL) under nitrogen was heated at 110 °C. After 3 h, the reaction was cooled to room temperature and diluted with EtOAc. The resulting mixture was washed with water. The organic layer was concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–40% EtOAc in petroleum ether) provided the product as a yellow solid (168 mg). LC-MS: (ESI, *m/z*): $[M+H]^+ = 538$.

[1538] **Intermediate 152:** (3-(Bis(4-methoxybenzyl)amino)-6-(2,2-difluoroethyl)-2-fluoro-5-methylphenyl)boronic acid



[1539] Step 1: (*E*)-3-Bromo-4-(2-ethoxyvinyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline

[1540] A solution of 3-bromo-2-fluoro-4-iodo-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline (5.03 g, 8.82 mmol), (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.37 g, 22.1 mmol), K_2CO_3 (2.42 g, 17.5 mmol) and $Pd(dppf)Cl_2$ (642 mg, 0.880 mmol) in 1,4-dioxane (50 mL) and water (10 mL) was heated at 90 °C under nitrogen. After 4 h, the reaction was cooled to

room temperature and diluted with EtOAc. The mixture was washed with water, and the organic was concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–10% EtOAc in petroleum ether) afforded product as a yellow solid (3.36 g). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 514.

[1541] Step 2: 2-(4-(Bis(4-methoxybenzyl)amino)-2-bromo-3-fluoro-6-methylphenyl)acetaldehyde

[1542] To an ice-cooled solution of (*E*)-3-bromo-4-(2-ethoxyvinyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline (2.12 g, 4.12 mmol) in THF (12 mL) under nitrogen was added aqueous HCl (3 mL, 12 M). The reaction was warmed to room temperature for 2 h. The resulting mixture was diluted with EtOAc and washed with water. The organic layer was concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–30% EtOAc in petroleum ether) furnished product as a yellow oil (667 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 486.

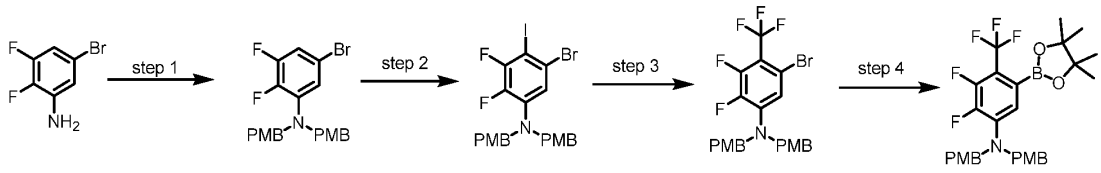
[1543] Step 3: 3-Bromo-4-(2,2-difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline

[1544] To an ice-cooled solution of 2-[4-[bis[(4-methoxyphenyl)methyl]amino]-2-bromo-3-fluoro-6-methyl-phenyl]acetaldehyde (667 mg, 1.37 mmol) in DCM (8 mL) under nitrogen was added DAST (1.55 g, 9.63 mmol). The reaction was warmed to room temperature for 30 min. Saturated aqueous NH_4Cl solution was added, and the mixture was extracted with EtOAc. The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–50% EtOAc in petroleum ether) provided product as a yellow oil (574 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 508.

[1545] Step 4: (3-(Bis(4-methoxybenzyl)amino)-6-(2,2-difluoroethyl)-2-fluoro-5-methylphenyl)boronic acid

[1546] To a solution of 3-bromo-4-(2,2-difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-methylaniline (1.21 g, 2.38 mmol) and $(iPrO)_3B$ (2.23 g, 11.8 mmol) in THF (15 mL) was added *n*-BuLi (4.84 mL, 12.1 mmol) at –60 °C. After 30 min, MeOH was added, and the reaction was warmed to room temperature. The mixture was concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–10% MeOH in DCM) afforded product as a yellow solid (821 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 474.

[1547] **Intermediate 153:** 2,3-Difluoro-*N*,*N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline



[1548] Step 1: 5-Bromo-2,3-difluoro-*N,N*-bis(4-methoxybenzyl)aniline

[1549] To an ice-cooled solution of 5-bromo-2,3-difluoro-aniline (0.50 g, 2.4 mmol) in DMF (10 mL) was added NaH (384 mg, 9.6 mmol, 60% in mineral oil). The solution was warmed to room temperature for 1 hour. PMBCl (1.13g, 7.21 mmol) was then added. After 4 h, the excess NaH was quenched by the addition of saturated aqueous NH_4Cl solution, and the resulting mixture was extracted with EtOAc. The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–5% ethyl acetate in petroleum ether) furnished product as an oil (0.90 g). LC-MS: (ESI, m/z): $[M+H]^+ = 448$.

[1550] Step 2: 5-Bromo-2,3-difluoro-4-iodo-*N,N*-bis(4-methoxybenzyl)aniline

[1551] A solution of 5-bromo-2,3-difluoro-N,N-bis[(4-methoxyphenyl)methyl]aniline (0.90 g, 2.0 mmol) and NIS (676 mg, 3.02 mmol) in acetic acid (10 mL) was stirred at room temperature for 2 hours. The reaction was concentrated under vacuum, and the resulting residue was purified by flash column chromatography on silica gel (gradient: 0–5% ethyl acetate in petroleum ether) to yield as a yellow oil (0.80 g). LC-MS: (ESI, m/z): $[M+H]^+ = 574$.

[1552] Step 3: 5-Bromo-2,3-difluoro-*N,N*-bis(4-methoxybenzyl)-4-(trifluoromethyl)aniline

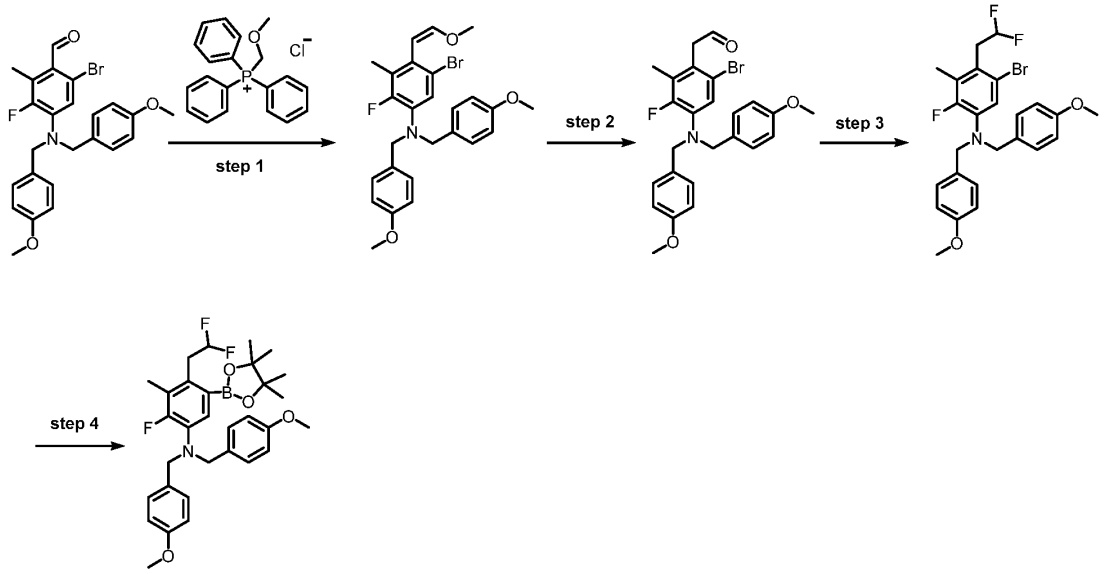
[1553] To a solution of 5-bromo-2,3-difluoro-4-iodo-*N,N*-bis[(4-methoxyphenyl)methyl]aniline (0.900 g, 1.57 mmol) and methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (1.50 g, 7.85 mmol) in DMA (9 mL) was added CuI (0.30 g, 1.6 mmol) under nitrogen at room temperature. The reaction was heated to 90 °C for 4 hours. The reaction mixture was cooled to room temperature and partitioned between water and EtOAc. The separated organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–10% ethyl acetate in petroleum ether) afforded the product as a brown oil (0.60 g). LC-MS: (ESI, m/z): $[M+H]^+ = 516$.

[1554] Step 4: 2,3-Difluoro-*N,N*-bis(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline

[1555] A solution of 5-bromo-2,3-difluoro-N,N-bis[(4-methoxyphenyl)methyl]-4-(trifluoromethyl)aniline (0.50 mg, 0.97 mmol), Pin_2B_2 (739 mg, 2.91 mmol), $PdCl_2$(dppf) (71 mg, 0.10 mmol) and KOAc (285 mg, 2.91 mmol) in 1,4-dioxane (5 mL) was heated at 100 °C under nitrogen for 4 hours. The reaction was cooled to room temperature, diluted with water, and

extracted with EtOAc. The organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–10% ethyl acetate in petroleum ether) provided product as a white solid (260 mg). LC-MS: (ESI, m/z): $[M+H]^+$ = 564.

[1556] **Intermediate 154:** 4-(2,2-Difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[1557] Step 1: 5-Bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-4-(2-methoxyvinyl)-3-methylaniline

[1558] To an ice-cooled solution of (methoxymethyl)triphenylphosphonium chloride (2.04 g, 5.95 mmol) in tetrahydrofuran (30 mL) was added *t*-BuOK (7.40 mL, 7.40 mmol, 1M in THF). The reaction was warmed to room temperature for 0.5 hour. The reaction was cooled to 0 °C before the addition of 4-(bis(4-methoxybenzyl)amino)-6-bromo-3-fluoro-2-methylbenzaldehyde (1.41 g, 2.99 mmol, Intermediate 114, step 3). The solution was then warmed to room temperature for 2 hours. Saturated aqueous NH_4Cl solution was added, and the resulting mixture was extracted with EtOAc. The combined organic was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–11% EtOAc in petroleum ether) provided product as a yellow oil (1.44 g). LC-MS: (ESI, m/z): $[M+H]^+$ = 500/502. ^1H NMR (400 MHz, $CDCl_3$, *ppm*) δ 7.26 – 7.22 (m, 4H), 6.82 (d, *J* = 8.8 Hz, 4H), 6.55 (d, *J* = 13.2 Hz, 1H), 6.14 (d, *J* = 6.8 Hz, 0.5H), 5.55 (d, *J* = 13.2 Hz, 1H), 5.18 (d, – = 6.8 Hz, 0.5H), 4.27 - 4.23 (m, 4H), 3.78 (s, 6H), 3.71 – 3.67 (m, 3H), 2.28 – 2.21 (m, 3H).

[1559] Step 2: 2-(4-(Bis(4-methoxybenzyl)amino)-6-bromo-3-fluoro-2-methylphenyl)acetaldehyde

[1560] To a solution of 5-bromo-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-4-(2-methoxyvinyl)-3-methylaniline (1.29 g, 2.58 mmol) in tetrahydrofuran (15 mL) was added concentrated hydrochloric acid (1.5 mL, 36%) at –15 ºC. After 1 h, the solution was warmed to room temperature for 5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–11% EtOAc in petroleum ether) provided product as a colorless oil (890 mg). LC-MS: (ESI, m/z): $[M+H]^+$ = 486/488.

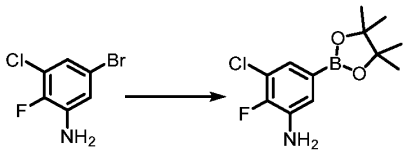
[1561] Step 3: 5-Bromo-4-(2,2-difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline

[1562] To a solution of 2-(4-(bis(4-methoxybenzyl)amino)-6-bromo-3-fluoro-2-methylphenyl)acetaldehyde (0.50 g, 1.0 mmol) in dichloromethane (15 mL) under nitrogen was added DAST (3.20 mL, 26.2 mmol) at –10 °C. The solution was warmed to room temperature for 3 hours. Saturated aqueous $NaHCO_3$ solution was added, and the resulting mixture was extracted with DCM. The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–7% EtOAc in petroleum ether) afforded product as a white solid (518 mg). LC-MS: (ESI, m/z): $[M+H]^+$ = 508/510.

[1563] Step 4: 4-(2,2-Difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

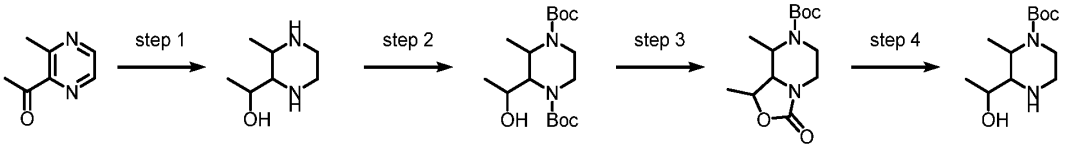
[1564] Under nitrogen, a solution of 5-bromo-4-(2,2-difluoroethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methylaniline (518 mg, 1.02 mmol), $PdCl_2$(dppf) (140 mg, 0.18 mmol), Pin_2B_2 (712 mg, 2.80 mmol) and KOAc (0.30 g, 3.1 mmol) in 1,4-dioxane (12 mL) was stirred at 85 °C. After 7 h, the reaction was cooled to room temperature and filtered. The filtrate was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel eluting (gradient: 0–5% EtOAc in petroleum ether) afforded product as an colorless oil (504 mg). LC-MS: (ESI, m/z): $[M+H]^+$ = 556. ^{1}H NMR (400 MHz, $CDCl_3$, *ppm*) δ 7.44 – 7.29 (m, 4H), 6.81 – 6.76 (m, 4H), 6.–1 – 5.72 (m, 2H), 4.47 - 4.26 (m, 4H), 3.77 (s, 6H), 3.50 – 3.43 (m, 2H), 2.25 (s, 3H), 1.27 – 2.26 (m, 12H).

[1565] **Intermediate 155:** 3-Chloro-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline



[1566] Under nitrogen, a solution of 5-bromo-3-chloro-2-fluoroaniline (0.20 g, 0.89 mmol, intermediate 135, step 1), Pin_2B_2 (339 mg, 1.34 mmol), $Pd(dppf)Cl_2$ (65 mg, 0.090 mmol) and KOAc (175 mg, 1.78 mmol) in 1,2-dimethoxyethane (8 mL) was stirred at 100 °C overnight. The mixture cooled to room temperature and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–20% EtOAc in petroleum ether) afforded product as a yellow oil (230 mg). LC-MS: (ESI, m/z): $[M+H]^+ = 272$.

[1567] **Intermediate 156:** *tert*-Butyl 3-(1-hydroxyethyl)-2-methylpiperazine-1-carboxylate



[1568] Step 1: 1-(3-Methylpiperazin-2-yl)ethan-1-ol

[1569] Under hydrogen (20 atm), a mixture of 1-(3-methylpyrazin-2-yl)ethan-1-one (10.0 g, 73.5 mmol) and PtO_2 (3.34 g, 14.7 mmol) in methanol (150 mL) was stirred overnight at 80 °C. The resulting mixture was cooled to room temperature and filtered over Celite. The filter cake was washed with methanol, and the filtrate was concentrated under vacuum to afford the crude titled compound as a light yellow oil (10 g). LC-MS: (ESI, *m/z*): $[M+H]^+ = 145$.

[1570] Step 2: Di-*tert*-butyl 2-(1-hydroxyethyl)-3-methylpiperazine-1,4-dicarboxylate

[1571] To an ice-cooled solution of 1-(3-methylpiperazin-2-yl) ethan-1-ol (10.0 g, 69.4 mmol) and DIPEA (57.2 mL, 347 mmol) in dichloromethane (200 mL) was added a solution of $(Boc)_2O$ (45.4 g, 208 mmol) in dichloromethane (100 mL) dropwise. The solution was warmed to room temperature for 2 hours. The reaction mixture was diluted with water and extracted with dichloromethane. The combined organic was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0–10% methanol in dichloromethane) afforded product as a light yellow oil (15 g). LC-MS: (ESI, *m/z*): $[M+H]^+ = 345$.

[1572] Step 3: *tert*-Butyl 1,8-dimethyl-3-oxotetrahydro-3*H*-oxazolo[3,4-a]pyrazine-7(1*H*)-carboxylate

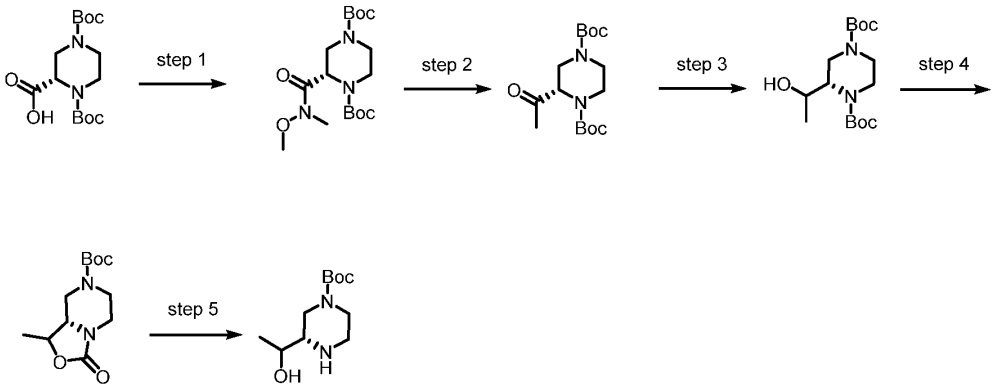
[1573] To an ice-cooled solution of di-*tert*-butyl 2-(1-hydroxyethyl)-3-methylpiperazine-1,4-dicarboxylate (5.00 g, 14.5 mmol) in tetrahydrofuran (10 mL) was added NaH (1.16 g, 29.0 mmol, 60% dispersion in mineral oil) in 3 portions. The reaction was warmed to room temperature. After 3 h, the saturated aqueous NH_4Cl solution was added. The reaction mixture

was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford the crude product as a brown solid (3.5 g). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 271.

[1574] Step 4: *tert*-Butyl 3-(1-hydroxyethyl)-2-methylpiperazine-1-carboxylate

[1575] To a solution of *tert*-butyl 1,8-dimethyl-3-oxotetrahydro-3*H*-oxazolo[3,4-a]pyrazine-7(1*H*)-carboxylate (3.5 g, crude) in ethanol (60 mL) was added a solution of NaOH (2.60 g, 65.0 mmol) in water (20 mL) at room temperature. The reaction was heated at 80 °C for 3 h. Ethanol was removed under reduced pressure, and the resulting residue was diluted with water. The solution was neutralized to pH = 8 with HCl (1M) and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum to afford the crude product as an off white solid (2.6 g). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 245.

[1576] **Intermediate 157:** *tert*-Butyl (*S*)-3-((*S*)-1-hydroxyethyl)piperazine-1-carboxylate



[1577] Step 1: Di-*tert*-butyl (*S*)-2-(methoxy(methyl)carbamoyl)piperazine-1,4-dicarboxylate

[1578] Under nitrogen, a solution of (*S*)-1,4-bis(tert-butoxycarbonyl)piperazine-2-carboxylic acid (5.01 g, 15.2 mmol), *N*,*O*-dimethylhydroxylamine (1.63 g, 16.7 mmol), HATU (7.50 g, 19.7 mmol) and DIPEA (3.91 g, 30.3 mmol) in DCM (2 mL) was stirred overnight at room temperature. Saturated aqueous NH_4Cl solution was added to the reaction, and resulting mixture was extracted with DCM. The combined organic was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–70% EtOAc in petroleum ether) afforded product as a white solid (5.41 g). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 374.

[1579] Step 2: Di-*tert*-butyl (*S*)-2-acetylpiperazine-1,4-dicarboxylate

[1580] To an ice-cooled solution of di-*tert*-butyl (*S*)-2-(methoxy(methyl)carbamoyl) piperazine-1,4-dicarboxylate (5.41 g, 14.5 mmol) in Et_2O (50 mL) was added MeMgBr (24.2 mL, 3M in Et_2O) under nitrogen. After 2 h, the reaction was quenched by saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic was dried over anhydrous sodium

sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–50% EtOAc in petroleum ether) afforded the product as a white solid (2.24 g). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 329.

[1581] Step 3: Di-*tert*-butyl (*S*)-2-((*R*)-1-hydroxyethyl)piperazine-1,4-dicarboxylate

[1582] To an ice-cooled solution of di-*tert*-butyl (*S*)-2-acetylpiperazine-1,4-dicarboxylate (2.21 g, 6.70 mmol) in CH_3OH (22 mL) was added $NaBH_4$ (380 mg, 10.1 mmol). The reaction was warmed to room temperature for 1 h. Water was added to the reaction, and the reaction was concentrated under vacuum to remove CH_3OH. The resulting solution was partitioned between water and EtOAc. The separated organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. Purification by flash column chromatography on silica gel (gradient: 0%–50% EtOAc in petroleum ether) to afford the titled compound as a white solid (2.21 g). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 331.

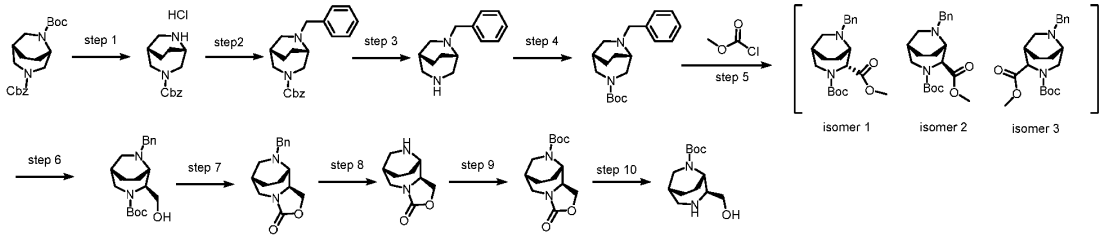
[1583] Step 4: *tert*-Butyl (1*S*,8a*S*)-1-methyl-3-oxotetrahydro-3*H*-oxazolo[3,4-*a*]pyrazine-7(1*H*)-carboxylate

[1584] To an ice-cooled solution of di-*tert*-butyl (*S*)-2-((*R*)-1-hydroxyethyl)piperazine-1,4-dicarboxylate (2.28 g, 6.90 mmol) in THF (25 mL) was added NaH (553 mg, 13.8 mmol) under nitrogen. The solution was warmed to room temperature for 1 h, before the addition of saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-60% ACN in water (0.05% NH_4HCO_3)) to afford the titled compound as a white solid (1.46 g). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 201.

[1585] Step 5: *tert*-Butyl (3S)-3-(1-hydroxyethyl)piperazine-1-carboxylate

[1586] A solution of *tert*-butyl (1*S*,8a*S*)-1-methyl-3-oxotetrahydro-3*H*-oxazolo[3,4-*a*] pyrazine-7(1*H*)-carboxylate (1.45 g, 5.67 mmol) and NaOH (2.27 g, 56.8 mmol) in EtOH (15 mL) and water (3 mL) was stirred at 80 °C for 2 h. The reaction was cooled to room temperature, and the resulting solution was concentrated under vacuum, and filtered. t The solid was washed with DCM, and the filtrate was concentrated under vacuum to afford crude product as a white oil (1.48 g), which was used without further purification. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 231.

[1587] **Intermediate 158:** *tert*-Butyl (1*R*,4*S*,5*S*)-4-(hydroxymethyl)-3,6-diazabicyclo[3.2.2]nonane-6-carboxylate



[1588] Step 1: Benzyl (1*S*,5*S*)-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate HCl salt

[1589] To a solution of 3-benzyl 6-(tert-butyl) (1*R*,5*S*)-3,6-diazabicyclo[3.2.2]nonane-3,6-dicarboxylate (40.0 g, 111 mmol) in dichloromethane (40 mL) was added HCl (40 mL, 4 M in 1,4-dioxane). The resulting solution was stirred for 3 h at room temperature. The solvent was concentrated under vacuum to afford 43 g (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 261.

[1590] Step 2: Benzyl (1*S*,5*S*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate

[1591] A solution of benzyl (1*S*,5*S*)-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate HCl salt (43 g, 146 mmol), benzyl bromide (23.6 mL, 198 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (42.0 g, 326 mmol) in *N*,*N*-dimethylformamide (40 mL) was stirred at 80 °C for 1 h. The reaction was cooled to room temperature, diluted with EtOAc and washed with water. The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc / petroleum ether) to afford 50 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 351.

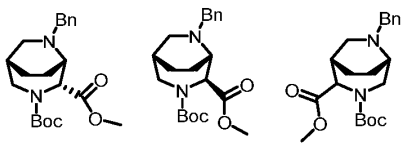
[1592] Step 3: (1*R*,5*S*)-6-Benzyl-3,6-diazabicyclo[3.2.2]nonane

[1593] A solution of benzyl (1*S*,5*S*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate (30.0 g, 85.6 mmol) in TFA (300 mL) was stirred for 3 h at 70 °C. The solvent was concentrated under vacuum to afford 27 g (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 217.

[1594] Step 4: *tert*-Butyl (1*S*,5*S*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate

[1595] To a solution of (1*R*,5*S*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane (27 g, 125 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (95.2 g, 437 mmol) in dichloromethane (270 mL) was added $(Boc)_2O$ (24.2 g, 187 mmol). The resulting solution was stirred for 30 min at room temperature. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc / petroleum ether) to afford 16 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 317.

[1596] Step 5: 3-(*tert*-Butyl) 4-methyl (1*S*,4*S*,5*S*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-3,4-dicarboxylate, 3-(*tert*-butyl) 4-methyl (1*S*,4*R*,5*S*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-3,4-dicarboxylate and 3-(*tert*-butyl) 2-methyl (1*S*,5*S*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-2,3-dicarboxylate (mixture of two isomers)



isomer 1 isomer 2 isomer 3

[1597] Under nitrogen, to a solution of *tert*-butyl (1*S*,5*S*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate (15 g, 47 mmol) and N^1,N^1,N^2,N^2-tetramethylethane-1,2-diamine (11.0 g, 94.9 mmol) in diethyl ether (150 mL) was added *s*-BuLi (73.1 mL, 1.3 M in cHex) at -78 °C. The resulting solution was stirred for 1.5 h at -55°C. The reaction system was recooled to -78 °C and methyl chloroformate (11.2 g, 118 mmol) in diethyl ether (100 mL) was added. The reaction was stirred overnight at room temperature. The reaction was quenched with NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The crude was purified by flash chromatography on silica gel (gradient: 0-10% EtOAc / petroleum ether) to afford 1.2 g of isomer 1 (the first peak), 1.7 g of isomer 2 (the second peak) and 2.0 g of isomer 3 (the third peak) as yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 375.

[1598] isomer 1: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.37 – 7.01 (m, 5H), 4.82 – 4.66 (m, 1H), 4.25 – 3.95 (m, 1H), 3.71 – 3.57 (m, 5H), 3.52 – 3.47 (m, 1H), 3.24 – 3.12 (m, 1H), 2.61 – 2.49 (m, 1H), 2.20 – 1.98 (m, 2H), 1.99 – 1.94 (m, 1H), 1.77 – 1.43 (m, 3H), 1.37 (d, *J* = 15.0 Hz, 9H).

[1599] isomer 2: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.52 – 7.09 (m, 5H), 5.13 – 4.94 (m, 1H), 4.28 – 4.13 (m, 1H), 3.76 – 3.70 (m, 1H), 3.64 – 3.52 (m, 4H), 3.30 – 3.25 (m, 1H), 3.15 – 2.99 (m, 1H), 2.84 – 2.80 (m, 1H), 2.46 – 2.38 (m, 1H), 2.22 – 2.16 (m, 1H), 2.02 – 1.84 (m, 1H), 1.59 – 1.46 (m, 3H), 1.41 (d, *J* = 7.1 Hz, 9H).

[1600] isomer 3: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.41 – 7.12 (m, 5H), 4.99 – 4.65 (m, 1H), 4.19 – 3.80 (m, 1H), 3.77 – 3.68 (m, 1H), 3.67 – 3.57 (m, 4H), 3.52 – 3.29 (m, 1H), 3.06 – 2.60 (m, 3H), 2.55 – 2.40 (m, 1H), 1.93 – 1.50 (m, 4H), 1.45 – 1.34 (m, 9H).

[1601] Step 6: *tert*-Butyl (1*S*,4*S*,5*S*)-6-benzyl-4-(hydroxymethyl)-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate

[1602] Under nitrogen, to a solution of 3-(*tert*-butyl) 4-methyl (1*S*,4*S*,5*S*)-6-benzyl-3,6-diazabicyclo[3.2.2]nonane-3,4-dicarboxylate (isomer 2, 1.6 g, 4.3 mmol) in tetrahydrofuran (20 mL) was added $LiAlH_4$ (1.7 mL, 2.5 M in THF) at 0 °C. The resulting solution was stirred for 30 min at 0 °C. The mixture was quenched by Na_2SO_4•$10H_2O$ and filtered. The filtrate was evaporated under vacuum to afford 1.4 g (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 347.

[1603] Step 7: (6*S*,9*S*,9a*S*)-10-Benzylhexahydro-1*H*,3*H*-9,6-(epiminomethano)oxazolo[3,4-*a*]azepin-3-one

[1604] Under nitrogen, to a solution of *tert*-butyl (1*S*,4*S*,5*S*)-6-benzyl-4-(hydroxymethyl)-3,6-diazabicyclo[3.2.2]nonane-3-carboxylate (1.4 g, 4.0 mmol) in tetrahydrofuran (20 mL) was added NaH (324 mg, 8.09 mmol, 60% in mineral oil) at 0 °C. The resulting solution was stirred for 2 h at room temperature. The reaction was quenched with NH_4Cl aqueous and extracted with EtOAc.

The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-80% MeOH in water (0.05% NH_4HCO_3)) to afford 781 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 273$.

[1605] Step 8: (6*S*,9*S*,9a*S*)-Hexahydro-1*H*,3*H*-9,6-(epiminomethano)oxazolo[3,4-*a*]azepin-3-one

[1606] Under hydrogen (1atm), a solution of (6*S*,9*S*,9a*S*)-10-benzylhexahydro-1*H*,3*H*-9,6-(epiminomethano) oxazolo [3,4-*a*] azepin-3-one (680 mg, 2.50 mmol) in methyl alcohol (20.0 mL) was added Pd/C (136 mg). The resulting solution was stirred for 1 h at room temperature. The solids were filtered. The solvent was evaporated under vacuum to afford 475 mg (crude) of the title compound as a yellow solid. LCMS: (ESI): $[M+H]^+ = 183$.

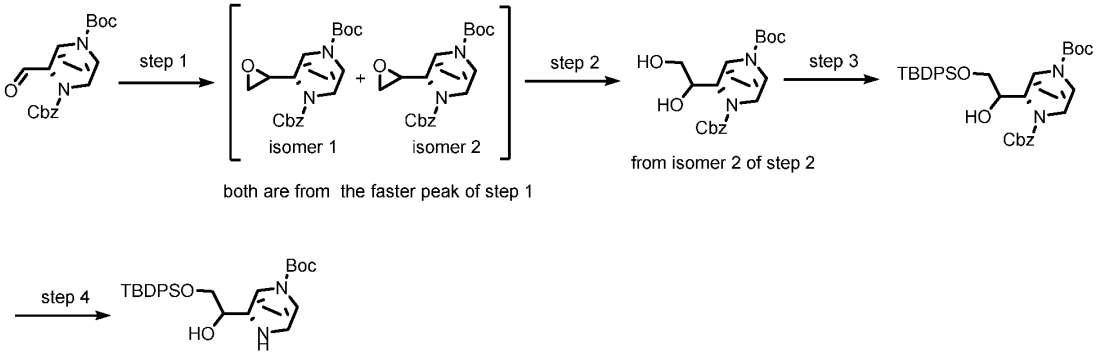
[1607] Step 9: *tert*-Butyl (6*S*,9*S*,9a*S*)-3-oxohexahydro-1*H*,3*H*-9,6-(epiminomethano)oxazolo[3,4-*a*]azepine-10-carboxylate

[1608] A solution of (6*S*,9*S*,9a*S*)-hexahydro-1*H*,3*H*-9,6-(epiminomethano)oxazolo[3,4-*a*]azepin-3-one (475 mg, 2.61 mmol), $(Boc)_2O$ (853 mg, 3.91 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (1.01 g, 7.83 mmol) in dichloromethane (10 mL) was stirred for 30 min at room temperature. The reaction was diluted with water and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford 706 mg (crude) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 283$.

[1609] Step 10: *tert*-Butyl (1*R*,4*S*,5*S*)-4-(hydroxymethyl)-3,6-diazabicyclo[3.2.2]nonane-6-carboxylate

[1610] To a solution of *tert*-butyl (6*S*,9*S*,9a*S*)-3-oxohexahydro-1*H*,3*H*-9,6-(epiminomethano) oxazolo[3,4-*a*]azepine-10-carboxylate (173 mg, 0.610 mmol) in ethanol (5.0 mL) was added NaOH (244 mg, 6.10 mmol) in water (1.0 mL). The resulting solution was stirred for 1 h at 80 °C. Solvent was evaporated under vacuum. The solid was washed with DCM several times. The combined DCM layers were evaporated under vacuum to afford 85 mg (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 257$. The crude was used for next step without further purification.

[1611] **Intermediate 159:** *tert*-Butyl (1*S*,2*S*,5*R*)-2-(2-((tert-butyldiphenylsilyl)oxy)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[1612] Step 1: 3-Benzyl 8-(*tert*-butyl) (1*S*,2*S*,5*R*)-2-(oxiran-2-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (two isomers)

[1613] To a solution of trimethylsulfonium iodide (12.0 g, 58.9 mmol) in dimethyl sulfoxide (100 mL) and tetrahydrofuran (20 mL) was added NaH (2.17 g, 54.3 mmol, 60% in mineral oil) at room temperature. The solution was stirred for 1 hour at room temperature. A solution of 3-benzyl 8-(*tert*-butyl) (1*S*,2*S*,5*R*)-2-formyl-3,8-diazabicyclo [3.2.1]octane-3,8-dicarboxylate (5.01 g, 13.4 mmol, intermediate 163, the faster peak of step 2) in tetrahydrofuran (20 mL) was then added at room temperature, and the mixture was stirred for an additional 2 hours. The reaction was quenched by aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-30% EtOAc / petroleum ether) to afford 0.83 g isomer 1 (the faster peak) and 2.01 g isomer 2 (the slower peak) as light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 389$.

[1614] Step 2: 3-Benzyl 8-(*tert*-butyl) (1*S*,2*S*,5*R*)-2-(1,2-dihydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (isomer 2)

[1615] To a solution of 3-benzyl 8-(*tert*-butyl) (1*S*,2*S*,5*R*)-2-(oxiran-2-yl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (1.96 g, 5.05 mmol) (isomer 2 of last step) in tetrahydrofuran (18 mL) was added aqueous H_2SO_4 solution (10%, 2 mL). The solution was stirred at 50 °C for 16 hours. The solution was cooled to room temperature and adjusted pH to ~10 by aqueous NaOH solution (10%). DIPEA (2.31 g, 17.9 mmol) and $(Boc)_2O$ (1.64 g, 7.59 mmol) was then added. The resulting solution was stirred at room temperature for 2 hours. The solution was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-4% MeOH / DCM) to afford 1.52 g of the title compound as light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 407$.

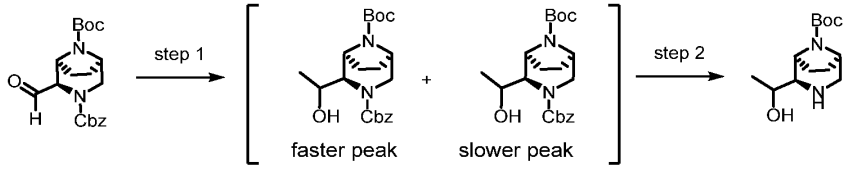
[1616] Step 3: 3-Benzyl 8-(*tert*-butyl) (1*S*,2*S*,5*R*)-2-(2-((tert-butyldiphenylsilyl)oxy)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (isomer 2)

[1617] To a solution of 3-benzyl 8-(*tert*-butyl) (1*S*,2*S*,5*R*)-2-(1,2-dihydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (1.51 g, 3.71 mmol), DMAP (0.91 g, 7.46 mmol) and DIPEA (2.45 g, 19.0 mmol) in *N*,*N*-Dimethylformamide (20 mL) was added *tert*-butylchlorodiphenylsilane (2.24 g, 8.15 mmol). The solution was stirred at room temperature for 16 hours. The solution was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-25% EtOAc / petroleum ether) to afford 2.22 g of the title compound as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 645.

[1618] Step 4: *tert*-Butyl (1*S*,2*S*,5*R*)-2-(2-((tert-butyldiphenylsilyl)oxy)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[1619] Under hydrogen (1 atm), a solution of 3-benzyl 8-(*tert*-butyl) (1*S*,2*S*,5*R*)-2-(2-((tert-butyldiphenylsilyl)oxy)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (2.22 g, 3.44 mmol) and Pd/C (10%, 517 mg, 0.490 mmol) in methyl alcohol (50 mL) was stirred at room temperature for 1.5 hours. The reaction was filtered, and the filtrate was concentrated under vacuum to afford 1.57 g (crude) of the title compound as crude white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 511. The crude was used for next step without further purification.

[1620] **Intermediate 160:** *tert*-Butyl (1*R*,2*R*,5*S*)-2-(1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[1621] Step 1: 3-Benzyl 8-(*tert*-butyl) (1*R*,2*R*,5*S*)-2-(1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate

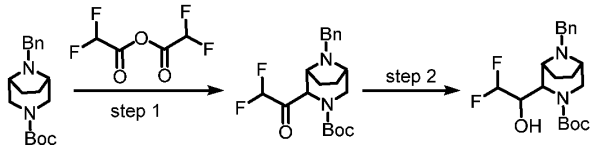
[1622] Under nitrogen, to a solution of 3-benzyl 8-(*tert*-butyl) (1*R*,2*R*,5*S*)-2-formyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (1.51 g, 4.01 mmol, intermediate 159, step 1, the slower peak) in THF (15 mL) was added MeMgBr (10 mL, 3 M in Et_2O) at -40 °C, and the mixture was stirred for 2 h at -40 °C. The resulting solution was partitioned between water and EtOAc. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on –silica gel (gradient: 0 - 45% EtOAc / petroleum ether) to afford 780 mg of the faster peak and 488 mg of the slower peak as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 391.

[1623] Step 2: *tert*-Butyl (1*R*,2*R*,5*S*)-2-(1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[1624] Under hydrogen, a solution of 3-benzyl 8-(*tert*-butyl) (1*R*,2*R*,5*S*)-2-(1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (2.74 g, 7.02 mmol) (the faster peak from last step) in MeOH (18 mL) was added Pd/C (880 mg, 10%), and the mixture was stirred at room temperature for 2.5 h. After filtration, the filtrate was concentrated under vacuum to afford 1.64 g (crude) of the title compound as a white solid LC-MS: (ESI, *m/z*): $[M+H]^+$ = 257.

[1625] Analogous to method described as above, the other isomers were prepared from the slower peak of step 1.

[1626] **Intermediate 161:** *tert*-Butyl (1*R*,5*S*)-8-benzyl-2-(2,2-difluoro-1-hydroxyethyl)-3,8-diazabicyclo [3.2.1] octane-3-carboxylate



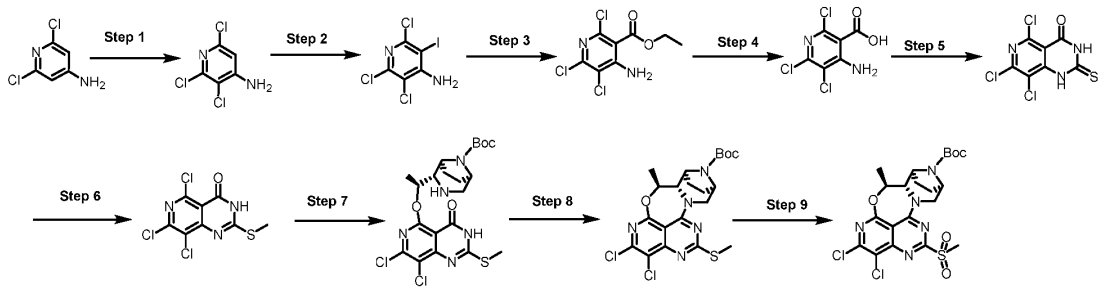
[1627] Step 1: *tert*-Butyl (1*R*,5*S*)-8-benzyl-2-(2,2-difluoroacetyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

[1628] Under nitrogen, to a solution of *tert*-butyl (1*R*,5*S*)-8-benzyl-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (2.00 g, 6.61 mmol) and TMEDA (1.54 g, 13.3 mmol) in diethyl ether (20.0 mL) was added *s*-BuLi (10.2 mL, 1.3 M in Hex) at -78 °C. The resulting solution was stirred for 1.5 h at -78 °C. Then 2,2-difluoroacetic anhydride (2.88 g, 16.5 mmol) in diethyl ether (5.00 mL) was added at -78 °C, and the mixture was stirred overnight at room temperature. The reaction was quenched with NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum The residue was purified by flash chromatography on silica gel eluting (gradient: 0%-50% EtOAc in petroleum ether) to afford 1.3 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 381.

[1629] Step 2: *tert*-Butyl (1*R*,5*S*)-8-benzyl-2-(2,2-difluoro-1-hydroxyethyl)-3,8-diazabicyclo [3.2.1] octane-3-carboxylate

[1630] Under nitrogen, to a solution of *tert*-butyl (1*R*,5*S*)-8-benzyl-2-(2,2-difluoroacetyl)-3,8-diazabicyclo [3.2.1] octane-3-carboxylate (6.0 g, 15.7 mmol) in tetrahydrofuran (60 mL) was added $LiAlH_4$ (4.7 mL, 1 M in THF) at 0 °C. The resulting solution was stirred at 0 °C for 1 h. The mixture was quenched by $Na_2SO_4 \cdot 10H_2O$ and filtered. The filtrate was concentrated under vacuum to afford 4.6 g (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $M+H]^+$ = 383. The crude was used for next step without further purification.

[1631] **Intermediate 162:** *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1,2-dichloro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[1632] Step 1: 2,3,6-Trichloropyridin-4-amine

[1633] A solution of 2,6-dichloropyridin-4-amine (20.0 g, 123 mmol) and NCS (16.4 g, 123 mmol) in tetrahydrofuran (500mL) was stirred at 50 °C for 24 hours. The solvent was concentrated under vacuum. The residue was diluted with water, and the resulting solution was extracted with EtOAc. The combined organic layers were concentrated under vacuum. The crude product was slurried with ether/ EtOAc (10:1) and filtered to afford 21 g of the title compound (crude) as an off-white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 197.

[1634] Step 2: 2,3,6-Trichloro-5-iodopyridin-4-amine

[1635] To a stirred mixture of 2,3,6-trichloropyridin-4-amine (22 g, 111 mmol) in ACN (200 mL) was added NIS (30 g, 134 mmol) and TsOH (2.18 g, 11 mmol) at room temperature. The solution was stirred for 2 h at 70 °C. The reaction system was cooled to room temperature, diluted with aqueous Na_2HSO_3 and extracted with EtOAc. The combined organic layers were washed sequentially with water and brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (gradient: 0%-30% EtOAc/petroleum ether) to afford 35 g of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 323.

[1636] Step 3: Ethyl 4-amino-2,5,6-trichloronicotinate

[1637] Under carbon monoxide atmosphere, a solution of 2,3,6-trichloro-5-iodo-pyridin-4-amine (8.0 g, 24.7 mmol), $Pd(PPh_3)_2Cl_2$ (1.74 g, 2.47 mmol) and triethylamine (7.51 g, 74.2 mmol) in ethanol (80 mL) was stirred for 48 h at 80 °C. The resulting mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% EtOAc/DCM) to yield 3.7 g of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ =269.

[1638] Step 4: 4-Amino-2,5,6-trichloronicotinic acid

[1639] A solution of ethyl 4-amino-2,5,6-trichloro-pyridine-3-carboxylate (3.0 g, 11 mmol) and NaOH (890 mg, 22 mmol) in EtOH (20 mL) and water (60 mL) was stirred for 2 h at room

temperature. The resulting mixture was filtered. The filtrate was acidified to pH ~3 with HCl. The precipitated solids were collected by filtration to afford 1.5 g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 241.

[1640] Step 5: 5,7,8-Trichloro-2-thioxo-2,3-dihydropyrido[4,3-d]pyrimidin-4(1*H*)-one

[1641] To a solution of 4-amino-2,5,6-trichloropyridine-3-carboxylic acid (8.5 g, 35 mmol) and pyridine (20 mL) in ACN (100 mL) was added ethoxycarbonyl isothiocyanate (18.5 g, 141 mmol). The solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum. The residue was diluted with water and the precipitated solid was collected by filtration to afford 8.7 g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 282.

[1642] Step 6: 5,7,8-Trichloro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3*H*)-one

[1643] To a stirred mixture of 5,7,8-trichloro-2-sulfanylidene-1H,3H-pyrido[4,3-d]pyrimidin-4-one (8.7 g, 31 mmol) and NaOMe (4.99 g, 92.4 mmol) in DMF (100 mL) was added CH_3I (3.06 g, 21.6 mmol) dropwise at 0 °C. The solution was stirred for 2 h at room temperature. The resulting mixture was diluted with water, and the resulting solution was extracted with CH_2Cl_2. The combined organic layers were concentrated under vacuum to afford 6.3 g (crude) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 296.

[1644] Step 7: *tert*-Butyl (1*S*,2*S*,5*R*)-2-((*S*)-1-((7,8-dichloro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[1645] Under nitrogen, to a solution of *tert*-butyl (1S,2S,5R)-2-((S)-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (156 mg, 0.610 mmol) in tetrahydrofuran (4 mL) was added NaH (81 mg, 2.02 mmol, 60% in mineral oil) at 0 °C. The resulting solution was stirred at room temperature for 0.5 h. Then 5,7,8-trichloro-2-methylsulfanyl-3H-pyrido[4,3-d] pyrimidin-4-one (0.20 g, 0.67 mmol) was added, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with water, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-60% EA/PE) to yield 180 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 516.

[1646] Step 8: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1,2-dichloro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

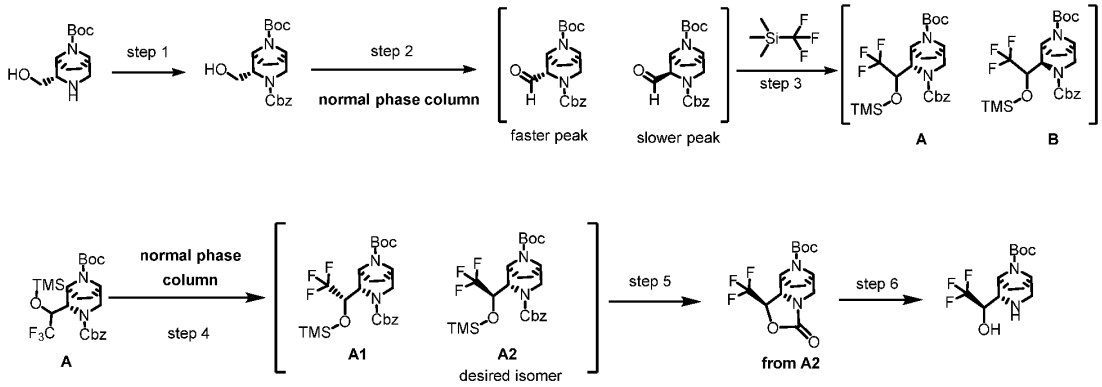
[1647] To a solution of *tert*-butyl (1*S*,2*S*,5*R*)-2-((*S*)-1-((7,8-dichloro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (2.0 g, 3.87 mmol) and DIPEA (2.5 g, 19 mmol) in dichloromethane (20 mL) was added BOPCl (2.95 g, 11.6 mmol) at room temperature. The resulting solution was stirred at room temperature for 2

h. The solvent was concentrated under vacuum, and the residue was purified by flash chromatography on silica gel (gradient: 0%-20% EtOAc /petroleum ether) to yield 1.5 g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 498.

[1648] Step 9: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1,2-dichloro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1649] Under nitrogen, to a solution of *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1,2-dichloro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (0.050 g, 0.10 mmol) in ethyl acetate (2 mL) was added m-CPBA (17.3 mg, 0.10 mmol) at 0 °C. The resulting solution was stirred at room temperature for 2 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica (gradient: 0%-20% EtOAc /petroleum ether) to afford 45 mg as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 530.

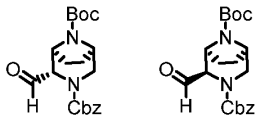
[1650] **Intermediate 163:** *tert*-Butyl (1R,2S,5S)-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate



[1651] Step 1: 3-Benzyl 8-(*tert*-butyl) (1*R*,2*S*,5*S*)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate

[1652] To a solution of *tert*-butyl (1*R*,2*S*,5*S*)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (5.00 g, 20.6 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (5.33 g, 41.3 mmol) in dichloromethane (50 mL) was added CbzCl (4.57 g, 26.9 mmol) at 0 °C. The resulting solution was stirred for 1 h at room temperature. The reaction was quenched with water and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc / petroleum ether) to afford 7.7 g of the title compound as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 377.

[1653] Step 2: 3-Benzyl 8-(*tert*-butyl) (1*R*,2*S*,5*S*)-2-formyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate and 3-benzyl 8-(*tert*-butyl) (1*R*,2*R*,5*S*)-2-formyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



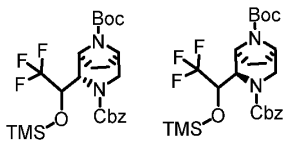
faster peak slower peak

[1654] Under nitrogen, to a solution of oxalyl dichloride (18.4 mL, 2 M in DCM) in dichloromethane (10 mL) was added DMSO (5.73 g, 73.5 mmol) in dichloromethane (10.0 mL) at -78 °C. The resulting solution was stirred for 30 min at -78 °C. Then 3-benzyl 8-(*tert*-butyl) (1*R*,2*S*,5*S*)-2-(hydroxymethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (6.9 g, 18 mmol) in dichloromethane (70 mL) was added at -78 °C, and the mixture was stirred for 1 h. Triethylamine (11.1 g, 110 mmol) was added at -78 °C. The reaction system was warmed to room temperature and stirred an additional 1 h. The reaction was diluted with water and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc / petroleum ether) to afford 1.46 g of the faster peak and 2.9 g of the slower peak as colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 375. Note: crude material does not epimerize.

[1655] **Faster peak:** ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.43 (d– *J* = 3.8 Hz, 1H), 7.38 - 736 (s, 5H), 5.12 (s, 2H), 4.23 (s, 1H), 4.08 (s, 1H), 3.78 (s, 1H), 3.57 (d, *J* = 12.1 Hz, 1H), 3.16 – 3.20 (m, 1H), 2.00 – 1.86 (m, 2H), 1.79 – 1.73 (m, 2H), 1.42 (s, 9H).

[1656] **Slower peak:** ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 7.45 – 7.23 (m, 5H), 5.15 – 5.00 (m, 2H), 4.76 (t, *J* = 8.1 Hz, 1H), 4.60 -4.64 (m, 1H), 4.22 – 3.98 (m, 1H), 3.75 – 3.58 (m, 1H), 3.18 – 3.06 (m, 1H), 2.09 – 1.80 (m, 2H), 1.82 – 1.52 (m, 2H), 1.36 (s, 9H).

[1657] Step 3: 3-Benzyl 8-(*tert*-butyl) (1*R*,2*S*,5*S*)-2-(2,2,2-trifluoro-1-((trimethylsilyl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate and 3-benzyl 8-(*tert*-butyl) (1*R*,2*R*,5*S*)-2-(2,2,2-trifluoro-1-((trimethylsilyl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



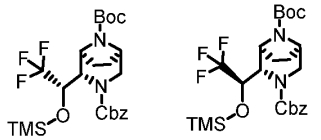
A B

[1658] A solution of 3-benzyl 8-(*tert*-butyl) (1*R*,2*S*,5*S*)-2-formyl-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (faster peak of step 2) (1.46 g, 3.90 mmol), trimethyl(trifluoromethyl)silane (1.11 g, 7.82 mmol) and LiOAc (258 mg, 3.90 mmol) in *N*,*N*-

dimethylformamide (15.0 mL) was stirred for 1 h at room temperature. The reaction was diluted with EtOAc and washed with water. The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford 2 g (crude) of the **compound A** as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 517.

[1659] Analogous to method described as above, 3.80 g crude **compound B** was prepared from 2.80 g of slower peak of step 2.

[1660] Step 4: 3-Benzyl 8-(*tert*-butyl) (1*R*,2*S*,5*S*)-2-((*S*)-2,2,2-trifluoro-1-((trimethylsilyl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate and 3-benzyl 8-(*tert*-butyl) (1*R*,2*S*,5*S*)-2-((*R*)-2,2,2-trifluoro-1-((trimethylsilyl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate



A1 **A2**
desired isomer

[1661] The mixture of diastereomers of 3-Benzyl 8-(*tert*-butyl) (1*R*,2*S*,5*S*)-2-(2,2,2-trifluoro-1-((trimethylsilyl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (6.5 g crude, compound A of last step) was separated by flash chromatography on silica gel (gradient: 0-15% EtOAc in petroleum ether) to afford 3.2 g compound A1 (the faster peak) and 810 mg compound A2 (the slower peak, desired isomer) as yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 517.

[1662] **Compound A1**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.46 – 7.11 (m, 5H), 5.07 (s, 2H), 4.87 (s, 1H), 4.38 (d, *J* = 46.1 Hz, 1H), 4.24 – 3.93 (m, 3H), 3.17 – 2.83 (m, 1H), 2.43 (d, *J* = 8.9 Hz, 1H), 1.86 (s, 2H), 1.56 (s, 1H), 1.33 (s, 9H), 0.09 (s, 9H).

[1663] **Compound A2**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.49 – 7.19 (m, 5H), 4.99 (d, *J* = 8.0 Hz, 2H), 4.70 (d, *J* = 29.2 Hz, 2H), 4.28 (d, *J* = 16.8 Hz, 1H), 4.11 (s, 2H), 2.69 (d, *J* = 16.1 Hz, 1H), 2.02 (d, *J* = 13.2 Hz, 1H), 1.88 (d, *J* = 27.8 Hz, 2H), 1.54 (d, *J* = 10.9 Hz, 1H), 1.31 (d, *J* = 9.6 Hz, 9H), 0.07 (s, 9H).

[1664] Step 5: *tert*-Butyl (1*R*,6*S*,9*R*,9a*S*)-3-oxo-1-(trifluoromethyl)hexahydro-1*H*,3*H*-6,9-epiminooxazolo[3,4-*a*]azepine-10-carboxylate

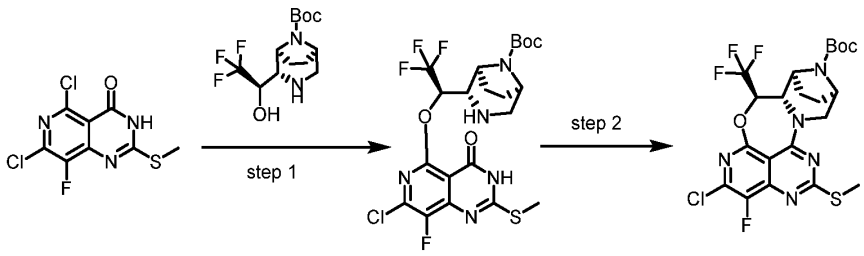
[1665] A solution of 3-benzyl 8-(*tert*-butyl) (1*R*,2*S*,5*S*)-2-((*R*)-2,2,2-trifluoro-1-((trimethylsilyl) oxy) ethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (compound A2 of last step) (0.80 g, 1.6 mmol) and TBAF (1.60 mL, 1 M in THF) in tetrahydrofuran (10.0 mL) was stirred for overnight at room temperature. The reaction system was diluted with EtOAc and washed with water. The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-100%

MeOH in water (0.05% NH_4HCO_3)) to afford 480 mg of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 337.

[1666] Step 6: *tert*-Butyl (1*R*,2*S*,5*S*)-2-((*R*)-2,2,2-trifluoro-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[1667] To a solution of *tert*-butyl (1*R*,6*S*,9*R*,9a*S*)-3-oxo-1-(trifluoromethyl)hexahydro-1*H*,3*H*-6,9-epiminooxazolo[3,4-*a*]azepine-10-carboxylate (480 mg, 1.4 mmol) in ethanol (5.0 mL) was added NaOH (571 mg, 14.3 mmol) in water (1.0 mL). The resulting solution was stirred for 1 h at 80 °C. Solvent was evaporated under vacuum. The residue was dissolved in DCM, and the suspension was filtered. The solvent was evaporated under vacuum to afford 460 mg (crude) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 311. ^1H NMR (300 MHz, DMSO-d_6) δ 3.95 (br, 2H), 3.67 (br, 1H), 2.90-2.80 (br, 1H), 2.80-2.70 (m, 1H), 2.68-2.60 (m, 1H), 2.25 (br, 1H), 1.95-1.85 (m, 1H), 1.82-1.52 (m, 3H), 1.40 (s, 9H).

[1668] **Intermediate 164:** *tert*-Butyl (5R,5aS,6S,9R)-2-chloro-1-fluoro-12-(methylthio)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



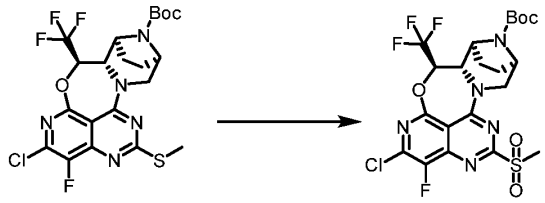
[1669] Step 1: *tert*-Butyl (1*S*,2*S*,5*R*)-2-((*R*)-1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)-2,2,2-trifluoroethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[1670] Under nitrogen, to a solution of *tert*-butyl (1*R*,2*S*,5*S*)-2-((*R*)-2,2,2-trifluoro-1-hydroxyethyl)-3,8-diazabicyclo [3.2.1]octane-8-carboxylate (460 mg, 1.5 mmol, intermediate 163) in tetrahydrofuran (10.0 mL) was added NaH (356 mg, 8.90 mmol, 60% in mineral oil) at 0 °C. The resulting solution was stirred for 30 min at room temperature. Then 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (621 mg, 2.22 mmol) was added at 0 °C. The solution was stirred overnight at room temperature. The mixture was quenched with NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford 1.10 g (crude) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 554.

[1671] Step 2: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(methylthi°)-5-(trifluoromethyl)-5a,6,7,8,9,10°hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

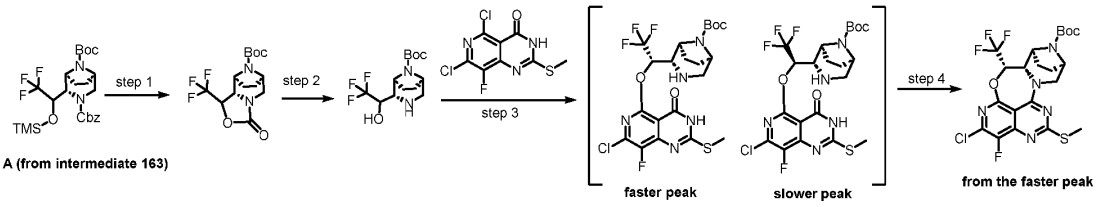
[1672] A solution of *tert*-butyl (1*S*,2*S*,5*R*)-2-((*R*)-1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)-2,2,2-trifluoroethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (0.70 g, 1.3 mmol), BOPCl (1.2 g, 5.06 mmol) and DIPEA (2.46 g, 19.0 mmol) in dichloromethane (15.0 mL) was stirred overnight at room temperature. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-25% EtOAc in petroleum ether) to afford 548 mg of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$= 536. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.74 – 5.69 (m, 1H), 5.24 (d, J = 13.3 Hz, 1H), 4.44 (d, J = 10.0 Hz, 1H), 4.31 (d, J = 18.1 Hz, 2H), 3.20 (d, J = 13.3 Hz, 1H), 2.58 (s, 3H), 1.89 (s, 4H), 1.46 (s, 9H).

[1673] **Intermediate 165:** *tert*-Butyl (5R,5aS,6S,9R)-2-chloro-1-fluoro-12-(methylsulfonyl)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[1674] Under nitrogen, to a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(methylthio°)-5-(trifluoromethyl)-5a,6,7,8,9,10°hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (80.0 mg, 0.150 mmol, intermediate 164) in ethyl acetate (2.0 mL) was added 3-chlorobenzoperoxoic acid (77.2 mg, 0.450 mmol) at 0 °C. The resulting solution was stirred for 1 h at room temperature. The solution was quenched with $Na_2S_2O_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc / petroleum ether) to afford 51.0 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 568.

[1675] **Intermediate 166:** *tert*-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-12-(methylthio)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab] heptalene-14-carboxylate



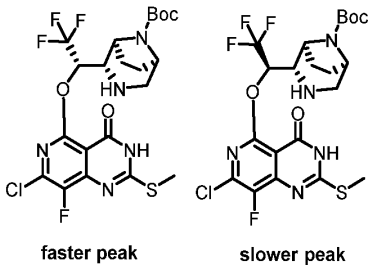
[1676] Step 1: *tert*-Butyl (6S,9R,9aS)-3-oxo-1-(trifluoromethyl)hexahydro-1H,3H-6,9-epiminooxazolo[3,4-a]azepine-10-carboxylate

[1677] To a solution of 3-benzyl 8-(*tert*-butyl) (1*R*,2*S*,5*S*)-2-(2,2,2-trifluoro-1-((trimethylsilyl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (2.00 g, 3.87 mmol, intermediate 163, step 3, compound A) in tetrahydrofuran (15.0 mL) was added tetrabutylammonium fluoride (3.90 mL, 1 M in THF) at room temperature. The resulting solution was stirred overnight at room temperature. The reaction system was diluted with EtOAc, washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-100% MeOH in water (0.05% NH_4HCO_3)) to afford 1.80 g (minor TBAF contaminant) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 337.

[1678] Step 2: *tert*-Butyl (1*R*,2*S*,5*S*)-2-(2,2,2-trifluoro-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[1679] A solution of *tert*-butyl (6*S*,9*R*,9a*S*)-3-oxo-1-(trifluoromethyl)hexahydro-1*H*,3*H*-6,9-epiminooxazolo[3,4-*a*]azepine-10-carboxylate (1.70 g, 5.05 mmol) and NaOH (2.01 g, 50.2 mmol) in ethanol (25.0 mL) and water (5.0 mL) was stirred for 1 h at 80 °C. Solid was filtered, and the filtrate was evaporated under vacuum to afford 850 mg (crude) the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 311. The crude was use for next step without further purification.

[1680] Step 3: *tert*-Butyl (1*S*,2*S*,5*R*)-2-((*S*)-1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)-2,2,2-trifluoroethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate **&** *tert*-butyl (1*S*,2*S*,5*R*)-2-((*R*)-1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)-2,2,2-trifluoroethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate



[1681] Under nitrogen, to a solution of *tert*-butyl (1*R*,2*S*,5*S*)-2-(2,2,2-trifluoro-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (0.30 g, 0.97 mmol) in tetrahydrofuran (10.0 mL) was added NaH (232 mg, 5.81 mmol, 60% in mineral oil) at 0 °C. The resulting solution was stirred for 30 min at 0 °C. Then 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (405 mg, 1.45 mmol) was added at 0 °C, and the mixture was stirred for 3 h at room temperature, the reaction was quenched with NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc / petroleum ether and then 10% MeOH / DCM) to afford 0.40 g of the **faster peak** (EtOAc / petroleum ether fraction) and 0.17 g of the **slower peak** (MeOH / DCM fraction) as yellow solids. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 554.

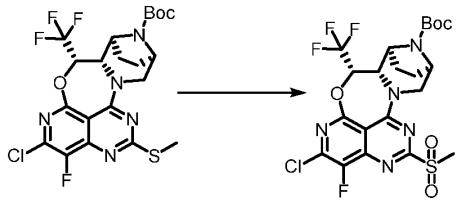
[1682] **Faster peak:** ^1H NMR (500 MHz, DMSO-d_6) δ 5.41 (s, 1H), 4.15 – 3.91 (m, 3H), 3.28 (s, 1H), 2.81 (s, 1H), 2.64 – 2.58 (m, 1H), 2.39 (d, *J* = 4.7 Hz, 3H), 1.75 – 1.64 (m, 4H), 1.43 (s, 9H).

[1683] **Slower peak:** ^1H NMR (3–0 MHz, DMSO-d_6) δ 6.06 - 5.63 (m, 1H), 4.13 – 3.94 (m, 3H), 3.17 (s, 2H), 2.87 – 2.75 (m, 1H), 2.59 (d, *J* = 2.7 Hz, 3H), 2.28 – 2.05 (m, 1H), 1.85 – 1.61 (m, 3H), 1.41 (d, *J* = 9.7 Hz, 9H).

[1684] Step 4: *tert*-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-12-(methylthio)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

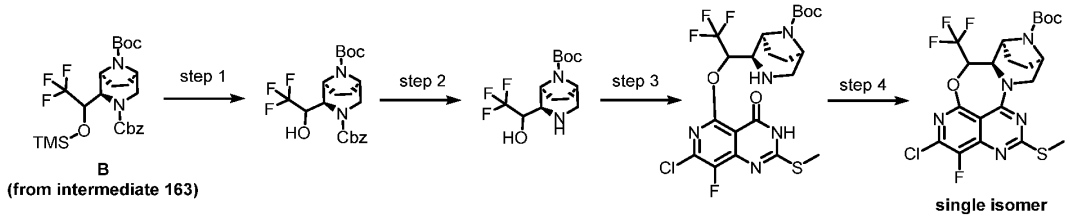
[1685] A solution of *tert*-butyl (1*S*,2*S*,5*R*)-2-((*S*)-1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)-2,2,2-trifluoroethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and *tert*-butyl (1*S*,2*S*,5*R*)-2-((*R*)-1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)-2,2,2-trifluoroethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (the faster peak of last step) (400 mg, 0.724 mmol), bis(2-oxooxazolidin-3-yl)phosphinic chloride (735 mg, 2.89 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (1.40 g, 10.8 mmol) in 1,2-dichloroethane (10.0 mL) was stirred for 8 h at 60 °C. The solid was filtered, and the filtrate was evaporated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc / petroleum ether) to afford 0.080 g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 536.

[1686] **Intermediate 167:** *tert*-Butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-12-(methylsulfonyl)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[1687] Under nitrogen, to a solution of *tert*-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-12-(methylthio)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (0.080 g, 0.15 mmol) in ethyl acetate (2.0 mL) was added 3-chlorobenzoperoxoic acid (77.2 mg, 0.450 mmol) at 0 °C. The resulting solution was stirred for 1 h at room temperature. The reaction was quenched with $Na_2S_2O_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc / petroleum ether) to afford 51.0 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 568.

[1688] **Intermediate 168:** *tert*-Butyl (5aR,6S,9R)-2-chloro-1-fluoro-12-(methylthio)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[1689] Step 1: 3-Benzyl 8-(*tert*-butyl) (1*R*,2*R*,5*S*)-2-(2,2,2-trifluoro-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (mixture of two isomers, ~1:15 by FNMR)

[1690] To a solution of 3-benzyl 8-(*tert*-butyl) (1*R*,2*R*,5*S*)-2-(2,2,2-trifluoro-1-((trimethylsilyl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (intermediate 163, step 3, compound B) (3.80 g, 7.36 mmol) in tetrahydrofuran (40.0 mL) was added tetrabutylammonium fluoride (7.4 mL, 1 M in THF) at room temperature. The solution was stirred overnight at room temperature. The reaction system was diluted with EtOAc and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude was purified by C18 column (solvent gradient: 0-100% MeOH in water (0.05% NH_4HCO_3)) to afford 2.4 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 445.

[1691] Step 2: *tert*-Butyl (1*R*,2*R*,5*S*)-2-(2,2,2-trifluoro-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[1692] Under hydrogen (1atm), to a solution of 3-benzyl 8-(*tert*-butyl) (1*R*,2*R*,5*S*)-2-(2,2,2-trifluoro-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-3,8-dicarboxylate (2.35 g, 5.29 mmol) in methyl alcohol (30.0 mL) was added Pd/C (522 mg, 10%). The resulting solution was stirred for 1 h at room temperature. The solid was filtered, and the filtrate was evaporated under vacuum to afford 1.6 g (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 311$.

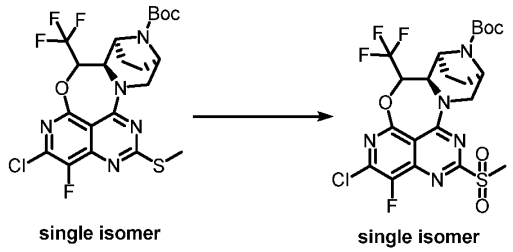
[1693] Step 3: *tert*-Butyl (1*S*,2*R*,5*R*)-2-(1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)-2,2,2-trifluoroethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[1694] Under nitrogen, to a solution of *tert*-butyl (1*R*,2*R*,5*S*)-2-(2,2,2-trifluoro-1-hydroxyethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.0 g, 3.2 mmol) in tetrahydrofuran (20.0 mL) was added NaH (774 mg, 19.4 mmol, 60% in mineral oil) at 0 °C. The resulting solution was stirred for 30 min at 0 °C. Then 5,7-dichloro-8-fluoro-2-(methylthio)pyrido [4,3-*d*]pyrimidin-4(3*H*)-one (1.35 g, 4.82 mmol) was added at 0 °C, and the mixture was stirred for 3 h at room temperature. The reaction system was quenched with NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH / DCM) to afford 1.5 g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 554$.

[1695] Step 4: *tert*-Butyl (5a*R*,6*S*,9*R*)-2-chloro-1-fluoro-12-(methylthio)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

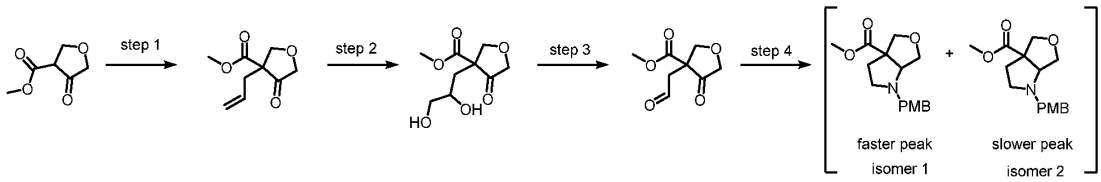
[1696] A solution of *tert*-butyl (1*S*,2*R*,5*R*)-2-(1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-*d*]pyrimidin-5-yl)oxy)-2,2,2-trifluoroethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.5 g, 2.7 mmol), bis(2-oxooxazolidin-3-yl)phosphinic chloride (2.76 g, 10.9 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (5.25 g, 40.7 mmol) in dichloromethane (30 mL) was stirred overnight at room temperature. The solvent was evaporated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc / petroleum ether) to afford 764 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 536$. Note: only one isomer was obtained.

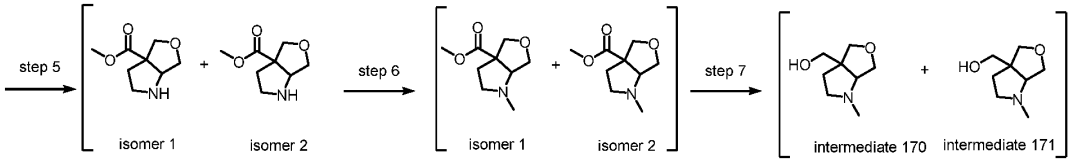
[1697] **Intermediate 169:** *tert*-Butyl (5aR,6S,9R)-2-chloro-1-fluoro-12-(methylsulfonyl)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab] heptalene-14-carboxylate



[1698] Under nitrogen, to a solution of tert-butyl (5aR,6S,9R)-2-chloro-1-fluoro-12-(methylthio)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab] heptalene-14-carboxylate (0.70 g, 1.3 mmol) in ethyl acetate (15 mL) was added 3-chlorobenzoperoxoic acid (679 mg, 3.93 mmol) at 0 °C. The resulting solution was stirred for 1 h at room temperature. The reaction was quenched with $Na_2S_2O_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc / petroleum ether) to afford 430 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 568.

[1699] **Intermediates 170 & 171:** (1-Methyltetrahydro-1*H*-furo[3,4-*b*]pyrrol-3a(4*H*)-yl)methanol (two isomers)





[1700] Step 1: Methyl 3-allyl-4-oxotetrahydrofuran-3-carboxylate

[1701] Under nitrogen, a mixture of methyl 4-oxotetrahydrofuran-3-carboxylate (25.0 g, 173 mmol), 3-bromoprop-1-ene (45.0 mL, 520 mmol) and K_2CO_3 (47.9 g, 347 mmol) in tetrahydrofuran (600 mL) was stirred overnight at 60 °C. The resulting mixture was filtered and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-60% ethyl acetate in petroleum ether) to afford the title compound (20.3 g, 63.5% yield) as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 185. ^1H NMR (400 MHz, DMSO-*d6*, ppm) δ 5.80 – 5.61 (m, 1H), 5.18 – 5.03 (m, 2H), 4.48 (d, J = 9.6 Hz, 1H), 4.16 – 3.95 (m,

3H), 3.67 (s, 3H), 2.69 – 2.56 (m, 1H), 2.48 – 2.37 (m, 1H). ^{13}C NMR (101 MHz, DMSO-*d6*, ppm) δ 210.45, 169.08, 132.80, 119.79, 73.40, 70.75, 59.20, 53.17, 36.08.

[1702] Step 2: Methyl 3-(2,3-dihydroxypropyl)-4-oxotetrahydrofuran-3-carboxylate

[1703] To a solution of methyl 3-allyl-4-oxotetrahydrofuran-3-carboxylate (5.00 g, 27.2 mmol) and NMO (6.36 g, 54.3 mmol) in acetone (40 mL) and water (5 mL) was added $K_2OsO_4.2H_2O$ (500 mg, 1.36 mmol) at 0 °C, and the mixture was stirred for 6 hours at room temperature. The reaction was quenched with solid $Na_2S_2O_3$. The resulting mixture was filtered and the filtrate was concentrated under vacuum to afford the title compound (6.50 g, crude) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 219.

[1704] Step 3: Methyl 4-oxo-3-(2-oxoethyl)tetrahydrofuran-3-carboxylate

[1705] To a mixture of methyl 3-(2,3-dihydroxypropyl)-4-oxotetrahydrofuran-3-carboxylate (6.50 g, crude) in acetone (54 mL) and water (6 mL) and was added $NaIO_4$ (8.82 g, 41.2 mmol) at 0 °C and stirred for 3 hours at 50 °C. The resulting mixture was filtered and the filtrate was concentrated under vacuum. The residue was re-dissolved in dichloromethane, dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound (4.20 g, crude) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 187.

[1706] Step4: Methyl 1-(4-methoxybenzyl)tetrahydro-1*H*-furo[3,4-*b*]pyrrole-3a(4*H*)-carboxylate (two isomers)

[1707] To a solution of methyl 4-oxo-3-(2-oxoethyl) tetrahydrofuran-3-carboxylate (2.00 g, crude) and (4-methoxyphenyl)methanamine (1.47 g, 10.7 mmol) in dichloromethane (10 mL) was added $NaBH_3CN$ (2.03 g, 32.2mmol) in portions at 0 °C and stirred for 1 hour at room temperature. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-60% ethyl acetate in petroleum ether) to afford a mixture of isomers (990 mg, 31.7% yield) as a colorless oil. Two isomers were separated by chiral prep. HPLC with the following conditions: (Column: CHIRALPAK IH, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.1% DEA) -H–C, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 70; Wave Length: 220/254 nm; RT1(min): 6.443; RT2(min): 8.6–; Sample Solvent: EtOH--HPLC; Injection Volume: 0.5 mL; Number Of Runs: 21) to afford **isomer 1** (340 mg, 10.9% yield, the faster peak) and **isomer 2** (300 mg, 9.60% yield, the slower peak) as colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 292.

[1708] Step 5: Methyl tetrahydro-1*H*-furo[3,4-*b*]pyrrole-3a(4*H*)-carboxylate (two isomers)

[1709] Under hydrogen, a mixture of methyl 1-(4-methoxybenzyl)tetrahydro-1*H*-furo[3,4-*b*]pyrrole-3a(4*H*)-carboxylate (340 mg, 1.16 mmol, **isomer 1 of last Step**) and 10%Pd/C (124.

mg, 0.120 mmol) in methanol (30 mL) was stirred overnight at room temperature. The resulting mixture was filtered over celite. The filtrate was concentrated under vacuum to afford the title compound (230 mg, crude) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 172.

[1710] Analogous to method described as above, **isomer 2** (200 mg, crude) was prepared from **isomer 2 of the last step** (300 mg, 1.03 mmol) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 172.

[1711] Step 6: Methyl 1-methyltetrahydro-1*H*-furo[3,4-*b*]pyrrole-3a(4*H*)-carboxylate (two isomers)

[1712] To a mixture of methyl tetrahydro-1*H*-furo[3,4-*b*]pyrrole-3a(4*H*)-carboxylate (100 mg, crude, **isomer 1 of last step**) and polyformaldehyde (87.2 mg, 0.968 mmol) in dichloromethane (5 mL) was added $NaBH(OAc)_3$ (618 mg, 2.92 mmol) in portions at 0 °C, and the mixture was stirred for 1 hour at room temperature. The reaction was quenched with $Na_2SO_4.10H_2O$ and filtered. The filtrate was concentrated under vacuum to afford the title compound (140 mg, crude) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 186.

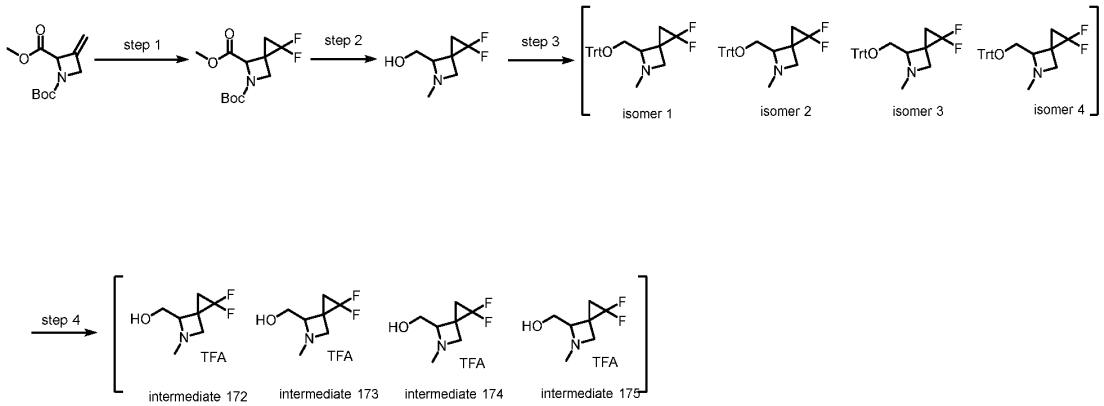
[1713] Analogous to the method described as above, **isomer 2** (150 mg, crude) was prepared from **isomer 2 of the last step** (100 mg, crude) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 186.

[1714] Step 7: (1-methyltetrahydro-1*H*-furo[3,4-*b*]pyrrol-3a(4*H*)-yl)methanol(two isomers)

[1715] To a solution of methyl-1-methyltetrahydro-1*H*-furo[3,4-*b*]pyrrole-3a(4*H*)-carboxylate (140 mg, crude, **isomer 1 of the last step**) in tetrahydrofuran (5 mL) was added $LiAlH_4$ (2.5M solution in tetrahydrofuran, 0.3 mL, 0.750 mmol) at 0 °C, and the mixture was stirred for 1 hour at room temperature. The reaction was quenched with $Na_2SO_4.10H_2O$ and filtered over celite. The filtrate was concentrated under vacuum to afford **intermediate 170** (90.0 mg, crude) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 158.

[1716] Analogous to the method described as above, **intermediate 171** (100 mg, crude) was prepared from **isomer 2 of the last step** (150 mg, crude) as a light yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 158.

[1717] **Intermediates 172, 173, 174, & 175:** (1,1-Difluoro-5-methyl-5-azaspiro[2.3] hexan-4-yl)methanol (4 isomers)



[1718] Step 1: 5-(*tert*-Butyl) 4-methyl 1,1-difluoro-5-azaspiro[2.3]hexane-4,5-dicarboxylate

[1719] A solution of 1-(*tert*-butyl) 2-methyl 3-methyleneazetidine-1,2-dicarboxylate (750 mg, 3.30 mmol), $TMSCF_3$ (1.88 g, 13.2 mmol) and NaI (248 mg, 1.65 mmol) in tetrahydrofuran (5.00 mL) was stirred for overnight at 70 °C. The reaction was cooled to room temperature, quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-40% EtOAc in petroleum ether) to afford 541 mg (59.1% yield) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 278$.

[1720] Step 2: (1,1-Difluoro-5-methyl-5-azaspiro[2.3]hexan-4-yl)methanol

[1721] Under nitrogen, to a solution of 5-(*tert*-butyl) 4-methyl 1,1-difluoro-5-azaspiro[2.3]hexane-4,5-dicarboxylate (541 mg, 1.95 mmol) in tetrahydrofuran (5.00 mL) was added $LiAlH_4$ (1.9 mL, 1M in THF) at 0 °C. The resulting solution was stirred for 2 h at 60 °C. The mixture was quenched by $Na_2SO_4.10H_2O$ and filtrated. The solvent was remove by blowing N_2 to afford 259 mg (81.3% yield) of the title compound as a yellow crude oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 164$.

[1722] Step 3: 1,1-Difluoro-5-methyl-4-((trityloxy)methyl)-5-azaspiro[2.3]hexane

[1723] To a solution of (1,1-difluoro-5-methyl-5-azaspiro[2.3]hexan-4-yl)methanol (259 mg, 1.59 mmol) and Et_3N (482 mg, 4.77 mmol) in dichloromethane (5.00 mL) was added (chloromethanetriyl)tribenzene (663 mg, 2.38 mmol). The resulting solution was stirred overnight at room temperature. The reaction was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc in petroleum ether) to afford 61.0 mg of the **faster peak** (mixture of two isomers) and 326 mg of the **slower peak** (mixture of two isomers) as yellow solids. The faster peak was separated by chiral prep. HPLC (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase – Hex(0.5% 2M NH_3-MeOH)--HP–, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min;

Gradient: isocratic 99; Wave Length: 220/254 nm; RT1(min): 5.907; RT2(min): 6.8–; Sample Solvent: EtOH--HPLC; Injection Volume: 0.3 mL; Number Of Runs: 24) to afford 20.0 mg (3.10% yield) of isomer 1 and 23 mg (3.60% yield) of isomer 2. The slower peak was separated by chiral prep. HPLC (Column: SB 2cm Hex(0.05% DEA): IPA=1000: 1; Mobil–Phase A: Hex(0.1% DEA)--H–C, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 1000: 1; Wave Length: 220/254 nm; RT1(min): 12.27; RT2(min): 16.–; Sample Solvent: EtOH--HPLC; Number Of Runs: 10) to afford 113 mg (17.6% yield) of isomer 3 and 105 mg (16.3% yield) of isomer 4.

[1724] **Isomer 1**: ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ 7.42 – 7.36 (m, 6H), 7.35 – 7.33 (m, 6H), 7.30 – 7.23 (m, 3H), 3.51 (s, 1H), 3.44 (d, J = 7.4 Hz, 1H), 3.15 (t, J = 9.0 Hz, 1H), 2.97 (t, J = 7.3 Hz, 1H), 2.90 – 2.83 (m, 1H), 2.53 (s, 3H), 1.47 – 1.42 (m, 2H).

[1725] **Isomer 2**: ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ 7.41 – 7.37 (m, 6H), 7.35 – 7.33 (m, 6H), 7.30 – 7.23 (m, 3H), 3.51 (s, 1H), 3.44 (d, J = 7.4 Hz, 1H), 3.15 (t, J = 9.0 Hz, 1H), 2.97 (t, J = 7.3 Hz, 1H), 2.90 – 2.84 (m, 1H), 2.53 (s, 3H), 1.47 – 1.42 (m, 2H).

[1726] **Isomer 3**: ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ 7.40 – 7.32 (m, 12H), 7.32 – 7.24 (m, 3H), 3.39 (t, J = 6.0 Hz, 1H), 3.35 – 3.29 (m, 1H), 3.16 – 3.12 (m, 1H), 3.08 (d, J = 7.6 Hz, 1H), 2.84 – 2.81 (m, 1H), 2.36 (s, 3H), 1.40 – 1.33 (m, 2H).

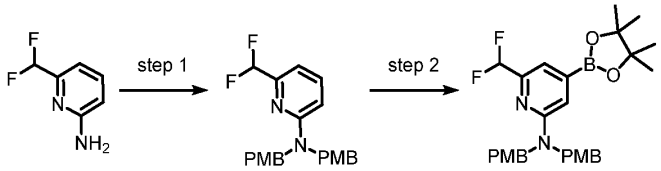
[1727] **Isomer 4**: ^{1}H NMR (500 MHz, DMSO-d_6, ppm) δ 7.40 – 7.32 (m, 12H), 7.32 – 7.24 (m, 3H), 3.39 (t, J = 6.1 Hz, 1H), 3.34 (s, 1H), 3.16 – 3.12 (m, 1H), 3.08 (d, J = 7.6 Hz, 1H), 2.84 – 2.81 (m, 1H), 2.36 (s, 3H), 1.42 – 1.29 (m, 2H).

[1728] Step 4: (1,1-Difluoro-5-methyl-5-azaspiro[2.3]hexan-4-yl)methanol

[1729] To a solution of 1,1-difluoro-5-methyl-4-((trityloxy)methyl)-5-azaspiro[2.3]hexane (20.0 mg, 0.0500 mmol) (isomer 1 of step 3) in dichloromethane (1.50 mL) was added TFA (0.500 mL). The resulting solution was stirred for 1 h at room temperature. Solvent was evaporated under vacuum to afford 44.0 mg (crude) **intermediate 172** as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 164. The crude was used for next step without further purification.

[1730] Analogous to the method described above, **intermediates 173, 174, and 175** were prepared from isomers 2, 3, and 4, respectively, of step 3.

[1731] **Intermediate 176**: 6-(Difluoromethyl)-*N,N-bis*(4-methoxybenzyl)-4-(4,4,5,5-tetramethyl-dioxaborolan-2-yl)pyridin-2-amine



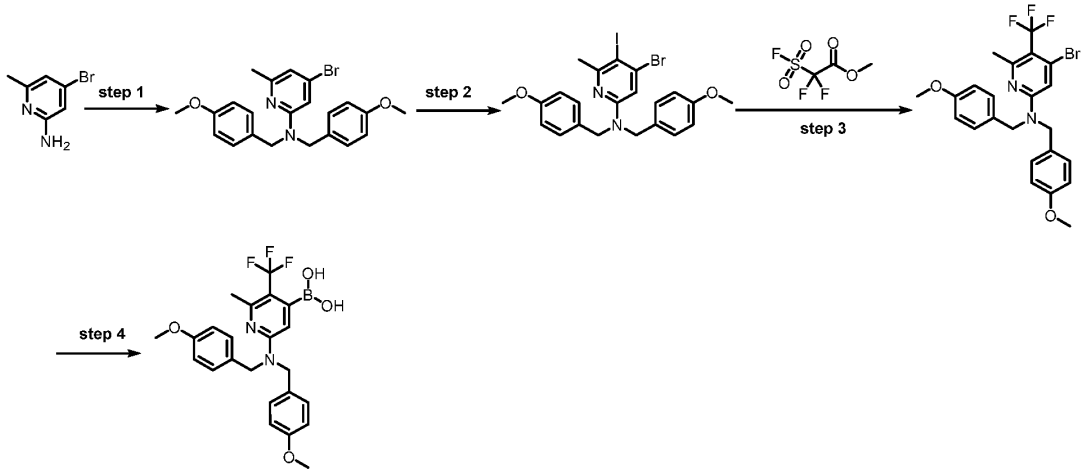
[1732] Step 1: 6-(Difluoromethyl)-*N,N-bis*(4-methoxybenzyl)pyridin-2-amine

[1733] To a solution of 6-(difluoromethyl)pyridin-2-amine (200 mg, 1.39 mmol) in *N,N*-dimethylformamide (8 mL) was added NaH (60% dispersion in mineral oil, 278 mg, 6.94 mmol) in portions at 0 °C and stirred for 30 minutes at room temperature. Then PMBCl (541 mg, 3.47 mmol) was added and stirred for 2 hours at room temperature. The reaction was quenched with saturated NH_4Cl aqueous solution. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (500 mg, 93.7% yield) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 385$.

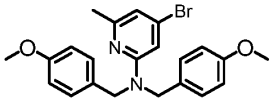
[1734] Step 2: 6-(Difluoromethyl)-*N,N-bis*(4-methoxybenzyl)-4-(4,4,5,5-tetramethyl-dioxaborolan-2-yl)pyridin-2-amine

[1735] Under nitrogen, a solution of Pin_2B_2 '661 mg, 2.60 mmol)' 4,4'-di-*tert*-butyl-2,2'-bipyridine (69.8 mg, 0.260 mmol) and methoxy(cyclooctadiene)iridium(I) dimer (86.2 mg, 0.130 mmol) in hexane (30 mL) was stirred for 10 minutes at 50 °C to afford a dark-red solution. Then a suspension of 6-(difluoromethyl)-*N,N-bis*(4-methoxybenzyl)pyridin-2-amine (500 mg, 1.3 mmol) in hexane (10 mL) was added, and the mixture was stirred for 3 hours at 50 °C. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (370 mg, 55.7% yield) as a colorless oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 511$. ^1H NMR (300 MHz, DMSO-*d6*, ppm) δ 7.23 – 7.12 (m, 4H), 7.02 (s, 1H), 6.98 – 6.55 (m, 6H), 4.70 (s, 4H), 3.72 (s, 6H), 1.26 (s, 12H).

Intermediate 177: (6-(Bis(4-methoxybenzyl) amino)-2-methyl-3-(trifluoromethyl) pyridin-4-yl) boronic acid

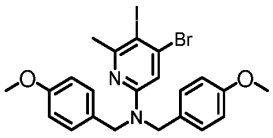


[1736] Step 1: 4-Bromo-*N*, *N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine



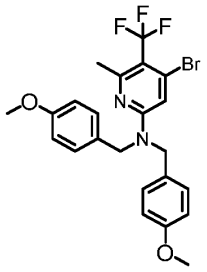
[1737] Under nitrogen, to a solution of 4-bromo-6-methylpyridin-2-amine (1.0 g, 5.35mmol) was added NaH (535mg, 13.4mmol, 60% oil suspension) at 0 °C. The mixture was stirred for 20 min. PMBCl (1.85g, 11.8mmol) was added and the mixture was allowed to warm to room temperature and stirred additional 1 hour. The reaction was quenched with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (2.20g, 94.7% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 427.

[1738] Step 2: 4-Bromo-5-iodo-*N*, *N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine



[1739] A solution of 4-bromo-*N*, *N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (2.10 g, 4.91 mmol) and NIS (1.11 g, 4.91 mmol) in acetic acid (20mL) was stirred at room temperature for 30 min. The reaction was quenched by water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (2.60g, 89% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 553.

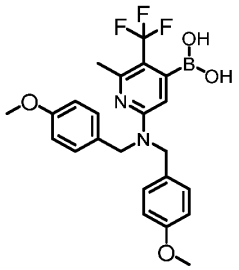
[1740] Step 3: 4-Bromo-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine



[1741] Under nitrogen, a solution of 4-bromo-5-iodo-*N*, *N*-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (2.58 g, 4.66 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl) acetate (5.94 mL, 46.6 mmol) and CuI (8.86 g, 46.6 mmol) in *N*, *N*-dimethylacetamide (25mL) was stirred at 90 °C for 1 hour. The solution was cooled to room temperature. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was diluted with

EtOAc, washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (1.92 g, 71% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 495$.

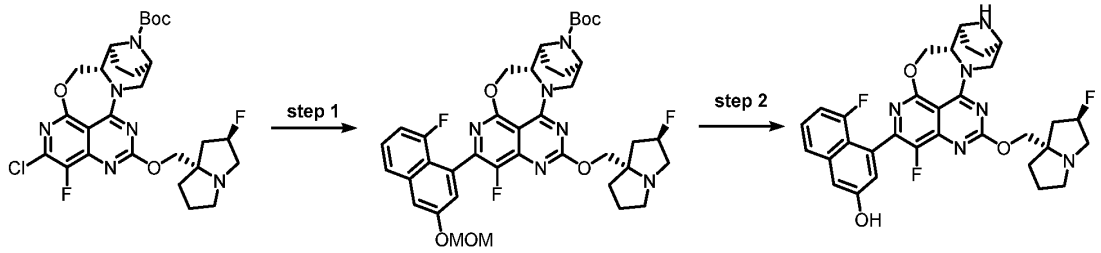
[1742] Step 4: (6-(Bis(4-methoxybenzyl) amino)-2-methyl-3-(trifluoromethyl) pyridin-4-yl) boronic acid



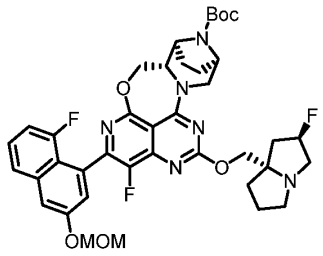
Under nitrogen, to a solution of 4-bromo-*N*, *N*-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl) pyridin-2-amine (1.83 g, 3.69 mmol) and triisopropyl borate (1.28 mL, 5.54 mmol) in tetrahydrofuran (20mL) was added a solution of *n*-BuLi (2.77 mL, 1.6 M in hexane) at -78 °C, and the mixture was stirred at -78 °C for 1 hour. The reaction was quenched with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-40% EtOAc in petroleum ether) to afford the title compound (562mg, 31.3% yield) as a white oil. LC-MS: (ESI, m/z): $[M+H]^+ = 461$.

[1743] COMPOUNDS

[1744] **Example 1:** Compound 1

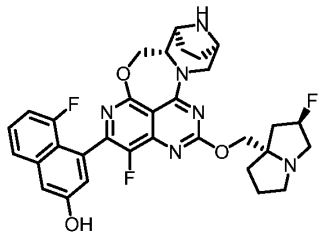


[1745] Step 1: *tert*-Butyl (5a*S*,6*S*,9*R*)-1-fluoro-2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



[1746] Under nitrogen, a solution of *tert*-butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (40.6 mg, 0.0700 mmol, **intermediate 9**), $Pd(PPh_3)_4$ (39.5 mg, 0.0300 mmol), 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (34.1 mg, 0.100 mmol, **intermediate 25**), Cs_2CO_3 (66.9 mg, 0.210 mmol) and H_2O (0.5 mL) in 1.4-dioxane (5 mL) was stirred for 1.5 h at 95°C. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL*2). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with CH_3OH/DCM (0-10%) to afford the title compound (40.6 mg,77.7 %) as white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 750.

[1747] Step 2: 5-Fluoro-4-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol (Compound 1)



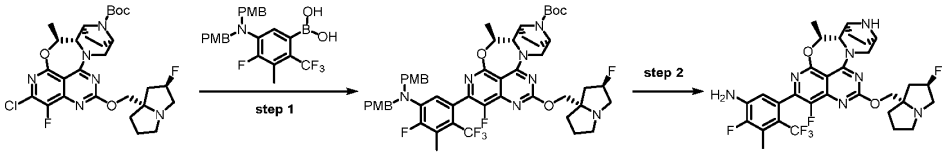
[1748] A solution of *tert*-butyl (5a*S*,6*S*,9*R*)-1-fluoro-2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (40.6 mg, 0.0542mmol) in TFA (1mL) and DCM (4mL) was stirred at room temperature for 1.5 hours and then concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate:60 mL/min; Gradient:14 B to 48 B in 7 min; 254 nm; R_{T1}:6.7) to afford the title compound 12.3 mg (37.5 % yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 604. ^1H NMR (400 MHz, DMSO-d_6, ppm) δ 10.18 (s, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.49 – 7.30 (m, 2H), 7.22 – 6.86 (m, 2H), 5.50

– 5.08 (m, 1H), 4.86- 4.76 (m, 1H), 4.53 (d, *J* = 13.0 Hz, 1H), 4.46 – 4.34 (m, 1H), 4.16 - 4.06 (m, 1H), 4.05 – 3.95 (m, 2H), 3.61 (d, *J* = 5.9 Hz, 1H), 3.55 – 3.49 (m, 1H), 3.16 – 2.99 (m, 4H), 2.88 – 2.89 (m, 2H), 2.17 – 2.10 (m, 1H), 2.11 – 1.94 (m, 2H), 1.93 – 1.49 (m, 7H).

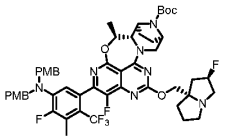
[1749] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Example **1**.

Cmpd. No.	^{1}H NMR	MS (M+H)$^+$
2	^{1}H NMR (300 MHz, DMSO-*d*$_6$, ppm) δ 8.21 – 8.14 (m, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.76 – 7.48 (m, 4H), 5.28 (d, *J* = 54.3 Hz, 1H), 4.84 (d, *J* = 13.2 Hz, 1H), 4.58 – 4.31(m, 2H), 4.16 – 3.96 (m, 3H), 3.68 - 3.58 (m, 2H), 3.16 – 3.01 (m, 4H), 2.83-2.77 (m, 2H), 2.15 (d, *J* = 5.5 Hz, 1H), 2.07 – 1.92 (m, 2H), 1.92 – 1.50 (m, 7H).	606
3	^{1}H NMR (400 MHz, DMSO-*d*$_6$, ppm) δ 10.12 (s, 1H), 7.87 – 7.85 (m, 1H), 7.45 – 7.42 (m, 2H), 7.31 (s, 1H), 7.08 (dd, *J* = 39.0, 2.6 Hz, 1H), 5.56 – 5.09 (m, 1H), 4.94 – 4.73 (m, 1H), 4.59 – 4.46 (m, 1H), 4.48 – 4.34 (m, 1H), 4.09 (dd, *J* = 10.3, 5.6 Hz, 1H), 4.04 – 3.94 (m, 2H), 3.74 (d, *J* = 46.7 Hz, 1H), 3.61 (d, *J* = 5.9 Hz, 1H), 3.51 (d, *J* = 5.9 Hz, 1H), 3.16 – 2.99 (m, 4H), 2.86 – 2.81 (m, 2H), 2.09 – 1.92 (m, 3H), 1.83 – 1.51 (m, 7H).	611
4	^{1}H NMR (300 MHz, DMSO-*d*$_6$, *ppm*): δ 8.16 (d, J = 2.8 Hz, 1H), 7.95 (dd, J = 8.8, 5.2 Hz, 1H), 7.24 – 7.11 (m, 1H), 5.27 (d, J = 54 Hz, 1H), 4.82 (dd, J = 12.9, 2.2 Hz, 1H), 4.51-4.35 (m, 2H), 4.21 – 4.17 (m, 1H), 4.01 (d, J = 10.3 Hz, 2H), 3.78-3.69 (m, 3H), 3.51 – 3.59 (m, 3H), 3.15-3.01 (m, 3H), 2.98-2.93 (m, 1H), 2.82 (q, J = 8.5, 8.0 Hz, 1H), 2.13 (s, 1H), 2.06 – 1.92 (m, 2H), 1.92– 1.66 (m, 7H).	593
5	^{1}H NMR (300 MHz, DMSO-*d*$_6$, *ppm*): δ 9.89 (s, 1H), 7.65 (d, J = 9 Hz, 1H), 7.42 – 7.31 (m, 1H), 7.26 (t, J = 2.5 Hz, 1H), 7.13 (t, J = 9 Hz, 1H), 7.00 (d, J = 2.6 Hz, 1H), 6.89 (d, J = 2.6 Hz, 1H), 5.38 (s, 1H), 5.20 (s, 1H), 4.78 - 4.28 (m, 2H), 4.14 - 4.01 (m, 3H), 3.63 (s, 2H), 3.12 - 3.01 (m, 4H), 2.90 – 2.77 (m, 1H), 2.46 – 2.33 (m, 1H), 2.32 - 2.18 (m, 2H), 2.08 - 1.98 (m, 2H), 1.94-1.65 (m, 7H), 0.92 - 0.83 (m, 3H).	615

[1750] **Example 6:** Compound 6

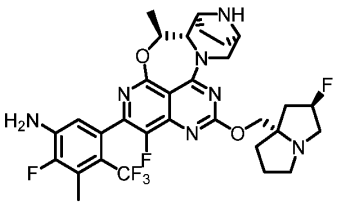


[1751] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



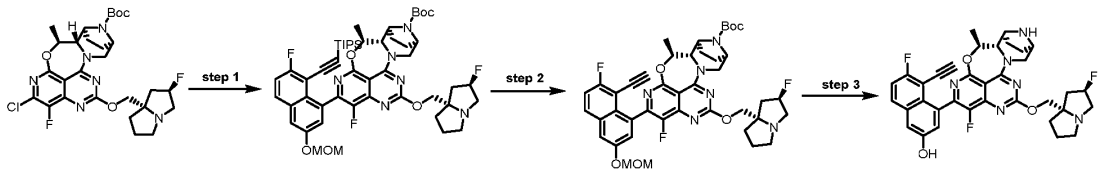
[1752] Under nitrogen, a solution of (5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (161 mg, 0.338 mmol, **intermediate 20**), tert-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (80.2 mg, 0.131 mmol, **intermediate 12**), K_3PO_4 (1.6 mL, 1.5 M in water) and cataCXium A Pd G3 (19.9 mg, 0.0300 mmol) in THF (8 mL) was stirred for 6 hours at 60°C. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with MeOH/DCM (0-10%) to yield 130 mg (77.9% yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 990.

[1753] Step 2: 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (Compound 6)

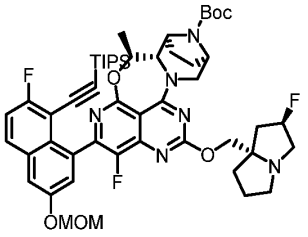


[1754] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (130 mg, 0.130 mmol) in TFA (4 mL) was stirred at 50 °C for 3 hours and then concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 59% B in 10 min, 59% B; Wave Length: 254/220 nm; R_{T1}(min): 7.35) to yield 29.1 mg (33.4% yield) of the title compound as a light yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 650. ^1H NMR (300 MHz, DMSO-d_6) δ 6.59 (d, *J* = 3.0 Hz, 1H), 6.02 (s, 2H), 5.28 (d, *J* = 55.5 Hz, 1H), 5.08 (d, *J* = 12.6 Hz, 1H), 4.51 (t, *J* = 7.6 Hz, 1H), 4.10 – 3.93 (m, 3H), 3.56 (s, 1H), 3.44 (d, *J* = 4.8 Hz, 1H), 3.08 – 2.99 (m, 4H), 2.88 – 2.81 (m, 1H), 2.31 (s, 3H), 2.13 (s, 1H), 2.07 – 1.94 (m, 2H), 1.85-1.76 (m, 4H), 1.70 – 1.50 (m, 3H), 1.42 (d, *J* = 6.2 Hz, 3H).

[1755] **Example 7:** Compound 7

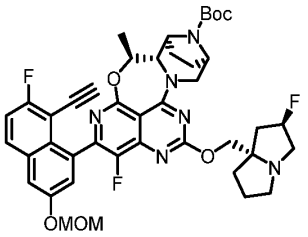


[1756] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



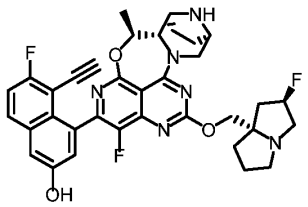
[1757] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (280 mg, 0.470 mmol, **intermediate 12**), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (363 mg, 0.710 mmol, **intermediate 43**), cataCXium A Pd G3 (68.9 mg, 0.0900 mmol) and K_3PO_4 (0.6 mL, 1.5 M in H_2O) in THF (5 mL) was stirred for 3 h at 60°C. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-7% MeOH / DCM) to afford 315 mg (70.7% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 943$.

[1758] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



[1759] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (315 mg, 0.334 mmol) and CsF (257 mg, 1.69 mmol) in DMF (3 mL) was stirred at room temperature for 1 hour. The resulting solution was diluted with EtOAc and washed with water. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the title compound (320 mg, crude) as a yellow solid which was used for next step without further purification. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 787.

[1760] Step 3: 5-Ethynyl-6-fluoro-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol (Compound 7)



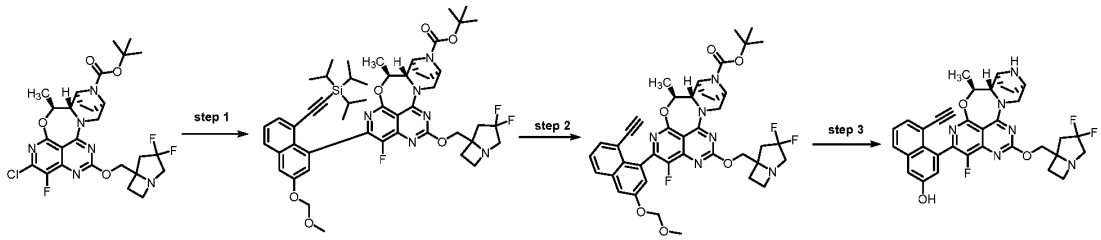
[1761] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (311 mg, 0.390 mmol) and HCl/1,4 -dioxane (1.0 mL, 4 M) in ACN (3 mL) was stirred at 0°C for 2 hours. The reaction mixture was adjusted to pH ~ 8 with solid $NaHCO_3$. The solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by C18 column (solvent gradient: 0-70% CH_3OH in water (0.05% NH_4HCO_3)) to afford 116.1 mg (45.9% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 643. ^1H NMR (300 MHz, DMSO-d_6, ppm): δ 10.13 (s, 1H), 8.01-7.97 (m, 1H), 7.49-7.43 (m, 1H), 7.37 (s, 1H), 7.19 (d, J = 2.5 Hz, 1H), 5.38 (s, 1H), 5.23 – 5.09 (m, 1H), 4.48-4.41 (m, 1H), 4.25 (d, J = 1.1 Hz, 1H), 4.14-4.09 (m, 1H), 4.04 – 3.93 (m, 2H), 3.60 (s, 1H), 3.46 (s, 1H), 3.15-3.09 (m, 2H), 3.05-2.85 (m, 2H), 2.95-2.83 (m, 1H), 2.15 (s, 1H), 2.03-1.98 (m, 2H), 1.96-1.77 (m, 5H), 1.69-1.57 (m, 3H), 1.53 – 1.41 (m, 3H).

[1762] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Examples **6** and **7**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
8	^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 8.22 – 8.14 (m, 1H), 8.13 – 8.04 (m, 1H), 7.76 – 7.47 (m, 4H), 5.43 – 5.05 (m, 2H), 4.64 – 4.64 (m, 1H), 4.17 – 3.91 (m, 3H), 3.65 – 3.41 (m, 2H), 3.19 – 2.93 (m, 4H), 2.91 – 2.75 (m, 1H), 2.24 – 1.92 (m, 3H), 1.92 – 1.34 (m, 5H).	619
9	^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 10.22 (s, 1H), 7.65 (dd, J = 8.4, 4.9 Hz, 1H), 7.47- 7.38 (m, 1H), 7.36 – 7.31 (m, 1H), 7.21 – 6.91 (m, 2H), 5.28 (d, J = 54.2 Hz, 1H), 5.10 (d, J = 12.6 Hz, 1H), 4.63 – 4.48 (m, 1H), 4.11 (dd, J = 10.3, 2.6 Hz, 1H), 4.05 – 3.93 (m, 2H), 3.58 (d, J = 5.6 Hz, 1H), 3.45 (d, J = 6.1 Hz, 1H), 3.15 – 3.02 (m, 3H), 3.01 (s, 1H), 2.92 – 2.74 (m, 2H), 2.21 – 2.08 (m, 1H), 2.15 – 2.01 (m, 2H), 1.81 (dd, J = 22.8, 11.2 Hz, 4H), 1.69 – 1.63 (m, 1H), 1.63 – 1.52 (m, 2H), 1.44 (dd, J = 6.4, 2.7 Hz, 3H).	
10	^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 9.95 – 9.79 (m, 1H), 7.70 – 7.58 (m, 1H), 7.42 – 7.28 (m, 1H), 7.27 – 7.20 (m, 1H), 7.18 – 7.04 (m, 1H), 7.03 – 6.78 (m, 1H), 5.45 – 5.00 (m, 2H), 4.64 – 4.39 (m, 1H), 4.10 (d, J = 10.4 Hz, 1H), 4.05 – 3.90 (m, 2H), 3.63 – 3.40 (m, 2H), 3.16 – 2.94 (m, 4H), 2.89 – 2.74 (m, 1H), 2.46 – 2.34 (m, 1H), 2.32 – 2.09 (m, 2H), 2.07 – 1.92 (m, 2H), 1.91 – 1.73 (m, 4H), 1.72 – 1.49 (m, 3H), 1.46 – 1.35 (m, 3H), 1.22 (s, 1H), 1.00 – 0.89 (m, 1H), 0.86 – 0.71 (m, 2H).	629
11	^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 10.11 (s, 1H), 7.93 – 7.82 (m, 1H), 7.52 – 7.36 (m, 2H), 7.35 – 7.25 (m, 1H), 7.16 – 6.95 (m, 1H), 5.39 – 5.08 (m, 2H), 4.56 – 4.39 (m, 1H), 4.16 – 4.04 (m, 1H), 4.03 – 3.93 (m, 2H), 3.90 (s, 1H), 3.67 – 3.55 (m, 2H), 3.53 – 3.44 (m, 1H), 3.16 – 2.95 (m, 4H), 2.88 – 2.78 (m, 1H), 2.19 – 1.94 (m, 3H), 1.90 – 1.51 (m, 7H), 1.49 – 1.37 (m, 3H).	625
12	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.97 (t, J = 7.8 Hz, 1H), 6.86 (dd, J = 8.2, 1.8 Hz, 1H), 6.71-6.63 (m, 1H), 5.56-5.27 (m, 3H), 5.07 (dd, J = 12.9, 2.5 Hz, 1H), 4.52 (dd, J = 8.4, 6.1 Hz, 1H), 4.10 (d, J = 10.3 Hz, 1H), 4.00 (d, J = 10.3 Hz, 1H), 3.93 (dd, J = 8.8, 1.4 Hz, 1H), 3.55 (s, 1H), 3.43 (d, J = 5.7 Hz, 1H), 3.18 – 3.00 (m, 4H),2.88 – 2.77 (m, 1H), 2.18 – 2.01 (m, 3H),1.88 – 1.72 (m, 4H), 1.79 -1.61 (m, 3H), 1.43 (d, J = 6.3 Hz, 3H).	568
13	^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 7.19 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 6.4 Hz, 1H), 5.37 – 5.19 (m, 3H), 5.00 – 4.89 (m, 1H), 4.54 – 4.49 (m, 1H), 4.00 (d, J = 10.3 Hz, 1H), 3.89 (d, J = 10.3 Hz, 1H), 3.81 (d, J = 8.6 Hz, 1H), 3.44 (s, 1H), 3.34 (d, J = 5.4 Hz, 1H), 2.99 (d, J = 6.2 Hz, 2H), 2.88 (d, J = 9.2 Hz, 2H), 2.72 (d, J = 7.6 Hz, 1H), 2.12 (d, J = 2.1 Hz, 3H), 2.04 (d, J = 5.9 Hz, 1H), 1.91 (d, J = 12.5 Hz, 2H), 1.80 – 1.73 (m, 4H), 1.50 (d, J = 14.3 Hz, 3H), 1.34 (d, J = 6.3 Hz, 3H).	582
14	^{1}H NMR (300 MHz, DMSO-d_6, *ppm*): δ 7.45 (d, J = 12.0 Hz, 1H), 6.76 (d, J = 8.6 Hz, 1H), 6.09 (s, 2H), 5.36- 5.18 (s, 1H), 5.07 (dd, J = 12.8, 2.6 Hz, 1H), 4.52 (dd, J = 8.7, 6.3 Hz, 1H), 4.08 (d, J = 10.4 Hz, 1H), 4.03 – 3.90 (m, 2H), 3.56 (s, 1H), 3.44 (d, J = 5.8 Hz, 1H), 3.17 – 2.96 (m, 4H), 2.86 – 2.74 (m, 1H), 2.14 (d, J = 4.5 Hz, 1H), 2.11-1.91 (m, 2H), 1.90 – 1.71 (m, 4H), 1.72 – 1.50 (m, 3H), 1.42 (d, J = 6.3 Hz, 3H).	636
15	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.67 – 6.48 (m, 3H), 5.37 – 5.19 (m, 1H), 5.10 – 5.01 (m, 1H), 4.58 – 4.46 (m, 1H), 4.11 – 3.95 (m, 3H), 3.60 – 3.51 (m, 1H), 3.49 – 3.41 (m, 1H), 3.12 – 2.94 (m, 4H), 2.87 – 2.68 (m, 2H), 2.16 – 1.90 (m, 3H), 1.88 – 1.70 (m, 4H), 1.68 – 1.50 (m, 3H), 1.43 (d, J = 6.3 Hz, 3H)	654

16	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.57 (s, 1H), 6.41 – 6.16 (m, 1H), 5.86 (s, 2H), 5.41 – 5.16 (m, 1H), 5.08 (d, J = 11.4 Hz, 1H), 4.57 – 4.44 (m, 1H), 4.13 – 3.86 (m, 3H), 3.61 – 3.53 (m, 1H), 3.48 – 3.39 (m, 1H), 3.16 – 2.93 (m, 4H), 2.88 – 2.68 (m, 2H), 2.33 (s, 3H), 2.19 – 1.90 (m, 3H), 1.89 – 1.71 (m, 4H), 1.69 – 1.49 (m, 3H), 1.43 (d, J = 6.3 Hz, 3H).	632
17	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.55 (d, J = 14.4 Hz, 1H), 6.45 – 6.30 (m, 3H), 5.41 – 5.29 (m, 1H), 5.12 – 5.03 (m, 1H), 4.60 – 4.47 (m, 1H), 4.14 – 3.92 (m, 3H), 3.62 – 3.52 (m, 1H), 3.50 – 3.42 (m, 1H), 3.17 – 3.06 (m, 2H), 3.05 – 2.97 (m, 2H), 2.89 – 2.77 (m, 1H), 2.19 – 2.11 (m, 1H), 2.08 – 1.94 (m, 2H), 1.90 – 1.73 (m, 4H), 1.71 – 1.51 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H).	636
18	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.53 – 6.30 (m, 1H), 5.45 – 5.15 (m, 3H), 5.15 – 5.00 (m, 1H), 4.60 – 4.47 (m, 1H), 4.11 (d, J = 10.2 Hz, 1H), 4.05 – 3.87 (m, 2H), 3.61 – 3.55 (m, 1H), 3.50 – 3.41 (m, 1H), 3.13 – 3.05 (m, 4H), 2.92 – 2.67 (m, 2H), 2.32 – 2.11 (m, 4H), 2.07 –2.02 (m, 2H), 1.89 – 1.71 (m, 4H), 1.70 – 1.57 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H).	600

[1763] **Example 19:** Compound 19



[1764] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-2-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1765] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (150 mg, 0.250 mmol, **intermediate 13, the faster peak**), triisopropyl((6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane (311 mg, 0.630 mmol, **intermediate 26**), cataCXium A Pd G3 (36.6 mg, 0.0500 mmol) and K_3PO_4 (0.5mL, 1.5M in water) in THF (2.5 mL) was stirred at 60°C overnight. The solid was filtered off and the filtrate was concentrated under vacuum. The residue was purified by reverse phase chromatography (gradient: 0–80% ACN in water (0.05% NH_4HCO_3)) to afford 215 mg, (92.1% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ =929.

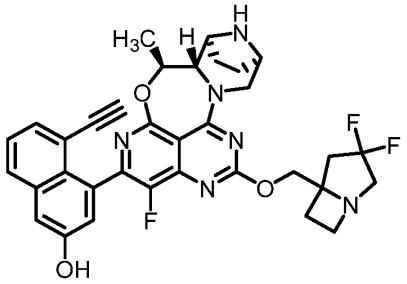
[1766] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-2-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1767] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-2-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (215 mg, 0.230 mmol) and CsF (341 mg, 2.24 mmol) in DMF (2 mL) was stirred at room temperature for 1.5 h. The resulting reaction mixture was purified directly by reverse phase chromatography (gradient: 0-80% ACN in water (0.05% NH_4HCO_3)) to afford 181 mg, (96.2% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 773.

[1768] Step 3: 4-((5*S*,5a*S*,6*S*,9*R*)-12-((3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-ethynylnaphthalen-2-ol (Compound 19)

[1769] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-2-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (170 mg, 0.220 mmol) in HCl/1,4 -dioxane (0.8 mL, 4M) and ACN (2.5 mL) was stirred at 0°C for 1 h and then concentrated under vacuum at 0°C. The crude product was purified by reverse phase chromatography (gradient: 0-50% ACN in water (0.05% NH_4HCO_3)) to afford 83.1 mg (59.1% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 629. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 10.09 (s, 1H), 7.90 – 7.81 (m, 1H), 7.51 – 7.36 (m, 2H), 7.30 (d, J = 2.6 Hz, 1H), 7.16 – 6.95 (m, 1H), 5.14 (d, J = 12.7 Hz, 1H), 4.57 – 4.40 (m, 1H), 4.39 – 4.24 (m, 2H), 4.01 – 3.92 (m, 1H), 3.75 (d, J = 87.3 Hz, 1H), 3.59 – 3.41 (m, 3H), 3.27 – 2.76 (m, 5H), 2.74 – 2.52 (m, 1H), 2.46 – 2.23 (m, 3H), 1.92 – 1.49 (m, 4H), 1.43 (t, J = 6.0 Hz, 3H).

[1770] **Example 20:** Compound 20



[1771] Analogous to the method described for **Example 19**, 84.4 mg **Example 20** were prepared from *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (150 mg, 0.250 mmol, **intermediate 13, the slower peak**). LC-MS: (ESI, *m/z*): $[M+H]^+$= 629. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 10.10 (s, 1H), 7.91 – 7.81 (m, 1H), 7.51 – 7.35 (m, 2H), 7.31 (d, J = 2.6 Hz, 1H), 7.15 – 6.97 (m, 1H),

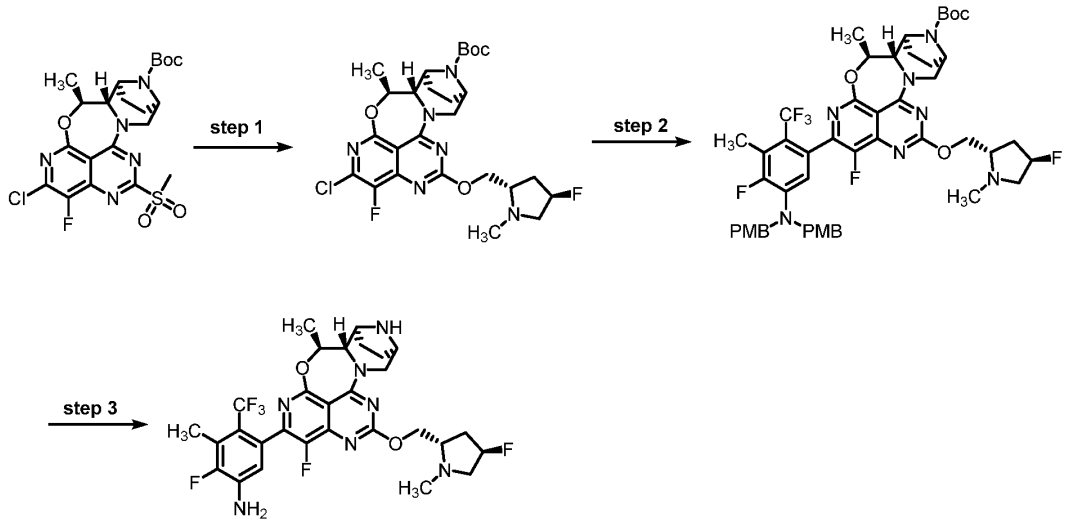
5.21 – 5.10 (m, 1H), 4.58 – 4.41 (m, 1H), 4.40 – 4.22 (m, 2H), 3.98 (d, J = 8.7 Hz, 1H), 3.90 – 3.59 (m, 2H), 3.59 – 3.42 (m, 2H), 3.27 – 2.97 (m, 4H), 2.74 – 2.52 (m, 1H), 2.46 – 2.23 (m, 3H), 1.95 – 1.50 (m, 4H), 1.43 (t, J = 6.0 Hz, 3H).

[1772] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Examples **19** and **20**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
21 (Isomer 1)	^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 8.23 – 8.14 (m, 1H), 8.12 – 8.04 (m, 1H), 7.76 – 7.47 (m, 4H), 5.21 – 5.08 (m, 1H), 4.65 – 4.47 (m, 1H), 4.39 (d, J = 10.9 Hz, 1H), 4.35 – 4.26 (m, 1H), 3.99 (t, J = 8.0 Hz, 1H), 3.65 – 3.43 (m, 3H), 3.22 (d, J = 8.5 Hz, 1H), 3.14 (s, 1H), 3.12 – 3.00 (m, 2H), 2.75 – 2.57 (m, 1H), 2.47 – 2.24 (m, 3H), 1.93 – 1.79 (m, 1H), 1.78 – 1.52 (m, 3H), 1.44 (t, J = 6.7 Hz, 3H), 1.23 (s, 1H).	623
21 (Isomer 2)	^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 8.23 – 8.14 (m, 1H), 8.12 – 8.05 (m, 1H), 7.77 – 7.47 (m, 4H), 5.22 (d, J = 13.5 Hz, 1H), 4.75 – 4.57 (m, 1H), 4.45 – 4.28 (m, 2H), 4.26 – 4.15 (m, 1H), 3.94 (s, 1H), 3.85 – 3.72 (m, 1H), 3.54 (s, 1H), 3.28 – 2.99 (m, 4H), 2.75 – 2.54 (m, 1H), 2.48 – 2.24 (m, 3H), 2.05 – 1.62 (m, 4H), 1.46 (t, J = 6.5 Hz, 3H), 1.23 (s, 1H).	623
22	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.29 – 8.14 (m, 2H), 7.74 – 7.50 (m, 3H), 5.21 – 5.11 (m, 1H), 4.51 (dd, J = 9.1, 6.4 Hz, 1H), 4.51 – 4.24 (m, 2H), 4.08 (t, J = 1.3 Hz, 1H), 3.98 (d, J = 8.8 Hz, 1H), 3.71-3.58 (m, 2H), 3.47 (s, 1H), 3.23 (d, J = 8.7 Hz, 1H), 3.19 (dd, J = 22.5, 15.5 Hz, 1H), 2.98-2.78 (m, 2H),2.72-2.61 (m, 2H),2.43 – 2.30 (m, 3H), 1.85 (d, J = 10.1 Hz, 1H), 1.68 – 1.59 (m, 3H), 1.45 (t, J = 6.8 Hz, 3H).	630
23	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.69 (dd, J = 8.2, 2.2 Hz, 1H), 6.46 (dd, J = 5.7, 2.2 Hz, 1H), 5.20 (s, 2H), 5.11 (dd, J = 12.9, 2.5 Hz, 1H), 4.54 (dd, J = 8.5, 6.2 Hz, 1H), 4.40 (d, *J* = 11.0 Hz, 2H), 4.32 (d, J = 11.0 Hz, 1H), 3.96 (dd, J = 8.7, 1.4 Hz, 2H), 3.49 – 3.16 (m, 2H), 3.10 – 2.98 (m, 2H), 2.79 (s, 1H), 2.74 – 2.53 (m, 1H), 2.51 – 2.35 (m, 2H), 2.31-2.29(m, 1H), 2.21 (s, 3H), 1.82 (s, 1H), 1.60 (dd, J = 23.7, 8.2 Hz, 3H), 1.46 (d, J = 6.3 Hz, 3H).	586
23	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.69 (dd, J = 8.3, 2.2 Hz, 1H), 6.46 (dd, J = 5.7, 2.2 Hz, 1H), 5.20 (s, 2H), 5.11 (dd, J = 12.8, 2.5 Hz, 1H), 4.62 – 4.47 (m, 1H), 4.40 (d, J = 11.0 Hz, 1H), 4.31 (d, J = 11.1 Hz, 1H), 3.96 (dd, J = 8.8, 1.4 Hz, 1H), 3.56 (dd, J = 5.4, 4.2 Hz, 2H), 3.49 – 3.41 (m, 1H), 3.30 – 3.18 (m, 2H), 3.12 – 2.98 (m, 2H), 2.78 (s, 1H), 2.74 – 2.52 (m, 1H), 2.50 – 2.27 (m, 2H), 2.25 (s, 1H), 2.2-2.1 (m, 3H),1.85-1.74 (m, 1H), 1.60 (dd, J = 23.7, 8.2 Hz, 3H), 1.46 (d, J = 6.3 Hz, 3H).	586
24	^{1}H NMR (300 MHz, DMSO-d6, ppm) δ 8.25 (s, 1H), 6.60 (d, J = 6.0 Hz, 1H), 6.01 (s, 2H), 5.09 (d, J = 12.6 Hz, 1H), 4.53 (s, 1H), 4.36 – 4.29 (m, 2H), 3.96 (d, J = 8.6 Hz, 1H), 3.61 – 3.44 (m, 3H), 3.28 – 3.03 (d, J = 14.3 Hz, 4H), 2.71 – 2.50 (m, 1H), 2.48 – 2.32 (m, 2H), 2.30 (s, 4H), 1.81 (s, 1H), 1.63 (s, 3H), 1.42 (d, J = 6.3 Hz, 3H)	654

25	^{1}H NMR (400 MHz, DMSO-*d6*, *ppm*): δ 9.95 (s, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.43 (t, J = 8.1 Hz, 1H), 7.29 – 7.20 (m, 2H), 7.18 (d, J = 2.5 Hz, 1H), 5.14 (dd, J = 12 Hz, J =4 Hz, 1H), 4.66 – 4.54 (m, 1H), 4.43 – 4.22 (m, 2H), 3.99 (d, J = 8.7 Hz, 1H), 3.59 (m, 3H), 3.23 (d, J = 8.8 Hz, 1H), 3.14 (m, 1H), 3.11 – 3.02 (m, 2H), 2.65 (m, 1H), 2.46 – 2.33 (m, 3H), 1.84 (m 1H), 1.67 (m, 3H), 1.46 (d, J = 6.3 Hz, 3H).	605

[1773] **Example 26:** Compound 26



[1774] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1775] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (100 mg, 0.190 mmol, **intermediate 11**) and ((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methanol (31.1 mg, 0.230 mmol, **intermediate 35**) in toluene (1 mL) was added *t*-BuONa (37.4 mg, 0.390 mmol) at 0°C. The reaction was stirred at room temperature for 1 hour. Water was added and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0–4% MeOH in DCM) to afford 112 mg (85.7% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 567.

[1776] Step 2: *tert*-Butyl (5S,5aS,6S,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1777] Under nitrogen, a mixture of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (25.3 mg, 0.0400 mmol), (5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (50.0 mg, 0.105mmol, **intermediate 20**), K_3PO_4 (1.5 M in H_2O, 0.2 mL) and cataCXium A Pd G3 (6.5mg, 0.0100mmol) in tetrahydrofuran (1mL) was stirred at 60°C for 1 hour. Water was added and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-100% EtOAc/petroleum ether) to afford 12 mg (23.8% yield) of the title compound as a brown solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 965.

[1778] Step 3: 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (Compound 26)

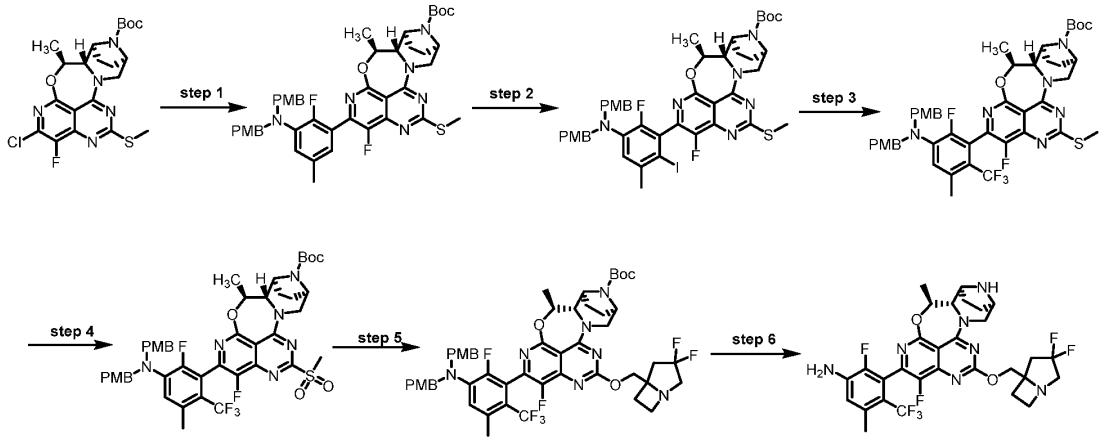
[1779] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (12.0 mg, 0.0100 mmol) in 2,2,2-trifluoroacetic acid (1 mL) was stirred at 50°C for 1 hour. Concentrated under reduced pressure. The residue was purified by Prep-HPLC (XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A:Water(10mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:31% B to 53% B in 8 min; 53% B; Wavelength: 254/220 nm; R_T(min): 8) to yield 2.5 mg (32.2% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 624. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.54 (m, 1H), 6.02 (s, 2H), 5.32 – 5.07 (m, 2H), 4.54 (m, 1H), 4.44 (m, 1H), 4.29 (m, 1H), 3.95 (m, 1H), 3.59 – 3.50 (m, 1H), 3.49 – 3.36 (m, 2H), 3.03 (m, 1H), 2.93 (m, 1H), 2.77 (s, 1H), 2.41 (s, 3H), 2.32 (s, 3H), 2.22 – 1.92 (m, 2H), 1.92 – 1.75 (m, 2H), 1.59 (m, 3H), 1.44 (m, 3H).

[1780] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Example **26**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
27	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 8.22 – 8.15 (m, 1H), 8.12 – 8.05 (m, 1H), 7.76 – 7.47 (m, 4H), 5.13 (d, J = 12.7 Hz, 1H), 4.54 (dd, J = 13.8, 7.7, 6.8 Hz, 1H), 4.23 – 4.12 (m, 2H), 3.98 (t, J = 8.9 Hz, 1H), 3.59 (s, 1H), 3.45 (d, J = 6.1 Hz, 1H), 3.15 – 3.00 (m, 3H), 2.81 (s, 1H), 2.72 (d, J = 12.0 Hz, 1H), 2.13 (d, J = 11.7 Hz, 1H), 2.09 (d, J = 5.5 Hz, 1H), 1.91 (d, J = 13.1 Hz, 1H), 1.82 (s, 2H), 1.67 – 1.55 (m, 6H), 1.44-1.26 (m, 4H).	663

28	^{1}H NMR (300 MHz, DMSO-d6, ppm) δ 9.88 (s, 1H), 7.63 – 7.63 (m, 1H), 7.37 – 7.32 (m, 1H), 7.26 – 7.24 (m, 1H), 7.18 – 7.04 (m, 1H), 7.00 (d, J = 2.6 Hz, 1H), 5.16 – 5.11 (m, 1H), 4.66 (d, J = 2.8 Hz, 2H), 4.54 – 4.51 (m, 2H), 3.96 (t, J = 8.3 Hz, 1H), 3.60 (s, 3H), 3.44 (s, 1H), 3.04 (t, J = 11.1 Hz, 1H), 2.84 (s, 1H), 2.39 (t, J = 7.4 Hz, 1H), 2.32 – 2.04 (m, 1H), 1.83 (d, J = 4.8 Hz, 3H), 1.73 – 1.61 (m, 3H), 1.60 (s, 2H), 1.56 – 1.36 (m, 3H), 0.94 (t, J = 7.4 Hz, 1H), 0.77 (t, J = 7.4 Hz, 2H).	585
29	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.61 (s, 1H), 6.02 (s, 2H), 5.69 (s, 1H), 5.51 (s, 1H), 5.11 (d, J = 11.2 Hz, 1H), 4.54 (s, 1H), 4.36 (d, J = 11.0 Hz, 1H), 4.13 (d, J = 10.9 Hz, 1H), 3.65 (m, 2H), 3.45 (d, J = 5.7 Hz, 1H), 3.05-3.01 (m, 3H), 2.99 – 2.84 (m, 2H), 2.45 – 2.40 (m, 1H), 2.36-2.29 (m, 4H), 2.28 – 2.06 (m, 1H), 1.88-1.77 (m, 1H), 1.75-1.63 (m, 3H), 1.44 (dd, J = 6.3 Hz, 3H).	636
30	^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 9.46 (s, 1H), 8.61 (d, J = 1.1 Hz, 1H), 8.30 – 8.23 (m, 1H), 7.90 – 7.71 (m, 3H), 5.21 – 5.07 (m, 1H), 4.68 – 4.54 (m, 1H), 4.27 – 4.14 (m, 2H), 4.00 (d, J = 8.8 Hz, 1H), 3.60 (s, 1H), 3.53 – 3.43 (m, 1H), 3.17 – 2.97 (m, 3H), 2.84 (s, 1H), 2.73 (d, J = 11.9 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.18 – 2.05 (m, 1H), 2.05 – 1.96 (m, 1H), 1.96 – 1.88 (m, 1H), 1.88 – 1.54 (m, 8H), 1.53 – 1.42 (m, 4H).	630
31	^{1}H NMR (400 MHz, DMSO-d_6) 6.60 (m, 1H), 6.46 (s, 2H), 5.09 (m, 1H), 4.53 (m, 1H), 4.40 (m, 1H), 4.13 (m, 1H), 3.97 (m, 1H), 3.61 (m. 6H), 3.50 (m, 5H), 2.32 (s, 3H), 2.14 – 2.01 (m, 1H), 1.84 – 1.69 (m, 6H), 1.44 (d, *J* = 6.3 Hz, 3H), 1.31 (m, 1H).	648
32	^{1}H NMR (300 MHz, DMSO-d_6) δ 7.99 – 7.90 (m, 1H), 7.85 – 7.73 (m, 1H), 7.65 – 7.51 (m, 4H), 7.46 (d, *J* = 8.1 Hz, 2H), 6.68 – 6.40 (m, 1H), 6.01 (s, 2H), 5.16 – 5.00 (m, 1H), 4.59 – 4.45 (m, 3H), 4.28 – 4.18 (m, 1H), 4.11 – 4.00 (m, 2H), 3.97 – 3.87 (m, 1H), 3.60 – 3.54 (m, 1H), 3.50 – 3.41 (m, 1H), 3.20 – 3.12 (m, 1H), 3.08 – 2.95 (m, 2H), 2.90 – 2.77 (m, 2H), 2.30 (s, 3H), 2.25 – 2.14 (m, 1H), 1.97 – 1.70 (m, 6H), 1.70-1.51 (m, 3H), 1.42 (d, *J* = 6.3 Hz, 3H).	839

[1781] **Example 33**: Compound 33



[1782] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(*bis*(4-methoxybenzyl)amino)-2-fluoro-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1783] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-

methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (300 mg, 0.620 mmol, **intermediate 10**), 2-fluoro-*N*,*N*-*bis*(4-methoxybenzyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilineand (612 mg, 0.124 mmol, **intermediate19**), K_3PO_4 (0.5 mL, 1.5 M in H_2O) and cataCXium A Pd G3 (90.8 mg, 0.120 mmol) in THF (2.5 mL) was stirred for 3 h at 60°C. The resulting solution was partitioned between water and EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-80% ACN in water (0.05% NH_4HCO_3)) to afford 219 mg (43.4% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 811.

[1784] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1785] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(*bis*(4-methoxybenzyl)amino)-2-fluoro-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (206 mg, 0.250 mmol) in AcOH (2.5 mL) was added NIS (63.9 mg, 0.280 mmol). The solution was stirred at room temperature for 1.5 hours, quenched with $Na_2S_2O_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-40% EtOAc / petroleum ether) to afford 203 mg (85.3% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 937.

[1786] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(*bis*(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1787] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (195 mg, 0.210 mmol), $Cu(O_2CCF_2SO_2F)_2$ (1.30 g, 3.12 mmol) and Cu powder (200 mg, 3.14 mmol) was stirred for 30 min at 90°C. The resulting mixture was cooled to room, diluted with EtOAc (30 mL), washed with water. The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-40% EtOAc /petroleum ether) to afford 149 mg (81.4% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 879.

[1788] Step 4: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-

hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1789] Under nitrogen, a solution of *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(*bis*(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (129 mg, 0.150 mmol) and m-CPBA (76.1 mg, 0.440 mmol) in EtOAc (3 mL) was stirred for 3 h at room temperature. The reaction was quenched with saturated aq. $NaHCO_3$, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-50% EtOAc/petroleum ether) to afford 120 mg (89.8% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 911$.

[1790] Step 5: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1791] Under nitrogen, to a solution of *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (101 mg, 0.110 mmol) and ((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methanol (21.0 mg, 0.130 mmol, **intermediate 6**) in PhMe (2.5 mL) was added t-BuONa (21.0 mg, 0.220 mmol) at 0 °C. The resulting solution was stirred for 1 h at room temperature. The resulting solution was added water (10 mL), extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-7% MeOH/DCM) to afford 88.0 mg (80.6% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 994$.

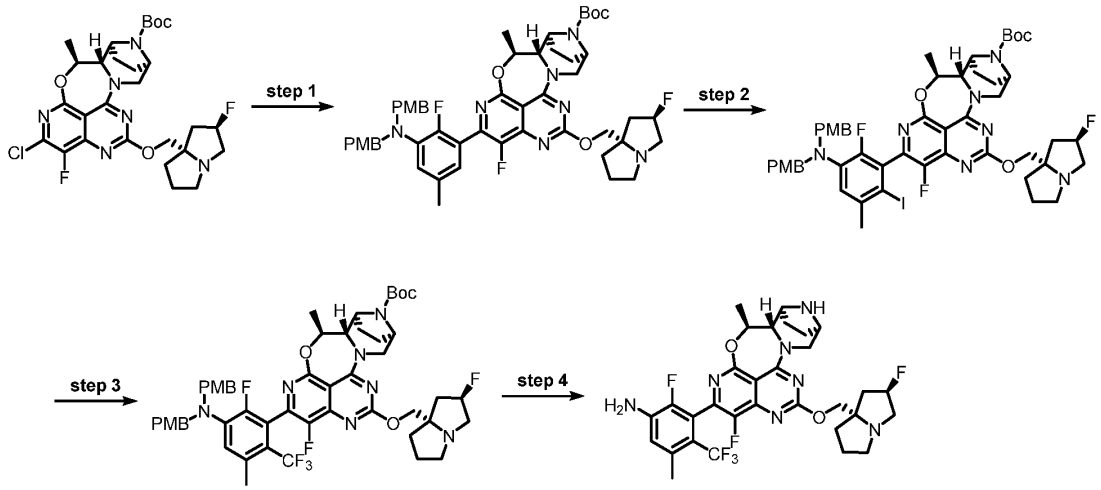
[1792] Step 6: 3-((5*S*,5a*S*,6*S*,9*R*)-12-((3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-5-methyl-4-(trifluoromethyl)aniline (Compound 33)

[1793] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (88.0 mg, 0.0900 mmol) in TFA (2.5 mL) was stirred at 50 °C for 3.5 hours. The solvent was concentrated under vacuum. The residue was

purified by C18 column (solvent gradient: 0-90% ACN in water (0.05% NH_4HCO_3)) to yield 23.5 mg (40.6% yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 654. ^1H NMR (300 MHz, DMSO-d_6, ppm): δ 6.82 (d, J = 8.8 Hz, 1H), 5.99 (d, J = 11.6 Hz, 2H), 5.19 – 5.07 (m, 1H), 4.69-4.58 (m, 1H), 4.45 – 4.31 (m, 2H), 4.00 (t, J = 8.1 Hz, 1H), 3.72-3.63 (m, 1H), 3.53 (d, J = 5.9, 5.3 Hz, 2H), 3.23 -3.07 (m, 4H), 2.73 – 2.52 (m, 1H), 2.50 – 2.24 (m, 6H),1.85 (s, 1H), 1.72-1.67 (m, 3H), 1.57-1.44 (m, 3H)

[1794] This compound was evaluated as a mixture of diastereomers.

[1795] **Example 34:** Compound 34



[1796] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1797] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (410 mg, 0.690 mmol, **intermediate 12**), 2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (680 mg, 1.39 mmol, **intermediate 19**), K_3PO_4 aqueous (0.5 mL, 1.5 M in H_2O) and cata CXium A Pd G3 (102 mg, 0.140 mmol) in THF (2.5 mL) was stirred for 3 h at 60 °C. The resulting solution was cooled to room temperature, diluted with water (10 mL), and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% MeOH/DCM) to afford 383 mg (59.7% yield) of the title compound as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 922.

[1798] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1799] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (371 mg, 0.400 mmol) and NIS (90.7 mg, 0.400 mmol) in acetic acid (2.5 mL) was stirred at room temperature for 2 hours. The resulting solution was quenched with aq. $Na_2S_2O_3$, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-9% MeOH/DCM) to afford 144 mg (34.2% yield) of the title compound as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1048.

[1800] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1801] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (133 mg, 0.130 mmol), $Cu(O_2CCF_2SO_2F)_2$ (794 mg, 1.90 mmol) and Cu (123 mg, 1.92 mmol) in DMF (2.5 mL) was stirred for 30 min at 90°C. The resulting solution was cooled to room temperature, diluted with EtOAc and washed with water. The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase chromatography (solvent gradient: 0-100% MeOH in water (0.05% NH_4HCO_3)) to yield 86.0 mg (68.4% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 990.

[1802] Step 4: 2-Fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline (Compound 34)

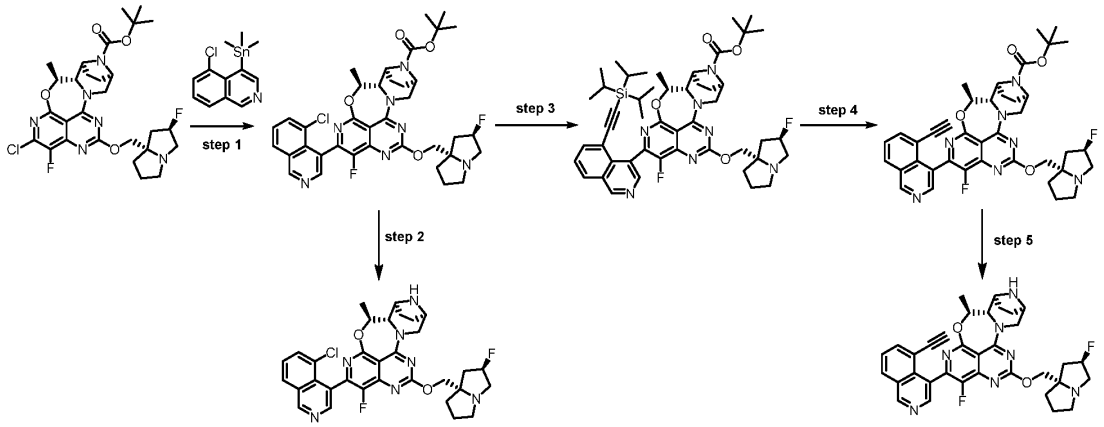
[1803] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (72.1 mg, 0.0729 mmol) in TFA (3.5 mL) was

stirred at 50°C for 4 hours and then concentrated under vacuum. The residue was purified by reverse phase chromatography (solvent gradient: 0-40% MeOH in water (0.1% FA)) to yield 1.2 mg (2.5 % yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 650. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 8.22 (s, 2H), 6.79 (d, J = 8.8 Hz, 1H), 5.97 (d, J = 11.3 Hz, 2H), 5.36 (s, 1H), 5.18-5.05 (m, 1H), 4.60 – 4.47 (m, 1H), 4.09 (dd, J = 10.3, 4.7 Hz, 1H), 4.05 – 3.90 (m, 1H), 3.59 (s, 1H), 3.46 (s, 1H), 3.12 – 3.02 (m, 4H), 2.99 (s, 1H), 2.35-2.31 (m, 3H), 2.13 (s, 1H), 2.00 (d, J = 16.1 Hz, 2H), 1.88-1.46 (m, 7H), 1.42 (d, J = 6.3 Hz, 3H).

[1804] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Example **34**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
35	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 7.37 (dd, J = 8.7, 5.7 Hz, 1H), 6.96 (t, J = 8.6 Hz, 1H), 6.10 (d, J = 9.8 Hz, 2H), 5.38 (s, 1H), 5.16-5.03 (m, 1H), 4.56 (s, 2H), 4.17 – 3.96 (m, 3H), 3.50 (s, 2H), 3.12-3.05 (m, 3H), 3.01 – 2.93 (m, 1H), 2.91 – 2.83 (m, 1H),2.29 – 2.23 (m, 1H),2.01 (s, 2H), 1.93 – 1.73 (m, 4H), 1.65 – 1.52 (m, 3H), 1.59 – 1.42 (m, 3H).	636
36	^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 6.82 (d, *J* = 8.8 Hz, 1H), 6.01 (d, *J* = 8.6 Hz, 2H), 5.41 (d, *J* = 54.4 Hz, 1H), 5.14 - 4.99 (m, 1H), 4.72 - 4.54 (m, 2H), 4.44 – 4.11 (m, 5H), 3.57 - 3.47 (m, 1H), 3.46 - 3.35 (m, 3H), 3.03 (s, 2H), 2.34 (m, 3H), 2.25 – 2.11 (m, 2H), 2.07 – 1.75 (m, 8H).	636

[1805] **Example 38 and 39:** Compounds 38 and 39



[1806] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-chloroisoquinolin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1807] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (150 mg, 0.250 mmol, **intermediate 12**), 5-chloro-4-(trimethylstannyl)isoquinoline (301 mg, 0.920 mmol, **intermediate 21**), BINAP (31.6 mg, 0.0500 mmol), CuI (14.4 mg, 0.0800

mmol) and $Pd(dppf)Cl_2$ (19.5 mg, 0.0300 mmol) in toluene (2 mL) was stirred at 90°C overnight. The resulting reaction mixture was extracted with EtOAc (20 mL), washed with water (2*20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase chromatography (gradient: 0-100% ACN in water (0.1% FA)) to afford 145 mg (79.5% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ =720.

[1808] Step 2: (5*S*,5a*S*,6*S*,9*R*)-2-(5-Chloroisoquinolin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene (Compound 38)

[1809] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-chloroisoquinolin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (20.0 mg, 0.0300 mmol) in HCl/1,4-dioxane (0.3 mL, 4M) and ACN (1 mL) was stirred at 0°C for 1.5 h. Then the mixture was concentrated under vacuum at 0°C. The residue was adjusted to pH~8 with $NaHCO_3$ (aq.) and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by reverse phase chromatography (gradient: 0-80% ACN in water (0.05% NH_4HCO_3)) to afford 7.4 mg, (42.3% yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 620. ^1H NMR (400 MHz, DMSO-d_6, *ppm*) δ 9.53 (d, J = 3.6 Hz, 1H), 8.50 (d, J = 36.9 Hz, 1H), 8.33 – 8.26 (m, 1H), 7.97 – 7.88 (m, 1H), 7.80 – 7.70 (m, 1H), 5.41 – 5.03 (m, 2H), 4.64 – 4.44 (m, 1H), 4.09 (d, J = 10.3 Hz, 1H), 4.05 – 3.90 (m, 2H), 3.70 – 3.53 (m, 1H), 3.51 – 3.41 (m, 1H), 3.16 – 2.91 (m, 4H), 2.89 – 2.75 (m, 1H), 2.22 – 2.09 (m, 1H), 2.08 – 1.92 (m, 2H), 1.90 – 1.50 (m, 7H), 1.43 (t, J = 5.7 Hz, 3H).

[1810] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-2-(5-((triisopropylsilyl)ethynyl)isoquinolin-4-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1811] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-chloroisoquinolin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (110 mg, 0.150 mmol, **from step 1**), ethynyltriisopropylsilane (139 mg, 0.760 mmol), $Pd(CH_3CN)_2Cl_2$ (7.90 mg, 0.0300 mmol), X-Phos (43.8 mg, 0.0900 mmol) and Cs_2CO_3 (99.7 mg, 0.310 mmol) in ACN (2mL) was stirred at 95°C overnight, then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-18%

MeOH / DCM) to afford 40.0 mg (30.2% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ =866.

[1812] Step 4: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-ethynylisoquinolin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1813] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-2-(5-((triisopropylsilyl)ethynyl)isoquinolin-4-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (37.1 mg, 0.0400 mmol) and CsF (64.9 mg, 0.424 mmol) in DMF (1.5 mL) was stirred at room temperature for 1 h. The reaction mixture was purified directly by reverse phase chromatography (gradient: 0-80% ACN in water (0.05% NH_4HCO_3)) to afford the title compound 29.2 mg (74.4% yield) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 710.

[1814] Step 5: (5*S*,5a*S*,6*S*,9*R*)-2-(5-Ethynylisoquinolin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene (Compound 39)

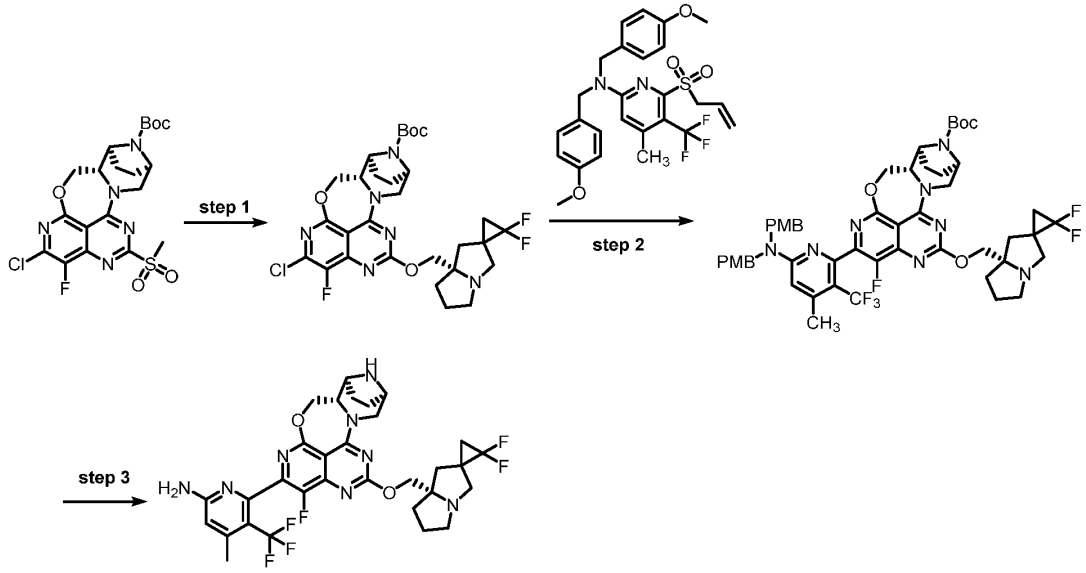
[1815] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-ethynylisoquinolin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (21.3mg, 0.0300mmol) in HCl/1,4-dioxane (0.5 mL, 4M) and ACN (1.5 mL) was stirred at 0°C for 1.5 h. Then the mixture was concentrated under vacuum at 0°C. The mixture was adjusted to pH ~ 8 with $NaHCO_3$ (aq.) and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum.The crude product was purified by reverse phase chromatography (gradient: 0-50% ACN in water (0.05% NH_4HCO_3)) to afford 7.9 mg (42.7% yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 610. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 9.49 (s, 1H), 8.49 (d, J = 29.7 Hz, 1H), 8.36 – 8.28 (m, 1H), 8.03 – 7.92 (m, 1H), 7.84 – 7.70 (m, 1H), 5.46 – 5.00 (m, 2H), 4.61 – 4.37 (m, 1H), 4.16 – 3.80 (m, 4H), 3.58 (s, 1H), 3.45 (s, 1H), 3.25 – 2.94 (m, 4H), 2.90 – 2.69 (m, 1H), 2.21 – 2.10 (m, 1H), 2.09 – 1.92 (m, 2H), 1.91 – 1.50 (m, 7H), 1.43 (t, J = 6.1 Hz, 3H).

[1816] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Examples **38** and **39**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
40	^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 9.49 (s, 1H), 8.49 (d, J = 29.7 Hz, 1H), 8.37 – 8.29 (m, 1H), 8.04 – 7.91 (m, 1H), 7.80 – 7.68 (m, 1H), 5.24 – 5.13 (m, 1H), 4.64 – 4.43 (m, 1H), 4.17 (d, J = 2.8 Hz, 3H), 4.12 – 3.84 (m, 1H), 3.80 (s, 1H), 3.70 – 3.61 (m, 1H), 3.22 – 2.96 (m, 3H), 2.77 – 2.67 (m, 1H), 2.60 – 2.52 (m, 1H), 2.14 – 1.49 (m, 12H), 1.48 – 1.37 (m, 3H).	654

41	^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 7.62 (d, J = 8.4 Hz, 1H), 7.53 – 7.39 (m, 2H), 7.12 – 7.03 (m, 1H), 6.76 (s, 1H), 6.09 (s, 2H), 5.45 – 5.04 (m, 2H), 4.64 – 4.47 (m, 1H), 4.13 (d, J = 10.3 Hz, 1H), 4.04 - 3.91 (m, 2H), 3.64 – 3.42 (m, 2H), 3.11 -3.05 (m, 3H), 3.02 (d, J = 5.5 Hz, 1H), 2.92 – 2.81 (m, 1H), 2.16 (d, J = 5.4 Hz, 1H), 2.07 – 1.95 (m, 2H), 1.93 – 1.74 (m, 4H), 1.73 - 1.48 (m, 3H), 1.45 (d, J = 6.3 Hz, 3H).	601

[1817] **Example 42:** Compound 42



[1818] Step 1: *tert*-Butyl (5a*S*,6*S*,9*R*)-2-chloro-12-(((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1819] To a solution of ((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol (163 mg, 0.800 mmol, **intermediate 33**), *tert*-butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (201 mg, 0.400 mmol, **intermediate 8**) in toluene (2 mL) was added t-BuONa (77.1 mg, 0.800 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, water (20 mL) and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The resulting residue was purified by flash chromatography on silica gel eluting with CH_3OH/DCM (0-10%) to afford the title compound (301 mg, crude) as light yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 624.

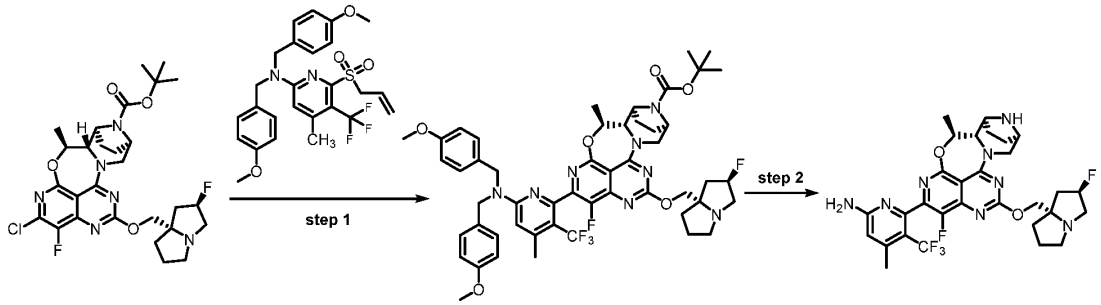
[1820] Step 2: *tert*-Butyl (5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-(((7a'S)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1821] Under nitrogen, a solution of 6-(allylsulfonyl)-*N*,*N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (501 mg, 0.0300 mmol, **intermediate 17**), $Pd(OAc)_2$ (5.60 mg, 0.0250 mmol), Pt-Bu_2MeHBF_4 (35.6 mg, 0.144 mmol), Cs_2CO_3 (357 mg, 0.0400 mmol) and *tert*-butyl (5a*S*,6*S*,9*R*)-2-chloro-12-(((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (301 mg, 0.0200 mmol) in 1,4-dioxane (5 mL) was stirred overnight at 120°C. The reaction mixture was cooled to room temperature, diluted with water (20 mL) and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with CH_3OH/DCM (0-10%) to afford the title compound (206 mg, 48.6% yield) as yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 1003.

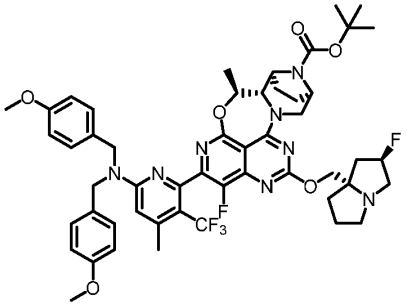
[1822] Step 3: 6-((5a*S*,6*S*,9*R*)-12-(((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Compound 42)

[1823] A solution of *tert*-butyl (5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-12-(((7a'S)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (70.6 mg, 0.0700 mmol) in TFA (3 mL) was stirred at 50°C for 3 hours. Then the mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A:water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:14 B to 47 B in 7 min; 254 nm; R_{T1}:6.8) to afford the title compound (21.5mg, 46.1% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 663. ^1H NMR (300 MHz, DMSO-d_6, ppm) δ 6.76 (s, 2H), 6.46 (s, 1H), 4.77 (dd, *J* = 13.1, 2.2 Hz, 1H), 4.49 (dd, *J* = 13.3, 2.0 Hz, 1H), 4.33 (dd, *J* = 13.3, 7.6 Hz, 1H), 4.15 (d, *J* = 1.8 Hz, 2H), 3.97 (d, *J* = 7.2 Hz, 1H), 3.58 (d, *J* = 5.6 Hz, 1H), 3.54 – 3.45 (m, 1H), 3.14 – 2.93 (m, 3H), 2.75 – 2.65 (m, 2H), 2.59 – 2.50 (m, 1H), 2.33 (d, *J* = 2.2 Hz, 3H), 2.12 – 1.38 (m, 11H).

[1824] **Example 43:** 6 Compound 43

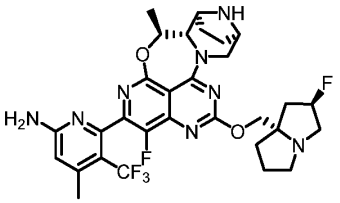


[1825] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



[1826] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (300 mg, 0.510 mmol, **intermediate 12**), 6-(allylsulfonyl)-*N*,*N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (395 mg, 0.760 mmol, **intermediate 17**), $Pd(OAc)_2$ (11.4 mg, 0.0500 mmol), $P(t\text{-}Bu)_2MeHBF_4$ (25.1 mg, 0.100 mmol) and Cs_2CO_3 (330 mg, 1.01 mmol) in 1,4-dioxane (3.5 mL) was stirred at 120°C overnight. Then the mixture was concentrated under vacuum. The residue was purified by reverse phase chromatography (gradient: 0-100% ACN in water (0.05% NH_4HCO_3)) to afford 158 mg (32.1% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ =973.

[1827] Step 2: 6-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Compound 43)



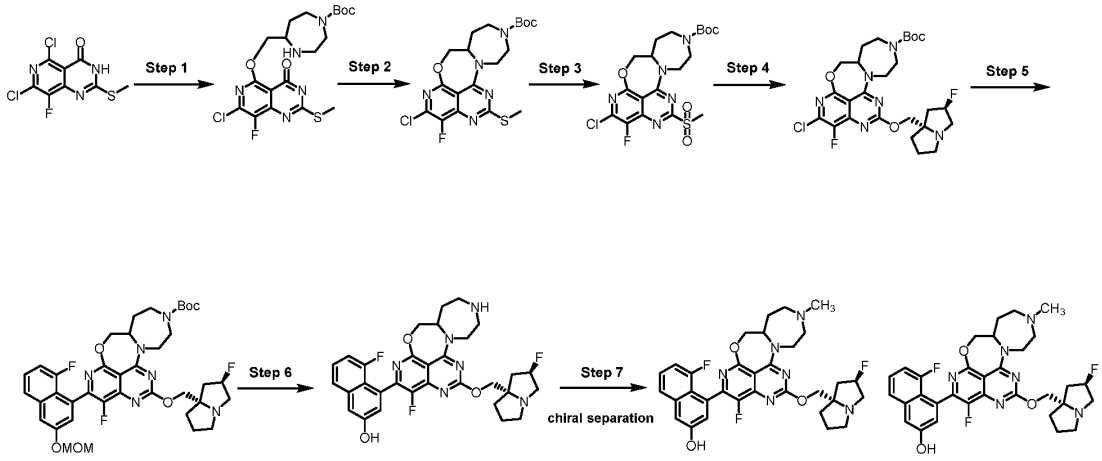
[1828] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (153 mg, 0.160 mmol) in TFA (5 mL) was stirred at 50°C for 4 h. Then the mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 48% B in 9 min, 48% B; Wave Length: 254/220 nm; R_{T1}(min): 8.9) to afford 58.8 mg (56.9% yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 633. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 6.82 (s, 2H), 6.48 (s, 1H), 5.29 (d, J = 54.4 Hz, 1H), 5.15 – 5.03 (m, 1H), 4.56 – 4.43 (m, 1H), 4.09 (d, J = 10.3 Hz, 1H), 4.04 – 3.90 (m, 2H), 3.57 (s, 1H), 3.49 – 3.41 (m, 1H), 3.17 – 3.03 (m, 3H), 3.00 (s, 1H), 2.92 – 2.75 (m, 1H), 2.40 – 2.31 (m, 3H), 2.18 – 2.12 (m, 1H), 2.08 – 1.97 (m, 2H), 1.93 – 1.72 (m, 4H), 1.71 – 1.51 (m, 3H), 1.43 (d, J = 6.3 Hz, 3H).

[1829] Each compound in Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Examples **42** and **43**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
44	^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 6.79 (s, 2H), 6.47 (s, 1H), 5.39 – 5.18 (m, 1H), 4.78 (d, *J* = 12.8 Hz, 1H), 4.50 (dd, *J* = 13.3, 2.0 Hz, 1H), 4.34 (dd, *J* = 13.2, 7.6 Hz, 1H), 4.09 (d, *J* = 10.4 Hz, 1H), 4.02 – 3.95 (m, 2H), 3.59 (d, *J* = 5.8 Hz, 1H), 3.53 – 3.47 (m, 1H), 3.12 – 2.93 (m, 4H), 2.88 – 2.77 (m, 1H), 2.73 (s, 1H), 2.37 – 2.32 (m, 3H), 2.12 (d, *J* = 4.5 Hz, 1H), 2.11 – 1.90 (m, 2H), 1.87 – 1.51 (m, 7H).	619
45 (Isomer 1)	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.68 (s, 2H), 6.36 (s, 1H), 4.99 (dd, J = 12.9, 2.5 Hz, 1H), 4.42-4.54 (m, 1H), 4.40-4.25 (m, 2H), 3.84 (d, J = 8.7 Hz, 1H), 3.50-3.43 (m, 2H), 3.33 (d, J = 5.7 Hz, 1H), 3.28-3.21 (m, 1H), 3.10-3.02 (m, 3H), 2.78 – 2.86 (m, 1H), 2.62 – 2.40 (m, 2H), 2.38 – 2.16 (m, 4H), 1.88-1.78 (m, 1H) 1.68-1.58 (m, 3H), 1.31 (d, J = 6.3 Hz, 3H)	637
45 (Isomer 2)	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.86 (s, 2H), 6.46 (s, 1H), 5.12 (dd, J = 12.9, 2.5 Hz, 1H), 4.62-4.44 (m, 1H), 4.40-4.25 (m, 2H), 3.86 (d, J = 8.7 Hz, 1H), 3.68-3.57 (m, 3H), 3.33-3.02 (m, 4H), 2.78 – 2.86 (m, 1H), 2.52 – 2.30 (m, 6H), 1.88-1.78 (m, 1H) 1.78-1.58 (m, 3H), 1.46-1.37 (d, J = 6.3 Hz, 3H)	637

47	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.80 (s, 2H), 6.48 (s, 1H), 5.10 (d, J = 12.2 Hz, 1H), 4.49 (s, 1H), 4.21 – 4.10 (m, 2H), 3.96 (d, J = 8.7 Hz, 1H), 3.68-3.57 (m, 1H), 3.44 (d, J = 5.7 Hz, 1H), 3.16 – 2.98 (m, 3H), 2.72 (d, J = 11.6 Hz, 1H), 2.35 (s, 3H), 2.10 (dd, J = 13.4, 5.6 Hz, 1H), 2.08 - 1.99 (m, 1H), 1.95 - 1.86 (d, J = 13.3 Hz, 1H), 1.84 - 1.76 (m, 4H), 1.72 - 1.51 (m, 6H), 1.59 – 1.40 (m, 3H).	677
48	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.80 (s, 2H), 6.48 (s, 1H), 5.08 (d, J = 12.6 Hz, 1H), 4.91 (s, 2H), 4.49 (dd, J = 8.6, 6.3 Hz, 1H), 4.07 – 3.91 (m, 3H), 3.56 (m, 2H), 3.44 (d, J = 5.7 Hz, 1H), 3.19 (d, J = 14.1 Hz, 1H), 3.07-2.94 (m, 2H), 2.65 – 2.55 (m, 2H), 2.30 – 2.24 (m, 4H), 2.03-1.90 (m, 1H), 1.88-1.57 (m, 7H), 1.43 (d, J = 6.3 Hz, 3H).	627

[1830] **Example 49:** Compound 49 (two unknown single isomers)



[1831] Step 1: *tert*-Butyl 5-(((7-chloro-8-fluoro-2-(methylthio)-4-oxo-4-pyrido[3,4-e]pyrimidin-5-yl)oxy)methyl)-1,4-diazepane-1-carboxylate

[1832] Under nitrogen, to a solution of *tert*-butyl 5-(hydroxymethyl)-1,4-diazepane-1-carboxylate (280mg, 1.22mmol, **intermediate 38**) in tetrahydrofuran (2 mL) was added NaH (316mg, 4.86mmol, 60% in mineral oil) at 0 °C. The resulting solution was stirred at room temperature for 0.5 h. Then 5,7-dichloro-8-fluoro-2-methylsulfanyl-3H-pyrido[4,3-d]pyrimidin-4-one (409mg, 1.46mmol, **intermediate 2**) was added. The resulting mixture was stirred for 2 hours at room temperature. The reaction mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% MeOH/DCM) to yield 480mg (83.6% yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 473$.

[1833] Step 2: *tert*-Butyl 2-chloro-1-fluoro-12-(methylthio)-5,5a,6,7,9,10-hexahydro-8*H*-4-oxa-3,8,10a,11,13-pentaazanaphtho[1,8-ab]heptalene-8-carboxylate

[1834] A mixture of *tert*-butyl rac-(5*S*)-5-[(7-chloro-8-fluoro-2-methylsulfanyl-4-oxo-3*H*-pyrido[4,3-d]pyrimidin-5-yl)oxymethyl]-1,4-diazepane-1-carboxylate (100 mg, 0.210mmol),

BOPCl (80.6mg, 0.320mmol) and DIEPA (136mg, 1.05mmol) in DCE (2mL) was stirred overnight at room temperature. The resulting mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 120mg (crude) as brown solid which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ =456.

[1835] Step 3: *tert*-Butyl 2-chloro-1-fluoro-12-(methylsulfonyl)-5,5a,6,7,9,10-hexahydro-8*H*-4-oxa-3,8,10a,11,13-pentaazanaphtho[1,8-ab]heptalene-8-carboxylate

[1836] To a solution of *tert*-butyl 13-chloro-14-fluoro-17-methylsulfanyl-10-oxa-2,5,12,16,18-pentazatetracyclo[9.7.1.02,8.015,19]nonadeca-1(18),11(19),12,14,16-pentaene-5-carboxylate (104mg, 0.230mmol) in EtOAc (3mL) was added m-CPBA (118mg, 0.680mmol) at 0°C. The resulting mixture was stirred overnight at room temperature. The reaction mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-50% EtOAc / petroleum ether) to yield 61 mg (54 % yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 488.

[1837] Step 4: *tert*-Butyl 2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,5a,6,7,9,10-hexahydro-8*H*-4-oxa-3,8,10a,11,13-pentaazanaphtho[1,8-ab]heptalene-8-carboxylate

[1838] To a solution of *tert*-butyl 13-chloro-14-fluoro-17-methylsulfonyl-10-oxa-2,5,12,16,18-pentazatetracyclo[9.7.1.02,8.015,19]nonadeca-1(18),11(19),12,14,16-pentaene-5-carboxylate (105mg, 0.220mmol), [*rac*-(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (68.5mg, 0.430mmol, **intermediate 5**) in toluene (3mL) was added *t*-BuONa (41.4mg, 0.430mmol) at 0°C. The resulting mixture was stirred overnight at room temperature. The reaction mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% MeOH/DCM) to yield 40 mg (32.8 % yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 567.

[1839] Step 5: *tert*-Butyl 1-fluoro-2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,5a,6,7,9,10-hexahydro-8*H*-4-oxa-3,8,10a,11,13-pentaazanaphtho[1,8-ab]heptalene-8-carboxylate

[1840] A solution of *tert*-butyl 13-chloro-14-fluoro-17-[[rac-(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-10-oxa-2,5,12,16,18-pentazatetracyclo[9.7.1.02,8.015,19]nonadeca-1(18),11(19),12,14,16-pentaene-5-carboxylate

(50mg, 0.09mmol), 2-(8-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (44mg, 0.13mmol, **intermediate 25**), Cs_2CO_3 (86.2mg, 0.260mmol), $Pd(PPh_3)_4$ (51mg, 0.040mmol) in 1.4-dioxane (2 mL) and water (0.4 mL) was stirred for 3 hours at 95°C. The reaction mixture was partitioned between water and EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% MeOH/DCM) to yield 45 mg (69.3 % yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 737.

[1841] Step 6: 5-Fluoro-4-(1-fluoro-12-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,8,10a,11,13-pentaazanaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol

[1842] A solution of *tert*-butyl 14-fluoro-13-[8-fluoro-3-(methoxymethoxy)-1-naphthyl]-17-[[rac-(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-10-oxa-2,5,12,16,18-pentazatetracyclo[9.7.1.02,8.015,19]nonadeca-1(18),11(19),12,14,16-pentaene-5-carboxylate (80mg, 0.110mmol) and HCl (1mL, 4M in dioxane) in DCE (2mL) was stirred for 2 hours at room temperature. The resulting mixture was concentrated under reduced pressure to afford 60 mg (crude) which was used for next step without further purification. LC-MS: (ESI, *m/z*): $[M+H]^+$= 593.

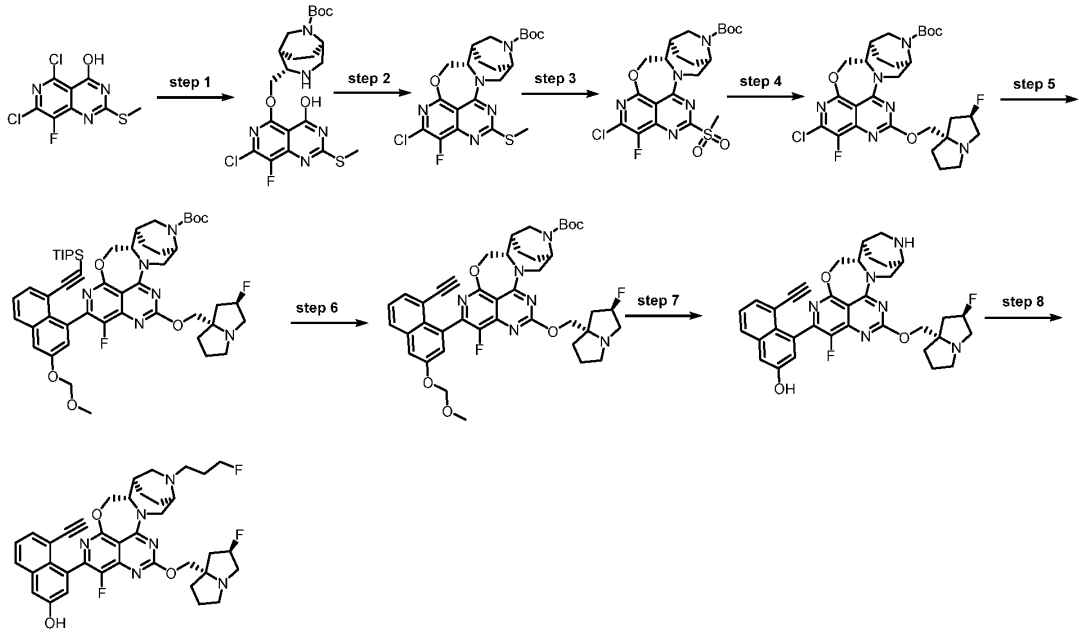
[1843] Step 7: 5-Fluoro-4-(1-fluoro-12-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-8-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,8,10a,11,13-pentaazanaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol (two unknown single isomers)

[1844] A solution of 5-fluoro-4-[14-fluoro-17-[[rac-(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-10-oxa-2,5,12,16,18-pentazatetracyclo[9.7.1.02,8.015,19]nonadeca-1(18),11(19),12,14,16-pentaen-13-yl]naphthalen-2-ol (60.0mg, 0.1mmol), HCHO (0.1 mL, 40% in water) and NaOAc (8.3mg, 0.1mmol) in DCM (2mL) was stirred 1h at room temperature. Then $NaBH(AcO)_3$ (32.2mg, 0.150mmol) was added. The resulting mixture was stirred overnight at room temperature. The reaction mixture was partitioned between water and DCM. The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude product was separated by Prep-CHIRAL HPLC with the following conditions: (Column: CHIRAL ART Cellulose-SC, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1(0.5% 2M NH3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 21 min; Wave Length: 220/254 nm; RT1(min): 12.52; RT2(min): 17.38; Sample Solvent: EtOH-HPLC; Injection Volume: 1 mL; Number Of Runs: 1) to yield 5.7 mg (9.3% yield) **Compound 49a** and 7.8 mg (12.7% yield) of **Compound 49b** as white solids.

[1845] **Compound 49a:** LC-MS: (ESI, m/z): $[M+H]^+$= 607. ^{1}H NMR (300 MHz, DMSO-d_6, *ppm*): δ 10.22 (d, J = 9.4 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.44 (m, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.14 (m, 1H), 7.02 (m, 1H), 5.29 (d, J = 54.5 Hz, 1H), 4.84 (t, J = 12.6 Hz, 1H), 4.52 (m, 2H), 4.15 (m, 2H), 4.02 (m, 1H), 3.54 – 3.41 (m, 1H), 3.10 (d, J = 6.7 Hz, 2H), 3.01 (s, 1H), 2.82 (t, J = 8.1 Hz, 2H), 2.67 (d, J = 11.5 Hz, 3H), 2.30 (d, J = 2.3 Hz, 3H), 2.15 (d, J = 6.7 Hz, 1H), 2.10 – 1.93 (m, 3H), 1.93 – 1.63 (m, 4H).

[1846] **Compound 49b:** LC-MS: (ESI, m/z): $[M+H]^+$= 607. ^{1}H NMR (300 MHz, DMSO-d_6, *ppm*): δ 10.22 (d, J = 9.1 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.43 (m, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.02 (m, 1H), 5.28 (d, J = 54.3 Hz, 1H), 4.93 – 4.80 (m, 1H), 4.65 – 4.41 (m, 2H), 4.26 – 4.09 (m, 2H), 4.04 (d, J = 10.6 Hz, 1H), 3.54 – 3.41 (m, 1H), 3.10 (s, 2H), 3.00 (s, 1H), 2.89 – 2.75 (m, 2H), 2.69 (s, 3H), 2.30 (s, 3H), 2.14 (s, 1H), 2.06 – 1.89 (m, 3H), 1.89 – 1.61 (m, 4H).

[1847] **Example of 50:** Compound 50



[1848] Step 1: *tert*-Butyl (1*R*,2*S*,5*R*)-2-(((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)methyl)-3,6-diazabicyclo[3.2.2]nonane-6-carboxylate

[1849] To a solution of *tert*-butyl (1*R*,2*S*,5*R*)-2-(hydroxymethyl)-3,6-diazabicyclo[3.2.2]nonane-6-carboxylate (460 mg, 1.79 mmol, **intermediate 39**) in tetrahydrofuran (10mL) was added NaH (431mg, 10.8mmol, 60% in mineral oil) at 0°C. The mixture was stirred at room temperature for 20 min. Then 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-ol (600 mg, 2.15 mmol, **intermediate 2**) was added and

the mixture was allowed to warm to room temperature and stirred at room temperature overnight. The reaction mixture was quenched with water. The precipitated solids were collected by filtration, washed with water and dried in oven to yield 1.20 g (crude) the title compound as a yellow solid which was used for next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+ = 500$.

[1850] Step 2: *tert*-Butyl (5a*S*,6*R*,9*R*)-2-chloro-1-fluoro-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalene-14-carboxylate

[1851] A solution of *tert*-butyl (1*R*,2*S*,5*R*)-2-(((7-chloro-8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-5-yl)oxy)methyl)-3,6-diazabicyclo[3.2.2]nonane-6-carboxylate (1.17 g, 2.34 mmol), BOPCl (2.97 g, 11.7 mmol) and DIPEA (3.02 g, 23.4 mmol) in DCE (12 mL) was stirred at room temperature for 4 hours. The resulting mixture was partitioned between water and EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient:0-40% EtOAc/petroleum ether) to afford 600 mg (46.9% yield) of the title compound as a light yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 482$

[1852] Step 3: *tert*-Butyl (5a*S*,6*R*,9*R*)-2-chloro-1-fluoro-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalene-14-carboxylate

[1853] To a solution of *tert*-butyl (5a*S*,6*R*,9*R*)-2-chloro-1-fluoro-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalene-14-carboxylate (430 mg, 0.894 mmol) in ethyl acetate (10 mL) was added mCPBA (308 mg, 1.79 mmol) portion wise at 0°C. The resulting solution was stirred at room temperature for 1 h. The reaction mixture was quenched with aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient:0-50% EtOAc/petroleum ether) to afford 422 mg (92.0% yield) of the title compound as a light yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 514$.

[1854] Step 4: *tert*-Butyl (5a*S*,6*R*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalene-14-carboxylate

[1855] To a solution of *tert*-butyl (5a*S*,6*R*,9*R*)-2-chloro-1-fluoro-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalene-14-carboxylate (400 mg, 0.780mmol) and ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (149 mg, 0.930mmol, **intermediate 5**) in toluene (5mL) was added *t*-BuONa (149

mg, 1.56mmol) at 0°C. The reaction was stirred at room temperature for 1 hour. The resulting mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-5% MeOH in DCM) to afford 370 mg (78.4% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 593.

[1856] Step 5: *tert*-Butyl (5a*S*,6*R*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5H)-yl)methoxy)-2-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalene-14-carboxylate

[1857] Under nitrogen, a solution of *tert*-butyl (5a*S*,6*R*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalene-14-carboxylate (180 mg, 0.300 mmol), triisopropyl((6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane (300 mg, 0.610mmol), K_3PO_4(1.5 M in water, 0.4ml) and cataCXium A Pd G3 (44.2mg, 0.0600mmol) in tetrahydrofuran (5 mL) was stirred at 60°C for 2 hours. The solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was partitioned between water and EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-5% MeOH in DCM) to afford 259 mg (91.6% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 926.

[1858] Step 6: *tert*-Butyl (5a*S*,6*R*,9*R*)-2-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalene-14-carboxylate

[1859] A solution of *tert*-butyl (5a*S*,6*R*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-2-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalene-14-carboxylate (249 mg, 0.270 mmol) and CsF (409 mg, 2.69 mmol) in *N*,*N*-dimethylacetamide (2 mL) was stirred at room temperature for 2 hours. The solid was filtered off. The filtrate was purified by reverse phase chromatography on pre-packed C18 column (solvent gradient: 0-100% ACN in water (0.05% NH_4HCO_3)) to yield 198 mg (95.7% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 769.

[1860] Step 7: 5-Ethynyl-4-((5a*S*,6*R*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol

[1861] To a solution of *tert*-butyl (5a*S*,6*R*,9*R*)-2-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalene-14-carboxylate (188mg, 0.250mmol) in acetonitrile (1.5mL) was added 4 M HCl/dioxane (0.5 mL) at 0°C. The reaction was stirred at 0°C for 3 hours and concentrated under reduced pressure. The residue was purified by reverse phase chromatography on pre-packed C18 column (solvent gradient: 0-50% ACN in water (0.05% NH_4HCO_3)) to yield 147 mg (89.7% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 625$.

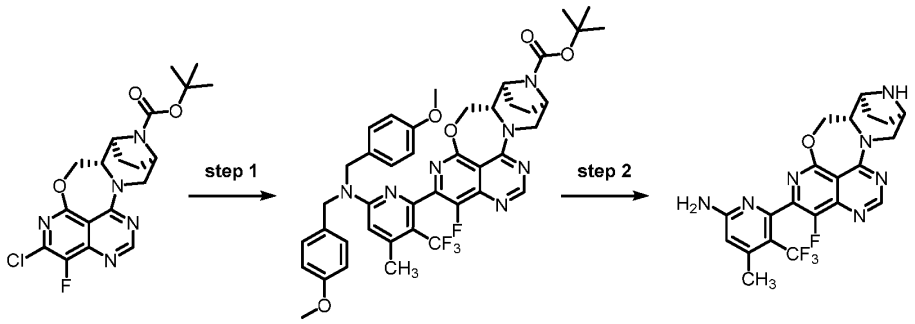
[1862] Step 8: 5-Ethynyl-4-((5a*S*,6*R*,9*R*)-1-fluoro-14-(3-fluoropropyl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol (Compound 50)

[1863] A solution of 5-ethynyl-4-((5a*S*,6*R*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-ethanonaphtho[1,8-ab]heptalen-2-yl)naphthalen-2-ol (75.0 mg, 0.120mmol), 1-iodo-3-fluoropropane (45.1 mg, 0.240mmol) and DIPEA (77.4 mg, 0.600mmol) in acetonitrile (1.5 mL) was stirred at 50°C overnight. Then the mixture was concentrated under vacuum. The crude was purified by Prep-HPLC (XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A:Water(10mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:32% B to 57% B in 9 min; 57% B; Wavelength: 254/220 nm; R_T(min): 7.9) to yield 24.4mg (29.6% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 685$. ^{1}H NMR (300 MHz, DMSO-*d6*) δ 10.12 (m, 1H), 7.87 (m, 1H), 7.51 – 7.35 (m, 2H), 7.31 (m, 1H), 7.10 (m, 1H), 5.28 (m, 1H), 5.10 – 4.93 (m, 1H), 4.66 – 4.41 (m, 4H), 4.24 (s, 1H), 4.13 (m, 1H), 3.97 (m, 1H), 3.49 (s, 1H), 3.25 (m, 1H), 3.07 (m, 5H), 2.88 – 2.69 (m, 3H), 2.56 (m, 1H), 2.38 (s, 1H), 2.17 – 1.96 (m, 3H), 1.83 (m, 6H), 1.51 (m, 3H).

[1864] The compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Examples **49** and **50**.

Cmpd. No.	^{1}H NMR	MS (M+H)$^+$
51	^{1}H NMR (300 MHz, DMSO-*d6*) δ 10.10 (s, 1H), 7.85 (m, 1H), 7.48 – 7.35 (m, 2H), 7.30 (m, 1H), 7.09 (m, 1H), 5.27 (m, 1H), 5.07 – 4.92 (m, 1H), 4.65 (m, 2H), 4.56 – 4.37 (m, 2H), 4.28 m, 2H), 4.24 – 4.05 (m, 2H), 3.96 (m, 1H), 3.73 (s, 1H), 3.47 (s, 1H), 3.24 – 2.67 (m, 10H), 2.35 (s, 1H), 2.13 (m, 1H), 2.01 (m, 2H), 1.94 – 1.65 (m, 4H), 1.65 – 1.30 (m, 3H).	695

[1865] **Example 52:** Compound 52



[1866]

Step 1: *tert*-Butyl (5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

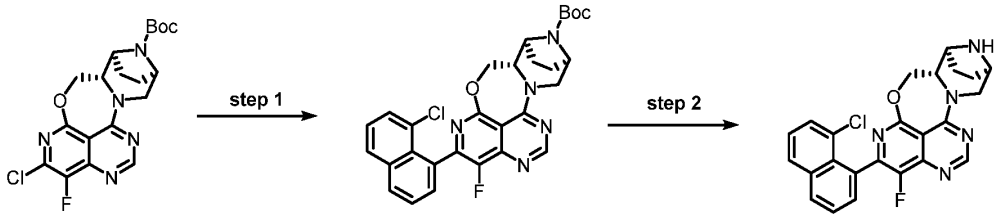
[1867] Under nitrogen, a solution of *tert*-butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (55.1 mg, 0.130 mmol, **intermediate14**), *N*,*N*-bis(4-methoxybenzyl)-4-methyl-6-(tributylstannyl)-5-(trifluoromethyl)pyridin-2-amine (168 mg, 0.240 mmol, **intermediate 42**), $Pd(PPh_3)_4$ (30.1 mg, 0.0300 mmol), LiCl (14.1 mg, 0.340 mmol) and CuI (3.20 mg, 0.0200 mmol) in 1,4-dioxane (1 mL) was stirred for 2 days at 110°C. Then the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0-65%) to afford the title compound (63.9 mg, 42.7% yield) as a light yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 802$.

[1868] Step 2: 6-((5a*S*,6*S*,9*R*)-1-Fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Compound 52)

[1869] A solution of *tert*-butyl (5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (63.9 mg,0.0558 mmol) in TFA (3 mL) was stirred at 50°C for 4 hours. Then the mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30×150mm 5um; Mobile Phase A:Water (10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60

mL/min; Gradient:12 B to 42 B in 7 min; 254 nm; R_{T1}:6.5) to afford the title compound (9.7mg, 26.4% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 462. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 8.63 (s, 1H), 6.81 (s, 2H), 6.47 (s, 1H), 4.91 (dd, J = 13.1, 2.2 Hz, 1H), 4.52 (dd, J = 13.3, 2.1 Hz, 1H), 4.39 (dd, J = 13.3, 7.7 Hz, 1H), 4.00 (d, J = 7.4 Hz, 1H), 3.56 (d, J = 5.3 Hz, 1H), 3.50 (d, J = 5.7 Hz, 1H), 3.03 (d, J = 12.3 Hz, 1H), 2.37 – 2.30 (m, 3H), 1.67 (d, J = 10.5 Hz, 2H), 1.64 – 1.41 (m, 2H).

[1870] **Example 53:** Compound 53



[1871] Step 1: *tert*-Butyl (5a*S*,6*S*,9*R*)-2-(8-chloronaphthalen-1-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

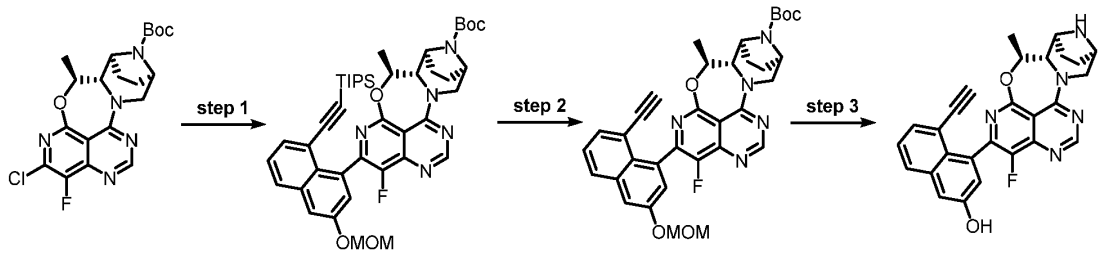
[1872] Under nitrogen, a solution of *tert*-butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (60.2 mg, 0.140 mmol, **intermediate 14**), 2-(8-chloronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (103 mg, 0.360 mmol, **intermediate 41**), $Pd(PPh_3)_2Cl_2$ (20.1 mg, 0.0300 mmol) and KF (24.8 mg, 0.430 mmol) in acetonitrile (1.5 mL) and water (0.3 mL) was stirred overnight at 100°C. Then the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0-75%) to afford the title compound (37.3 mg, 47.7% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 548.

[1873] Step 2: (5a*S*,6*S*,9*R*)-2-(8-Chloronaphthalen-1-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene (Compound 53)

[1874] A solution of *tert*-butyl (5a*S*,6*S*,9*R*)-2-(8-chloronaphthalen-1-yl)-1-fluoro-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (37. 3mg, 0.0700 mmol) and TFA (0.5 mL) in DCM (2 mL) was stirred at room temperature for 1 hour. Then the mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: Xselect CSH F-Phenyl OBD column, 19*250, 5um; Mobile Phase A: Water (0.05% FA), Mobile Phase B: ACN; Flow rate:25 mL/min; Gradient:3 B to 20 B in 9 min; 254 nm; R_{T1}:7.55) to afford the title compound (11.3 mg, 33.6% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 448. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 8.68 (d, J = 1.8 Hz, 1H), 8.25 – 8.14 (m, 1H), 8.10 (dd, J = 8.1, 1.4 Hz, 1H), 7.79 – 7.50 (m,

4H), 5.04 – 4.94 (m, 1H), 4.63 – 4.37 (m, 2H), 4.08 (t, J = 9.5 Hz, 1H), 3.64 (s, 1H), 3.57 (s, 1H), 3.16 – 3.03 (m, 1H), 1.80 – 1.54 (m, 4H).

[1875] **Example 54:** Compound 54



[1876] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1877] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (90.6 mg, 0.210 mmol, **intermediate 15**), $Pd(dppf)Cl_2$ (15.9 mg, 0.0200 mmol), triisopropyl((6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane (133 mg, 0.270 mmol, **intermediate 26**) and Cs_2CO_3 (230 mg, 0.710 mmol) in 1.4-dioxane (1.5 mL) and H_2O (0.4 mL) was stirred for 1.5 h at 95°C. The reaction mixture was partitioned between water and EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0-65%) to afford the title compound (131 mg, 81.8% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 768.

[1878] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1879] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (111 mg, 0.140 mmol) and CsF (219 mg, 1.44 mmol) in DMF (2 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc (15 mL) and washed with H_2O. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with EtOAc/petroleum ether (0-75%) to afford the title compound (80.6 mg, 91.5% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 612.

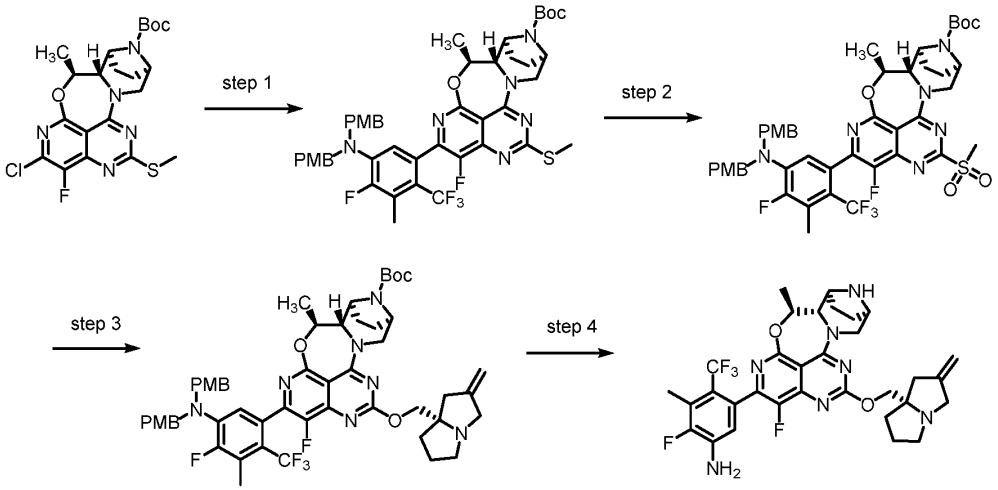
[1880] Step 3: 5-ethynyl-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)naphthalen-2-ol (Compound 54)

[1881] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (80.6 mg, 0.130 mmol) in ACN (2 mL) was added HCl (1 mL, 4 M in dioxane) at 0°C. The reaction mixture was stirred at 0°C for 1 hour. Then the mixture was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 10% B to 40% B in 10 min, 40% B; Wave Length: 220/254 nm; R_{T1}(min): 11.93;) to afford the title compound (14.1 mg, 22.9% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 468. ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 10.14 (s, 1H), 8.67 (s, 1H), 7.88- 7.86 (m, 1H), 7.53 – 7.37 (m, 2H), 7.33 (t, *J* = 2.1 Hz, 1H), 7.10 (dd, *J* = 54.9, 2.6 Hz, 1H), 5.29 – 5.27 (m, 1H), 4.60 – 4.46 (m, 1H), 4.04 – 3.96 (m, 1H), 3.72 (d, *J* = 136.1 Hz, 2H), 3.46 (t, *J* = 6.8 Hz, 1H), 3.04 (t, *J* = 11.7 Hz, 1H), 2.82 (s, 1H), 1.84 – 1.80 (m, 1H), 1.78 – 1.62 (m, 2H), 1.62 – 1.51 (m, 1H), 1.45 (dd, *J* = 8.0, 6.3 Hz, 3H).

[1882] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Examples **53** and **54**.

Cmpd. No.	^{1}H NMR	MS (M+H)$^+$
55	^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 8.66 (s, 1H), 7.93 (s, 2H), 7.36 (dd, J = 8.5, 5.8 Hz, 1H), 7.04 (t, J = 8.8 Hz, 1H), 4.94 (dd, J = 13.3, 2.3 Hz, 1H), 4.55 (dd, J = 13.4, 2.2 Hz, 1H), 4.44 (dd, J = 13.3, 7.3 Hz, 1H), 4.05 (d, J = 7.0 Hz, 1H), 3.71 – 3.59 (m, 2H), 3.18 – 3.03 (m, 1H), 1.85 – 1.48 (m, 4H).	454
56	^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 8.69 (s, 1H), 8.28 – 8.15 (m, 2H), 7.73 – 7.52 (m, 3H), 5.31 – 5.21 (m, 1H), 4.60 – 4.45 (m, 1H), 4.36 – 3.91 (m, 2H), 3.56 (d, *J* = 5.3 Hz, 1H), 3.47 (t, *J* = 7.5 Hz, 1H), 3.05 (t, *J* = 12.6 Hz, 1H), 2.81 – 2.76 (m, 1H), 1.91 – 1.51 (m, 4H), 1.46 (dd, *J* = 9.9, 6.3 Hz, 3H).	470

[1883] **Example 57:** Compound 57



[1884] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1885] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho [1,8-*ab*]heptalene-14-carboxylate (701 mg, 1.45 mmol, intermediate 46) and (5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (1.73 g, 3.63 mmol, intermediate 20) in THF (9 mL) was added cataCXium A Pd G_3 (317 mg, 0.440 mmol) and K_3PO_4 (1.8 mL, 1.5 M in H_2O) at room temperature. The resulting solution was stirred for 3 h at 60°C. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-100% CH_3CN in water (0.05% NH_4HCO_3)) to yield 941 mg (73.7% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 879$.

[1886] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1887] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (910 mg, 1.04 mmol) in DCM (10 mL) was added m-CPBA (537 mg, 3.11 mmol) at 0 °C. The resulting solution was stirred for 2 h at room temperature. The solution was diluted with $NaHCO_3$ solution and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel

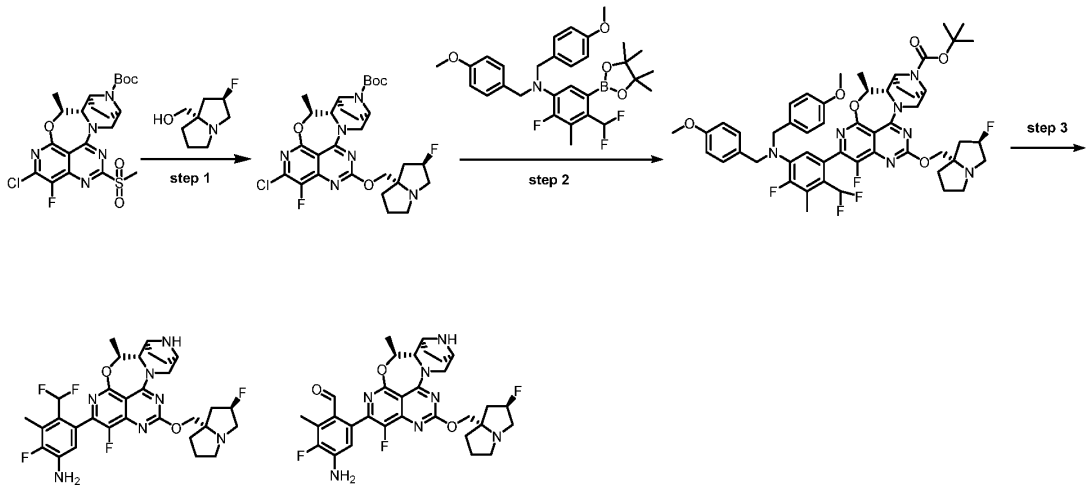
(gradient: 0-51% EtOAc in petroleum ether) to afford 378 mg (33.3% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 911.

[1888] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((*S*)-2-methylenetetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1889] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7, 8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*] heptalene-14-carboxylate (100 mg, 0.110 mmol) and (*S*)-(2-methylenetetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methanol (20.2 mg, 0.130 mmol, intermediate 36) in toluene (1.5 mL) was added t-BuONa (21.1 mg, 0.220 mmol) at 0 °C. The resulting solution was stirred for 1 h at room temperature. The solution was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-8% MeOH in DCM) to yield 91 mg (84.1% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 984.

[1890] Step 4: 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-(((*S*)-2-methylenetetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl) aniline (Compound 57) Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((*S*)-2-methylenetetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (90.8 mg, 0.0900 mmol) in TFA (5 mL) was stirred for 3 h at 50°C. The resulting solution was concentrated under vacuum. The crude product was purified by Prep-HPLC(Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 55% B in 9 min, 55% B; Wave Length: 254/220 nm; R_{T1}(min): 8.6;) to yield 20.1 mg (33.1% yield) of the title compound as a while solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 634. ^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.61 (s, 1H), 6.02 (s, 2H), 5.10 (dd, J = 13.1, 2.5 Hz, 1H), 4.93 (s, 2H), 4.58-4.52 (m, 1H), 4.03-3.94 (m, 3H), 3.66-3.55 (m, 3H), 3.23 (s, 1H), 3.11-2.98 (m, 2H), 2.67-2.56 (m, 2H), 2.41 (s, 1H), 2.32 (s, 3H), 1.98-1.33 (m, 8H), 1.44 (d, J = 6.3 Hz, 3H).

[1891] **Example 58 and 59:** Compounds 58 and 59



[1892] Step1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

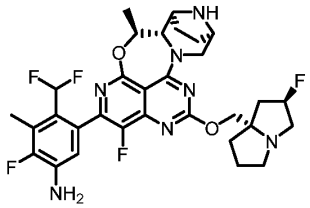
[1893] Under nitrogen, to a solution of ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (37.5 mg, 0.240 mmol, intermediate 5) and *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (60.6 mg, 0.120 mmol, intermediate 11) in toluene (1.5 mL) was added t-BuONa (22.6 mg, 0.240 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 hour, quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with CH_3OH/DCM (0-10%) to afford the title compound (40.6 mg, 58.1% yield) as light yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 593$.

[1894] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-2-(difluoromethyl)-4-fluoro-3-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

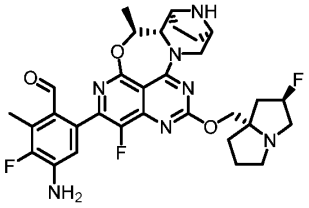
[1895] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (100 mg, 0.170 mmol), 4-(difluoromethyl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (201 mg, 0.370 mmol, intermediate 56), cataCXium A Pd G3 (28.7 mg, 0.0400 mmol) and K_3PO_4 (313 mg, 1.47 mmol)

in Tetrahydrofuran (6 mL) and Water (1 mL) was stirred at 60°C for 3 hours. The solution was concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-7% MeOH in DCM) to afford 136 mg (83% yield) of the title compound as yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 972.

[1896] Step 3: 4-(Difluoromethyl)-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methylaniline (Compound 58) and 4-Amino-3-fluoro-6-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-methylbenzaldehyde(Compound 59)



58



59

[1897] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-2-(difluoromethyl)-4-fluoro-3-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (80.3 mg, 0.0800 mmol) in 2,2,2-trifluoroacetic acid (1 mL) was stirred at room temperature for 1 hour. The solution was concentrated under vacuum in cold water. The residue was purified by reverse phase flash chromatography on pre-packed C18 column (gradient: 0-55% CH_3CN in water (0.05% NH_4HCO_3)). The fraction that contained desired product (Compound 58) was extracted with DCM, dried over anhydrous sodium sulfate and concentrated under vacuum (in cold water) to afford 10.2 mg (20% yield) of the title compound as a light yellow solid.

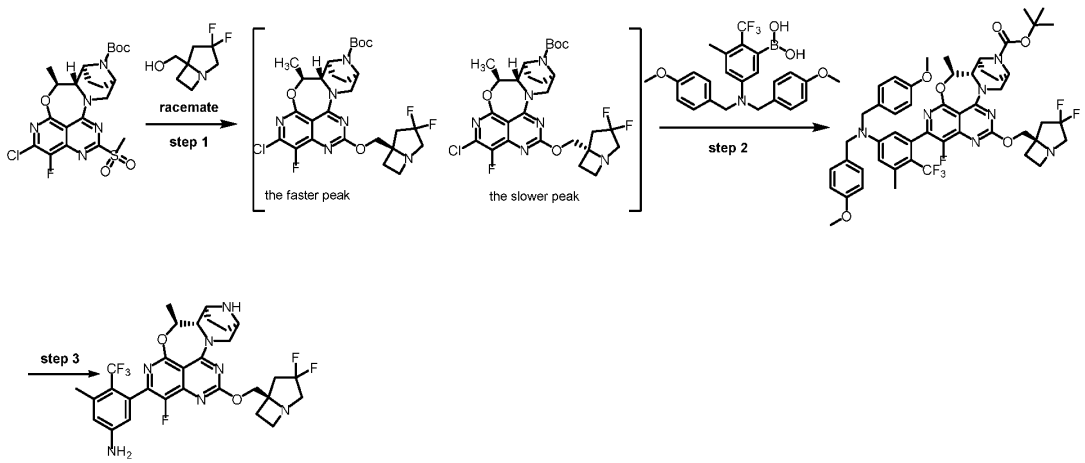
[1898] When the solvent was concentrated under reduce pressure after reverse phase column directly, compound **58** hydrolyzed to **59**.

[1899] **58:** LC-MS: (ESI, m/z): $[M+H]^+$ = 632. ^1H NMR (400 MHz, DMSO-*d6, ppm*) δ 6.71 - 6.45 (m, 2H), 5.78 (s, 2H), 5.29 (d, *J* = 54.0 Hz, 1H), 5.13 - 5.10 (m, 1H), 4.56 - 4.52 (m, 1H), 4.13 - 3.97 (m, 3H), 3.66 - 3.51 (m, 2H), 3.18 - 3.02 (m, 4H), 2.90 - 2.83 (m, 1H), 2.35 (s, 3H), 2.17 - 2.00 (m, 3H), 1.88 - 1.61 (m, 7H), 1.46 - 1.44 (m, 3H).

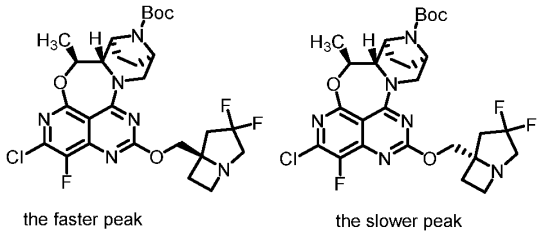
[1900] **59:** LC-MS: (ESI, m/z): $[M+H]^+$ = 610. ^1H NMR (300 MHz, DMSO-*d6, ppm*) δ 9.63 (s, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.41 (s, 2H), 5.27 (d, *J* = 54.0 Hz, 1H), 5.11 - 5.08 (m, 1H), 4.54

- 4.51 (m, 1H), 4.13 - 3.94 (m, 3H), 3.58 - 3.44 (m, 2H), 3.16 - 3.00 (m, 4H), 2.90 - 2.78 (m, 2H), 2.49 (s, 3H), 2.16 - 2.00 (m, 3H), 1.91 - 1.58 (m, 7H), 1.48 - 1.46 (m, 3H).

[1901] **Example 60:** Compound 60



[1902] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate



[1903] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (3.50 g, 6.81 mmol, intermediate 11) and (3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methanol (1.30 g, 7.97 mmol, intermediate 6A) in toluene (35 mL) was added t-BuONa (1.30 g, 13.5 mmol) at 0°C. The resulting solution was stirred at room temperature for 1h, the reaction was quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0%-6% MeOH/DCM) to afford 2.06 g (50.7% yield) of a mixture of two diastereoisomers as a white solid. The diastereoisomers were separated by Chiral-Prep-HPLC (Column: CHIRALPAK IE-3, 4.6*50 mm, 3 um; Mobile Phase A: Hex(0.1%DEA): EtOH=50: 50; Flow rate: 1 mL/min; Gradient: 0% B to 0% B; Injection Volume: 5ul mL) to afford yield 643 mg of the faster peak and 676 mg of the slower peak as white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 597.

[1904] The faster peak (desired isomer): ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 5.18 (d, J = 13.2 Hz, 1H), 4.64 (t, J = 7.6 Hz, 1H), 4.44 – 4.29 (m, 3H), 4.16 (s, 1H), 3.99 (d, J = 9.0 Hz, 1H), 3.54 (dd, J = 9.0, 4.7 Hz, 1H), 3.33 – 3.15 (m, 1H), 3.15 (d, J = 4.4 Hz, 1H), 3.13 – 2.98 (m, 2H), 2.75 – 2.52 (m, 1H), 2.50 – 2.38 (m, 1H), 2.41 – 2.25 (m, 1H), 1.87 (s, 3H), 1.73 (s, 1H), 1.50 (d, J = 6.3 Hz, 3H), 1.47 (s, 9H).

[1905] The slower peak: ^{1}H NMR (300 MHz, DMSO-d_6, ppm): ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 5.18 (d, J = 13.2 Hz, 1H), 4.64 (t, J = 7.6 Hz, 1H), 4.44 – 4.29 (m, 3H), 4.16 (s, 1H), 3.99 (d, J = 9.0 Hz, 1H), 3.54 (dd, J = 9.0, 4.7 Hz, 1H), 3.33 – 3.15 (m, 1H), 3.15 (d, J = 4.4 Hz, 1H), 3.13 – 2.98 (m, 2H), 2.75 – 2.52 (m, 1H), 2.50 – 2.38 (m, 1H), 2.41 – 2.25 (m, 1H), 1.87 (s, 3H), 1.73 (s, 1H), 1.50 (d, J = 6.3 Hz, 3H), 1.47 (s, 9H).

[1906] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

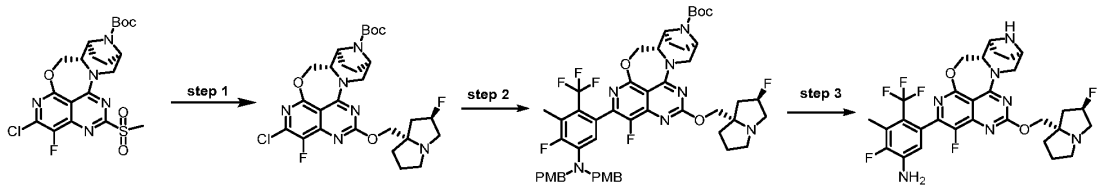
[1907] Under nitrogen, a solution of (5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (84.6 mg, 0.180 mmol, intermediate 52), *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (55.0 mg, 0.0900 mmol, the faster peak of from step 1), cataCXium A Pd G_3 (13.4 mg, 0.0200 mmol) and K_3PO_4(1.5 M in water) (0.2 mL) in tetrahydrofuran (2 mL) was stirred at 60 °C for 1 hour. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was diluted with water and was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-90% EtOAc in petroleum ether) to afford the title compound (75 mg, 82.6% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 976.

[1908] Step 3: 3-((5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline (Compound 60)

[1909] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (75.0 mg, 0.0800 mmol) in 2,2,2-trifluoroacetic acid (1 mL) was stirred at 50 °C for 1 hour. The solvent was concentrated under vacuum. The crude was purified by Prep-HPLC with the following conditions:(Column: XBridge Prep OBD C18 Column, 30*150

mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 51% B in 9 min, 51% B; Wave Length: 254/220 nm; R_{T1}(min): 8.18) to afford the title compound (28.1 mg, 57.4 % yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 636. ^1H NMR (300 MHz, DMSO-d6) δ 6.60 (d, J = 2.2 Hz, 1H), 6.30 (d, J = 43.8 Hz, 1H), 5.89 (s, 2H), 5.13 (d, J = 13.0 Hz, 1H), 4.56 (dd, J = 8.6, 6.3 Hz, 1H), 4.48 – 4.24 (m, 2H), 4.00 (d, J = 8.7 Hz, 1H), 3.67 (s, 1H), 3.54 (d, J = 5.5 Hz, 2H), 3.23 (d, J = 8.8 Hz, 1H), 3.20 – 3.03 (m, 3H), 2.78 – 2.56 (m, 2H), 2.39 (d, J = 23.0 Hz, 6H), 1.84 (d, J = 10.7 Hz, 1H), 1.80-1.55 (m, 3H), 1.45 (d, J = 6.3 Hz, 3H).

[1910] **Example 61:** Compound 61



[1911] Step 1: *tert* -Butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1912] Under nitrogen, to a mixture of *tert* -butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (201 mg, 0.401 mmol, intermediate 11) and ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (128 mg, 0.802 mmol, intermediate 5) in toluene (2 mL) was added t-BuONa (77.1 mg, 0.802 mmol) at 0°C. The solution was stirred at room temperature for 1 hour. The reaction system was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The resulting residue was purified by flash chromatography on silica gel eluting with CH_3OH/DCM (0-10%) to afford the title compound (151 mg, 64.8% yield) as light yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 579. ^1H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 5.29 (d, J = 54.2 Hz, 1H), 4.89 (d, J = 13.4 Hz, 1H), 4.72 – 4.62 (m, 1H), 4.48 (dd, J = 13.3, 7.3 Hz, 1H), 4.40 – 4.25 (m, 2H), 4.19 – 3.95 (m, 3H), 3.15 – 2.97 (m, 4H), 2.89 – 2.76 (m, 1H), 2.17 – 2.11 (m, 1H), 2.07 – 2.02 (m, 1H), 1.94 – 1.62 (m, 8H), 1.45 (s, 9H).

[1913] Step 2: *tert*-Butyl (5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

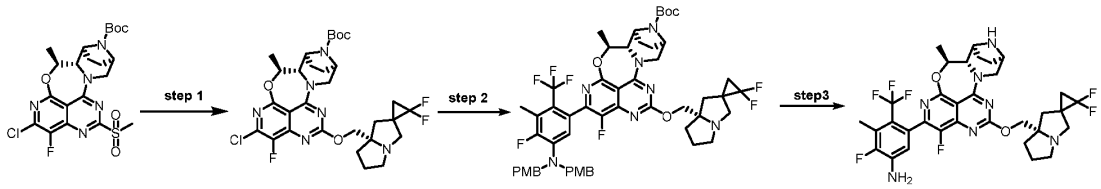
[1914] Under nitrogen, a solution of *tert*-butyl (5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-

3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (150 mg, 0.260 mmol), (5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (371 mg, 0.780 mmol, intermediate 20), cataCXium A Pd G3 (37.8 mg, 0.0500 mmol) and K_3PO_4 (0.4 mL, 1.5 M in water) in THF (2 mL) was stirred at 60 °C for 3 h. The solvent was concentrated under vacuum. The resulting residue was purified by reverse phase chromatography (gradient: 0–100 % acetonitrile in water (0.1% FA)) to yield 202 mg (79.8% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 956.

[1915] Step 3: 2-Fluoro-5-((5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (Compound 61)

[1916] A solution of *tert*-butyl (5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (201 mg, 0.210 mmol) in TFA (9.5 mL) was stirred at 50 °C for 4 h. The reaction mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 45% B in 10 min, 45% B; Wave Length: 254/220 nm; R_{T1}(min): 8.9) to yield 50.3 mg (37.7% yield) of the title compound as a light yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 636. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 6.57 (s, 1H), 5.99 (s, 2H), 5.44 – 5.11 (m, 1H), 4.78 (d, J = 12.9 Hz, 1H), 4.59 – 4.44 (m, 1H), 4.42 – 4.27 (m, 1H), 4.08 (d, J = 10.4 Hz, 1H), 3.97 (d, J = 10.3 Hz, 2H), 3.65 – 3.54 (m, 1H), 3.54 – 3.43 (m, 1H), 3.18 – 2.93 (m, 4H), 2.90 – 2.68 (m, 2H), 2.39 – 2.23 (m, 3H), 2.19 – 2.08 (m, 1H), 2.07 – 1.91 (m, 2H), 1.90 – 1.40 (m, 7H).

[1917] **Example 62:** Compound 62



[1918] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-12-(((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1919] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-

methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (301 mg, 0.590 mmol, intermediate 11) and [rac-(8S)-1',1'-difluorospiro[2,3,5,7-tetrahydro-1*H*-pyrrolizine-6,2'-cyclopropane]-8-yl]methanol (238 mg, 1.17 mmol, intermediate 33) in toluene (3 mL) was added t-BuONa (111 mg, 1.16 mmol) at 0°C. The resulting solution was stirred for 1 h at room temperature. The solution was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0%-10% MeOH / DCM) to afford 231 mg (61.9 % yield) of the title compound as white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 637.

[1920] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-(((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1921] Under nitrogen, a solution of tert-butyl (5S,5aS,6S,9R)-2-chloro-12-(((7a'S)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (121 mg, 0.190 mmol), (5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (217 mg, 0.450 mmol, intermediate 20), cataCXium A Pd G3 (29.2 mg, 0.0400 mmol) and K_3PO_4 (0.4 mL, 1.5 M in H_2O) in THF (2 mL) was stirred for 3 hours at 60 °C. The solution was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH in DCM) to afford 141 mg (71.8% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1034.

[1922] Step 3: 5-((5*S*,5a*S*,6*S*,9*R*)-12-(((7a'*S*)-2,2-Difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (Compound 62)

[1923] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-(((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (141 mg, 0.140 mmol) in TFA (5 mL) was stirred at 50 °C for 4 hours. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30 x 150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 39% B to 59% B in 10 min,

59% B; Wave Length: 254/220 nm; RT1(min): 10.0) to afford 17.8 mg (18.6% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 694. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 6.53 (d, *J* = 56.7 Hz, 1H), 6.01 (s, 2H), 5.13 – 5.03 (m, 1H), 4.59 – 4.47 (m, 1H), 4.22 – 4.10 (m, 2H), 3.95 (d, *J* = 8.7 Hz, 1H), 3.56 (d, *J* = 5.5 Hz, 1H), 3.44 (d, *J* = 6.1 Hz, 1H), 3.09 (s, 1H), 3.01 (s, 2H), 2.72 (d, *J* = 11.9 Hz, 1H), 2.55 (d, *J* = 8.6 Hz, 1H), 2.32 (d, *J* = 3.3 Hz, 3H), 2.11 – 2.03 (m, 1H), 2.02 – 1.93 (m, 1H), 1.90 (d, *J* = 13.3 Hz, 1H), 1.86 – 1.71 (m, 3H), 1.70 – 1.51 (m, 5H), 1.50 – 1.39 (m, 4H).

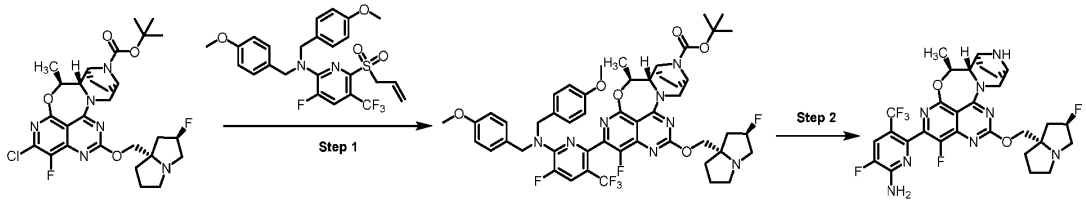
[1924] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Examples **60**, **61**, and **62**.

Cmpd. No.	**^{1}H NMR**	**MS (M+H)$^+$**
64	^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 6.86 – 6.39 (m, 2H), 6.02 (s, 2H), 5.14 – 5.00 (m, 1H), 4.54 – 4.51 (m, 1H), 4.13 – 3.89 (m, 3H), 3.70 (d, *J* = 14.8 Hz, 1H), 3.60 – 3.52 (m, 1H), 3.45 (d, *J* = 6.1 Hz, 1H), 3.27 (s, 1H), 3.09 – 2.85 (m, 3H), 2.62 – 2.53 (m, 2H), 2.32 (s, 4H), 1.95 (m, 1H), 1.90 - 1.52 (m, 7H), 1.43 (m, 3H).	662
65	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.70 – 6.37 (m, 1H), 6.02 (s, 2H), 5.18 – 5.01 (m, 1H), 4.60 – 4.28 (m, 3H), 3.96 (d, J = 8.7 Hz, 1H), 3.61 – 3.51 (m, 1H), 3.49 – 3.43 (m, 1H), 3.42 – 3.35 (m, 1H), 3.03 (d, J = 13.2 Hz, 1H), 2.99 – 2.89 (m, 1H), 2.81 (s, 1H), 2.76 – 2.62 (m, 1H), 2.61 – 2.53 (m, 1H), 2.38 (s, 3H), 2.32 (t, J = 2.5 Hz, 3H), 2.29 – 2.07 (m, 1H), 1.89 – 1.75 (m, 1H), 1.68 – 1.52 (m, 3H), 1.44 (d, 3H).	642
66	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.53 (d, J = 58.5 Hz, 1H), 6.01 (s, 2H), 5.17 – 5.04 (m, 1H), 4.57 – 4.50 (m, 1H), 4.47 – 4.29 (m, 2H), 3.95 (d, J = 8.8 Hz, 1H), 3.63 – 3.50 (m, 1H), 3.44 (d, J = 6.1 Hz, 1H), 3.41 – 3.34 (m, 1H), 3.03 (d, J = 12.8 Hz, 1H), 2.99 – 2.79 (m, 1H), 2.74 – 2.59 (m, 1H), 2.59 – 2.53 (m, 1H), 2.48 – 2.42 (m, 1H), 2.37 (s, 3H), 2.32 (d, J = 3.4 Hz, 3H), 2.27 – 2.12 (m, 1H), 1.87 – 1.74 (m, 1H), 1.73 – 1.48 (m, 3H), 1.43 (d, 3H).	642
67	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.57 (s, 1H), 6.35-6.16 (m, 1H), 5.87 (s, 2H), 5.08 (dd, J = 12.8, 2.5 Hz, 1H), 4.55-4.49 (m, 1H), 4.41-4.36 (m, 1H), 4.13-4.09 (m, 1H), 3.95 (d, J = 8.8 Hz, 1H), 3.61-.40 (m, 6H), 3.13 (t, J = 10.4 Hz, 1H), 3.06-2.81 (m, 4H), 2.33 (s, 3H), 2.13-2.00 (m, 1H), 1.83-1.50 (m, 6H), 1.42 (d, J = 6.3 Hz, 3H), 1.35-1.19 (m, 1H), 1.13 (s, 1H).	630
68	^{1}H NMR (300 MHz, DMSO-d_6, *ppm*) δ 6.63 – 6.56 (s, 1H), 6.37-6.23 (m, 1H), 5.88 (s, 2H), 5.09 (dd, J = 12.8, 2.5 Hz, 1H), 4.60 – 4.45 (m, 1H), 4.17 (d, J = 2.6 Hz, 2H), 3.95 (d, J = 8.8 Hz, 1H), 3.58 (s, 1H), 3.45 (d, J = 5.7 Hz, 1H), 3.12-3.00 (m, 3H), 2.78-2.64 (m, 2H), 2.56 (d, J = 7.8 Hz, 1H), 2.35 (d, J = 2.6 Hz, 3H), 2.15 – 1.85 (m, 2H), 1.92-1.81 (m, 1H), 1.75-1.71 (m, 2H), 1.69 – 1.54 (m, 6H), 1.58 – 1.40 (m, 4H).	676
69	^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) *δ* 6.64 – 6.51 (m, 1H), 6.28 (d, J = 45.1 Hz, 1H), 5.87 (s, 2H), 5.16 – 4.99 (m, 1H), 4.62 – 4.44 (m, 1H), 4.19 – 4.02 (m, 2H), 4.00 – 3.89 (m, 1H), 3.60 (s, 1H), 3.53 – 3.43 (m, 1H), 3.41 – 3.34 (m, 1H), 3.30 – 3.23 (m, 1H), 3.17 – 2.96 (m, 3H), 2.78 – 2.62 (m, 1H), 2.46 – 2.22 (m, 5H), 2.09 – 1.95 (m, 1H), 1.93 – 1.50 (m, 7H), 1.48 – 1.36 (m, 3H).	650

70	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 7.45 (d, J = 12.0 Hz, 1H), 6.76 (d, J = 8.6 Hz, 1H), 6.09 (s, 2H), 5.12-5.02 (m, 1H), 4.54-4.49 (m, 1H), 4.41-4.36 (m, 1H), 4.14-4.08 (m, 1H), 3.94 (d, J = 8.4 Hz, 1H), 3.65-3.40 (m, 6H), 3.13 (t, J = 10.4 Hz, 1H), 3.06-2.83 (m, 4H), 2.74-2.71 (m, 1H), 2.12-2.01 (m, 1H), 1.84-1.52 (m, 6H), 1.42 (d, J = 6.3 Hz, 3H), 1.34-1.22 (m, 1H).	634
71	^{1}H NMR (300 MHz, DMSO-d6) δ 7.48 (d, J = 12.0 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 6.11 (s, 2H), 5.13 (dd, J = 13.1, 2.5 Hz, 1H), 4.57 (dd, J = 8.7, 6.3 Hz, 1H), 4.42 – 4.26 (m, 2H), 4.01 (d, J = 8.5 Hz, 1H), 3.66 (s, 1H), 3.54 (d, J = 5.4 Hz, 2H), 3.23 (d, J = 8.9 Hz, 1H), 3.19 – 3.13 (m, 1H), 3.13 – 3.02 (m, 2H), 2.75 – 2.56 (m, 2H), 2.47 – 2.22 (m, 3H), 1.84 (d, J = 10.3 Hz, 1H), 1.77 – 1.54 (m, 3H), 1.45 (d, J = 6.3 Hz, 3H).	640
72	^{1}H-NMR (300 MHz, $CDCl_3$, *ppm*) δ 7.50 (d, *J* = 6 Hz, 1H), 6.73 (d, *J* = 9 Hz, 1H), 6.64 (s, 1H), 5.46 – 5.35 (m, 1H), 5.22 (s, 1H), 4.41 – 4.14 (m, 3H), 4.02 (s, 3H), 3.8 – 3.53 (m, 2H), 3.46 – 3.17 (m, 3H), 3.16 – 2.93 (m, 2H), 2.43 – 2.13 (m, 3H), 2.11 – 1.87 (m, 4H), 1.85 – 1.65 (m, 3H), 1.57 (d, *J* = 6Hz, 3H).	618
73	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 7.23 (d, *J* = 13.6 Hz, 1H), 6.68 (d, *J* = 9.0 Hz, 1H), 5.70 (s, 2H), 5.40 – 5.15 (m, 2H), 4.66 – 4.61 (m, 1H), 4.17 - 4.04 (m, 3H), 3.89 - 3.74 (m, 2H), 3.27 - 3.09 (m, 6H), 2.92 - 2.88 (m, 1H), 2.19 – 1.69 (m, 9H), 1.53 - 1.47 (m, 3H), 1.33 - 1.24 (m, 2H).	632
74	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.62 (d, *J* = 2.7 Hz, 1H), 6.47 (d, *J* = 2.7 Hz, 1H), 5.40 – 5.17 (m, 3H), 5.08 (d, *J* = 12 Hz, 1H), 4.61 – 4.48 (m, 1H), 4.14 – 3.91 (m, 3H), 3.57 (s, 1H), 3.45 (d, *J* = 5.4 Hz, 1H), 3.20 – 3.07 (m, 2H), 3.06 – 2.97 (m, 2H), 2.86 – 2.74 (m, 2H), 2.25 (s, 3H), 2.16 (d, *J* = 4.4 Hz, 1H), 2.02 (m, 2H), 1.93 – 1.75 (m, 4H), 1.72 – 1.52 (m, 3H), 1.44 (d, *J* = 6.3 Hz, 3H).	598
75	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.65 - 6.62 (m, 1H), 6.30 - 5.92 (m, 1H), 5.38 - 5.09 (m, 4H), 4.57 - 4.52 (m, 1H), 4.10 - 3.97 (m, 3H), 3.63 - 3.49 (m, 2H), 3.18 - 3.01 (m, 6H), 2.89 - 2.83 (m, 1H), 2.22 (s, 3H), 2.21 - 1.99 (m, 3H), 1.87 - 1.60 (m, 7H), 1.45 - 1.43 (m, 3H).	646
76	^{1}H NMR (300 MHz, DMSO-d_6, *ppm*) δ 6.71 (d, *J* = 9.4 Hz, 1H), 5.40 (d, *J* = 10.2 Hz, 2H), 5.20 (s, 1H), 5.08 (dd, *J* = 12.8, 2.5 Hz, 1H), 4.62 – 4.47 (m, 1H), 4.16 – 3.98 (m, 2H), 3.95 (d, *J* = 8.7 Hz, 1H), 3.58 (s, 1H), 3.45 (d, *J* = 5.8 Hz, 1H), 3.15 – 3.07 (m, 2H), 3.07 – 2.97 (m, 2H), 2.89 – 2.80 (m, 2H), 2.26 (d, *J* = 2.6 Hz, 3H), 2.16 (d, *J* = 4.7 Hz, 1H), 2.02 (dd, *J* = 14.4, 4.9 Hz, 2H), 1.91 – 1.69 (m, 4H), 1.73 – 1.50 (m, 3H), 1.45 (d, *J* = 6.3 Hz, 3H).	616
77	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.55 (d, J = 14.3, 1H), 6.37 (s, 3H), 5.09 (dd, J = 12.9, 2.6 Hz, 1H), 4.56-4.52 (m, 1H), 4.43-4.33 (m, 1H), 4.16-4.13 (m, 1H), 3.96 (d, J = 8.8 Hz, 1H), 3.64 – 3.41 (m, 6H), 3.15 (t, J = 10.4 Hz, 1H), 3.08 – 2.78 (m, 4H), 2.14 – 1.99 (m, 1H), 1.82-1.73 (m, 2H), 1.66-1.54 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H), 1.37-1.24 (m, 1H).	634
78	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 9.01 (d, *J* = 5.2 Hz, 1H), 8.85 (s, 1H), 7.96 (d, *J* = 5.2 Hz, 1H), 5.11 (d, *J* = 9 Hz, 1H), 4.65 – 4.52 (m, 1H), 4.48 – 4.25 (m, 2H), 3.99 (d, *J* = 8.6 Hz, 1H), 3.62 – 3.50 (m, 2H), 3.46 (d, *J* = 5.8 Hz, 1H), 3.27 – 3.17 (m, 1H), 3.15 (d, *J* = 4.5 Hz, 1H), 3.06 (d, *J* = 13.3 Hz, 2H), 2.81 (s, 1H), 2.75 – 2.58 (m, 2H), 2.44 – 2.30 (m, 2H), 1.81 (d, *J* = 10.5 Hz, 1H), 1.73 – 1.52 (m, 3H), 1.45 (d, *J* = 6.3 Hz, 3H).	608
79	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 7.60 – 7.46 (m, 2H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.28 – 7.15(m, 1H), 6.85 (s, 1H), 6.60 (s, 2H), 5.19 – 5.08 (m, 1H), 4.66 – 4.52 (m, 1H), 4.45 – 4.28 (m, 2H), 3.98 (d, *J* = 8.6 Hz, 1H), 3.65-3.49 (m, 2H), 3.46 (d, *J* = 5.5 Hz, 1H), 3.22 (d, *J* = 8.8 Hz, 1H), 3.14 (s, 1H), 3.05 (d, *J* = 14.1 Hz, 2H), 2.74 (d, *J* = 18.8 Hz, 1H), 2.69 – 2.57 (m, 1H), 2.47 – 2.21 (m, 3H), 1.92 – 1.78 (m, 1H), 1.74 – 1.51 (m, 3H), 1.45 (d, *J* = 6.3 Hz, 3H).	605

80	^{1}H NMR (300 MHz, DMSO-*d*$_6$, *ppm*) δ 9.88 (s, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.43 – 7.30 (m, 1H), 7.26 (t, J = 3.3 Hz, 1H), 7.13 (dd, J = 15.2, 7.1 Hz, 1H), 7.01 (d, J = 2.6 Hz, 1H), 5.12 (d, J = 12.5 Hz, 1H), 4.91 (s, 2H), 4.59-4.53 (m, 1H), 4.06-3.95 (m, 3H), 3.56 (d, J = 13.9 Hz, 3H), 3.45 (s, 1H), 3.12 – 2.94 (m, 2H), 2.79 (s, 1H), 2.67 – 2.53 (m, 1H), 2.47 – 2.31 (m, 2H), 2.29 – 2.09 (m, 2H), 1.97-1.83 (m, 3H), 1.70-1.65 (m, 4H), 1.43 (t, J = 5.1 Hz, 3H), 1.25 (s, 1H),0.96 (t, J = 7.4 Hz, 1H), 0.80 (t, J = 7.4 Hz, 2H).	623
81	^{1}H NMR (300 MHz, DMSO-*d*$_6$, *ppm*) δ 10.15 (s, 1H), 8.01-7.92 (m, 1H), 7.52-7.45 (m, 1H), 7.40 – 7.34 (m, 1H), 7.19 (d, J = 2.5 Hz, 1H), 5.29 (d, J = 54 Hz,1H), 4.83 (dd, J = 18.4, 13.2 Hz, 1H), 4.54 (dd, J = 14.2, 12.1 Hz, 1H), 4.38-4.31 (m, 1H), 4.17 – 4.05 (m, 2H), 4.05 – 3.94 (m, 2H), 3.62 (s, 1H), 3.53 (s, 1H), 3.11-3.01 (m, 4H), 2.85-2.76 (m, 2H), 2.14 (s, 1H), 2.03 (d, J = 9.7 Hz, 2H), 1.90 – 1.61 (m, 7H).	629
82	^{1}H NMR (400 MHz, DMSO-*d*$_6$, *ppm*) *δ* 7.90 (d, J = 8.3 Hz, 1H), 7.63 – 7.48 (m, 1H), 7.47 – 7.19 (m, 2H), 5.29 (d, J = 54.4 Hz, 1H), 5.16 – 5.05 (m, 1H), 4.65 – 4.47 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 4.06 – 3.91 (m, 2H), 3.64 – 3.53 (m, 1H), 3.51 – 3.42 (m, 1H), 3.17 – 3.03 (m, 3H), 3.01 (s, 1H), 2.91 – 2.77 (m, 1H), 2.24 – 2.12 (m, 1H), 2.11 – 1.93 (m, 2H), 1.91 – 1.73 (m, 4H), 1.72 – 1.51 (m, 3H), 1.50 – 1.37 (m, 3H).	637
83	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.57 (s, 2H), 5.27 (d, 1H), 5.14 – 5.04 (m, 1H), 4.98 (s, 2H), 4.60 – 4.43 (m, 1H), 4.17 – 3.98 (m, 2H), 3.94 (d, J = 8.8 Hz, 1H), 3.62 – 3.53 (m, 1H), 3.49 – 3.41 (m, 1H), 3.20 – 3.07 (m, 2H), 3.07 – 2.95 (m, 2H), 2.90 – 2.72 (m, 4H), 2.72 – 2.55 (m, 2H), 2.30 – 2.11 (m, 1H), 2.10 – 1.98 (m, 2H), 1.97 – 1.73 (m, 6H), 1.72 – 1.51 (m, 3H), 1.45 (d, J = 6.3 Hz, 3H).	590

[1925] **Example 84**: Compound 84



[1926] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-5fluoro-3-(trifluoromethyl)pyridin-2-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1927] Under nitrogen, a solution of *tert*-butyl rac-(4R,7S,8S,9S)-13-chloro-14-fluoro-9-methyl-17-[[rac-(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-10-oxa-2,12,16,18,20-pentazapentacyclo[9.7.1.14,7.02,8.015,19]icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (10.0 mg, 0.02 mmol), $Pd(OAc)_2$ (1.89 mg, 0.01 mmol, Example 58, step 1), 6-allylsulfonyl-3-fluoro-N,N-bis[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)pyridin-2-amine (13.3 mg, 0.03 mmol, intermediate 64), $P(t\text{-}Bu)_2Me.HBF_4$ (0.42 mg) and Cs_2CO_3 (10.9 mg, 0.03 mmol) in 1,4-dioxane (2 mL) was stirred at 120 °C overnight. The resulting mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was

purified by flash chromatography on silica gel (gradient: 0%-5% MeOH/DCM) to yield 12 mg (72.8% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 977.

[1928] Step 2: 3-Fluoro-6-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-(trifluoromethyl)pyridin-2-amine (Compound 84)

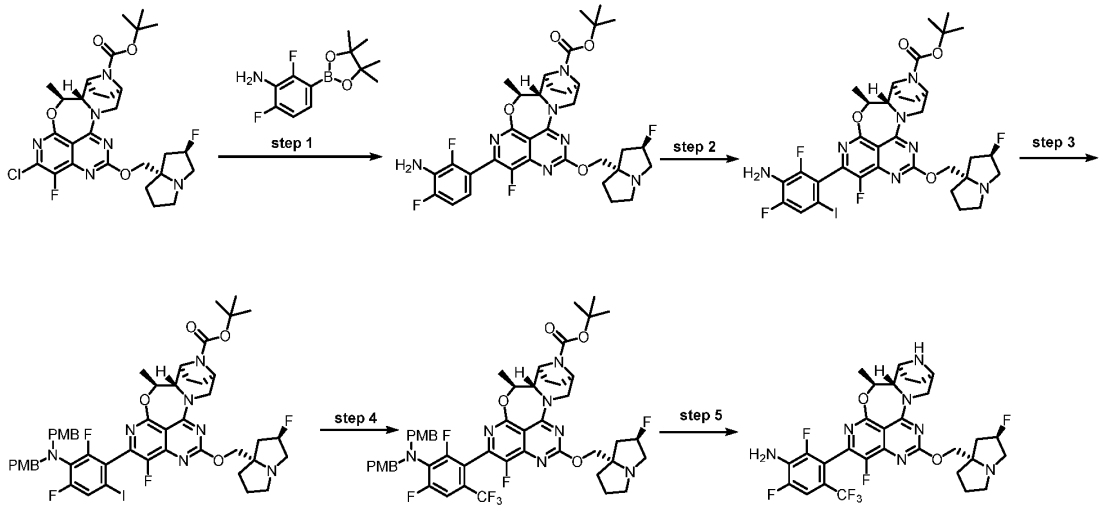
[1929] A solution of *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-5-fluoro-3-(trifluoromethyl)pyridin-2-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (12.0 mg, 0.01 mmol) in TFA (2 mL) was stirred at 50 °C for 4 hours. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC (conditions: Column: XBridge Prep OBD C18 Column, 30×150 mm 5um; Mobile Phase A:Water(10 mmol/L NH_4HCO_3), Mobile Phase B:ACN; Flow rate:60 mL/min; Gradient:12 B to 42 B in 7 min; 254 nm; RT1:6.5) to afford the title compound (1.5 mg, 19.2% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$= 637. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*): δ 7.86 (m, 1H), 7.26 (s, 2H), 5.34 (s, 1H), 5.17 – 5.06 (m, 1H), 4.50 (m, 1H), 4.09 (m, 1H), 4.05 – 3.89 (m, 2H), 3.56 (s, 2H), 3.09 (s, 2H), 3.02 (d, *J* = 13.2 Hz, 2H), 2.82 (d, *J* = 7.9 Hz, 2H), 2.25 – 1.94 (m, 3H), 1.81 (m, 4H), 1.64 (s, 2H), 1.55 (s, 1H), 1.43 (m, 3H).

[1930] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Example **84**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
85	^{1}H NMR (400 MHz, DMSO-d_6, *ppm*): δ 7.76 (d, *J* = 8.9 Hz, 1H), 7.42 – 7.20 (m, 1H), 6.91 (s, 2H), 6.62 (d, *J* = 8.8 Hz, 1H), 5.43 – 5.19 (m, 1H), 5.09 (m, 1H), 4.49 (m, 1H), 4.09 (d, *J* = 10.3 Hz, 1H), 4.06 – 3.93 (m, 2H), 3.50 – 3.37 (m, 1H), 3.18 – 3.04 (m, 1H), 3.03 (d, *J* = 12.5 Hz, 2H), 2.91 – 2.75 (m, 2H), 2.22 – 2.10 (m, 2H), 2.10 – 2.02 (m, 1H), 1.99 (m, 1H), 1.91 – 1.72 (m, 4H), 1.65 (m, 2H), 1.55 (m, 1H), 1.43 (d, *J* = 6.3 Hz, 3H).	619
86	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 7.87-7.78 (m, 1H), 7.27 (s, 2H), 5.10 (d, J = 12.0 Hz, 1H), 4.56-4.45 (m, 1H), 4.22-4.11 (m, 2H), 3.96 (d, J = 8.7 Hz, 1H), 3.60-3.55 (m, 1H), 3.44 (d, J = 6.2 Hz, 1H), 3.09-2.97 (m, 3H), 2.75-2.68 (m, 2H), 2.56-2.53 (m, 1H), 2.13-2.05 (m, 1H), 2.02-1.94 (m, 1H), 1.93-1.86 (m, 1H), 1.84-1.76 (m, 2H), 1.74-1.71(m, 1H), 1.66-1.45 (m, 5H), 1.48-1.45 (d, J = 6.3 Hz, 4H).	681
87	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 7.87 (d, J = 11.2 Hz, 1H), 7.28 (s, 2H), 5.17 – 5.07 (m, 1H), 4.54-4.48 (m, 1H), 4.35 (q, J = 12.0 Hz, 2H), 4.02 – 3.93 (m, 1H), 3.71-3.57 (m, 2H), 3.45 (d, J = 5.4 Hz, 1H), 3.25- 3.17 (m, 1H), 3.14-2.99 (m, 3H), 2.77 – 2.60 (m, 2H), 2.46 – 2.29 (m, 3H), 1.91-1.78 (m, 1H), 1.75-1.51 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H).	641

88	^{1}H NMR (300 MHz, DMSO-d_6, *ppm*) δ 8.79 (dd, *J* = 6.5, 5.0 Hz, 1H), 7.68 (dd, *J* = 9.8, 5.0 Hz, 1H), 5.32 – 5.06 (m, 1H), 4.52 (m, 1H), 4.35 (q, J = 11.0 Hz, 1H), 4.00 (dd, J = 12.6, 9.5 Hz, 2H), 3.60 – 3.51 (m, 1H), 3.45 – 3.37 (m, 1H), 3.23 – 3.03 (m, 3H), 3.03 – 2.90 (m, 2H), 2.84 – 2.64 (m, 2H), 2.59 (d, J = 2.3 Hz, 3H), 2.48 – 2.26 (m, 2H), 1.99 – 1.78 (m, 1H), 1.75 – 1.53 (m, 4H), 1.45 (dd, J = 8.2, 6.3 Hz, 3H).	622
89	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 7.93 (d, *J* = 8.4 Hz, 1H), 7.83 – 7.59 (m, 2H), 7.50 – 7.29 (m, 2H), 5.15 (dd, *J* = 12.8, 2.5 Hz, 1H), 4.72 – 4.53 (m, 1H), 4.37 (m, 2H), 4.10 – 3.90 (m, 4H), 3.60 – 3.45 (m, 4H), 3.26 – 3.00 (m, 4H), 2.82 – 2.59 (m, 2H), 2.42 – 2.25 (m, 2H), 1.83 (d, *J* = 10.9 Hz, 1H), 1.64 (m, 3H), 1.45 (d, *J* = 6.3 Hz, 3H).	620

[1931] **Example 90:** Compound 90



[1932] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluorophenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1933] Under nitrogen, a solution of 2,6-difluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (305 mg, 1.19 mmol, intermediate 62), *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (354 mg, 0.597 mmol, Example 58, step 1), cataCXium A Pd G_3 (86.9 mg, 0.120 mmol) and K_3PO_4 (1.5 M in water) (1.2 mL) in tetrahydrofuran (6 mL) was stirred at 60 °C for 1 hour. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-5%

MeOH in DCM) to afford the title compound (390 mg, 95.3% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 686.

[1934] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-6-iodophenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1935] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluorophenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (390 mg, 0.570 mmol), NIS (384 mg, 1.71 mmol) and TsOH (78.3 mg, 0.460 mmol) in *N*,*N*-dimethylacetamide (6 mL) was stirred at room temperature overnight. Additional NIS (384 mg, 1.71 mmol) and TsOH (78.3 mg, 0.460 mmol) were added, and the mixture was stirred at room temperature for another 1 hour. The solution was loaded to reverse phase column directly and eluted with 0-90% acetonitrile in water (0.5% NH_4HCO_3) to afford the title compound (486 mg, 94.1% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 812.

[1936] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-6-iodophenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1937] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-6-iodophenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (580 mg, 0.710 mmol) was added NaH (71.5 mg, 1.79 mmol, 60% suspension in oil) at 0 °C. The mixture was stirred for 15 min before PMBCl (247 mg, 1.57 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-5% MeOH in DCM) to afford the title compound (320 mg, 39.4% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 1052.

[1938] Step 4: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

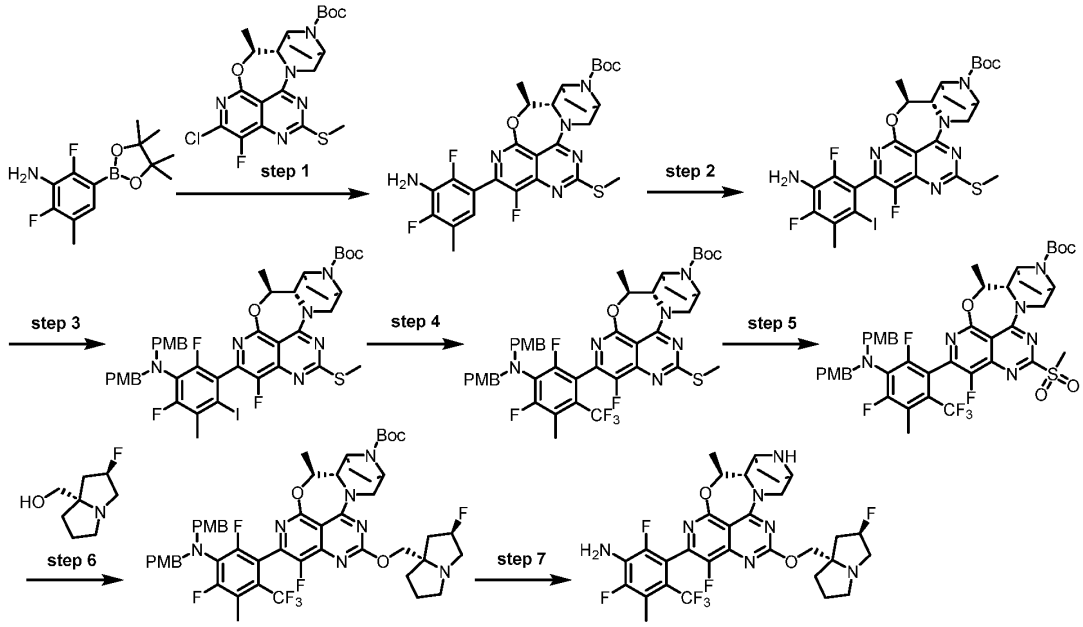
[1939] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-6-iodophenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-

1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (320 mg, 0.300 mmol) in *N*,*N*-dimethylacetamide (10 mL) was added copper 2,2-difluoro-2-(fluorosulfonyl)acetate (1.90 g, 4.56 mmol) and Cu (292 mg, 4.56 mmol) at 0 °C was added. The reaction was stirred at 90 °C for 30 min. The solution was cooled to room temperature. The reaction mixture was extracted with EtOAc and washed with water. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-5% MeOH in DCM) to afford the title compound (200 mg, 58.7% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 994.

[1940] Step 5: 2,6-Difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline (Compound 90)

[1941] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (120 mg, 0.120 mmol) in 2,2,2-trifluoroacetic acid (1.5 mL) was stirred at 50 °C for 1 hour. The solvent was concentrated under vacuum. The crude were purified by Prep-HPLC with the following conditions:(Column: XBridge Prep OBD C18 Column, 19*250 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH; Flow rate: 25 mL/min; Gradient: 60% B to 85% B in 9 min, 85% B; Wave Length: 220/254 nm; R_{T1}(min): 9.03) to afford the title compound (24.1 mg, 30.5% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 654. ^{1}H NMR (300 MHz, DMSO-d6) δ 7.55 – 7.39 (m, 1H), 6.23 (d, J = 9.3 Hz, 2H), 5.27 (d, J = 54.4 Hz, 1H), 5.14 – 5.00 (m, 1H), 4.62 – 4.46 (m, 1H), 4.14 – 3.90 (m, 3H), 3.56 (s, 1H), 3.43 (d, J = 5.9 Hz, 1H), 3.16 – 2.92 (m, 4H), 2.92 – 2.67 (m, 2H), 2.28 – 1.93 (m, 3H), 1.93 – 1.48 (m, 7H) , 1.42 (dd, J = 6.4, 3.1 Hz, 3H).

[1942] **Example 91:** Compound 91



[1943] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1944] Under nitrogen, to a solution of 2,6-difluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (280 mg, 1.04 mmol, intermediate 31), *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (501 mg, 1.04 mmol, intermediate 46) and cataCXium A Pd G3 (75.7 mg, 0.100 mmol) in tetrahydrofuran (5.4 mL) and Water (1.1 mL) was added K_3PO_4 (1.5 M solution in H_2O, 1.1 mL, 1.65 mmol) at room temperature. The resulting mixture was stirred for 3 hours at 90°C. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-26% EtOAc in petroleum ether) to afford the title compound (260 mg, 42.5% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 589$.

[1945] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1946] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (260 mg, 0.440 mmol), TsOH (9.2 mg, 0.0500 mmol and NIS (130 mg, 0.580 mmol) in N,N-dimethylformamide (3 mL) was stirred at room temperature for 1 hour. The solvent was concentrated under vacuum. The residue was

purified by flash chromatography on silica gel (gradient: 0-14% EtOAc in petroleum ether) to afford the title compound (320 mg, 98.3% yield) as a brown solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 715.

[1947] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1948] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (320 mg, 0.448 mmol) in N,N-dimethylformamide (5 mL) was added NaH (90.0 mg, 2.25 mmol, 60% suspension in oil) and the mixture was stirred at 0 °C for 30 minutes. Then PMBCl (175 mg, 1.12 mmol) was added and the mixture was stirred at room temperature for 5 hours. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-14% EtOAc in petroleum ether) to afford the title compound (400 mg, 65.5% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 955.

[1949] Step 4: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1950] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (370 mg, 0.390 mmol) and CuI (74.0 mg, 0.390 mmol) in N,N-dimethylacetamide (5 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.25 mL, 1.93 mmol). The resulting solution was stirred at 90°C for 3 hours. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc in petroleum ether) to afford the title compound (280 mg, 74.9% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 897.

[1951] Step 5: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1952] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-

hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (300 mg, 0.330 mmol) in EtOAc (5 mL) was added m-CPBA (174 mg, 1.01 mmol) at 0 °C. The solution was stirred at room temperature for 3 hours. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with 0-54% EtOAc in petroleum ether to afford the title compound (192 mg, 49.4% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 929.

[1953] Step 6: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1954] To a solution of ((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methanol (42.8 mg, 0.270 mmol, intermediate 14) in tetrahydrofuran (3 mL) was added NaH (30.0 mg, 0.75 mmol, 60% suspension in oil) at 0 °C and the mixture was stirred for 30 minutes at room temperature. Then *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (192 mg, 0.210 mmol) was added and the mixture was stirred at room temperature for 2 hours. The reaction system was quenched with aqueous NH_4Cl and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-55% EtOAc in petroleum ether) to afford the title compound (120 mg, 57.6% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 1008.

[1955] Step 7: 2,6-Difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline

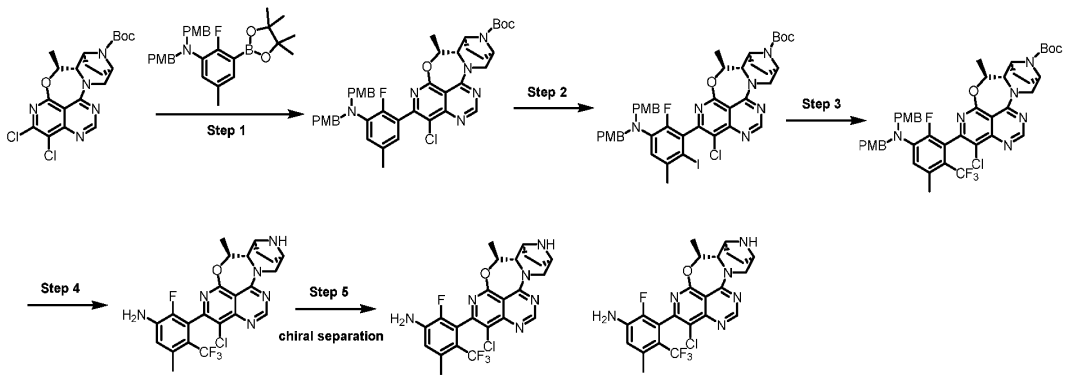
[1956] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (120 mg, 0.120 mmol) in TFA (5 mL) was stirred at 50 °C for 2 hours. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 55% B in 9 min, 55% B; Wave Length: 254/220 nm; R_{T1}(min): 8.8) to afford the title compound (18.2 mg, 22.6% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 668. ^1H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.16 (d, J = 10.7 Hz,

2H), 5.29 (d, J = 54.3 Hz, 1H), 5.16 – 5.01 (m, 1H), 4.66 – 4.50 (m, 1H), 4.18 – 3.94 (m, 3H), 3.71 – 3.46 (m, 2H), 3.07 (dd, J = 24.1, 9.1 Hz, 4H), 2.92 – 2.71 (m, 1H), 2.30 (s, 3H), 2.23 – 2.12 (m, 1H), 2.11 – 1.94 (m, 2H), 1.93 – 1.52 (m, 7H), 1.44 (d, J = 6.3 Hz, 3H).

[1957] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Example **91**.

Cmpd. No.	^{1}H NMR	MS (M+H)$^+$
92 (Isomer 1)	^{1}H NMR (300 MHz, CD_3OD-*d6, ppm*) δ 6.87 (d, J = 8.8 Hz, 1H), 5.37 (d, J = 13.3 Hz, 1H), 4.58-4.56 (m, 1H), 4.51 (s, 2H), 4.09 (m, 1H), 3.79 – 3.67 (m, 2H), 3.63-3.55 (s, 1H), 3.42-3.35 (m, 2H), 3.29-3.20 (m, 1H), 3.18-3.10 (m, 1H), 2.79 – 2.49 (m, 4H), 2.53 – 2.38 (m, 3H), 2.13-2.07 (m, 1H), 1.82-1.73 (m, 3H), 1.59 (dd, J = 6.4, 2.2 Hz, 3H), 1.31 (s, 1H)	654
92 (Isomer 2)	^{1}H NMR (300 MHz, CD_3OD-*d6, ppm*) δ 6.87 (d, J = 8.8 Hz, 1H), 5.44-5.39 (m, 1H), 4.61-4.46 (m, 3H), 4.16-4.11 (m, 1H), 3.83 – 3.63 (m, 3H), 3.52-3.35 (m, 2H), 3.30-3.16 (m, 2H), 2.74-2.46 (m, 4H), 2.46-2.35 (m, 3H), 2.18-2.04 (m, 1H), 1.98 -1.73 (m, 3H), 1.62-1.57 (m, 3H), 1.31 (s, 1H).	654

[1958] **Examples 93, 94, and 95**: Compounds 93, 94, and 95



[1959] Step 1: *tert*-Butyl(5S,5aS,6S,9R)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methylphenyl)-1-chloro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1960] Under nitrogen, a solution of 2-fluoro-N,N-bis[(4-methoxyphenyl)methyl]-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (217 mg, 0.44 mmol, intermediate 19), tert-butyl rac-(4R,7S,8S,9S)-13,14-dichloro-9-methyl-10-oxa-2,12,16,18,20-pentazapentacyclo[9.7.1.14,7.02,8.015,19]icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (100 mg, 0.22 mmol, intermediate 47), Cs_2CO_3 (216 mg, 0.66 mmol) and $Pd(PPh_3)_4$ (128 mg, 0.11 mmol) in dioxane and water (0.5 mL) was stirred for 1 h at 95 °C. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% MeOH/DCM) to yield 160 mg (92.6% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$= 781.

[1961] Step 2: *tert*-Butyl(5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-1-chloro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1962] To a solution of tert-butyl rac-(4R,7S,8S,9S)-13-[3-[bis[(4-methoxyphenyl)methyl]amino]-2-fluoro-5-methyl-phenyl]-14-chloro-9-methyl-10-oxa-2,12,16,18,20-pentazapentacyclo[9.7.1.14,7.02,8.015,19]icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (200 mg, 0.26 mmol) in acetic acid (3 mL) was added NIS (57.6 mg, 0.26 mmol). The resulting mixture was stirred for 1h at room temperature. The reaction system was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% MeOH/DCM) to yield 165 mg (71.1% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$= 907.

[1963] Step 3: *tert*-Butyl(5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-chloro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

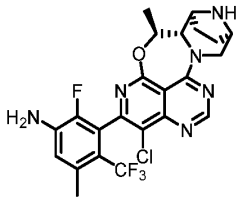
[1964] Under nitrogen, to a solution of methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (1.1 g, 26.5 mmol) in N,N-dimethylformamide (6 mL) was added tert-butyl rac-(4R,7S,8S,9S)-13-[3-[bis[(4-methoxyphenyl)methyl]amino]-2-fluoro-6-iodo-5-methyl-phenyl]-14-chloro-9-methyl-10-oxa-2,12,16,18,20-pentazapentacyclo[9.7.1.14,7.02,8.015,19]icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (160 mg, 0.18 mmol) and CuI (34.2 mg, 0.18 mmol) at 0 °C. The resulting solution was stirred at 90 °C for 30 min. The resulting mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by reverse phase chromatography (gradient: 0–60 % acetonitrile in water (0.1% NH_4HCO_3)) to afford 120 mg (80.1% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$= 849.

[1965] Step 4: 3-((5*S*,5a*S*,6*S*,9*R*)-1-chloro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-5-methyl-4-(trifluoromethyl)aniline (mixture of two atropisomers) (Compound 93)

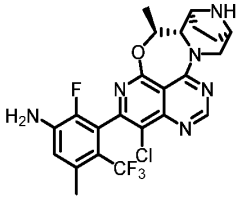
[1966] A solution of tert-butyl rac-(4R,7S,8S,9S)-13-[3-[bis[(4-methoxyphenyl)methyl]amino]-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl]-14-chloro-9-methyl-10-oxa-2,12,16,18,20-pentazapentacyclo[9.7.1.14,7.02,8.015,19]icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (30.0 mg, 0.04 mmol) in TFA (1.5 mL) was stirred at 50 °C for 4 hours. The solvent was concentrated under vacuum and the residue was purified by Prep-HPLC ((Column: XSelect CSH Fluoro Phenyl, 30*150 mm, 5μm; Mobile Phase

A: Water(10 mmol/L NH4HCO3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 55% B in 9.5 min, 55% B; Wave Length: 254/220 nm; RT1(min): 7.98; Number Of Runs: 0) to afford 8.2 mg (45.6% yield) of Compound **93** (mixture of atropisomers) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$= 509. ^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 8.71 (s, 1H), 6.89 – 6.64 (m, 1H), 5.95 (d, *J* = 13.0 Hz, 2H), 5.24 – 5.08 (m, 1H), 4.75 – 4.51 (m, 1H), 4.00 (t, *J* = 8.3 Hz, 1H), 3.54 (s, 1H), 3.43 (s, 1H), 3.02 (d, *J* = 12.7 Hz, 1H), 2.76 (s, 1H), 2.38 – 2.21 (m, 3H), 1.79 (d, *J* = 8.9 Hz, 1H), 1.65 (m, 3H), 1.44 (d, *J* = 6.3 Hz, 3H).

[1967] Step 5: 3-((5*S*,5a*S*,6*S*,9*R*)-1-chloro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-2-fluoro-5-methyl-4-(trifluoromethyl)aniline (two single atropisomers)



94



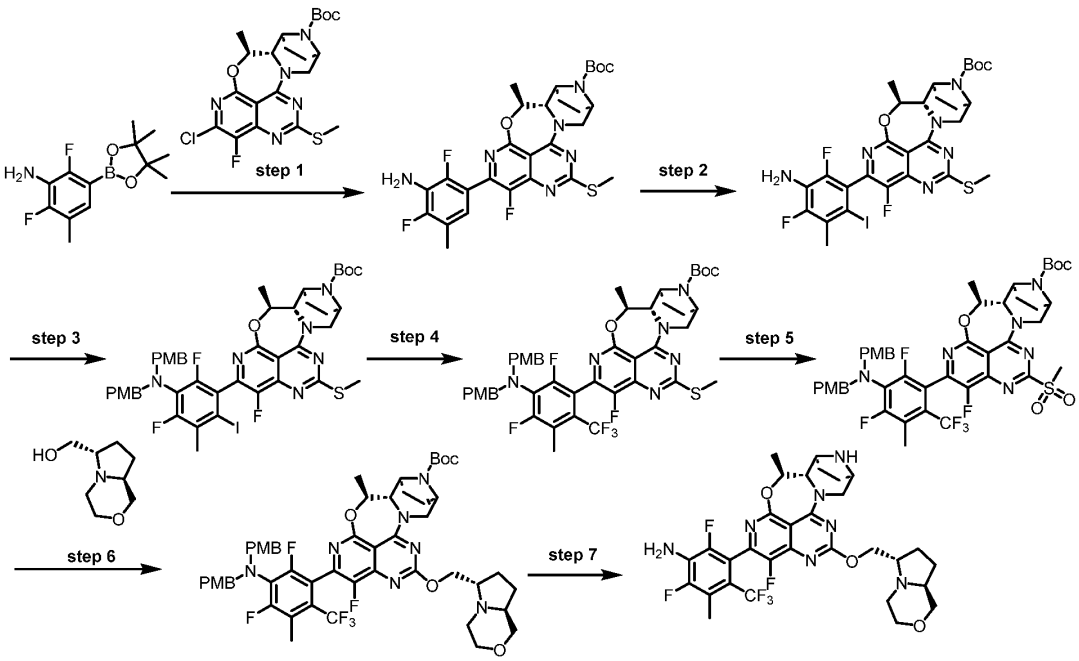
95

[1968] 60 mg the product from step 4 was separated by Chiral Prep-HPLC Column: (CHIRALPAK ID, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2 M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 30% B to 30% B in 20 min; Wave Length: 220/254 nm; RT1(min): 10.613; RT2(min): 16.407; Sample Solvent: EtOH--HPLC; Injection Volume: 0.8 mL; Number Of Runs: 4) to afford 18.5 mg (17.2% yield) faster peak and 20.5 mg (19% yield) slower peak as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$= 509.

[1969] **94:** ^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 8.73 (s, 1H), 6.80 (m, 1H), 5.97 (d, *J* = 17.4 Hz, 2H), 5.22 (m, 1H), 4.66 (m, 1H), 4.02 (t, *J* = 9.6 Hz, 1H), 3.64 – 3.42 (m, 2H), 3.05 (d, *J* = 12.5 Hz, 1H), 2.34 (m, 3H), 1.84 (m, 1H), 1.79 – 1.51 (m, 3H), 1.45 (d, *J* = 6.3 Hz, 3H).

[1970] **95:** ^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 8.73 (s, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 5.95 (s, 2H), 5.21 (m, 1H), 4.65 (m, 1H), 4.00 (dd, *J* = 8.7, 1.5 Hz, 1H), 3.51 (m, 5.9 Hz, 2H), 3.04 (d, *J* = 12.7 Hz, 1H), 2.82 (s, 1H), 2.36 (m, 3H), 1.93 – 1.79 (m, 1H), 1.74 – 1.51 (m, 3H), 1.45 (d, *J* = 6.4 Hz, 3H).

[1971] **Example 96:** Compound 96



[1972] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1973] Under nitrogen, to a mixture of 2,6-difluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (280 mg, 1.04 mmol), *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (501 mg, 1.04 mmol) and cataCXium A Pd G3 (75.7 mg, 0.100 mmol) in tetrahydrofuran (5.4 mL) and water (1.1 mL) was added K_3PO_4 (1.5M in H_2O, 1.1 mL). The resulting mixture was stirred for 3 hours at 90°C. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-26% EtOAc in petroleum ether) to afford the title compound (260 mg, 42.5% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 589.

[1974] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1975] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (260 mg, 0.440 mmol), TsOH (9.2 mg, 0.0500 mmol and NIS (130 mg, 0.580 mmol) in N,N-dimethylformamide (3 mL) was stirred at room temperature for 1 hour. The solvent was concentrated under vacuum. The residue was

purified by flash chromatography on silica gel (gradient: 0-14% EtOAc in petroleum ether) to afford the title compound (320 mg, 98.3% yield) as a brown solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 715.

[1976] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1977] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (320 mg, 0.448 mmol) in N,N-dimethylformamide (5 mL) was added NaH (90.0 mg, 2.25 mmol, 60% suspension in mineral oil), and the mixture was stirred at 0 °C for 30 minutes. Then PMBCl (175 mg, 1.12 mmol) was added, and the mixture was stirred at room temperature for 5 hours. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-14% EtOAc in petroleum ether) to afford the title compound (400 mg, 65.5% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 955.

[1978] Step 4: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1979] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (370 mg, 0.390 mmol) and CuI (74.0 mg, 0.390 mmol) in N,N-dimethylacetamide (5 mL) was added methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.25 mL, 1.93 mmol), and the mixture was stirred at 90°C for 3 hours. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc in petroleum ether) to afford the title compound (280 mg, 74.9% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 897.

[1980] Step 5: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[1981] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (300 mg, 0.330 mmol) in EtOAc (5 mL) was added m-CPBA (174 mg, 1.01 mmol) in batches at 0 °C, and the mixture was stirred at room temperature for 3 hours. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-54% EtOAc in petroleum ether) to afford the title compound (192 mg, 49.4% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 929.

[1982] Step 6: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

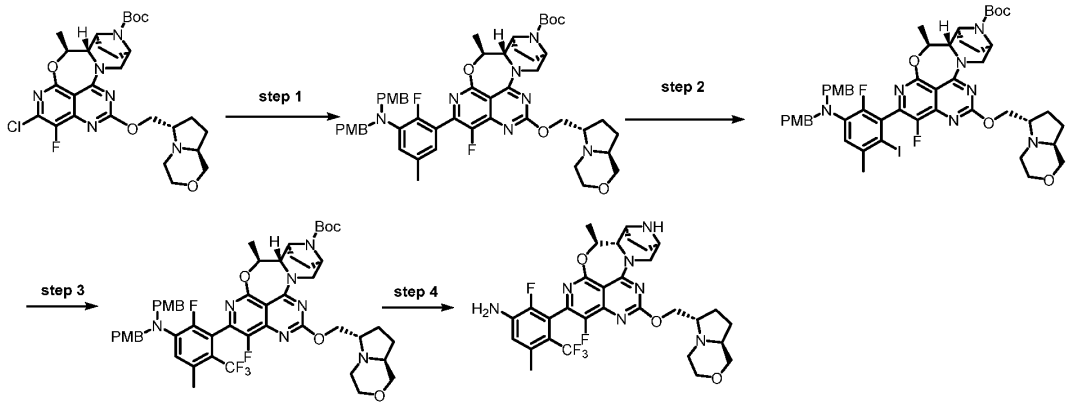
[1983] Under nitrogen, to a solution of ((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)methanol (55.0 mg, 0.350 mmol) in tetrahydrofuran (3 mL) was added NaH (65.0 mg, 1.63 mmol, 60% suspension in mineral oil) at 0 °C. The solution was stirred for 30 minutes at room temperature. Then *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (192 mg, 0.210 mmol) was added and the mixture was stirred at room temperature for 2 hours. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-55% EtOAc in petroleum ether) to afford the title compound (190 mg, 37.9% yield) as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+$ = 1009.

[1984] Step 7: 2,6-Difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline (Compound 96)

[1985] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (190 mg, 0.120 mmol) in TFA (5 mL) was stirred at 50 °C for 2 hours. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase

B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; R_{T1}(min): 8.9) to afford the title compound (32.5 mg, 30.2% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 668. ^1H NMR (300 MHz, DMSO-d6) δ 6.14 (d, J = 10.6 Hz, 2H), 5.13 – 5.01 (m, 1H), 4.61 – 4.47 (m, 1H), 4.45 – 4.34 (m, 1H), 4.18 – 4.08 (m, 1H), 4.00 – 3.90 (m, 1H), 3.65 – 3.38 (m, 6H), 3.19 – 2.64 (m, 6H), 2.30 (s, 3H), 2.14 – 1.97 (m, 1H), 1.87 – 1.48 (m, 6H), 1.42 (d, J = 6.3 Hz, 3H), 1.36 – 1.17 (m, 1H).

[1986] **Example 97:** Compound 97



[1987] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methylphenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1988] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (700 mg, 1.18 mmol), 2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.16 g, 2.37 mmol), cataCXium A Pd G3 (173 mg, 0.240 mmol) and K_3PO_4 (2.5 mL, 1.5 M in water) in THF (10 mL) was stirred at 60 °C for 3 h. The solution was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH in DCM) to yield 1.18 g (93.1% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 920.

[1989] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-

5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1990] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methylphenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (1.08 g, 1.01 mmol) in AcOH (10 mL) was added NIS (239 mg, 1.06 mmol) at room temperature. The mixture was stirred at room temperature for 0.5 h. The solution was cooled to 0 °C and quenched with saturated $Na_2S_2O_3$ solution. The solution diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH in DCM) to yield 845 mg (71.8% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 1046.

[1991] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

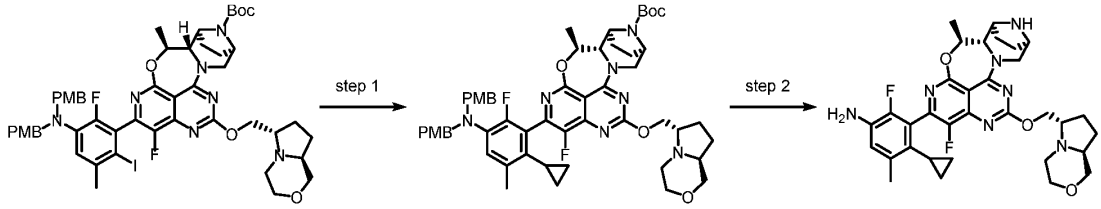
[1992] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (150 mg, 0.140 mmol), $Cu(O_2CCF_2SO_2F)_2$ (898 mg, 1.46 mmol) and Cu (138 mg, 2.15 mmol) in DMF (5 mL) was stirred at room temperature for 1 h. The solution was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by reverse phase chromatography (gradient: 0–100 % MeOH in water (0.05% ammonium acid carbonate) to yield 129 mg (91% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 988.

[1993] Step 4: 2-Fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline (Compound 97)

[1994] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (129 mg, 0.130 mmol) in TFA (5.5 mL) was stirred at 50 °C for 4 h. The solution was concentrated under vacuum. The crude

product was purified by Prep-HPLC with the following conditions: (Column: Xselect CSH C18 OBD Column 30*150mm 5μm, n; Mobile Phase A: Water(0.1%FA), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 7% B to 20% B in 8 min, 20% B; Wave Length: 254/220 nm; R_{T1}(min): 8; Number Of Runs: 0) to yield 37.7 mg (44.3% yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 648. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 6.80 (d, J = 8.8 Hz, 1H), 5.97 (d, J = 11.3 Hz, 2H), 5.17 – 4.98 (m, 1H), 4.64 – 4.46 (m, 1H), 4.45 – 4.32 (m, 1H), 4.19 – 4.06 (m, 1H), 4.01 – 3.88 (m, 1H), 3.68 – 3.38 (m, 6H), 3.13 (t, J = 10.4 Hz, 1H), 3.08 – 2.91 (m, 2H), 2.90 – 2.77 (m, 2H), 2.39 – 2.28 (m, 3H), 2.15 – 1.98 (m, 1H), 1.88 – 1.48 (m, 6H), 1.42 (d, J = 6.3 Hz, 3H), 1.37 – 1.24 (m, 1H).

[1995] **Example 98:** Compound 98



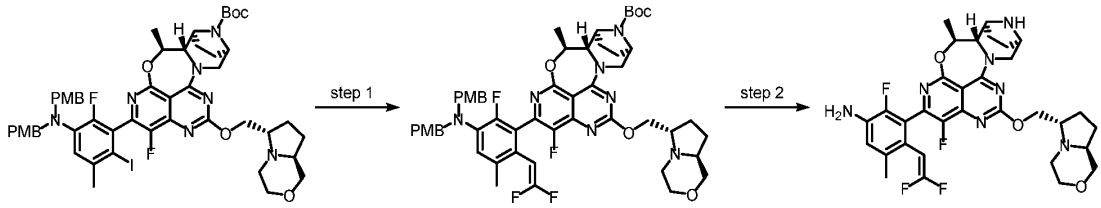
[1996] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-6-cyclopropyl-2-fluoro-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[1997] Under nitrogen, a solution of *tert*- butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (112 mg, 0.110 mmol, Example 97, step 2), 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (26.6 mg, 0.160 mmol), K_2CO_3 (14.6 mg, 0.110 mmol) and Pd(dppf)Cl_2 (3.9 mg, 0.0100 mmol) in 1,4-dioxane (1 mL) and water (0.2 mL) was stirred for 16 hours at 90 °C. The solution was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH in DCM) to afford 43.1 mg (25.5% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 960.

[1998] Step 2: 4-Cyclopropyl-2-fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methylaniline (Compound 98)

[1999] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-6-cyclopropyl-2-fluoro-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (34.8 mg, 0.0100 mmol) in TFA (4 mL) was stirred at 50 °C for 3 hours. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: YMC-Actus Triart C18 ExRS, 30 x 150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; R_{T1}(min): 8.9) to afford 2.8 mg (12.4 % yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 620. ^1H NMR (300 MHz, DMSO-d_6) δ 6.67 (d, *J* = 9.2 Hz, 1H), 5.12 (d, *J* = 12.6 Hz, 1H), 5.01 (d, *J* = 9.1 Hz, 2H), 4.65 – 4.31 (m, 2H), 4.15– 4.13 (m, 1H), 3.97 (d, *J* = 9.0 Hz, 1H), 3.64 – 3.82 (m, 1H), 3.54 (d, *J* = 12.7 Hz, 3H), 3.45 (t, *J* = 5.5 Hz, 2H), 3.15 (t, *J* = 10.4 Hz, 1H), 3.09 – 2.79 (m, 5H), 2.28 (d, *J* = 6.7 Hz, 3H), 2.08 (s, 1H), 1.91 – 1.74 (m, 2H), 1.72 – 1.48 (m, 5H), 1.44 (d, *J* = 6.2 Hz, 3H), 1.31 – 1.24 (m, 1H), 0.53 (t, *J* = 8.2 Hz, 1H), 0.40 – 0.18 (m, 1H), 0.17 – 0.01 (m, 1H), -0.18 (d, *J* = 5.5 Hz, 1H).

[2000] **Example 99:** Compound 99



[2001] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-6-(2,2-difluorovinyl)-2-fluoro-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

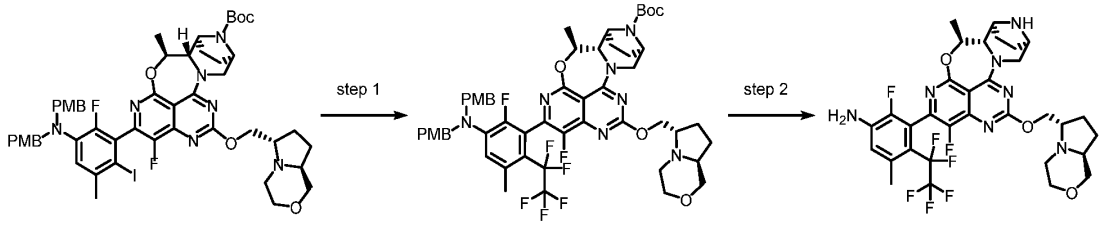
[2002] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (112 mg, 0.110 mmol, Example 97, step 2), 2-(2,2-difluorovinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (40.6 mg, 0.210 mmol), K_2CO_3 (29.6 mg, 0.210 mmol) and Pd(dppf)Cl_2 (7.83 mg, 0.0100 mmol) in 1,4-dioxane (1.5 mL) and water (0.2 mL) was stirred for 2 hours at 90 °C. The solution was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10%

MeOH in DCM) to afford the title compound 104 mg (85.1 % yield) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 982.

[2003] Step 2: 4-(2,2-Difluorovinyl)-2-fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methylaniline (Compound 99)

[2004] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-6-(2,2-difluorovinyl)-2-fluoro-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (30.1 mg, 0.0305 mmol) in TFA (4 mL) stirred at 50 °C for 3 hours. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep Phenyl OBD Column, 19 x 250 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 40% B to 70% B in 7 min, 70% B; Wave Length: 254/220 nm; R_{T1}(min): 6.5) to afford 4.6 mg (23.5% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 642. ^1H NMR (400 MHz, DMSO-d_6) δ 6.76 – 6.73 (m, 1H), 5.48 – 5.27 (m, 3H), 5.10 (d, *J* = 12.9 Hz, 1H), 4.57 (d, *J* = 28.9 Hz, 1H), 4.41 – 4.39 (m, 1H), 4.15 – 4.12 (m, 1H), 3.97 (d, *J* = 8.3 Hz, 1H), 3.67 – 3.59 (m, 1H), 3.55 (s, 2H), 3.52 (d, *J* = 3.2 Hz, 1H), 3.49 – 3.40 (m, 2H), 3.15 (t, *J* = 10.4 Hz, 1H), 3.07 – 2.94 (m, 2H), 2.88 (d, *J* = 14.1 Hz, 2H), 2.36 – 2.18 (m, 1H), 2.14 (d, *J* = 8.3 Hz, 4H), 1.78 – 1.73 (m, 2H), 1.64 (d, *J* = 7.8 Hz, 4H), 1.51 – 1.39 (m, 3H), 1.38 – 1.20 (m, 1H).

[2005] **Example 100:** Compound 100



[2006] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(perfluoroethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

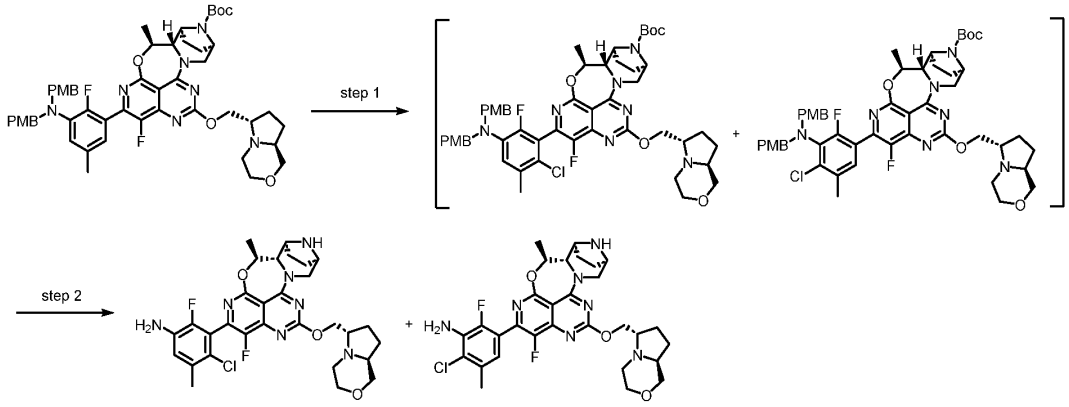
[2007] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (143 mg, 0.140

mmol, Example 97, step 2), trimethyl(perfluoroethyl)silane (525 mg, 2.73 mmol), KF (15.9 mg, 0.270 mmol) and CuI (143 mg, 0.750 mmol) in DMF (5 mL) was stirred for 3 hours at 50 °C. The solution was cooled to room temperature, diluted with ethyl acetate and washed with water. The separated organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-15% MeOH in DCM) to afford 152 mg (84.4% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1038.

[2008] Step 2: 2-Fluoro-3-(((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(perfluoroethyl)aniline (Compound 100)

[2009] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methyl-6-(perfluoroethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (136 mg, 0.130 mmol) in TFA (5 mL) was stirred at 50 °C for 3 hours. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: XBridge Shield RP18 OBD Column, 30 x 150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 32% B to 44% B in 10 min, 44% B; Wave Length: 254/220 nm; R_{T1}(min): 10) to afford 11.2 mg (12.3% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 698. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.82 (d, *J* = 9.1 Hz, 1H), 6.04 (d, *J* = 10.3 Hz, 2H), 5.09 (t, *J* = 10.8 Hz, 1H), 4.69 – 4.30 (m, 2H), 4.14 (s, 1H), 3.96 (d, *J* = 8.5 Hz, 1H), 3.59 – 3.50 (m, 6H), 3.22 – 2.78 (m, 6H), 2.33 (s, 3H), 2.08 (s, 1H), 1.91 – 1.49 (m, 6H), 1.50 – 1.36 (m, 3H), 1.31 (s, 1H).

[2010] **Examples 101 & 102:** Compounds 101 and 102



[2011] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-6-chloro-2-fluoro-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2012] *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-4-chloro-2-fluoro-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2013] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (100 mg, 0.110 mmol, Example 97, step 1) in AcOH (1.5 mL) was added NCS (17.5 mg, 0.130 mmol). The mixture was stirred at room temperature overnight. The solution was cooled to 0 °C and quenched with saturated $Na_2S_2O_3$ solution. The solution diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH in DCM) to yield 78.9 mg (76.1% yield) of the mixture title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 955.

[2014] Step 2: 4-Chloro-2-fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methylaniline (Compound 101) **&** 2-Chloro-6-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methylaniline (Compound 102)

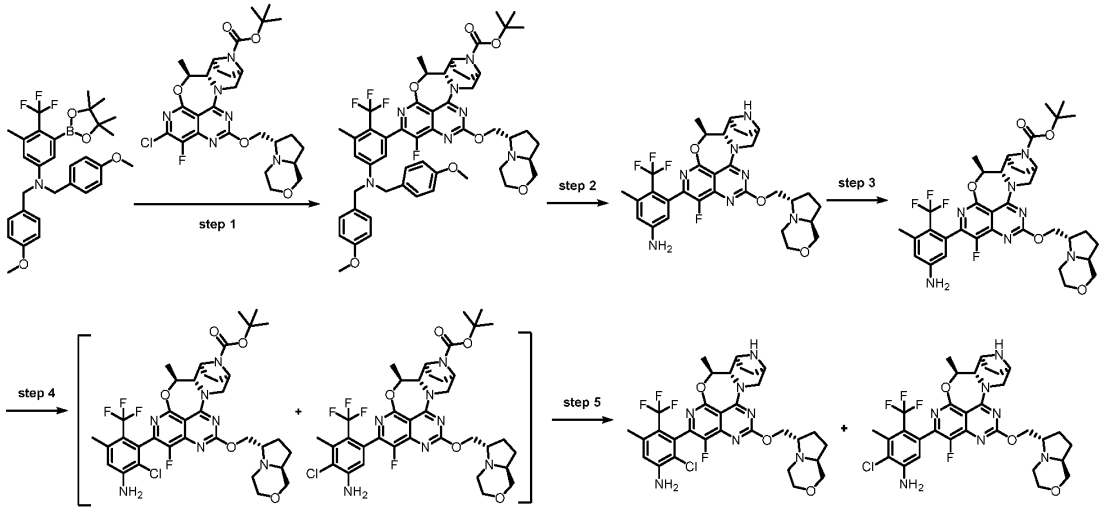
[2015] A solution of *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-6-chloro-2-fluoro-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate and *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-4-chloro-2-fluoro-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate mixture (78.9 mg, 0.0827 mmol) in TFA (3.5 mL) was stirred at 50 °C for 4 h. The solution was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L

NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; R_{T1}(min): 8.9) to yield 14.5 mg (28.5% yield) of 101 and 1.0 mg (1.7% yield) of 101 as a white solid.

[2016] **101**: LC-MS: (ESI, *m/z*): $[M+H]^+$= 614. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 6.84 (d, J = 9.4 Hz, 1H), 5.37 (d, J = 8.7 Hz, 2H), 5.20 – 5.01 (m, 1H), 4.67 – 4.52 (m, 1H), 4.50 – 4.33 (m, 1H), 4.24 – 4.08 (m, 1H), 4.03 – 3.91 (m, 1H), 3.70 – 3.39 (m, 6H), 3.15 (t, J = 10.3 Hz, 1H), 3.08 – 2.92 (m, 2H), 2.92 – 2.78 (m, 2H), 2.24 (d, J = 8.6 Hz, 3H), 2.16 – 1.99 (m, 1H), 1.91 – 1.50 (m, 6H), 1.45 (d, J = 6.3 Hz, 3H), 1.38 – 1.26 (m, 1H).

[2017] **102**: LC-MS: (ESI, *m/z*): $[M+H]^+$= 614. ^{1}H NMR (400 MHz, DMSO-d_6, *ppm*) δ 6.70 (d, J = 6.9 Hz, 1H), 5.49 (s, 2H), 5.17 – 5.03 (m, 1H), 4.68 – 4.49 (m, 1H), 4.48 – 4.37 (m, 1H), 4.22 – 4.07 (m, 1H), 4.03 – 3.92 (m, 1H), 3.68 – 3.41 (m, 6H), 3.15 (t, J = 10.3 Hz, 1H), 3.09 – 2.93 (m, 2H), 2.93 – 2.80 (m, 2H), 2.30 (s, 3H), 2.17 – 1.97 (m, 1H), 1.90 – 1.52 (m, 6H), 1.46 (d, J = 6.4 Hz, 3H), 1.39 – 1.26 (m, 1H).

[2018] **Example 103:** Compound 103



[2019] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2020] Under nitrogen, a mixture of *N*,*N*-*bis*(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline (90.0 mg, 0.170 mmol), *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (39.3 mg, 0.0700 mmol), cataCXium A Pd G3 (9.70 mg, 0.0100 mmol) and K_3PO_4 (70.6 mg, 0.330 mmol) in tetrahydrofuran (1 mL) and water

(0.2 mL) was stirred at 60 °C for 1 hour. The resulting solution was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% ethyl acetate in petroleum ether) to afford 70.5 mg (42.8% yield) of the title compound as a yellow oil. LC-MS: (ESI, m/z): $[M+H]^+ = 970$.

[2021] Step 2: 3-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline

[2022] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (60.5 mg, 0.0600 mmol) in 2,2,2-trifluoroacetic acid (5 mL) was stirred at 50°C for 3 hours. The solvent was concentrated under vacuum. The residue was neutralized by saturated $NaHCO_3$ aqueous solution and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-100% CH_3CN in water (0.05% NH_4HCO_3)) to afford 33.5 mg (76.2% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 630$.

[2023] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2024] A solution of 3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline (33.5 mg, 0.0500 mmol), Boc_2O (13.9 mg, 0.0600 mmol) and DIPEA (13.7 mg, 0.110 mmol) in dichloromethane (1 mL) was stirred at room temperature for 1 hour. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford 25.0 mg (64.4 % yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 730$.

[2025] Step 4: *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2-chloro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate **&** *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-4-

chloro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2026] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (14.6 mg, 0.0200 mmol) and NCS (4.0 mg, 0.0300 mmol) in acetic acid (1 mL) was stirred at room temperature for 36 hours. The reaction was quenched with saturated $Na_2S_2O_3$ aqueous solution. The resulting solution was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to yield 12.9 mg (mixture, 85.6 % yield) of the title compounds as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 764.

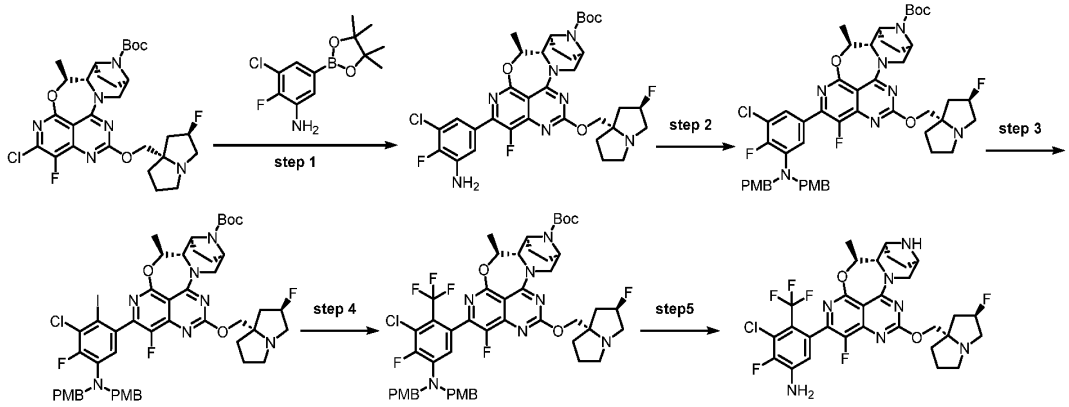
[2027] Step 5: 2-Chloro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline **&** 2-chloro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline

[2028] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2-chloro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate and *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-4-chloro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (mixture, 12.9 mg, 0.0169 mmol) in dichloromethane (1 mL) was added 2,2,2-trifluoroacetic acid (0.2 mL). The resulting solution was stirred at room temperature for 1 hour. The solvent was concentrated under vacuum. The residue was neutralized by saturated $NaHCO_3$ aqueous solution and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; RT2(min): 9.0) to yield 1.2 mg (10.7% yield, the faster peak) of **103a** and 1.2 mg (10.7% yield, the slower peak) of **103b** as while solids.

[2029] **103a:** LC-MS: (ESI, m/z): $[M+H]^+$ = 664. ^1H NMR (300 MHz, DMSO-*d6, ppm,*) δ 6.86 (s, 1H), 6.16 (d, J = 9.9 Hz, 2H), 5.09 (d, J = 12.4 Hz, 1H), 4.53 (t, J = 6.2 Hz, 1H), 4.46 – 4.37 (m, 1H), 4.18 – 4.10 (m, 1H), 3.96 (d, J = 8.7 Hz, 1H), 3.64 – 3.59 (m, 1H), 3.57 – 3.45 (m, 4H), 3.15 (t, J = 10.3 Hz, 2H), 3.07 – 2.94 (m, 2H), 2.87 (d, J = 12.5 Hz, 2H), 2.74 (s, 1H), 2.44 – 2.30 (m, 3H), 2.14 – 2.02 (m, 1H), 1.82 – 1.57 (m, 5H), 1.44 (d, J = 6.3 Hz, 3H), 1.38 – 1.27 (m, 1H), 1.24 (s, 1H).

[2030] **103b:** LC-MS: (ESI, m/z): $[M+H]^+$ = 664. ^1H NMR (300 MHz, DMSO-*d6, ppm,*) δ 6.68 – 6.53 (m, 1H), 6.22 (s, 2H), 5.09 (d, J = 11.5 Hz, 1H), 4.58 – 4.48 (m, 1H), 4.45 – 4.35 (m, 1H), 4.18 – 4.09 (m, 1H), 3.96 (d, J = 8.7 Hz, 1H), 3.64 – 3.44 (m, 5H), 3.20 – 3.09 (m, 2H), 3.07 – 2.95 (m, 2H), 2.89 (s, 2H), 2.46 (s, 3H), 2.08 (s, 1H), 1.78 (t, J = 7.9 Hz, 2H), 1.62 (d, J = 12.6 Hz, 3H), 1.44 (d, J = 6.3 Hz, 3H), 1.37 – 1.29 (m, 1H), 1.24 (s, 1H).

[2031] **Example 104:** Compound 104



[2032] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-5-chloro-4-fluorophenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2033] Under nitrogen, a stirred solution of 3-chloro-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (220 mg, 0.810 mmol, intermediate 76), *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (400 mg, 0.670 mmol), Catacxium A Pd G_3 (98.2 mg, 0.130 mmol) and aqueous K_3PO_4 (2.25 mL, 1.5 mol/L in water) in tetrahydrofuran (11.2 mL) was stirred at 60°C overnight. The reaction system was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel

(gradient: 0-20% MeOH in CH_2Cl_2) to afford 250 mg (52.8 % yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 702.

[2034] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-5-chloro-4-fluorophenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2035] Under nitrogen, to a stirred solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-5-chloro-4-fluorophenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (250 mg, 0.360 mmol) in N,N-dimethylformamide (5 mL) was added NaH (42.7 mg, 1.78 mmol, 60% suspension in mineral oil) at 0°C. The solution was stirred at 25°C for 0.5 h, then PMB-Cl (126 mg, 0.800 mmol) was added and the resulting solution was stirred at 25°C for 5 h. The resulting solution was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-100% CH_3CN in water (0.05% TFA)) to afford of the title compound 170 mg (50.7% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 942.

[2036] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-iodophenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2037] Under nitrogen, to a stirred solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-5-chloro-4-fluorophenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (170 mg, 0.180 mmol) in N,N-dimethylformamide (5 mL) was added I_2 (183 mg, 0.720 mmol) and AgOAc (120 mg, 0.720 mmol). The solution was stirred for 1 h at 25°C. The resulting solution was quenched with aqueous $Na_2S_2O_3$ solution and extracted with EtOAc. The combined organic layers were washed with saturated NaCl solution, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-100% CH_3CN in water (0.05% TFA)) to afford of the title compound 88.0 mg (45.7% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 1068.

[2038] Step 4: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-

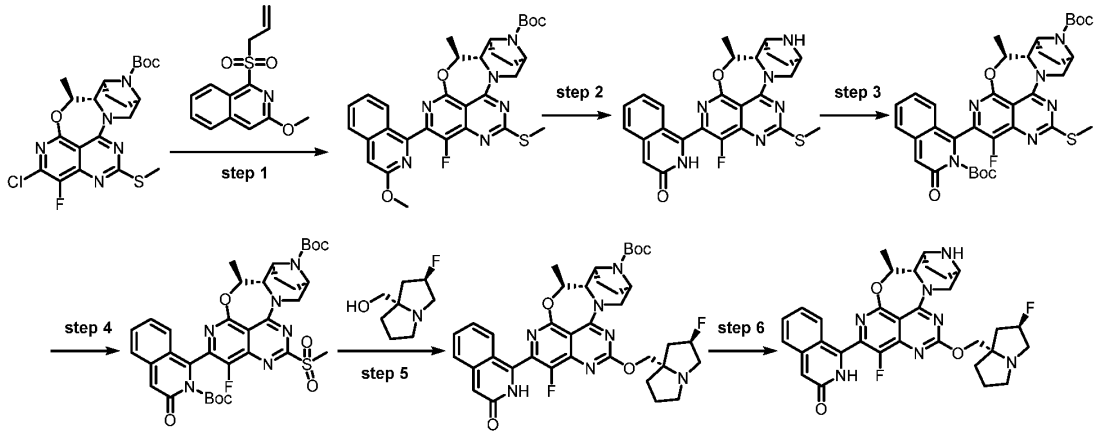
7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2039] Under nitrogen, to a stirred solution of $Cu(FSO_2CF_2COO)_2$ (297 mg, 1.24 mmol), Cu (78.5 mg, 1.24 mmol) in N,N-dimethylformamide (2.5 mL) was added *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-iodophenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (88.0 mg, 0.0800 mmol) at 0°C. The solution was stirred for 1 h at 25°C. The resulting solution was diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with saturated NaCl solution, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-100% CH_3CN in water (0.05% TFA)) to afford of the title compound 32.0 mg (38.4% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 1010$.

[2040] Step 5: 3-Chloro-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-(trifluoromethyl)aniline (Compound 104)

[2041] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-3-chloro-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (32.0 mg, 0.0300 mmol) in 2,2,2-trifluoroacetic acid (3 mL) was stirred for 1 h at 25°C. The mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 11% B to 41% B in 7 min, 41% B; Wave Length: 254/220 nm; R_{T1}(min): 5.72) to afford 4.7 mg (22.1% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 670$. ^1H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.66 (d, *J* = 39.8 Hz, 1H), 6.47 (s, 2H), 5.28 (d, *J* = 54.3 Hz, 1H), 5.07 (d, *J* = 12.7 Hz, 1H), 4.53 (m, 1H), 4.17 – 3.86 (m, 3H), 3.57 (s, 1H), 3.44 (s, 1H), 3.16 – 2.95 (m, 4H), 2.90 – 2.55 (m, 2H), 2.15 (d, *J* = 4.9 Hz, 1H), 2.02 (d, *J* = 13.5 Hz, 2H), 1.90 – 1.70 (m, 4H), 1.69 – 1.5 (m, 3H), 1.43 (d, *J* = 6.3 Hz, 3H).

[2042] **Example 105:** Compound 105



[2043] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(3-methoxyisoquinolin-1-yl)-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2044] Under nitrogen, a solution of 1-(allylsulfonyl)-3-methoxyisoquinoline (82.0 mg, 0.310 mmol, intermediate 77), *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (100 mg, 0.210 mmol), $Pd(OAc)_2$ (4.7 mg, 0.0200 mmol), P(t-Bu)$_2$Me.HBF_4 (10.3 mg, 0.0400 mmol), Cs_2CO_3 (135 mg, 0.410 mmol) in 1,4-dioxane (3 mL) was stirred at 120°C overnight. The mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-60% EtOAc in petroleum ether) to afford 58.0 mg (46.2% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 605$.

[2045] Step 2: 1-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)isoquinolin-3(2*H*)-one

[2046] A stirred solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(3-methoxyisoquinolin-1-yl)-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (200 mg, 0.332 mmol) in HBr/AcOH (8 mL, 36% in AcOH) was stirred overnight at 80°C. The mixture was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-100% CH_3CN in water (0.05% TFA)) to yield 110 mg (67.9% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 491$.

[2047] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(*tert*-butoxycarbonyl)-3-oxo-2,3-dihydroisoquinolin-1-yl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2048] Under nitrogen, to a stirred solution of 1-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)isoquinolin-3(2*H*)-one (90.0 mg, 0.183 mmol) in DMF (3 mL) was added DMAP (2.3 mg, 0.0180 mmol) and di-*tert*-butyl dicarbonate (80.1 mg, 0.365 mmol) at 0°C. The resulting solution was stirred at 25°C for 5 h. The mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-40% EtOAc in petroleum ether) to afford 120 mg (87.4% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 691$.

[2049] Step 4: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(*tert*-butoxycarbonyl)-3-oxo-2,3-dihydroisoquinolin-1-yl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2050] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(*tert*-butoxycarbonyl)-3-oxo-2,3-dihydroisoquinolin-1-yl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (100 mg, 0.169 mmol) in CH_2Cl_2 (8 mL) was added *m*-CPBA (87.6 mg, 0.507 mmol) in batches at 0°C. The resulting solution was stirred at 25°C for 3 h. The reaction mixture was quenched with aqueous $Na_2S_2O_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-60% EtOAc in petroleum ether) to afford 90 mg (85.4% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 723$.

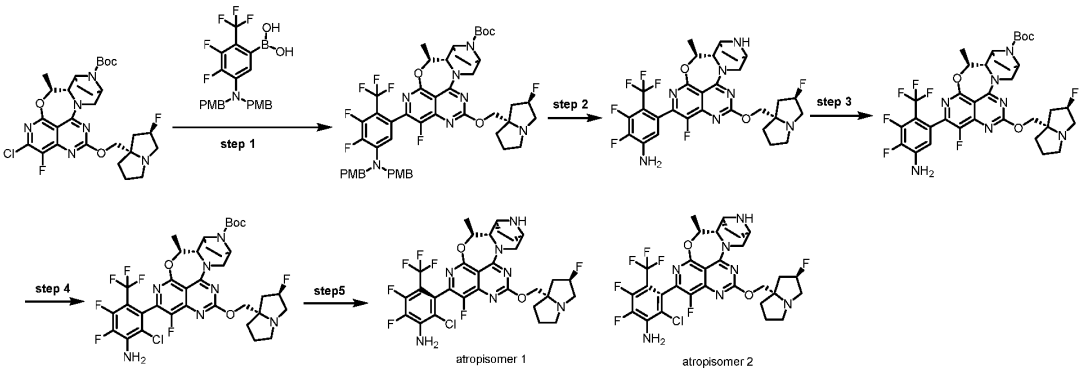
[2051] Step 5: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-2-(3-oxo-2,3-dihydroisoquinolin-1-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2052] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(*tert*-butoxycarbonyl)-3-oxo-2,3-dihydroisoquinolin-1-yl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (75.0 mg, 0.104 mmol) in toluene (5 mL) were added *t*-BuONa (19.9 mg, 0.208 mmol) and ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (24.8 mg, 0.156 mmol) at 0°C. The resulting solution was stirred at 25°C for 1 h. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-60% MeOH in CH_2Cl_2) to afford 82.0 mg (95.2% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+ = 702$.

[2053] Step 6: 1-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)isoquinolin-3(2*H*)-one (Compound 105)

[2054] Under nitrogen, to a stirred solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-2-(3-oxo-2,3-dihydroisoquinolin-1-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (82.0 mg, 0.117 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.6 mL). The resulting solution was stirred at 25°C for 1 h. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep C18 OBD Column, 30*100 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 30% B to 60% B in 10 min, 60% B; Wavelength: 254/220 nm; R_{T1}(min): 7.5) to yield 9.4 mg (0.120% yield) of the title compound as yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 602. ^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 11.5 – 10.5 (m, 1H), 7.92 – 7.78 (m, 1H), 7.62 (dd, *J* = 8.3, 6.5 Hz, 2H), 7.39 – 7.21 (m, 1H), 7.08 (s, 1H), 5.45 – 5.03 (m, 2H), 4.66 – 4.49 (m, 1H), 4.13 (d, *J* = 10.3 Hz, 1H), 4.09 – 3.86 (m, 2H), 3.59 (s, 1H), 3.46 (d, *J* = 5.6 Hz, 1H), 3.19 – 2.96 (m, 4H), 2.92 – 2.79 (m, 1H), 2.16 (d, *J* = 5.4 Hz, 1H), 2.13 – 1.97 (m, 2H), 1.97 – 1.75 (m, 4H), 1.75 – 1.54 (m, 3H), 1.45 (d, *J* = 6.3 Hz, 3H).

[2055] **Example 106:** Compound 106



[2056] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-3,4-difluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2057] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (308 mg, 0.520 mmol), (5-(bis(4-methoxybenzyl)amino)-3,4-difluoro-2-

(trifluoromethyl)phenyl)boronic acid (500 mg, 1.04 mmol), cataCXium A Pd G_3 (75.7 mg, 0.100 mmol) and K_3PO_4 (1.5 M in water) (1.1 mL, 1.65 mmol) in tetrahydrofuran (5 mL) was stirred at 60 °C for 2 h. The solution was concentrated under vacuum. The residual was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-100% MeOH in water (0.05% NH_4HCO_3)) to afford the title compound (299 mg, 57.9% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 994.

[2058] Step 2: 2,3-Difluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-(trifluoromethyl)aniline

[2059] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-3,4-difluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (200 mg, 0.200 mmol) in 2,2,2-trifluoroacetic acid (2 mL) was stirred at 50 °C for 1.5 h. The solvent was evaporated under vacuum to afford the title compound (150 mg, crude) as a yellow solid. The crude product was used for the next step without further purification. LC-MS: (ESI, m/z): $[M+H]^+$ = 654.

[2060] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-3,4-difluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

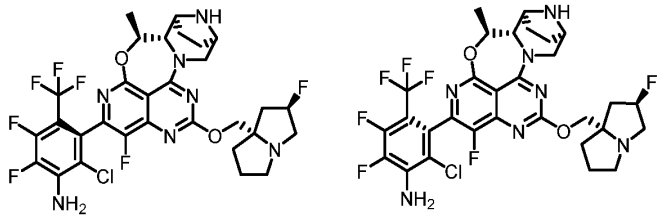
[2061] A solution of 2,3-difluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-(trifluoromethyl)aniline (150 mg, 0.230 mmol), Boc_2O (75.0 mg, 0.340 mmol) and DIPEA (88.9 mg, 0.690 mmol) in dichloromethane (2 mL) was stirred at room temperature for 1 h. The solvent was evaporated under vacuum. The residue was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-100% MeOH in water (0.05% NH_4HCO_3)) to afford the title compound (75.0 mg, 43.4 % yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 754.

[2062] Step 4: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2-chloro-4,5-difluoro-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2063] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-3,4-difluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-

methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (50.0 mg, 0.0700 mmol) and NCS (53.0 mg, 0.400 mmol) in 1-methyl-2-pyrrolidinone (1 mL) was stirred at 80 °C for 2 h. The resulting mixture was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-100% MeOH in water (0.05% NH_4HCO_3)) to afford the title compound (49.0 mg, 93.7% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 788.

[2064] Step 5: 2-Chloro-5,6-difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-(trifluoromethyl)aniline

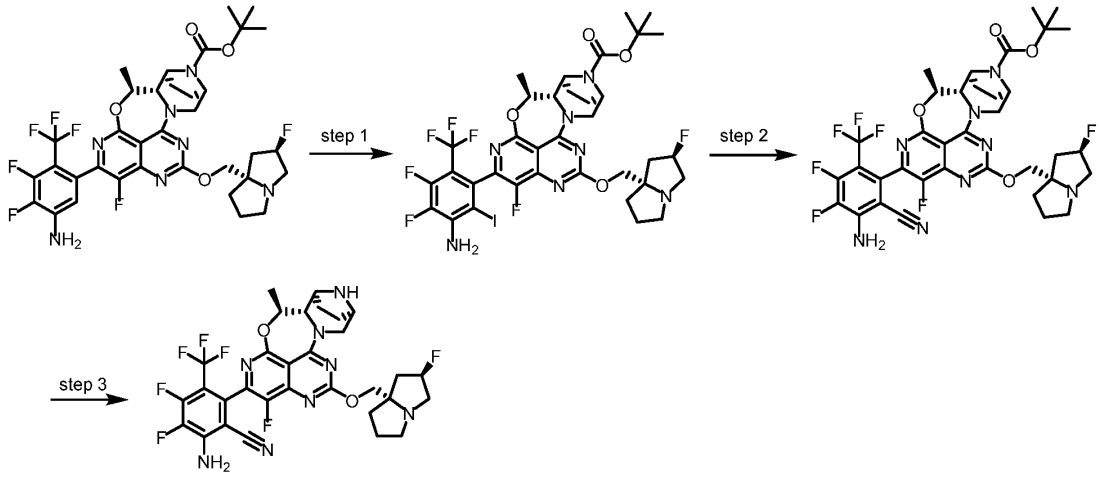


[2065] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2-chloro-4,5-difluoro-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (49.0 mg, 0.0600 mmol) in dichloromethane (1.5 mL) was added TFA (0.5 mL). The solution was stirred at room temperature for 30 min. Solvent was evaporated under vacuum. The residue was purified by prep HPLC with the following conditions: (Column: XBridge BEH130 Prep C18 OBD Column, 19*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 33% B to 50% B in 10 min; Wave Length: 254 nm; R_{T1}(min): 8.4, R_{T2}(min): 9.1; Number Of Runs: 2) to afford **106a** (7.30 mg, 17.1% yield) (the faster peak, atropisomer 1) and **106b** (5.00 mg, 11.7% yield) (the slower peak, atropisomer 2) as white solids. LC-MS: (ESI, m/z): $[M+H]^+$ = 688.

[2066] **106a**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.86 (s, 2H), 5.28 (d, J = 54 Hz, 1H), 5.09 – 5.05 (m, 1H), 4.57 – 4.53 (m, 1H), 4.14 – 3.89 (m, 3H), 3.58 (d, J = 5.6 Hz, 1H), 3.45 (d, J = 6.2 Hz, 1H), 3.20 – 2.99 (m, 4H), 2.84 – 2.82 (m, 1H), 2.76 (s, 1H), 2.20 – 1.93 (m, 3H), 1.91 – 1.73 (m, 4H), 1.74 – 1.64 (m, 2H), 1.56 – 1.53 (m, 1H), 1.44 (d, J = 6.3 Hz, 3H).

[2067] **106b**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.83 (s, 2H), 5.28 (d, J = 54 Hz, 1H), 5.09 – 5.06 (m, 1H), 4.57 – 4.53 (m, 1H), 4.14 – 3.92 (m, 3H), 3.58 – 3.44 (m, 2H), 3.16 – 2.97 (m, 4H), 2.84 – 2.80 (m, 1H), 2.76 (s, 1H), 2.19 – 1.95 (m, 3H), 1.90 – 1.73 (m, 4H), 1.75 – 1.61 (m, 2H), 1.61 – 1.49 (m, 1H), 1.44 (d, J = 6.3 Hz, 3H).

[2068] **Example 107:** Compound 107



[2069] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-4,5-difluoro-2-iodo-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2070] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-3,4-difluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (150 mg, 0.200 mmol, Example 97, step 1) and NIS (537.8 mg, 2.39 mmol) in acetic acid (2 mL) was stirred at room temperature for overnight. The mixture was poured into water. The product was extracted with DCM, and the combined organic layers were washed with aqueous saturated aqueous sodium thiosulfate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH in DCM) to yield the title compound (91.0 mg, 52% yield) as a yellow solid. LC-MS (ESI, m/z): $[M+H]^+$ = 880.

[2071] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2-cyano-4,5-difluoro-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

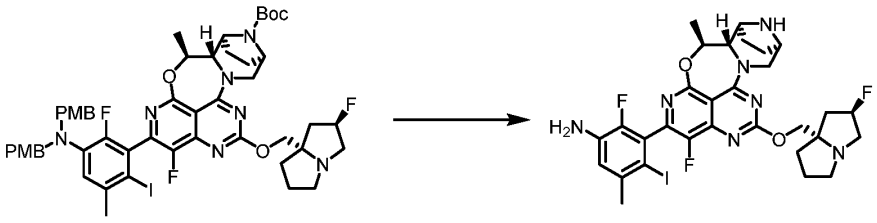
[2072] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-4,5-difluoro-2-iodo-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (80.0 mg, 0.0900 mmol) in 1-methyl-2-pyrrolidinone (1.5 mL) was added $Zn(CN)_2$ (46.4 mg, 0.400 mmol) and $Pd(PPh_3)_4$ (20.1 mg, 0.0200 mmol). The solution was reacted under microwave irradiation at 100 °C for 2 h. The

resulting mixture was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-100% ACN in water (0.05% NH_4HCO_3)) to yield the title compound (46.0 mg, 64.9 % yield) as a white solid. LC-MS (ESI, m/z): $[M+H]^+$ = 779.

[2073] Step 3: 2-Amino-3,4-difluoro-6-((5*S*,5a*S*,6*S*,9R)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-(trifluoromethyl)benzonitrile

[2074] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2-cyano-4,5-difluoro-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (46.0 mg, 0.0600 mmol) in dichloromethane (5 mL) was added TFA (1 mL). The solution was stirred at room temperature for 1 h. Solvent was evaporated under vacuum. The residue was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient:0-100% ACN in water (0.05% NH_4HCO_3)) to yield the title compound (5.80 mg, 14.5% yield) as a white solid. LC-MS (ESI, m/z): $[M+H]^+$ = 679. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.55 (s, 2H), 5.28 (d, *J* = 54.3 Hz, 1H), 5.08 (d, *J* = 12.9 Hz, 1H), 4.58 (s, 1H), 4.18 – 3.88 (m, 3H), 3.57 (s, 1H), 3.45 (s, 1H), 3.04 (d, *J* = 24.9 Hz, 4H), 2.83 (s, 1H), 2.15 (s, 1H), 2.04 (s, 2H), 1.79 – 1.53 (m, 7H), 1.44 (s, 3H).

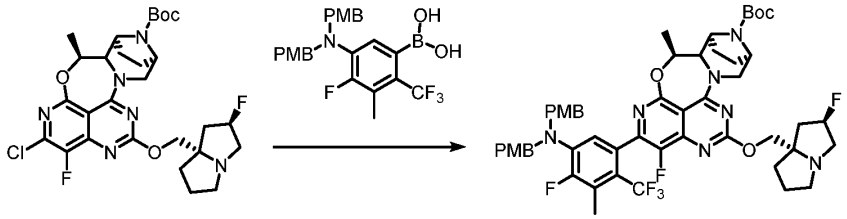
[2075] **Example 108:** Compound 108



[2076] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2-fluoro-6-iodo-5-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (71.0 mg, 0.0700 mmol) in TFA (2.5 mL) was stirred at 50 °C for 4 hours. The reaction was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 47% B in 10 min, 47% B; Wave Length: 254/220 nm; R_{T1}(min): 9.13) to yield 17.0 mg (35.5% yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 623. ^{1}H NMR (300 MHz, DMSO-d_6, *ppm*) δ 6.89 (d, J = 8.8 Hz, 1H), 5.39 (d, J = 11.3 Hz, 2H), 5.36 (s, 1H), 5.18-5.02 (m, 1H), 4.60 – 4.47 (m, 1H), 4.15-

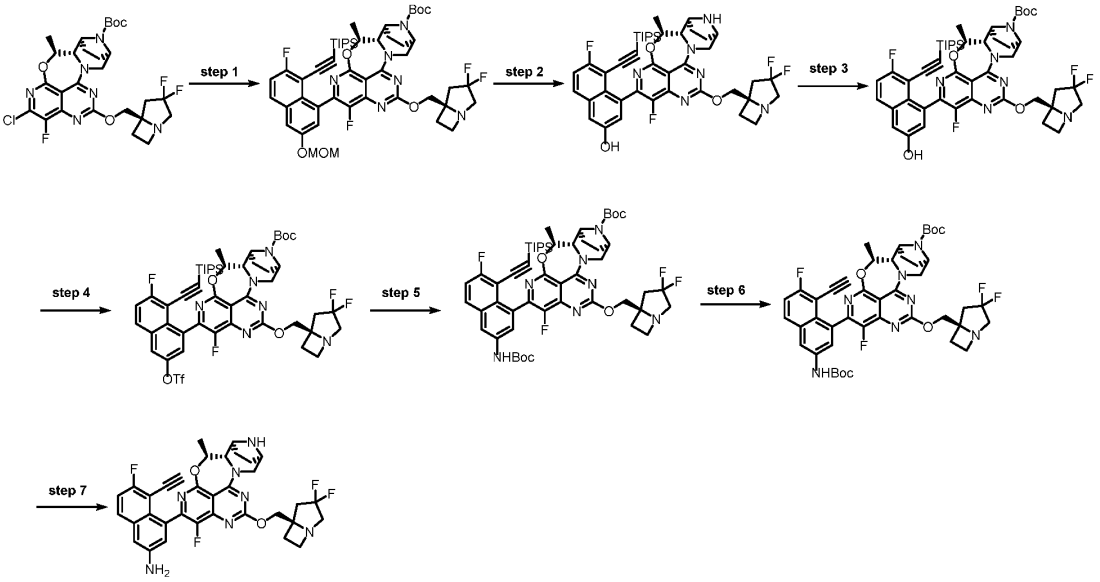
3.95 (m, 3H), 3.59 (s, 1H), 3.46 (s, 1H), 3.19 – 3.02 (m, 4H), 2.99-2.82 (m, 2H),2.32 (d, J = 2.7 Hz, 3H), 2.13 (s, 1H), 2.05 (d, J = 16.1 Hz, 2H), 1.89-1.75 (m, 4H),1.71-1.52 (m, 3H), 1.42 (d, J = 6.3 Hz).

[2077] **Example 109 :** *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate



[2078] Under nitrogen, to a solution of (5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (130.5 mg, 0.274 mmol), *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (80.7 mg, 0.136 mmol) and cataCXium A Pd G3 (20.1 mg, 0.0276 mmol) in THF (8 mL) was added K_3PO_4 (1.6 mL, 1.5 M in water). The resulting solution was stirred for 4 hours at 60 °C. The solution was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase chromatography (gradient: 0–95% acetonitrile in water (0.05% NH_4HCO_3) to afford 118 mg (87.5% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): [M+H]+ = 990. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.16 (d, J = 8.1 Hz, 4H), 6.86 (d, J = 8.1 Hz, 4H), 6.71 (d, J = 29.2 Hz, 1H), 5.44 – 5.04 (m, 2H), 4.56 (s, 1H), 4.33 (d, J = 19.3 Hz, 5H), 4.17 – 3.98 (m, 3H), 3.94 (s, 1H), 3.71 (s, 6H),–3.16 – 2.92 (m, 4H), 2.88 - 2.75 (m, 1H), 2.35 (s, 3H), 2.16 - 2.09 (m, 1H), 2.07 – 1.94 (m, 2H), 1.92 – 1.62 (m, 7H), 1.45 (s, 12H).

[2079] **Example 110:** Compound 110



[2080] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2081] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (100 mg, 0.168 mmol), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (215 mg, 0.420 mmol) and cataCXium A Pd G3 (24.1 mg, 0.0331 mmol) in THF (2 mL) was added K_3PO_4 (0.4 mL, 1.5 M in H_2O) at room temperature. The resulting solution was stirred for 16 hours at 60 °C. The solution was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH in DCM) to afford the title compound 141 mg (88.9% yield) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 947$.

[2082] Step 2: 4-((5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol

[2083] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-2-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-

3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (141 mg, 0.149 mmol) in DCM (3 mL) was added HCl in 1,4-dioxane (1 mL, 4 M), and the mixture was stirred at room temperature for 3 hours. The solvent was concentrated under vacuum. The residue was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0–80 % acetonitrile in water (0.05% NH_4HCO_3) to afford the title compound 102 mg (85.9% yield) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 803.

[2084] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-2-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2085] To a solution of 4-((5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (102 mg, 0.125 mmol) and DIPEA (48.1 mg, 0.372 mmol) in DCM (2 mL) was added $(Boc)_2O$ (41.2 mg, 0.190 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 hours. The solution was diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-70% EtOAc / petroleum ether) to afford the title compound 81.0 mg (72.0% yield) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 903.

[2086] Step 4: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-2-(7-fluoro-3-(((trifluoromethyl)sulfonyl)oxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2087] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-2-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (50.2 mg, 0.0554 mmol) and DIPEA (42.6 mg, 0.222 mmol) in DCM (2 mL) was added Tf_2O (15.6 mg, 0.0554 mmol) at -60 °C and the mixture was stirred at -60 °C for 1 hour. The solution was warmed to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH in DCM) to afford the title compound 23.4 mg (40.1% yield) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1035.

[2088] Step 5: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2089] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-2-(7-fluoro-3-(((trifluoromethyl)sulfonyl)oxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (21.5 mg, 0.0208 mmol), $Pd_2(dba)_3$ (0.5 mg, 0.546 μmol), Xantphos (1.0 mg, 1.73 μmol), Cs_2CO_3 (20.3 mg, 0.0623 mmol) and $BocNH_2$ (3.7 mg, 0.0316 mmol) in 1,4-dioxane (2 mL) was stirred for 3 hours at 100 °C. The solution was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH in DCM) to afford 15.3 mg (73.5% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1002.

[2090] Step 6: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-((tert-butoxycarbonyl)amino)-8-ethynyl-7-fluoronaphthalen-1-yl)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

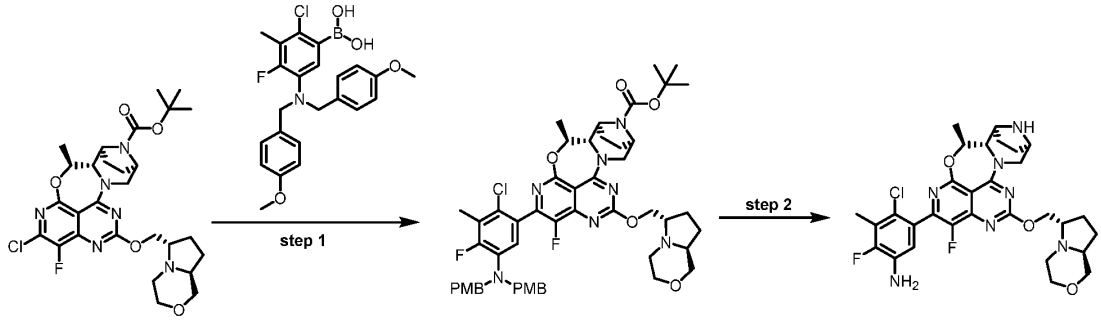
[2091] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (15.3 mg, 0.0153 mmol) in DMF (1.5 mL) was added CsF (11.3 mg, 0.0745 mmol). The solution was stirred at room temperature for 1 hour. The solution was diluted with ethyl acetate and washed with water. The separated organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound 11 mg (crude) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 846.

[2092] Step 7: 4-((5*S*,5a*S*,6*S*,9*R*)-12-(((*R*)-3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-ethynyl-6-fluoronaphthalen-2-amine (Compound 110)

[2093] To a solution of TFA (0.05mL) in HFIP (1 mL) was added *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-((tert-butoxycarbonyl)amino)-8-ethynyl-7-fluoronaphthalen-1-yl)-12-(((*R*)-3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (9.1 mg, 0.0106mmol), and the mixture was stirred for 2 hours at room temperature. The reaction mixture

was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 23% B to 48% B in 9.5 min, 48% B; Wave Length: 254/220 nm; R_{T1}(min): 8.2) to afford the title compound 4.9 mg (69.6% yield) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 646. ^1H NMR (400 MHz, DMSO-d_6) δ 7.77 – 7.72 (m, 1H), 7.35 – 7.29 (m, 1H), 7.11 – 6.90 (m, 2H), 5.63 (d, *J* = 12.1 Hz, 2H), 5.17 – 5.13 (m, 1H), 4.49 – 4.43 (m, 1H), 4.40 – 4.27 (m, 2H), 4.20 – 3.87 (m, 2H), 3.56 (d, *J* = 15.7 Hz, 2H), 3.46 (t, *J* = 6.2 Hz, 1H), 3.32 – 3.21 (m, 1H), 3.17 – 3.00 (m, 3H), 2.81 (s, 1H), 2.71 – 2.59 (m, 1H), 2.48 – 2.28 (m, 3H), 1.84 (t, *J* = 10.1 Hz, 1H), 1.79 – 1.52 (m, 3H), 1.45 (t, *J* = 6.9 Hz, 3H).

[2094] **Example 111:** Compound 111



[2095] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-2-chloro-4-fluoro-3-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2096] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (150 mg, 0.250 mmol), (5-(bis(4-methoxybenzyl)amino)-2-chloro-4-fluoro-3-methylphenyl)boronic acid (224 mg, 0.500 mmol, Intermediate 69), cataCXium A Pd G_3 (36.8 mg, 0.0500 mmol) and K_3PO_4 (1.5 M in water) (0.5 mL, 0.750 mmol) in tetrahydrofuran (2.5 mL) was stirred at 60 °C for 1.5 h. The solvent was concentrated under vacuum. The crude product was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-100% CH_3CN in water (0.05% NH_4HCO_3)) to afford 290 mg the title compound (60% purity). The crude product was repurified by flash chromatography on silica gel (gradient: 0-50% EtOAc in petroleum ether, 0-10% MeOH in DCM) to afford the title compound (180 mg, 74.3% yield) as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 954.

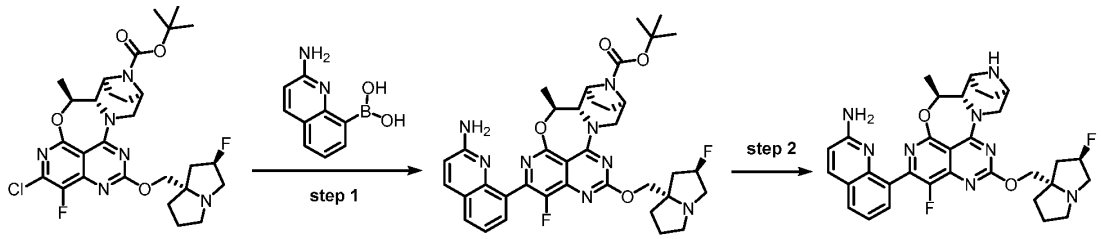
[2097] Step 2: 4-Chloro-2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methylaniline ((Compound 111)

[2098] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-2-chloro-4-fluoro-3-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (175 mg, 0.180 mmol) in 2,2,2-trifluoroacetic acid (2 mL) was stirred at 50 °C for 1 h. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: XBridge BEH C18 OBD Prep Column, 19*250 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 50% B to 80% B in 7 min, 80% B; Wave Length: 254/220 nm; R_T(min): 6.4) to yield the title compound (19.3 mg, 17.1% yield) as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$= 614. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.70 (d, *J* = 9.3 Hz, 1H), 5.40 (s, 2H), 5.10 – 5.06 (m, 1H), 4.63 – 4.48 (m, 1H), 4.43 – 4.38 (m, 1H), 4.16 – 4.10 (m, 1H), 3.94 (d, *J* = 8.7 Hz, 1H), 3.64 – 3.60 (m, 1H), 3.59 – 3.43 (m, 5H), 3.14 (t, *J* = 10.4 Hz, 1H), 3.04 – 2.86 (m, 5H), 2.26 (d, *J* = 2.4 Hz, 3H), 2.17 – 1.99 (m, 1H), 1.90 – 1.70 (m, 2H), 1.64 – 1.58 (m, 4H), 1.44 (d, *J* = 6.3 Hz, 3H), 1.37 – 1.24 (m, 1H).

[2099] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Example **111**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
112	^{1}H NMR (300 MHz, DMSO-d6) δ 6.82 (s, 2H), 6.23 (s, 1H), 5.09 (d, J = 12.0 Hz, 1H), 4.61 – 4.48 (m, 1H), 4.41 (dd, J = 10.9, 5.3 Hz, 1H), 4.14 (dd, J = 10.9, 5.9 Hz, 1H), 3.96 (d, J = 8.7 Hz, 1H), 3.62 (dd, J = 10.9, 3.5 Hz, 1H), 3.53 (d, J = 12.8 Hz, 3H), 3.45 (s, 2H), 3.21 – 3.15 (m, 1H), 3.09 – 2.92 (m, 2H), 2.94 – 2.79 (m, 2H), 2.74 (s, 1H), 2.49 – 2.43 (m, 3H), 2.19 – 1.99 (m, 1H), 1.90 – 1.73 (m, 2H), 1.76 – 1.54 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H), 1.35-1.20 (m, 1H).	631
113	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.66 (d, *J* = 8.7 Hz, 1H), 5.37 (br, 2H), 5.12 - 5.08 (m, 1H), 4.54 – 4.52 (m, 1H), 4.44 - 4.42 (m, 1H), 4.16 – 4.13 (m, 1H), 3.97 - 3.94 (m, 1H), 3.77 - 3.43 (m, 8H), 3.19 - 2.86 (m, 5H), 2.24 (s, 3H), 2.17 – 2.08 (m, 1H), 1.83 - 1.55 (m, 6H), 1.44 (d, *J* = 6.3 Hz, 3H), 1.40 - 1.33 (m, 1H).	662

[2100] **Example 114:** Compound 114



[2101] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-aminoquinolin-8-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2102] Under nitrogen, to a mixture of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (62.7 mg, 0.110 mmol), (2-aminoquinolin-8-yl)boronic acid (40.0 mg, 0.210 mmol, intermediate 72) and cataCXium A Pd G3 (15.4 mg, 0.0200 mmol) in tetrahydrofuran (2.5 mL) was added a solution of K_3PO_4 (67.4 mg, 0.320 mmol) in water (0.5 mL) at room temperature. The solution was stirred at 60°C for 5 hours. The resulting solution was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on a pre-packed C18 column (gradient: 0-70% CH_3CN in water (0.05% NH_4HCO_3) to afford 21.0 mg (28.3% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 701$.

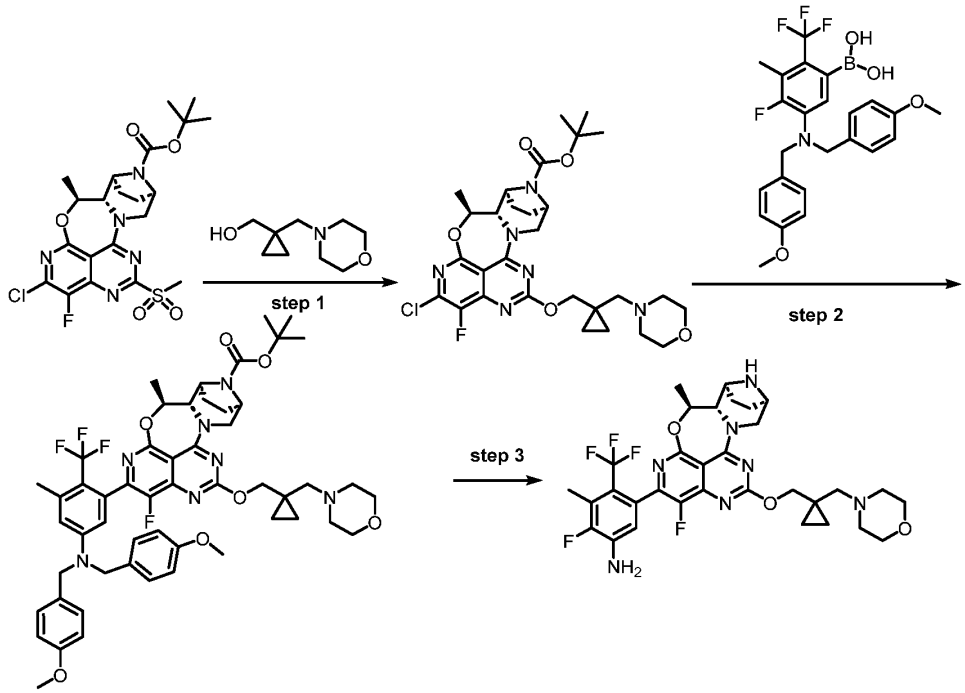
[2103] Step 2: 8-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)quinolin-2-amine (Compound 114)

[2104] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-aminoquinolin-8-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (20.0 mg, 0.0500 mmol) in dichloromethane was added 2,2,2-trifluoroacetic acid (3 mL) at room temperature. The solution was stirred for 1 hour. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 20% B to 45% B in 7 min; Wave Length: 254 nm; RT1(min): 8.3; Number Of Runs: 2) to yield 4.4 mg (25.7% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+ = 601$. ^1H NMR (300 MHz, DMSO-*d6, ppm*) δ 7.96 (d, J = 8.9 Hz, 1H), 7.78-7.70 (m, 1H), 7.51-7.43 (m, 1H), 7.25 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.9 Hz, 1H), 6.32 (s, 2H), 5.29 (d, J = 54.4 Hz, 1H), 5.18-5.06 (m, 1H), 4.58 – 4.45 (m, 1H), 4.13 (d, J = 10.3 Hz, 1H), 4.06 – 3.93 (m, 2H), 3.59 (s, 1H), 3.46 (d, J = 5.6 Hz, 1H), 3.15 – 2.98 (m, 4H), 2.84 (d, J = 6.7 Hz, 1H), 2.21 – 2.12 (m, 1H), 2.10 – 1.97 (m, 2H), 1.89 – 1.59 (m, 7H), 1.46 (d, J = 6.3 Hz, 3H), 1.24 (s, 1H).

[2105] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Example **114**.

Cmpd. No.	^{1}H NMR	MS (M+H)$^+$
115	^{1}H NMR (300 MHz, DMSO-d6) δ 7.20 (d, J = 2.3 Hz, 1H), 6.75 (s, 1H), 6.52 (d, J = 2.5 Hz, 2H), 5.27 (d, J = 54.2 Hz, 1H), 5.07 (d, J = 12.1 Hz, 1H), 4.51 (dd, J = 8.7, 6.3 Hz, 1H), 4.09 (d, J = 10.3 Hz, 1H), 3.97 (dd, J = 14.4, 9.5 Hz, 2H), 3.56 (s, 1H), 3.51 – 3.40 (m, 1H), 3.18 – 2.89 (m, 4H), 2.82 (d, J = 6.4 Hz, 1H), 2.14 (d, J = 5.2 Hz, 1H), 2.01 (d, J = 12.7 Hz, 2H), 1.95 – 1.44 (m, 7H), 1.42 (d, J = 6.3 Hz, 3H).	686
116	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 7.79 – 7.76 (m, 1H), 7.60 (s, 2H), 7.31 – 7.26 (m, 1H), 7.13 (t, J = 7.7 Hz, 1H), 5.39 – 5.20 (m, 1H), 5.13 – 5.05 (m, 1H), 4.57 – 4.46 (m, 1H), 4.11 (d, J = 10.3 Hz, 1H), 4.02 (d, J = 10.3 Hz, 1H), 3.97 – 3.93 (m, 1H), 3.57 (d, J = 5.6 Hz, 1H), 3.46 (d, J = 5.9 Hz, 1H), 3.15 – 3.07 (m, 2H), 3.06 – 2.99 (m, 2H), 2.88 – 2.79 (m, 1H), 2.75 (s, 1H), 2.20 – 2.11 (m, 1H), 2.10 – 2.04 (m, 1H), 2.03 – 1.96 (m, 1H), 1.89 – 1.73 (m, 4H), 1.70 – 1.54 (m, 3H), 1.45 (d, J = 6.3 Hz, 3H).	607
117	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 7.19 (d, J = 8.6 Hz, 1H), 6.63 – 6.56 (m, 1H), 6.36 – 6.09 (m, 1H), 5.42 – 5.30 (m, 1H), 5.24 – 4.92 (m, 3H), 4.58 – 4.44 (m, 1H), 4.16 – 3.89 (m, 3H), 3.63 – 3.54 (m, 1H), 3.44 (d, J = 5.9 Hz, 1H), 3.19 – 2.95 (m, 4H), 2.92 – 2.71 (m, 1H), 2.24 – 2.12 (m, 1H), 2.11 – 1.94 (m, 2H), 1.93 – 1.51 (m, 6H), 1.43 (d, J = 6.3 Hz, 3H), 1.24 (s, 2H), 1.04 (s, 9H).	606

[2106] **Example 118:** Compound 118



[2107] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2108] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-

methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (200 mg, 0.389 mmol) and (1-(morpholinomethyl)cyclopropyl)methanol (80.0 mg, 0.467 mmol) in toluene (10 mL) was added *tert*-butoxysodium (75.0 mg, 0.780 mmol) at 0 °C. The solution was stirred at room temperature for 2 hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-15% methanol in dichloromethane) to afford 176 mg (74.7% yield) of the title compound as a yellow solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 605.

[2109] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2110] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (136 mg, 0.225 mmol), (5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (214 mg, 0.449 mmol) and cataCXium A Pd G3 (32.8 mg, 0.0451 mmol) in tetrahydrofuran (4 mL) was added a solution of K_3PO_4 (143 mg, 0.674 mmol) in water (0.8 mL). This solution was stirred at 60°C for 5 hours. The resulting solution was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-15% methanol in dichloromethane) to afford 186 mg (82.6 % yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 1002.

[2111] Step 3: 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (Compound 118)

[2112] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (170 mg, 0.170 mmol) in 2,2,2-trifluoroacetic acid (5 mL) was stirred at 50°C for 1 hour. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: YMC-Actus Triart C18 ExRS, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min,

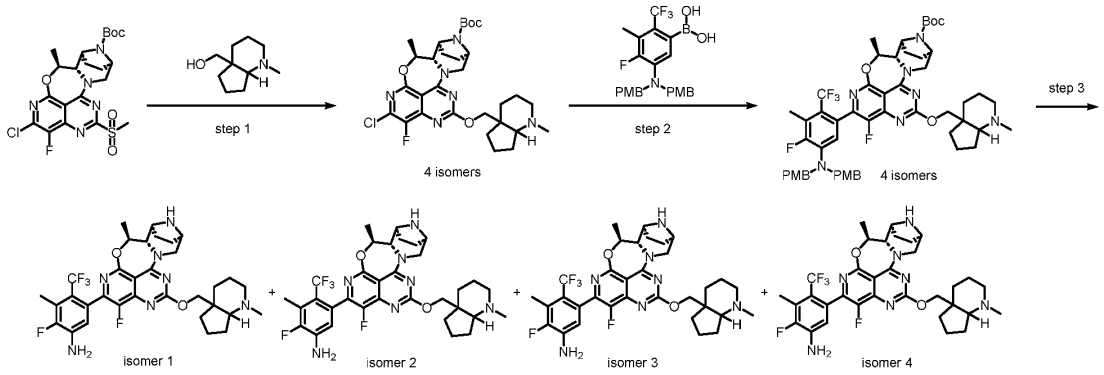
42% B; Wave Length: 254/220 nm; RT1(min): 8.5) to yield 47.7 mg (42.5% yield) of the title compound as a white solid. LC-MS: (ESI, m/z): $[M+H]^+$ = 662. ^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.64 – 6.40 (m, 1H), 6.00 (s, 2H), 5.11 – 5.04 (m, 1H), 4.58 – 4.43 (m, 1H), 4.34 – 4.18 (m, 2H), 3.93 (d, J = 8.7 Hz, 1H), 3.63 – 3.39 (m, 6H), 3.00 (d, J = 12.8 Hz, 1H), 2.75 (s, 1H), 2.44 – 2.20 (m, 9H), 1.80 (s, 1H), 1.57 (d, J = 26.3 Hz, 3H), 1.42 (d, J = 6.3 Hz, 3H), 0.63 (d, J = 5.2 Hz, 2H), 0.41 (t, J = 2.9 Hz, 2H).

[2113] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for Example **118**.

Cmpd. No.	**^{1}H NMR**	**MS $(M+H)^+$**
119 (isomer 1)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.67 – 6.45 (m, 1H), 6.02 (br, 2H), 5.12 - 5.07 (m, 1H), 4.55 – 4.50 (m, 1H), 4.42 - 4.37 (m, 1H), 4.31 - 4.27 (m, 1H), 3.98 – 3.95 (m, 1H), 3.59 - 3.57 (m, 1H), 3.48 - 3.46 (m, 1H), 3.06 - 3.02 (m, 1H), 2.83 – 2.78 (m, 1H), 2.32 – 2.28 (m, 4H), 2.27 - 2.19 (m, 2H), 2.08 – 1.53 (m, 11H), 1.45 - 1.39 (m, 4H).	682
119 (isomer 2)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.68 – 6.45 (m, 1H), 6.02 (br, 2H), 5.11 - 5.06 (m, 1H), 4.55 – 4.50 (m, 1H), 4.40 - 4.35 (m, 1H), 4.16 - 4.10 (m, 1H), 3.98 – 3.94 (m, 1H), 3.56 - 3.53 (m, 1H), 3.45 - 3.40 (m, 2H), 3.31 - 3.23 (m, 1H), 3.10 – 3.00 (m, 2H), 2.86 - 2.78 (m, 2H), 2.32 (s, 3H), 2.16 – 1.45 (m, 12H), 1.43 (d, *J* = 6.3 Hz, 3H).	682
120	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.67 – 6.46 (m, 1H), 6.01 (br, 2H), 5.27 - 5.21 (m, 1H), 5.11 - 5.07 (m, 1H), 4.55 – 4.39 (m, 2H), 4.21 - 4.16 (m, 1H), 3.97 - 3.94 (m, 1H), 3.75 - 3.18 (m, 6H), 3.05 - 3.01 (m, 1H), 2.32 (s, 3H), 2.16 – 1.94 (m, 4H), 1.82 - 1.46 (m, 6H), 1.43 (d, *J* = 6.3 Hz, 3H).	662
121 (isomer 1)	^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 6.61 – 6.47 (m, 1H), 6.02 (br, 2H), 5.10 - 5.06 (m, 1H), 4.55 – 4.51 (m, 1H), 4.38 - 4.32 (m, 2H), 3.96 – 3.92 (m, 2H), 3.82 - 3.78 (m, 1H), 3.55 - 3.54 (m, 1H), 3.44 - 3.43 (m, 1H), 3.24 - 3.20 (m, 1H), 3.06 – 2.99 (m, 3H), 2.82 - 2.78 (m, 1H), 2.32 (s, 3H), 2.08 – 1.95 (m, 3H), 1.87 - 1.54 (m, 7H), 1.43 (d, *J* = 6.4 Hz, 3H), 1.28 - 1.23 (m, 1H).	648
121 (isomer 2)	^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 6.65 – 6.44 (m, 1H), 6.02 (br, 2H), 5.10 - 5.07 (m, 1H), 4.84 – 4.79 (m, 1H), 4.55 – 4.51 (m, 1H), 4.36 - 4.32 (m, 1H), 4.05 – 3.94 (m, 2H), 3.74 - 3.71 (m, 1H), 3.60 - 3.54 (m, 2H), 3.44 - 3.43 (m, 1H), 3.03 – 2.77 (m, 4H), 2.37 - 2.32 (m, 4H), 2.21 – 2.06 (m, 2H), 1.87 - 1.55 (m, 7H), 1.43 (d, *J* = 6.4 Hz, 3H), 1.38 - 1.34 (m, 1H).	648
122	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.68 – 6.40 (m, 1H), 6.01 (s, 2H), 5.36 – 4.99 (m, 2H), 4.61 – 4.44 (m, 1H), 4.09 (s, 2H), 3.95 (d, J = 8.7 Hz, 1H), 3.62 – 3.41 (m, 2H), 3.19 (s, 1H), 3.11 – 2.96 (m, 3H), 2.46 – 2.25 (m, 5H), 1.99 – 1.71 (m, 4H), 1.70 – 1.51 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H), 1.12 (d, J = 6.7 Hz, 3H).	664
123	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.74 – 6.37 (m, 1H), 6.02 (s, 2H), 5.19 – 5.00 (m, 1H), 4.62 – 4.46 (m, 1H), 4.41 – 4.28 (m, 1H), 4.23 – 4.10 (m, 1H), 3.96 (d, J = 8.8 Hz, 1H), 3.69 – 3.53 (m, 3H), 3.50 – 3.35 (m, 2H), 3.20 – 3.09 (m, 2H), 3.09 – 2.98 (m, 2H), 2.84 (s, 3H), 2.33 (s, 3H), 2.13 – 1.76 (m, 4H), 1.74 – 1.52 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H).	67

124	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.67 – 6.39 (m, 1H), 6.02 (s, 2H), 5.09 (d, J = 13.0 Hz, 1H), 4.60 – 4.47 (m, 1H), 4.44 – 4.19 (m, 2H), 3.96 (d, J = 8.8 Hz, 1H), 3.58 (s, 1H), 3.50 – 3.41 (m, 3H), 3.40 – 3.35 (m, 1H), 3.31 – 3.27 (m, 1H), 3.27 – 3.14 (m, 2H), 3.03 (d, J = 13.0 Hz, 1H), 2.83 (s, 3H), 2.32 (s, 3H), 2.19 – 2.04 (m, 1H), 2.02 – 1.75 (m, 2H), 1.74 – 1.48 (m, 5H), 1.44 (d, J = 6.3 Hz, 3H)	675
125	^{1}H NMR (300 MHz, DMSO-d6) δ 6.54 (dd, J = 14.3, 2.2 Hz, 1H), 6.34 (d, J = 5.0 Hz, 3H), 5.07 (dd, J = 12.9, 2.5 Hz, 1H), 4.62 – 4.32 (m, 2H), 4.23 – 4.07 (m, 1H), 3.94 (d, J = 8.8 Hz, 1H), 3.70 – 3.39 (m, 4H), 3.34 (s, 1H), 3.28 (s, 1H), 3.01 (d, J = 12.7 Hz, 1H), 2.86 – 2.65 (m, 3H), 2.14 – 1.94 (m, 1H), 1.78 (d, J = 7.3 Hz, 2H), 1.73 – 1.46 (m, 4H), 1.42 (d, J = 6.3 Hz, 3H), 1.38 – 1.26 (m, 1H), 1.19 (d, J = 1.6 Hz, 3H), 1.06 (s, 3H).	662

[2114] **Example 126:** Compound 126 (four isomers)



[2115] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-((1-methyloctahydro-4a*H*-cyclopenta[*b*]pyridin-4a-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (four isomers)

[2116] To a solution of (1-methyloctahydro-4a*H*-cyclopenta[*b*]pyridin-4a-*yl*)methanol (0.60 g, 3.5 mmol, intermediate 95) in tetrahydrofuran (20 mL) was added NaH (60% dispersion in mineral oil, 425 mg, 10.6 mmol) at 0 °C, and the mixture was stirred for 30 minutes at room temperature. Then *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (907 mg, 1.77 mmol) was added at room temperature, and the mixture was stirred for 2 hours. The reaction was quenched with NH_4Cl solution. The resulting solution was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-15% methanol in dichloromethane) to afford two fractions as yellow solids. The faster peak (80 mg, mixture of **isomer 1** and **isomer 2**). The slower peak (380 mg, mixture of **isomer 3** and **isomer 4**). **Isomer 1** and **isomer 2** was separated by Chiral-Prep-HPLC with the following conditions (Column: CHI–LPAK ID, 2*25 cm, 5 μm; Mo–le Phase A: Hex(0.1% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 15; Wave Length: 220/254 nm; RT1(min): 13.88; RT2(min):

17.661; Injection Volume: 0.4 mL; Number Of Runs: 11) to afford **isomer 1** (35 mg, the faster peak) and **isomer 2** (30 mg, the slower peak) as white solids. **Isomer 3** and **isomer 4** was separated by Chiral-Prep-HPLC with the following conditions: (Column: CHI–LPAK ID, 2*25 cm, 5 μm; Mo–le Phase A: Hex(0.1% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 10; Wave Length: 220/254 nm; RT1(min): 12.978; RT2(min): 15.578; Injection Volume: 0.8 mL; Number Of Runs: 16) to afford **isomer 3** (150 mg, the faster peak) and **isomer 4** (150 mg, the slower peak) as white solids. LC-MS: (ESI, *m/z*): $[M+H]^+ = 603$.

[2117] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-methyloctahydro-4a*H*-cyclopenta[*b*]pyridin-4a-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (four isomers)

[2118] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-((1-methyloctahydro-4a*H*-cyclopenta[*b*]pyridin-4a-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (35 mg, 0.058 mmol, **isomer 1 of last step**), (5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (55.4 mg, 0.116 mmol), K_3PO_4 (1.5M aqueous solution, 0.2 mL, 0.300 mmol) and cataCXium A Pd G3 (8.50 mg, 0.0116 mmol) in tetrahydrofuran (1 mL) was stirred for 3 hours at 60 °C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-15% methanol in dichloromethane) to afford the title compound (31 mg, 53%, **isomer 1**) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 1000$.

[2119] Analogous to method described as above, **isomer 2** (42 mg), **isomer 3** (185 mg) and **isomer 4** (180 mg) were obtained as brown solids.

[2120] Step 3: 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-methyloctahydro-4a*H*-cyclopenta[*b*]pyridin-4a-*yl*)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (four isomers)

[2121] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl) amino)-4-fluoro-3-methyl-2-(trifluoromethyl) phenyl)-1-fluoro-5-methyl-12-((1-methyloctahydro-4a*H*-cyclopenta[*b*]pyridin-4a-yl) methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*] heptalene-14-carboxylate (31mg, 0.031 mmol, **isomer 1 of last step**) in TFA (10 mL) was stirred for 1 hour at room temperature. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep

OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 43% B to 67% B in 9 min; Wave Length: 254nm/220nm nm; RT1(min): 8) to afford **Isomer 1** (6.4 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 660.

[2122] Analogous to method described as above, **Isomer 2,** (5.9 mg), **Isomer 3** (116 mg) and **Isomer 4** (62.9 mg) were obtained as white solids. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 660.

[2123] **Isomer 1:** ^{1}H NMR (300 MHz, CD_3OD, *ppm*) δ 6.74 – 6.47 (m, 1H), 5.68 – 5.53 (m, 1H), 4.81 – 4.69 (m, 1H), 4.64 (d, J = 11.1 Hz, 1H), 4.52 (d, J = 11.0 Hz, 1H), 4.43 – 4.30 (m, 3H), 4.30 – 4.20 (m, 1H), 3.58 – 3.40 (m, 2H), 3.30 – 3.15 (m, 1H), 2.99 – 2.83 (m, 3H), 2.41 (s, 3H), 2.37 – 2.28 (m, 1H), 2.27 – 2.02 (m, 6H), 2.02 – 1.83 (m, 5H), 1.83 – 1.70 (m, 2H), 1.63 (d, J = 6.3 Hz, 3H).

[2124] **Isomer 2**: ^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.71 – 6.38 (m, 1H), 6.02 (s, 2H), 5.08 (d, J = 12.9, 2.5 Hz, 1H), 4.63 – 4.48 (m, 1H), 4.40 (d, J = 10.7 Hz, 1H), 4.15 (d, J = 10.7 Hz, 1H), 3.95 (d, J = 8.6 Hz, 1H), 3.61 – 3.50 (m, 1H), 3.45 (d, J = 5.7 Hz, 1H), 3.03 (d, J = 12.8 Hz, 1H), 2.71 – 2.60 (m, 1H), 2.48 – 2.40 (m, 2H), 2.32 (s, 3H), 2.29 – 2.11 (s, 4H), 1.90 – 1.75 (m, 2H), 1.74 – 1.47 (m, 10H), 1.47 – 1.33 (m, 4H).

[2125] **Isomer 3**: ^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.67 – 6.41 (m, 1H), 6.02 (s, 2H), 5.08 (d, J = 12.8 Hz, 1H), 4.80 – 4.62 (m, 1H), 4.60 – 4.45 (m, 1H), 4.20 – 3.99 (m, 1H), 3.94 (d, J = 8.6 Hz, 1H), 3.63 – 3.50 (m, 1H), 3.50 – 3.40 (m, 1H), 3.02 (d, J = 12.8 Hz, 1H), 2.97 – 2.76 (m, 2H), 2.33 (s, 3H), 2.17 – 2.01 (m, 4H), 1.98 – 1.88 (m, 1H), 1.87 – 1.51 (m, 10H), 1.51 – 1.32 (m, 5H), 1.28 – 1.09 (m, 1H), 1.08 – 0.91 (m, 1H).

Isomer 4: ^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.71 – 6.38 (m, 1H), 6.02 (s, 2H), 5.16 – 4.99 (m, 1H), 4.70 – 4.48 (m, 2H), 4.13 (d, J = 11.2 Hz, 1H), 3.94 (d, J = 8.6 Hz, 1H), 3.62 – 3.40 (m, 2H), 3.11 – 2.76 (m, 3H), 2.32 (s, 3H), 2.19 – 2.02 (m, 4H), 1.99 – 1.87 (m, 1H), 1.87 – 1.51 (m, 10H), 1.51 – 1.32 (m, 5H), 1.29 – 0.91 (m, 2H).

[2126] Each compound in Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 126**.

Cmpd. No.	**^{1}H NMR**	**MS (M+H)$^+$**
127 (isomer 1)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.65 – 6.44 (m, 1H), 6.04 (br, 2H), 5.12 – 5.08 (m, 1H), 4.72 – 4.51 (m, 3H), 4.27 – 4.25 (m, 2H), 4.00 – 3.97 (m, 1H), 3.62 –3.61 (m, 1H), 3.50 – 3.48 (m, 1H), 3.08 – 3.04 (m, 1H), 2.82 – 2.76 (m, 2H), 2.34 – 2.32 (m, 6H), 2.03 – 1.58 (m, 10H), 1.44 (d, *J* = 6.3 Hz, 3H).	652

127 (isomer 2)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.65 – 6.43 (m, 1H), 6.04 (br, 2H), 5.13 – 5.08 (m, 1H), 4.72 – 4.51 (m, 3H), 4.29 – 4.27 (m, 2H), 4.02 – 3.99 (m, 1H), 3.65 – 3.63 (m, 1H), 3.53 – 3.49 (m, 1H), 3.10 – 3.06 (m, 1H), 2.83 – 2.77 (m, 2H), 2.34 – 2.32 (m, 6H), 2.03 – 1.60 (m, 10H), 1.44 (d, *J* = 6.3 Hz, 3H).	652
128	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.70 – 6.40 (m, 1H), 6.30 – 5.79 (m, 3H), 5.15 – 4.94 (m, 1H), 4.64 – 4.33 (m, 3H), 4.33 – 4.05 (m, 1H), 3.99 – 3.89 (m, 1H), 3.69 – 3.48 (m, 3H), 3.16 – 2.99 (m, 3H), 2.89 – 2.79 (m, 2H), 2.79 – 2.72 (m, 1H), 2.32 (s, 3H), 1.98 – 1.56 (m, 4H), 1.43 (d, J = 6.3 Hz, 3H).	642
129	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.67 – 6.43 (m, 1H), 6.03 (s, 2H), 5.17 – 5.06 (m, 1H), 4.61 – 4.45 (m, 2H), 3.96 (d, J = 8.7 Hz, 2H), 3.65 (d, J = 11.6 Hz, 1H), 3.55 – 3.48 (m, 2H), 3.47 – 3.42 (m, 1H), 3.26 – 3.20 (m, 3H), 3.10 – 2.89 (m, 4H), 2.37 – 2.21 (m, 4H), 2.17 – 2.05 (m, 1H), 1.94 – 1.73 (m, 1H), 1.65 – 1.52 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H), 0.82 (d, J = 6.1 Hz, 3H), 0.72 – 0.63 (m, 1H), 0.60 – 0.45 (m, 2H), 0.40 – 0.30 (m, 1H).	676
130 (isomer 1)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.76 – 6.38 (m, 1H), 6.03 (s, 2H), 5.77 – 5.52 (m, 1H), 5.13 – 5.04 (m, 1H), 4.60 – 4.46 (m, 1H), 4.15 – 4.01 (m, 2H), 3.95 (d, J = 8.8 Hz, 1H), 3.61 – 3.53 (m, 1H), 3.46 – 3.42 (m, 1H), 3.08 – 2.88 (m, 3H), 2.77 – 2.64 (m, 1H), 2.32 (s, 3H), 2.13 – 1.94 (m, 2H), 1.93 – 1.74 (m, 5H), 1.74 – 1.50 (m, 5H), 1.44 (d, J = 6.3 Hz, 3H).	682
130 (isomer 2)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.69 – 6.38 (m, 1H), 6.02 (s, 2H), 5.78 – 5.51 (m, 1H), 5.15 – 5.02 (m, 1H), 4.59 – 4.46 (m, 1H), 4.13 – 4.01 (m, 2H), 4.00 – 3.92 (m, 1H), 3.61 – 3.50 (m, 1H), 3.45 (d, J = 5.7 Hz, 1H), 3.09 – 2.92 (m, 3H), 2.75 – 2.64 (m, 1H), 2.33 (s, 3H), 2.12 – 1.93 (m, 2H), 1.92 – 1.75 (m, 5H), 1.73 – 1.51 (m, 5H), 1.44 (d, J = 6.3 Hz, 3H).	682
131 (isomer 1)	^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 6.71 – 6.38 (m, 1H), 6.03 (s, 2H), 5.16 – 5.03 (m, 1H), 4.62 – 4.46 (m, 1H), 4.44 – 4.32 (m, 1H), 4.32 – 4.20 (m, 1H), 3.96 (d, J = 8.7 Hz, 1H), 3.61 – 3.54 (m, 1H), 3.49 – 3.41 (m, 3H), 3.41 – 3.36 (m, 1H), 3.30 – 3.16 (m, 3H), 3.04 (d, J = 12.8 Hz, 1H), 2.83 (s, 3H), 2.33 (s, 3H), 2.19 – 2.05 (m, 1H), 2.05 – 1.88 (m, 2H), 1.88 – 1.75 (m, 1H), 1.75 – 1.60 (m, 3H), 1.60 – 1.46 (m, 2H), 1.44 (d, J = 6.4 Hz, 3H).	675
131 (isomer 2)	^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 6.67 – 6.42 (m, 1H), 6.02 (s, 2H), 5.14 – 5.03 (m, 1H), 4.61 – 4.48 (m, 1H), 4.45 – 4.31 (m, 1H), 4.31 – 4.17 (m, 1H), 3.96 (d, J = 8.8 Hz, 1H), 3.67 – 3.54 (m, 1H), 3.46 (d, J = 6.5 Hz, 1H), 3.44 – 3.36 (m, 3H), 3.31 – 3.29 (m, 1H), 3.29 – 3.15 (m, 2H), 3.03 (d, J = 12.8 Hz, 1H), 2.83 (s, 3H), 2.33 (s, 3H), 2.18 – 2.05 (m, 1H), 2.05 – 1.89 (m, 1H), 1.89 – 1.77 (m, 1H), 1.75 – 1.61 (m, 3H), 1.61 – 1.47 (m, 2H), 1.44 (d, J = 6.3 Hz, 3H).	675
131 (isomer 3)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.70 – 6.38 (m, 1H), 6.02 (s, 2H), 5.08 (d, J = 12.2 Hz, 1H), 4.63 – 4.46 (m, 1H), 4.42 – 4.28 (m, 1H), 4.22 – 4.07 (m, 1H), 4.03 – 3.86 (m, 1H), 3.69 – 3.50 (m, 3H), 3.50 – 3.36 (m, 2H), 3.22 – 2.96 (m, 5H), 2.83 (s, 3H), 2.32 (s, 3H), 2.09 – 1.95 (m, 1H), 1.95 – 1.76 (m, 3H), 1.74 – 1.50 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H).	675

131 (isomer 4)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.74 – 6.37 (m, 1H), 6.03 (s, 2H), 5.22 – 5.00 (m, 1H), 4.66 – 4.47 (m, 1H), 4.44 – 4.28 (m, 1H), 4.25 – 4.10 (m, 1H), 3.97 (d, J = 8.8 Hz, 1H), 3.72 – 3.35 (m, 5H), 3.22 – 2.97 (m, 4H), 2.84 (s, 3H), 2.32 (s, 3H), 2.12 – 1.75 (m, 4H), 1.75 – 1.50 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H).	675
132	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.52 (d, *J* = 40.6 Hz, 1H), 6.03 (s, 2H), 5.09 (d, *J* = 12.3 Hz, 1H), 4.65 – 4.54 (m, 3H), 4.29 (s, 1H), 4.08 (d, *J* = 7.5 Hz, 1H), 3.95 (d, *J* = 9.0 Hz, 1H), 3.62 – 3.51 (m, 3H), 3.44 (d, *J* = 5.4 Hz, 1H), 3.17 (d, *J* = 1.2 Hz, 1H), 3.03 (d, *J* = 12.6 Hz, 1H), 2.35 (s, 6H), 1.88 – 1.75 (m, 3H), 1.64 (s, 3H), 1.42 (d, *J* = 6.3 Hz, 3H)	634
133 (isomer 1)	^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 6.72 – 6.46 (m, 1H), 6.03 (br, 2H), 5.11 – 5.07 (m, 1H), 4.55 – 4.53 (m, 1H), 4.41 – 4.38 (m, 1H), 4.11 – 4.07 (m, 1H), 3.97 – 3.95 (m, 1H), 3.58 – 3.57 (m, 1H), 3.47 – 3.41 (m, 2H), 3.13 – 3.11 (m, 1H), 3.07 – 3.05 (m, 1H), 3.05 (s, 3H), 2.90 – 2.88 (m, 1H), 2.82 (s, 3H), 2.80 – 2.65 (m, 2H), 2.32 (s, 3H), 2.08 – 2.05 (m, 1H), 1.90 – 1.82 (m, 2H), 1.66 – 1.33 (m, 8H), 1.43 (d, *J* = 6.0 Hz, 3H), 1.22 – 1.18 (m, 1H).	717
133 (isomer 2)	^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 6.71 – 6.46 (m, 1H), 6.02 (br, 2H), 5.11 – 5.08 (m, 1H), 4.55 – 4.53 (m, 1H), 4.40 – 4.38 (m, 1H), 4.27 – 4.24 (m, 1H), 3.96 – 3.94 (m, 1H), 3.58 – 3.57 (m, 1H), 3.44 – 3.43 (m, 1H), 3.29 – 3.27 (m, 1H), 3.13 – 3.11 (m, 1H), 3.04 – 3.02 (m, 1H), 3.02 (s, 3H), 2.80 (s, 3H), 2.67 – 2.61 (m, 2H), 2.32 (s, 3H), 2.10 – 2.07 (m, 2H), 1.89 – 1.50 (m, 10H), 1.43 (d, *J* = 6.0 Hz, 3H), 1.35 – 1.26 (m, 2H).	717
133 (isomer 3)	^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 6.66 – 6.42 (m, 1H), 6.05 (br, 2H), 5.11 – 5.09 (m, 1H), 4.55 – 4.53 (m, 1H), 4.39 – 4.37 (m, 1H), 4.24 – 4.21 (m, 1H), 3.97 – 3.95 (m, 1H), 3.57 – 3.56 (m, 1H), 3.46 – 3.45 (m, 1H), 3.05 – 2.97 (m, 3H), 3.01 (s, 3H), 2.83 – 2.79 (m, 4H), 2.65 – 2.62 (m, 1H), 2.50 – 2.46 (m, 1H), 2.38 – 2.32 (m, 4H), 1.88 – 1.51 (m, 10H), 1.44 (d, *J* = 6.4 Hz, 3H), 1.41 – 1.35 (m, 1H), 1.26 – 1.22 (m, 1H).	717
133 (isomer 4)	^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 6.64 – 6.46 (m, 1H), 6.02 (br, 2H), 5.10 – 5.06 (m, 1H), 4.55 – 4.53 (m, 1H), 4.36 – 4.34 (m, 1H), 4.05 – 4.03 (m, 1H), 3.96 – 3.94 (m, 1H), 3.55 – 3.53 (m, 1H), 3.44 – 3.42 (m, 1H), 3.21 – 3.19 (m, 1H), 3.03 – 2.98 (m, 4H), 2.90 – 2.87 (m, 2H), 2.80 (s, 3H), 2.80 – 2.73 (m, 2H), 2.32 (s, 3H), 2.06 – 2.03 (m, 1H), 1.85 – 1.43 (m, 11H), 1.43 (d, *J* = 6.0 Hz, 3H).	717
134 (isomer 1)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.73 – 6.34 (m, 1H), 6.01 (s, 2H), 5.16 – 5.01 (m, 1H), 4.62 – 4.40 (m, 2H), 4.30 (d, J = 11.1 Hz, 1H), 3.99 – 3.76 (m, 3H), 3.62 – 3.51 (m, 1H), 3.51 – 3.35 (m, 3H), 3.01 (d, J = 12.7 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.73 – 2.57 (m, 2H), 2.39 – 2.24 (m, 5H), 1.96 – 1.72 (m, 3H), 1.71 – 1.46 (m, 4H), 1.41 (d, J = 6.5 Hz, 3H).	648
134 (isomer 2)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.69 – 6.36 (m, 1H), 6.01 (s, 2H), 5.08 (d, J = 12.7 Hz, 1H), 4.64 – 4.24 (m, 3H), 4.01 – 3.73 (m, 3H), 3.59 – 3.51 (m, 1H), 3.50 – 3.36 (m, 3H), 3.01 (d, J = 12.7 Hz, 1H), 2.87 – 2.76 (m, 1H), 2.73 – 2.58 (m, 2H), 2.39 – 2.23 (m, 6H), 2.00 – 1.72 (m, 2H), 1.72 – 1.45 (m, 4H), 1.42 (d, J = 6.3 Hz, 3H).	648

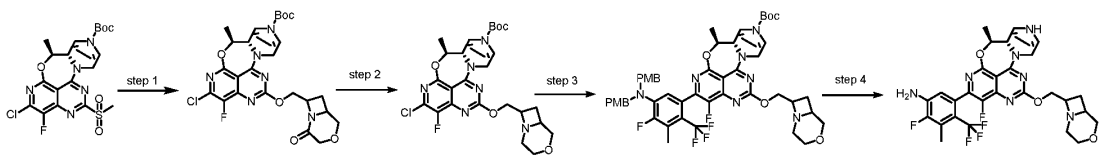
135	^{1}H NMR (300 MHz, DMSO-d6) δ 6.52 (d, J = 39.5 Hz, 1H), 6.01 (s, 2H), 5.09 (dd, J = 12.9, 2.5 Hz, 1H), 4.65 – 4.37 (m, 3H), 4.17 (d, J = 4.6 Hz, 1H), 3.94 (d, J = 8.8 Hz, 1H), 3.81 (dd, J = 12.4, 4.9 Hz, 1H), 3.53 (s, 1H), 3.43 – 3.39 (m, 1H), 3.35 (s, 1H), 3.23 (d, J = 12.3 Hz, 1H), 3.01 (d, J = 12.5 Hz, 2H), 2.92 – 2.78 (m, 2H), 2.74 (s, 1H), 2.30 (s, 3H), 2.11 – 1.96 (m, 2H), 1.86 – 1.48 (m, 5H), 1.42 (d, J = 6.3 Hz, 3H).	634
136	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.52 (d, *J* = 39.4 Hz, 1H), 6.01 (s, 2H), 5.07 (d, *J* = 11.7 Hz, 1H), 4.62 – 4.46 (m, 1H), 4.23 (d, *J* = 4.2 Hz, 1H), 4.08 (d, *J* = 8.0 Hz, 1H), 3.93 (d, *J* = 8.9 Hz, 2H), 3.76 – 3.68 (m, 1H), 3.53 (s, 1H), 3.46 – 3.36 (m, 3H), 3.1– – 2.85 (m, 4H), 2.56 (d, *J* = 4.1 Hz, 1H), 2.30 (s, 3H), 2.05 - 1.89 (m, 2H), 1.78 (d, *J* = 10.3 Hz, 1H), 1.58 (d, *J* = 32.3 Hz, 3H), 1.42 (d, *J* = 6.3 Hz, 3H).	634
137 (isomer 1)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.70 – 6.39 (m, 1H), 6.03 (s, 2H), 5.15 – 5.01 (m, 1H), 4.61 (d, J = 10.1 Hz, 1H), 4.55 (t, J = 7.6 Hz, 1H), 4.25 (d, J = 10.1 Hz, 1H), 3.97 (d, J = 8.7 Hz, 1H), 3.78 – 3.68 (m, 1H), 3.60 (s, 1H), 3.49 (s, 1H), 3.46 – 3.37 (m, 1H), 3.19 (m, 1H), 3.03 (d, J = 13.0 Hz, 1H), 2.99 – 2.89 (m, 5H), 2.86 – 2.77 (m, 1H), 2.34 (s, 3H), 1.90 (m, 3H), 1.78 – 1.51 (m, 5H), 1.44 (d, J = 6.3 Hz, 3H).	675
137 (isomer 2)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.72 – 6.42 (m, 1H), 6.03 (s, 2H), 5.14 – 5.01 (m, 1H), 4.61– 4.55 (m, 2H), 4.25 (d, J = 10.1 Hz, 1H), 3.97 (d, J = 8.7 Hz, 1H), 3.78 – 3.70 (m, 1H), 3.62 (s, 1H), 3.49 (s, 1H), 3.44 – 3.37 (m, 1H), 3.20 (m, 1H), 3.04 (d, J = 13.0 Hz, 1H), 2.98 – 2.89 (m, 5H), 2.85 – 2.76 (m, 1H), 2.33 (s, 3H), 1.91 (m, 3H), 1.78 – 1.52 (m, 5H), 1.43 (d, J = 6.3 Hz, 3H).	675
138	^{1}H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 6.68 – 6.32 (m, 1H), 6.02 (s, 2H), 5.16 – 5.04 (m, 1H), 4.61 – 4.46 (m, 1H), 4.43 – 4.31 (m, 2H), 3.95 (d, J = 8.8 Hz, 1H), 3.64 – 3.50 (m, 5H), 3.44 (d, J = 5.6 Hz, 1H), 3.02 (d, J = 12.8 Hz, 1H), 2.83 – 2.68 (m, 1H), 2.48 – 2.42 (m, 2H), 2.42 – 2.35 (m, 4H), 2.32 (s, 3H), 1.98 – 1.86 (m, 2H), 1.84 – 1.75 (m, 1H), 1.71 – 1.50 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H).	636
139	^{1}H NMR (400 MHz, DMSO-d_6) δ 6.54 (d, *J* = 60.8 Hz, 1H), 6.03 (s, 2H), 5.49 (s, 1H), 5.35 (d, *J* = 4.7 Hz, 1H), 5.08 (dd, *J* = 13.1, 2.5 Hz, 1H), 4.54 (dd, *J* = 8.7, 6.2 Hz, 1H), 4.16 (s, 2H), 3.95 (d, *J* = 8.8 Hz, 1H), 3.57 (d, *J* = 5.4 Hz, 2H),3.44 (d, *J* = 6.2 Hz, 1H), 3.28 (s, 1H), 3.03 (d, *J* = 12.7 Hz, 1H), 2.92 (dd, *J* = 12.5, 4.0 Hz, 1H), 2.87 – 2.79 (m, 1H), 2.43 – 2.28 (m, 5H), 2.05 (dd, *J* = 14.7, 4.7 Hz, 1H), 2.00 – 1.88 (m, 1H), 1.79 (d, *J* = 10.9 Hz, 1H), 1.64 (s, 2H), 1.54 (t, *J* = 5.7 Hz, 1H), 1.44 (d, *J* = 6.3 Hz, 3H).	668
140	^{1}H NMR (300 MHz, DMSO-d6) δ 6.54 (d, J = 40.2 Hz, 1H), 6.02 (s, 2H), 5.43 (s, 1H), 5.26 (s, 1H), 5.09 (dd, J = 12.9, 2.5 Hz, 1H), 4.53 (dd, J = 8.7, 6.3 Hz, 1H), 4.27 – 4.08 (m, 2H), 3.95 (d, J = 8.8 Hz, 1H), 3.56 (d, J = 4.9 Hz, 1H), 3.49 – 3.38 (m, 2H), 3.25 – 3.06 (m, 2H), 3.06 – 2.95 (m, 2H), 2.83 (s, 1H), 2.35 (d, J = 18.0 Hz, 4H), 2.26 – 2.12 (m, 2H), 2.12 – 1.99 (m, 1H), 1.78 (d, J = 10.0 Hz, 1H), 1.72 – 1.49 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H).	668

141	^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 6.53 (d, J = 60.5 Hz, 1H), 6.03 (s, 2H), 5.55 – 5.25 (m 2H), 5.20 – 5.01 (m, 1H), 4.64 – 4.41 (m, 1H), 4.28 – 4.06 (m, 2H), 3.95 (d, J = 8.8 Hz, 1H), 3.56 (d, J = 4.9 Hz, 1H), 3.48 – 3.39 (m, 2H), 3.22 – 3.15 (m, 1H), 3.11 (d, J = 10.2 Hz, 1H), 3.08 – 2.97 (m, 2H), 2.67 (s,1H), 2.43 – 2.25 (m, 4H), 2.19 (t, J = 12.0 Hz, 2H), 2.12 – 1.99 (m, 1H), 1.80 (s, 1H), 1.59 (d, J = 40.5 Hz, 3H), 1.43 (dd, J = 6.5, 3.1 Hz, 3H).	668
142	^{1}H NMR (300 MHz, DMSO-d6) δ 6.53 (d, J = 38.0 Hz, 1H), 6.02 (s, 2H), 5.42 (s, 1H), 5.24 (s, 1H), 5.08 (d, J = 13.2 Hz, 1H), 4.52 (d, J = 6.6 Hz, 1H), 4.04 (d, J = 5.1 Hz, 2H), 3.95 (d, J = 7.2 Hz, 1H), 3.57 (d, J = 5.6 Hz, 1H), 3.44 (s, 1H), 3.24 (s, 2H), 3.19 – 2.97 (m, 3H), 2.32 (s, 4H), 2.22 (d, J = 22.5 Hz, 3H), 1.88 – 1.73 (m, 1H), 1.63 (s, 3H), 1.45 (d, J = 6.2 Hz, 3H), 1.24 (s, 1H).	668
143 (isomer 1)	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.54 (d, J = 41.3 Hz, 1H), 6.03 (s, 2H), 5.50 – 5.19 (m, 1H), 5.19 – 4.80 (m, 2H), 4.71 – 4.49 (m, 1H), 4.35 (d, J = 10.6 Hz, 1H), 4.10 (d, J = 10.9 Hz, 1H), 3.96 (d, J = 8.8 Hz, 1H), 3.58 (s, 1H), 3.45 (d, J = 5.8 Hz, 1H), 3.24 – 3.07 (m, 2H), 3.08-2.84 (m, 3H), 2.68 – 2.55 (m, 1H), 2.32 (s, 3H), 2.14 – 1.97 (m, 1H), 1.89 – 1.73 (m, 3H), 1.72 – 1.50 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H).	668
143 (isomer 2)	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.54 (d, J = 40.8 Hz, 1H), 6.03 (s, 2H), 5.55 – 5.04 (m, 3H), 4.56 (dd, J = 8.6, 6.3 Hz, 1H), 4.27 – 4.12 (m, 2H), 3.99 (d, J = 8.8 Hz, 1H), 3.64 (s, 1H), 3.51 (d, J = 5.7 Hz, 1H), 3.29 – 3.16 (m, 1H), 3.07 (d, J = 12.2 Hz, 2H), 3.02 – 2.89 (m, 1H), 2.82 – 2.69 (m, 1H), 2.52 (s, 1H), 2.32 (s, 3H), 2.02 (s, 1H), 1.93 – 1.76 (m, 4H), 1.75 – 1.52 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H).	668
143 (isomer 3)	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.54 (d, J = 40.8 Hz, 1H), 6.03 (s, 2H), 5.53 – 5.01 (m, 3H), 4.62 – 4.46 (m, 1H), 4.26 – 4.18 (m, 1H), 4.14 (dd, J = 10.7, 3.6 Hz, 1H), 3.96 (d, J = 8.7 Hz, 1H), 3.57 (s, 1H), 3.52 – 3.41 (m, 1H), 3.24 (d, J = 13.3 Hz, 1H), 3.03 (d, J = 12.4 Hz, 2H), 2.97 (d, J = 6.5 Hz, 1H), 2.86 – 2.68 (m, 1H), 2.30 (d, J = 13.3 Hz, 3H), 2.02 (d, J = 9.6 Hz, 1H), 1.92 – 1.73 (m, 4H), 1.72 – 1.51 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H).	668
144	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.80 – 6.25 (m, 1H), 6.03 (s, 2H), 5.16 – 5.00 (m, 1H), 4.93 – 4.69 (m, 1H), 4.60 (s, 4H), 4.57 – 4.36 (m, 3H), 3.96 (d, J = 8.7 Hz, 1H), 3.58 – 3.50 (m, 1H), 3.48 – 3.38 (m, 2H), 3.35 (s, 4H), 3.02 (d, J = 12.8 Hz, 1H), 2.87 – 2.70 (m, 1H), 2.70 – 2.62 (m, 1H), 2.32 (s, 3H), 1.90-1.75 (m, 1H), 1.73 – 1.50 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H).	666
145	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.68 – 6.37 (m, 1H), 6.02 (s, 2H), 5.06 (d, J = 12.8, 2.5 Hz, 1H), 4.94 – 4.67 (m, 1H), 4.58 (s, 4H), 4.55 – 4.35 (m, 3H), 3.94 (d, J = 8.7 Hz, 1H), 3.56 – 3.48 (m, 1H), 3.48 – 3.39 (m, 2H), 3.35 (s, 4H), 3.01 (d, J = 12.8 Hz, 1H), 2.73 (d, J = 5.1 Hz, 1H), 2.65 (d, J = 5.2 Hz, 1H) , 2.30 (s, 3H), 1.82 – 1.71 (m, 1H), 1.71 – 1.48 (m, 3H), 1.42 (d, J = 6.3 Hz, 3H).	666
146	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) 6.67 – 6.37 (m, 1H), 6.02 (s, 2H), 5.07 (m, 1H), 4.95 – 4.68 (m, 1H), 4.66 – 4.35 (m, 5H), 3.94 (d, J = 8.8 Hz, 1H), 3.59 – 3.40 (m, 6H), 3.09 – 2.91 (m, 5H), 2.86 – 2.65 (m, 3H), 2.30 (s, 3H), 1.87 – 1.73 (m, 1H), 1.71 – 1.49 (m, 3H), 1.42 (d, J = 6.3 Hz, 3H).	684

149	^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 6.67 – 6.46 (m, 1H), 6.03 (s, 2H), 5.10 – 5.06 (m, 1H), 4.61 – 4.50 (m, 5H), 4.36 – 4.35 (m, 2H), 3.96 – 3.94 (m, 1H), 3.60 – 3.43 (m, 6H), 3.03 – 3.00 (m, 1H), 2.76 – 2.75 (m, 1H), 2.54 – 2.51 (m, 4H), 2.35 – 2.23 (m, 5H), 1.88 – 1.84 (m, 1H), 1.72 – 1.55 (m, 3H), 1.44 (d, *J* = 6.4 Hz, 3H).	678
150 (isomer 1)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.68 – 6.38 (m, 1H), 6.37 – 6.15 (m, 1H), 6.14 – 5.91 (m, 2H), 5.17 – 5.03 (m, 1H), 4.64 – 4.46 (m, 1H), 4.39 – 4.20 (m, 2H), 3.96 (d, J = 8.7 Hz, 1H), 3.56 (d, J = 5.5 Hz, 1H), 3.49 – 3.40 (m, 1H), 3.03 (d, J = 12.8 Hz, 1H), 2.91 – 2.64 (m, 3H), 2.41 – 2.27 (m, 6H), 2.24 – 1.99 (m, 2H), 1.96 – 1.77 (m, 2H), 1.76 – 1.68 (m, 3H), 1.68 – 1.49 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H).	670
150 (isomer 2)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.68 – 6.40 (m, 1H), 6.38 – 6.13 (m, 1H), 6.09 – 5.91 (m, 2H), 5.16 – 4.99 (m, 1H), 4.60 – 4.44 (m, 1H), 4.39 – 4.17 (m, 2H), 3.94 (d, J = 8.7 Hz, 1H), 3.55 (d, J = 5.3 Hz, 1H), 3.43 (d, J = 5.7 Hz, 1H), 3.01 (d, J = 12.7 Hz, 1H), 2.91 – 2.66 (m, 3H), 2.41 – 2.23 (m, 6H), 2.21 – 1.97 (m, 2H), 1.95 – 1.48 (m, 8H), 1.42 (d, J = 6.3 Hz, 3H).	670
151 (isomer 1)	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.54 (d, J = 57.1 Hz, 1H), 6.04 (s, 2H), 5.18 – 5.03 (m, 1H), 4.76 (s, 1H), 4.66 (s, 1H), 4.59 – 4.50 (m, 1H), 4.31 – 4.22 (m, 1H), 3.97 (d, J = 8.8 Hz, 1H), 3.84 – 3.71 (m, 1H), 3.59 (s, 1H), 3.53 – 3.38 (m, 4H), 3.11 – 2.92 (m, 3H), 2.81 – 2.65 (m, 1H), 2.46 (d, J = 11.5 Hz, 1H), 2.38 – 2.28 (m, 3H), 2.12 – 1.98 (m, 1H), 1.93 – 1.74 (m, 2H), 1.73 – 1.51 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H).	634
151 (isomer 2)	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.52 (d, J = 40.7 Hz, 1H), 6.01 (s, 2H), 5.07 (d, J = 12.7 Hz, 1H), 4.62 – 4.43 (m, 1H), 4.37 – 4.16 (m, 2H), 4.07 – 3.88 (m, 2H), 3.85 – 3.68 (m, 1H), 3.66 – 3.49 (m, 2H), 3.47 – 3.36 (m, 2H), 3.08 – 2.89 (m, 2H), 2.89 – 2.78 (m, 1H), 2.60 – 2.52 (m, 2H), 2.30 (s, 3H), 2.27 – 2.14 (m, 1H), 1.93 – 1.71 (m, 1H), 1.70 – 1.48 (m, 4H), 1.42 (d, J = 6.3 Hz, 3H).	634
152 (isomer 1)	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.54 (d, J = 56.7 Hz, 1H), 6.03 (s, 2H), 5.40 – 5.17 (m, 1H), 5.14 – 5.01 (m, 1H), 4.64 – 4.37 (m, 3H), 4.02 – 3.89 (m, 1H), 3.62 – 3.49 (m, 2H), 3.48 – 3.41 (m, 1H), 3.09 – 2.95 (m, 2H), 2.94 – 2.82 (m, 2H), 2.39 – 2.27 (m, 3H), 2.24 – 2.07 (m, 1H), 1.93 – 1.75 (m, 4H), 1.74 – 1.60 (m, 3H), 1.60 – 1.47 (m, 2H), 1.44 (d, J = 6.3 Hz, 3H).	650
152 (isomer 2)	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.54 (d, J = 58.4 Hz, 1H), 6.03 (s, 2H), 5.39 – 5.15 (m, 1H), 5.13 – 5.04 (m, 1H), 4.61 – 4.49 (m, 1H), 4.48 – 4.35 (m, 2H), 4.02 – 3.86 (m, 1H), 3.60 – 3.49 (m, 1H), 3.47 – 3.41 (m, 1H), 3.30 – 3.23 (m, 1H), 3.22 – 3.14 (m, 1H), 3.12 – 2.97 (m, 2H), 2.84 – 2.80 (m, 1H), 2.37 – 2.30 (m, 3H), 2.29 – 2.20 (m, 1H), 1.93 – 1.71 (m, 4H), 1.71 – 1.50 (m, 5H), 1.44 (d, J = 6.3 Hz, 3H).	650
153 (isomer 1)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.53 (d, J = 57.7 Hz, 1H), 6.03 (s, 2H), 5.09 (m, 1H), 4.53 (m, 1H), 4.22 (m, 2H), 3.96 (d, J = 8.8 Hz, 1H), 3.68 (m, 1H), 3.50 (m, 2H), 3.31 – 3.14 (m, 3H), 3.02 (d, J = 12.8 Hz, 1H), 2.84 (s, 1H), 2.48 – 2.28 (m, 4H), 2.23 – 2.01 (m, 3H), 1.80 (d, J = 11.5 Hz, 1H), 1.76 – 1.49 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H).	668

153 (isomer 2)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.55 (d, J = 57.7 Hz, 1H), 6.04 (s, 2H), 5.09 (m, 1H), 4.53 (m, 1H), 4.23 (m, 2H), 3.97 (d, J = 8.8 Hz, 1H), 3.68 (m, 1H), 3.52 (m, 2H), 3.31 – 3.15 (m, 3H), 3.01 (d, J = 12.8 Hz, 1H), 2.85 (s, 1H), 2.48 – 2.29 (m, 4H), 2.23 – 2.02 (m, 3H), 1.81 (d, J = 11.5 Hz, 1H), 1.76 – 1.47 (m, 4H), 1.43 (d, J = 6.3 Hz, 3H).	668
153 (isomer 3)	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.54 (d, J = 40.3 Hz, 1H), 6.03 (s, 2H), 5.09 (m, 1H), 4.65 – 4.32 (m, 2H), 3.96 (d, J = 8.7 Hz, 1H), 3.68 – 3.41 (m, 2H), 3.32 – 3.15 (m, 2H), 3.06 – 2.86 (m, 2H), 2.84 – 2.72 (m, 1H), 2.30 (d, J = 13.6 Hz, 4H), 2.15 – 1.98 (m, 3H), 1.97 – 1.72 (m, 4H), 1.80 – 1.47 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H).	668
154	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.53 (d, J = 55.9 Hz, 1H), 6.03 (s, 2H), 5.09 (m, 1H), 4.53 (m, 1H), 4.48 – 4.29 (m, 2H), 3.95 (d, J = 8.8 Hz, 1H), 3.66 – 3.53 (m, 4H), 3.52 – 3.40 (m, 2H), 3.32 – 3.13 (m, 3H), 3.02 (d, J = 12.8 Hz, 1H), 2.89 (m, 1H), 2.84 – 2.66 (m, 2H), 2.32 (d, J = 3.5 Hz, 3H), 2.11 – 1.93 (m, 1H), 1.89 – 1.48 (m, 5H), 1.44 (d, J = 6.3 Hz, 3H), 1.35 – 1.17 (m, 3H).	662
155	^{1}H NMR (400 MHz, DMSO-d_6) δ 6.58 (d, J = 20.7 Hz, 3H), 5.11 – 5.08 (m, 1H), 4.64 – 4.48 (m, 1H), 4.44 – 4.23 (m, 2H), 3.97 (d, J = 8.8 Hz, 1H), 3.56 – 3.52 (m, 2H), 3.45 (d, J = 6.0 Hz, 1H), 3.25 – 3.21(m, 1H), 3.15 – 2.99 (m, 3H), 2.77 (s, 1H), 2.71 – 2.58 (m, 1H), 2.49 – 2.26 (m, 3H), 1.80 (d, J = 11.7 Hz, 1H), 1.74 – 1.52 (m, 3H), 1.45 (d, J = 6.3 Hz, 3H)**.**	658
156	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.70 – 6.55 (m, 1H), 6.28 – 5.83 (m, 1H), 5.24 (s, 2H), 5.05 – 5.17 (m, 1H), 4.61 – 4.44 (m, 1H), 4.36 – 4.16 (m, 2H), 3.97 (d, J = 8.9 Hz, 1H), 3.67 – 3.60 (m, 1H), 3.54 – 3.49 (m, 6H), 3.13 – 2.91 (m, 3H), 2.45 – 2.32 (m, 4H), 2.32 – 2.23 (m, 2H), 2.20 (s, 3H), 1.92 – 1.74 (m, 1H), 1.74 – 1.52 (m, 3H), 1.43 (d, J = 6.3 Hz, 3H), 0.68 – 0.59 (m, 2H), 0.48 – 0.38 (m, 2H).	658
157	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.62 – 6.50 (m, 2H), 6.37 (s, 2H), 5.09 (d, J = 12.6 Hz, 1H), 4.62 – 4.40 (m, 2H), 4.27 – 4.17 (m, 1H), 4.01 – 3.92 (m, 1H), 3.66 – 3.39 (m, 5H), 3.14 – 2.80 (m, 3H), 2.67 – 2.52 (m, 2H), 2.15 – 1.70 (m, 4H), 1.70 – 1.47 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H), 1.14 (s, 3H), 1.08 (s, 3H).	662
158	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.78 – 6.58 (m, 1H), 6.41 – 5.91 (m, 1H), 5.73 (s, 2H), 5.12 (d, J = 12.0 Hz, 1H), 4.64 – 4.50 (m, 1H), 4.48 – 4.36 (m, 1H), 4.21 – 4.09 (m, 1H), 3.99 (d, J = 8.9 Hz, 1H), 3.74 – 3.41 (m, 7H), 3.22 – 2.93 (m, 5H), 2.92 – 2.81 (m, 2H), 2.20 – 1.99 (m, 1H), 1.94 – 1.52 (m, 6H), 1.45 (d, J = 6.3 Hz, 3H), 1.39 – 1.20 (m, 1H).	648

[2127] **Example 159:** Compound 159 (two diastereomers)



[2128] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-((2-oxo-4-oxa-1-azabicyclo[4.2.0]octan-8-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2129] Under nitrogen, to a solution of *tert*-butyl rac-(4*R*,7*S*,8*S*,9*S*)-13-chloro-14-fluoro-9-methyl-17-methylsulfonyl-10-oxa-2,12,16,18,20-pentazapentacyclo[9.7.1.14,7.02,8.015,19]icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (300 mg, 0.580 mmol) and 8-(hydroxymethyl)-4-oxa-1-azabicyclo[4.2.0]octan-2-one (175 mg, 1.11 mmol, intermediate 111) in toluene (3 mL) was added t-BuONa (112 mg, 1.17 mmol) at 0 °C. The resulting solution was stirred for 1h at room temperature. The resulting solution was dilute with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-6% MeOH / DCM) to afford 257 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 591.

[2130] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-((4-oxa-1-azabicyclo[4.2.0]octan-8-yl)methoxy)-2-chloro-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2131] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-((2-oxo-4-oxa-1-azabicyclo[4.2.0]octan-8-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (257 mg, 0.430 mmol) in THF (6 mL) was added DIBAL-H (6.0 mL, 1 M in THF) at -20 °C. The resulting solution was slowly warmed to room temperature and stirred at room temperature for 1 h. The reaction was quenched by $Na_2SO_4.10\ H_2O$. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-6% MeOH / DCM) to afford 83.0 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 577.

[2132] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-((4-oxa-1-azabicyclo[4.2.0]octan-8-yl)methoxy)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2133] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-((4-oxa-1-azabicyclo[4.2.0]octan-8-yl)methoxy)-2-chloro-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (83.0 mg, 0.140 mmol), [5-[bis[(4-methoxyphenyl)methyl]amino]-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl]boronic acid (137 mg, 0.290 mmol), cataCXium A Pd G3 (21.0 mg, 0.0300 mmol) and K_3PO_4 (0.5 mL, 1.5 M in H_2O) in THF (2.5 mL) was stirred for 3 h at 60 °C.

The resulting solution was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The resulting residue was purified by C18 column (solvent gradient: 0-70% ACN in water (0.05% NH_4HCO_3)) to yield 94.1 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 974.

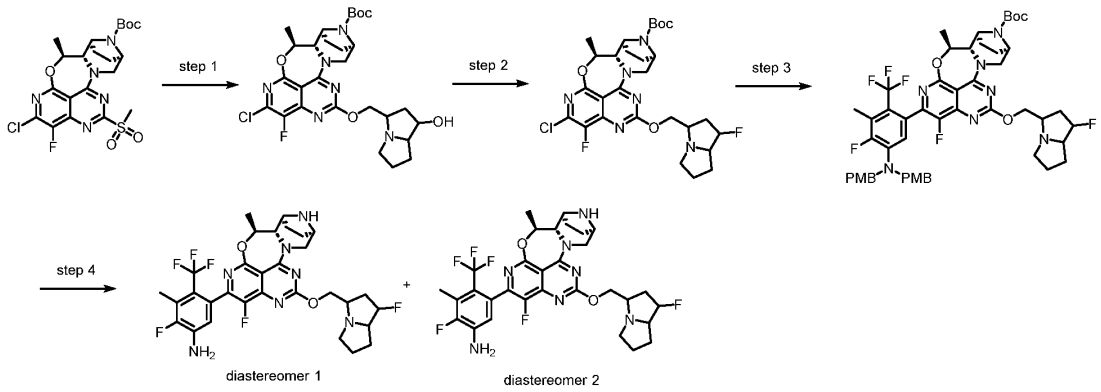
[2134] Step 4: 5-((5*S*,5a*S*,6*S*,9*R*)-12-((4-Oxa-1-azabicyclo[4.2.0]octan-8-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (two diastereomers)

[2135] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-((4-oxa-1-azabicyclo[4.2.0]octan-8-yl)methoxy)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (94.1 mg, 0.100 mmol) in TFA (3.5 mL) was stirred at room temperature for 1 hour. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 21% B to 41% B in 10.5 min; Wave Length: 220 nm; R_{T1}(min): 10) to afford product 18.1 mg (mixture of two diastereomers) as a white solid. The two diastereomers were separated by Chiral-Prep-HPLC (conditions: Column: CHIR–PAK IE, 2*25 cm, 5 μm; Mob–e Phase A: MtBE(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; 25% B; Wave Length: 220/–4 nm; R_{T1}(min): 9.377; R_{T2}(min): 11.805; Sample Solvent: EtOH--HPLC) to afford 3.1 mg **159 (diastereomer 1)** and 2.8 mg **159 (diastereomer 2)** as white solids.

[2136] **159 (diastereomer 1):** LC-MS: (ESI, *m/z*): $[M+H]^+$ = 634. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.60 (s, 1H), 6.02 (s, 2H), 5.09 (d, J = 12.7 Hz, 1H), 4.53 (dd, J = 8.7, 6.3 Hz, 1H), 4.40 – 4.17 (m, 3H),3.96 (d, J = 8.6 Hz, 1H), 3.80-3.74 (m, 1H), 3.74 – 3.57 (m, 2H), 3.57 – 3.42 (m, 4H), 3.02 (d, J = 12.8 Hz, 1H), 2.83 – 2.67 (m, 2H), 2.32 (d, J = 2.8 Hz, 3H), 2.10 (dt, J = 10.5, 7.2 Hz, 1H), 1.81 (s, 1H), 1.75 – 1.44 (m, 8H).

[2137] **159 (diastereomer 2):** LC-MS: (ESI, *m/z*): $[M+H]^+$ = 634. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.61 (s, 1H), 6.03 (s, 2H), 5.09 (d, J = 12.7 Hz, 1H), 4.54 (dd, J = 8.7, 6.3 Hz, 1H), 4.41 – 4.18 (m, 3H),3.97 (d, J = 8.6 Hz, 1H), 3.81-3.75 (m, 1H), 3.74 – 3.41 (m, 6H), 3.01 (d, J = 12.8 Hz, 1H), 2.81 – 2.68 (m, 2H), 2.31 (d, J = 2.8 Hz, 3H), 2.10 (dt, J = 10.5, 7.2 Hz, 1H), 1.80 (s, 1H), 1.74 – 1.43 (m, 8H).

[2138] **Example 160:** Compound 160 (two diastereomers)



[2139] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-((1-hydroxyhexahydro-1*H*-pyrrolizin-3-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2140] Under nitrogen, to a solution of 3-(hydroxymethyl)-2,3,5,6,7,8-hexahydro-1*H*-pyrrolizin-1-ol (459 mg, 2.92 mmol, intermediate 112) in THF (15 mL) was added NaH (312 mg, 7.80 mmol) at 0 °C, and the mixture was stirred for 30 min at 0 °C. Then *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*] heptalene-14-carboxylate (1.00 g, 1.95 mmol) was added, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with saturated NH_4Cl aqueous, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0%-20% MeOH / DCM) to afford 246 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 591$

[2141] Step 2: *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-((1-fluorohexahydro-1*H*-pyrrolizin-3-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2142] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-((1-hydroxyhexahydro-1*H*-pyrrolizin-3-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (246 mg, 0.420 mmol) in DCM (2.5 mL) was added DAST (408 mg, 2.53 mmol) at -78 °C. The resulting solution was slowly warmed to room temperature and stirred for 2 h at room temperature. The reaction was quenched with saturated NH_4Cl aqueous, extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-95% MeOH in water (0.05% NH_4HCO_3)) to afford 54.2 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 592$.

[2143] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-fluorohexahydro-1*H*-pyrrolizin-3-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2144] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-((1-fluorohexahydro-1*H*-pyrrolizin-3-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (54.2 mg, 0.0900 mmol), [5-[bis[(4-methoxyphenyl)methyl]amino]-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl]boronic acid (87.5 mg, 0.180 mmol), cataCXium A Pd G3 (13.4 mg, 0.0200 mmol) and K_3PO_4 (0.2 mL, 1.5 M in H_2O) in THF (0.5 mL) was stirred for 1.5 h at 60 °C. The resulting solution was partitioned between water and EtOAc. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% MeOH / DCM) to afford 63.3 mg of the title compound as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 990.

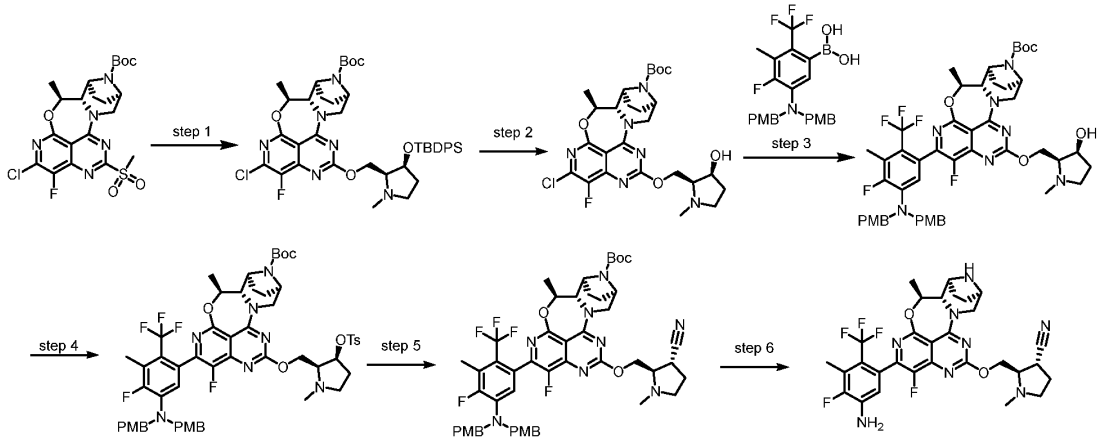
[2145] Step 7: 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-((1-fluorohexahydro-1*H*-pyrrolizin-3-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (two diastereomers)

[2146] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-fluorohexahydro-1*H*-pyrrolizin-3-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (63.3 mg, 0.0600 mmol) in TFA (2.5 mL) was stirred at room temperature for 40 min. The solvent was concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-85% CH_3OH in water (0.05% NH_4HCO_3)) to afford 35.6 mg as the mixture of two diastereomers. The mixture diastereomers were separated by Chiral-Prep-HPLC (conditions: Column: CHIRALPAK IE, –25 cm, 5 μm; Mobile Phase – Hex: DCM=3: 1(0.5% 2 M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; 20% in 24 min; Wave Length: 220/2– nm; R_{T1}(min): 16.594; R_{T2}(min): 19.762; Sample Solvent: EtOH--HPLC) to afford 6.9 mg of **160 (diastereomer 1)** and 6.8 mg of **160 (diastereomer 2)** as white solids.

[2147] **160 (diastereomer 1) :**LC-MS: (ESI, *m/z*): $[M+H]^+$ = 650. ^1H NMR (300 MHz, DMSO-d_6, ppm): δ 6.51 (d, J = 41.4 Hz, 1H), 6.01 (s, 2H), 5.18 – 4.77 (m, 2H), 4.60 – 4.46 (m, 1H), 4.39 – 4.28 (m, 1H), 4.12 – 4.01 (m, 1H), 3.9– (d, J = 8.8 Hz, 1H), 3.56 (s, 1H), 3.52 – 3.40 (m, 2H), 3.25 - 3.11 (m, 1H), 3.02 (d, J = 12.8 Hz, 1H), 2.95 – 2.83 (m, 1H), 2.79 – 2.66 (m, 1H), 2.30 (s, 4H), 1.99 – 1.76 (m, 3H), 1.74 – 1.49 (m, 5H), 1.51 – 1.30 (m, 4H).

[2148] **160 (diastereomer 2):** LC-MS: (ESI, *m/z*): $[M+H]^+$ = 650. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.52 (d, J = 40.4 Hz, 1H), 6.01 (s, 2H), 5.16 – 4.80 (m, 2H), 4.61 – 4.43 (m, 1H), 4.43 – 4.27 (m, 1H), 4.17 – 4.03 (m, 1H), 3.94 (d, J = 8.8 Hz, 1H), 3.57 – 3.46 (m, 1H), 3.48 – 3.37–(m, 2H), 3.23 – 3.09 (m, 1H), 3.01 (d, J = 12.7 Hz, 1H), 2.94 - 2.82 (m, 1H), 2.84 – 2.63 (m, 1H), 2.44 – 2.19 (m, 4H), 1.99 – 1.73 (m, 3H), 1.73 - 1.48 (m, 5H), 1.50 – 1.29 (m, 4H).

[2149] **Example 161:** Compound 161



[2150] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-(((2*S*,3*S*)-3-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-2-chloro-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2151] Under nitrogen, to a solution of ((2*S*,3*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methanol (400mg, 1.08mmol, intermediate 113) and *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (463mg, 0.900mmol) in toluene (1mL) was added *t*-BuONa (173mg, 1.80mmol) at 0 °C, and the mixture was stirred at room temperature overnight. The solvent was concentrated under vacuum. The crude product was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-80% EtOAc / petroleum ether) to afford the title compound (413 mg) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 803.

[2152] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*S*,3*S*)-3-hydroxy-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2153] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-(((2*S*,3*S*)-3-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-2-chloro-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-

3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (390mg, 0.490mmol) and TBAF (2.43mL, 2.43mmol) in tetrahydrofuran (5mL) was stirred at room temperature for 1 hour. The reaction was quenched by water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-5% MeOH/DCM) to afford the title compound (190 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 565$.

[2154] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*S*,3*S*)-3-hydroxy-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2155] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*S*,3*S*)-3-hydroxy-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (170mg, 0.300mmol), (5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (287.18mg, 0.6000mmol), cataCXium A Pd G_3 (43.8mg, 0.0600mmol) and K_3PO_4 (1.5M in water) (0.1mL) in tetrahydrofuran (5mL) was stirred at 60 °C for 2 hours. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH in DCM) to afford the title compound (224 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 962$.

[2156] Step 4: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((2*S*,3*S*)-1-methyl-3-(tosyloxy)pyrrolidin-2-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2157] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*S*,3*S*)-3-hydroxy-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (180mg, 0.190mmol) in dichloromethane (4mL) was added Et_3N (56.7mg, 0.560mmol), TsCl (39.1mg, 0.210mmol) and 4-DMAP (1.1mg, 0.0090mmol) at 0 °C. The reaction was stirred at room temperature overnight. The reaction was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue

was purified by flash chromatography on silica gel (gradient: 0-5% MeOH in DCM) to afford the title compound (126 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1116.

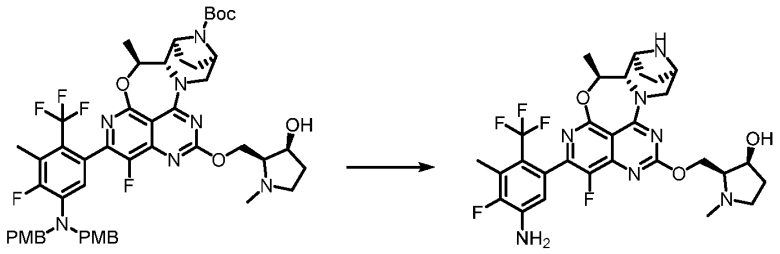
[2158] Step 5: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-(((2*R*,3*R*)-3-cyano-1-methylpyrrolidin-2-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2159] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(((2*S*,3*S*)-1-methyl-3-(tosyloxy)pyrrolidin-2-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (100mg, 0.103 mmol) in dimethyl sulfoxide (1mL) was added NaCN (21.9mg, 0.450mmol) at room temperature. The resulting solution was stirred for 2 hours at 55 °C. Then additional NaCN (219mg, 4.50mmol) was added, and the mixture was stirred at 55 °C overnight. The reaction was quenched with water, extracted with Et_2O. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-70% EtOAc / petroleum ether) to afford the title compound (28 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 971.

[2160] Step 6: (2*R*,3*R*)-2-((((5*S*,5a*S*,6*S*,9*R*)-2-(5-Amino-4°fluoro-3-methyl-2-(trifluoromethyl)°henyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-12-yl)oxy)methyl)-1-methylpyrrolidine-3-carbonitrile

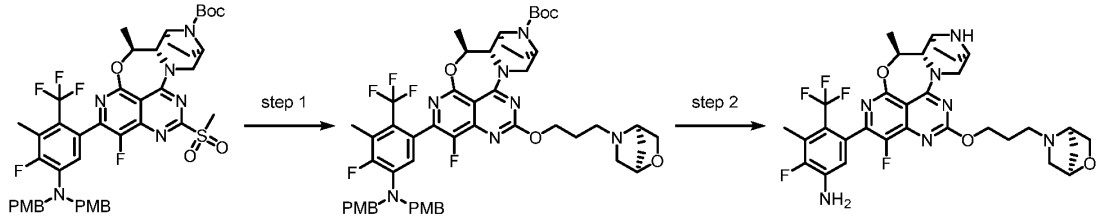
[2161] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-(((2*R*,3*R*)-3-cyano-1-methylpyrrolidin-2-yl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (31.0mg, 0.0300mmol) in 2,2,2-trifluoroacetic acid (2mL) was stirred at room temperature for 1 hour. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: Xselect CSH F-Phenyl OBD column, 30*250 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 39% B to 61% B in 10 min, 61% B; Wave Length: 254/220 nm; R_{T1}(min): 8.5) to afford the title compound (3.8 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 631. ^1H NMR (300 MHz, DMSO-d6) δ 6.55 (d, J = 37.2 Hz, 1H), 6.02 (s, 2H), 5.11 (d, J = 12.3 Hz, 1H), 4.59 – 4.29 (m, 3H), 3.97 (d, J = 8.8 Hz, 1H), 3.71 (s, 1H), 3.45 (d, J = 5.6 Hz, 1H), 3.25 (s, 2H), 3.10 – 2.99 (m, 2H), 2.85 (d, J = 5.2 Hz, 1H), 2.39 (s, 4H), 2.32 (s, 3H), 2.24 – 2.08 (m, 1H), 2.05 – 1.90 (m, 1H), 1.82 (s, 1H), 1.62 (d, J = 12.2 Hz, 3H), 1.44 (d, J = 6.3 Hz, 3H).

[2162] **Example 162:** Compound 162



[2163] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2S,3S)-3-hydroxy-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (20.0mg, 0.0208mmol, from **compound 161**) in 2,2,2-trifluoroacetic acid (2mL) was stirred at room temperature for 1 hours. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; R_{T1}(min): 8.9) to afford the title compound (1.2 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 622. ^{1}H NMR (300 MHz, DMSO-d6) δ 6.54 (d, J = 40.0 Hz, 1H), 6.03 (s, 2H), 5.20 – 5.05 (m, 1H), 4.81 (d, J = 6.1 Hz, 1H), 4.62 – 4.47 (m, 2H), 4.35 – 4.18 (m, 2H), 3.96 (d, J = 8.8 Hz, 1H), 3.53 (d, J = 10.0 Hz, 1H), 3.44 (d, J = 5.7 Hz, 1H), 3.09 – 2.93 (m, 2H), 2.76 (s, 1H), 2.46 – 2.37 (m, 1H), 2.32 (d, J = 3.7 Hz, 6H), 2.16 – 1.98 (m, 2H), 1.82 (s, 1H), 1.74 – 1.51 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H).

[2164] **Example 163:** Compound 163



[2165] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-(3-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2166] Under nitrogen, to a solution of 3-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propan-1-ol (62.1 mg, 0.400 mmol, intermediate 114) in THF (2.5 mL) was added NaH (35.2 mg, 0.880 mmol) at 0 °C, and the mixture was stirred for 20 min. Then *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl) amino)-4-fluoro-3-methyl-2-(trifluoromethyl) phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-

methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (80.1 mg, 0.0900 mmol, intermediate 113) was added at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction system was quenched with NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% MeOH/DCM) to afford 52.5 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 988.

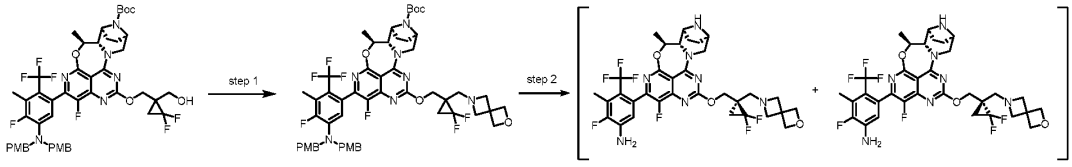
[2167] Step 2: 5-((5*S*,5a*S*,6*S*,9*R*)-12-(3-((1*R*,4*R*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline

[2168] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-12-(3-((1*R*,4*R*)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl)propoxy)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (52.5 mg, 0.0500 mmol) in TFA (2.5 mL) was stirred at room temperature for 1 h. Then the solution was concentrated under vacuum. The crude product was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; R_{T1}(min): 9 to afford 10.4 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 648. ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 6.52 (d, J = 38.2 Hz, 1H), 6.00 (s, 2H), 5.17 – 5.01 (m, 1H), 4.59 – 4.44 (m, 1H), 4.38 (t, J = 6.5 Hz, 2H), 4.33 – 4.26 (m, 1H), 3.93 (d, J = 8.8 Hz, 1H), 3.81 (d, J = 7.4 Hz, 1H), 3.53 (s, 1H), 3.49 – 3.39 (m, 3H), 3.00 (d, J = 12.7 Hz, 1H), 2.84 – 2.70 (m, 2H), 2.70 – 2.54 (m, 2H), 2.37 (d, J = 9.8 Hz, 1H), 2.31 (s, 3H), 1.90 – 1.49 (m, 8H), 1.42 (d, J = 6.3 Hz, 3H).

[2169] **Example 164**: Compound 164 was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 163**.

[2170] **164:** ^1H NMR (400 MHz, DMSO-d6, ppm): δ 6.54 (d, J = 40.3 Hz, 1H), 6.02 (s, 2H), 5.19 – 5.03 (m, 1H), 4.67 – 4.48 (m, 1H), 4.46 – 4.26 (m, 3H), 3.97 (d, J = 8.8 Hz, 1H), 3.84 (d, J = 7.4 Hz, 1H), 3.58 (s, 1H), 3.55 – 3.45 (m, 3H), 3.04 (d, J = 12.9 Hz, 1H), 2.81 (d, J = 9.8 Hz, 1H), 2.77 – 2.58 (m, 2H), 2.44 (d, J = 9.9 Hz, 1H), 2.37 – 2.28 (m, 3H), 1.93 – 1.78 (m, 3H), 1.77 – 1.50 (m, 5H), 1.44 (d, J = 6.3 Hz, 3H).

[2171] **Example 165**: Compound 165 (mixture and two separate diastereomers)



[2172] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-((1-((2-oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-2,2-difluorocyclopropyl)methoxy)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (two isomers)

[2173] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (240 mg, 0.248 mmol, intermediate 118) and NMO (58.0 mg, 0.496 mmol) in dichloromethane (5 mL) was added TPAP (43.6 mg, 0.124 mmol) at 0°C, and the mixture was stirred for 1 hour at room temperature. The resulting mixture was filtered and the filter cake was washed with dichloromethane. To the combined filtrate was added NaOAc (305 mg, 3.72 mmol) and 2-oxa-6-azaspiro [3.3]heptane (369 mg, 3.72 mmol) at room temperature, and the mixture was stirred for 1 hour at 60 °C. Then the mixture was cooled to ambient temperature and $NaBH_3CN$ (234 mg, 3.72 mmol) was added, and the mixture was stirred overnight at room temperature. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by reverse phase flash chromatography on pre-packed C18 column (gradient: 0-100% CH_3CN in water (0.05% NH_4HCO_3)) to afford the title compound (200 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1050.

[2174] Step 2: ((5*S*,5a*S*,6*S*,9*R*)-12-((1-((2-Oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-2,2-difluorocyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (two isomers)

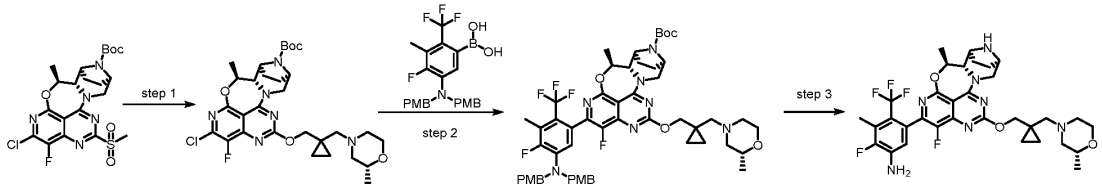
[2175] A solution of *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-12-((1-((2-oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-2,2-difluorocyclopropyl)methoxy)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (200 mg, 0.190 mmol, mixture of diastereomers) in 2,2,2-trifluoroacetic acid (20 mL) was stirred for 30 minutes at room temperature. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 17% B to 42% B in 9 min; Wave Length: 254nm/220nm; RT1(min): 9.6) to afford **165 (mixture of diastereomers** with respect to the difluorocyclopropyl stereogenic center) (25.1 mg). LC-MS: (ESI, *m/z*): $[M+H]^+$ = 710. ^1H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 6.68 – 6.37 (m, 1H), 6.04 (s,

2H), 5.14 – 5.02 (m, 1H), 4.70 – 4.42 (m, 6H), 4.32 – 4.21 (m, 1H), 3.96 (d, J = 8.6 Hz, 1H), 3.56 (d, J = 5.6 Hz, 1H), 3.45 (d, J = 6.1 Hz, 1H), 3.38 – 3.35 (m, 1H), 3.33 – 3.30 (m, 1H), 3.03 (d, J = 12.8 Hz, 1H), 2.91 – 2.69 (m, 1H), 2.67 – 2.52 (m, 3H), 2.32 (s, 3H), 1.85 – 1.75 (m, 1H), 1.75 – 1.58 (m, 3H), 1.58 – 1.47 (m, 2H), 1.44 (d, J = 6.3 Hz, 3H).

[2176] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 165**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
166	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.54 (d, J = 39.0 Hz, 1H), 6.03 (s, 2H), 5.17 – 5.02 (m, 1H), 4.66 – 4.48 (m, 2H), 4.42 (t, J = 11.2 Hz, 1H), 4.31 (s, 1H), 3.97 (d, J = 8.7 Hz, 1H), 3.78 (t, J = 6.9 Hz, 1H), 3.63 – 3.54 (m, 1H), 3.53 – 3.38 (m, 3H), 3.04 (d, J = 12.8 Hz, 1H), 2.92 – 2.68 (m, 3H), 2.48 – 2.40 (m, 2H), 2.32 (s, 3H), 1.90 – 1.48 (m, 8H), 1.44 (d, J = 6.3 Hz, 3H).	710
167	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.54 (d, J = 59.6 Hz, 1H), 6.04 (s, 2H), 5.11 (m, 1H), 4.72 – 4.35 (m, 3H), 3.99 (d, J = 8.8 Hz, 1H), 3.68 – 3.44 (m, 6H), 3.06 (d, J = 12.9 Hz, 1H), 2.79 – 2.65 (m, 1H), 2.47 – 2.23 (m, 8H), 1.88 – 1.49 (m, 6H), 1.45 (d, J = 6.3 Hz, 3H).	698

[2177] **Example 168**: Compound 168



[2178] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-((1-(((*R*)-2-methylmorpholino)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2179] To a solution of (*R*)-(1-((3-methylmorpholino)methyl)cyclopropyl)methanol (360 mg, crude) in THF (5 mL) was added NaH (60% dispersion in mineral oil, 156 mg, 3.90 mmol) in portions at 0°C, and the mixture was stirred for 30 minutes at room temperature. Then *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (200 mg, 0.390 mmol) was added, and the mixture was stirred for 1 hour at room temperature. The reaction was quenched with saturated NH_4Cl aqueous solution. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (139 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 619.

[2180] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-(((*R*)-2-

methylmorpholino)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2181] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-((1-(((*R*)-2-methylmorpholino)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (139 mg, 0.225 mmol), (5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (215 mg, 0.450 mmol), K_3PO_4 (1.5M aqueous solution, 0.8 mL, 1.20 mmol) and cataCXium A Pd G3 (32.8 mg, 0.0450 mmol) in THF (4 mL) was stirred for 1 hour at 60 °C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-60% ethyl acetate in petroleum ether) to afford the title compound (210 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1016.

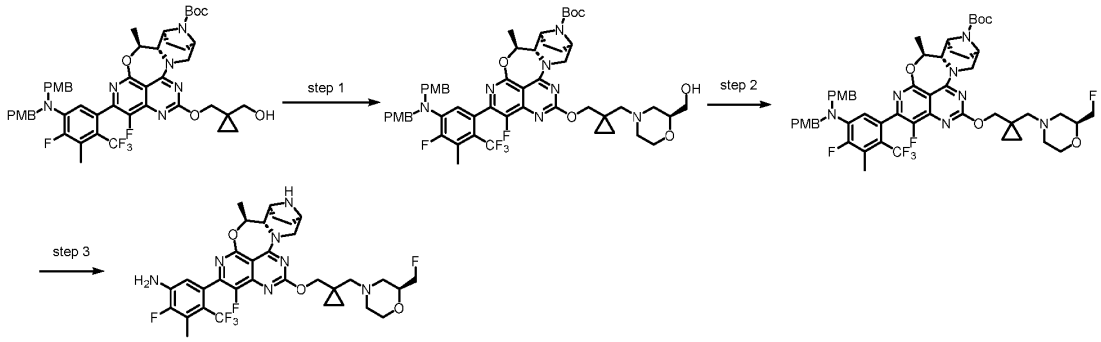
[2182] Step 3: 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-(((*R*)-2-methylmorpholino) methyl)cyclopropyl) methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline

[2183] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl) amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-(((*R*)-2-methylmorpholino)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (210 mg, 0.207 mmol) in 2,2,2-trifluoroacetic acid (20 mL) was stirred for 30 minutes at room temperature. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 19*250 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 62% B to 84% B in 9 min, 84% B; Wave Length: 220/254 nm; RT1(min): 6.77) to afford the title compound (20.0 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 676. ^{1}H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 6.64 – 6.38 (m, 1H), 6.01 (s, 2H), 5.16 – 4.99 (m, 1H), 4.56 – 4.44 (m, 1H), 4.26 (s, 2H), 3.93 (d, J = 8.7 Hz, 1H), 3.73 – 3.63 (m, 1H), 3.57 – 3.50 (m, 1H), 3.50 – 3.39 (m, 4H), 3.00 (d, J = 12.7 Hz, 1H), 2.84 – 2.68 (m, 2H), 2.35 – 2.17 (m, 5H), 1.97 – 1.85 (m, 1H), 1.85 – 1.73 (m, 1H), 1.69 – 1.50 (m, 4H), 1.42 (d, J = 6.3 Hz, 3H), 0.99 (d, J = 6.2 Hz, 3H), 0.70 – 0.54 (m, 2H), 0.51 – 0.29 (m, 2H).

Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 168.**

Cmpd. No.	^{1}H NMR	MS (M+H)$^+$
169	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.68 – 6.41 (m, 1H), 6.03 (s, 2H), 5.09 (d, J = 12.7 Hz, 1H), 4.60 – 4.45 (m, 1H), 4.40 – 4.26 (m, 2H), 4.20 (d, J = 10.8 Hz, 1H), 3.94 (d, J = 8.7 Hz, 1H), 3.78 (d, J = 7.5 Hz, 1H), 3.65 – 3.52 (m, 1H), 3.52 – 3.40 (m, 3H), 3.01 (d, J = 12.8 Hz, 1H), 2.91 – 2.73 (m, 2H), 2.65 (d, J = 12.6 Hz, 1H), 2.48 – 2.36 (m, 1H), 2.32 (s, 3H), 1.91 – 1.74 (m, 1H), 1.74 – 1.50 (m, 5H), 1.44 (d, J = 6.3 Hz, 3H), 0.66 – 0.54 (m, 2H), 0.54 – 0.34 (m, 2H).	674
170	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.75 – 6.30 (m, 1H), 6.01 (s, 2H), 5.13 – 5.02 (m, 1H), 4.58 – 4.43 (m, 1H), 4.38 – 4.10 (m, 3H), 3.93 (d, *J* = 8.7 Hz, 1H), 3.76 (d, *J* = 7.5 Hz, 1H), 3.50 – 3.38 (m, 4H), 3.00 (d, *J* = 12.8 Hz, 1H), 2.88 – 2.78 (m, 2H), 2.60 (d, *J* = 12.6 Hz, 1H), 2.54 – 2.48 (m, 1H), 2.30 (s, 3H), 1.90 – 1.75 (m, 1H), 1.74 – 1.48 (m, 5H), 1.51 (d, *J* = 8.7 Hz, 3H), 0.65 – 0.50 (m, 2H), 0.50 – 0.34 (m, 2H).	674

[2184] **Example 171:** Compound 171



[2185] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-(((*S*)-2-(hydroxymethyl)morpholino)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2186] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (200 mg, 0.214 mmol, intermediate 122) and NMO (50.2 mg, 0.428 mmol) in dichloromethane (4 mL) was added TPAP (37.6 mg, 0.107 mmol) at 0 °C, and the mixture was stirred for 1 hour at room temperature. The resulting mixture was filtered and the filter cake was washed with dichloromethane. To the combined filtrate were added NaOAc (264 mg, 3.22 mmol) and a solution of (*S*)-morpholin-2-ylmethanol in dichloromethane (4 mL) at room temperature, and the mixture was stirred for 1 hour. Then $NaBH_3CN$ (202 mg, 3.22 mmol) was added at room temperature, and the mixture was stirred overnight. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was

purified twice by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) and reverse phase flash chromatography on pre-packed C18 column (gradient: 0-50% CH_3CN in water (0.05% NH_4HCO_3)) to afford the title compound (85.0 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1032.

[2187] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-(((*S*)-2-(fluoromethyl)morpholino)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2188] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl) amino)-4-fluoro-3-methyl-2-(trifluoromethyl) phenyl)-1-fluoro-12-((1-(((*S*)-2-(hydroxymethyl)morpholino)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (85.0 mg, 0.0824 mmol) in dichloromethane (2 mL) was added DAST (66.4 mg, 0.412 mmol) dropwise at -60 °C, and the mixture was stirred for 1 hour at room temperature. The reaction was quenched by saturated $NaHCO_3$ solution at 0°C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified twice by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) and reverse phase flash chromatography on pre-packed C18 column (gradient: 0-50% CH_3CN in water (0.05% NH_4HCO_3)) to afford the title compound (32.0 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1034.

[2189] Step 3: 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-((1-(((*S*)-2-(fluoromethyl)morpholino)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline

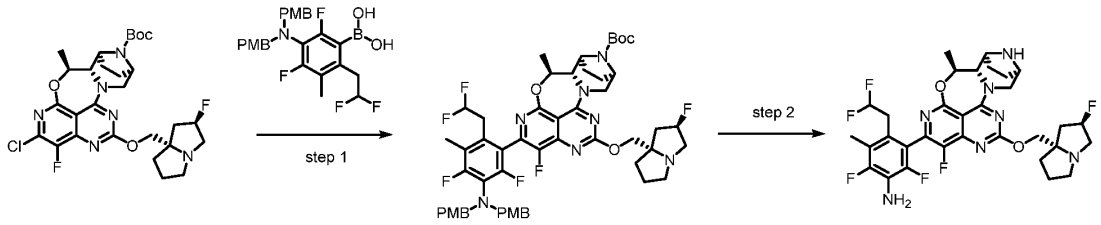
[2190] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-((1-(((*S*)-2-(fluoromethyl)morpholino)methyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (32.0 mg, 0.0309 mmol) in 2,2,2-trifluoroacetic acid (10 mL) was stirred for 1 hour at room temperature. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 9) to afford the title compound (7.0 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 694. ^1H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 6.70 –

6.40 (m, 1H), 6.03 (s, 2H), 5.09 (d, J = 12.9 Hz, 1H), 4.56 – 4.49 (m, 1H), 4.49 – 4.43 (m, 1H), 4.34 – 4.22 (m, 3H), 3.95 (d, J = 8.7 Hz, 1H), 3.78 (d, J = 11.1 Hz, 1H), 3.70 – 3.59 (m, 1H), 3.59 – 3.48 (m, 2H), 3.48 – 3.40 (m, 2H), 3.02 (d, J = 12.9 Hz, 1H), 2.92 – 2.76 (m, 2H), 2.30 – 2.23 (m, 5H), 2.06 – 1.93 (m, 1H), 1.90 – 1.74 (m, 2H), 1.73 – 1.52 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H), 0.72 – 0.61 (m, 2H), 0.48 – 0.38 (m, 2H).

[2191] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 171**.

Cmpd. No.	^{1}H NMR	MS (M+H)$^+$
172	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.71 – 6.39 (m, 1H), 6.04 (s, 2H), 5.09 (d, J = 12.9 Hz, 1H), 4.60 – 4.49 (m, 1H), 4.48 – 4.42 (m, 1H), 4.38 – 4.16 (m, 3H), 3.95 (d, J = 8.7 Hz, 1H), 3.78 (d, J = 11.1 Hz, 1H), 3.69 – 3.40 (m, 5H), 3.02 (d, J = 12.6 Hz, 1H), 2.85 (d, J = 11.1 Hz, 1H), 2.76 (d, J = 11.7 Hz, 1H), 2.34 – 2.28 (m, 5H), 2.06 – 1.92 (m, 1H), 1.89 – 1.74 (m, 2H), 1.72 – 1.52 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H), 0.70 – 0.62 (m, 2H), 0.49 – 0.39 (m, 2H).	694
173	^{1}H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 6.68 – 6.38 (m, 1H), 6.03 (s, 2H), 5.36 – 4.94 (m, 2H), 4.62 – 4.44 (m, 1H), 4.17 (s, 2H), 3.94 (d, J = 8.7 Hz, 1H), 3.69 – 3.52 (m, 3H), 3.46 – 3.42 (m, 1H), 3.17 – 3.08 (m, 1H), 3.07 – 2.96 (m, 2H), 2.47 (s, 2H), 2.32 (s, 3H), 1.88 – 1.72 (m, 1H), 1.72 – 1.49 (m, 3H), 1.43 (d, J = 6.3 Hz, 3H), 0.60 – 0.39 (m, 4H).	650
174	^{1}H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 1H NMR (300 MHz, DMSO-d6) δ 6.70 – 6.34 (m, 1H), 6.01 (s, 2H), 5.06 (d, J = 12.7 Hz, 1H), 4.66 – 4.41 (m, 6H), 4.14 (s, 2H), 3.92 (d, J = 8.7 Hz, 1H), 3.59 – 3.48 (m, 1H), 3.42 (d, J = 5.8 Hz, 1H), 3.26 (s, 4H), 2.99 (d, J = 12.9 Hz, 1H), 2.38 – 2.24 (m, 5H), 1.86 – 1.72 (m, 1H), 1.72 – 1.48 (m, 3H), 1.42 (d, J = 6.3 Hz, 3H), 0.55 – 0.46 (m, 2H), 0.44 – 0.35 (m, 2H).	674

[2192] **Example 175:** Compound 175



[2193] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-6-(2,2-difluoroethyl)-2,4-difluoro-5-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2194] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (75.1 mg, 0.130 mmol), (3-(*bis*(4-methoxybenzyl)amino)-6-(2,2-difluoroethyl)-2,4-

difluoro-5-methylphenyl) boronic acid (155 mg, 0.321 mmol, intermediate 124), K_3PO_4 (0.19 mL, 1.5 M in H_2O) and Xphos Pd G3 (21.4 mg, 0.0300 mmol) in 2-methyl-2-butanol (1 mL) was stirred for 3 h at room temperature. The resulting solution was partitioned between water and EtOAc. The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0%-10% MeOH/DCM) to afford 84.1 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 764.

[2195] Step 2: 4-(2,2-Difluoroethyl)-2,6-difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methylaniline

[2196] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)- 2-(3-(bis(4-methoxybenzyl) amino)-6-(2,2-difluoroethyl)-2,4-difluoro-5-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (80.1 mg, 0.0800 mmol) in TFA (3 mL) was stirred for 30 min at room temperature. The resulting solution was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; R_{T1}(min): 8.9) to yield 40.5 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 664. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 5.80-6.47 (m, 1H), 5.41-5.21 (m, 3H), 5.16-5.07 (m, 1H), 4.78-4.57 (m, 1H), 4.18-3.92 (m, 3H), 3.62-3.54 (m, 1H), 3.45 (d, J = 5.8 Hz, 1H), 3.25-3.04 (m, 4H), 3.03-2.98 (m, 2H), 2.85-2.73 (m, 2H), 2.25-2.17 (m, 3H), 2.12-2.09 (m, 1H), 2.02-1.94 (m, 2H), 1.92-1.74 (m, 4H), 1.69-1.54 (m, 3H), 1.52-1.44 (m, 3H).

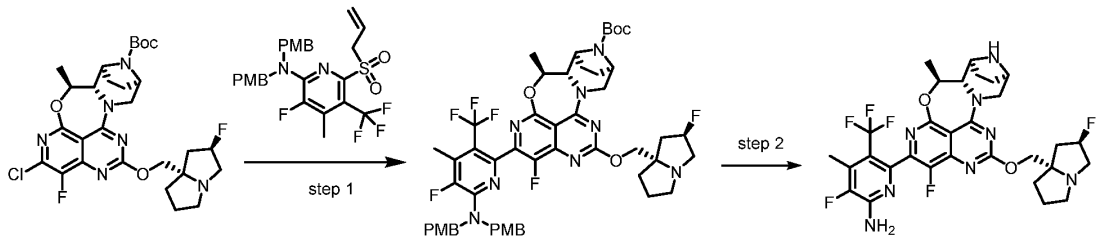
[2197] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 175**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
176	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 13.30 (s, 1H), 7.78 – 7.63 (m, 2H), 5.29 (d, *J* = 54.3 Hz, 1H), 5.12 (d, *J* = 12.6 Hz, 1H), 4.59 (s, 1H), 4.15 – 3.98 (m, 3H), 3.59 (s, 1H), 3.47 (s, 1H), 3.12 – 3.01 (m, 4H), 2.87 -2.78 (m, 2H), 2.54 (s, 3H), 2.16 (d, *J* = 4.9 Hz, 1H), 2.06 – 1.95 (m, 2H), 1.91 – 1.74 (m, 4H), 1.77 – 1.51 (m, 3H), 1.46 (s, 3H).	623
177	^{1} H NMR (300 MHz, DMSO-d6) δ 6.48 (d, J = 3.8 Hz, 1H), 6.31 (s, 2H), 5.29 (d, J = 54.4 Hz, 1H), 5.17 – 5.00 (m, 1H), 4.56 (dd, J = 8.7, 6.2 Hz, 1H), 4.12 (d, J = 10.3 Hz, 1H), 3.99 (dd, J = 18.2, 9.5 Hz, 2H), 3.57 (s, 1H), 3.45 (d, J = 5.7 Hz, 1H), 3.14 – 2.92 (m, 4H), 2.88 – 2.77 (m, 1H), 2.29 (s, 3H), 2.23 – 1.93 (m, 3H), 1.93 – 1.72 (m, 4H), 1.58 (dd, J = 25.2, 7.1 Hz, 3H), 1.46 (d, J = 6.3 Hz, 3H).	583

178	^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 8.09 (s, 1H), 6.93 (s, 1H), 6.29 (s, 2H), 5.28 (d, *J* = 54.0 Hz, 1H), 5.09 – 5.06 (m, 1H), 4.56 – 4.52 (m, 1H), 4.11 – 4.08 (m, 1H), 4.02 – 3.95 (m, 2H), 3.57 – 3.56 (m, 1H), 3.45 – 3.43 (m, 1H), 3.13 – 3.01 (m, 4H), 2.84 – 2.79 (m, 2H), 2.14 – 1.98 (m, 3H), 1.86 – 1.54 (m, 7H), 1.44 (d, *J* = 6.4 Hz, 3H).	619
179	^{1}H NMR (400 MHz, DMSO-*d6, ppm*) δ 7.44 – 7.42 (m, 2H), 7.01 – 6.96 (m, 1H), 6.68 (s, 1H), 6.54 – 6.48 (m, 2H), 5.27 (d, *J* = 54.0 Hz, 1H), 5.14 – 5.11 (m, 1H), 4.57 – 4.55 (m, 1H), 4.13 – 3.97 (m, 3H), 3.59 – 3.44 (m, 2H), 3.10 – 3.01 (m, 4H), 2.84 – 2.82 (m, 1H), 2.38 – 2.36 (m, 1H), 2.28 – 2.06 (m, 4H), 1.87 – 1.56 (m, 7H), 1.43 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 7.6 Hz, 1H), 0.78 (t, *J* = 7.6 Hz, 2H).	629
180	^{1}H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 6.73 – 6.46 (m, 1H), 6.38 – 6.18 (m, 2H), 5.29 (d, J = 54.3 Hz, 1H), 5.02 – 5.18 (m, 1H), 4.60 – 4.31 (m, 1H), 4.19 – 3.86 (m, 3H), 3.61 – 3.52 (m, 1H), 3.50 – 3.35 (m, 3H), 3.28 (s, 1H), 3.19 (s, 3H), 3.14 – 2.95 (m, 4H), 2.90 – 2.77 (m, 1H), 2.21 – 2.11 (m, 1H), 2.10 – 1.95 (m, 2H), 1.92 – 1.72 (m, 4H), 1.70 – 1.50 (m, 3H), 1.49 – 1.36 (m, 3H).	660
181 (isomer 1)	^{1}H NMR (400 MHz, DMSO-*d$_6$*) *δ* 7.15 (d, J = 13.0 Hz, 1H), 6.82 – 6.66 (m, 1H), 6.06 (t, J = 4.5 Hz, 1H), 5.38 – 5.20 (s, 3H), 5.09 (d, J = 12.0 Hz, 1H), 4.61 – 4.52 (m, 1H), 4.11 (d, J = 10.3 Hz, 1H), 4.05 – 3.91 (m, 2H), 3.57 (s, 1H), 3.44 (s, 1H), 3.11 – 3.02 (m, 5H), 2.82 (s, 2H), 2.16 (d, J = 4.9 Hz, 1H), 2.03 (d, J = 12.2 Hz, 2H), 1.82 – 1.69 (m, 4H), 1.62-1.53 (m, 2H), 1.51 –1.49 (m, 1H), 1.44 (d, J = 6.3 Hz, 3H), 1.27– 1.15 (m, 3H).	646
181 (isomer 2)	^{1}H NMR (400 MHz, DMSO-*d$_6$*) *δ* 7.15 (d, J = 13.0 Hz, 1H), 6.82 – 6.66 (m, 1H), 6.06 (t, J = 4.5 Hz, 1H), 5.38 – 5.20 (s, 3H), 5.09 (d, J = 12.0 Hz, 1H), 4.61 – 4.52 (m, 1H), 4.11 (d, J = 10.3 Hz, 1H), 4.09 – 4.02 (m, 1H), 4.00 – 3.92 (m, 1H), 3.57 (s, 1H), 3.44 (s, 1H), 3.11 – 3.06 (m, 2H), 3.14 – 2.92 (m, 3H), 2.85 – 2.82 (m, 1H), 2.77 (s, 1H), 2.16 (d, J = 4.9 Hz, 1H), 2.03 (d, J = 12.2 Hz, 2H), 1.82 – 1.69 (m, 4H), 1.62 –1.49 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H), 1.27– 1.15 (m, 3H).	646
182	^{1}H NMR (300 MHz, DMSO-d6) δ 6.75 (dd, J = 9.3, 2.0 Hz, 1H), 5.44 – 5.18 (m, 3H), 5.18 – 5.03 (m, 1H), 4.66 – 4.48 (m, 1H), 4.15 – 3.92 (m, 3H), 3.66 – 3.43 (m, 4H), 3.14 – 2.97 (m, 4H), 2.91 – 2.77 (m, 1H), 2.25 (d, J = 6.5 Hz, 3H), 2.20 – 2.12 (m, 1H), 2.10 – 1.96 (m, 2H), 1.90 – 1.73 (m, 5.3 Hz, 4H), 1.70 – 1.50 (m, 3H), 1.44 (dd, J = 6.4, 2.6 Hz, 3H).	664
183	^{1}H NMR (300 MHz, DMSO-*d$_6$*, ppm): δ 6.67 (d, J = 8.0 Hz, 1H), 5.88 (s, 2H), 5.36-5.21 (m, 1H), 5.14-5.07 (m, 1H), 4.62-4.50 (m, 1H), 4.11 (d, J = 10.2 Hz, 1H), 4.05-3.96 (m, 2H), 3.73-3.54 (m, 3H), 3.50 (d, J = 6.3 Hz, 1H), 3.14-2.99 (m, 4H), 2.86-2.81 (m, 1H), 2.21-2.12 (m, 1H), 2.11-2.04 (m, 1H), 2.03-1.95 (m, 1H), 1.93-1.76 (m, 4H), 1.73-1.53 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H).	668
184	^{1}H NMR (400 MHz, DMSO-*d$_6$, ppm*) δ 6.28 (d, J = 35.8 Hz, 3H), 5.29 (d, J = 54.3 Hz, 1H), 5.12 – 5.06 (m, 1H), 4.58 – 4.51 (m, 1H), 4.10 (d, J = 10.3 Hz, 1H), 3.99 – 3.93 (m, 2H), 3.63 (s, 3H), 3.57 (d, J = 5.6 Hz, 1H), 3.45 (d, J = 6.0 Hz, 1H), 3.16 – 3.07 (m, 2H), 3.02 (d, J = 9.5 Hz, 2H), 2.84 (t, J = 8.0 Hz, 1H), 2.14 (d, J = 4.8 Hz, 1H), 2.06 (s, 1H), 1.98 (d, J = 15.6 Hz, 1H), 1.87 – 1.81 (m, 4H), 1.71 – 1.50 (m, 3H), 1.45 (d, J = 6.4 Hz, 3H).	649
185	^{1}H NMR (300 MHz, DMSO-*d$_6$*) δ 6.32 (s, 1H), 6.17 (s, 2H), 5.30 (d, *J* = 54.4 Hz, 1H), 5.14 (d, *J* = 13.0 Hz, 1H), 4.62 – 4.57 (m, 1H), 4.19 – 3.98 (m, 3H), 3.75 (d, *J* = 5.1 Hz, 1H), 3.69 – 3.60 (m, 2H), 3.54 (d, *J* = 15.1 Hz, 2H), 3.13 (d, *J* = 10.3 Hz, 3H), 3.03 (s, 1H), 2.85 (d, *J* = 7.3 Hz, 1H), 2.38 (s, 2H), 2.17 (d, *J* = 5.0 Hz, 1H), 2.04 (d, *J* = 12.5 Hz, 2H), 1.91 – 1.70 (m, 7H), 1.68 – 1.42 (m, 3H).	647

186	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.84 – 6.69 (m 1H), 6.37 – 5.83 (m, 1H), 5.72 (s, 2H), 5.48 – 5.08 (m, 2H), 4.74 – 4.57 (m, 1H), 4.22 – 4.12 (m, 2H), 4.08 (d, J = 10.5 Hz, 1H), 3.98 (s, 1H), 3.90 – 3.78 (m, 1H), 3.23 (s, 1H), 3.21 – 3.07 (m, 4H), 3.07 (s, 1H), 2.94 – 2.80 (m, 1H), 2.22 – 2.15 (m, 1H), 2.14 – 1.99 (m, 2H), 1.98 – 1.60 (m, 7H), 1.45 (d, J = 6.3 Hz, 3H).	666
187	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.12 (d, J = 12.4 Hz, 1H), 6.92 – 6.74 (m, 1H), 6.43 – 5.82 (m, 1H), 5.62 – 5.16 (m, 4H), 4.84 – 4.60 (m, 1H), 4.47 – 4.16 (m, 4H), 4.15 – 4.02 (m, 1H), 3.44 – 3.31 (m, 4H), 3.15 – 2.81 (m, 3H), 2.42 – 2.11 (m, 3H), 2.09 – 1.69 (m, 8H), 1.49 (d, J = 6.3 Hz, 3H).	632
188	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.67 (t, J = 74.4 Hz, 1H), 6.39 (s, 1H), 6.18 (s, 2H), 5.29 (d, J = 54.3 Hz, 1H), 5.14 – 5.02 (m, 1H), 4.61 – 4.44 (m, 1H), 4.11 (d, J = 10.3 Hz, 1H), 4.06 – 3.89 (m, 2H), 3.57 (s, 1H), 3.49 – 3.42 (m, 1H), 3.19 – 2.97 (m, 4H), 2.92 – 2.70 (m, 2H), 2.30 (s, 3H), 2.24 – 2.12 (m, 1H), 2.11 – 2.93 (m, 2H), 1.92 – 1.73 (m, 4H), 1.72 – 1.51 (m, 3H), 1.45 (d, J = 6.3 Hz, 3H).	631
189	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.30 (d, J = 1.3 Hz, 1H), 6.12 – 5.81 (m, 3H), 5.43 – 5.14 (m, 1H), 5.12 – 5.07 (m, 1H), 4.56 – 4.51 (m, 1H), 4.16 – 4.03 (m, 2H), 3.99 – 3.94 (m, 1H), 3.57 (d, J = 5.3 Hz, 1H), 3.44 (d, J = 5.7 Hz, 1H), 3.19 – 3.03 (m, 4H), 3.03 – 2.86 (m, 3H), 2.84 – 2.81 (m, 1H), 2.37 (s, 3H), 2.16 (d, J = 4.5 Hz, 1H), 2.04 – 1.98 (m, 2H), 1.91 – 1.67 (m, 4H), 1.62 (d, J = 9.3 Hz, 3H), 1.44 (d, J = 6.3 Hz, 3H).	629
190	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.71-6.62 (m, 1H), 6.36-5.95 (m, 1H), 5.72 (s, 2H), 5.36-5.18 (m, 1H), 5.13-5.04 (m, 1H), 4.62-4.44 (m, 1H), 4.09 (d, J = 10.3 Hz, 1H), 4.02-3.83 (m, 2H), 3.42-3.59 (m, 3H), 3.13-2.92 (m, 6H), 2.86-2.75 (m, 1H), 2.17-1.96 (m, 3H), 1.92-1.73 (m, 4H), 1.71-1.49 (m, 3H), 1.43 (d, J = 6.3 Hz, 3H).	650

[2198] **Example 191**: Compound 191



[2199] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-5-fluoro-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2200] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (60.2 mg, 0.100 mmol), 6-(allylsulfonyl)-3-fluoro-*N*,*N*-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (82.0 mg, 0.150 mmol, intermediate 129), $Pd(OAc)_2$ (1.14 mg, 0.010 mmol), $P(t\text{-}Bu)_2MeHBF_4$ (2.52 mg, 0.0100 mmol) and Cs_2CO_3 (66.2 mg, 0.200 mmol) in 1,4-doxane (1 mL) was stirred for 2 h at 120 °C. The resulting reaction was cooled to

room and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-90% ACN in water (0.05% NH_4HCO_3)) to afford 35.1 mg of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 991.

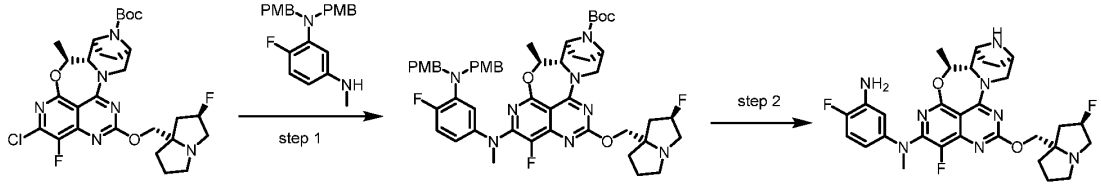
[2201] Step 2: 3-Fluoro-6-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

[2202] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(*bis*(4-methoxybenzyl)amino)-5-fluoro-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (35.1 mg, 0.0400 mmol) in TFA (2 mL) was stirred at 50 °C for 4 h. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 31% B to 47% B in 8.5 min; Wave Length: 254/220 nm; R_{T1}(min): 6.5) to yield 9.30 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 651. ^1H NMR (300 MHz, DMSO-d_6, ppm): δ 7.15 (s, 2H), 5.36-5.18 (m, 1H), 5.07 (d, J = 12.7 Hz, 1H), 4.53-4.46 (m, 1H), 4.07-3.96 (m, 3H), 3.55-3.42 (m, 2H), 3.12-3.01 (m, 4H), 2.80-2.71 (m, 2H), 2.35-2.26 (m, 3H), 2.13-2.07 (m, 1H), 2.04-1.96 (m, 2H), 1.95-1.76 (m, 4H), 1.69-1.59 (m, 3H), 1.41 (d, J = 6.3 Hz, 3H).

[2203] **Example 192**: Compound **192** was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 191**.

[2204] ^1H NMR (300 MHz, DMSO-d6, ppm): δ 7.18 (s, 2H), 5.15-5.07 (m, 1H), 4.54-4.45 (m, 1H), 4.21-4.13 (m, 2H), 3.96 (d, J = 8.7 Hz, 1H), 3.58-3.55 (m, 1H), 3.44 (d, J = 6.1 Hz, 1H), 3.10-2.97 (m, 3H), 2.83-2.85 (m, 1H), 2.72 (d, J = 11.9 Hz, 1H), 2.45-2.23 (m, 3H), 2.13-2.03 (m, 1H), 2.01-1.97 (m, 1H), 1.90 (d, J = 13.3 Hz, 1H), 1.85-1.73 (m, 3H), 1.78-1.56 (m, 5H), 1.48-1.38 (m, 4H). MS $(M+H)^+$ 695.

[2205] **Example 193**: Compound 193



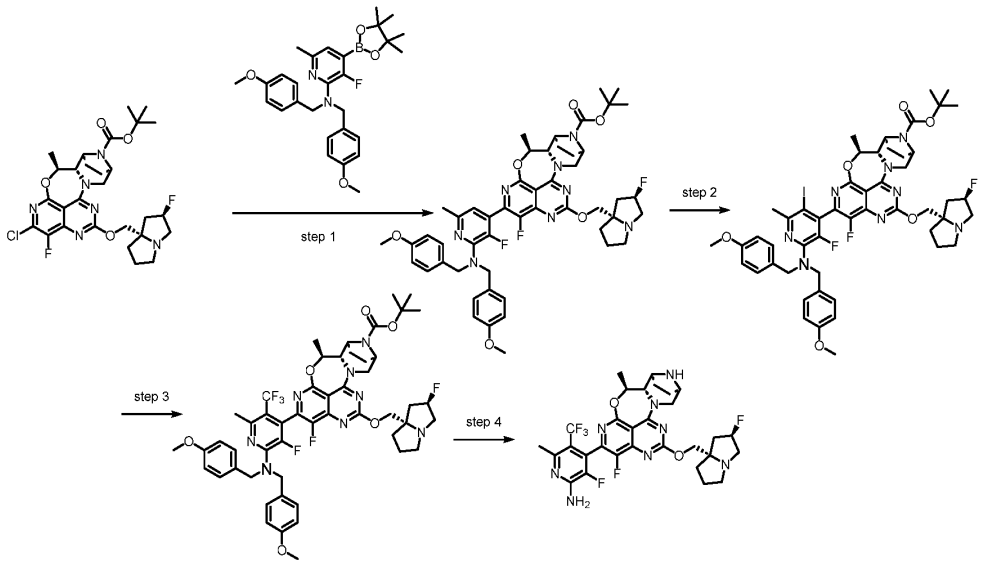
[2206] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-((3-(*bis*(4-methoxybenzyl) amino)-4-fluorophenyl)(methyl)amino)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2207] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (150 mg, 0.250 mmol) , 4-fluoro-N^3,N^3-*bis*(4-methoxybenzyl)-N^1-methylbenzene-1,3-diamine (190 mg, crude, intermediate 137), Cs_2CO_3 (326 mg, 1.00 mmol) , $Pd(OAc)_2$ (28.0 mg, 0.125 mmol) and Xantphos (57.8 mg, 0.100 mmol) in 1,4-dioxane (5 mL) was stirred for 1 hour at 110 °C. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (110 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 938.

[2208] Step 2: 4-fluoro-N^1-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-N^1-methylbenzene-1,3-diamine

[2209] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-((3-(*bis*(4-methoxybenzyl)amino)-4-fluorophenyl)(methyl)amino)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (100 mg, 0.110 mmol) in 2,2,2-trifluoroacetic acid (10 mL) was stirred for 1 hour at room temperature. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 17% B to 42% B in 9 min; Wave Length: 254nm/220nm; RT1(min): 8.9) to afford the title compound (23.3 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 597. ^{1}H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 7.04 – 6.82 (m, 1H), 6.58 – 6.41 (m, 1H), 6.38 – 6.26 (m, 1H), 5.35 (d, *J* = 53.5 Hz, 1H), 5.16 (s, 2H), 5.07 – 4.96 (m, 1H), 4.53 – 4.41 (m, 1H), 4.07 – 3.84 (m, 3H), 3.62 – 3.54 (m, 1H), 3.54 – 3.45 (m, 1H), 3.30 (s, 3H), 3.14 – 3.02 (m, 2H), 3.01 – 2.92 (m, 2H), 2.87 – 2.73 (m, 1H), 2.15 – 2.04 (m, 1H), 2.04 – 1.92 (m, 2H), 1.88 – 1.69 (m, 4H), 1.68 – 1.51 (m, 3H), 1.44 (d, *J* = 6.3 Hz, 3H).

[2210] **Example 194:** Compound 194



[2211] Step1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-6-methylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2212] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (93.9mg, 0.160mmol), 3-fluoro-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (130mg, 0.263mmol, intermediate 125), cataCXium A Pd G_3 (23.1mg, 0.0300mmol) and K_3PO_4 (1.5M in water, 0.3mL) in tetrahydrofuran (1.5mL) was stirred at 60 °C for 2 hours. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-100% EtOAc in petroleum ether) to afford the title compound (180 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 923$.

[2213] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-5-iodo-6-methylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2214] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-6-methylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-

methanonaphtho[1,8-ab]heptalene-14-carboxylate (170mg, 0.180mmol) and NIS (41.4mg, 0.180mmol) in acetic acid (2mL) was stirred at room temperature for 1 hour. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-5% MeOH in DCM) to afford the title compound (141 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1049.

[2215] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

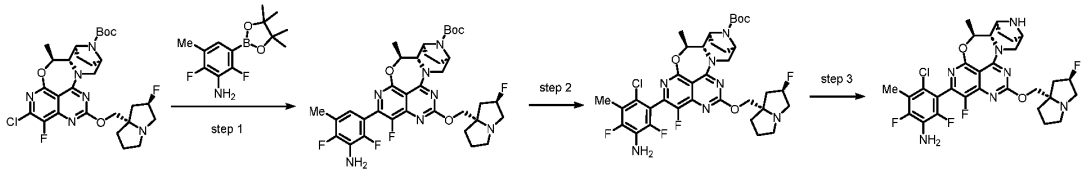
[2216] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-3-fluoro-5-iodo-6-methylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (120mg, 0.110mmol), copper(II) 2,2-difluoro-2-(fluorosulfonyl)acetate (716mg, 1.72mmol) and Cu (110mg, 1.72mmol) was added *N*,*N*-Dimethylacetamide (2mL) at 0 °C. The reaction was stirred at room temperature for 1 hour. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The crude product was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-100% EtOAc in petroleum ether) to afford the title compound (75 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 991.

[2217] Step 4: 3-Fluoro-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[2218] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (70.0mg, 0.0700mmol) in 2,2,2-trifluoroacetic acid (2mL) was stirred at 50 °C for 1 hour. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 22% B to 42% B in 10 min; Wave Length: 220 nm; R_{T1}(min): 9.7) to afford the title compound (17.1 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 651. ^1H NMR (300 MHz, DMSO-d6) δ 7.18 (d, J = 10.9 Hz, 2H), 5.27 (d, J = 54.4 Hz, 1H), 5.11 – 5.03 (m, 1H),

4.63 – 4.50 (m, 1H), 4.16 – 3.88 (m, 3H), 3.53 (d, J = 17.8 Hz, 1H), 3.43 (s, 1H), 3.16 – 2.92 (m, 4H), 2.86 – 2.76 (m, 1H), 2.46 – 2.38 (m, 3H), 2.14 (d, J = 5.2 Hz, 1H), 2.01 (d, J = 11.8 Hz, 2H), 1.92 – 1.48 (m, 7H), 1.42 (d, J = 6.3 Hz, 3H).

[2219] **Example 195:** Compound 195



[2220] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-5-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2221] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (100 mg, 0.169 mmol), 2,6-difluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (68.1 mg, 0.253 mmol), K_3PO_4 (1.5M in H_2O, 0.6 mL, 0.900 mmol) and cataCXium A Pd G3 (24.6 mg, 0.0338 mmol) in tetrahydrofuran (3 mL) was stirred for 3 hours at 90 °C. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (77.0 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 700.

[2222] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-6-chloro-2,4-difluoro-5-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

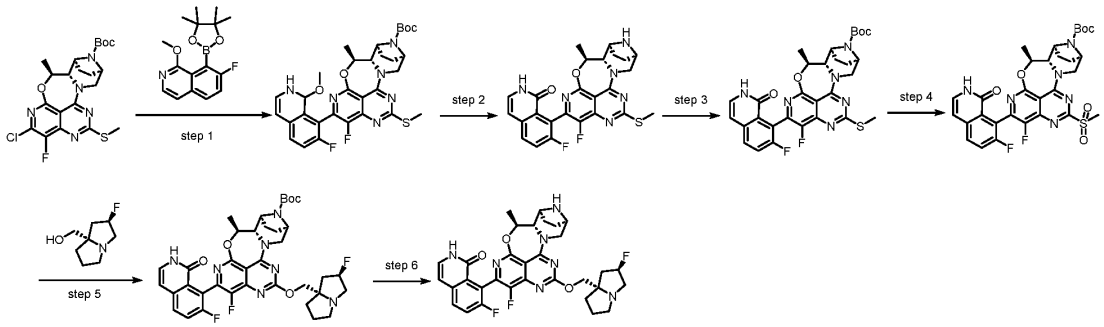
[2223] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (110 mg, 0.157 mmol) in AcOH (10 mL) was added NCS (41.9 mg, 0.314 mmol) at room temperature and the solution was stirred for 24 hours at room temperature. The reaction was quenched with saturated $Na_2S_2O_3$ aqueous solution. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10%

methanol in dichloromethane) to afford the title compound (110 mg) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 734.

[2224] Step 3: 4-Chloro-2,6-difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methylaniline

[2225] To a solution of *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-6-chloro-2,4-difluoro-5-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (110 mg, 0.149 mmol) in dichloromethane (10 mL) was added 2,2,2-trifluoroacetic acid (2 mL) at room temperature, and the mixture was stirred for 1 hour. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min; Wave Length: 254/220 nm; RT1(min): 8.9) to afford the title compound (29.5 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 635. ^{1}H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 5.52 (d, J = 8.2 Hz, 2H), 5.29 (d, J = 54.3 Hz, 1H), 5.08 (d, J = 12.6 Hz, 1H), 4.67 – 4.50 (m, 1H), 4.17 – 3.91 (m, 3H), 3.63 – 3.41 (m, 2H), 3.18 – 2.94 (m, 4H), 2.91 – 2.68 (m, 2H), 2.32 – 2.19 (m, 3H), 2.19 – 2.12 (m, 1H), 2.10 – 1.94 (m, 2H), 1.91 – 1.73 (m, 4H), 1.73 – 1.51 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H).

[2226] **Example 196:** Compound 196



[2227] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-1-methoxyisoquinolin-8-yl)-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2228] Under nitrogen, a solution of 7-fluoro-1-methoxy-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline (269mg, 0.890mmol, intermediate 140), *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (357mg, 0.740mmol) and cataCXium A Pd G_3 (107mg, 0.150mmol) in tetrahydrofuran (7.5mL) and

K_3PO_4 (1.5 M in water, 1.5mL) was stirred at 60 °C overnight. The resulting mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc, washed with water and dried over anhydrous Na_2SO_4. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-70% EtOAc in petroleum ether) to afford the title compound (255mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 623$.

[2229] Step 2: 7-Fluoro-8-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)isoquinolin-1-ol

[2230] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-1-methoxyisoquinolin-8-yl)-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (255mg, 0.410mmol) in 40% HBr/AcOH (5mL) was stirred at 80 °C for 1 hour. Solvent was evaporated and the residue was purified by flash chromatography on silica gel (gradient: 0-20% MeOH in DCM) to afford the title compound (175 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 509$.

[2231] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-1-hydroxyisoquinolin-8-yl)-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2232] A solution of 7-fluoro-8-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab] heptalen-2-yl)isoquinolin-1-ol (230 mg, 0.450mmol), Boc_2O (197mg, 0.900mmol) and DIPEA (875mg, 6.78mmol) in dichloromethane (5mL) was stirred at room temperature for 1 hour. The resulting mixture was diluted with EtOAc, washed with brine and dried over anhydrous sodium sulfate. The solvent was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-100% EtOAc in petroleum ether) to afford the title compound (148 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 609$.

[2233] Step 4: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-1-hydroxyisoquinolin-8-yl)-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2234] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-1-hydroxyisoquinolin-8-yl)-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (135mg, 0.220mmol) in ethyl acetate (2mL) was added 3-chlorobenzoperoxoic acid (38.3mg, 0.220mmol) in EtOAc (0.5ml) at 0 °C. The resulting solution was stirred for 3h at room temperature. The reaction was quenched with $NaHCO_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over

anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% EtOAc / petroleum ether) afford the title compound (136 mg) as a pink solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 641.

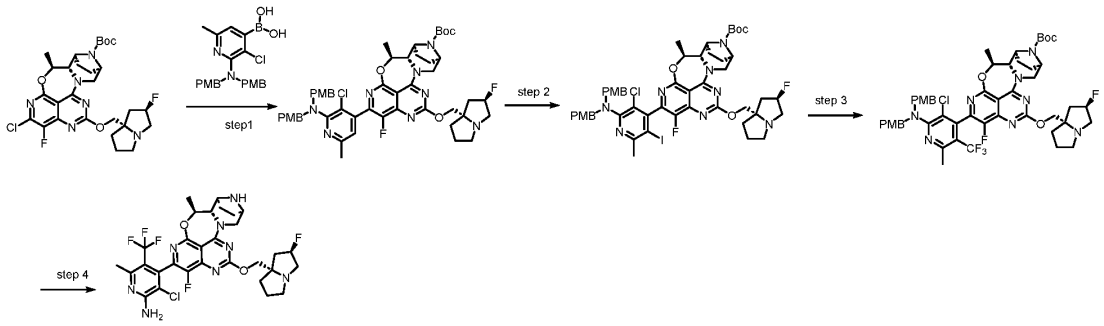
[2235] Step 5: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-1-oxo-1,2-dihydroisoquinolin-8-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2236] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-1-hydroxyisoquinolin-8-yl)-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab] heptalene-14-carboxylate(125mg, 0.200mmol) and ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (37.2mg, 0.230mmol) in toluene (1.5mL) was added *t*-BuONa (37.4mg, 0.390mmol) at 0 °C. The reaction was stirred at room temperature for 2 hours. Then the solvent was evaporated and the residue was purified by C18 column (solvent gradient: 0-100% ACN in water (0.05% NH_4HCO_3)) to afford the title compound (62 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 720.

[2237] Step 6: 7-Fluoro-8-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)isoquinolin-1(2*H*)-one

[2238] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(7-fluoro-1-oxo-1,2-dihydroisoquinolin-8-yl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (62.0mg, 0.0900mmol) in 2,2,2-trifluoroacetic acid (2mL) and DCM (4mL) was stirred at room for 1 hour. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water(10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9) to afford the title compound (19.9 mg) as a light yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 620. ^1H NMR (300 MHz, DMSO-d6) δ 11.18 – 11.04 (m, 1H), 7.88 (dd, J = 8.9, 5.4 Hz, 1H), 7.79 – 7.61 (m, 1H), 7.24 – 7.09 (m, 1H), 6.64 (dd, J = 7.1, 5.0 Hz, 1H), 5.38 – 5.02 (m, 2H), 4.57 – 4.41 (m, 1H), 4.18 – 3.86 (m, 3H), 3.57 (s, 1H), 3.44 (t, J = 6.6 Hz, 1H), 3.21 – 2.93 (m, 4H), 2.81 (q, J = 8.0 Hz, 2H), 2.16 (dd, J = 12.2, 8.2 Hz, 1H), 2.10 – 1.95 (m, 2H), 1.99 – 1.46 (m, 7H), 1.41 (t, J = 6.3 Hz, 3H).

[2239] **Example 197:** Compound 197



[2240] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-chloro-6-methylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2241] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (300 mg, 0.620 mmol), (2-(bis(4-methoxybenzyl)amino)-3-chloro-6-methylpyridin-4-yl)boronic acid (1.01 g, 2.34 mmol, intermediate 141), K_3PO_4 (1.0 mL, 1.5 M in H_2O) and cataCXium A Pd G3 (50.1 mg, 0.0700 mmol) in THF (5 mL) was stirred for 1.5 h at 60°C. The resulting solution was partitioned between water and EtOAc. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0 - 12% MeOH / DCM) to afford 280 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 939$.

[2242] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-chloro-5-iodo-6-methylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2243] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-chloro-6-methylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (270 mg, 0.290 mmol) and NIS (97.0 mg, 0.430 mmol) in AcOH (3 mL) was stirred for 25 min at room temperature. The reaction was quenched with $Na_2S_2O_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-13% MeOH / DCM) to afford 281 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 1065$.

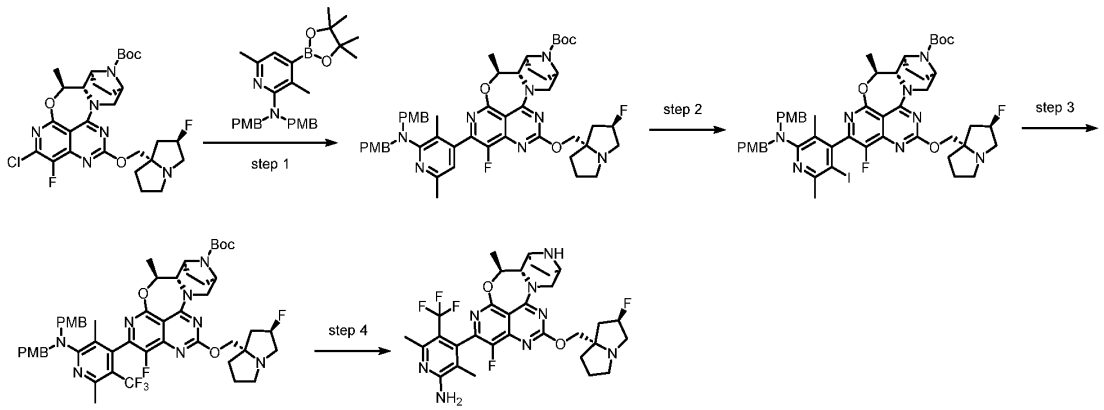
[2244] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-chloro-6-methyl-5-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2245] Under nitrogen, to a mixture of *tert* -butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-3-chloro-5-iodo-6-methylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (270 mg, 0.250 mmol), Cu powder (162 mg, 2.53 mmol) and $Cu(O_2CCF_2SO_2F)_2$ (1.06 g, 2.54 mmol) was added DMF (4 mL) at 0°C, and the mixture was stirred for 1 h at room temperature. The resulting mixture was diluted with EtOAc, washed with water. The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-13% MeOH / DCM) to afford 196 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1007.

[2246] Step 4: 3-Chloro-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[2247] A solution of *tert* -butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-chloro-6-methyl-5-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (180 mg, 0.180 mmol) in TFA (4 mL) was stirred at 50 °C for 1.5 h. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC (conditions: Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min; Wave Length: 254/220 nm; R_{T1} (min): 8.9) to afford 11.1 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 668 .LC-MS: (ESI, *m/z*): $[M+H]^+$ = 668. ^1H NMR (400 MHz, DMSO-d_6) δ 7.28 (s, 2H), 5.29 (d, J = 54.5 Hz, 1H), 5.15 – 4.91 (m, 1H) , 4.55 (d, J = 2.1 Hz, 1H), 4.10 (d, J = 10.2 Hz, 1H), 4.01 (d, J = 10.4 Hz, 2H), 3.51 (d, J = 53.3 Hz, 2H), 3.29 – 2.91 (m, 4H), 2.83 (d, J = 8.1 Hz, 2H), 2.48 (d, J = 2.5 Hz, 2H), 2.09 (d, J = 30.1 Hz, 2H), 2.00 (d, J = 6.3 Hz, 1H), 1.93 – 1.69 (m, 4H), 1.61 (d, J = 54.3 Hz, 2H), 1.52 – 1.46 (m, 1H) , 1.44 (d, J = 6.3 Hz, 3H).

[2248] **Example 198:** Compound 198



[2249] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3,6-dimethylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2250] Under nitrogen, a solution of *N*,*N*-bis(4-methoxybenzyl)-3,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (417 mg, 0.850 mmol, intermediate 142), *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (251 mg, 0.420 mmol), cataCXium A Pd G3 (69.2 mg, 0.0900 mmol) and K_3PO_4 (3 mL, 1.5M in H_2O) in THF (15 mL) was stirred for 3 hours at 60°C. The resulting mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-15% MeOH / DCM) to afford 286 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 919$.

[2251] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-5-iodo-3,6-dimethylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2252] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-3,6-dimethylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (356 mg, 0.390 mmol) and NIS (123 mg, 0.550 mmol) in AcOH (3 mL) was stirred at room temperature for 0.5 h. The solution was quenched by $Na_2S_2O_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified

by flash chromatography on silica gel (gradient: 0-15% MeOH / DCM) to afford 382 mg of the title compound as white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1045.

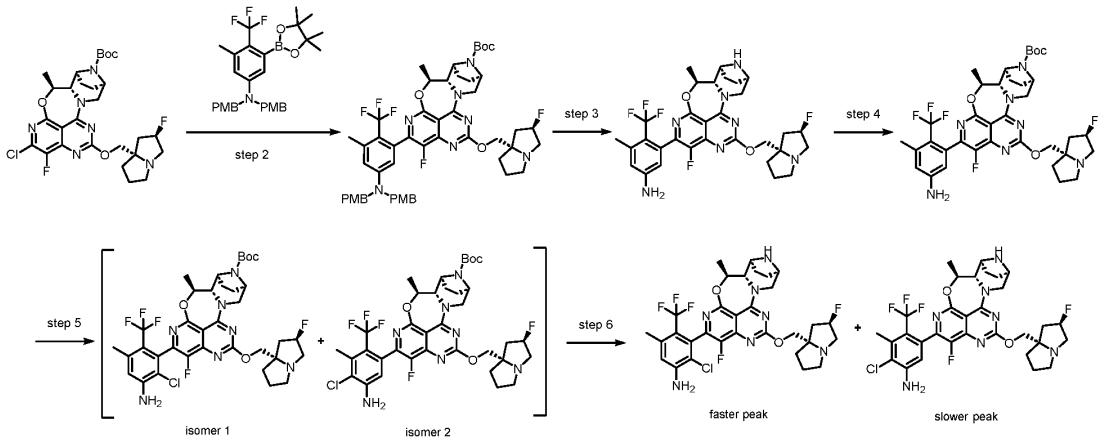
[2253] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3,6-dimethyl-5-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2254] Under nitrogen, to a mixture of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-5-iodo-3,6-dimethylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (305 mg, 0.290 mmol), $Cu(O_2CCF_2SO_2F)_2$ (608 mg, 1.46 mmol) and Cu powder (149 mg, 2.33 mmol) was added DMF (15 mL) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. The resulting reaction was diluted with EtOAc, washed with water. The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash (0-70% EtOAc in petroleum ether and then 0-15% MeOH / DCM) to afford 289 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 987.

[2255] Step 4: 4-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3,6-dimethyl-5-(trifluoromethyl)pyridin-2-amine

[2256] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3,6-dimethyl-5-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (286 mg, 0.290 mmol) in TFA (5 mL) was stirred at 50°C for 3 h. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 23% B to 48% B in 9 min; Wave Length: 254nm/220nm; R_{T1}(min): 8.7) to afford 25.8 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 647. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.63 (d, *J* = 13.2 Hz, 2H), 5.42 – 5.18 (m, 1H), 5.12 –5.04 (m, 1H), 4.54 – 4.49 (m, 1H), 4.13 – 4.07(m, 1H), 4.06 – 3.87 (m, 2H), 3.58 (d, *J* = 5.6 Hz, 1H), 3.45 (d, *J* = 6.1 Hz, 1H), 3.16 – 2.98 (m, 4H), 2.89 – 2.77 (m, 2H), 2.45 – 2.37 (m, 3H), 2.18 – 1.93 (m, 3H), 1.91 – 1.85 (m, 3H), 1.79 (d, *J* = 22.4 Hz, 3H), 1.71 – 1.60 (m, 2H), 1.57 (s, 2H), 1.43 (d, *J* = 6.3 Hz, 3H).

[2257] **Examples 199 and 200**: Compound 199 and 200



[2258] Step 1: *tert*-Butyl (5S,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2259] Under nitrogen, a mixture of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (190 mg, 0.320 mmol), *N*,*N*-*bis*(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline (434 mg, 0.800 mmol, intermediate 143), K_3PO_4 (1.5M in H_2O, 1.1 mL, 1.65 mmol) and cataCXium A Pd G3 (46.6 mg, 0.0640 mmol) in tetrahydrofuran (5.5 mL) was stirred for 1 hour at 60 °C. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (354 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 972$.

[2260] Step 2: 3-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline

[2261] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl) amino)-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (354 mg, 0.364 mmol) in 2,2,2-trifluoroacetic acid (20 mL) was stirred for 1 hour at room temperature. The solvent was concentrated under vacuum. The residue was neutralized by saturated $NaHCO_3$ aqueous solution and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and

concentrated under vacuum to afford the title compound (240 mg, crude) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 632.

[2262] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2263] To a solution of 3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline (220 mg, 0.350 mmol) and DIPEA (90.0 mg, 0.700 mmol) in dichloromethane (5 mL) was added a solution of $(Boc)_2O$ (91.3 mg, 0.420 mmol) in dichloromethane (1 mL) at 0 °C, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (181 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 732.

[2264] Step 4: Mixture of *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2-chloro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate **(isomer 1) & (isomer 2)**

[2265] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (160 mg, 0.220 mmol) in acetic acid (2 mL) was added NCS (35.1 mg, 0.260 mmol) at room temperature, and the mixture was stirred for 48 hours at room temperature. The reaction was quenched by saturated $Na_2S_2O_3$ aqueous solution. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (136 mg, **mixture of isomer 1 and isomer 2**) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 766.

[2266] Step 5: 2-Chloro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline **(199)** and 2-chloro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-

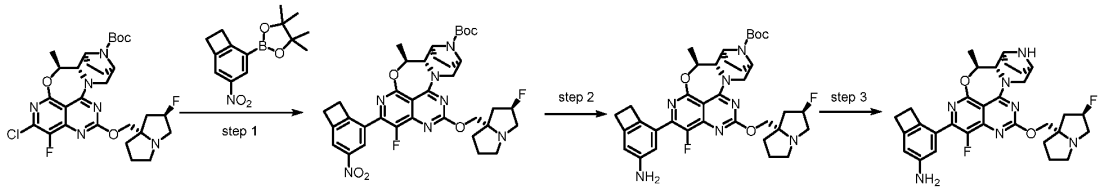
yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline **(200)**

[2267] To a solution of mixture of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2-chloro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate and *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-4-chloro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (136 mg, 0.177 mmol) in dichloromethane (5 mL) was added 2,2,2-trifluoroacetic acid (1 mL) at room temperature, and the mixture was stirred for 1 hour. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9; RT2(min): 9.0) to afford **199** (19.0 mg, the faster peak) and **200** (24.2 mg, the slower peak) as white solids.

[2268] **199:** LC-MS: (ESI, *m/z*): $[M+H]^+$ = 666. ^1H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.86 (s, 1H), 6.18 (d, J = 10.0 Hz, 2H), 5.30 (d, J = 54.4 Hz, 1H), 5.11 (d, J = 13.0 Hz, 1H), 4.69 – 4.49 (m, 1H), 4.14 – 3.99 (m, 3H), 3.72 – 3.68 (m, 1H), 3.59 – 3.53 (m, 1H), 3.15 – 3.05 (m, 3H), 3.04 – 2.99 (m, 1H), 2.92 – 2.77 (m, 2H), 2.42 – 2.32 (m, 3H), 2.20 – 2.15 (m, 1H), 2.10 – 2.00 (m, 2H), 1.96 – 1.56 (m, 7H), 1.44 (d, J = 6.3 Hz, 3H).

[2269] **200:** LC-MS (ESI, *m/z*): $[M+H]^+$ = 666. ^1H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.71 – 6.50 (m, 1H), 6.24 (s, 2H), 5.29 (d, J = 54.5 Hz, 1H), 5.15 – 5.03 (m, 1H), 4.59 – 4.49 (m, 1H), 4.15 – 3.91 (m, 3H), 3.61 – 3.54 (m, 1H), 3.48 – 3.42 (m, 1H), 3.18 – 2.98 (m, 4H), 2.90 – 2.71 (m, 2H), 2.46 (s, 3H), 2.23 – 2.11 (m, 1H), 2.11 – 1.94 (m, 2H), 1.93 – 1.73 (m, 4H), 1.73 – 1.51 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H).

[2270] **Example 201**: Compound 201



[2271] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-2-(4-nitrobicyclo[4.2.0]octa-1(6),2,4-trien-2-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2272] Under nitrogen, a solution of 4,4,5,5-tetramethyl-2-(4-nitrobicyclo[4.2.0]octa-1(6),2,4-trien-2-yl)-1,3,2-dioxaborolane (87.5 mg, 0.324 mmol, intermediate 144), *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate(76.3 mg, 0.131 mmol), K_3PO_4 (0.254 mL, 1.5 M in water) and cataCXium A Pd G_3 (18.6 mg, 0.0260 mmol) in THF (1.27 mL) was stirred for 1 h at 60°C. The resulting solution was partitioned between water and EtOAc. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% MeOH / DCM) to afford 114 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 706.

[2273] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(4-aminobicyclo[4.2.0]octa-1(6),2,4-trien-2-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

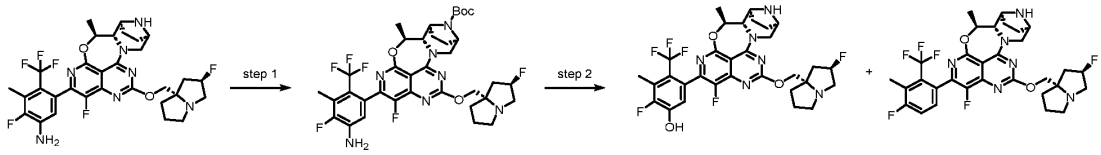
[2274] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methoxy)-5-methyl-2-(4-nitrobicyclo[4.2.0]octa-1(6),2,4-trien-2-yl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (50.0 mg, 0.0700 mmol), Fe (19.8 mg, 0.350 mmol) and NH_4Cl (37.5 mg, 0.710 mmol) in EtOH (1.40 mL) and H_2O (0.600 mL) was stirred for 1 h at 80°C. After filtration, the filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% MeOH / DCM) to afford 40.0 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 676.

[2275] Step 3: 5-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)bicyclo[4.2.0]octa-1(6),2,4-trien-3-amine

[2276] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(4-aminobicyclo[4.2.0]octa-1(6),2,4-trien-2-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (30.0 mg, 0.0400 mmol) in DCM (1 mL) and TFA (1 mL) was stirred for 1 h at room temperature. The solvent was concentrated under vacuum. The residue was purified by PREP-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 17% B to 42% B in 9 min; Wave Length: 254nm/220nm; RT1(min): 9.6) to afford 3.10 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 576. ^1H NMR (300 MHz, DMSO-d_6) δ 7.07 (d, *J* = 1.8 Hz, 1H), 6.45 (d, *J* = 1.8 Hz, 1H), 5.29 (d, *J* = 54.9 Hz, 2H),

5.06 (s, 2H), 4.52 (p, J = 6.3 Hz, 1H), 4.11 (d, J = 10.3 Hz, 1H), 4.01 (d, J = 10.3 Hz, 1H), 3.93 (d, J = 8.7 Hz, 1H), 3.57 (s, 1H), 3.45 (d, J = 5.5 Hz, 1H), 3.19 – 3.07 (m, 4H), 3.00 (d, J = 9.3 Hz, 5H), 2.84 (q, J = 8.4, 7.9 Hz, 1H), 2.16 (d, J = 5.4 Hz, 1H), 2.03 (d, J = 10.3 Hz, 2H), 1.80 (dd, J = 12.0, 7.2 Hz, 4H), 1.60 (q, J = 15.9, 12.7 Hz, 3H), 1.46 (d, J = 6.3 Hz, 3H).

[2277] **Examples 202 and 203**: Compounds 202 and 203



[2278] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2279] A solution of 2-fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (200 mg, 0.310 mmol, Example 6), di-*tert*-butyl dicarbonate (100 mg, 0.460 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (119 mg, 0.920 mmol) in dichloromethane (2 mL) was stirred for 30 min at room temperature. The solvent was evaporated under vacuum and the residual was purified by flash chromatography on silica gel (gradient: 0%-10% MeOH / DCM) to afford 181 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 750.

Step 2: 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)phenol and (5*S*,5a*S*,6*S*,9*R*)-1-fluoro-2-(4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene

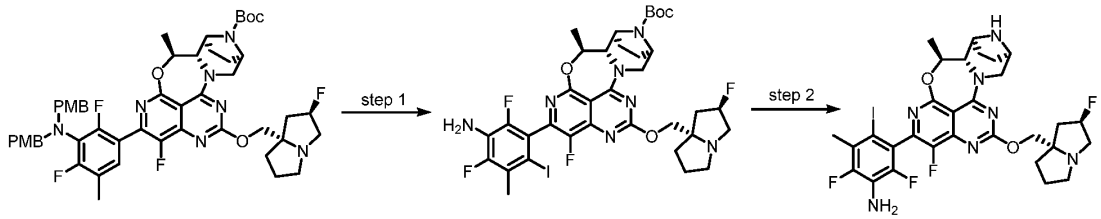
[2280] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-amino-4-fluoro-3-methyl-2-(trifluoromethyl) phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (150 mg, 0.200 mmol) and 35% H_2SO_4 (2.50 mL) in water (1.76 mL) was added $NaNO_2$ (15.2 mg, 0.220 mmol) at -5~0 °C. Then $Cu(NO_3)_2.3H_2O$ (676 mg, 2.80 mmol) in water (1.80 mL) and Cu_2O (34.4 mg, 0.240 mmol) was added, and the mixture was stirred for 15 min at room temperature. The reaction was quenched by $NaHCO_3$ aqueous and extracted with DCM. The combined organic layers were dried over

anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by prep. HPLC (Column: XBridge BEH C18 OBD Prep Column, 19*250 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: MeOH--HPLC; Flow rate: 25 mL/min; Gradient: 20% B to 54% B in 10 min, 54% B; Wave Length: 254/220 nm; RT1(min): 9.68) to yield **202** 4.50 mg and **203** 5.30 mg of as white solids.

[2281] **202**: LC-MS: (ESI, *m/z*): $[M+H]^+$ = 651. ^1H NMR (300 MHz, DMSO-d_6) δ 6.80 (d, *J* = 31.5 Hz, 1H), 5.29 (d, *J* = 54.3 Hz, 1H), 5.09 (d, *J* = 12.7 Hz, 1H), 4.55 (s, 1H), 4.19 – 3.88 (m, 3H), 3.72 – 3.49 (m, 2H), 3.20 – 2.91 (m, 5H), 2.90 – 2.79 (m, 1H), 2.38 (s, 3H), 2.15 (d, *J* = 4.9 Hz, 1H), 2.08 – 1.98 (m, 2H), 1.94 – 1.73 (m, 4H), 1.65 (s, 3H), 1.44 (d, *J* = 6.3 Hz, 3H).

[2282] **203**: LC-MS: (ESI, *m/z*): $[M+H]^+$ = 635. ^1H NMR (300 MHz, DMSO-d_6) δ 7.63 (t, *J* = 8.9 Hz, 1H), 7.36 (d, *J* = 40.8 Hz, 1H), 5.29 (d, *J* = 54.2 Hz, 1H), 5.08 (d, *J* = 12.6 Hz, 1H), 4.54 (s, 1H), 4.10 (d, *J* = 10.4 Hz, 1H), 4.06 – 3.80 (m, 2H), 3.58 (s, 1H), 3.45 (s, 1H), 3.17 – 2.95 (m, 5H), 2.83 (m, 1H), 2.46 – 2.39 (m, 3H), 2.15 (d, *J* = 4.9 Hz, 1H), 2.12 – 1.97 (m, 2H), 1.90 – 1.72 (m, 4H), 1.63 (d, *J* = 14.4 Hz, 3H), 1.44 (d, *J* = 6.3 Hz, 3H).

[2283] **Example 204**: Compound 204



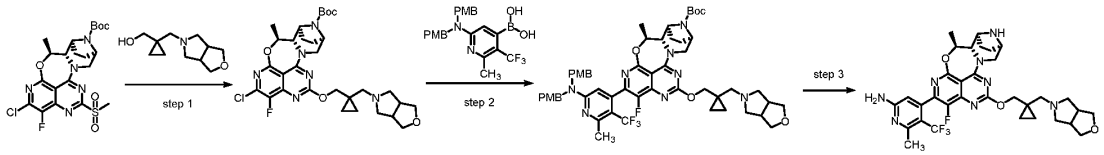
[2284] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2285] A solution of *tert*-butyl (4*R*,7*S*,8*S*,9*S*)-13-[3-[bis[(4-methoxyphenyl) methyl] amino]-2,4-difluoro-5-methyl-phenyl]-14-fluoro-17-[[(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-9-methyl-10-oxa-2,12,16,18,20-pentazapentacyclo[9.7.1.14,7.02,8.015,19]icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (90. 5 mg, 0.100 mmol) and NIS (109 mg, 0.480 mmol) in AcOH (1.5 mL) was stirred at room temperature for 1 h. The reaction was quenched by $Na_2S_2O_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% MeOH / DCM) to afford 66.1 mg of the title compound as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 826.

[2286] Step 2: 2,6-Difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-4-iodo-5-methylaniline

[2287] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (66.2 mg, 0.0800 mmol) and TFA (1 mL) in DCM (4 mL) was stirred at room temperature for 1 h. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC (conditions: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL / min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; R_{T1}(min): 8.9) to afford 26.2 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 726. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 5.56 – 5.47 (m, 1H), 5.29 (d, J = 54.4 Hz, 1H), 5.16 – 5.03 (m, 1H), 4.66 – 4.49 (m, 1H), 4.21 – 3.94 (m, 3H), 3.61 (s, 1H), 3.48 (d, J = 5.5 Hz, 1H), 3.17 – 2.97 (m, 4H), 2.91- 2.79 (m, 1H), 2.32 – 2.25 (m, 3H), 2.20 – 2.13 (m, 1H), 2.09 – 1.95 (m, 2H), 1.92 – 1.57 (m, 7H), 1.45 (d, J = 6.2 Hz, 3H).

[2288] **Example 205**: Compound 205



[2289] Step1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-((1-((tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5(3*H*)-yl)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2290] To a solution of (1-((tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5(3*H*)-yl)methyl)cyclopropyl)methanol (360 mg, crude, intermediate 145) in THF (5 mL) was added NaH (60% dispersion in mineral oil, 156 mg, 3.90 mmol) in portions at 0°C, and the mixture was stirred for 30 minutes at room temperature. Then *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*] heptalene-14-carboxylate (200 mg, 0.390 mmol) was added, and the mixture was stirred for 1 hour at room temperature. The reaction was quenched with saturated NH_4Cl aqueous solution. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on

silica gel (gradient: 0-90% ethyl acetate in petroleum ether) to afford the title compound (100 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 632.

[2291] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(*bis*(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-5-methyl-12-((1-((tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5(3*H*)-yl)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2292] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-((1-((tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5(3*H*)-yl)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (100 mg, 0.158 mmol), (6-(*bis*(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)boronic acid (190 mg, 0.412 mmol), K_3PO_4 (1.5M aqueous solution, 0.5 mL, 0.75 mmol) and cataCXium A Pd G3 (23.0 mg, 0.0316 mmol) in THF (2.5 mL) was stirred for 3 hours at 60 °C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-100% ethyl acetate in petroleum ether) to afford the title compound (140 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1011.

[2293] Step 3: 4-((5*S*,5a*S*,6*S*,9*R*)-1-Fluoro-5-methyl-12-((1-((tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5(3*H*)-yl)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[2294] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(*bis*(4-methoxybenzyl) amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-5-methyl-12-((1-((tetrahydro-1*H*-furo[3,4-*c*]pyrrol-5(3*H*)-yl)methyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (140 mg, 0.138 mmol) in 2,2,2-trifluoroacetic acid (20 mL) was stirred for 3 hours at 50 °C. The solvent was concentrated under vacuum. The residue was purified by reverse phase chromatography (gradient: 0-50 % acetonitrile in water (0.05% NH_4HCO_3)) and Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min; Wave Length: 254/220 nm; RT1(min): 9) to afford the title compound (8.20 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 671. ^1H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 6.83 (s, 2H), 6.23 (s, 1H), 5.17 – 5.02 (m, 1H), 4.60 – 4.46 (m, 1H), 4.36 – 4.20 (m, 2H), 3.95 (d, J = 8.7 Hz, 1H), 3.72 (t, J = 7.4 Hz, 2H), 3.62 –3.51 (m, 1H), 3.49 – 3.36 (m, 2H), 3.02 (d, J = 12.7 Hz, 1H), 3.71 – 3.58 (m, 3H), 2.48 –

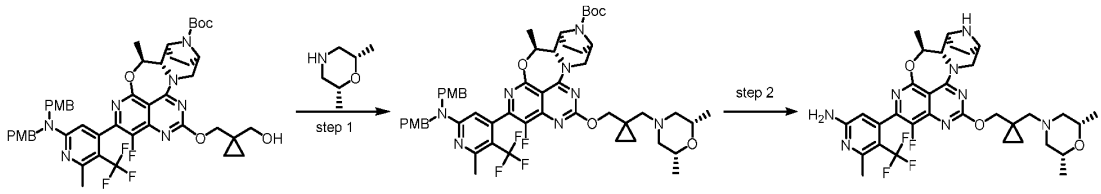
2.43 (m, 5H), 2.41 – 2.25 (m, 4H), 1.88 – 1.73 (m, 1H), 1.71 – 1.49 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H), 0.69 – 0.57 (m, 2H), 0.48 – 0.32 (m, 2H).

[2295] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 205**.

Cmpd. No.	^{1}H NMR	MS (M+H)$^+$
206	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.83 (s, 2H), 6.23 (s, 1H), 5.16 – 5.04 (m, 1H), 4.60 – 4.48 (m, 1H), 4.44 (d, J = 10.8 Hz, 1H), 4.31 (d, J = 10.8 Hz, 1H), 3.99 – 3.92 (m, 1H), 3.58 – 3.43 (m, 6H), 3.18 – 2.92 (m, 4H), 2.49 – 2.44 (m, 3H), 2.37 – 2.23 (m, 2H), 1.84 – 1.53 (m, 8H), 1.44 (d, J = 6.3 Hz, 3H), 0.66 – 0.55 (m, 2H), 0.50 – 0.41 (m, 2H).	671
207	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.83 (s, 2H), 6.23 (s, 1H), 5.11 (d, *J* = 12.6 Hz, 1H), 4.51 (m, 1H), 4.40 (d, *J* = 10.7 Hz, 1H), 4.25 (d, *J* = 10.9 Hz, 1H), 4.16 (s, 2H), 3.96 (d, *J* = 8.8 Hz, 1H), 3.55 (s, 1H), 3.52 (d, *J* = 12.6 Hz, 2H), 3.02 (m, 1H),2.62 (t, *J* = 10.8 Hz, 2H), 2.47 (d, *J* = 2.3 Hz, 3H), 2.31 (d, *J* = 12.7 Hz, 1H), 2.25 – 2.07 (m, 3H), 1.73 (d, *J* = 9.7 Hz, 3H), 1.61 (s, 4H), 1.44 (d, *J* = 6.3 Hz, 3H), 0.61 (s, 2H), 0.38 (s, 2H).	671
208	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.83 (s, 2H), 6.23 (s, 1H), 5.16 – 5.04 (m, 1H), 4.60 – 4.48 (m, 1H), 4.39 – 4.26 (m, 2H), 4.20 (d, J = 10.8 Hz, 1H), 3.96 (d, J = 8.5 Hz, 1H), 3.78 (d, J = 7.5 Hz, 1H), 3.65 – 3.53 (m, 1H), 3.53 – 3.37 (m, 4H), 3.02 (d, J = 12.7 Hz, 1H), 2.85 (d, J = 9.8 Hz, 1H), 2.76 – 2.59 (m, 1H), 2.48 – 2.32 (m, 5H), 1.88 – 1.74 (m, 1H), 1.73 – 1.57 (m, 3H), 1.57 – 1.48 (m, 2H), 1.44 (d, J = 6.3 Hz, 3H), 0.79 – 0.52 (m, 2H), 0.52 – 0.36 (m, 2H).	657
209	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.84 (s, 2H), 6.23 (s, 1H), 5.19 – 4.97 (m, 1H), 4.61 – 4.45 (m, 1H), 4.37 – 4.16 (m, 3H), 3.95 (d, J = 8.7 Hz, 1H), 3.78 (d, J = 7.4 Hz, 1H), 3.59 – 3.52 (m, 1H), 3.52 – 3.41 (m, 3H), 3.02 (d, J = 12.7 Hz, 1H), 2.88 – 2.77 (m, 1H), 2.62 (d, J = 12.6 Hz, 1H), 2.51 – 2.43 (m, 4H), 2.42 – 2.37 (m, 1H), 1.91 – 1.76 (m, 1H), 1.76 – 1.45 (m, 5H), 1.44 (d, J = 6.3 Hz, 3H), 0.65 – 0.53 (m, 2H), 0.51 – 0.45 (m, 1H), 0.45 – 0.37 (m, 1H).	657
210	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.84 (s, 2H), 6.23 (s, 1H), 5.20 – 5.00 (m, 1H), 4.63 – 4.46 (m, 1H), 4.38 – 4.17 (m, 2H), 3.97 (d, J = 8.7 Hz, 1H), 3.68 – 3.44 (m, 6H), 3.04 (d, J = 12.8 Hz, 1H), 2.49 – 2.44 (m, 3H), 2.39 (s, 4H), 2.30 (s, 2H), 1.90 – 1.77 (m, 1H), 1.75 – 1.51 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H), 0.71 – 0.60 (m, 2H), 0.48 – 0.37 (m, 2H).	645
211	^{1}H NMR (300 MHz, DMSO-d6, ppm) δ 6.83 (s, 2H), 6.23 (s, 1H), 5.09 (d, J = 12.6 Hz, 1H), 4.58 – 4.48 (m, 1H), 4.38 – 4.20 (m, 2H), 4.06 – 3.92 (m, 2H), 3.75 – 3.60 (m, 1H), 3.64 – 3.60 (m, 1H), 3.28 – 3.49 (m, 1H), 3.44 (d, J = 6.0 Hz, 1H), 3.02 (d, J = 12.7 Hz, 1H), 2.96 – 2.84 (m, 3H), 2.71 – 2.58 (m, 2H), 2.55 – 2.52 (m, 1H), 2.48 (s, 3H), 1.90 – 1.77 (m, 3H), 1.70 – 1.52 (m, 5H), 1.44 (d, J = 6.3 Hz, 3H), 0.67 – 0.55 (m, 2H), 0.52 – 0.38 (m, 2H).	671
212	^{1}H NMR (300 MHz, DMSO-d6, ppm) δ 6.83 (s, 2H), 6.23 (s, 1H), 5.10 (d, J = 12.8 Hz, 1H), 4.61 – 4.45 (m, 1H), 4.36 – 4.18 (m, 2H), 3.96 (d, J = 8.8 Hz, 1H), 3.66 – 3.50 (m, 3H), 3.48 – 3.41 (m, 1H), 3.02 (d, J = 12.7 Hz, 1H), 2.48 – 2.41 (m, 6H), 2.37 (s, 3H), 2.36 – 2.24 (m, 1H), 1.89 – 1.74 (m, 1H), 1.74 – 1.50 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H), 0.68 – 0.61 (m, 2H), 0.61 – 0.54 (m, 2H), 0.48 – 0.36 (m, 4H).	671

213	^{1}H NMR (300 MHz, DMSO-d6, ppm): δ 6.84 (s, 2H), 6.23 (s, 1H), 5.13 – 5.04 (m, 1H), 4.57 – 4.49 (m, 1H), 4.28 (s, 2H), 3.95 (d, J = 8.6 Hz, 1H), 3.70 (d, J = 10.9 Hz, 1H), 3.56 (s, 1H), 3.44 (d, J = 6.1 Hz, 3H), 3.02 (d, J = 12.7 Hz, 1H), 2.88 – 2.67 (m, 3H), 2.47 (d, J = 2.4 Hz, 3H), 2.35 – 2.20 (m, 2H), 1.99 – 1.88 (m, 1H), 1.80 (d, J = 10.8 Hz, 1H), 1.69 – 1.58 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H), 1.01 (d, J = 6.2 Hz, 3H), 0.64 (d, J = 4.3 Hz, 2H), 0.43 (d, J = 4.5 Hz, 2H).	659
214	^{1}H NMR (300 MHz, DMSO-d6) δ 6.84 (s, 2H), 6.23 (s, 1H), 5.10 (dd, J = 12.9, 2.5 Hz, 1H), 4.63 – 4.47 (m, 1H), 4.41 – 4.27 (m, 2H), 3.97 (d, J = 8.7 Hz, 1H), 3.55 (d, J = 11.0 Hz, 2H), 3.45 (d, J = 5.4 Hz, 1H), 3.27 – 3.17 (m, 1H), 3.15 (d, J = 3.8 Hz, 1H), 3.11 – 2.98 (m, 2H), 2.87 (s, 1H), 2.75 – 2.57 (m, 1H), 2.49 – 2.44 (m, 3H), 2.36 (d, J = 33.4 Hz, 3H), 1.80 (d, J = 10.6 Hz, 1H), 1.58 (dd, J = 28.5, 8.2 Hz, 3H), 1.44 (d, J = 6.3 Hz, 3H).	637
215	^{1}H NMR (300 MHz, DMSO-d6) δ 6.81 (s, 2H), 6.21 (s, 1H), 5.27 (d, J = 54.4 Hz, 1H), 5.06 (dd, J = 12.9, 2.5 Hz, 1H), 4.57 – 4.46 (m, 1H), 4.08 (d, J = 10.3 Hz, 1H), 3.96 (dd, J = 14.8, 9.5 Hz, 2H), 3.55 (s, 1H), 3.43 (d, J = 5.8 Hz, 1H), 3.18 – 2.89 (m, 4H), 2.89 – 2.78 (m, 1H), 2.75 (d, J = 12.0 Hz, 1H), 2.48 – 2.40 (m, 3H), 2.19 – 2.05 (m, 1H), 2.00 (dd, J = 14.8, 4.8 Hz, 2H), 1.90 – 1.70 (m, 4H), 1.70 – 1.46 (m, 3H), 1.42 (d, J = 6.3 Hz, 3H).	633
216	^{1}H NMR (400 MHz, DMSO-d6, ppm): δ 6.84 (s, 1H), 6.23 (s, 2H), 5.16 – 4.99 (m, 1H), 4.63 – 4.45 (m, 1H), 4.24 – 4.09 (m, 2H), 3.96 (d, J = 8.8 Hz, 1H), 3.57 (s, 1H), 3.45 (d, J = 5.7 Hz, 1H), 3.18 – 2.94 (m, 3H), 2.80 – 2.66 (m, 1H), 2.57 (s, 1H), 2.47 (d, J = 2.4 Hz, 3H), 2.15 – 2.04 (m, 1H), 2.03 – 1.94 (m, 1H), 1.90 (d, J = 13.3 Hz, 1H), 1.86 – 1.74 (m, 3H), 1.74 – 1.49 (m, 6H), 1.44 (d, J = 6.2 Hz, 3H).	677
217	^{1}H NMR (400 MHz, DMSO-d6, ppm) δ 6.84 (s, 2H), 6.23 (s, 1H), 5.09 (m, 1H), 4.55 (m, 1H), 4.14 – 4.08 (d, J = 10.5 Hz, 1H), 3.97 (d, J = 8.8 Hz, 1H), 3.58 (s, 1H), 3.45 (d, J = 6.1 Hz, 1H), 3.16 – 3.06 (m, 1H), 3.03 (d, J = 12.6 Hz, 3H), 2.72 (m, 1H), 2.50 – 2.42 (m, 4H), 2.42 – 2.27 (m, 2H), 2.06 – 1.99 (m, 1H), 1.96 – 1.85 (m, 1H), 1.79 (m, 3H), 1.65 (s, 2H), 1.60 – 1.51 (m, 1H), 1.44 (d, J = 6.3 Hz, 3H).	651

[2296] **Example 218**: Compound 218



[2297] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-12-((1-(((2R,6S)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

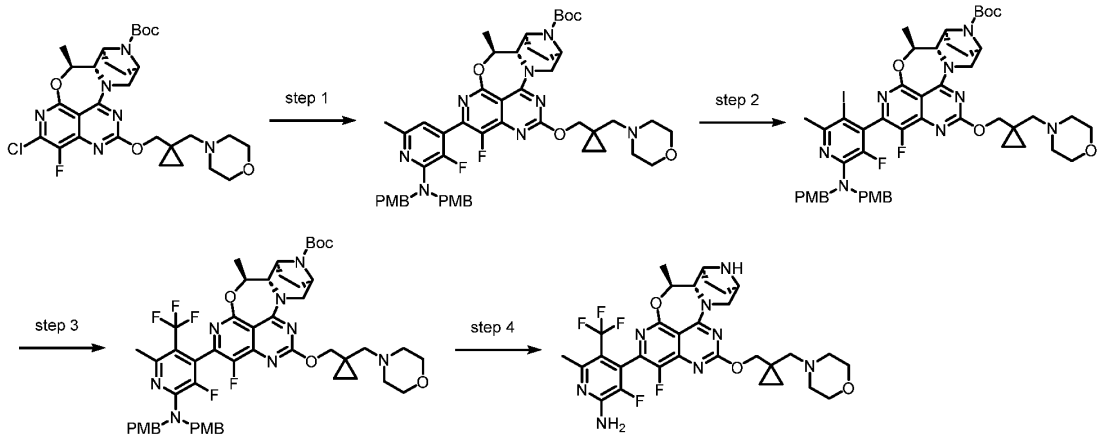
[2298] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-((1-(hydroxymethyl)cyclopropyl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (250 mg, 0.274

mmol, intermediate 150) in DCM (3.00 mL) was added NMO (64.0 mg, 0.548 mmol) in DCM (1.00 mL) and TPAP (48.0 mg, 0.550 mmol) in DCM (1.00mL) at 0 °C The resulting solution was stirred for 1 h at room temperature. After filtration, to the filtrate was added (2*R*,6*S*)-2,6-dimethylmorpholine (472 mg, 4.10 mmol) and NaOAc (336 mg, 4.10 mmol) at room temperature, and the mixture was stirred for 30 min. Then $NaBH_3CN$ (257 mg, 4.10 mmol) was added and the solution was stirred overnight. The resulting solution was quenched with water and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-100% MeOH in water (0.05% NH_4HCO_3)) to afford 144 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1013.

[2299] Step 2: 4-((5*S*,5a*S*,6*S*,9*R*)-12-((1-(((2*R*,6*S*)-2,6-Dimethylmorpholino)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[2300] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl) amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-12-((1-(((2*R*,6*S*)-2,6-dimethylmorpholino)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (63.4 mg, 0.0626 mmol) in TFA (0.300 mL) was stirred for overnight at room temperature. The solvent was evaporated under vacuum. The residue was purified by C18 column (solvent gradient: 0-100% ACN in water (0.05% NH_4HCO_3)) to yield 2.6 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 673. ^1H NMR (300 MHz, DMSO-d_6, ppm): δ 6.84 (s, 2H), 6.23 (s, 1H), 5.09 (d, *J* = 12.3 Hz, 1H), 4.60 – 4.44 (m, 1H), 4.27 (q, *J* = 10.9 Hz, 2H), 3.95 (d, *J* = 8.8 Hz, 1H), 3.60 – 3.38 (m, 5H), 3.01 (d, J = 12.7 Hz, 1H), 2.87 – 2.69 (m, 3H), 2.49 – 2.44 (m, 3H), 2.27 (s, 2H), 1.81 (s, 1H), 1.63 (s, 1H), 1.55 (t, *J* = 10.7 Hz, 2H), 1.44 (d, *J* = 6.3 Hz, 3H), 1.24 (s, 1H), 1.02 (d, *J* = 6.2 Hz, 5H), 0.64 (d, *J* = 4.5 Hz, 2H), 0.41 (d, *J* = 5.2 Hz, 2H).

[2301] **Example 219**: Compound 219



[2302] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-6-methylpyridin-4-yl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2303] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (150 mg, 0.263 mmol, from Compound 210), 3-fluoro-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (245 mg, 0.500 mmol), cataCXium A Pd G3 (36.1 mg, 0.0500 mmol) and K_3PO_4 (0.5 mL, 1.5 M in water) in THF (2.5 mL) was stirred at 60 °C for 2 h. The resulting solution was partitioned between water and EtOAc. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-100% ACN in water (0.05% NH_4HCO_3)) to afford 159 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 935$.

[2304] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-5-iodo-6-methylpyridin-4-yl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2305] Under nitrogen, to a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-3-fluoro-6-methylpyridin-4-yl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (147 mg, 0.157 mmol) in AcOH (1.5 mL) was added NIS (38.9 mg, 0.170 mmol) and the solution was stirred at room temperature for 30 min. The resulting solution was quenched by $Na_2S_2O_3$ aqueous and extracted with EtOAc.

The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0%-10% MeOH / DCM) to afford 142 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1061.

[2306] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-4-yl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2307] Under nitrogen, to a mixture of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-3-fluoro-5-iodo-6-methylpyridin-4-yl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl) cyclopropyl) methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (130.1 mg, 0.123 mmol), $Cu(O_2CCF_2SO_2F)_2$ (511 mg, 1.23 mmol) and Cu powder (78.5 mg, 1.23 mmol) was added DMF (3 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. The resulting reaction was diluted with EtOAc, washed with water. The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-90% MeOH in water (0.05% NH_4HCO_3)) to afford 116 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1003.

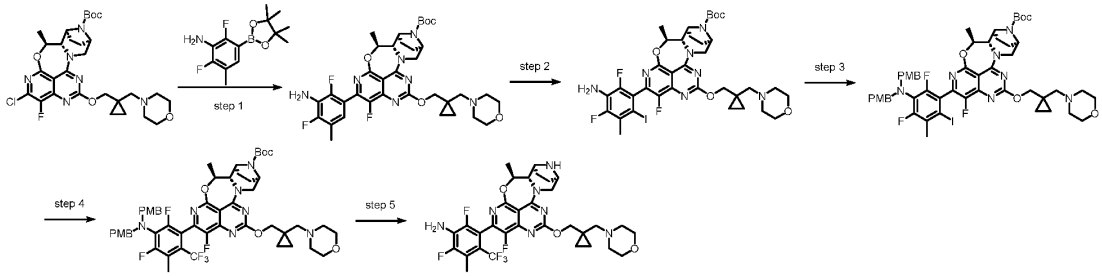
[2308] Step 4: 3-Fluoro-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[2309] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-4-yl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (115 mg, 0.115 mmol) in TFA (6 mL) was stirred at 50 °C for 4 h. Then the solution was concentrated under vacuum. The crude product was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 45% B in 9 min, 45% B; Wave Length: 254/220 nm; R_{T1}(min): 8.8) to afford 27.8 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 663. ^1H NMR (400 MHz, DMSO-d_6, ppm): δ 7.31 – 7.01 (m, 2H), 5.15 – 4.97 (m, 1H), 4.64 – 4.43 (m, 1H), 4.39 – 4.13 (m, 2H), 3.95 (t, J = 8.2 Hz, 1H), 3.62 – 3.39 (m, 6H), 3.01 (d, J = 12.8 Hz, 1H), 2.82 (s, 1H), 2.47 – 2.41 (m, 3H), 2.36 (s, 4H), 2.29 (s, 2H), 1.89 – 1.72 (m, 1H), 1.71 – 1.48 (m, 3H), 1.42 (d, J = 6.2 Hz, 3H), 0.69 – 0.57 (m, 2H), 0.45 – 0.35 (m, 2H).

[2310] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 219**.

Cmpd. No.	^{1}H NMR	MS (M+H)$^+$
220	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.32 – 7.08 (m, 2H), 5.17 – 4.98 (m, 1H), 4.66 – 4.47 (m, 1H), 4.44 – 4.24 (m, 2H), 4.03 – 3.88 (m, 1H), 3.61 – 3.40 (m, 3H), 3.21 (d, J = 8.7 Hz, 1H), 3.15 – 2.97 (m, 3H), 2.73 – 2.52 (m, 1H), 2.47 – 2.24 (m, 6H), 1.71 (m, 4H), 1.92 – 1.48 (d, J = 6.3 Hz, 3H).	655
221	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.19 (d, J = 11.4 Hz, 2H), 5.07 (d, J = 13.2 Hz, 1H), 4.69 – 4.44 (m, 1H), 4.27 – 4.06 (m, 2H), 3.95 (t, J = 8.2 Hz, 1H), 3.50 (d, J = 40.1 Hz, 2H), 3.16 – 2.92 (m, 3H), 2.82 (s, 1H), 2.70 (d, J = 11.8 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.47 – 2.39 (m, 3H), 2.12 – 1.89 (m, 3H), 1.87 – 1.45 (m, 9H), 1.42 (d, J = 6.2 Hz, 3H).	695
222	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 7.32 – 7.02 (m, 2H), 5.07 (d, J = 12.4 Hz, 1H), 4.65 – 4.42 (m, 1H), 4.39 – 4.12 (m, 3H), 4.02 – 3.87 (m, 1H), 3.76 (d, J = 7.6 Hz, 1H), 3.59 – 3.49 (m, 1H), 3.50 – 3.33 (m, 3H), 3.01 (d, J = 13.1 Hz, 1H), 2.83 (d, J = 9.7 Hz, 1H), 2.74 – 2.58 (m, 1H), 2.47 – 2.22 (m, 5H), 1.85 – 1.71 (m, 1H), 1.70 – 1.58 (m, 3H), 1.55 – 1.46 (m, 2H), 1.42 (d, J = 6.3 Hz, 3H), 0.62 – 0.34 (m, 4H).	675
223	^{1}H NMR (300 MHz, DMSO-*d6,* ppm) δ 7.33 – 7.07 (m, 2H), 5.18 – 5.00 (m, 1H), 4.67 – 4.49 (m, 1H), 4.40 – 4.18 (m, 3H), 3.97 (t, J = 8.1 Hz, 1H), 3.78 (d, J = 7.4 Hz, 1H), 3.64 – 3.54 (m, 1H), 3.54 – 3.39 (m, 4H), 3.04 (d, J = 12.9 Hz, 1H), 2.85 (d, J = 9.7 Hz, 1H), 2.70 – 2.56 (m, 2H), 2.49 – 2.30 (m, 4H), 1.90 – 1.75 (m, 1H), 1.75 – 1.59 (m, 3H), 1.59 – 1.49 (m, 2H), 1.44 (d, J = 6.3 Hz, 3H), 0.66 – 0.53 (m, 2H), 0.53 – 0.37 (m, 2H).	675

[2311] **Example 224:** Compound 224



[2312] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-5-methylphenyl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2313] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (300 mg, 0.496 mmol, from Compound 210), 2,6-difluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (266.8 mg, 0.990 mmol), K_3PO_4 (1.5M in H_2O, 2 mL, 0.600 mmol) and cataCXium A Pd G3 (72.2 mg, 0.100 mmol) in tetrahydrofuran (10 mL) was stirred for 3 hours at 60 °C. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer

was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-60% ethyl acetate in petroleum ether) to afford the title compound (250 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 712.

[2314] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2315] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-5-methylphenyl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl) cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (250 mg, 0.352 mmol) in acetic acid (10 mL) was added NIS (94.8 mg, 0.420 mmol) at room temperature. The mixture was stirred at room temperature for 1 hour. The reaction was quenched with $Na_2S_2O_3$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (180 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 838.

[2316] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(*bis*(4-methoxybenzyl)amino)-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2317] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (180 mg, 0.215 mmol)] in *N,N*-dimethylformamide (10 mL) was added NaH (60% dispersion in mineral oil, 43.0 mg, 1.08 mmol) at 0 °C, and the mixture was stirred for 30 minutes at room temperature. Then PMBCl (86.5 mg, 0.550 mmol) was added, and the mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl aqueous solution. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (150 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1078.

[2318] Step 4: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2319] Under nitrogen, to a mixture of $Cu(O_2CCF_2SO_2F)_2$ (551 mg, 1.32 mmol) and copper (84.3 mg, 1.32 mmol) was added an ice cooled solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl) amino)-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (142 mg, 0.132 mmol) in DMF (10 mL) at 0 °C, and the mixture was stirred for 1 hour at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (105 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1020.

[2320] Step 5: 2,6-Difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline

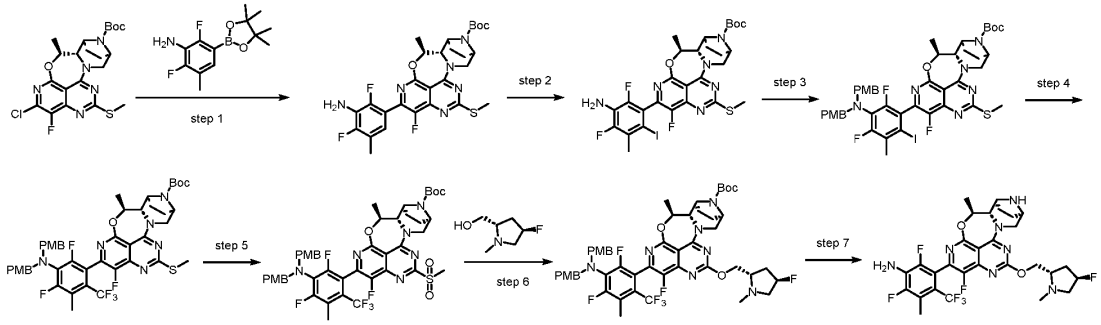
[2321] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-(morpholinomethyl)cyclopropyl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (100 mg, 0.098 mmol) in 2,2,2-trifluoroacetic acid (10 mL) was stirred for 1 hour at room temperature. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 26% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9) to afford the title compound (9.5 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 680. ^{1}H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 6.28 – 6.10 (m, 2H), 5.10 (d, J = 13.3 Hz, 1H), 4.60 – 4.50 (m, 1H), 4.37 – 4.19 (m, 2H), 4.01 – 3.90 (m, 1H), 3.61 – 3.49 (m, 5H), 3.48 – 3.41 (m, 2H), 3.03 (d, J = 12.8 Hz, 1H), 2.90 – 2.75 (m, 1H), 2.42 – 2.32 (m, 5H), 2.31 (s, 3H), 1.90 – 1.74 (m, 1H), 1.72 – 1.51 (m, 3H), 1.44 (d, J = 6.3 Hz, 3H), 0.72 – 0.59 (m, 2H), 0.47 – 0.32 (m, 2H).

[2322] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described **for Example 224**.

Cmpd. No.	**^{1}H NMR**	**MS $(M+H)^+$**
225	^{1}H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.18 – 6.14 (m, 1H), 5.16 – 5.12 (m, 1H), 4.67 – 4.62 (m, 1H), 4.22 – 4.04 (m, 3H), 3.81 – 3.62 (m, 2H), 3.19 – 3.03 (m, 3H), 2.77 – 2.72 (m, 1H), 2.38 – 2.31 (m, 4H), 2.10 – 1.46 (m, 15H).	712

226	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.79 (d, J = 8.8 Hz, 1H), 5.97 (d, J = 11.5 Hz, 2H), 5.17 – 4.96 (m, 1H), 4.61 – 4.43 (m, 1H), 4.38 – 4.15 (m, 2H), 3.94 (t, J = 7.9 Hz, 1H), 3.57 – 3.48 (m, 5H), 3.47 – 3.39 (m, 1H), 3.01 (d, J = 13.1 Hz, 1H), 2.43 – 2.23 (m, 9H), 1.89 – 1.72 (m, 1H), 1.71 – 1.47 (m, 3H), 1.42 (d, J = 6.3 Hz, 3H), 0.69 – 0.53 (m, 2H), 0.47 – 0.32 (m, 2H).	662
227	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.81 (d, J = 8.8 Hz, 1H), 5.54-5.38 (m, 1H), 4.66-4.48 (m, 2H), 4.37-4.23 (m, 2H), 4.09-3.91 (m, 3H), 3.82 (s, 1H), 3.73-3.42 (m, 2H), 3.32-3.26 (m, 1H), 3.06-2.97 (m, 1H), 2.84-2.73 (m, 1H), 2.60-2.53 (m, 4H), 2.37-2.24 (m, 2H), 2.19-2.08 (m, 2H), 1.86-1.69 (m, 3H), 1.65-1.52 (m, 3H), 1.54-1.45 (m, 2H), 1.28 (s, 2H).	694

[2323] **Example 228**: Compound 228



[2324] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2325] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (501 mg, 1.04 mmol), 2,6-difluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (280 mg, 1.04 mmol), K_3PO_4 (1.5M in H_2O, 1.1 mL) and cataCXium A Pd G3 (75.7 mg, 0.100 mmol) in tetrahydrofuran (5.5 mL) was stirred for 3 hours at 90 °C. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc in petroleum ether) to afford the title compound (260 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 589.

[2326] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2327] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (260 mg, 0.441 mmol) and TsOH.H_2O (9.2

mg, 0.050 mmol) in N,N-dimethylformamide (3 mL) was added and NIS (130 mg, 0.580 mmol) at room temperature. The solution was stirred for 1 hour at room temperature. The reaction was quenched with saturated $Na_2S_2O_3$ aqueous solution. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (320 mg) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 715$.

[2328] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(*bis*(4-methoxybenzyl)amino)-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2329] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-amino-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*] heptalene-14-carboxylate (320 mg, 0.447 mmol) in N,N-dimethylformamide (5 mL) was added NaH (60% dispersion in mineral oil, 90.0 mg, 2.25 mmol) at 0 °C, and the mixture was stirred for 30 minutes at room temperature. Then PMBCl (175 mg, 1.12 mmol) was added, and the mixture was stirred for 5 hours at room temperature. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc in petroleum ether) to afford the title compound (400 mg) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 955$.

[2330] Step 4: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(*bis*(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2331] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(*bis*(4-methoxybenzyl) amino)-2,4-difluoro-6-iodo-5-methylphenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (370 mg, 0.387 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.25 mL, 1.93 mmol) and CuI (74.0 mg, 0.390 mmol) in *N,N*-dimethylacetamide (5 mL) was stirred for 3 hours at 90°C. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-30% EtOAc in petroleum ether) to afford the title compound (280 mg) as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+ = 897$.

[2332] Step 5: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(*bis*(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-

hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2333] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(*bis*(4-methoxybenzyl) amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (300 mg, 0.334 mmol) in EtOAc (5 mL) was added *m*CPBA (174 mg, 1.01 mmol) at 0 °C in 3 portions, and the mixture was stirred for 3 hours at room temperature. The reaction was quenched with saturated $Na_2S_2O_3$ aqueous solution, diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-60% EtOAc in petroleum ether) to afford the title compound (192 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 929$.

[2334] Step 6: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(*bis*(4-methoxybenzyl)amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2335] To a solution of ((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methanol (21.6 mg, 0.162 mmol) in tetrahydrofuran (2 mL) was added NaH (60% dispersion in mineral oil, 25.9 mg, 0.648 mmol) at 0 °C, and the mixture was stirred for 30 minutes at room temperature. Then *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(*bis*(4-methoxybenzyl) amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (100 mg, 0.108 mmol) was added, and the mixture was stirred for 2 hours at room temperature. The reaction was quenched with saturated NH_4Cl aqueous solution, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-100% EtOAc in petroleum ether) to afford the title compound (100 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 982$.

[2336] Step 7: 2,6-Difluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline

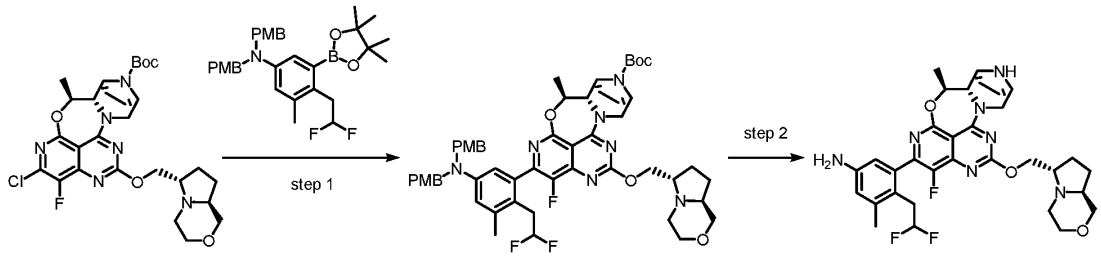
[2337] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(*bis*(4-methoxybenzyl) amino)-2,4-difluoro-5-methyl-6-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*S*,4*R*)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (100 mg, 0.102 mmol) in 2,2,2-trifluoroacetic

acid (10 mL) was stirred for 1 hour at room temperature. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min; Wave Length: 254/220 nm; RT1(min): 8) to afford the title compound (8.9 mg) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 642. ^1H NMR (300 MHz, DMSO-*d6*, ppm) δ 6.56 – 6.11 (m, 2H), 5.38 – 4.70 (m, 2H), 4.49 – 4.25 (m, 1H), 4.25 – 4.10 (m, 1H), 4.09 – 3.87 (m, 1H), 3.84 – 3.61 (m, 1H), 3.59 – 3.34 (m, 4H), 3.06 – 2.70 (m, 2H), 2.42 – 2.35 (m, 3H), 2.32 (s, 3H), 2.26 – 2.00 (m, 2H), 2.00 – 1.89 (m, 1H), 1.89 – 1.75 (m, 1H), 1.75 – 1.50 (m, 2H), 1.39 – 1.13 (m, 3H).

[2338] **Example 229**: Compound **229**, was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 228.**

[2339] **229:** ^1H NMR: (400 MHz, DMSO-*d6,* ppm) δ 6.76 (d, *J* = 86.0 Hz, 1H), 6.18 – 6.15 (m, 2H), 5.09 –5.06 (m, 1H), 4.57 – 4.54 (m, 1H), 4.08 – 3.96 (m, 3H), 3.72 – 3.69 (m, 1H), 3.57 – 3.55 (m, 1H), 3.45 – 3.43 (m, 1H), 3.27 – 3.25 (m, 1H), 3.05 – 2.99 (m, 2H), 2.58 – 2.54 (m, 2H), 2.34 –2.30 (m, 4H), 1.96 – 1.54 (m, 8H), 1.43 (d, *J* = 6.4 Hz, 3H). **MS (M+H)$^+$**: 680

[2340] **Example 230**: Compound 230



[2341] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-2-(2,2-difluoroethyl)-3-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

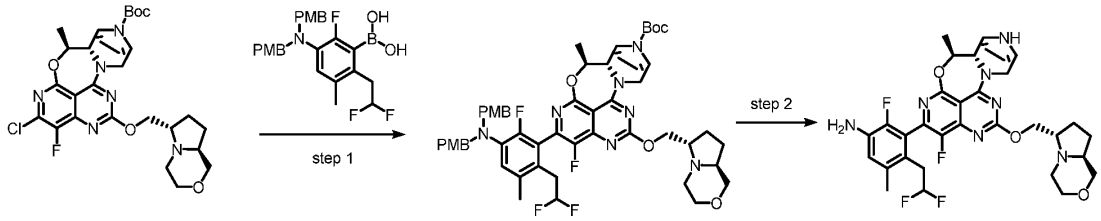
[2342] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (261 mg, 0.440 mmol), 4-(2,2-difluoroethyl)-*N,N*-bis(4-methoxybenzyl)-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (220 mg, 0.372 mmol, intermediate 151), cataCXium A Pd G3 (60.1 mg, 0.0800 mmol) and K_3PO_4 (1 mL, 1.5 M in H2O) in THF (5 mL) was stirred for 3 h at 60°C. The resulting mixture was diluted with EtOAc and washed with water. The organic layer was concentrated under vacuum. The residue was purified by flash

chromatography on silica gel (gradient: 0-15% MeOH / DCM) to afford 315 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 996.

[2343] Step 2: 4-(2,2-Difluoroethyl)-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methylaniline

[2344] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-2-(2,2-difluoroethyl)-3-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (20.1 mg, 0.0208 mmol) in TFA (2 mL) was stirred at room temperature for 1 h. The solvent was concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-90% ACN in water (0.05% NH_4HCO_3)) to afford 9.8 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 626. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.60 – 6.47 (m, 1H), 6.42 (s, 1H), 6.26 – 5.79 (m, 1H), 5.29 – 5.00 (m, 3H), 4.63 – 4.47 (m, 1H), 4.42 (dd, J = 11.0, 5.3 Hz, 1H), 4.14 (dd, J = 10.9, 5.9 Hz, 1H), 3.97 (d, J = 9.0 Hz, 1H), 3.63 (dd, J = 11.0, 3.6 Hz, 1H), 3.59 – 3.48 (m, 3H), 3.45 (t, J = 5.2 Hz, 2H), 3.15 (t, J = 10.5 Hz, 1H), 3.01 (dd, J = 19.2, 9.7 Hz, 4H), 2.95 – 2.80 (m, 3H), 2.25 (s, 3H), 2.14 – 1.97 (m, 1H), 1.90 – 1.71 (m, 2H), 1.70 – 1.50 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H), 1.37 – 1.19 (m, 1H).

[2345] **Example 231**: Compound 231



[2346] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl)amino)-6-(2,2-difluoroethyl)-2-fluoro-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

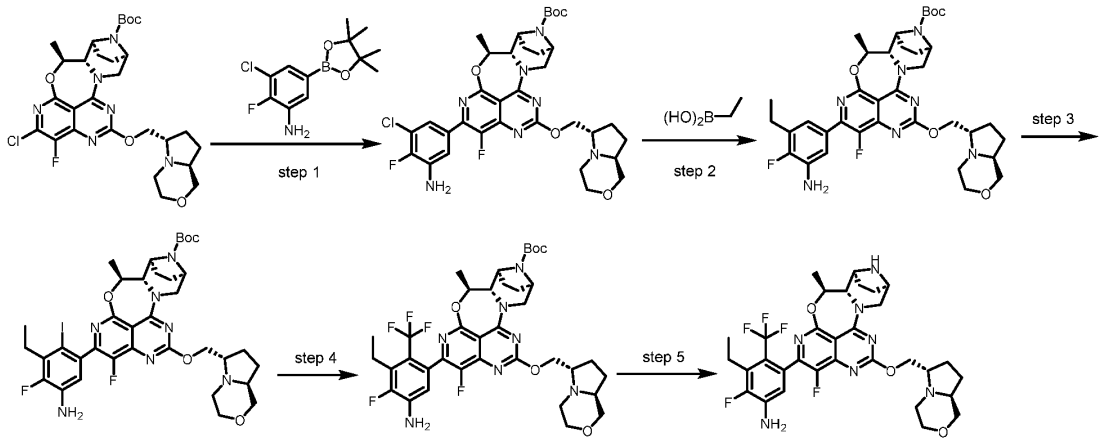
[2347] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (20.2 mg, 0.0342 mmol), (3-(bis(4-methoxybenzyl)amino)-6-(2,2-difluoroethyl)-2-fluoro-5-methylphenyl)boronic acid (120 mg, 0.203 mmol, intermediate 152), cataCXiun A Pd G3 (5.1 mg, 0.00700mmol) and K_3PO_4 (0.3mL, 1.5 M in H_2O) in THF (1.5 mL) was stirred at 60°C for 3 h. The resulting solution was partitioned between water and EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was

purified by flash chromatography on silica gel eluting (gradient: 0-15% MeOH / DCM) to afford 28.0 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 984.

[2348] Step 2: 4-(2,2-Difluoroethyl)-2-fluoro-3-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-methylaniline

[2349] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(3-(bis(4-methoxybenzyl) amino)-6-(2,2-difluoroethyl)-2-fluoro-5-methylphenyl)-1-fluoro-12-(((6*S*,8a*S*)-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (28.0 mg, 0.0285 mmol) in TFA (3 mL) was stirred at room temperature for 1.5 h. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30 x 150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; R_{T1}(min): 9) to afford 4.7 mg of the title compound as a white solid LC-MS: (ESI, *m/z*): $[M+H]^+$ = 644. ^1H NMR (400 MHz, DMSO-d_6) δ 6.74 (d, J = 9.2 Hz, 1H), 6.40 – 5.74 (m, 1H), 5.23 (s, 2H), 5.11 (dd, J = 12.9, 2.6 Hz, 1H), 4.64 – 4.52 (m, 1H), 4.50 – 4.36 (m, 1H), 4.14 (dd, J = 10.9, 5.8 Hz, 1H), 3.98 (d, J = 9.1 Hz, 1H), 3.70 – 3.39 (m, 6H), 3.23 – 2.67 (m, 8H), 2.23 (d, J = 7.5 Hz, 3H), 2.18 – 1.94 (m, 1H), 1.93 – 1.51 (m, 6H), 1.44 (dd, J = 6.4, 2.1 Hz, 3H), 1.39 – 1.25 (m, 1H).

[2350] **Example 232:** Compound 232



[2351] Step 1: *tert*-Butyl (5S,5aS,6S,9R)-2-(3-amino-5-chloro-4-fluorophenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2352] Under nitrogen, a solution of 3-chloro-2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (55.0 mg, 0.200 mmol, intermediate 155), *tert*-butyl (5S,5aS,6S,9R)-2-chloro-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (120 mg, 0.203 mmol), K_3PO_4 (aqueous, 1 mL, 1.5 mmol) and cataCXium A Pd G3 (15.0 mg, 0.020 mmol) in THF (2 mL) was stirred at 60 °C for two hours. The reaction system was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-12% methanol in dichloromethane) to yield 130 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 700.

[2353] Step 2: *tert*-Butyl (5S,5aS,6S,9R)-2-(3-amino-5-ethyl-4-fluorophenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2354] Under nitrogen, a solution of ethylboronic acid (264.0 mg, 3.57 mmol), *tert*-butyl (5S,5aS,6S,9R)-2-(3-amino-5-chloro-4-fluorophenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (500 mg, 0.714 mmol), BI-DIME (47.0 mg, 0.140 mmol), $Pd_2(dba)_3$ (66.0 mg, 0.070 mmol) and K_3PO_4 (1.52 g, 7.14 mmol) in toluene (8 mL) was stirred at 110°C for two hours. The solvent was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-12% methanol in dichloromethane) to yield 537 mg (crude) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 694.

[2355] Step 3: *tert*-Butyl (5S,5aS,6S,9R)-2-(5-amino-3-ethyl-4-fluoro-2-iodophenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2356] A solution of *tert*-butyl (5S,5aS,6S,9R)-2-(3-amino-5-ethyl-4-fluorophenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (119.0 mg, 0.170 mmol) and NIS (42.0 mg, 0.190 mmol) in acetic acid (2 mL) was stirred for two hours at room temperature. The reaction was quenched with $Na_2S_2O_3$, diluted with water and extracted with ethyl acetate. The combined organic layers were concentrated under reduced pressure. The residual was purified by flash chromatography on silica gel (gradient: 0-

15% methanol in dichloromethane) to yield 30 mg of the title compound as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 820.

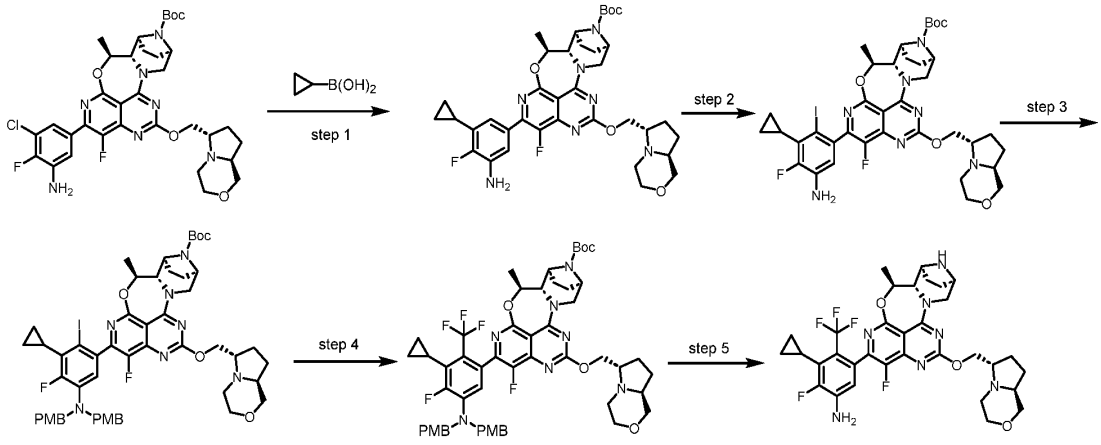
[2357] Step 4: *tert*-Butyl (5S,5aS,6S,9R)-2-(5-amino-3-ethyl-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2358] Under nitrogen, to a solution of 2,2-difluoro-2-(fluorosulfonyl) acetate copper(II) (81.0mg, 0.190 mmol) and Cu (12.0 mg, 0.190 mmol) in N,N-dimethyl formamide (1.5mL) was added tert-butyl (5S,5aS,6S,9R)-2-(5-amino-3-ethyl-4-fluoro-2-iodophenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (30.0 mg, 0.0366 mmol) at -78°C. The reaction was warmed to room temperature and stirred additional 1 h. The solution was loaded on C18 column and eluted with acetonitrile and water containing 0.05%NH_4HCO_3(gradient:0-70% ACN in water) to yield 30 mg of the title compound as brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 762.

[2359] Step 5: 3-Ethyl-2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline

[2360] A solution of tert-butyl (5S,5aS,6S,9R)-2-(5-amino-3-ethyl-4-fluoro-2-(trifluoromethyl) phenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (30.0 mg, 0.0394 mmol) in TFA (3mL) was stirred for 10 minutes at room temperature. The solvent was removed under vacuum. The residual was purified by reverse phase chromatography eluting with acetonitrile and water containing 0.05%NH_4HCO_3 (0-60%) to yield 30 mg crude product. The crude was further purified by prep-HPLC to afford 1 mg of title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 662. ^{1}H-NMR (300 MHz, DMSO-d6) δ : 6.69 – 6.39 (m, 1H), 6.01 (s, 2H), 5.06 (d, J = 12.9 Hz, 1H), 4.58 – 4.42 (m, 1H), 4.43 – 4.31 (m, 1H), 4.17 – 4.04 (m, 1H), 3.93 (d, J = 8.9 Hz, 1H), 3.71 – 3.63 (m, 2H), 3.64 – 3.59 (m, 2H), 3.59 – 3.55 (m, 1H), 3.55 – 3.50 (m, 1H), 3.50 – 3.45 (m, 1H), 3.13 (t, J = 10.4 Hz, 1H), 3.07 – 2.88 (m, 2H), 2.89 – 2.79 (m, 2H), 2.79 – 2.66 (m, 2H), 2.16 – 1.94 (m, 2H), 1.87 – 1.69 (m, 2H), 1.68 – 1.49 (m, 4H), 1.48 – 1.37 (m, 3H), 1.19 – 1.17 (m, 3H).

[2361] **Example 233:** Compound 233



[2362] Step 1: *tert*-Butyl (5S,5aS,6S,9R)-2-(3-amino-5-cyclopropyl-4-fluorophenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2363] Under nitrogen, a solution of cyclopropylboronic acid (307 mg, 3.57 mmol), tert-butyl (5S,5aS,6S,9R)-2-(3-amino-5-chloro-4-fluorophenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (500 mg, 0.714 mmol, from Example 235, step 1), BI-DIME (47.0 mg, 0.140 mmol), $Pd_2(dba)_3$ (66.0 mg, 0.070 mmol), and K_3PO_4 (1.52 g, 7.14 mmol) in toluene (8 mL) was stirred at 110°C for two hours. The solution was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-15% methanol in dichloromethane) to yield 491 mg (crude) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 706$.

[2364] Step 2: *tert*-Butyl (5S,5aS,6S,9R)-2-(5-amino-3-cyclopropyl-4-fluoro-2-iodophenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2365] A solution of tert-butyl (5S,5aS,6S,9R)-2-(3-amino-5-cyclopropyl-4-fluorophenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (490 mg, 0.694 mmol), NIS (187.7 mg, 0.830 mmol) in acetic acid (2.5 mL) was stirred for two hours at room temperature. The reaction was quenched with $Na_2S_2O_3$, diluted with water and extracted with ethyl acetate. The combined organic layers were concentrated under reduced pressure. The residual was purified by flash chromatography on silica

gel (gradient: 0-9% methanol in dichloromethane) to yield 280 mg crude product as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 832.

[2366] Step 3: *tert*-Butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-cyclopropyl-4-fluoro-2-iodophenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2367] Under nitrogen, to a solution of *tert*-butyl (5S,5aS,6S,9R)-2-(5-amino-3-cyclopropyl-4-fluoro-2-iodophenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (220.4 mg, 0.312 mmol) in N,N-dimethylformamide (8 mL) was added NaH (80.0 mg, 3.33 mmol) at 0 °C. The solution was stirred at 0 °C for 30 min, then PMBCl (230.0 mg, 1.47mmol) was added. The solution was stirred additional 1h at room temperature. The reaction was quenched with ice water, extracted with ethyl acetate. The concentrated organic layers were concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0-9% methanol in dichloromethane) to yield 230 mg crude product as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1072.

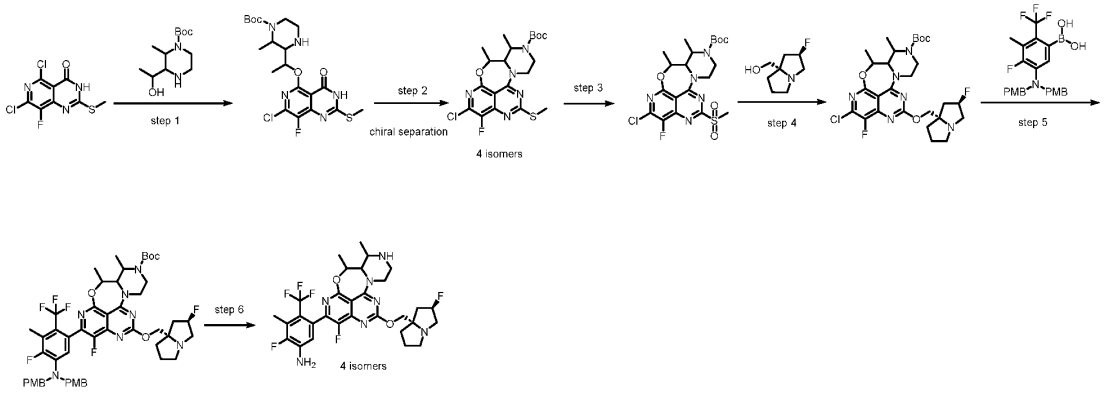
[2368] Step 4: *tert*-Butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-cyclopropyl-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2369] Under nitrogen, to a solution of 2,2-difluoro-2-(fluorosulfonyl) acetate copper(II) (1.06 g, 2.54 mmol) and Cu (156.8 mg, 2.49 mmol) in *N*, *N*-dimethylformamide (5 mL) was added *tert*-butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl)amino)-3-cyclopropyl-4-fluoro-2-iodophenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (230.0 mg, 0.214 mmol) at -78°C. The reaction was allowed to warm to room temperature and stirred additional 1h. The solution was diluted with water, extracted with EtOAc. The combined organic layers were concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to yield 220 mg crude product as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1014.

[2370] Step 5: 3-Cyclopropyl-2-fluoro-5-((5S,5aS,6S,9R)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-4-(trifluoromethyl)aniline

[2371] A solution of tert-butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl) amino)-3-cyclopropyl-4-fluoro-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((6S,8aS)-hexahydro-1H-pyrrolo[2,1-c][1,4]oxazin-6-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (220.0 mg, 0.217 mmol) in 2,2,2-trifluoroacetic acid (5 mL) was stirred for one hour at room temperature. The reaction was concentrated under reduced pressure. The residual was purified by prep-HPLC to yield 10.3 mg product as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 674. ^{1}H-NMR (300 MHz, DMSO-d6) δ: 6.11 (s, 1H), 5.70 (s, 2H), 5.07 (dd, J = 12.8, 2.5 Hz, 1H), 4.49 (s, 1H), 4.39 (dd, J = 10.9, 5.4 Hz, 1H), 4.12 (dd, J = 10.9, 5.9 Hz, 1H), 3.94 (d, J = 8.7 Hz, 1H), 3.62 (dd, J = 10.9, 3.5 Hz, 1H), 3.58 – 3.47 (m, 3H), 3.47 – 3.38 (m, 1H), 3.14 (t, J = 10.3 Hz, 1H), 3.07 – 2.76 (m, 5H), 2.23 – 1.94 (m, 2H), 1.91 – 1.50 (m, 6H), 1.43 (d, J = 6.3 Hz, 3H), 1.39 – 1.15 (m, 2H), 1.01 (d, J = 8.4 Hz, 2H), 0.73 (s, 2H).

[2372] **Example 234:** Compound 234 (four isomers)



[2373] Step 1: *tert*-Butyl 3-(1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-2-methylpiperazine-1-carboxylate

[2374] To a solution of *tert*-butyl 3-(1-hydroxyethyl)-2-methylpiperazine-1-carboxylate (1.30 g, crude, intermediate 156) in tetrahydrofuran (50 mL) was added NaH (60% dispersion in mineral oil, 1.28 g, 32.0 mmol) in 3 portions at 0°C, and the mixture was stirred for 30 minutes at room temperature. Then 5,7-dichloro-8-fluoro-2-methylsulfanyl-3*H*-pyrido[4,3-d]pyrimidin-4-one (2.24 g, 8.00 mmol) was added at room temperature, and the mixture was stirred for 2 hours. The reaction was quenched with saturated NH_4Cl aqueous solution. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum to afford the title compound (1.65 g, crude) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 488.

[2375] Step 2: *tert*-Butyl 2-chloro-1-fluoro-5,6-dimethyl-11-(methylthio)-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-*de*]naphthalene-7(5*H*)-carboxylate (four isomers)

[2376] To a mixture of *tert*-butyl 3-(1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-2-methylpiperazine-1-carboxylate (1.65 g, crude) and DIPEA (9.00 mL, 54.5 mmol) in dichloromethane (150 mL) was added BOPCl (3.44 g, 13.5 mmol) at room temperature, and the mixture was stirred overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-50% ethyl acetate in petroleum ether) to afford 130 mg of the faster peak (mixture of **isomer 1** and **isomer 2**) and 700 mg of the slower peak (mixture of **isomer 3** and **isomer 4**) as yellow solids. **Isomer 1** and **isomer 2** was separated by Chiral-Prep-HPLC with the following conditions: (Column: CHIRALPAK IG, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 20% B to 20% B in 21 min; Wave Length: 220/254 nm; RT1(min): 10.91; RT2(min): 15.006; Sample Solvent: EtOH--HPLC; Injection Volume: 0.8 mL; Number Of Runs: 9) to afford **isomer 1** (50.0 mg, the faster peak) and **isomer 2** (50.0 mg, the slower peak) as white solids. **Isomer 3** and **isomer 4** was separated by Chiral-Prep-HPLC with the following conditions: (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex(0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: 15% B to 15% B in 16 min; Wave Length: 220/254 nm; RT1(min): 9.282; RT2(min): 10.762; Sample Solvent: EtOH--HPLC; Injection Volume: 0.3 mL; Number Of Runs: 54) to afford **isomer 3** (230 mg, the faster peak) and **isomer 4** (150 mg, the slower peak) as white solids.

[2377] **Isomer 1**: LC-MS: (ESI, *m/z*): $[M+H]^+$ = 470. ^{1}H NMR (300 MHz, $CDCl_3$, *ppm*) δ 5.39 – 5.14 (m, 1H), 4.93 – 4.52 (m, 2H), 4.17 – 3.87 (m, 1H), 3.85 – 3.61 (m, 1H), 3.21 – 2.88 (m, 2H), 2.61 (s, 3H), 1.75 – 1.59 (m, 3H), 1.50 (d, J = 4.9 Hz, 9H), 1.24 (d, J = 6.4 Hz, 3H).

[2378] **Isomer 2**: LC-MS: (ESI, *m/z*): $[M+H]^+$ = 470. ^{1}H NMR (300 MHz, $CDCl_3$, *ppm*) 5.44 – 5.11 (m, 1H), 4.95 – 4.48 (m, 2H), 4.21 – 3.90 (m, 1H), 3.86 – 3.58 (m, 1H), 3.04 (s, 2H), 2.61 (s, 3H), 1.72 – 1.57 (m, 3H), 1.50 (s, 9H), 1.25 (d, J = 6.4 Hz, 3H).

[2379] **Isomer 3**: LC-MS: (ESI, *m/z*): $[M+H]^+$ = 470.^{1} H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 5.19 – 5.00 (m, 1H), 4.90 – 4.76 (m, 1H), 4.68 – 4.46 (m, 1H), 4.09 – 3.98 (m, 1H), 3.98 – 3.76 (m, 1H), 3.16 – 2.90 (m, 2H), 2.54 (s, 3H), 1.48 (d, J = 6.6 Hz, 3H), 1.42 (s, 9H), 1.16 – 1.02 (m, 3H).

[2380] **Isomer 4**: LC-MS: (ESI, *m/z*): $[M+H]^+$ = 470. ^{1}H NMR (300 MHz, DMSO-*d6*, *ppm*) δ 5.21 – 5.01 (m, 1H), 4.93 – 4.76 (m, 1H), 4.70 – 4.44 (m, 1H), 4.09 – 3.97 (m, 1H), 3.97 – 3.75

(m, 1H), 3.17 – 2.88 (m, 2H), 2.54 (s, 3H), 1.48 (d, J = 6.6 Hz, 3H), 1.42 (s, 9H), 1.18 – 0.99 (m, 3H).

[2381] Step 3: *tert*-Butyl 2-chloro-1-fluoro-5,6-dimethyl-11-(methylsulfonyl)-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo [4,5] cyclohepta[1,2,3-*de*] naphthalene-7(5*H*)-carboxylate (four isomers)

[2382] To a solution of *tert*-butyl 2-chloro-1-fluoro-5,6-dimethyl-11-(methylthio)-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-*de*]naphthalene-7(5*H*)-carboxylate (50.0 mg, 0.106 mmol, **isomer 1 of last step**) in ethyl acetate (3 mL) was added *m*CPBA (85% purity, 64.6 mg, 0.318 mmol) at 0 °C, and the mixture was stirred for 3 hours at room temperature. The reaction was quenched with saturated $Na_2S_2O_3$ solution, diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with (gradient: 0-60% ethyl acetate in petroleum ether) to afford the title compound (52.0 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 503.

[2383] Analogous to method described as above, another 3 isomers were prepared with the corresponding isomers of last step.

[2384] Step 4: *tert*-Butyl 2-chloro-1-fluoro-11-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methoxy)-5,6-dimethyl-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-*de*]naphthalene-7(5*H*)-carboxylate (four isomers)

[2385] To a solution of ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methanol (32.9 mg, 0.207 mmol) in tetrahydrofuran (2 mL) was added NaH (60% dispersion in mineral oil, 24.7 mg, 0.618 mmol) at 0 °C and stirred for 30 minutes at room temperature. Then *tert*-butyl 2-chloro-1-fluoro-5,6-dimethyl-11-(methylsulfonyl)-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-*de*]naphthalene-7(5*H*)-carboxylate (52.0 mg, 0.103 mmol, **the first isomer of last step**) was added at room temperature and stirred for 2 hours. The reaction was quenched with NH_4Cl solution. The resulting solution was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (55.0 mg) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 581.

[2386] Analogous to method described as above, another 3 isomers were prepared with the corresponding isomers of last step.

[2387] Step 5: *tert*-Butyl 2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-11-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-

yl)methoxy)-5,6-dimethyl-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-*de*]naphthalene-7(5*H*)-carboxylate (four isomers)

[2388] Under nitrogen, a solution of *tert*-butyl 2-chloro-1-fluoro-11-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6-dimethyl-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-*de*]naphthalene-7(5*H*)-carboxylate (55.0 mg, 0.0947 mmol, **the first isomer of last step**), (5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (90.8 mg, 0.190 mmol), K_3PO_4 (1.5M aqueous solution, 0.3 mL, 0.450 mmol) and cataCXium A Pd G3 (13.8 mg, 0.0189 mmol) in tetrahydrofuran (1.5 mL) was stirred for 3 hours at 60 °C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (35.0 mg) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 978.

[2389] Analogous to the method described above, another 3 isomers were prepared with the corresponding isomers of last step.

[2390] Step 6: 2-Fluoro-5-(1-fluoro-11-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6-dimethyl-5,5a,6,7,8,9-hexahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-*de*]naphthalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (four isomers)

[2391] A solution of *tert*-butyl 2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-11-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5,6-dimethyl-5a,6,8,9-tetrahydro-4-oxa-3,7,9a,10,12-pentaazabenzo[4,5]cyclohepta[1,2,3-*de*]naphthalene-7(5*H*)-carboxylate (35.0 mg, 0.0358 mmol, **the first isomer of last step**) in TFA (10 mL) was stirred for 1 hour at room temperature. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 15% B to 45% B in 9 min, 45% B; Wave Length: 254/220 nm; RT1(min): 8.6) to afford **234 (isomer 1)** (2.0 mg) as a white solid.

[2392] Analogous to method described as above, another 3 isomers were prepared with the corresponding isomers of the last step.

[2393] **234 (isomer 1):** LC-MS: (ESI, *m/z*): $[M+H]^+$ = 638. ^1H NMR (300 MHz, DMSO-*d6*, ppm) δ 6.72 – 6.44 (m, 1H), 6.01 (s, 2H), 5.28 (d, J = 54.3 Hz, 1H), 5.04 (d, J = 12.2 Hz, 1H), 4.80 – 4.70 (m, 1H), 4.15 – 3.95 (m, 3H), 3.60 – 3.49 (m, 1H), 3.20 – 2.91 (m, 4H), 2.90 – 2.71

(m, 3H), 2.31 (s, 3H), 2.19 – 2.12 (m, 1H), 2.10 – 1.94 (m, 2H), 1.92 – 1.70 (m, 2H), 1.46 (d, J = 6.6 Hz, 3H), 1.27 – 1.22 (m, 1H), 1.13 (d, J = 6.6 Hz, 3H).

[2394] **234 (isomer 2):** LC-MS: (ESI, *m/z*): $[M+H]^+$ = 638. ^{1}H NMR (300 MHz, DMSO-*d6*, ppm) δ 6.70 – 6.43 (m, 1H), 6.01 (s, 2H), 5.28 (d, J = 54.3 Hz, 1H), 5.03 (d, J = 12.2 Hz, 1H), 4.79 – 4.68 (m, 1H), 4.11 (d, J = 10.3 Hz, 1H), 4.04 – 3.93 (m, 2H), 3.58 – 3.46 (m, 1H), 3.19 – 2.98 (m, 4H), 2.98 – 2.69 (m, 3H), 2.32 (s, 3H), 2.21 – 2.12 (m, 1H), 2.07 – 1.93 (m, 2H), 1.92 – 1.69 (m, 2H), 1.46 (d, J = 6.6 Hz, 3H), 1.28 – 1.22 (m, 1H), 1.12 (d, J = 6.6 Hz, 3H).

[2395] **234 (isomer 3):** LC-MS: (ESI, *m/z*): $[M+H]^+$ = 638. ^{1}H NMR (300 MHz, DMSO-*d6*, ppm) δ 6.66 – 6.46 (m, 1H), 5.99 (s, 2H), 5.46 – 4.77 (m, 2H), 4.77 – 4.62 (m, 1H), 4.14 – 3.93 (m, 2H), 3.54 (d, J = 9.0 Hz, 1H), 3.16 – 2.74 (m, 7H), 2.71 – 2.57 (m, 1H), 2.51 – 2.50 (m, 1H), 2.31 (s, 3H), 2.15 – 2.07 (m, 1H), 2.07 – 1.90 (m, 2H), 1.89 – 1.66 (m, 3H), 1.61 – 1.40 (m, 3H), 1.19 (d, J = 6.2 Hz, 3H).

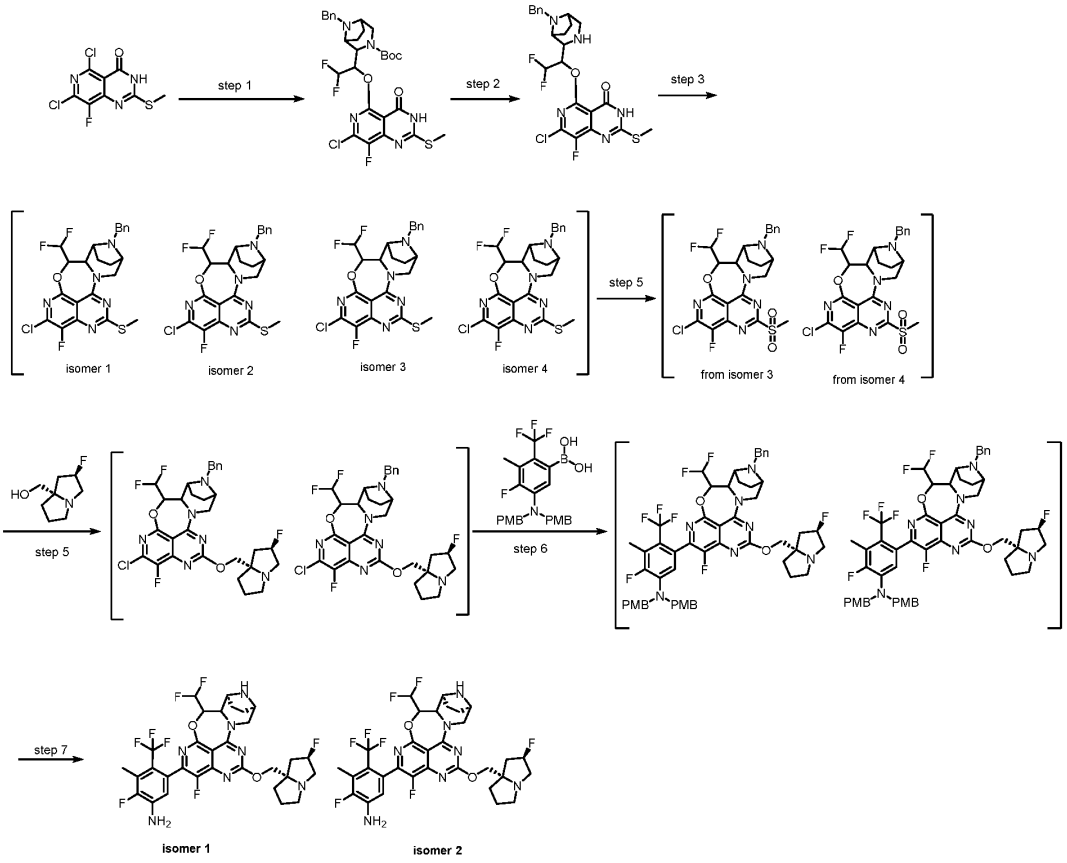
[2396] **234 (isomer 4):** LC-MS: (ESI, *m/z*): $[M+H]^+$ = 638. ^{1}H NMR (300 MHz, DMSO-*d6*, ppm) δ 6.70 – 6.41 (m, 1H), 6.01 (s, 2H), 5.49 – 4.83 (m, 2H), 4.78 – 4.62 (m, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.98 (d, J = 10.4 Hz, 1H), 3.56 (d, J = 9.0 Hz, 1H), 3.18 – 2.76 (m, 7H), 2.70 – 2.52 (m, 2H), 2.34 (s, 3H), 2.21 – 2.11 (m, 1H), 2.10 – 1.92 (m, 2H), 1.92 – 1.66 (m, 3H), 1.60 – 1.39 (m, 3H), 1.21 (d, J = 6.2 Hz, 3H).

[2397] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 234**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
235 (isomer 1)	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.54 (d, J = 30.2 Hz, 1H), 5.98 (s, 2H), 5.26 (d, J = 54.3 Hz, 1H), 5.02 (d, J = 12.8 Hz, 1H), 4.80 – 4.67 (m, 1H), 4.11 (d, J = 10.4 Hz, 1H), 3.97 (d, J = 10.4 Hz, 1H), 3.81 (d, J = 10.2 Hz, 1H), 3.23 (s, 1H), 3.17 – 2.90 (m, 5H), 2.89 – 2.57 (m, 3H), 2.35 – 2.27 (m, 3H), 2.16 – 2.08 (d, J = 4.7 Hz, 1H), 2.06 – 1.92 (m, 2H), 1.87 – 1.71 (m, 3H), 1.42 (d, J = 6.6 Hz, 3H).	624
235 (isomer 2)	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.56 (s, 1H), 5.98 (s, 2H), 5.27 (d, J = 54.2 Hz, 1H), 4.90 (s, 1H), 4.59 – 4.41 (m, 1H), 4.11 (d, J = 10.4 Hz, 1H), 3.99 (d, J = 10.4 Hz, 1H), 3.87 (t, J = 9.3 Hz, 1H), 3.17 – 2.92 (m, 6H), 2.89 – 2.74 (m, 2H), 2.54 (s, 1H), 2.35 – 2.27 (m, 3H), 2.17 – 1.92 (m, 3H), 1.90 – 1.67 (m, 3H), 1.35 (d, J = 6.4 Hz, 3H).	624
236	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.57 (s, 1H), 6.01 (s, 2H), 5.38 (s, 1H), 5.27 – 5.20 (m, 1H), 4.61 – 4.55 (m, 1H), 4.44 (d, *J* = 13.1 Hz, 1H), 4.16 (d, *J* = 10.4 Hz, 1H), 4.08 (d, *J* = 4.4 Hz, 1H), 4.00 (d, *J* = 10.4 Hz, 1H), 3.32 – 3.18 (m, 2H), 3.18 – 2.92 (m, 5H), 2.87 – 2.79 (m, 1H), 2.32 (s, 3H), 2.24 – 2.11 (m, 2H), 2.11 – 1.91 (m, 2H), 1.86 – 1.74 (m, 4H), 1.62 – 1.46 (m, 2H), 1.26 (d, *J* = 12.0 Hz, 1H).	650

237 (isomer 1)	^{1}H NMR (400 MHz, DMSO-d6) δ 6.55 (d, J = 50.4 Hz, 1H), 5.98 (s, 2H), 5.44 – 5.14 (m, 1H), 4.97 – 4.52 (m, 1H), 4.28 (d, J = 13.3 Hz, 1H), 4.11 (d, J = 10.3 Hz, 1H), 3.99 (d, J = 10.3 Hz, 1H), 3.85 – 3.63 (m, 3H), 3.41 (dd, J = 13.3, 4.1 Hz, 1H), 3.17 – 3.04 (m, 2H), 3.01 (s, 1H), 2.89 – 2.76 (m, 1H), 2.72 – 2.57 (m, 1H), 2.32 (t, J = 2.6 Hz, 3H), 2.21 – 2.08 (m, 1H), 2.07 – 1.97 (m, 2H), 1.91 – 1.6 (m, 7H), 1.41 (d, J = 6.6 Hz, 3H).	650
237 (isomer 2)	^{1}H NMR (400 MHz, DMSO-d_6) δ 6.55 (d, J = 54.4 Hz, 1H), 6.00 (s, 2H), 5.45 – 5.09 (m, 1H), 4.66 (s, 1H), 4.41 (d, J = 13.1 Hz, 1H), 4.12 (d, J = 10.4 Hz, 1H), 3.98 (d, J = 10.4 Hz, 1H), 3.77 (s, 1H), 3.65 (s, 1H), 3.38 (s, 1H), 3.25 (s, 1H), 3.17 – 3.04 (m, 2H), 3.02 (s, 1H), 2.89 – 2.78 (m, 1H), 2.39 – 2.27 (m, 3H), 2.21 – 2.10 (m, 1H), 2.09 – 1.94 (m, 2H), 1.91 – 1.63 (m, 7H), 1.56 (d, J = 6.4 Hz, 3H).	650

[2398] **Example 238**: Compound 238 (two isomers)



[2399] Step 1: *tert*-Butyl 8-benzyl-2-(1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)-2,2-difluoroethyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate

[2400] Under nitrogen, to a solution of *tert*-butyl (1*R*,5*S*)-8-benzyl-2-(2,2-difluoro-1-hydroxyethyl)-3,8-diazabicyclo [3.2.1] octane-3-carboxylate (4.60 g, 12.0 mmol, intermediate 161) in tetrahydrofuran (50.0 mL) was added NaH (2.89 g, 72.2 mmol, 60% in mineral oil) at 0 °C. The resulting solution was stirred for 30 min at 0 °C. Then 5,7-dichloro-8-fluoro-2-

(methylthio) pyrido[4,3-d] pyrimidin-4(3*H*)-one (4.60 g, 12.0 mmol) was added at 0 °C. The solution was stirred for 3 h at room temperature. The reaction was quenched with NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0-10% MeOH / DCM) to afford 2.90 g of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 626.

[2401] Step 2: 5-(1-(8-Benzyl-3,8-diazabicyclo[3.2.1]octan-2-yl)-2,2-difluoroethoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(*3H*)-one

[2402] To a solution of *tert*-butyl 8-benzyl-2-(1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d] pyrimidin-5-yl)oxy)-2,2-difluoroethyl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (2.90 g, 4.63 mmol) in dichloromethane (60.0 mL) was added TFA (20.0 mL). The resulting solution was stirred for 30 min at room temperature. The solvent was evaporated under vacuum. The residue was dissolved in DCM, washed with aqueous $NaHCO_3$. The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford 2.60 g (crude) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 526.

[2403] Step 3: 14-Benzyl-2-chloro-5-(difluoromethyl)-1-fluoro-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene

[2404] A solution of 5-(1-(8-benzyl-3,8-diazabicyclo[3.2.1]octan-2-yl)-2,2-difluoroethoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(*3H*)-one (2.60 g, 4.94 mmol), bis(2-oxooxazolidin-3-yl)phosphinic chloride (5.04 g, 19.8 mmol) and DIPEA (9.60 g, 74.4 mmol) in 1,2-dichloroethane (30.0 mL) was stirred for 2 h at 60 °C. The solvent was evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0% - 30% EtOAc / petroleum ether) to afford 230 mg of the faster peak and 610 mg of the slower peak as yellow solids. The faster peak was separated by PREP_SFC (Column: Lux 3μ Cellulose-4 4.6*50mm, 3μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH: ACN=1: 1; Flow rate: 100 mL/min; Gradient: isocratic 50% B; Column Temperature (°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 3.42; RT2(min): 4.43; Sample Solvent: MeOH; Injection Volume: 4 mL) to yield 174.0 mg isomer 1 and 92.0 mg isomer 2. The slower peak was separated by PREP_SFC (Column: CHIRALPAK IG 3*25 cm, 5 μm; Mobile Phase A: CO_2, Mobile Phase B: MeOH: ACN=2: 1; Flow rate: 100 mL/min; Gradient: isocratic 40% B; Column Temperature (°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 3.87; RT2(min): 5.27; Sample Solvent: MeOH; Injection Volume: 1.5 mL; Number of Runs: 22) to yield 312 mg isomer 3 and 310 mg isomer 4.

[2405] Step 4: 14-Benzyl-2-chloro-5-(difluoromethyl)-1-fluoro-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene

[2406] To a solution of 14-benzyl-2-chloro-5-(difluoromethyl)-1-fluoro-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene (isomer 3 of last step) (265 mg, 0.522 mmol) in EtOAc (2.00 mL) was added m-CPBA (269 mg, 1.57 mmol) at 0°C. The resulting solution was stirred for 1 h at room temperature. The reaction was quenched with $Na_2O_3S_2$ aqueous and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to afford 501mg (crude) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 540$.

[2407] Analogous to the method described as above, another isomer was prepared with isomer 4 of last step.

[2408] Step 5: 14-Benzyl-2-chloro-5-(difluoromethyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene (two isomers)

[2409] To a solution of 14-benzyl-2-chloro-5-(difluoromethyl)-1-fluoro-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*] heptalene (501 mg, 0.930 mmol) and ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methanol (178 mg, 1.86 mmol) in toluene (5.00 mL) was added t-BuONa (178 mg, 1.86 mmol) at 0 °C. The resulting solution was stirred for 30 min at room temperature. The solvent was concentrated under vacuum at 0°C. The residue was purified by flash chromatography on silica gel eluting (gradient: 0%-20% MeOH / DCM) to afford 225 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 619$.

[2410] Analogous to method described as above, the other isomers were prepared with the corresponding isomers of last step.

[2411] Step 6: 5-(14-Benzyl-5-(difluoromethyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)aniline (two isomers)

[2412] Under nitrogen, a solution of 14-benzyl-2-chloro-5-(difluoromethyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*] heptalene (256 mg, 0.414 mmol), (5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl) boronic acid (493 mg, 1.03 mmol), K_3PO_4 (0.830 mL, 1.5 M in water) and cataCXium A Pd G_3 (60.2 mg, 0.0800

mmol) in THF (4.00 mL) was stirred for 1 h at 60°C. The resulting solution was partitioned between water and EtOAc. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0% -20% MeOH / DCM) to afford 306 mg of the title compound as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1016.

[2413] Analogous to method described as above, the other isomers were prepared with the corresponding isomers of last step.

[2414] Step 7: 5-((6*S*,9*R*)-5-(difluoromethyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline (two isomers)

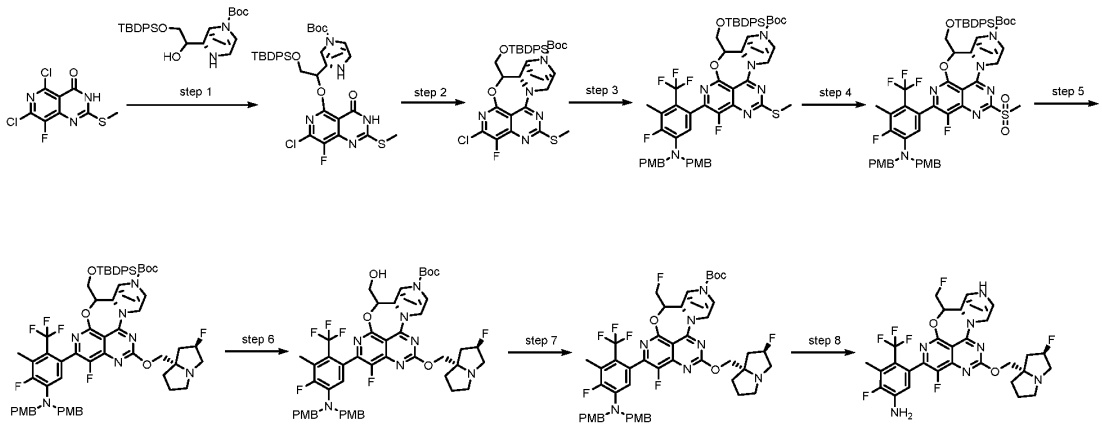
[2415] To a solution of 5-(14-benzyl-5-(difluoromethyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-*N*,*N*-bis(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)aniline (240 mg, 0.236 mmol) in MeOH (30.0 mL) was added 10% Pd/C (240 mg) and HCl (0.300 ml, 12 M in water). The resulting solution was stirred for 1 h at room temperature. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by prep. HPLC (Column: XBridge Prep OBD C18, Column, 30*150 mm: 5μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: CAN; Flow rate: 60 mL/min; Gradient: 39% B to 56% B in 9 min; Wave Length: 254/220 nm; RT1(min): 8.6) to afford 21.2 mg of **238 (isomer 1)** (head piece from isomer 3 of step 3) as a white solid.

[2416] Analogous to method described as above, the other isomer **238 (isomer 2)** (head piece from isomer 4 of step 3) was prepared.

[2417] **238 (isomer 1):** LC-MS: (ESI, *m/z*): $[M+H]^+$ = 686. ^1H NMR (300 MHz, DMSO-d_6) δ 7.06 (t, *J* = 53.2 Hz, 1H), 6.69 – 6.63 (m, 1H), 6.01 (s, 2H), 5.54 – 5.07 (m, 2H), 4.38 (d, *J* = 13.2 Hz, 1H), 4.12 (d, *J* = 10.4 Hz, 1H), 4.07 (s, 1H), 3.98 (d, *J* = 10.4 Hz, 1H), 3.91 (s, 1H), 3.73 (s, 1H), 3.10 (d, *J* = 8.2 Hz, 2H), 3.00 (s, 1H), 2.90 (s, 1H), 2.82 (d, *J* = 6.8 Hz, 1H), 2.37 – 2.31 (m, 3H), 2.14 (d, *J* = 7.8 Hz, 1H), 2.03 (s, 1H), 1.99 (s, 1H), 1.93 – 1.53 (m, 7H).

[2418] **238 (isomer 2)**: LC-MS: (ESI, *m/z*): $[M+H]^+$ = 686. ^1H NMR (300 MHz, Methanol-d_4) δ 7.08 (t, *J* = 53.1 Hz, 1H), 6.80 – 6.47 (m, 1H), 5.31 (d, *J* = 53.9 Hz, 1H), 5.11 (dd, *J* = 20.5, 9.8 Hz, 1H), 4.57 (d, *J* = 13.4 Hz, 1H), 4.26 (d, *J* = 1.7 Hz, 2H), 4.08 (d, *J* = 5.4 Hz, 1H), 3.93 (d, *J* = 6.2 Hz, 1H), 3.81 (s, 1H), 3.50 (d, *J* = 13.4 Hz, 1H), 3.28 – 3.10 (m, 3H), 3.09 – 2.90(m, 1H), 2.55– 2.31 (m, 3H), 2.29-2.19 (m, 3H), 2.13– 1.99 (m, 3H), 1.99– 1.70 (m, 4H).

[2419] **Example 239:** Compound 239



[2420] Step 1: *tert*-Butyl (1*S*,2*S*,5*R*)-2-(2-((tert-butyldiphenylsilyl)oxy)-1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate

[2421] Under nitrogen, to a solution of *tert*-butyl (1*S*,2*S*,5*R*)-2-(2-((tert-butyldiphenylsilyl) oxy)-1-hydroxyethyl)-3,8-diazabicyclo [3.2.1] octane-8-carboxylate (1.56 g, 3.05 mmol, intermediate 159) in tetrahydrofuran (35 mL) was added NaH (60%) (1.03 g, 25.8 mmol) at 0°C. The solution was stirred at room temperature for 0.5 hour. Then 5,7-dichloro-8-fluoro-2-(methylthio) pyrido [4,3-d] pyrimidin-4(3*H*)-one (2.11 g, 7.53 mmol) was added and the solution was stirred at room temperature for 16 hours. The reaction was quenched with aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-7% MeOH / DCM) to afford 1.44 g of the title compound as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 754.

[2422] Step 2: *tert*-Butyl (5a*S*,6*S*,9*R*)-5-(((*tert*-butyldiphenylsilyl) oxy)methyl)-2-chloro-1-fluoro-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2423] A solution of *tert*-butyl (1*S*,2*S*,5*R*)-2-(2-((tert-butyldiphenylsilyl) oxy)-1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (1.44 g, 1.98 mmol), BOPCl (1.11 g, 4.35 mmol) and DIPEA (1.49 g, 11.6 mmol) in dichloromethane (40 mL) was stirred at room temperature for 16 hours. The reaction was quenched with water and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc / petroleum ether) to afford 1.14 g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 736.

[2424] Step 3: *tert*-Butyl (5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-fluoro-12-(methylthio)-

5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2425] Under nitrogen, a solution of *tert*-butyl (5a*S*,6*S*,9*R*)-5-(((*tert*-butyldiphenylsilyl) oxy) methyl)-2-chloro-1-fluoro-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab] heptalene-14-carboxylate (400 mg, 0.543 mmol), (5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (674 mg, 1.41 mmol), cataCxium A Pd G3 (115 mg, 0.160 mmol) and K_3PO_4 (2 mL, 1.5 M in H_2O) in tetrahydrofuran (10 mL) was stirred at 60°C for 3 hours. The solution was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-20% EtOAc / petroleum ether) to afford 497 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1133.

[2426] Step 4: *tert*-Butyl (5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl) amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-fluoro-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2427] Under nitrogen, to a solution of *tert*-butyl (5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl) amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-fluoro-12-(methylthio)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (497 mg, 0.439 mmol) in dichloromethane (8 mL) was added m-CPBA (232 mg, 1.34 mmol) at 0°C. The solution was stirred at room temperature for 1 hour. The reaction was quenched with aqueous $Na_2S_2O_3$ solution, extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-40% EtOAc / petroleum ether) to afford 383 mg of the title compound as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1165.

[2428] Step 5: *tert*-Butyl (5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2429] Under nitrogen, to a solution of ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methanol (95.3 mg, 0.600 mmol) in tetrahydrofuran (8 mL) was added NaH (60%) (76.2 mg, 1.91 mmol) at 0°C and stirred at room temperature for 0.5 hour. Then *tert*-butyl (5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl) amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-fluoro-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-

3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (370 mg, 0.318 mmol) was added. The solution was stirred at room temperature for 2 hours. The reaction was quenched with aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-4% MeOH / DCM) to afford 251 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 1244$.

[2430] Step 6: *tert*-Butyl (5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl) amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-(hydroxymethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2431] To a solution of *tert*-butyl (5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl) amino)-4-fluoro-3-methyl-2-(trifluoromethyl) phenyl)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (250 mg, 0.201 mmol) in tetrahydrofuran (6 mL) was added TBAF (1 M in THF, 1.5 mL) and the solution was stirred at room temperature for 2 hours. Then the reaction was diluted with water, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-5% MeOH / DCM) to afford 170 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 1006$.

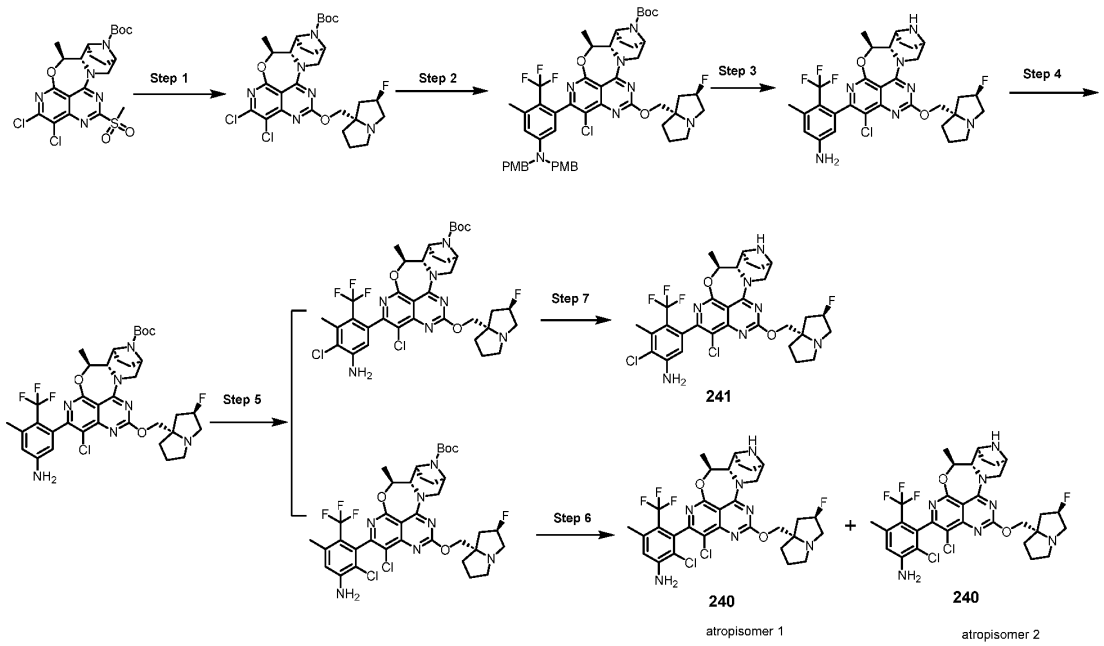
[2432] Step 7: *tert*-Butyl (5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl) amino)-4-fluoro-3-methyl-2-(trifluoromethyl) phenyl)-1-fluoro-5-(fluoromethyl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl) methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab] heptalene-14-carboxylate

[2433] Under nitrogen, to a solution of *tert*-butyl (5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-(hydroxymethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (170 mg, 0.169mmol) in dichloromethane (5 mL) was added DAST (854 mg, 5.30 mmol) at 0°C. The solution was stirred at room temperature for 16 hours. The reaction was quenched with aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-6% MeOH / DCM) to afford 80 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 1008$.

[2434] Step 8: 2-Fluoro-5-((5a*S*,6*S*,9*R*)-1-fluoro-5-(fluoromethyl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline

[2435] A solution of *tert*-butyl (5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-(fluoromethyl)-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (75.1 mg, 0.0745 mmol) in 2,2,2-trifluoroacetic acid (4 mL) was stirred at room temperature for 2 hours. The solution was concentrated under vacuum. The residue was purified by prep-HPLC with the following conditions: (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 36% B to 55% B in 9 min; Wave Length: 254/220 nm; RT1(min): 8.2; Number of Runs:2) to afford 22.6 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 668. ^1H NMR (400 MHz, DMSO-*d6, ppm*) δ 6.56 (d, *J* = 50.4 Hz, 1H), 6.01 (s, 2H), 5.27 (d, *J* = 54.0 Hz, 1H), 5.08 – 4.80 (m, 3H), 4.45 – 4.42 (m, 1H), 4.13 – 4.11 (m, 1H), 3.98 – 3.96 (m, 1H), 3.77 – 3.61 (m, 3H), 3.38 – 3.35 (m, 1H), 3.13 – 3.01 (m, 3H), 2.85 – 2.75 (m, 2H), 2.33 (s, 3H), 2.14 – 1.95 (m, 3H), 1.87 – 1.65 (m, 7H).

[2436] **Examples 240 and 241:** Compounds 240 (two atropisomers) and 241



[2437] Step 1: *tert*-Butyl (5S,5aS,6S,9R)-1,2-dichloro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2438] Under nitrogen, to a solution of ((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl) methanol (225mg, 1.41mmol) in tetrahydrofuran (2 mL) was added 60% NaH (189mg, 4.71mmol) at 0 °C. The resulting solution was stirred at room temperature for 30 min. Then *tert*-butyl rac-(4R,7*S*,8*S*,9*S*)-13,14-dichloro-9-methyl-17-methylsulfonyl-10-oxa-2,12,16,18,20-pentazapentacyclo[9.7.1.14,7.02,8.015,19]icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (500mg, 0.94mmol, intermediate 162) was added. The solution was stirred at 25°C for 2 hours. The reaction mixture was partitioned between saturated aqueous NH_4Cl and EtOAc. The separated organic layer was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% MeOH/DCM) to yield 400 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 609.

[2439] Step 2: *tert*-Butyl (5S,5aS,6S,9R)-2-(5-(bis(4-methoxybenzyl) amino)-3-methyl-2-(trifluoromethyl)phenyl)-1-chloro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2440] Under nitrogen, a solution of *tert*-butyl rac-(4R,7S,8S,9S)-13,14-dichloro-9-methyl-17-[[rac-(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-10-oxa-2,12,16,18,20-pentazapentacyclo[9.7.1.14,7.02,8.015,19]icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (257mg, 0.42mmol), [5-[bis[(4-methoxyphenyl)methyl]amino]-3-methyl-2-(trifluoromethyl)phenyl]boronic acid (490mg, 0.53mmol), cataCxium A Pd G3 (61.4mg, 0.08mmol) and K_3PO_4 (1mL, 1.5 M in H_2O) in tetrahydrofuran (5mL) was stirred at 60°C for 2 hours. The reaction mixture was diluted with water, extracted with EtOAc. The combined organic layers were concentrated under vacuum. The residue was purified by flash chromatography on silica (gradient: 0%-10% MeOH/DCM) to afford 380mg as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 988.

[2441] Step 3: 3-((5S,5aS,6S,9R)-1-Chloro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline

[2442] A solution of *tert*-butyl rac-(4*R*,7*S*,8*S*,9*S*)-13-[5-[bis[(4-methoxyphenyl) methyl]amino]-3-methyl-2-(trifluoromethyl)phenyl]-14-chloro-9-methyl-17-[[rac-(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-10-oxa-2,12,16,18,20-pentazapentacyclo[9.7.1.14,7.02,8.015,19]icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (260mg, 0.30mmol) in TFA (2.5mL) was stirred at 25 °C for 4 hours. The resulting mixture was

concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% MeOH/DCM) to yield 100 mg of the title compound as a yellow liquid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 648.

[2443] Step 4: *tert*-Butyl (5S,5aS,6S,9R)-2-(5-amino-3-methyl-2-(trifluoromethyl)phenyl)-1-chloro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2444] Under nitrogen, to a solution of 3-((5S,5aS,6S,9R)-1-chloro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline (10mg, 0.02mmol) in DCM (5mL) was added DIPEA (9.95mg, 0.08mmol) and $(Boc)_2O$ (6.73mg, 0.03mmol).The resulting mixture was stirred for 2h at room temperature. The solution was diluted with water, extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (gradient: 0%-20% MeOH/DCM) to yield 11 mg of the title compound as a yellow liquid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 748.

[2445] Step 5: *tert*-Butyl (5S,5aS,6S,9R)-2-(3-amino-2-chloro-5-methyl-6-(trifluoromethyl)phenyl)-1-chloro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate **&** *tert*-Butyl (5S,5aS,6S,9R)-2-(5-amino-4-chloro-3-methyl-2-(trifluoromethyl)phenyl)-1-chloro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (two isomers)

[2446] A solution of *tert*-butyl rac-(4*R*,7*S*,8*S*,9*S*)-13-[5-amino-3-methyl-2-(trifluoromethyl) phenyl]-14-chloro-9-methyl-17-[[rac-(2*R*,8*S*)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methoxy]-10-oxa-2,12,16,18,20-pentazapentacyclo [9.7.1.14,7.02,8.015,19]icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (160mg, 0.21mmol) and NCS (34mg, 0.26mmol) in acetic acid (2mL) was stirred at 25 degrees C for 36 hours. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (gradient: 0%-20% MeOH/DCM) to yield 110 mg (**isomer 1**) and 25 mg (**isomer 2**) as yellow solids. LC-MS: (ESI, *m/z*): $[M+H]^+$= 782.

[2447] Step 6: 2-Chloro-3-((5S,5aS,6S,9R)-1-chloro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-5-methyl-4-(trifluoromethyl)aniline (two atropisomers)

[2448] A solution of *tert*-butyl (5S,5aS,6S,9R)-2-(3-amino-2-chloro-5-methyl-6-(trifluoromethyl) phenyl)-1-chloro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (30mg, 0.05mmol) in TFA (3mL) was stirred at 25 °C for 1 hour. The residue was purified by Prep-HPLC ((Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 52% B to 82% B in 7 min, 82% B; Wave Length: 254 nm; RT1(min): 6.5) to afford 2.3 mg **240 (atropisomer 1)** and 3.0 mg **240 (atropisomer 2)** as white solids. LC-MS: (ESI, *m/z*): $[M+H]^+$= 682.

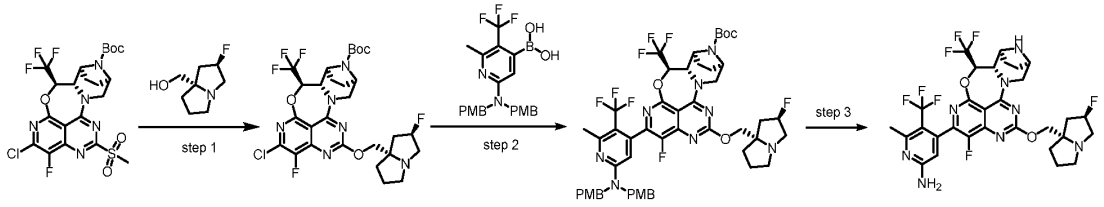
[2449] **240 (atropisomer 1):** ^{1}H NMR (300 MHz, DMSO-*d6,* ppm) δ 6.84 (s, 1H), 6.15 (s, 2H), 5.41 – 4.96 (m, 2H), 4.64 – 4.46 (m, 1H), 4.21 – 3.93 (m, 3H), 3.51 (m, 2H), 3.21 –2.93 (m, 5H), 2.34 (m, 3H), 2.21 – 1.95 (m, 3H), 1.94 – 1.52 (m, 7H), 1.52 – 1.43 (m, 3H).

[2450] **240 (atropisomer 2):** ^{1}H NMR (300 MHz, DMSO-*d6,* ppm) δ 6.84 (s, 1H), 6.16 (s, 2H), 5.45 – 4.97 (m, 2H), 4.64 – 4.40 (m, 1H), 4.25 – 3.90 (m, 3H), 3.53 (m, 2H), 3.24 –2.94 (m, 5H), 2.37 (m, 3H), 2.21 – 1.94 (m, 2H), 1.93 – 1.55 (m, 8H), 1.54 – 1.41 (m, 3H).

[2451] Step 7: 2-Chloro-5-((5S,5aS,6S,9R)-1-chloro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline

[2452] A solution of *tert*-butyl (5S,5aS,6S,9R)-2-(5-amino-4-chloro-3-methyl-2-(trifluoromethyl)phenyl)-1-chloro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (25mg, 0.03mmol) in TFA (3mL) was stirred at 25 °C for 1 hour. The solvent was remove under reduce pressure. The residue was purified by Prep-HPLC ((Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 52% B to 82% B in 7 min, 82% B; Wave Length: 254 nm; RT1(min): 6.5) to afford 3.0 mg of Compound **241** as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$= 682. ^{1}H NMR (300 MHz, DMSO-*d6,* ppm) δ 6.56 (s, 1H), 6.30 (d, J = 41.4 Hz, 2H), 5.42 – 4.99 (m, 3H), 4.70 – 4.50 (m, 1H), 4.22 – 3.90 (m, 2H), 3.62 (d, J = 5.2 Hz, 1H), 3.50 (t, J = 5.5 Hz, 1H), 3.19 – 2.77 (m, 5H), 2.48 – 2.39 (m, 4H), 2.24 – 1.96 (m, 3H), 1.95 – 1.53 (m, 7H), 1.44 (d, J = 6.3 Hz, 3H).

[2453] **Example 242**: Compounds 242



[2454] Step 1: *tert*-Butyl (5R,5aS,6S,9R)-2-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2455] Under nitrogen, a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(methylsulfonyl)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab] heptalene-14-carboxylate (40.0 mg, 0.0704 mmol, **intermediate 165**) and ((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (12.3 mg, 0.0800 mmol) in toluene (1.00 mL) was added t-BuONa (13.5 mg, 0.140 mmol) at 0 °C. The resulting solution was stirred for 20 min at room temperature. The solvent was evaporated under vacuum at 0 °C. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH / DCM) to afford 25.0 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 674.

[2456] Step 2: *tert*-Butyl (5R,5aS,6S,9R)-2-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2457] Under nitrogen, a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (73.0 mg, 0.112 mmol), (6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)boronic acid (104 mg, 0.230 mmol), cataCXium A Pd G_3 (16.4 mg, 0.0200 mmol) and K_3PO_4 (0.230 mL, 1.5 M in water) in tetrahydrofuran (1.10 mL) was stirred for 1 h at 60 °C. Solvent was evaporated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH / DCM) to afford 89.0 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1027.

[2458] Step 3: 4-((5*R*,5a*S*,6*S*,9*R*)-1-Fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

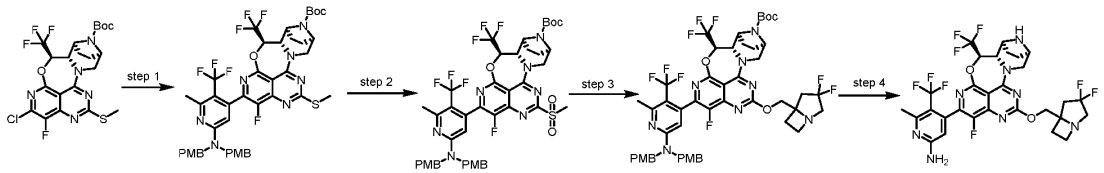
[2459] A solution of *tert*-butyl (5R,5aS,6S,9R)-2-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (85.0 mg, 0.0828 mmol) in 2,2,2-trifluoroacetic acid (1.00 mL) was stirred for 3 h at 50 °C. The solvent was evaporated under vacuum. The residue was purified by prep. HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min, 42% B; Wave Length: 254/220 nm; RT1(min): 8.9) to afford 16.2 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 687. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.88 (s, 2H), 6.22 (s, 1H), 5.66 – 5.61 (m, 1H), 5.38 (s, 1H), 5.20 – 5.13 (m, 1H), 4.39 (d, *J* = 9.6 Hz, 1H), 4.15 – 4.03 (m, 2H), 3.60 – 3.52 (m, 2H), 3.17 – 3.01 (m, 5H), 2.87 – 2.82 (m, 1H), 2.48 (d, *J* = 2.3 Hz, 3H), 2.15 (s, 1H), 2.05 – 1.96 (m, 2H), 1.92 – 1.75 (m, 5H), 1.75 – 1.52 (m, 2H).

[2460] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 242**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
243	^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 6.87 (s, 2H), 6.28 (s, 1H), 5.73 (d, *J* = 7.2 Hz, 1H), 5.28 (d, *J* = 54 Hz, 1H), 4.60 (d, *J* = 2.1 Hz, 1H), 4.25 – 3.99 (m, 3H), 3.67 – 3.53 (m, 2H), 3.28 (s, 1H), 3.16 – 3.00 (m, 4H), 2.84 – 2.82 (m, 1H), 2.48 (d, *J* = 2.3 Hz, 3H), 2.15 (d, *J* = 4.1 Hz, 1H), 2.08 – 1.97 (m, 2H), 1.86 – 1.62 (m, 6H), 1.40 (t, *J* = 9.5 Hz, 1H)	687
244	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.70 – 6.43 (m, 1H), 6.25 – 5.93 (m, 2H), 5.80 – 5.58 (m, 1H), 5.19 (d, *J* = 13.1, 2.5 Hz, 1H), 4.52 – 4.25 (m, 3H), 3.66 – 3.49 (m, 3H), 3.27 – 3.19 (m, 1H), 3.18 – 3.03 (m, 3H), 2.72 – 2.60 (m, 1H), 2.48 – 2.38 (m, 2H), 2.38 – 2.28 (m, 4H), 1.96 – 1.75 (m, 2H), 1.72 – 1.50 (m, 2H).	708
245	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.56 (s, 1H), 6.07 (s, 2H), 5.63 (s, 1H), 5.16 (d, J = 12.8 Hz, 1H), 4.52 – 4.29 (m, 2H), 4.24 – 4.08 (m, 1H), 3.70 – 3.39 (m, 6H), 3.21 – 3.06 (m, 2H), 3.05 – 2.92 (m, 1H), 2.92 – 2.78 (m, 2H), 2.39 – 2.26 (m, 3H), 2.19 – 1.98 (m, 1H), 1.96 – 1.71 (m, 3H), 1.70 – 1.48 (m, 3H), 1.40 – 1.19 (m, 1H).	702
246	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.60 (s, 1H), 6.04 (s, 2H), 5.73 (s, 1H), 5.28 (d, *J* = 53.7 Hz, 1H), 4.58 (d, *J* = 10.8 Hz, 1H), 4.24 (s, 1H), 4.15 (d, *J* = 10.2 Hz, 1H), 3.96 (d, *J* = 10.2 Hz, 1H), 3.66 – 3.53 (m, 2H), 3.27 (s, 1H), 3.16 – 3.04 (m, 3H), 3.00 (s, 1H), 2.86 – 2.82 (m, 1H), 2.33 (s, 3H), 2.15 – 2.14 (s, 1H), 2.04 (s, 1H), 2.00 – 1.96 (m, 1H), 1.85 – 1.61 (m, 6H), 1.42 – 1.39 (s, 1H).	704
247	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.55 (s, 1H), 6.07 (s, 2H), 5.63 (s, 1H), 5.37 – 5.13 (m, 2H), 4.37 (d, *J* = 10.5 Hz, 1H), 4.14 – 3.05 (m, 2H), 3.59 – 3.51 (m, 2H), 3.09 (s, 3H), 3.00 (s, 1H), 2.84 (s, 1H), 2.32 (s, 3H), 2.14 (s, 1H), 2.04 (s, 1H), 2.00 (s, 1H), 1.87 – 1.77 (m, 5H), 1.68 – 1.56 (m, 2H).	704

248	^{1}H NMR (300 MHz, DMSO-d_6) δ 6.57 (d, J = 19.2 Hz, 1H), 6.05 (s, 2H), 5.67 (t, J = 8.7 Hz, 1H), 5.28 (d, J = 53.7 Hz, 1H), 4.58 (d, J = 12.6 Hz, 1H), 4.15 (d, J = 10.5 Hz, 1H), 3.99 (d, J = 10.5 Hz, 1H), 3.90 (s, 1H), 3.66 (s, 2H), 3.45 (d, J = 2.1 Hz, 1H), 3.11 – 3.08 (m, 2H), 3.00 (s, 1H), 2.83 – 2.80 (m, 2H), 2.33 (s, 3H), 2.15 – 2.13 (m, 1H), 2.04 – 1.99 (m, 2H), 1.94 – 1.56 (m, 7H).	704
249	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.56 (s, 1H), 6.07 (s, 2H), 5.62 (s, 1H), 5.25 – 5.08 (m, 1H), 4.45 – 4.31 (m, 2H), 4.25 (d, J = 10.9 Hz, 1H), 3.64 – 3.47 (m, 6H), 3.10 (d, J = 12.8 Hz, 1H), 2.95 (s, 1H), 2.45 – 2.20 (m, 9H), 1.86 (s, 2H), 1.73 – 1.49 (m, 2H), 0.73 – 0.55 (m, 2H), 0.49 – 0.33 (m, 2H).	716
250	^{1}H NMR (400 MHz, DMSO-d_6) δ 6.73 – 6.56 (m, 1H), 6.31 – 5.82 (m, 1H), 5.79-5.61 (m, 1H), 5.43 – 5.09 (m, 4H), 4.39 (d, J = 9.8 Hz, 1H), 4.22 – 3.96 (m, 2H), 3.56 (d, J = 25.2 Hz, 2H), 3.32 – 2.92 (m, 7H), 2.89-2.82 (m, 1H), 2.23 (d, J = 2.6 Hz, 3H), 2.16 (d, J = 4.5 Hz, 1H), 2.10 – 1.91 (m, 2H), 1.88-1.71 (m, 5H), 1.69 – 1.45 (m,2H).	700
251	^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 10.17 (s, 1H), 7.92 – 7.85 (m, 1H), 7.51 – 7.39 (m, 2H), 7.37 – 7.32 (m, 1H), 7.18 – 6.98 (m, 1H), 5.66 – 5.19 (m, 3H), 4.40 (d, J = 9.7 Hz, 1H), 4.16 – 4.09 (m, 1H), 4.03 (d, J = 10.4 Hz, 1H), 3.93 (s, 1H), 3.58 (d, J = 20.8 Hz, 2H), 3.17 – 2.99 (m, 5H), 2.91 – 2.78 (m, 1H), 2.23 – 2.13 (m, 1H), 2.10 – 1.99 (m, 2H), 1.94 – 1.64 (m, 7H).	679

[2461] **Example 252:** Compound 252 (two isomers)



[2462] Step 1: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(methylthio)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2463] Under nitrogen, a solution of *tert*-butyl (5R,5aS,6S,9R)-2-chloro-1-fluoro-12-(methylthio)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (2.00 g, 3.73 mmol, intermediate 164), [6-[bis[(4-methoxyphenyl)methyl]amino]-2-methyl-3-(trifluoromethyl)-4-pyridyl]boronic acid (3.11 g, 6.74 mmol), cataCXium A Pd G3 (544 mg, 0.750 mmol) and K_3PO_4 (7.5 mL, 1.5 M in H_2O) in THF (37.4 mL) was stirred for 1 h at 60°C. The resulting solution was partitioned between water and EtOAc. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-40% EtOAc / petroleum ether) to afford 2.80 g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 916.

[2464] Step 2: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(methylsulfonyl)-5-(trifluoromethyl)-5a,6,7,8,9,10-

hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2465] To a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl) amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(methylthio)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (1.60 g, 1.75 mmol) in EtOAc (20 mL) was added m-CPBA (900 mg, 5.24 mmol) at 0 °C and stirred at room temperature for 1 h. The reaction was quenched with saturated $Na_2S_2O_3$ aqueous, extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0%-55% EtOAc/petroleum ether) to afford 1.29 g of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 948$.

[2466] Step 3: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2467] Under nitrogen, to a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*I*)-2-(6-(bis(4-methoxybenzyl) amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(methylsulfonyl)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (120 mg, 0.130 mmol) and (3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methanol (42.0 mg, 0.260 mmol) in toluene (5 mL) was added *t*-BuONa (24.0 mg, 0.250 mmol) at 0 °C, and the mixture was stirred for 1 h at room temperature. The resulting solution was partitioned between water and EtOAc. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-89% MeOH in water (0.05% NH_4HCO_3)) to afford 102 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 1031$.

[2468] Step 4: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2469] A solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(6-(bis(4-methoxybenzyl) amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (90.0 mg, 0.0900 mmol) in TFA (5 mL) was stirred at 50 °C for 3.5 h. The solvent was concentrated under vacuum. The crude product was purified by Prep-HPLC (Column: CHIRALPAK SB 2 x 25 cm, 5 μm; Mobile Phase A:

HEX(0.5% 2M NH_3-MeOH), Mobile Phase B: ETOH; Flow rate: 20 mL/min; Gradient: isocratic 20; Wave Length: 220/254 nm; R_{T1}(min): 10.427; R_{T2}(min): 12.233; Sample Solvent: EtOH) to afford **252 (isomer 1)** 10.4 mg (the faster peak) and **252 (isomer 2)** 9.8 mg (the slower peak) as white solids. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 691.

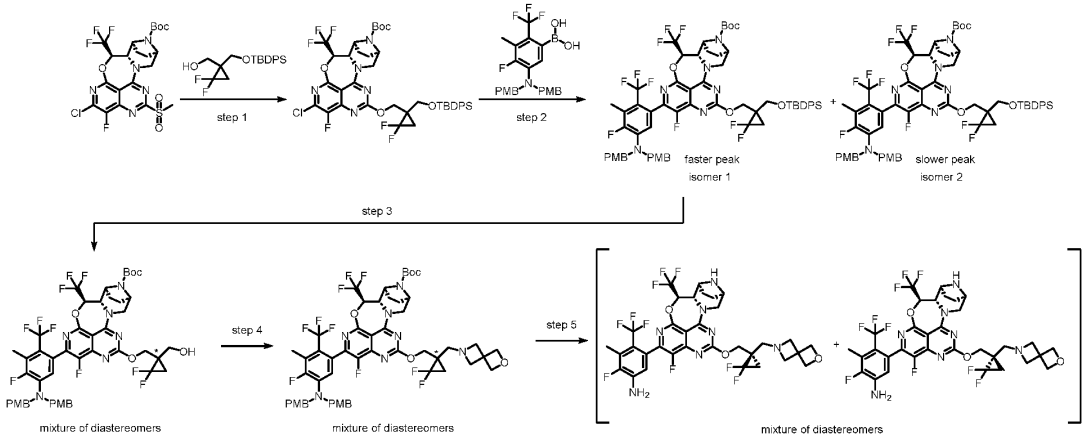
[2470] **252 (isomer 1):** ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 6.88 (s, 2H), 6.23 (s, 1H), 5.65 (t, J = 8.2 Hz, 1H), 5.19 (d, J = 12.7 Hz, 1H), 4.53 – 4.23 (m, 3H), 3.67 – 3.47 (m, 3H), 3.30 – 3.18 (m, 1H), 3.18 – 3.00 (m, 3H), 2.80 – 2.58 (m, 1H), 2.48 – 2.41 (m, 3H), 2.35 (dd, J = 10.8, 6.2 Hz, 2H), 2.30-2.15 (m, 1H), 1.88 (d, J = 19.6 Hz, 2H), 1.77 – 1.46 (m, 2H).

252 (isomer 2): ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.87 (s, 2H), 6.22 (s, 1H), 6.01 – 5.63 (m, 1H), 5.18 (dd, *J* = 12.9, 2.6 Hz, 1H), 4.50 – 4.20 (m, 3H), 3.72 – 3.43 (m, 3H), 3.22 (d, *J* = 8.7 Hz, 1H), 3.15 (d, *J* = 4.3 Hz, 2H), 3.08 (t, *J* = 5.3 Hz, 1H), 2.85 – 2.65 (m, 1H), 2.51 – 2.29 (m, 6H), 1.96 – 1.75 (m, 2H), 1.62 (dd, *J* = 15.2, 7.3 Hz, 2H).

Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 252**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
253	^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 6.87 (s, 2H), 6.22 (s, 1H), 5.66-5.62 (m, 1H), 5.23-5.14 (m, 1H), 4.46-4.37 (m, 2H), 4.19-4.16 (m, 1H), 3.74-3.65 (m, 1H), 3.61-3.49 (m, 4H), 3.45-3.38 (m, 1H), 3.31-3.29 (m, 1H), 3.21-3.18 (m, 2H), 3.05-2.98 (m, 1H), 2.93-2.85 (m, 2H), 2.46-2.42 (m, 3H), 2.14-2.03 (m, 1H), 1.90-1.77 (m, 3H), 1.68-1.57 (m, 3H), 1.36-1.29 (m, 1H).	685
254	^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.87 (s, 2H), 6.22 (s, 1H), 5.75 – 5.53 (m, 1H), 5.24 – 5.08 (m, 1H), 4.39 (d, J = 9.7 Hz, 1H), 4.28 – 4.12 (m, 2H), 3.67 – 3.46 (m, 2H), 3.20 – 2.94 (m, 3H), 2.72 (d, J = 11.8 Hz, 1H), 2.59 – 2.53 (m, 1H), 2.48 – 2.42 (m, 3H), 2.18 – 2.02 (m, 1H), 2.03 – 1.91 (m, 2H), 1.90 – 1.88 (m, 1H), 1.87 – 1.77 (m, 3H), 1.76 – 1.68 (m, 1H), 1.68 – 1.55 (m, 3H), 1.54 – 1.41 (m, 1H).	731

[2471] **Example 255**: Compound 255 (mixture and two separate diastereomers)



[2472] Step 1: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-12-((1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-2-chloro-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2473] To a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(methylsulfonyl)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (500 mg, 0.880 mmol, intermediate 165) and (1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methanol (497 mg, 1.32 mmol, intermediate 117) in toluene (3 mL) was added *t*BuONa (169 mg, 1.76 mmol) at 0 °C and the solution was stirred for 1 hour at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-100% EtOAc in petroleum ether) to afford the title compound (640 mg) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 865.

[2474] Step 2: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (two isomers)

[2475] Under nitrogen, a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-12-((1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-2-chloro-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (640 mg, 0.740 mmol), (5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)boronic acid (530 mg, 1.11 mmol), K_3PO_4 (1.5M aqueous solution, 2.5 mL, 3.75 mmol) and cataCXium A Pd G3 (108 mg, 0.148 mmol) in THF (12.5 mL) was stirred for 3 hours at 60 °C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford a mixture of two diastereomers (840 mg) as a light brown solid. The two diastereomers were separated by Chiral-Prep-SFC with the following conditions: (Column:((S, S)-WHELK-O1-Kromasil, 5*25 cm, 10 μm; Mobile Phase A: CO_2, Mobile Phase B: IPA; Flow rate: 90 mL/min; Gradient: isocratic 35% B; Column Temperature(°C): 35; Back Pressure(bar): 100; Wave Length: 220 nm; RT1(min): 18.95; RT2(min): 21.17; Sample Solvent: MEOH; Injection Volume: 1 mL; Number Of Runs: 40) to afford **isomer 1** (270 mg, the faster peak) and **isomer 2** (250 mg, the slower peak) as white solids. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1262.

[2476] Step 3: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (two isomers)

[2477] To a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((1-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-difluorocyclopropyl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (200 mg, 0.158 mmol, **isomer 1 of last step**) in tetrahydrofuran (4 mL) was added TBAF (1M solution in tetrahydrofuran, 0.5 mL), and the mixture was stirred for 2 hours at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (120 mg) as a light brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1023. It appears that isomerization took place in the TBDPS deprotection step to give a mixture of diastereomers of the title compound with respect to the stereogenic center of the difluorocyclopropyl moiety. This mixture was used as such in the following steps.

[2478] Step 4: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-12-((1-((2-oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-2,2-difluorocyclopropyl)methoxy)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (mixture of diastereomers)

[2479] To a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((2,2-difluoro-1-(hydroxymethyl)cyclopropyl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (50.0 mg, 0.0489 mmol, mixture of diastereomers) and NMO (11.5 mg, 0.0978 mmol) in dichloromethane (2 mL) was added TPAP (3.44 mg, 0.00978 mmol) at 0°C and the solution was stirred for 1 hour at room temperature. The resulting mixture was filtered and the filter cake was washed with dichloromethane. To the combined filtrate were added NaOAc (60.2 mg, 0.734 mmol) and 2-oxa-6-azaspiro [3.3]heptane (72.8 mg, 0.734 mmol) at room temperature and the solution was stirred for 1 hour at 60 °C. Then the mixture was cooled to ambient temperature and $NaBH_3CN$ (46.1 mg, 0.734 mmol) was added, and the mixture was stirred overnight at room temperature. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was

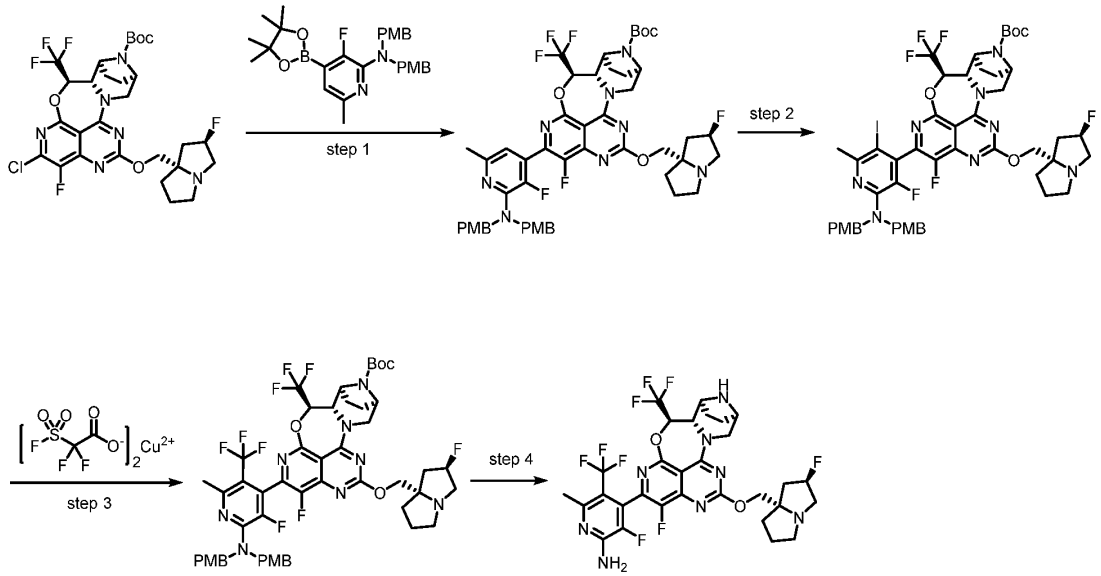
purified by reverse phase flash chromatography on pre-packed C18 column (gradient: 0-100% CH_3CN in water (0.05% NH_4HCO_3)) to afford the title compound (30.0 mg) as a mixture of diastereomers with respect to the stereogenic center of the difluorocyclopropyl moiety. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1105.

[2480] Step 5: 5-((5*R*,5a*S*,6*S*,9*R*)-12-((1-((2-Oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-2,2-difluorocyclopropyl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline

[2481] A solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-12-((1-((2-oxa-6-azaspiro[3.3]heptan-6-yl)methyl)-2,2-difluorocyclopropyl)methoxy)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (30.0 mg, 0.0271 mmol, mixture of diastereomers) in TFA (10 mL) was stirred for 30 minutes at room temperature. The solvent was concentrated under vacuum. The residue was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 42% B to 56% B in 10 min; Wave Length: 254nm/220nm nm; RT1(min): 8.5) to afford **255 (mixture of diastereomers)** (3.00 mg).

[2482] **255 (mixture of diastereomers):** LC-MS: (ESI, *m/z*): $[M+H]^+$ = 764. ^1H NMR (300 MHz, DMSO-*d6, ppm*) δ 6.69 – 6.40 (m, 1H), 6.08 (s, 2H), 5.78 – 5.53 (m, 1H), 5.17 (d, J = 12.8 Hz, 1H), 4.67 – 4.47 (m, 5H), 4.40 (d, J = 9.6 Hz, 1H), 4.36 – 4.22 (m, 1H), 3.66 – 3.48 (m, 2H), 3.43 – 3.37 (m, 1H), 3.13 (d, J = 12.9 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.53 (s, 4H), 2.33 (s, 3H), 1.92 – 1.79 (m, 2H), 1.79 – 1.41 (m, 4H).

[2483] **Example 256**: Compound 256



[2484] Step 1: *tert*-Butyl (5R,5aS,6S,9R)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-6-methylpyridin-4-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2485] Under nitrogen, a solution of *tert*-butyl (5R,5aS,6S,9R)-2-chloro-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate (100 mg, 0.155 mmol, Example 245, step 1), 3-fluoro-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (153 mg, 0.312 mmol), cataCxium A Pd G_3 (22.5 mg, 0.0309 mmol) and K_3PO_4 (0.310 mL, 1.5 M in water) in tetrahydrofuran (1.55 mL) was stirred for 1 h at 60 °C. The resulting solution was partitioned between water and EtOAc. The separated organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% 0-10% MeOH / DCM) to afford 140 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 977$.

[2486] Step 2: *tert*-Butyl (5R,5aS,6S,9R)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-5-iodo-6-methylpyridin-4-yl)-1-fluoro-12-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5H-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-ab]heptalene-14-carboxylate

[2487] A solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-3-fluoro-6-methylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-

methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (140 mg, 0.140 mmol) and 1-iodopyrrolidine-2,5-dione (32.3 mg, 0.140 mmol) in acetic acid (2.00 mL) was stirred for 1 h at room temperature. The solvent was evaporated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% MeOH / DCM) to afford 150 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1103.

[2488] Step 3: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

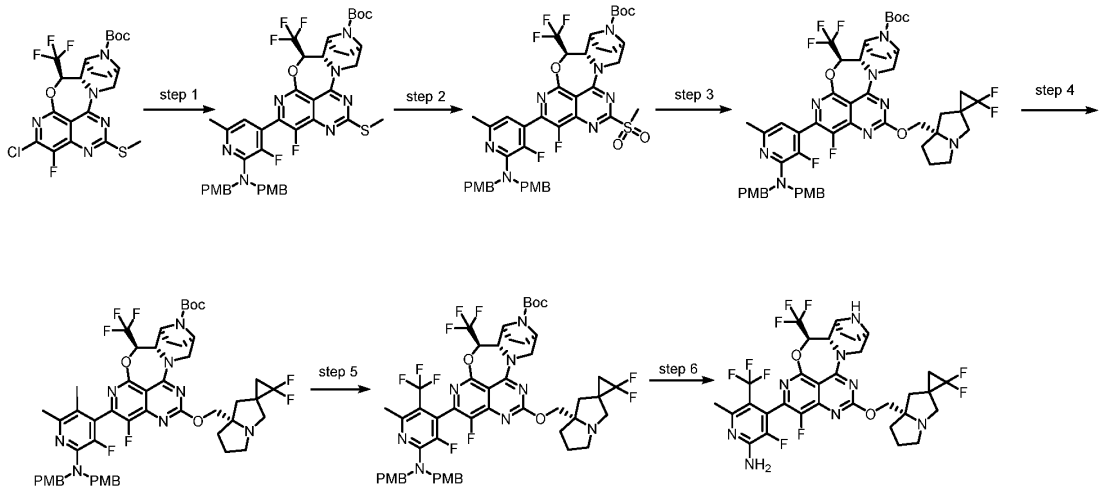
[2489] Under nitrogen, to a mixture of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-3-fluoro-5-iodo-6-methylpyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (184 mg, 0.170 mmol), $Cu(O_2CCF_2SO_2F)_2$ (1.05 g, 2.51 mmol) and copper (160 mg, 2.50 mmol) was added *N*,*N*-dimethylacetamide (5.00 mL) at 0 °C. The resulting solution was stirred for 1 h at room temperature. The resulting mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-100% EtOAc / petroleum ether) to afford 90.0 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1045.

[2490] Step 4: 3-Fluoro-4-((5*R*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[2491] A solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (85.0 mg, 0.0800 mmol) in 2,2,2-trifluoroacetic acid (1.00 mL) was stirred for 1 h at 50 °C. Solvent was evaporated under vacuum. The residue was purified by prep. HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 17% B to 42% B in 9 min; Wave Length: 254nm/220nm; RT1(min): 8.6) to afford 23.4 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 705. ^1H NMR (300 MHz, DMSO-d_6) δ 7.23 (d, *J* = 13.1 Hz, 2H), 5.68 – 5.65 (m, 1H), 5.38 – 5.13 (m, 2H), 4.39 (t, *J* = 9.9 Hz, 1H), 4.16 – 4.03 (m, 2H), 3.59 – 3.51 (m, 2H), 3.15 – 3.00 (m, 5H), 2.84

– 2.82 (m, 1H), 2.46 (s, 3H), 2.15 (s, 1H), 2.07 – 1.86 (m, 2H), 1.83 – 1.77 (m, 5H), 1.68 – 1.56 (m, 2H).

[2492] **Example 257**: Compound 257



[2493] Step 1: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-6-methylpyridin-4-yl)-1-fluoro-12-(methylthio)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2494] Under nitrogen, a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(methylthio)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (250 mg, 0.470 mmol, intermediate 164), 3-fluoro-*N*,*N*-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (575 mg, 1.17 mmol), cataCXium A Pd G3 (68.1 mg, 0.0900 mmol) and K_3PO_4 (1 mL, 1.5 M in H_2O) in THF (5 mL) was stirred at 60 °C for 2 h. The resulting solution was partitioned between water and EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-50% EtOAc / petroleum ether) to afford 568 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 866$.

[2495] Step 2: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-6-methylpyridin-4-yl)-1-fluoro-12-(methylsulfonyl)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2496] To a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-6-methylpyridin-4-yl)-1-fluoro-12-(methylthio)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (558 mg, 0.623 mmol) in ethyl acetate (10 mL) was added m-CPBA (335 mg, 1.94 mmol) at 0 °C. The solution was stirred at room temperature for 1 h. The reaction was quenched with aqueous

$Na_2S_2O_3$ and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-40% EtOAc / petroleum ether) to afford 355 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 898.

[2497] Step 3: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-6-methylpyridin-4-yl)-12-(((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2498] To a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-3-fluoro-6-methylpyridin-4-yl)-1-fluoro-12-(methylsulfonyl)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (343 mg, 0.382 mmol) and ((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methanol (93.1 mg, 0.460 mmol) in toluene (5 mL) was added t-BuONa (73.4 mg, 0.760 mmol) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. The resulting solution was partitioned between water and EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-80% ACN in water (0.05% NH_4HCO_3)) to afford 163 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1021.

[2499] Step 4: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-5-iodo-6-methylpyridin-4-yl)-12-(((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2500] To a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-6-methylpyridin-4-yl)-12-(((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (139 mg, 0.136 mmol) in AcOH (1.5 mL) was added NIS (30.6 mg, 0.140 mmol). The solution was stirred at room temperature for 20 min. The reaction was quenched with aqueous $Na_2S_2O_3$ and extracted with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0%-10% MeOH / DCM) to afford 128 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1147.

[2501] Step 5: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl)amino)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-4-yl)-12-(((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-

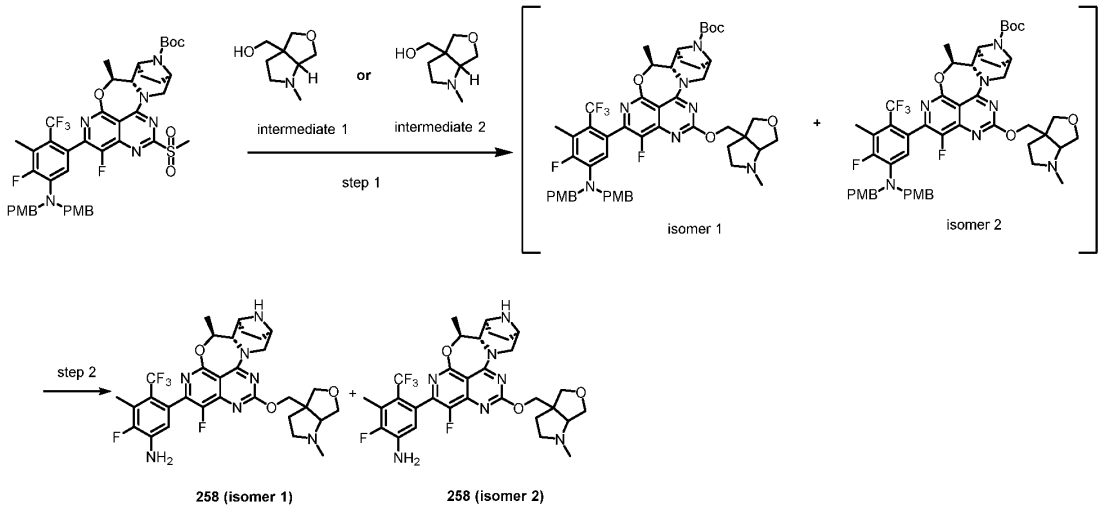
5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2502] Under nitrogen, to a mixture of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-3-fluoro-5-iodo-6-methylpyridin-4-yl)-12-(((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (115 mg, 0.100 mmol), $Cu(O_2CCF_2SO_2F)_2$ (419 mg, 1.00 mmol) and Cu (64.2 mg, 1.00 mmol) was added DMF (2.5 mL) at 0 °C. The solution was stirred at room temperature for 1 h. The resulting reaction was diluted with EtOAc and washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-80% MeOH in water (0.05% NH_4HCO_3)) to afford 135 mg of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1088.

[2503] Step 6: 4-((5*R*,5a*S*,6*S*,9*R*)-12-(((7a'*S*)-2,2-Difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza[6,9]methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[2504] A solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(2-(bis(4-methoxybenzyl) amino)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-4-yl)-12-(((7a'*S*)-2,2-difluorodihydro-1'*H*,3'*H*-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (116 mg, 0.107 mmol) in TFA (6 mL) was stirred at 50 °C for 3 h. Then the solution was concentrated under vacuum. The crude product was purified by Prep-HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 31% B to 53% B in 10 min; Wave Length: 254nm/220nm nm; R_{T1}(min): 8) to afford 54.4 mg of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 749. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 7.24 (d, J = 22.4 Hz, 2H), 5.78 – 5.63 (m, 1H), 5.25 – 5.11 (m, 1H), 4.50 – 4.33 (m, 1H), 4.29 – 4.15 (m, 2H), 3.65 – 3.57 (m, 1H), 3.56 – 3.49 (m, 1H), 3.20 – 3.07 (m, 2H), 3.06 – 2.98 (m, 1H), 2.96 (s, 1H), 2.72 (d, J = 11.8 Hz, 1H), 2.58 – 2.52 (m, 1H), 2.49 – 2.44 (m, 2.6 Hz, 3H), 2.14 – 2.04 (m, 1H), 2.03 – 1.96 (m, 1H), 1.91 (d, J = 13.3 Hz, 1H), 1.88 – 1.79 (m, 3H), 1.78 – 1.53 (m, 5H), 1.54 – 1.44 (m, 1H).

[2505] **Example 258**: Compound 258 (two isomers)



[2506] Step1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-methyltetrahydro-1*H*-furo[3,4-*b*]pyrrol-3a(4*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (two isomers)

[2507] To a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (60.0 mg, 0.0659 mmol, procedure has been included in previous version) and (1-methyltetrahydro-1*H*-furo[3,4-*b*]pyrrol-3a(4*H*)-yl)methanol (90.0 mg, crude, intermediate 170) in toluene (2 mL) was added *t*BuONa (12.7 mg, 0.132 mmol) at 0 °C, and the mixture was stirred for 1 hour at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (60.0 mg, 92.2 % yield, **isomer 1**) as a light yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 989$.

[2508] Analogous to the method described above, **isomer 2** (35.0 mg, 53.8% yield) was prepared from *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-(methylsulfonyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (60.0 mg, 0.0659 mmol) and intermediate 171 (100 mg, crude) as a light yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+ = 989$.

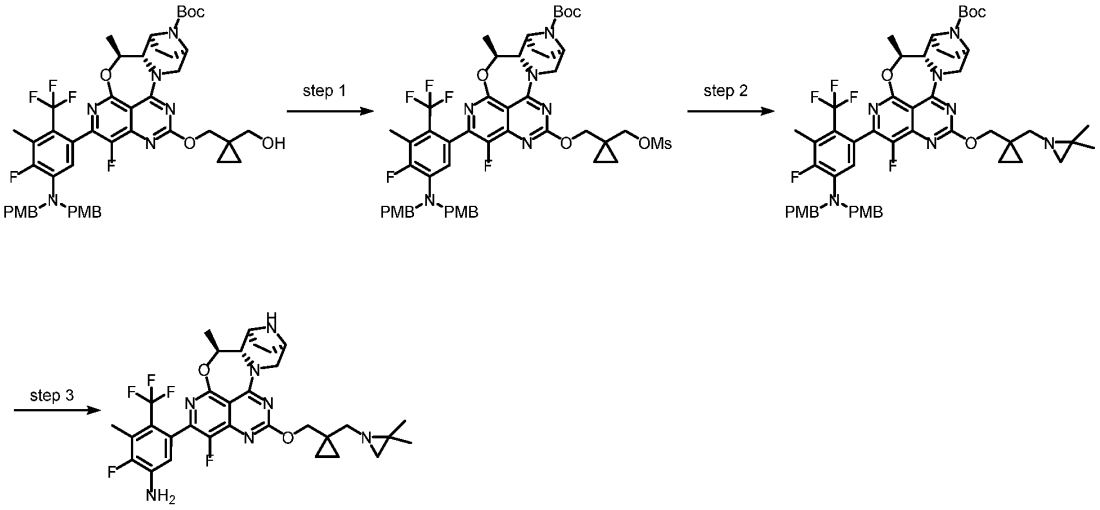
[2509] Step 2: 2-Fluoro-5-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-5-methyl-12-((1-methyltetrahydro-1*H*-furo[3,4-*b*]pyrrol-3a(4*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-

pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-3-methyl-4-(trifluoromethyl)aniline (two isomers).

[2510] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(*bis*(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-methyltetrahydro-1*H*-furo[3,4-*b*]pyrrol-3a(4*H*)-yl)methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (60.0 mg, 0.0607 mmol, **isomer 1 of the last step**) in 2,2,2-trifluoroacetic acid (10 mL) was stirred for 30 minutes at room temperature. The solvent was concentrated under vacuum. The residue was purified by prep. HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 50% B in 10 min; Wave Length: 254nm/220nm; RT1(min): 8.6) to afford **258 (isomer 1)** (18.3 mg, 46.5% yield) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 648. ^1H NMR (300 MHz, DMSO-*d6*, ppm) δ 6.67 – 6.41 (m, 1H), 6.03 (s, 2H), 5.09 (d, J = 12.6 Hz, 1H), 4.59 – 4.48 (m, 1H), 4.43 – 4.27 (m, 2H), 3.95 (d, J = 8.6 Hz, 1H), 3.80 – 3.67 (m, 2H), 3.59 – 3.53 (m, 2H), 3.54 – 3.40 (m, 2H), 3.03 (d, J = 12.9 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.75 – 2.68 (m, 1H), 2.47 – 2.37 (m, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 2.01 – 1.91 (m, 1H), 1.87 – 1.51 (m, 5H), 1.44 (d, J = 6.3 Hz, 3H).

[2511] Analogous to method described as above, **258 (isomer 2)** (10.1 mg, 44.0% yield) was prepared from (35.0 mg, 0.0354 mmol, **isomer 2 of the last step**) after purification by prep. HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 50% B in 10 min; Wave Length: 254nm/220nm; RT1(min): 8.1) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 648. ^1H NMR (300 MHz, DMSO-*d6*, ppm) δ 6.68 – 6.43 (m, 1H), 6.02 (s, 2H), 5.09 (d, J = 12.7 Hz, 1H), 4.60 – 4.48 (m, 1H), 4.45 – 4.25 (m, 2H), 3.95 (d, J = 8.7 Hz, 1H), 3.73 (d, J = 9.1 Hz, 2H), 3.62 – 3.43 (m, 4H), 3.03 (d, J = 12.8 Hz, 1H), 2.96 – 2.87 (m, 1H), 2.76 – 2.68 (m, 1H), 2.45 – 2.37 (m, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 2.00 – 1.90 (m, 1H), 1.83 – 1.53 (m, 5H), 1.44 (d, J = 6.3 Hz, 3H).

[2512] **Example 259**: Compound 259



[2513] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-5-methyl-12-((1-(((methylsulfonyl) oxy)methyl) cyclopropyl) methoxy)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2514] Under nitrogen, a solution of *tert*-butyl (4*R*,7*S*,8*S*,9*S*)-13-[5-[bis[(4-methoxyphenyl) methyl] amino]-4- fluoro-3-methyl-2-(trifluoromethyl) phenyl]-14-fluoro-17-[[1-(hydroxymethyl) cyclopropyl] methoxy]-9-methyl-10-oxa-2,12,16,18,20-pentazapentacyclo[9.7.1.14,7.02,8.015,19]icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (80.4 mg, 0.0900 mmol) in DCM (3 mL) was added DIPEA (55.3 mg, 0.430 mmol) at room temperature. Then Ms_2O (29.8 mg, 0.170 mmol) was added at 0 °C and stirred at room temperature for 1 hour. The solvent was concentrated under vacuum to afford 80.1 mg (crude) of the title compound as a yellow oil. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1011.

[2515] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((1-((2,2-dimethylaziridin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

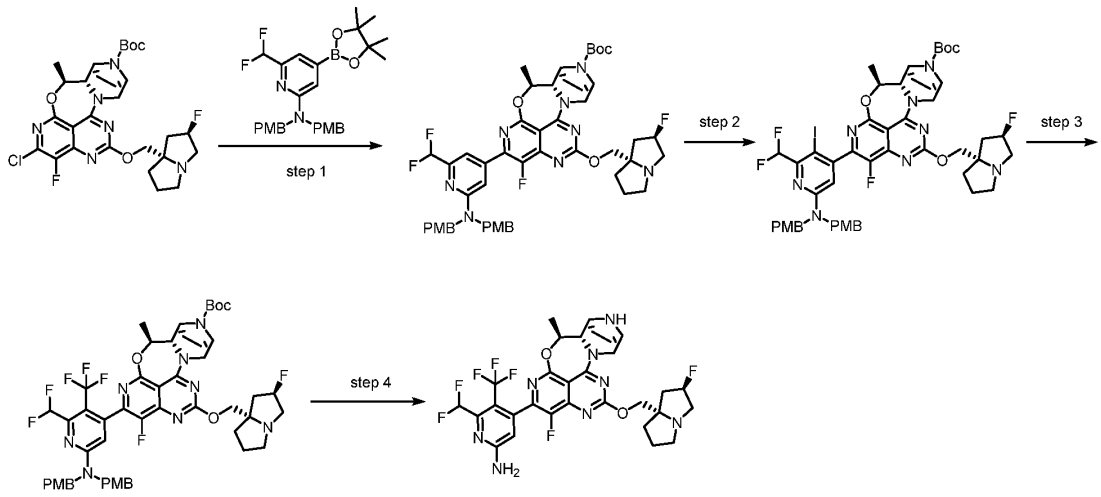
[2516] A solution of *tert*-butyl (4*R*,7*S*,8*S*,9*S*)-13-[5-[bis[(4-methoxyphenyl) methyl] amino]-4-fluoro-3-methyl-2- (trifluoromethyl) phenyl]-14-fluoro-9-methyl-17-[[1-(methylsulfonyloxymethyl) cyclopropyl] methoxy]-10-oxa-2,12,16,18,20-pentazapentacyclo [9.7.1.14,7.02,8.015,19] icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (80.1 mg, 0.0800 mmol), 2,2-dimethylaziridine (123 mg, 1.74 mmol) and K_2CO_3 (32.7 mg, 0.240 mmol) in DMF (3 mL) was stirred for 12 h at 70 °C. The resulting solution was partitioned between water and EtOAc. The organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting (gradient: 0%-

15% MeOH / DCM) to afford 44.7 mg (57.2% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 986.

[2517] Step 3: 5-((5*S*,5a*S*,6*S*,9*R*)-12-((1-((2,2-Dimethylaziridin-1-yl)methyl)cyclopropyl)methoxy)-1-fluoro-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline

[2518] A solution of *tert*-butyl (4*R*,7*S*,8*S*,9*S*)-13-[5-[bis[(4-methoxyphenyl) methyl] amino]-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl]-17-[[1-[(2,2-dimethylaziridin-1-yl)methyl]cyclopropyl]methoxy]-14-fluoro-9-methyl-10-oxa-2,12,16,18,20-pentazapentacyclo[9.7.1.14,7.02,8.015,19]icosa-1(18),11(19),12,14,16-pentaene-20-carboxylate (41.3 mg, 0.0400 mmol) in TFA (1.5 mL) was stirred at room temperature for 0.5 h. The solvent was concentrated under vacuum. The crude product was purified by prep. HPLC with the following conditions: (Column: XSelect CSH Fluoro Phenyl 30 x 150 mm, 5μm; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 14% B to 38% B in 10 min; Wave Length: 254nm/220nm nm; R_{T1}(min): 9.3) to afford 1.4 mg (5.17 % yield) of the title compound as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 646. ^1H NMR (300 MHz, DMSO-d_6, ppm) δ 6.73 – 6.36 (m, 1H), 6.02 (s, 2H), 5.10 (d, J = 12.7 Hz, 1H), 4.62 – 4.47 (m, 1H), 4.45 – 4.32 (m, 1H), 4.31 – 4.15 (m, 1H), 3.95 (d, J = 8.7 Hz, 1H), 3.55 (s, 1H), 3.52 (s, 1H), 3.48 – 3.41 (m, 1H), 3.02 (d, J = 12.9 Hz, 1H), 2.82 – 2.64 (m, 1H), 2.32 (s, 3H), 2.22 – 2.06 (m, 1H), 1.82 (s, 1H), 1.75 – 1.51 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H), 1.14 (s, 3H), 1.08 (s, 1H), 1.04 (s, 3H), 0.65 – 0.40 (m, 4H).

[2519] **Example 260:** Compound 260



[2520] Step 1: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(*bis*(4-methoxybenzyl)amino)-6-(difluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-

yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2521] Under nitrogen, a solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-chloro-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (390 mg, 0.724 mmol), 6-(difluoromethyl)-*N*,*N*-*bis*(4-methoxybenzyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (370 mg, 0.724 mmol, intermediate 7), K_3PO_4 (1.5M solution in H_2O, 2.4 mL, 3.60 mmol) and cataCXium A Pd G3 (105 mg, 0.145 mmol) in tetrahydrofuran (12 mL) was stirred for 2 hours at 60 °C. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (400 mg, 58.7% yield) as a brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 941. ^{1}H NMR (300 MHz, DMSO-*d6,* ppm) δ 7.38 (s, 1H), 7.31 – 7.13 (m, 5H), 7.10 – 6.66 (m, 5H), 5.44 – 5.03 (m, 2H), 4.77 (s, 4H), 4.67 – 4.52 (m, 1H), 4.28 (d, J = 9.8 Hz, 1H), 4.19 – 3.91 (m, 4H), 3.72 (s, 6H), 3.17 – 2.93 (m, 4H), 2.90 – 2.75 (m, 1H), 2.27 – 1.60 (m, 10H), 1.57 – 1.37 (m, 12H).

[2522] Step 2: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(*bis*(4-methoxybenzyl)amino)-2-(difluoromethyl)-3-iodopyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2523] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(2-(*bis*(4-methoxybenzyl)amino)-6-(difluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (100 mg, 0.106 mmol) and NIS (47.7 mg, 0.212 mmol) in acetic acid (2 mL) was stirred for 1 hour at room temperature. The reaction was quenched with saturated $Na_2S_2O_3$ aqueous solution. The reaction system was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-5% methanol in dichloromethane) to afford the title compound (80.0 mg, 70.6% yield) as a light brown solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1067. ^{1}H NMR (300 MHz, DMSO-*d6,* ppm) δ 7.20 (d, J = 8.3 Hz, 4H), 7.12 – 6.71 (m, 6H), 5.43 – 5.05 (m, 2H), 4.86 – 4.65 (m, 4H), 4.65 – 4.48 (m, 1H), 4.36 – 4.27 (m, 1H), 4.22 – 3.90 (m, 4H), 3.72 (s, 6H), 3.20 – 2.97 (m, 4H), 2.90 – 2.77 (m, 1H), 2.20 – 2.11 (m, 1H), 2.07 – 1.96 (m, 2H), 1.96 – 1.65 (m, 7H), 1.55 – 1.37 (m, 12H).

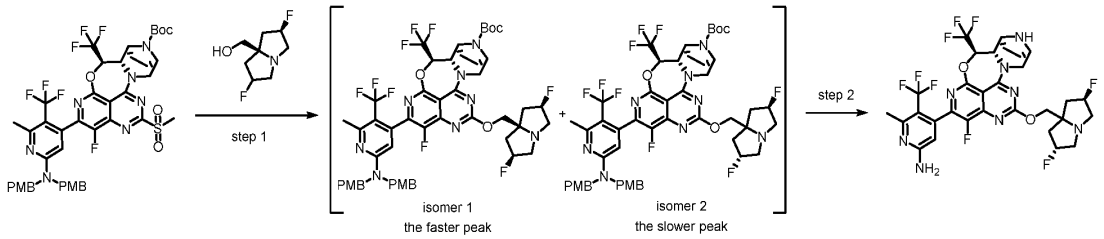
[2524] Step 3: *tert*-Butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(*bis*(4-methoxybenzyl)amino)-2-(difluoromethyl)-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2525] Under nitrogen, to a solid mixture of $Cu(O_2CCF_2SO_2F)_2$ (313 mg, 0.750 mmol) and Cu power (47.7 mg, 0.750 mmol) was added an ice-cold solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(*bis*(4-methoxybenzyl)amino)-2-(difluoromethyl)-3-iodopyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (80.0 mg, 0.0750 mmol) in *N*,*N*-dimethylacetamide (5 mL) at 0 °C and stirred for 1 hour at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-10% methanol in dichloromethane) to afford the title compound (50.0 mg, 66.1% yield) as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1009

[2526] Step 4: 6-(Difluoromethyl)-4-((5*S*,5a*S*,6*S*,9*R*)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-5-(trifluoromethyl)pyridin-2-amine

[2527] A solution of *tert*-butyl (5*S*,5a*S*,6*S*,9*R*)-2-(6-(*bis*(4-methoxybenzyl)amino)-2-(difluoromethyl)-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-*yl*)methoxy)-5-methyl-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (50.0 mg, 0.0496 mmol) in 2,2,2-trifluoroacetic acid (10 mL) was stirred for 1 hour at 50 °C. The solvent was concentrated under vacuum. The residue was purified by prep. HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3); Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 27% B to 50% B in 10 min; Wave Length: 254 nm; RT1(min): 8.6) to afford the title compound (8.20 mg, 24.7% yield) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 669. ^{1}H NMR (300 MHz, DMSO-*d6*, ppm) δ 7.36 (s, 2H), 6.98 (t, J = 53.4 Hz, 1H), 6.58 (s, 1H), 5.29 (d, J = 54.4 Hz, 1H), 5.08 (d, J = 12.7 Hz, 1H), 4.63 – 4.45 (m, 1H), 4.17 – 3.99 (m, 2H), 3.99 – 3.90 (m, 1H), 3.63 – 3.53 (m, 1H), 3.45 (d, J = 5.7 Hz, 1H), 3.17 – 3.08 (m, 2H), 3.07 – 2.96 (m, 2H), 2.93 – 2.76 (m, 1H), 2.20 – 2.11 (m, 1H), 2.08 – 1.94 (m, 2H), 1.91 – 1.73 (m, 4H), 1.73 – 1.52 (m, 4H), 1.44 (d, J = 6.3 Hz, 3H).

[2528] **Example 261:** Compound 261



[2529] Step 1: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(6-(*bis*(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-12-(((2*R*,6*S*,7a*r*)-2,6-difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate **&** *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(6-(*bis*(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-12-(((2*R*,6*R*)-2,6-difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2530] To a solution of ((2*R*,7a*R*)-2,6-difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methanol (120 mg, 0.677 mmol, the procedure has been included in previous version) in tetrahydrofuran (4 mL) was added NaH (60% dispersion in mineral oil, 52.8 mg, 1.32 mmol) at 0 °C, and the mixture was stirred for 30 minutes at room temperature. Then *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(6-(*bis*(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-1-fluoro-12-(methylsulfonyl)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (250 mg, 0.264 mmol) was added, and the mixture was stirred for 1 hour at room temperature. The reaction was quenched with saturated NH_4Cl aqueous solution. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (gradient: 0-50% ethyl acetate in petroleum ether) to afford a mixture of diastereomers (90.0 mg, 32.6% yield) as a yellow solid. Two diastereomers were separated by chiral prep. HPLC with the following conditions: (Column: CHIRALPAK ID, 2*25 cm, 5 μm; Mobile Phase A: Hex (0.1% TFA)--HPLC, Mobile Phase B: EtOH--HPLC; Flow rate: 20 mL/min; Gradient: isocratic 20; Wave Length: 220/254 nm; RT1(min): 8.461; RT2(min): 10.449; Sample Solvent: EtOH--HPLC; Injection Volume: 1.0 mL; Number Of Runs: 6) to afford **isomer 1** (9.00 mg, 3.26% yield, the faster peak) and **isomer 2** (50.0 mg, 18.1% yield, the slower peak) as white solids. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1045.

[2531] Step 2: 4-((5*R*,5a*S*,6*S*,9*R*)-12-(((2*R*,6*R*)-2,6-Difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-

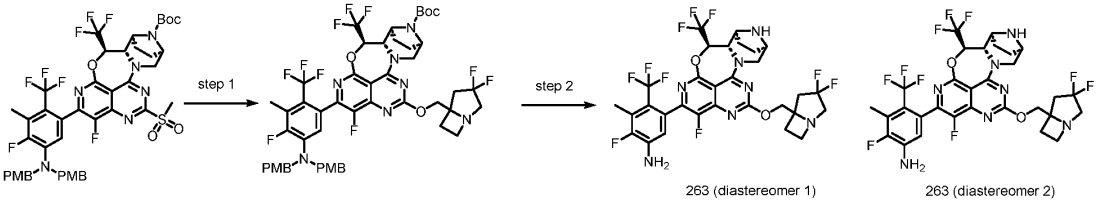
pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[2532] A solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(6-(*bis*(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-12-(((2*R*,6*R*)-2,6-difluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (50.0 mg, 0.0478 mmol, **isomer 2 of last step**) in 2,2,2-trifluoroacetic acid (10 mL) was stirred for 3 hours at 50 °C. The solvent was concentrated under vacuum. The residue was purified by prep. HPLC (Column: XBridge Prep OBD C18 Column, 30*150 mm, 5μm; Mobile Phase A: Water (10 mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min; Gradient: 28% B to 51% B in 9 min; Wave Length: 254nm/220nm; RT1(min): 8) to afford the title compound (12.3 mg, 36.5% yield) as a white solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 705. ^{1}H NMR (300 MHz, DMSO-*d6*, ppm) δ 6.87 (s, 2H), 6.23 (s, 1H), 5.73 – 5.56 (m, 1H), 5.51 – 5.41 (m, 1H), 5.33 – 5.23 (m, 1H), 5.23 – 5.11 (m, 1H), 4.40 (d, J = 9.7 Hz, 1H), 4.30 – 4.12 (m, 2H), 3.64 – 3.49 (m, 2H), 3.49 – 3.34 (m, 1H), 3.26 – 2.93 (m, 5H), 2.48 (s, 3H), 2.44 – 2.29 (m, 1H), 2.29 – 2.13 (m, 2H), 2.11 – 2.00 (m, 1H), 1.91 – 1.76 (m, 2H), 1.74 – 1.49 (m, 2H).

[2533] Each compound in the Table below was prepared following a similar experimental procedure (using appropriately substituted reagents) as described for **Example 261**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
262 (isomer 1)	^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 6.88 (s, 2H), 6.22 (s, 1H), 5.70 – 5.61 (m, 1H), 5.17 – 5.13 (m, 1H), 4.44 – 4.31 (m, 3H), 3.75 (q, *J* = 6.0 Hz, 1H), 3.57 (d, *J* = 5.9 Hz, 1H), 3.58 – 3.48 (m, 2H), 3.12 (d, *J* = 12.7 Hz, 1H), 3.05 (t, *J* = 7.2 Hz, 1H), 2.48 (d, *J* = 2.3 Hz, 3H), 2.42 (s, 3H), 1.84 (d, *J* = 8.7 Hz, 2H), 1.73 – 1.52 (m, 4H).	691
262 (isomer 2)	^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 6.88 (s, 2H), 6.22 (s, 1H), 5.70 – 5.61 (m, 1H), 5.17 – 5.13 (m, 1H), 4.44 – 4.31 (m, 3H), 3.77 – 3.74 (m, 1H), 3.57 (d, *J* = 5.9 Hz, 1H), 3.58 – 3.48 (m, 2H), 3.12 (d, *J* = 12.7 Hz, 1H), 3.05 (t, *J* = 7.2 Hz, 1H), 2.48 (d, *J* = 2.3 Hz, 3H), 2.42 (s, 3H), 1.84 (d, *J* = 8.7 Hz, 2H), 1.73 – 1.52 (m, 4H).	691
262 (isomer 3)	^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 6.86 (s, 2H), 6.21 (s, 1H), 5.67 – 5.62 (m, 1H), 5.17 – 5.12 (m, 1H), 4.45 – 4.35 (m, 3H), 3.67 – 3.52 (m, 3H), 3.44 – 3.40 (m, 1H), 3.18 – 3.08 (m, 2H), 2.46 (d, *J* = 2.3 Hz, 3H), 2.38 (s, 3H), 1.85 (d, *J* = 7.6 Hz, 2H), 1.81 – 1.49 (m, 4H).	691
262 (isomer 4)	^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 6.86 (s, 2H), 6.20 (s, 1H), 5.63 (t, *J* = 8.3 Hz, 1H), 5.16 – 5.12 (m, 1H), 4.47 – 4.29 (m, 3H), 3.65 – 3.47 (m, 3H), 3.44 – 3.40 (m, 1H), 3.18 – 3.05 (m, 2H), 2.46 (d, *J* = 2.3 Hz, 3H), 2.38 (s, 3H), 1.90 – 1.48 (m, 6H).	691

[2534] **Example 263:** Compound 263 (two diastereomers)



[2535] Step 1: *tert*-Butyl (5*R*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate

[2536] Under nitrogen, to a solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-1-fluoro-12-(methylsulfonyl)-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (300 mg, 0.310 mmol, the procedure has been included in previous version) and (3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methanol (127 mg, 0.780 mmol, the procedure has been included in previous version) in toluene (5 mL) was added *t*-BuONa (74.7 mg, 0.780 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. Then solution was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by C18 column (solvent gradient: 0-95% ACN in water (0.05% NH_4HCO_3)) to afford 198 mg (41.6% yield) of the title compound as a yellow solid. LC-MS: (ESI, *m/z*): $[M+H]^+$ = 1048.

[2537] Step 2: 5-((5*R*,5a*S*,6*S*,9*R*)-12-((3,3-Difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalen-2-yl)-2-fluoro-3-methyl-4-(trifluoromethyl)aniline

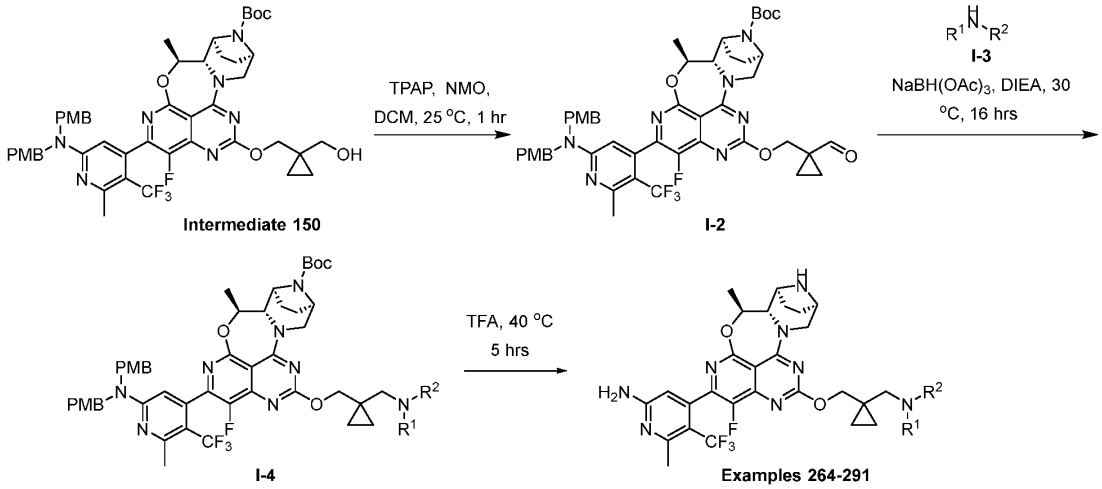
[2538] A solution of *tert*-butyl (5*R*,5a*S*,6*S*,9*R*)-2-(5-(bis(4-methoxybenzyl)amino)-4-fluoro-3-methyl-2-(trifluoromethyl)phenyl)-12-((3,3-difluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-1-fluoro-5-(trifluoromethyl)-5a,6,7,8,9,10-hexahydro-5*H*-4-oxa-3,10a,11,13,14-pentaaza-6,9-methanonaphtho[1,8-*ab*]heptalene-14-carboxylate (364 mg, 0.230 mmol) in TFA (3 mL) was stirred at room temperature for 1 h. The solvent was concentrated under vacuum and the crude product was purified by prep. HPLC (Column: XSelect CSH Fluoro Phenyl 30*150 mm, 5μm; Mobile Phase A: water (10mmol/L NH_4HCO_3), Mobile Phase B: ACN; Flow rate: 60 mL/min mL/min; Gradient: 29% B to 54% B in 10 min; Wave Length: 254nm/220nm; R_{T1}(min): 8.6) to afford 83.2 mg of the mixture product as a white solid. The mixture product was purified by chiral prep. HPLC (Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: Hex: DCM=3: 1 (0.5% 2M NH_3-MeOH)--HPLC, Mobile Phase B: IPA--HPLC; Flow rate: 20 mL /

min; Gradient: isocratic 5; Wave Length: 220/254 nm; R_{T1}(min): 13.123; R_{T2}(min): 18.513; Sample Solvent: EtOH--HPLC;) to afford 25.3 mg (15.6% yield) of **263 (diastereomer 1)** and 26.4 mg (16.3% yield) of **263 (diastereomer 2)** as white solids.

[2539] **263 (diastereomer 1):** LC-MS: (ESI, *m/z*): $[M+H]^+$ = 708. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.54 (s, 1H), 6.08 (s, 2H), 5.65 (s, 1H), 5.28 – 5.09 (m, 1H), 4.51 – 4.24 (m, 3H), 3.67 – 3.42 (m, 3H), 3.29 – 3.18 (m, 1H), 3.14 (s, 2H), 3.12 – 2.95 (m, 2H), 2.77 – 2.58 (m, 1H), 2.46 – 2.37 (m, 2H), 2.37 – 2.25 (m, 4H), 1.95 – 1.76 (m, 2H), 1.75 – 1.51 (m, 2H).

[2540] **263 (diastereomer 2):** LC-MS: (ESI, *m/z*): $[M+H]^+$ = 708. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 6.54 (s, 1H), 6.08 (s, 2H), 5.65 (s, 1H), 5.31 – 5.08 (m, 1H), 4.53 – 4.26 (m, 3H), 3.70 – 3.45 (m, 3H), 3.29 – 3.19 (m, 1H), 3.19 – 3.06 (m, 3H), 3.05 – 2.83 (m, 1H) 2.76 – 2.57 (m, 1H), 2.48 – 2.37 (m, 2H), 2.36 – 2.25 (m, 4H), 1.95 – 1.76 (m, 2H), 1.75 – 1.48 (m, 2H).

[2541] **Examples 264-291**: Compounds 264-291



[2542] General procedure

[2543] **Step 1:** To a vial containing a solution of **Intermediate 150** (0.050 mmol, 1.0 eq) in DCM (0.50 mL) were added TPAP (0.030 mmol, 0.50 eq) and NMO (0.10 mmol, 2.0 eq) under nitrogen. The vial was capped and stirred at 25 °C for 1 hr. The solution was directly used for next step (**Solution A**).

[2544] **Step 2:** To **Solution A** were added amine **I-3** (0.50 mmol, 10 eq), *N,N*-diisopropylethylamine (0.35 mmol, 7.0 eq) and $NaBH(OAc)_3$ (0.25 mmol, 5.0 eq). Then the reaction was stirred at 30 °C for 16 h. The solvent was concentrated under nitrogen gas flow. The residue was purified by prep-TLC (PE: EA=2:1, Rf =2/ 3) to give the protected reductive amination product **I-4**, which was directly used for next step.

[2545] **Step 3:** To a vial containing the residue of **I-4** (0.030 mmol, 1.0 eq) was added TFA (0.15 mL). The reaction mixture was stirred at 40 °C for 5 hrs. The solution was concentrated

under nitrogen flow gas. The residue was purified by prep-HPLC to give final product **I-5** as the TFA salt **(Examples 264-291)**.

Cmpd. No.	^{1}H NMR	MS $(M+H)^+$
264	N/A	691
265	N/A	657
266	N/A	721
267	N/A	713
268	N/A	671
269	N/A	679
270	N/A	691
271	N/A	695
272	N/A	677
273	^{1}H NMR (METHANOL-d4, 400 MHz) δ 6.5-6.6 (m, 1H), 5.5-5.6 (m, 1H), 4.7-4.8 (m, 1H), 4.3-4.5 (m, 7H), 4.2-4.3 (m, 1H), 4.0-4.1 (m, 2H), 3.7-3.8 (m, 1H), 3.4-3.5 (m, 2H), 3.38 (br s, 1H), 3.2-3.3 (m, 2H), 2.66 (s, 1H), 2.60 (d, 3H, J=2.0 Hz), 2.3-2.4 (m, 1H), 2.0-2.2 (m, 3H), 1.4-1.7 (m, 7H), 1.3-1.4 (m, 3H), 0.90 (br s, 4H)	659
274	^{1}H NMR (METHANOL-d4, 400 MHz) δ 6.5-6.7 (m, 1H), 6.0-6.4 (m, 1H), 5.5-5.6 (m, 1H), 4.6-4.8 (m, 2H), 4.5-4.6 (m, 2H), 4.1-4.5 (m, 8H), 3.4-3.5 (m, 4H), 2.6-2.7 (m, 4H), 2.2-2.4 (m, 1H), 2.0-2.2 (m, 3H), 1.61 (d, 3H, J=6.4 Hz), 1.3-1.4 (m, 1H), 0.9-0.9 (m, 4H)	665
275	N/A	691
276	N/A	679
277	N/A	677
278	N/A	657
279	N/A	691
280	N/A	671
281	N/A	671
282	N/A	685
283	N/A	647
284	N/A	647
285	^{1}H NMR (DMSO-d6, 400 MHz) δ 10.0-10.3 (m, 1H), 9.3-9.5 (m, 2H), 6.9-6.9 (m, 1H), 6.1-6.3 (m, 1H), 5.2-5.4 (m, 1H), 4.7-4.8 (m, 1H), 4.49 (br dd, 1H, J=6.3, 11.3 Hz), 4.1-4.3 (m, 7H), 3.3-3.4 (m, 6H), 2.47 (br d, 4H, J=2.0 Hz), 1.8-2.2 (m, 6H), 1.4-1.5 (m, 3H), 0.6-0.9 (m, 4H)	691
286	N/A	685
287	N/A	685
288	N/A	665
289	N/A	647
290	N/A	677
291	^{1}H NMR (DMSO-d6, 400 MHz) δ 10.1-10.3 (m, 1H), 9.2-9.5 (m, 2H), 6.8-7.0 (m, 2H), 6.2-6.3 (m, 1H), 5.2-5.5 (m, 2H), 4.7-4.8 (m, 1H), 4.0-4.3 (m, 8H), 3.38 (br s, 5H), 2.46 (br d, 5H, J=2.0 Hz), 1.8-2.1 (m, 5H), 1.5-1.5 (m, 3H), 1.0-1.1 (m, 1H), 0.7-1.0 (m, 4H)	677

[2546] **Example 500**: KRAS G12D LoEnz Biochemical Assay, BODIPY-GDP Exchange TR-FRET . Biochemical compound potencies are assessed by evaluating inhibition of SOS1-

mediated nucleotide exchange in KRAS G12D. In this assay, the SOS1-promoted exchange of fluorescently-labeled GDP (BOPIDY-GDP) is monitored by time-resolved fluorescence resonance energy transfer (TR-FRET). Compounds solubilized in DMSO are dispensed as concentration series into 384-well white assay plates. A preformed complex of biotin-tagged recombinant human KRAS (0.06 nM mutant G12D) and 0.06 nM terbium-labeled streptavidin (CisBIO) prepared in 10 uL/well assay buffer (20 mM HEPES, pH 7.5, 50 mM NaCl, 10 mM $MgCl_2$, 0.01% Tween-20 and 1 mM dithiothreitol) is added and allowed to incubate for 10-minutes at room temperature. The reaction is initiated with the addition of 5 uL 300 nM recombinant human SOS1 and 300 nM BODIPY-GDP in assay buffer. After a 120-minute incubation, the fluorescence is measured with excitation at 337 nm and emission at 490 and 520 nm. The TR-FRET ratio is determined as the fluorescence at 520 nm divided by the fluorescence at 490 nm multiplied by 10,000. The results are normalized to percent inhibition based on control samples: DMSO (0% inhibition) and control compound at a concentration that inhibits completely (100% inhibition). The normalized TR-FRET results are plotted against compound concentration, and the data are fit to a 4-parameter Hill equation to determine the IC_{50} values.

[2547] **Example 501**: KRAS WT Biochemical Assay, BODIPY-GDP Exchange TR-FRET. Biochemical compound potencies are assessed by evaluating inhibition of SOS1-mediated nucleotide exchange in KRAS WT. In this assay, the SOS1-promoted exchange of fluorescently-labeled GDP (BOPIDY-GDP) is monitored by time-resolved fluorescence resonance energy transfer (TR-FRET). Compounds solubilized in DMSO are dispensed as concentration series into 384-well white assay plates, and 5 uL assay buffer (20 mM HEPES, pH 7.5, 50 mM NaCl, 10 mM $MgCl_2$, 0.01% Tween-20 and 1 mM dithiothreitol) is added just prior to the start of the assay. A preformed complex of 3 nM biotin-tagged recombinant human KRAS WT and 0.3 nM terbium-labeled streptavidin (CisBIO) prepared in 5 uL/well assay buffer is added and allowed to incubate for 10-minutes at room temperature. The reaction is initiated with the addition of 5 uL 3 nM recombinant human SOS1 and 300 nM BODIPY-GDP in assay buffer. After a 60-minute incubation, the fluorescence is measured with excitation at 337 nm and emission at 490 and 520 nm. The TR-FRET ratio is determined as the fluorescence at 520 nm divided by the fluorescence at 490 nm multiplied by 10,000. The results are normalized to percent inhibition based on control samples: DMSO (0% inhibition) and control compound at a concentration that inhibits completely (100% inhibition). The normalized TR-FRET results are plotted against compound concentration, and the data are fit to a 4-parameter Hill equation to determine the IC_{50} values.

[2548] **Example 502**: KRAS WT Biochemical Assay, BODIPY-GDP Exchange TR-FRET. Biochemical compound potencies are assessed by evaluating inhibition of SOS1-mediated nucleotide exchange in KRAS WT. In this assay, the SOS1-promoted exchange of fluorescently-

labeled GDP (BOPIDY-GDP) is monitored by time-resolved fluorescence resonance energy transfer (TR-FRET). Compounds solubilized in DMSO are dispensed as concentration series into 384-well white assay plates. A preformed complex of 0.06 nM biotin-tagged recombinant human KRAS WT, 15 nM GDP and 0.06 nM terbium-labeled streptavidin (CisBIO) prepared in 10 uL/well assay buffer (20 mM HEPES, pH 7.5, 50 mM NaCl, 10 mM $MgCl_2$, 0.01% Tween-20 and 1 mM dithiothreitol) is added and allowed to incubate for 10-minutes at room temperature. The reaction is initiated with the addition of 5 uL 300 nM recombinant human SOS1 and 300 nM BODIPY-GDP in assay buffer. After a 120-minute incubation, the fluorescence is measured with excitation at 337 nm and emission at 490 and 520 nm. The TR-FRET ratio is determined as the fluorescence at 520 nm divided by the fluorescence at 490 nm multiplied by 10,000. The results are normalized to percent inhibition based on control samples: DMSO (0% inhibition) and control compound at a concentration that inhibits completely (100% inhibition). The normalized TR-FRET results are plotted against compound concentration, and the data are fit to a 4-parameter Hill equation to determine the IC_{50} values.

[2549] **Example 503**: KRAS 3D-Cell Proliferation Assays. Cellular potencies of compounds are assessed by evaluating inhibition of proliferation in 3D cultures of homozygous mutant KRAS G12D human pancreatic cell lines (AsPC-1 and HPAC) as compared to a KRAS wild type human lung adenocarcinoma cell line (PC-9 and/or H1975). Cells are seeded into 384-well black round-bottom, ultra-low attachment assay plates in 50 uL cell growth medium (RPMI-1640 with 10% fetal bovine serum and 2 mM L-glutamine). After overnight incubation at 37°C and 5% CO_2, compounds solubilized in DMSO are added as dilution series to the wells in a total volume of 150 nL (0.3% DMSO final). The cells are incubated for 7 days at 37°C and 5% CO_2. Cell proliferation is quantitated by addition of 40 uL/well of CellTiter-Glo® 3D (Promega), and the well contents are mixed 20x at high speed using liquid handling automation workstation (Bravo with 384-well head) and centrifuged at 1500 rpm for 2 minutes to eliminate bubbles. This reagent in combination with mechanical disruption releases the cellular ATP to promote activity in a luciferase-based enzyme/substrate chemiluminescent detection system. After a 30-minute incubation under ambient conditions with shaking and an additional 10 minutes without shaking, the luminescence is read on a plate reader (e.g., EnVision [PerkinElmer]). The results are normalized to percent inhibition based on the following control samples: DMSO (0% inhibition) and 1 μM staurosporine (100% inhibition). The normalized luminescence results are plotted against compound concentration, and the data are fit to a 4-parameter Hill equation to determine the IC_{50} values.

[2550] Table of Exemplary Compound Potencies.

Cmpd. No.	KRas(wt) GDP HTRF IC50	KRas (G12D) GDP HTRF IC50	Prolif PC9 3D ATP IC50	Prolif AsPC-1 3D ATP IC50	KRas HTRF IC50 [uM]	Prolif HPAC 3D ATP IC50 [uM]	Prolif H1975 3D ATP IC50 [uM]
1	0.008120	0.000120	16.900000	0.226000	NT	NT	NT
2	0.922000	0.015200	4.680000	0.565000	NT	NT	NT
3	0.000517	0.000058	20.000000	0.006720	0.000757	0.0112000	0.2020
4	9.570000	0.899000	13.300000	9.750000	NT	NT	NT
5	0.002120	0.000060	9.050000	0.006280	NT	0.0070600	1.4000
6	0.000480	0.000074	4.210000	0.000561	0.000548	0.0002470	0.6920
7	0.000296	0.000059	10.200000	0.001920	0.000288	0.0013600	0.1300
8	0.146000	0.001780	3.920000	0.072000	NT	0.0873000	4.3100
9	0.006510	0.000057	7.790000	0.019300	NT	0.0116000	2.0200
10	0.006460	0.000082	6.670000	0.004930	0.013300	0.0059600	2.2700
11	0.000380	0.000060	20.000000	0.002300	NT	0.0024100	0.1690
12	37.400000	0.379000	13.900000	16.600000	NT	NT	NT
13	1.540000	0.030700	3.530000	1.870000	1.770000	NT	NT
14	0.006580	0.000260	6.210000	0.005620	NT	0.0113000	2.5100
15	0.000448	0.000070	2.900000	0.001570	NT	NT	NT
16	0.000668	0.000138	20.000000	0.001300	0.000484	0.0007000	0.2550
17	0.000559	0.000133	7.910000	0.001710	0.001050	0.0006200	1.3400
18	7.850000	0.175000	7.910000	5.590000	NT	5.2200000	20.0000
19	0.001830	0.000080	8.800000	0.005050	NT	0.0033100	0.2170
20	0.006550	0.000120	8.680000	0.028700	NT	0.0077800	2.2200
21	3.890000	0.069900	7.700000	1.090000	NT	0.6980000	12.2000
21	1.400000	0.020300	8.130000	0.330000	NT	NT	NT
22	0.145000	0.002990	7.410000	0.060300	NT	0.1390000	20.0000
23	39.500000	0.725000	9.400000	14.000000	NT	NT	NT
23	94.500000	2.500000	20.000000	20.000000	NT	NT	NT
24	0.003280	0.000290	7.870000	0.004290	NT	0.0018900	6.7100
25	0.126000	0.002040	11.000000	0.464000	NT	0.0788000	10.7000
26	0.006010	0.000260	7.640000	0.005190	NT	0.0032400	1.5400
27	0.065200	0.000720	2.780000	0.032100	NT	0.0681000	2.3900
28	0.751000	0.009380	11.000000	0.363000	NT	0.2570000	20.0000
29	0.002930	0.000086	8.190000	0.004980	NT	0.0077600	6.1100
30	0.598000	0.019400	3.810000	0.166000	NT	0.1540000	2.8900
31	0.001550	0.000087	3.790000	0.001640	0.007110	0.0008080	0.4230
32	0.000579	0.000200	0.821000	0.003380	NT	NT	NT
33	0.007530	0.000230	3.920000	0.003720	NT	0.0012900	1.8500
34	0.002130	0.000235	6.950000	0.000692	0.004290	0.0005400	0.3400
35	0.015800	0.000570	9.170000	0.010600	NT	0.0074000	5.8700
36	0.046500	0.000980	6.110000	0.052400	NT	0.0314000	1.1300
38	0.697000	0.013900	7.380000	0.270000	NT	0.0961000	2.8300
39	0.076100	0.001780	20.000000	0.055800	NT	0.0358000	3.9700

40	0.086800	0.001300	15.700000	0.027700	NT	0.0360000	20.0000
41	0.296000	0.006350	20.000000	0.980000	NT	NT	NT
42	0.045200	0.000470	7.040000	0.122000	NT	NT	NT
43	0.016600	0.000598	20.000000	0.043400	NT	0.0168000	4.2900
44	0.059000	0.000680	20.000000	0.337000	NT	NT	NT
45	0.069400	0.000730	20.000000	0.112000	NT	NT	NT
45	0.319000	0.003160	20.000000	0.345000	NT	NT	NT
47	0.004430	0.000443	8.840000	0.003970	NT	0.0029500	1.5300
48	0.010500	0.000491	20.000000	0.008240	0.028500	0.0055200	5.7600
49	0.561000	0.808000	2.370000	20.000000	NT	NT	NT
49	0.331000	3.460000	4.240000	20.000000	NT	NT	NT
50	0.001690	0.000240	4.910000	0.013000	NT	0.0258000	0.4550
51	0.005600	0.000300	19.500000	0.051200	NT	0.0730000	1.8200
52	194.00000	2.140000	NT	NT	NT	NT	NT
53	200.00000	22.20000	NT	NT	NT	NT	NT
54	1.980000	0.017800	20.000000	2.090000	NT	3.4200000	20.0000
55	200.00000	22.20000	12.800000	20.000000	NT	NT	NT
56	46.500000	0.942000	20.000000	5.740000	NT	NT	NT
57	NT	0.000160	3.110000	0.000361	0.000633	0.0025900	0.2510
59	NT	0.000310	NT	NT	0.051400	0.1170000	10.5000
60	NT	0.000180	16.500000	0.003480	0.004550	0.0025900	0.7200
61	NT	0.000210	NT	0.044500	0.030500	0.0213000	2.6100
62	NT	0.000083	NT	0.000300	0.000290	0.0002610	0.1110
63	NT	0.000150	NT	NT	0.021700	0.0824000	20.8000
64	NT	0.000120	NT	0.000900	0.000738	0.0004600	0.2350
65	NT	0.001720	7.530000	0.064300	0.377000	0.0196000	7.9600
66	NT	0.002290	4.780000	0.041400	0.274000	0.0276000	7.1500
67	NT	0.000170	NT	NT	0.007530	0.0027900	0.6390
68	NT	0.000070	NT	NT	0.000112	0.0002050	0.1460
69	NT	0.000310	NT	0.021300	0.040900	0.0064200	1.2800
70	NT	0.000710	NT	0.044100	0.169000	0.0110000	1.7000
71	NT	0.003510	20.000000	0.132000	0.313000	NT	NT
72	NT	0.000280	NT	NT	0.012900	0.0031600	1.0600
73	NT	0.002600	NT	NT	0.036300	0.0163000	4.0900
74	NT	0.000330	NT	NT	0.030800	0.0057000	2.0400
75	NT	0.000130	NT	0.005200	0.011800	0.0027700	0.7970
76	NT	0.000130	5.710000	0.014100	0.014300	0.0046200	0.2480
77	NT	0.000240	NT	0.011900	0.021100	0.0027900	0.3580
78	NT	0.867000	20.000000	15.900000	200.0000	NT	NT
79	0.954000	0.022700	20.000000	4.040000	1.530000	NT	NT
80	0.003390	0.000068	4.050000	0.005080	0.003480	0.0027600	0.9240
81	NT	0.000085	20.000000	0.014700	0.000448	0.0124000	4.7800
82	NT	0.360000	NT	NT	23.50000	20.000000	20.0000
83	NT	0.001150	NT	NT	0.123000	0.0237000	2.2300

84	NT	0.024900	20.000000	1.160000	4.310000	NT	NT
85	NT	0.003280	20.000000	0.975000	0.678000	NT	NT
86	NT	0.004670	8.750000	0.144000	0.248000	0.1260000	5.4300
87	NT	0.068900	20.000000	4.030000	16.10000	1.4000000	20.0000
88	NT	1.470000	20.000000	20.000000	1.620000	NT	NT
89	NT	0.912000	NT	NT	1.650000	NT	NT
90	NT	0.000470	NT	0.018900	0.071600	0.0073000	1.1400
91	NT	0.000182	NT	0.001300	0.005710	0.0012500	0.9530
92	NT	0.001010	8.130000	0.017300	0.148000	0.0126000	20.0000
92	NT	0.000760	11.200000	0.006040	0.034900	0.0031000	0.3830
93	NT	0.073400	NT	NT	14.40000	0.8360000	20.0000
94	NT	2.300000	NT	NT	200.0000	2.2300000	15.2000
95	NT	0.026600	NT	0.200000	3.570000	0.2470000	6.7000
96	NT	0.000433	NT	0.005800	0.075800	0.0036900	0.9820
97	NT	0.000370	NT	0.010100	0.043700	0.0032100	0.5730
98	NT	0.004250	NT	NT	0.553000	0.0262000	2.7500
99	NT	0.002090	NT	NT	0.506000	0.0400000	5.0600
100	NT	0.001490	NT	NT	0.495000	0.0218000	3.9700
101	NT	0.003190	NT	NT	0.906000	0.0415000	8.4900
103	NT	0.000860	NT	NT	0.224000	0.0092900	3.4600
104	NT	0.000050	NT	0.001400	0.000710	0.0006500	0.2210
105	NT	0.141000	NT	NT	9.700000	2.0000000	20.0000
106	NT	0.001890	NT	NT	0.210000	0.0314000	0.7700
106	NT	0.000180	NT	0.005400	0.031100	0.0041900	0.6220
107	NT	0.001390	NT	NT	0.167000	0.0435000	4.8700
108	NT	0.000325	NT	NT	0.037600	0.0028500	0.7720
110	NT	0.000150	NT	NT	0.007750	0.0025800	0.5870
111	NT	0.000310	NT	NT	0.108000	0.0141000	1.8400
112	NT	0.000480	NT	0.031600	0.062800	0.0075900	1.4700
113	NT	0.000310	NT	NT	0.065600	0.0029100	1.1700
114	NT	0.135000	NT	NT	36.70000	2.0000000	20.0000
115	NT	0.000390	NT	NT	0.034100	0.0157000	2.7100
116	NT	0.002410	NT	NT	0.213000	0.5130000	20.0000
117	NT	0.004840	NT	NT	0.638000	0.1480000	4.7400
118	NT	0.000090	NT	0.000600	0.001760	0.0004300	0.5190
119 (isomer 1)	NT	0.004380	NT	NT	0.787000	0.0767000	3.1500
119 (isomer 2)	NT	0.000370	NT	NT	0.075000	0.0079500	1.7000
120	NT	0.000240	NT	NT	0.044500	0.0106000	1.5300
121 (isomer 1)	NT	0.000680	NT	NT	0.108000	0.0125000	1.3400
121 (isomer 2)	NT	0.000270	NT	0.041000	0.049300	0.0175000	0.5330
122	NT	0.000110	NT	NT	0.003720	0.0018400	0.4870
123	NT	0.000700	NT	NT	0.181000	0.0630000	13.9000

124	NT	0.001740	NT	NT	0.619000	0.2930000	12.2000
125	NT	0.000230	NT	0.010200	0.014700	0.0021400	1.2200
126 (isomer 1)	NT	0.000100	NT	0.000600	0.000420	0.0005100	0.7700
126 (isomer 2)	NT	0.000090	NT	NT	0.008080	0.0051500	1.7700
126 (isomer 3)	NT	0.000090	NT	NT	0.006310	0.0032800	1.4300
126 (isomer 4)	NT	0.000370	NT	NT	0.090300	0.0249000	2.2500
127 (isomer 1)	NT	0.000140	NT	NT	0.017900	0.0501000	6.0800
127 (isomer 2)	NT	0.000190	NT	NT	0.037700	0.0575000	7.9700
128	NT	0.000480	NT	NT	0.156000	0.0515000	5.0600
129	NT	0.000180	NT	0.001000	0.003870	0.0011000	1.1500
130 (isomer 1)	NT	0.002260	NT	NT	0.460000	0.0447000	2.8300
130 (isomer 2)	NT	0.000920	NT	NT	0.174000	0.0158000	2.9000
131 (isomer 1)	NT	0.013900	NT	NT	2.530000	1.4300000	20.0000
131 (isomer 2)	NT	0.001310	NT	NT	0.293000	0.3420000	20.0000
131 (isomer 3)	NT	0.002070	NT	NT	0.249000	0.0774000	8.8500
131 (isomer 4)	NT	0.001140	NT	NT	0.195000	0.0900000	6.8100
132	NT	0.001470	NT	NT	0.291000	0.0704000	14.2000
133 (isomer 1)	NT	0.000120	NT	NT	0.013600	0.0267000	2.6300
133 (isomer 2)	NT	0.000150	NT	NT	0.014400	0.0224000	1.6000
133 (isomer 3)	NT	0.000140	NT	NT	0.023300	0.0363000	0.6590
133 (isomer 4)	NT	0.000080	NT	NT	0.002300	0.0141000	2.0800
134 (isomer 1)	NT	0.000190	NT	NT	0.039400	0.0085900	2.5500
134 (isomer 2)	NT	0.000190	NT	NT	0.038100	0.0074500	1.9400
135	NT	0.000710	NT	NT	0.143000	0.0956000	20.0000
136	NT	0.000380	NT	0.200000	0.090800	0.0675000	12.3000
137 (isomer 1)	NT	0.002310	NT	NT	0.283000	0.1270000	20.0000
137 (isomer 2)	NT	0.002340	NT	NT	0.454000	0.1930000	20.0000
138	NT	0.000420	NT	NT	0.115000	0.0151000	2.5500
139	NT	0.002410	NT	NT	0.780000	0.1180000	8.5700
140	NT	0.000140	NT	0.004400	0.018400	0.0025300	2.0600
141	NT	0.000260	NT	NT	0.085000	0.0069200	6.2400

142	NT	0.000200	NT	NT	0.033200	0.0054500	3.5600
143 (isomer 1)	NT	0.000220	NT	NT	0.028100	0.0047200	0.9720
143 (isomer 2)	NT	0.000260	NT	0.004100	0.033500	0.0035200	1.1300
143 (isomer 3)	NT	0.000430	NT	NT	0.047300	0.0047700	1.0900
144	NT	0.000500	NT	NT	0.099500	0.0212000	7.5100
145	NT	0.000670	NT	NT	0.171000	0.0687000	5.1200
146	NT	0.000760	NT	NT	0.114000	1.7400000	20.0000
149	NT	0.018400	NT	NT	5.450000	0.1860000	20.0000
150 (isomer 1)	NT	0.000180	NT	NT	0.027500	0.0137000	3.7700
150 (isomer 2)	NT	0.000250	NT	NT	0.064500	0.0239000	2.8500
151 (isomer 1)	NT	0.001840	NT	NT	0.398000	0.3230000	20.0000
151 (isomer 2)	NT	0.000120	NT	NT	0.025500	0.0080400	1.6900
152 (isomer 1)	NT	0.000100	NT	NT	0.015700	0.0174000	0.7870
152 (isomer 2)	NT	0.003230	NT	NT	0.526000	0.2990000	6.3300
153 (isomer 1)	NT	0.000370	NT	NT	0.090900	0.0190000	4.7400
153 (isomer 2)	NT	0.000320	NT	NT	0.087600	0.0134000	4.1800
153 (isomer 3)	NT	0.000550	NT	NT	0.125000	0.0329000	4.4900
154	NT	0.000470	NT	NT	0.118000	0.0205000	4.1000
155	NT	0.000220	NT	NT	0.031500	0.0088400	4.7500
156	NT	NT	NT	0.009400	NT	0.0029400	0.7760
157	NT	0.000550	NT	NT	0.045600	0.0128000	2.1400
158	NT	0.003390	NT	NT	0.121000	0.0099400	13.8000
159 (diast. 1)	NT	0.000280	NT	NT	0.064000	0.0369000	4.3100
159 (diast. 2)	NT	0.000230	NT	NT	0.048100	0.0238000	1.2400
159 (mixture)	NT	0.000230	NT	NT	0.045200	0.0179000	3.7400
160 (diast. 1)	NT	0.000140	NT	NT	0.031300	0.0080700	1.0000
160 (diast. 2)	NT	0.000120	NT	NT	0.022500	0.0069700	0.7550
161	NT	0.007610	NT	NT	1.330000	0.0689000	13.0000
162	NT	0.000130	NT	0.200000	0.041300	0.0487000	9.4500
163	NT	0.000110	NT	NT	0.019600	0.0102000	1.1400
164	NT	0.000150	NT	NT	0.030600	0.0438000	7.1100
165 a	NT	0.000080	NT	0.000600	0.001140	0.0006300	0.3740

165 b	NT	0.000100	NT	0.000849	0.001430	0.0006600	0.4990
165 c	NT	0.000090	NT	0.001100	0.002190	0.0010900	0.4810
166 a	NT	0.000100	NT	NT	0.003680	0.0014400	1.2700
166 b	NT	0.000150	NT	NT	0.005380	0.0014900	0.4020
167 a	NT	0.000170	NT	NT	0.013600	0.0015800	1.1400
167 b	NT	0.000190	NT	NT	0.013800	0.0018200	1.0600
168	NT	0.000120	NT	0.000700	0.001680	0.0004720	0.6560
169	NT	0.000100	NT	NT	0.002310	0.0009200	0.4540
170	NT	0.000090	NT	0.000800	0.002160	0.0009200	0.5060
171	NT	0.000253	NT	NT	0.013700	0.0013300	0.9040
172	NT	0.000240	NT	NT	0.011100	0.0017200	0.8640
173	NT	0.000080	NT	NT	0.005950	0.0013300	0.9170
174	NT	0.003390	NT	0.001300	0.003040	0.0038600	0.2270
175	NT	0.003390	NT	NT	0.108000	0.0196000	2.3400
176	NT	0.002800	NT	0.200000	0.809000	0.1680000	15.2000
177	NT	0.126000	NT	NT	11.70000	4.4500000	20.0000
178	NT	NT	NT	NT	NT	0.1330000	9.2800
179	NT	0.006640	NT	NT	0.659000	0.2940000	8.4100
180	NT	0.017400	NT	NT	2.740000	2.0000000	20.0000
181 (isomer 1)	NT	0.159000	NT	NT	10.90000	2.0000000	12.3000
181 (isomer 2)	NT	0.050400	NT	NT	3.030000	0.9030000	7.2600
182	NT	0.000269	NT	0.008300	0.033900	0.0041200	1.9100
183	NT	0.000210	NT	0.004200	0.004460	0.0023200	0.8520
184	NT	0.001980	NT	NT	0.393000	0.1470000	20.0000
185	NT	0.001100	NT	NT	0.107000	0.0320000	4.9300
186	NT	0.000100	NT	0.008900	0.005610	0.0025800	1.0900
187	NT	0.000510	NT	NT	0.163000	0.0348000	18.9000
188	NT	0.001260	NT	NT	0.225000	0.0660000	10.1000
189	NT	0.002310	NT	NT	0.252000	0.0954000	20.0000
190	NT	0.000110	NT	0.012600	0.010100	0.0022000	1.5600
191	NT	0.000460	NT	NT	0.091100	0.0296000	1.4100
192	NT	NT	NT	NT	NT	0.0071700	1.2800
193	NT	32.80000	NT	NT	128.0000	2.0000000	20.0000
194	NT	0.000420	NT	0.002700	0.028900	0.0049900	0.9190
195	NT	0.000440	NT	NT	0.108000	0.0221000	1.3400
196	NT	0.248000	NT	NT	20.10000	20.000000	20.0000
197	NT	0.000460	NT	NT	0.059800	0.0097900	0.4680
198	NT	0.000620	NT	NT	0.085800	0.0130000	3.7200
199	NT	0.000170	NT	0.004060	0.009630	0.0009800	1.0500
200	NT	0.000100	NT	NT	0.006700	0.0068300	0.5930
201	NT	0.009190	NT	NT	1.620000	0.4070000	10.6000
202	NT	0.001980	NT	NT	0.214000	2.0000000	20.0000
203	NT	0.026800	NT	NT	1.590000	0.5200000	20.0000

204	NT	0.000385	NT	NT	0.069100	0.0189000	1.4200
205	NT	0.003390	NT	NT	0.008610	0.0033500	1.1300
206	NT	0.000170	NT	0.003600	0.024200	0.0031600	2.8400
207	NT	0.000360	NT	NT	0.043100	0.0023600	1.4200
208	NT	0.000310	NT	NT	0.024700	0.0048900	3.6300
209	NT	0.000240	NT	NT	0.018500	0.0034700	0.2820
210	NT	NT	NT	0.003600	NT	0.0018100	0.8680
211	NT	0.000210	NT	NT	0.017800	0.0014500	1.1500
212	NT	0.000560	NT	NT	0.039100	0.0016400	0.3890
213	NT	0.000310	NT	NT	0.013600	0.0012500	0.2950
214	NT	0.000420	NT	0.025400	0.055700	0.0080400	7.0300
215	NT	0.000210	NT	0.007800	0.007100	0.0025000	0.8310
216	NT	NT	NT	0.000600	NT	0.0008930	0.1610
217	NT	0.003390	NT	NT	0.242000	0.0388000	12.6000
218	NT	0.000290	NT	NT	0.014100	0.0013600	0.3840
219	NT	0.000460	NT	NT	0.047300	0.0036700	8.2800
220	NT	0.000920	NT	NT	0.149000	0.0118000	20.0000
221	NT	0.000390	NT	0.001200	0.009950	0.0014500	0.4980
222	NT	0.003390	NT	NT	0.045700	0.0057600	1.4800
223	NT	0.003390	NT	NT	0.051300	0.0064600	1.2300
224	NT	0.000180	NT	0.003500	0.012000	0.0027200	0.7110
225	NT	0.000250	NT	0.002900	0.004200	0.0011900	0.5610
226	NT	0.000400	NT	0.001200	0.008110	0.0008600	0.5680
227	NT	0.000210	NT	NT	0.000938	0.0005160	0.6790
228	NT	0.370000	NT	NT	4.880000	2.0000000	20.0000
229	NT	0.000360	NT	NT	0.012000	0.0018200	0.6390
230	NT	0.001130	NT	NT	0.213000	0.0284000	5.8400
231	NT	0.004600	NT	NT	1.240000	0.0398000	13.2000
232	NT	0.002860	NT	NT	0.277000	0.0770000	10.5000
233	NT	NT	NT	NT	NT	2.0000000	5.4000
234 (isomer 1)	NT	1.330000	NT	NT	23.30000	2.0000000	8.5700
234 (isomer 2)	NT	0.209000	NT	NT	0.513000	2.0000000	9.7500
234 (isomer 3)	NT	4.810000	NT	NT	4.570000	2.0000000	16.6000
234 (isomer 4)	NT	0.589000	NT	NT	0.510000	2.0000000	8.5000
235 (isomer 1)	NT	0.065800	NT	NT	0.143000	2.4200000	4.3400
235 (isomer 2)	NT	0.000480	NT	NT	0.002630	0.1360000	0.2620
236	NT	0.068000	NT	NT	0.830000	2.0000000	14.5000
237 (isomer 1)	NT	1.910000	NT	NT	1.020000	NT	NT
237 (isomer 2)	NT	0.000150	NT	0.200000	0.000350	0.0036300	1.0400

238 (isomer 1)	NT	7.700000	NT	NT	3.810000	2.0000000	13.5000
238 (isomer 2)	NT	13.00000	NT	NT	4.800000	2.0000000	20.0000
239	NT	0.000580	NT	NT	0.000940	0.0334000	0.5690
240 (atrop. 1)	NT	0.044900	NT	NT	1.080000	0.5940000	6.4800
240 (atrop. 2)	NT	0.000140	NT	0.001500	0.015100	0.0018800	1.0600
241	NT	0.000130	NT	NT	0.015400	0.0162000	1.2000
242	NT	0.000330	NT	0.007800	0.005290	0.0051100	1.0400
243	NT	0.581000	NT	NT	3.960000	2.0000000	20.0000
244	NT	0.000520	NT	NT	0.011900	0.0061400	0.2580
245	NT	0.000249	NT	0.003600	0.007440	0.0041300	0.7390
246	NT	0.311000	NT	NT	1.200000	2.0000000	20.0000
247	NT	0.000210	NT	0.001000	0.000959	0.0016400	0.6430
248	NT	0.001100	NT	0.027900	0.000522	0.0125000	0.2440
249	NT	0.000220	NT	0.001100	0.001370	0.0013700	0.4170
250	NT	0.000390	NT	NT	0.013600	0.0169000	0.9940
251	NT	0.000160	NT	0.001900	0.001050	0.0023000	0.2340
252 (isomer 1)	NT	0.001170	NT	NT	0.025000	0.0204000	7.7100
252 (isomer 2)	NT	0.005890	NT	NT	0.159000	0.1190000	20.0000
253	NT	0.001030	NT	0.064600	0.037100	0.0198000	5.0800
254	NT	0.000490	NT	0.002500	0.001250	0.0018600	0.1390
255 a	NT	0.000410	NT	0.006600	0.001390	0.0016600	0.1200
255 b	NT	0.000270	NT	0.004700	0.001170	0.0042100	0.3080
256	NT	0.000820	NT	NT	0.017000	0.0139000	0.0934
257	NT	0.000890	NT	0.008000	0.008410	0.0083700	5.0200
258 (isomer 1)	NT	0.000090	NT	0.008100	0.014900	0.0050000	1.5600
258 (isomer 2)	NT	0.000070	NT	0.006900	0.011000	0.0026800	1.5500
259	NT	0.000160	NT	NT	0.009710	0.0123000	1.9700
260	NT	0.000280	NT	NT	0.026200	0.0415000	3.2500
261	NT	0.002760	NT	NT	0.097100	0.1070000	6.1000
262 (isomer 1)	NT	0.031900	NT	NT	0.668000	0.4750000	20.0000
262 (isomer 2)	NT	0.007020	NT	NT	0.186000	0.1230000	20.0000
262 (isomer 3)	NT	0.041100	NT	NT	1.080000	0.9710000	20.0000
262 (isomer 4)	NT	0.001140	NT	NT	0.035100	0.0434000	4.3800
263 (diast. 1)	NT	0.000260	NT	0.007100	0.005490	0.0061400	0.7890
263 (diast. 2)	NT	0.000530	NT	NT	0.015400	0.0154000	0.3360

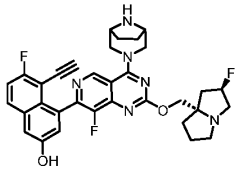
264	NT	0.000330	NT	NT	0.019200	0.0055600	11.0000
265	NT	0.000280	NT	NT	0.014100	0.0022400	6.2400
266	NT	0.003050	NT	NT	1.100000	NT	NT
267	NT	0.002980	NT	NT	0.609000	NT	NT
268	NT	0.000290	NT	NT	0.011900	0.0021700	1.7000
269	NT	0.000420	NT	NT	0.105000	NT	NT
270	NT	0.000260	NT	NT	0.010700	0.0025200	2.4800
271	NT	0.000510	NT	NT	0.056400	0.0044900	10.9000
272	NT	0.000380	NT	NT	0.024400	0.0045800	5.4800
273	NT	0.000290	NT	NT	0.017100	0.0065300	3.1900
274	NT	0.000340	NT	NT	0.025700	0.0075500	1.0700
275	NT	0.000480	NT	NT	0.023300	0.0032900	5.1800
276	NT	0.000260	NT	NT	0.008910	0.0018200	1.6200
277	NT	NT	NT	NT	NT	0.0020900	0.9740
278	NT	NT	NT	NT	NT	NT	NT
279	NT	NT	NT	NT	NT	0.0020200	1.2700
280	NT	NT	NT	NT	NT	0.0017700	1.3400
281	NT	NT	NT	NT	NT	0.0086000	2.4300
282	NT	NT	NT	NT	NT	0.0039600	2.4500
283	NT	NT	NT	NT	NT	0.0015800	0.5770
284	NT	NT	NT	NT	NT	0.0012300	0.4900
285	NT	NT	NT	NT	NT	0.0030500	0.6080
286	NT	NT	NT	NT	NT	NT	NT
287	NT	NT	NT	NT	NT	0.0057200	1.3800
288	NT	NT	NT	NT	NT	0.0188000	9.8100
289	NT	NT	NT	NT	NT	0.0031500	0.5730
290	NT	NT	NT	NT	NT	0.0025300	2.7800
291	NT	NT	NT	NT	NT	0.0040900	12.2000

NT = not tested

[2551] **Example 504**: Pharmacokinetic profiling.

[2552] The pharmacokinetics of Compound **6** were evaluated following a single intravenous bolus (IV) of solution at doses of 0.5 – 1 mg/kg and oral administration (PO) of solution at doses of 5 – 30 mg/kg in female CD-1 mice or male Sprague Dawley rats using a parallel study design. Blood samples for the IV dose group in mice were collected at 0.033, 0.083, 0.25, 0.5, 1, 3, and 8 hours post-dose, and plasma samples for the same group were collected at 8 hours post-dose. Blood samples for the PO dose group in mice were collected at 0.25, 0.5, 1, 3, 8, and 24 hours post-dose. Blood and plasma samples for the IV dose group in rats were collected at 0.033, 0.083, 0.25, 0.5, 1, 2, 4, 8, and 24 hours post-dose. Blood and plasma samples for PO dose groups in rats were collected at 0.083, 0.25, 0.5, 1, 2, 4, 8, and 24 hours post-dose. The vehicle used for IV dose groups was 10% DMSO, 35% PEG400, 55% Water, and for PO groups was 80% PEG400/20% EtOH. Plasma and blood concentrations were quantitated at Wuxi Inc. using a non-validated

LC/MS/MS method. The lower limits of quantitation (LLOQ) are 0.0079 μM for blood assays, and 0.0016 μM for plasma assays. Pharmacokinetic parameters were calculated by non-compartmental methods as described in Gibaldi and Perrier (Gibaldi and Perrier, 1982) using Phoenix® WinNonlin® version 8.3.4 (Certara L.P.). Following PO administration, percent bioavailability (% F) was determined for each animal by dividing the dose-normalized area under the plasma and blood concentration-time curve, extrapolated to infinity (AUCinf) obtained following each PO dose by the mean dose-normalized AUCinf of the animals dosed by IV injections. All PK parameters are presented as mean ± standard deviation (SD).

[2553] The pharmacokinetics of **Comparator Compound**  were evaluated following a single intravenous bolus (IV) of solution at a dose of 1 mg/kg and oral administration (PO) of solution at doses of 5 – 30 mg/kg in female CD-1 mice or male Sprague Dawley rats using a parallel study design. Blood samples for the IV dose group in mice were collected at 0.033, 0.083, 0.25, 0.5, 1, 3, and 8 hours post-dose, and plasma samples for the same group were collected at 8 hours post-dose. Blood samples for the PO dose group in mice were collected at 0.083, 0.25, 0.5, 1, 3, 8, and 24 hours post-dose. Blood and plasma samples for the IV dose group in rats were collected at 0.033, 0.083, 0.25, 0.5, 1, 2, 4, 8, and 24 hours post-dose. Blood and plasma samples for the PO dose group in rats were collected at 0.083, 0.25, 0.5, 1, 2, 4, 8, and 24 hours post-dose. For the IV group in rats, urine was collected from each animal from 0 – 8 and 8 – 24 hours post dose. The vehicle used for IV dose groups was 10% DMSO, 35% PEG400, 55% Water, and for PO groups was 80% PEG400/20% EtOH. Plasma and blood concentrations were quantitated at Wuxi Inc. using a non-validated LC/MS/MS method. The lower limits of quantitation (LLOQ) are 0.0085 μM for blood assays, 0.0017 μM for plasma assays (IV group in mice and PO group in rats), 0.0051 μM for plasma assays (IV group in rats), and 0.017 μM for urine assays. Pharmacokinetic parameters were calculated by non-compartmental methods as described in Gibaldi and Perrier (Gibaldi and Perrier, 1982) using Phoenix® WinNonlin® version 8.3.4 (Certara L.P.). Following PO administration, percent bioavailability (% F) was determined for each animal by dividing the dose-normalized area under the plasma and blood concentration-time curve, extrapolated to infinity (AUCinf) obtained following each PO dose by the mean dose-normalized AUCinf of the animals dosed by IV injections. All PK parameters are presented as mean ± standard deviation (SD).

[2554] The pharmacokinetics of Compound **81** were evaluated following a single intravenous bolus (IV) of solution at a dose of 0.5 mg/kg and oral administration (PO) of solution at a dose of

5 mg/kg in female CD-1 mice using a parallel study design. Blood samples for the IV dose group were collected at 0.033, 0.083, 0.25, 0.5, 1, 3, and 8 hours post-dose, and plasma samples for the same group were collected at 8 hours post-dose. Blood samples for the PO dose group were collected at 0.25, 0.5, 1, 3, 8, and 24 hours post-dose. The vehicle used for IV dose groups was 10% DMSO, 35% PEG400, 55% Water, and for PO groups was 80% PEG400/20% EtOH. Plasma and blood concentrations were quantitated at Wuxi Inc. using a non-validated LC/MS/MS method. The lower limits of quantitation (LLOQ) are 0.0081 μM for blood assays, and 0.0049 μM for plasma assays. Pharmacokinetic parameters were calculated by non-compartmental methods as described in Gibaldi and Perrier (Gibaldi and Perrier, 1982) using Phoenix® WinNonlin® version 8.3.4 (Certara L.P.). Following PO administration, percent bioavailability (% F) was determined for each animal by dividing the dose-normalized area under the blood concentration-time curve, extrapolated to infinity (AUCinf) obtained following each PO dose by the mean dose-normalized AUCinf of the animals dosed by IV injections. All PK parameters are presented as mean ± standard deviation (SD).

[2555] The pharmacokinetics of Compound **7** were evaluated following a single intravenous bolus (IV) of solution at doses of 0.5 – 1 mg/kg and oral administration (PO) of solution at doses of 5 – 30 mg/kg in female CD-1 mice or male Sprague Dawley rats using a parallel study design. Blood samples for the IV dose group in mice were collected at 0.033, 0.083, 0.25, 0.5, 1, 3, and 8 hours post-dose, and plasma samples for the same group were collected at 8 hours post-dose. Blood samples for the PO dose group in mice were collected at 0.25, 0.5, 1, 3, 8, and 24 hours post-dose. Blood and plasma samples for the IV dose group in rats were collected at 0.033, 0.083, 0.25, 0.5, 1, 2, 4, 8, and 24 hours post-dose. Blood and plasma samples for the PO dose group in rats were collected at 0.083, 0.25, 0.5, 1, 2, 4, 8, and 24 hours post-dose. The vehicle used for IV dose groups was 10% DMSO, 35% PEG400, 55% Water, and for PO groups was 80% PEG400/20% EtOH. Plasma and blood concentrations were quantitated at Wuxi Inc. using a non-validated LC/MS/MS method. The lower limits of quantitation (LLOQ) are 0.0079 μM for blood assays, and 0.0016 μM for plasma assays. Pharmacokinetic parameters were calculated by non-compartmental methods as described in Gibaldi and Perrier (Gibaldi and Perrier, 1982) using Phoenix® WinNonlin® version 8.3.4 (Certara L.P.). Following PO administration, percent bioavailability (% F) was determined for each animal by dividing the dose-normalized area under the plasma and blood concentration-time curve, extrapolated to infinity (AUCinf) obtained following each PO dose by the mean dose-normalized AUCinf of the animals dosed by IV injections. All PK parameters are presented as mean ± standard deviation (SD).

[2556] The pharmacokinetics of Compound **194** were evaluated following a single intravenous bolus (IV) of solution at a dose of 0.5 mg/kg and oral administration (PO) of solution at doses of

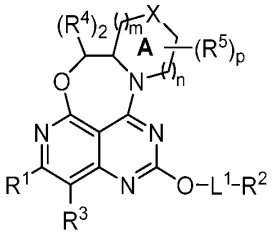
5 – 30 mg/kg in female CD-1 mice or male Sprague Dawley rats using a parallel study design. Blood samples for the IV dose group in mice were collected at 0.033, 0.083, 0.25, 0.5, 1, 3, and 8 hours post-dose, and plasma samples for the same group were collected at 8 hours post-dose. Blood samples for the PO dose group in mice were collected at 0.25, 0.5, 1, 3, 8, and 24 hours post-dose. Blood and plasma samples for the IV and PO dose groups in rats were collected at 0.033, 0.083, 0.25, 0.5, 1, 2, 4, 8, and 24 hours post-dose. The vehicle used for IV dose groups was 10% DMSO, 35% PEG400, 55% Water, and for PO groups was 80% PEG400/20% EtOH. Plasma and blood concentrations were quantitated at Pharmaron Inc. using a non-validated LC/MS/MS method. The lower limits of quantitation (LLOQ) are 0.0078 μM in mice and 0.0039 μM in rats for blood assays, and 0.0016 μM in mice and 0.00078 μM in rats for plasma assays. Pharmacokinetic parameters were calculated by non-compartmental methods as described in Gibaldi and Perrier (Gibaldi and Perrier, 1982) using Phoenix® WinNonlin® version 8.3.4 (Certara L.P.). Following PO administration, percent bioavailability (% F) was determined for each animal by dividing the dose-normalized area under the plasma and blood concentration-time curve, extrapolated to infinity (AUCinf) obtained following each PO dose by the mean dose-normalized AUCinf of the animals dosed by IV injections. All PK parameters are presented as mean ± standard deviation (SD).

[2557] The pharmacokinetics of compounds 6, 7, 81 and 194, and comparator compound are provided in Figure 1.

CLAIMS

What is claimed is:

1. A compound of formula (I):



(I),

or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

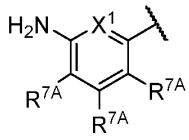
X is O or NR^6;

m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is formula  (E), wherein X^1 is N or CR^{7C} and R^{7C} is hydrogen or halogen;

each R^{7A} is independently halogen, CN, NH_2, $N(Me)_2$, R^{7B}-substituted or unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or unsubstituted cyclopropyl;

R^{7B} is CN, oxo, or C_{1-3} alkyl;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein

two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

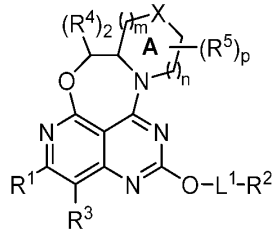
R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

2. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of claim 1, wherein X^1 is CR^{7C} and R^{7C} is hydrogen or halogen.

3. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of claim 1, wherein X^1 is N.

4. A compound of formula (I):



(I),

or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

X is O or NR^6;

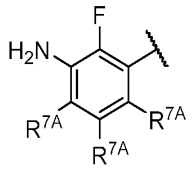
m is 1 or 2;

n is 1 or 2;

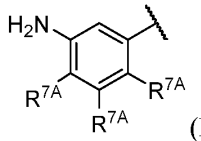
wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is (E2) or (E3)



(E2) or



(E3);

each R^{7A} is independently hydrogen, halogen, unsubstituted C_{1-3} alkyl or unsubstituted C_{1-3} haloalkyl;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;
R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and
R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

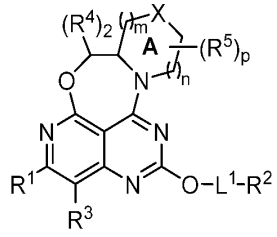
5. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of claim 4, wherein no more than one R^{7A} is hydrogen.

6. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of claim 4, wherein R^{7A} is not hydrogen.

7. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of claim 4, wherein at least one R^{7A} is halogen.

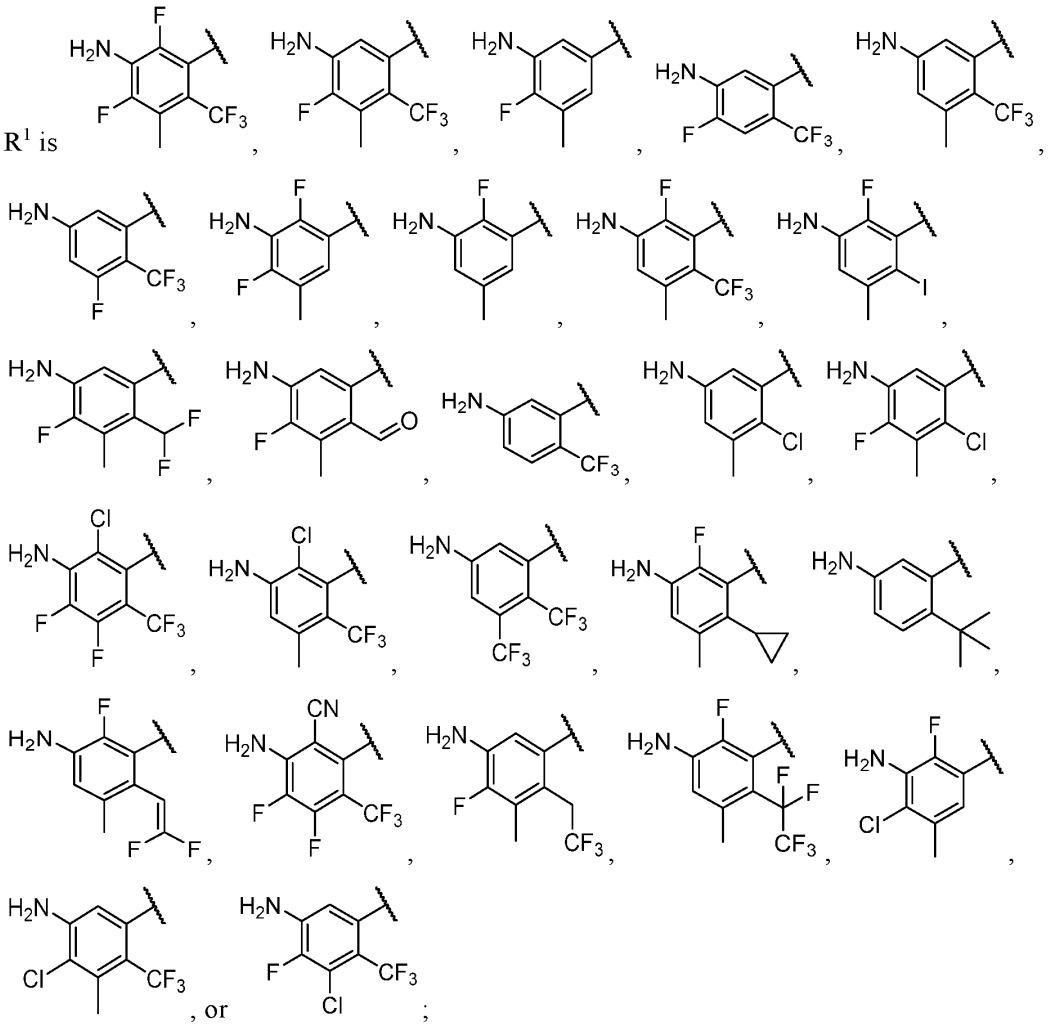
8. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of claim 4, wherein at least one R^{7A} is unsubstituted C1-3 haloalkyl.

9. A compound of formula (I):



(I),

or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein
X is O or NR^6;
m is 1 or 2;
n is 1 or 2;
wherein n and m together make a 6- or 7-membered ring Ring A;
p is 0, 1, or 2;

R^1 is  , or ;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

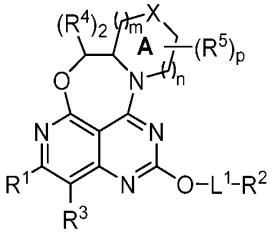
R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;
R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;
each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;
R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein
two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or
two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};
R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;
R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;
R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and
R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

10. A compound of formula (I):



(I),

or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein
X is O or NR^6;
m is 1 or 2;
n is 1 or 2;
wherein n and m together make a 6- or 7-membered ring Ring A;
p is 0, 1, or 2;
R^1 is R^{7A}-substituted phenyl or R^{7A}-substituted pyridinyl;
each R^{7A} is independently halogen, NH_2, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl;
L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

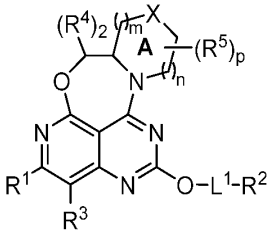
R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

11. A compound of formula (I):



(I),

or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

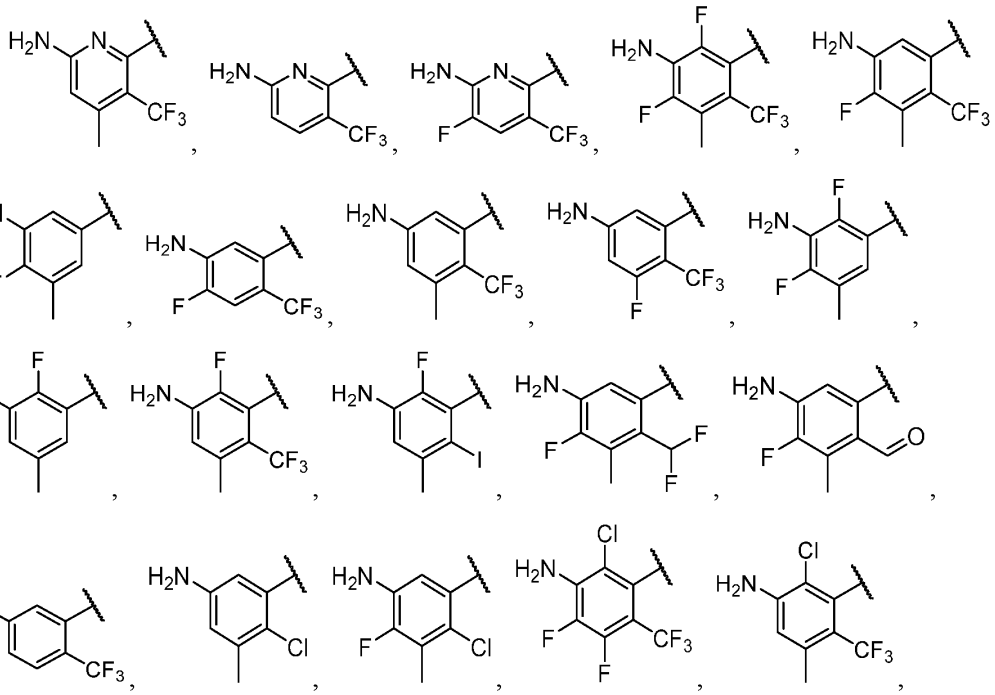
X is O or NR^6;

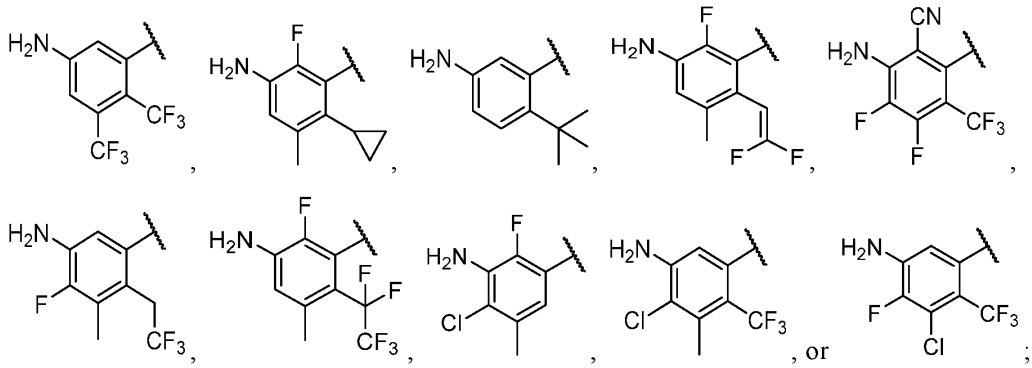
m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is 



L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

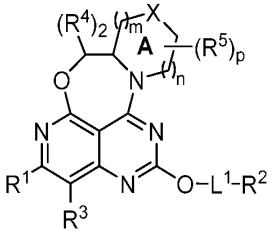
R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

12. A compound of formula (I):



(I),

or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

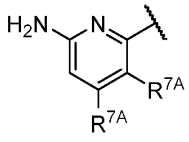
X is O or NR^6;

m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is of formula  (E1);

each R^{7A} is independently halogen, CN, NH_2, $N(Me)_2$, R^{7B}-substituted or unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or unsubstituted cyclopropyl;

R^{7B} is CN, oxo, or C_{1-3} alkyl;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein

two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

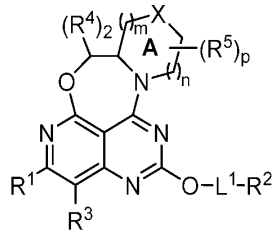
R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

13. A compound of formula (I):



(I),

or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, wherein

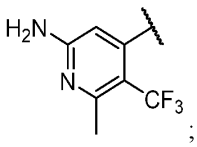
X is O or NR^6;

m is 1 or 2;

n is 1 or 2;

wherein n and m together make a 6- or 7-membered ring Ring A;

p is 0, 1, or 2;

R^1 is  ;

L^1 is R^{L1}-substituted or unsubstituted C_{1-4} alkylene;

R^{L1} is halogen or unsubstituted C_{1-3} alkyl, or wherein two R^{L1} together form an unsubstituted C_{3-4} cycloalkyl;

R^2 is R^9-substituted or unsubstituted 4-10 membered heterocycle comprising one or more heteroatoms selected from N, S, or O;

R^9 is independently halogen, CN, OH, OCF_3, $OCHF_2$, OCH_2F, R^{10}-substituted or unsubstituted C_{1-3} alkyl, R^{10}-substituted or unsubstituted C_{1-3} haloalkyl, unsubstituted C_{1-3} alkoxy, R^{10}-substituted or unsubstituted C_{1-3} alkylidene, or R^{10}-substituted or unsubstituted C_{3-4} cycloalkyl, or R^{10}-substituted or unsubstituted 3 or 4-membered heterocycle; or wherein two R^9 together form a R^{10}-substituted or unsubstituted C_{3-5} cycloalkyl or a R^{10}-substituted or unsubstituted C_{3-5} heterocycle comprising one or more oxygen atoms; or wherein two R^9 together form a bridge between two carbon atoms of the cycloalkyl or heterocycle, wherein the bridge comprises 1-3 carbons;

each R^{10} is independently hydrogen, oxo, CN, halogen, or C_{1-3} unsubstituted alkyl;

R^3 is hydrogen, -CN, halogen, unsubstituted C_{1-3} alkyl, or unsubstituted cyclopropyl;

each R^4 is independently hydrogen, methyl, or C_{1-3} haloalkyl;

R^5 is independently halogen, oxo, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl; or wherein

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons and optionally one heteroatom selected from O and N; or

two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises one of O or NR^{11};

R^{11} is hydrogen, $C(O)CH_3$, or unsubstituted C_{1-3} alkyl;

R^6 is hydrogen, R^{6A}-substituted or unsubstituted C_{1-6} alkyl, R^{6A}-substituted or unsubstituted C_{1-6} haloalkyl, R^{6A}-substituted or unsubstituted C_{1-6} alkenyl; R^{6A}-substituted or unsubstituted C_{1-6} alkynyl, or R^{6A}-substituted or unsubstituted 3-4 membered heterocycle;

R^{6A} is halogen, CN, OR^{6B}, SR^{6C}, $S(O)_2R^{6C}$, $C(O)R^{6B}$, unsubstituted C_{1-3} alkyl, unsubstituted C_{1-3} haloalkyl, or R^{6B}-substituted or unsubstituted 3-4 membered heterocycle; and

R^{6B} and R^{6C} are each independently C_{1-3} alkyl or C_{1-3} haloalkyl.

14. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-13, wherein each R^4 is hydrogen.

15. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-13, wherein one R^4 is hydrogen and one R^4 is methyl.

16. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-13, wherein R^4 is hydrogen and one R^4 is -CF_3.

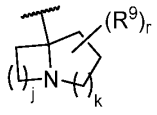
17. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-3 and 12, wherein each R^{7A} is independently halogen, NH_2, unsubstituted C_{1-3} alkyl, or unsubstituted C_{1-3} haloalkyl.

18. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-3, 10, 12, and 14-17, wherein at least one R^{7A} is NH_2.

19. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-18, wherein L^1 is methylene.

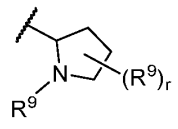
20. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-18, wherein L^1 is R^{L1}-substituted or unsubstituted C_{2-3} alkylene.

21. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-20, wherein R^2 is


(A),

or a stereoisomer thereof, wherein,
R^9 is halogen or R^{10}-substituted or unsubstituted C_{1-3} alkylidene
r is an integer of 0-12;
j is 1, 2, or 3; and
k is 1 or 2.

22. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-20, wherein R^2 is



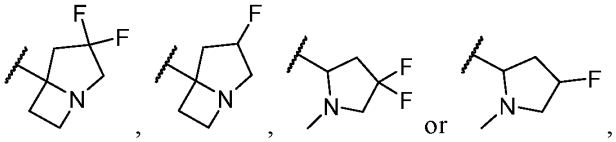
(B),

or a stereoisomer thereof, wherein

R^9 is independently halogen or unsubstituted C_{1-3} alkyl; and

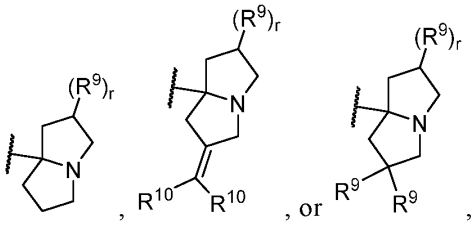
r is 1 or 2.

23. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-20, wherein R^2 is:



or a stereoisomer thereof.

24. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-20, wherein R^2 is:



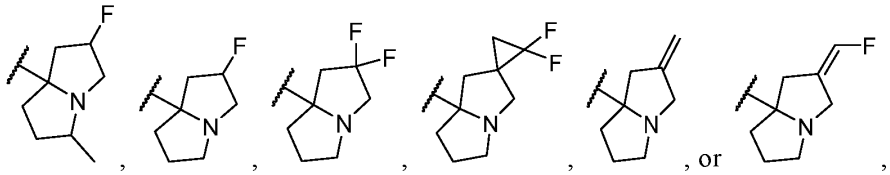
or a stereoisomer thereof, wherein

R^9 is independently halogen or R^{10}-substituted or unsubstituted C_{1-3} alkylidene;

each R^{10} is independently hydrogen or halogen; and

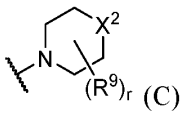
r is 1 or 2.

25. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-20, wherein R^2 is:



or a stereoisomer thereof.

26. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-20, wherein R^2 is:

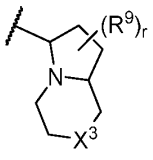


(C)

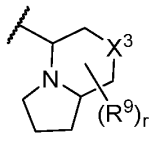
or a stereoisomer thereof,

wherein X^2 is CR^9 or O.

27. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-20, wherein R^2 is:



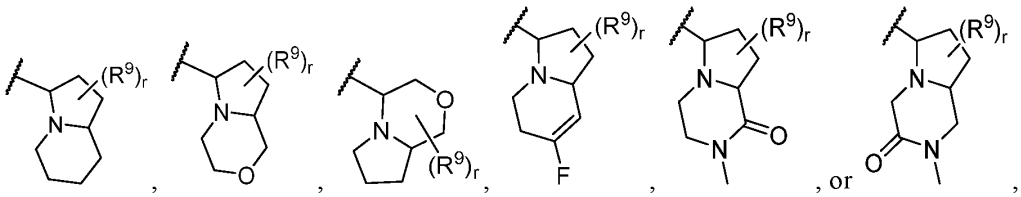
(D) or



(D1),

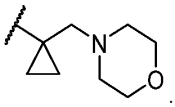
or a stereoisomer thereof, wherein X^3 is CR^9 , NR^9, or O.

28. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-20, wherein R^2 is:



or a stereoisomer thereof.

29. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-20, wherein R^2 is:



30. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-29, wherein R^3 is halogen.

31. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-30, wherein two R^5 together form a bridge between two carbon atoms of Ring A, wherein the bridge comprises 1-3 carbons.

32. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of claim 31, wherein the bridge comprises 2 carbon atoms.

33. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of claim 31, the bridge comprises 1 carbon atom.

34. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-33, wherein X is NR^6.

35. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of claim 34, wherein R^6 is hydrogen or R^{6A}-substituted or unsubstituted C_{1-3} alkyl.

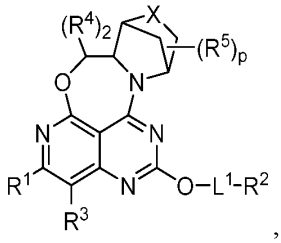
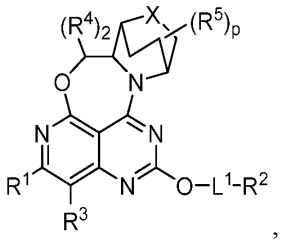
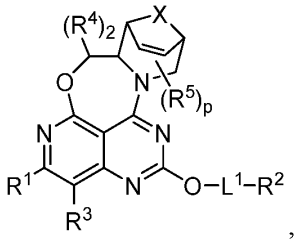
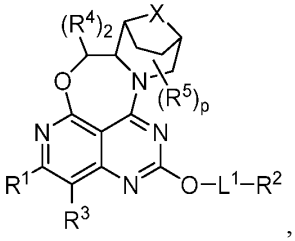
36. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of claim 34, wherein R^6 is R^{6A}-substituted or unsubstituted C_{1-3} alkyl.

37. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 34-36, wherein R^{6A} is halogen, CN, OH, OMe, OEt, OCF_3, SO_2Me, unsubstituted C_{1-3} alkyl, or 4-membered heterocycle.

38. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of claim 34, wherein R^6 is hydrogen.

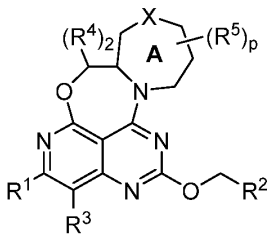
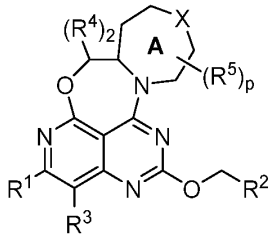
39. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-38, wherein R^2 is azetidinyl, oxetanyl, or thietanedioxide.

40. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-13, wherein the compound of formula (I) comprises formula:


,

,

, or

,

or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

41. The compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-13, wherein the compound of formula (I) comprises formula:


(IIIa) or

(IIIb),

or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

42. A compound selected from compounds 1-36, 38-45, 47-62, 64-108, 110-146, and 149-291 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

43. A compound selected from compounds 1-36, 38-45, 47-62, 64-108, and 110-125 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

44. A compound selected from compounds 126-146 and 149-291 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

45. A compound selected from compounds 6, 15, 24, 26, 29, 31-32, 57-59, 61-62, 64-66, 75-76, 91, 96, 104, 106, 111, 113, 118-124, 126-146, 149-156, 158-175, 181, 183, 186, 190-192, 195, 200, 204, 224-225, 228-229, 232-239, 241, 244-250, 255, 258-259, and 263 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

46. A compound selected from compounds 6, 12-18, 23-24, 26, 29, 31-36, 57-58, 60-62, 64-77, 90-97, 100-102, 104, 108, 111, 113, 115, 118-146, 149-175, 181-183, 186-187, 190, 195, 200, 204, 224-232, 234-239, 241, 244-250, 255, 258-259, and 263 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

47. A compound selected from compounds 6, 13-14, 16-18, 23-24, 26, 29, 31-34, 36, 57-62, 64-72, 74, 76, 91-104, 106-108, 111, 113, 115, 117-146, 149-154, 157, 159-174, 199, 200, 224-229, 234-241, 244-249, 255, 258-259, and 263 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

48. A compound selected from compounds 6, 12-18, 23-24, 26, 29, 31-36, 42-45, 47-48, 52, 57-58, 60-78, 84-88, 90-97, 100-104, 106, 108, 111-113, 115, 118-146, 149-175, 177-178, 181-183, 185-187, 189-192, 194-195, 197-200, 203-232, 234-250, and 252-291 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

49. A compound selected from compounds 6, 13-14, 16-18, 23-24, 26, 29, 31-34, 36, 42-45, 47-48, 52, 57-62, 64-72, 74, 76, 84-88, 91-104, 106-108, 111, 113, 115, 117-146, 149-154, 157, 159-174, 199, 200, 224-229, 234-241, 244-249, 255, 258-259, and 263 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

50. A compound selected from compounds 42-45, 47-48, and 52 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

51. A compound selected from compounds 112, 205-218, 242-243, 252-254, 261-262, and 264-291 in Table 1 or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

52. A pharmaceutical composition comprising a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-51, and one or more pharmaceutically acceptable excipients.

53. A method of treating cancer, the method comprising administering an effective amount of a compound or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof of any one of claims 1-51, or a pharmaceutical composition of claim 52.

54. The method of claim 53, wherein the cancer is characterized as comprising a KRas mutation.

55. The method of claim 54, wherein the KRas mutation corresponds to a $KRas^{G12D}$ mutation.

56. The method of any one of claims 53-55, further comprising testing a sample from the patient before administration for the absence or presence of a $KRas^{G12D}$ mutation.

57. The method of claim 56, wherein the compound, stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof or pharmaceutical composition is administered to the patient after the patient sample shows the presence of a $KRas^{G12D}$ mutation.

58. The method of any one of claims 53-57, wherein the cancer is tissue agnostic.

59. The method of any one of claims 53-57, wherein the cancer is pancreatic cancer, lung cancer, or colorectal cancer.

60. The method of claim 59, wherein the lung cancer is lung adenocarcinoma, NSCLC, or SCLC.

61. The method of claim 59, wherein the cancer is pancreatic cancer.

62. The method of claim 59, wherein the cancer is colorectal cancer.

63. The method of any one of claims 53-62, further comprising administering at least one additional therapeutic agent.

64. The method of claim 63, wherein the additional therapeutic agent comprises an epidermal growth factor receptor (EGFR) inhibitor, phosphatidylinositol kinase (PI3K) inhibitor, insulin-like growth factor receptor (IGF1R) inhibitor, a Janus kinase (JAK) inhibitor, a Met kinase inhibitor, a SRC family kinase inhibitor, a mitogen-activated protein kinase (MEK) inhibitor, an extracellular-signal-regulated kinase (ERK) inhibitor, a topoisomerase inhibitor, a taxane, an anti-metabolite agent, or an alkylating agent.

65. A compound according to any one of claims 1-51, or a stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, for use as a therapeutically active substance.

66. Use of a compound of any one of claims 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, for the therapeutic treatment of a cancer comprising a $KRas^{G12D}$ mutation.

67. Use of a compound according to any one of claims 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically salt thereof, in the manufacture of a medicament for inhibiting tumor metastasis.

68. Use of a compound of any one of claims 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, for the preparation of a medicament for the therapeutic treatment of a cancer comprising a $KRas^{G12D}$ mutation.

69. A compound according to any one of claims 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically salt thereof, for the therapeutic and/or prophylactic treatment of a cancer comprising a $KRas^{G12D}$ mutation.

70. A method for regulating activity of a KRas mutant protein, the method comprising reacting the mutant protein with a compound of any one of claims 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

71. A method for inhibiting proliferation of a cell population, the method comprising contacting the cell population with the compound of any one of claims 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof.

72. A method of claim 71, wherein the inhibition of proliferation is measured as a decrease in cell viability of the cell population.

73. A method for inhibiting tumor metastasis comprising administering to an individual in need thereof a therapeutically effective amount of the compound of any one of claims 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof to a subject in need thereof.

74. A compound of any one of claims 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in regulating activity of a KRas mutant protein.

75. A compound of any one of claims 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in inhibiting proliferation of a cell population.

76. The compound, stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt for use of claim 75, wherein the inhibition of proliferation is measured as a decrease in cell viability of the cell population.

77. A compound of any one of claims 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, for use in inhibiting tumor metastasis.

78. Use of a compound of any one of claims 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for regulating activity of a KRas mutant protein.

79. Use of a compound of any one of claims 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting proliferation of a cell population.

80. The use of claim 79, wherein the inhibition of proliferation is measured as a decrease in cell viability of the cell population.

81. Use of a compound of any one of claims 1-51, or stereoisomer, atropisomer, tautomer, or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting tumor metastasis.