

RAS INHIBITORS AND METHODS OF USE THEREOF**CROSS REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims the benefit of, and priority to, U.S. Provisional Patent Application No. 63/588,031, filed on October 5, 2023; U.S. Provisional Patent Application No. 63/667,196, filed on July 3, 2024; and U.S. Provisional Patent Application No. 63/696,429, filed on September 19, 2024; the content of each of which is hereby incorporated by reference herein in its entirety.

BACKGROUND

[0002] Ras proteins (e.g., K-Ras, H-Ras and N-Ras) play an important role in various human cancers and represent attractive targets for anticancer therapy. Dysregulation of Ras proteins by activating mutations, overexpression or upstream activation is commonly observed in human tumor cells, and activating mutations in Ras are often observed in human cancers. For example, activating mutations at codon 12 in Ras proteins function by inhibiting both GTPase-activating protein (GAP)-dependent and intrinsic hydrolysis rates of GTP, significantly altering the population of Ras mutant proteins to the "on" (GTP-bound) state (Ras(ON)), leading to oncogenic MAPK signaling. Ras proteins show a strong affinity for GTP, thereby allowing Ras to be activated even in the presence of low concentrations of this nucleotide. Mutations at codons 13 (e.g., G13D) and 61 (e.g., Q61K) of Ras are also responsible for oncogenic activity in some cancers.

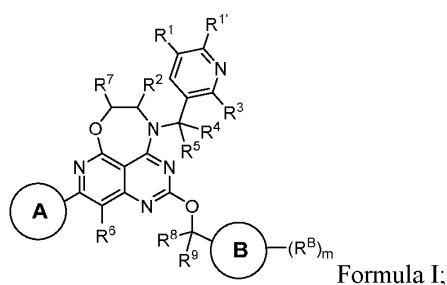
[0003] For example, oncogenic K-Ras mutations that stabilize GTP binding and lead to constitutive activation of K-Ras and downstream signaling have been reported in various types of cancers. K-Ras mutations at codons 12, 13, 61 and other positions of the K-Ras primary amino acid sequence have been observed in patient with pancreatic, colorectal, non-small cell lung, and small cell lung adenocarcinomas.

[0004] Despite extensive research and discovery efforts by the pharmaceutical industry to develop inhibitors of Ras (e.g., K-Ras) for treating cancer, no such inhibitor has yet demonstrated sufficient safety and/or efficacy to obtain regulatory approval. Thus, an unmet need exists to develop new pan-Ras inhibitors, for example inhibitors of activating Ras mutants, that show safety and efficacy profiles necessary for treating Ras-mediated cancers and other conditions that are affected by, associated with, or would benefit from inhibition of Ras.

SUMMARY

[0005] The disclosure is directed, in part, to compounds that inhibit Ras, for example, multiple mutated forms of Ras, for example, K-Ras. Also disclosed herein are pharmaceutical compositions comprising at least one disclosed compound and a pharmaceutically acceptable carrier. In some embodiments, the present disclosure provides a method of treating a disease or disorder characterized by aberrant Ras activity due to a Ras mutation (e.g., aberrant K-Ras activity due to a K-Ras mutation). In some embodiments, the disease or disorder is a cancer.

[0006] For example, disclosed herein is a compound represented by Formula I:



or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

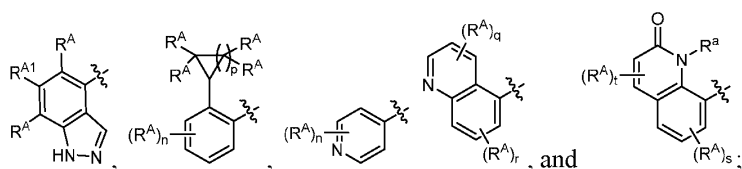
R^1 is selected from the group consisting of halogen, C₃-C₄cycloalkyl, C₁-C₆alkyl, C₂-C₆alkenyl, and C₂-C₆alkynyl; wherein cycloalkyl, alkyl, alkenyl, and alkynyl may optionally be substituted with one, two, or three halogens;

R^2 is hydrogen or C₁-C₆alkyl optionally substituted with one or more halogens or hydroxyl; and

ring A is selected from the group consisting of indazolyl, quinolinyl, quinolinonyl, benzothiophenyl, benzothiazolyl, pyrazolopyridyl, pyridyl, phenyl, and naphthyl, wherein ring A is substituted with one or more substituents each independently selected from R^A ;

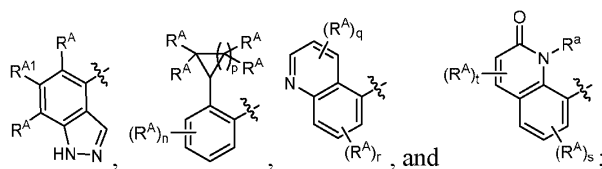
or:

R^1 is hydrogen; R^2 is C₁-C₆alkyl optionally substituted with one or more halogens or hydroxyl; and ring A is selected from the group consisting of:



or:

R^1 is hydrogen; R^2 is hydrogen; and ring A is selected from the group consisting of:



- R^A is independently selected for each occurrence from the group consisting of hydrogen, halogen, deuterium, hydroxyl, -CN, -NO₂, -NR^aR^b, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, and phenyl may optionally be substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, oxo, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;

- R^{A1} is selected from the group consisting of hydrogen, deuterium, chloro, -CN, -NO₂, -NR^aR^b, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, and phenyl may optionally be substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, oxo, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;

- $R^{1'}$ is hydrogen or halogen;

R^3 is selected from the group consisting of -NR^aR^b, halogen, C₁-C₂alkyl, and hydrogen, wherein alkyl may optionally be substituted with one, two, or three halogens;

R^4 is selected from the group consisting of hydrogen and C₁-C₂alkyl, wherein alkyl may optionally be substituted with one, two, or three halogens;

- R^5 is C₁-C₂alkyl optionally be substituted with one, two, or three halogens;

R^6 is selected from the group consisting of halogen, hydrogen, deuterium, and C₁-C₃alkyl;

R^7 is selected from the group consisting of hydrogen and C_1 - C_6 alkyl optionally substituted with one or more halogens or hydroxyl;

R^8 and R^9 are each independently selected from the group consisting of hydrogen, deuterium, and C_1 - C_3 alkyl;

5 Ring B is selected from the group consisting of 4-12 membered heterocyclyl containing at least one ring nitrogen;

R^B is independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, -CN, - NR^aR^b , -COOH, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, =CHF, and =CH- C_1 - C_6 alkyl; wherein C_1 - C_6 alkyl may optionally be substituted with one, two, or three
10 substituents each independently selected from the group consisting of hydroxyl, halogen, and C_1 - C_3 alkoxy; or

Ring B and R^B are absent and replaced with a substituent selected from the group consisting of - CH_2OH and C_3 - C_4 cycloalkyl, wherein cycloalkyl is substituted with a substituent selected from the group consisting of - CH_2OH and - CH_2 - NR^aR^b , and

15 R^a and R^b are each independently selected from the group consisting of hydrogen and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, and C_1 - C_6 alkoxy; or

R^a and R^b , together with the nitrogen to which they are attached, may be joined together
20 to form a 4-7 membered heterocyclyl optionally substituted by one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, - NR^aR^b , C_1 - C_6 alkyl, and C_1 - C_6 alkoxy;

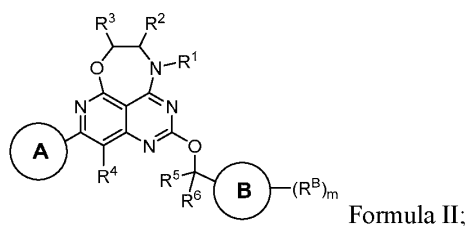
m and n are each independently 0, 1, 2, 3, or 4;

p is 1, 2, or 3;

25 q, r, and s are each independently 0, 1, 2, or 3; and

t is 0, 1, or 2.

[0007] Also disclosed herein is a compound represented by Formula II:



or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

- ring A is selected from the group consisting of indazolyl, quinolinyl, quinolinonyl, benzothiophenyl, benzothiazolyl, pyridinyl, pyrimidinyl, and phenyl; wherein ring A is substituted with one, two, or three substituents each independently selected from R^A ;
- R^A is independently selected for each occurrence from the group consisting of hydrogen, halogen, deuterium, hydroxyl, -CN, -NO₂, -NR^aR^b, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, and phenyl may optionally be substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, oxo, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;
- R^1 is selected from the group consisting of C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, -CH(CH₃)-(C₃-C₆cycloalkyl), -CH₂-(C₃-C₆cycloalkyl), phenyl, 5-membered heteroaryl, and -CR^cR^d-(5-membered heteroaryl); wherein alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, and heteroaryl may optionally be substituted with one, two, three, or four substituents each independently selected from R^{11} ;
- R^2 is selected from the group consisting of hydrogen, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, -CH(CH₃)-(C₃-C₆cycloalkyl), -CH₂-(C₃-C₆cycloalkyl), phenyl, 5-membered heteroaryl, and -CR^cR^d-(5-membered heteroaryl); wherein alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, and heteroaryl may optionally be substituted with one, two, three, or four substituents each independently selected from R^{22} ;
- R^{11} and R^{22} are independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, -CN, -NO₂, -NR^aR^b, oxo, C₁-C₆alkyl, C₁-C₆alkoxy, phenyl, -COOH, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl;

R^3 is selected from the group consisting of hydrogen and C_1 - C_6 alkyl optionally substituted with one or more halogens or hydroxyl;

R^4 is selected from the group consisting of halogen, hydrogen, deuterium, and C_1 - C_3 alkyl;

5 R^5 and R^6 are each independently selected from the group consisting of hydrogen, deuterium, and C_1 - C_3 alkyl;

Ring B is selected from the group consisting of 5-10 membered heterocyclyl containing at least one ring nitrogen;

10 R^B is independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, -CN, - NR^aR^b , C_1 - C_6 alkyl, and C_1 - C_6 alkoxy;

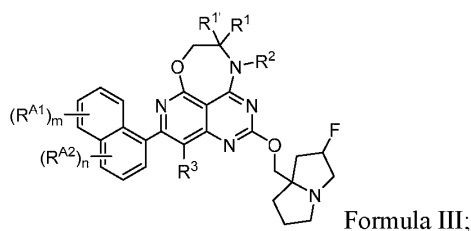
R^a and R^b are each independently selected from the group consisting of hydrogen and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, and C_1 - C_6 alkoxy; or

15 R^a and R^b , together with the nitrogen to which they are attached, may be joined together to form a 4-7 membered heterocyclyl optionally substituted by one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, - NR^aR^b , C_1 - C_6 alkyl, and C_1 - C_6 alkoxy; and

m is 0, 1, 2, 3, or 4;

20 wherein if ring A is benzothiophenyl, then R^1 is CH_3 or substituted C_1 - C_6 alkyl.

[0008] Further disclosed herein is a compound represented by Formula III:



or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

25 R^{A1} and R^{A2} are independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, -CN, - NO_2 , - NR^aR^b , C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, phenyl, - $C(=O)NR^aR^b$, - $NR^a(C=O)R^b$, - $O(C=O)NR^aR^b$, -

NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, and phenyl may optionally be substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, oxo, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;

R¹¹ is hydrogen and R¹ is selected from the group consisting of hydrogen, -CH₃, -CF₃, -CH₂CH₂OH, -CH₂C(CH₃)₂OH, C₂-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, phenyl, 5-membered heteroaryl, and -CR^cR^d-(5-membered heteroaryl); wherein alkyl is substituted with one, two, three, or four substituents each independently selected from R¹¹; and wherein alkenyl, alkynyl, cycloalkyl, phenyl, and heteroaryl may optionally be substituted with one, two, three, or four substituents each independently selected from R²²; and

R² is selected from the group consisting of hydrogen, -CH₃, -CH₂CH₂OH, -CH₂CH₂CH₂OH, -CH₂CH(CH₃)OH, -CH₂C(CH₃)₂OH, C₂-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃cycloalkyl, C₅-C₆cycloalkyl, phenyl, 5-membered heteroaryl, and -CR^cR^d-(5-membered heteroaryl); wherein alkyl is substituted with one, two, three, or four substituents each independently selected from R¹¹; and wherein alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, and heteroaryl may optionally be substituted with one, two, three, or four substituents each independently selected from R²²;

or:

R¹ and R¹¹, together with the carbon atom to which they are attached, may be joined together to form C₃-cycloalkyl optionally substituted with one, two or three halogens or hydroxyl; and R² is C₁-C₆alkyl substituted with one, two, or three substituents each independently selected from the group consisting of halogen, hydroxyl, cyano, -COOH, and C(=O)NR^aR^b; or

R¹ and R¹¹, together with the carbon atom to which they are attached, may be joined together to form C₄-cycloalkyl optionally substituted with one, two or three halogens or hydroxyl; and R² is C₁-C₆alkyl optionally substituted with one, two, or three substituents each independently selected from the group consisting of halogen, hydroxyl, cyano, -COOH, and C(=O)NR^aR^b;

R¹¹ is independently selected for each occurrence from the group consisting of halogen, deuterium, -CN, -NO₂, -NR^aR^b, oxo, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -COOH, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -

(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl;

R²² is independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, -CN, -NO₂, -NR^aR^b, oxo, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -COOH, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl;

R³ is selected from the group consisting of halogen, hydrogen, deuterium, and C₁-C₃alkyl;

R^a and R^b are each independently selected from the group consisting of hydrogen and C₁-C₆alkyl, wherein C₁-C₆alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, and C₁-C₆alkoxy; or

R^a and R^b, together with the nitrogen to which they are attached, may be joined together to form a 4-7 membered heterocyclyl optionally substituted by one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;

R^c and R^d are each independently selected from the group consisting of hydrogen and C₁-C₆alkyl;

m is 0, 1, 2, 3, or 4; and

n is 0, 1, or 2;

wherein:

if R¹ is hydrogen, then R² is not hydrogen, -CH₃, or CH₂CH₂OH; and

if R¹ is -CH₃, then R² is not hydrogen, -CH₃, -CH₂CF₂, -CH₂CF₃, or -CH₂CH(CH₃)OH.

[0009] Also disclosed herein are pharmaceutical compositions comprising at least one compound of the disclosure and at least one pharmaceutically acceptable excipient. In certain embodiments, the pharmaceutical compositions comprise at least one additional therapeutic agent.

[0010] Further disclosed herein are methods of treating a patient suffering from a condition, disease, or disorder that is affected by, associated with, or would benefit from inhibition of Ras

(e.g., K-Ras), comprising administering to the patient a therapeutically effective amount of a compound disclosed herein, or a pharmaceutical composition thereof.

[0011] For example, disclosed herein are methods of treating a Ras protein-related (e.g., a K-Ras protein-related) disease or disorder in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound disclosed herein, or a pharmaceutical composition thereof. For example, in some embodiments, the compounds and compositions disclosed herein may be used to treat a cancer having one or more Ras mutations (e.g., a K-Ras mutation). In some embodiments, the methods described herein may be useful to treat cancers including, but not limited to, pancreatic cancer, colorectal cancer, multiple myeloma, lung adenocarcinoma, melanoma, endometrial cancer, uterine cancer, thyroid, acute myelocytic leukemia, bladder carcinoma, gastric cancer, cervical cancer, and head and neck squamous cell carcinoma.

[0012] Also disclosed herein are methods of inhibiting a Ras protein (e.g., a K-Ras protein) in a cell or tissue, comprising contacting the cell or tissue with a therapeutically effective amount of a compound disclosed herein, or a pharmaceutical composition thereof.

DETAILED DESCRIPTION

[0013] The features and other details of the disclosure will now be more particularly described. Before further description of the present disclosure, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and as understood by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

Definitions

[0014] The term “treating” includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.

[0015] The term “alkyl” as used herein refers to a saturated straight or branched hydrocarbon. Exemplary alkyl groups include, but are not limited to, straight or branched hydrocarbons of 1-6, 1-4, or 1-3 carbon atoms, referred to herein as C₁₋₆alkyl, C₁₋₄alkyl, and C₁₋₃alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-butyl, 3-methyl-2-butyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-

butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.

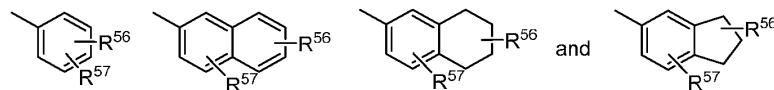
[0016] The term “alkenyl” as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond. Exemplary alkenyl groups include, but are not limited to, a straight or branched group of 2-6 or 3-4 carbon atoms, referred to herein as C₁-C₅alkenyl, C₂-C₆alkenyl, and C₃-C₄alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc.

[0017] The term “alkynyl” as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond. Exemplary alkynyl groups include, but are not limited to, straight or branched groups of 2-6, or 3-6 carbon atoms, referred to herein as C₂-C₆alkynyl, and C₃-C₆alkynyl, respectively. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, etc.

[0018] The term “alkoxy” as used herein refers to a straight or branched alkyl group attached to oxygen (alkyl-O-). Exemplary alkoxy groups include, but are not limited to, alkoxy groups of 1-6 or 2-6 carbon atoms, referred to herein as C₁-C₅alkoxy, C₁-C₆alkoxy, and C₂-C₆alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.

[0019] The term “aryl” refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 p electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C_{6–14} aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl”; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C₁₄ aryl”; *e.g.*, anthracyl). “Aryl” also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, and trinaphthalene. Particularly aryl groups include phenyl, naphthyl,

indenyl, and tetrahydronaphthyl. Examples of representative substituted aryls include the following



- wherein one of R^{56} and R^{57} may be hydrogen and at least one of R^{56} and R^{57} is each
- 5 independently selected from C_1 - C_8 alkyl, C_1 - C_8 haloalkyl, 4-10 membered heterocyclyl, alkanoyl, C_1 - C_8 alkoxy, heteroaryloxy, alkylamino, arylamino, heteroarylamino, $NR^{58}COR^{59}$, $NR^{58}SOR^{59}$, $NR^{58}SO_2R^{59}$, $COOalkyl$, $COOaryl$, $CONR^{58}R^{59}$, $CONR^{58}OR^{59}$, $NR^{58}R^{59}$, $SO_2NR^{58}R^{59}$, S-alkyl, SOalkyl, SO_2alkyl , Saryl, SOaryl, SO_2aryl ; or R^{56} and R^{57} may be joined
 - 10 to form a cyclic ring (saturated or unsaturated) from 5 to 8 atoms, optionally containing one or more heteroatoms selected from the group N, O, or S. R^{60} and R^{61} are each independently hydrogen, C_1 - C_8 alkyl, C_1 - C_4 haloalkyl, C_3 - C_{10} cycloalkyl, 4-10 membered heterocyclyl, C_6 - C_{10} aryl, substituted C_6 - C_{10} aryl, 5-10 membered heteroaryl, or substituted 5-10 membered heteroaryl.

[0020] The term “carbonyl” as used herein refers to the radical $-C(O)-$.

- 15 [0021] The term “cyano” as used herein refers to the radical $-CN$.

- [0022] The terms “cycloalkyl” or a “carbocyclic group” as used herein refers to a saturated or partially unsaturated hydrocarbon group of, for example, 3-6, or 4-6 carbons, referred to herein as C_3 - C_{10} cycloalkyl, C_3 -6cycloalkyl or C_4 -6cycloalkyl, respectively. Exemplary cycloalkyl groups include, but are not limited to, cyclohexyl, cyclopentyl, cyclopentenyl, cyclobutyl or cyclopropyl.
- 20

[0023] The terms “halo” or “halogen” as used herein refer to F, Cl, Br, or I.

- [0024] The terms “haloalkyl” as used herein refers to an alkyl radical in which the alkyl group is substituted with one or more halogens. Typical haloalkyl groups include, but are not limited to, trifluoromethyl (i.e., CF_3), difluoromethyl, fluoromethyl, chloromethyl, dichloromethyl, dibromoethyl, tribromomethyl, tetrafluoroethyl, and the like. Exemplary haloalkyl groups include, but are not limited to, straight or branched hydrocarbons of 1-6, 1-4, or 1-3 carbon atoms substituted with a halogen (i.e., Cl, F, Br and I), referred to herein as C_1 -6haloalkyl, C_{1-4} haloalkyl, and C_{1-3} haloalkyl, respectively.
- 25

- [0025] The term “hetero” when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbyl
- 30

groups described above such as alkyl, e.g., heteroalkyl, cycloalkyl, e.g., heterocyclyl, aryl, e.g., heteroaryl, cycloalkenyl, e.g., cycloheteroalkenyl, and the like having from 1 to 5, and particularly from 1 to 3 heteroatoms.

[0026] The terms “heteroaryl” or “heteroaromatic group” as used herein refers to an aromatic 5-10 membered ring system containing one or more heteroatoms, for example one to three heteroatoms, such as nitrogen, oxygen, and sulfur. The term may also be used to refer to a 5-7 membered monocyclic heteroaryl or an 8-10 membered bicyclic heteroaryl. Where possible, said heteroaryl ring may be linked to the adjacent radical through carbon or nitrogen. Examples of heteroaryl rings include but are not limited to furan, thiophene, pyrrole, pyrrolopyridine, indole, thiazole, oxazole, isothiazole, isoxazole, imidazole, benzoimidazole, imidazopyridine, pyrazole, triazole, pyridine or pyrimidine, etc.

[0027] The terms “heterocyclyl,” “heterocycle,” or “heterocyclic group” are art-recognized and refer to saturated or partially unsaturated 4-10 membered ring structures, whose ring structures include one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Where possible, heterocyclyl rings may be linked to the adjacent radical through carbon or nitrogen. The term may also be used to refer to 4-10 membered saturated or partially unsaturated ring structures that are bridged, fused or spirocyclic ring structures, whose ring structures include one to three heteroatoms, such as nitrogen, oxygen, and sulfur. Examples of heterocyclyl groups include, but are not limited to, pyrrolidine, piperidine, morpholine, thiomorpholine, piperazine, oxetane, azetidine, tetrahydrofuran, dihydrofuran, dihydropyran, tetrahydropyran, etc. In some embodiments, the heterocycle is a spiro heterocycle (e.g., 2,8-diazaspiro[4.5]decane). In some embodiments, the heterocycle is a bridged heterocycle (e.g., octahydro-1H-4,7-methanoisoindole). “Spiro heterocyclyl,” or “spiro heterocycle” refers to a polycyclic heterocyclyl with rings connected through one common atom (called a spiro atom), wherein the rings have one or more heteroatoms selected from the group consisting of N, O, and S(O)_m (wherein m is an integer of 0 to 2) as ring atoms.

[0028] The terms “hydroxy” and “hydroxyl” as used herein refers to the radical -OH.

[0029] The term “oxo” as used herein refers to the radical =O.

[0030] “Pharmaceutically or pharmacologically acceptable” include molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, and general safety and purity standards as required by FDA Office of Biologics standards.

[0031] The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

[0032] The term “pharmaceutical composition” as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers.

[0033] “Individual,” “patient,” or “subject” are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. The compounds of the disclosure can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, *e.g.*, domestic animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like). “Modulation” includes antagonism (*e.g.*, inhibition), inverse agonism, agonism, biased agonism, biased signal transduction, functionally selective agonism, partial antagonism and/or partial agonism.

[0034] In the present specification, the term “therapeutically effective amount” means the amount of the subject compound that will elicit the biological or medical response of a tissue, system or animal, (*e.g.*, mammal or human) that is being sought by the researcher, veterinarian, medical doctor or other clinician. The compounds of the disclosure are administered in therapeutically effective amounts to treat a disease. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect.

[0035] The term “pharmaceutically acceptable salt(s)” as used herein refers to salts of acidic or basic groups that may be present in compounds used in the compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, including, but not limited to, malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate,

oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts, particularly calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

[0036] The compounds of the disclosure may contain one or more chiral centers and, therefore, exist as stereoisomers. The term "stereoisomers" when used herein consist of all enantiomers or diastereomers. These compounds may be designated by the symbols "(+)," "(-)," "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. The present disclosure encompasses various stereoisomers of these compounds and mixtures thereof. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[0037] The compounds of the disclosure may contain one or more double bonds and, therefore, exist as geometric isomers resulting from the arrangement of substituents around a carbon-carbon double bond. The symbol $\equiv$ denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the "Z" or "E" configuration wherein the terms "Z" and "E" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "E" and "Z" isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond.

[0038] Compounds of the disclosure may contain a carbocyclic or heterocyclic ring and therefore, exist as geometric isomers resulting from the arrangement of substituents around the ring. The arrangement of substituents around a carbocyclic or heterocyclic ring are designated as being in the "Z" or "E" configuration wherein the terms "Z" and "E" are used in

accordance with IUPAC standards. Unless otherwise specified, structures depicting carbocyclic or heterocyclic rings encompass both “Z” and “E” isomers. Substituents around a carbocyclic or heterocyclic rings may also be referred to as “cis” or “trans”, where the term “cis” represents substituents on the same side of the plane of the ring and the term “trans” represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated “cis/trans.”

[0039] Individual enantiomers and diastereomers of compounds of the present disclosure can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3) direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well known methods, such as chiral-phase liquid chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations and may involve the use of chiral auxiliaries. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

[0040] The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the disclosure embrace both solvated and unsolvated forms. In one embodiment, the compound is amorphous. In one embodiment, the compound is a single polymorph. In another embodiment, the compound is a mixture of polymorphs. In another embodiment, the compound is in a crystalline form.

[0041] The disclosure also embraces isotopically labeled compounds of the disclosure which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number

usually found in nature. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively.

For example, a compound of the disclosure may have one or more H atom replaced with deuterium.

[0042] Certain isotopically labeled disclosed compounds (*e.g.*, those labeled with ^3H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^3H) and carbon-14 (*i.e.*, ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^2H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the disclosure can generally be prepared by following procedures analogous to those disclosed in the examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

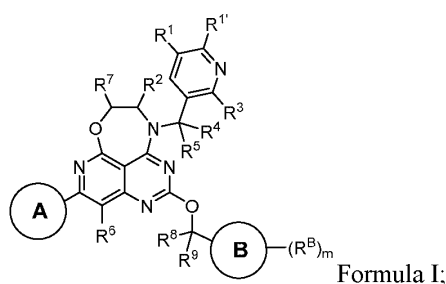
[0043] The term “prodrug” refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (such as by esterase, amidase, phosphatase, oxidative and or reductive metabolism) in various locations (such as in the intestinal lumen or upon transit of the intestine, blood or liver). Prodrugs are well known in the art (for example, see Rautio, Kumpulainen, *et al*, Nature Reviews Drug Discovery 2008, 7, 255). For example, if a compound of the disclosure or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C₁₋₈)alkyl, (C₂₋₁₂)alkylcarbonyloxymethyl, 1-(alkylcarbonyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkylcarbonyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁₋₂)alkylamino(C₂₋₃)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C₁₋₂)alkyl, N,N-di(C₁₋₂)alkylcarbamoyl-(C₁₋₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂₋₃)alkyl.

- [0044] Similarly, if a compound of the disclosure contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C₁₋₆)alkylcarbonyloxymethyl, 1-((C₁₋₆)alkylcarbonyloxy)ethyl, 1-methyl-1-((C₁₋₆)alkylcarbonyloxy)ethyl (C₁₋₆)alkoxycarbonyloxymethyl, N-(C₁₋₆)alkoxycarbonylaminomethyl, succinoyl, (C₁₋₆)alkylcarbonyl, α -amino(C₁₋₄)alkylcarbonyl, arylalkylcarbonyl and α -aminoalkylcarbonyl, or α -aminoalkylcarbonyl- α -aminoalkylcarbonyl, where each α -aminoalkylcarbonyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)₂, -P(O)(O(C₁₋₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).
- 10 [0045] If a compound of the disclosure incorporates an amine functional group, a prodrug can be formed, for example, by creation of an amide or carbamate, an N-alkylcarbonyloxyalkyl derivative, an (oxodioxolenyl)methyl derivative, an N-Mannich base, imine or enamine. In addition, a secondary amine can be metabolically cleaved to generate a bioactive primary amine, or a tertiary amine can be metabolically cleaved to generate a bioactive primary or
- 15 secondary amine. For examples, see Simpicio, *et al.*, *Molecules* 2008, 13, 519 and references therein.

I. Compounds

- [0046] The disclosure is directed, in part, to compounds that inhibit Ras, for example, multiple mutated forms of Ras, for example, K-Ras. In some embodiments, the present
- 20 disclosure provides a method of treating a disease or disorder characterized by aberrant Ras activity due to a Ras mutant (e.g., aberrant K-Ras activity due to a K-Ras mutant). In some embodiments, the disease or disorder is a cancer.

[0047] For example, disclosed herein is a compound represented by Formula I:



- 25 or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

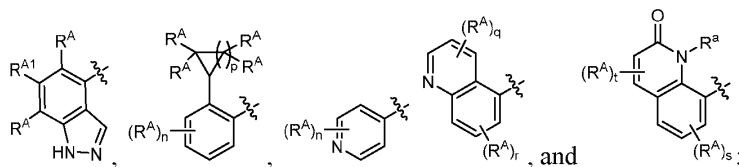
R^1 is selected from the group consisting of halogen, C₃-C₄cycloalkyl, C₁-C₆alkyl, C₂-C₆alkenyl, and C₂-C₆alkynyl; wherein cycloalkyl, alkyl, alkenyl, and alkynyl may optionally be substituted with one, two, or three halogens;

R^2 is hydrogen or C₁-C₆alkyl optionally substituted with one or more halogens or hydroxyl; and

ring A is selected from the group consisting of indazolyl, quinolinyl, quinolinonyl, benzothiophenyl, benzothiazolyl, pyrazolopyridyl, pyridyl, phenyl, and naphthyl, wherein ring A is substituted with one or more substituents each independently selected from R^A ;

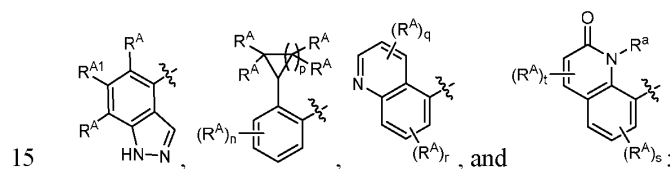
or:

R^1 is hydrogen; R^2 is C₁-C₆alkyl optionally substituted with one or more halogens or hydroxyl; and ring A is selected from the group consisting of:



or:

R^1 is hydrogen; R^2 is hydrogen; and ring A is selected from the group consisting of:



R^A is independently selected for each occurrence from the group consisting of hydrogen, halogen, deuterium, hydroxyl, -CN, -NO₂, -NR^aR^b, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, and phenyl may optionally be substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, oxo, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;

R^{A1} is selected from the group consisting of hydrogen, deuterium, chloro, -CN, -NO₂, -NR^aR^b, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -

5 C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, and phenyl may optionally be substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, oxo, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;

R^{1'} is hydrogen or halogen;

R³ is selected from the group consisting of -NR^aR^b, halogen, C₁-C₂alkyl, and hydrogen, wherein alkyl may optionally be substituted with one, two, or three halogens;

10 R⁴ is selected from the group consisting of hydrogen and C₁-C₂alkyl, wherein alkyl may optionally be substituted with one, two, or three halogens;

R⁵ is C₁-C₂alkyl optionally be substituted with one, two, or three halogens;

R⁶ is selected from the group consisting of halogen, hydrogen, deuterium, and C₁-C₃alkyl;

15 R⁷ is selected from the group consisting of hydrogen and C₁-C₆alkyl optionally substituted with one or more halogens or hydroxyl;

R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, deuterium, and C₁-C₃alkyl;

20 Ring B is selected from the group consisting of 4-12 membered heterocyclyl containing at least one ring nitrogen;

R^B is independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, -CN, -NR^aR^b, -COOH, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, =CHF, and =CH-C₁-C₆alkyl; wherein C₁-C₆alkyl may optionally be substituted with one, two, or three substituents each independently selected from the group consisting of hydroxyl, halogen, and C₁-C₃alkoxy; or

Ring B and R^B are absent and replaced with a substituent selected from the group consisting of -CH₂OH and C₃-C₄cycloalkyl, wherein cycloalkyl is substituted with a substituent selected from the group consisting of -CH₂OH and -CH₂-NR^aR^b, and

30 R^a and R^b are each independently selected from the group consisting of hydrogen and C₁-C₆alkyl, wherein C₁-C₆alkyl optionally substituted with one or more substituents each

independently selected from the group consisting of halogen, deuterium, hydroxyl, and C₁-C₆alkoxy; or

R^a and R^b, together with the nitrogen to which they are attached, may be joined together to form a 4-7 membered heterocyclyl optionally substituted by one or more substituents each
 5 independently selected from the group consisting of halogen, deuterium, hydroxyl, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;

m and n are each independently 0, 1, 2, 3, or 4;

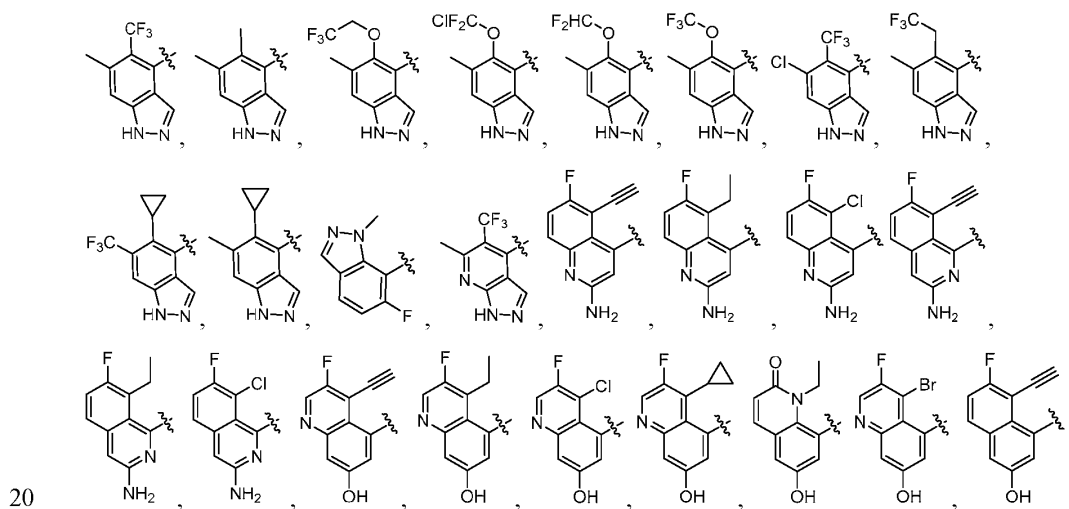
p is 1, 2, or 3;

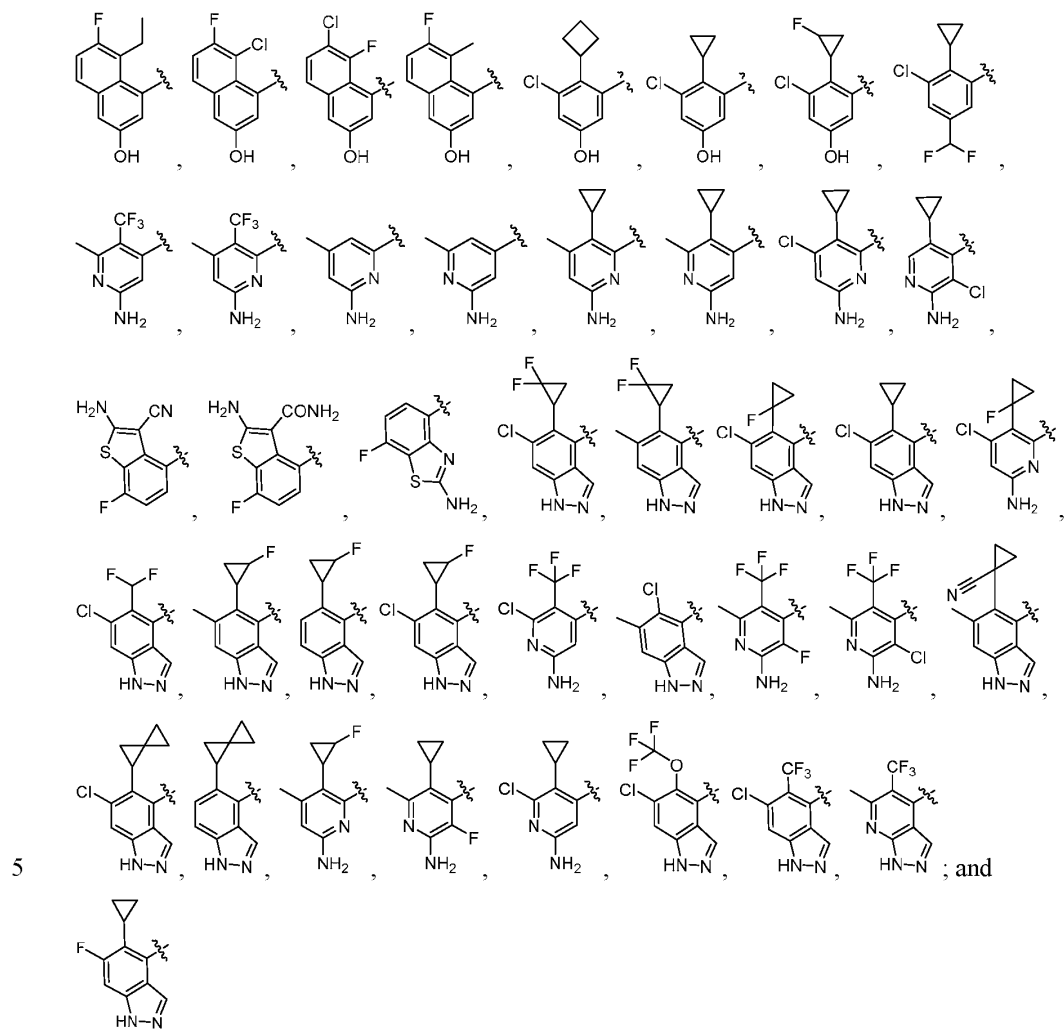
q, r, and s are each independently 0, 1, 2, or 3; and

10 t is 0, 1, or 2.

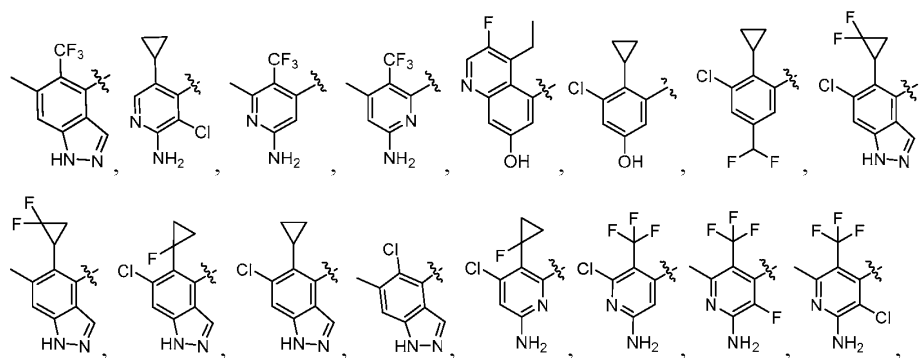
[0048] For example, in some embodiments R¹ is selected from the group consisting of fluoro, chloro, cyclopropyl, trifluoromethyl, -CH₂CH₂CH₃, and propenyl; and R² is hydrogen or -CH₃. In other embodiments, R^A is independently selected for each occurrence from the group consisting of, for example, halogen, hydroxyl, cyano, -NH₂, -C(O)NH₂, C₁-C₄alkyl, and C₂-C₄alkynyl, C₁-C₄alkoxy, and C₃-C₄cycloalkyl, wherein alkyl, alkynyl, alkoxy, and cycloalkyl
 15 may optionally be substituted with one, two, or three halogens or -CN.

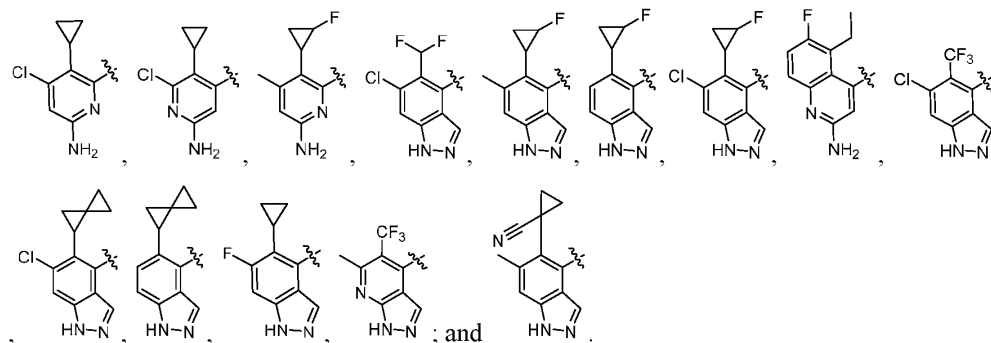
[0049] In some embodiments, or example, ring A is selected from the group consisting of:



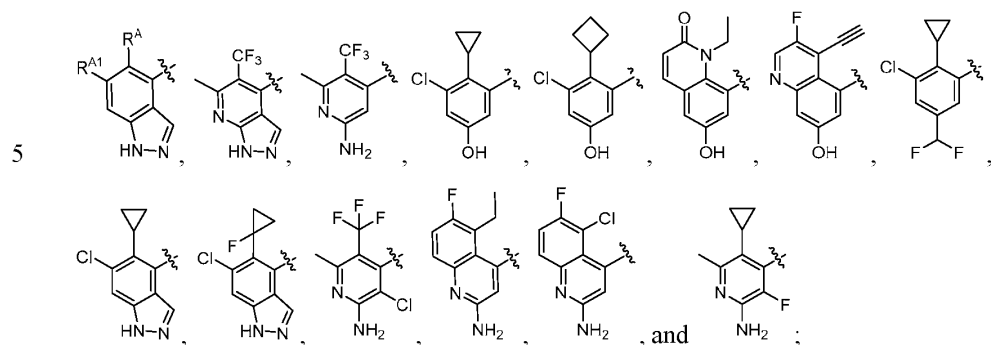


[0050] In other embodiments, ring A is selected from the group consisting of, for example



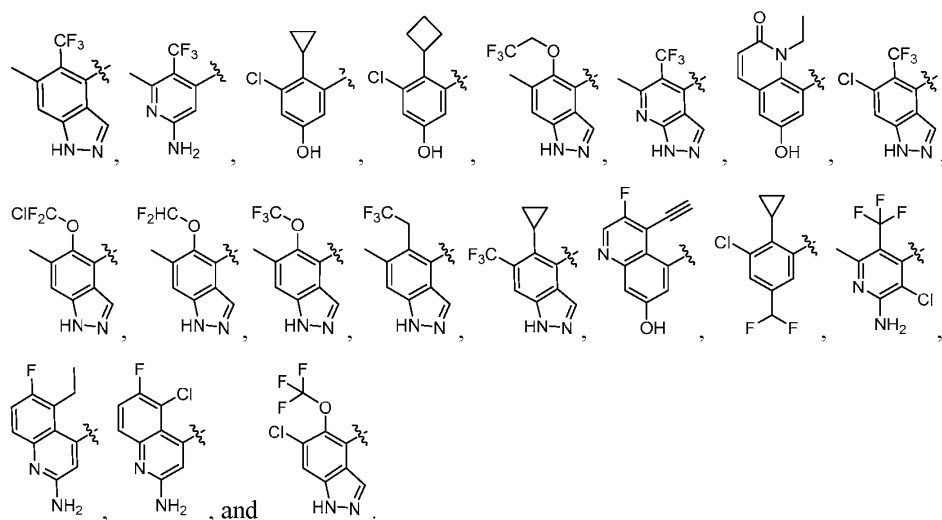


[0051] In still other embodiments, for example, R¹ is hydrogen and R² is -CH₃. For example, in certain embodiments ring A is selected from the group consisting of:

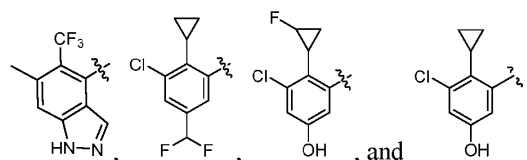


wherein: R^A is selected from the group consisting of C₁-C₃alkyl, C₁-C₃alkoxy, and C₃-C₄cycloalkyl; wherein alkyl and alkoxy are each substituted with one, two, or three halogens; and R^{A1} is selected from the group consisting of chloro, -CH₃, and -CF₃.

10 **[0052]** In some embodiments, ring A is selected from the group consisting of, for example:



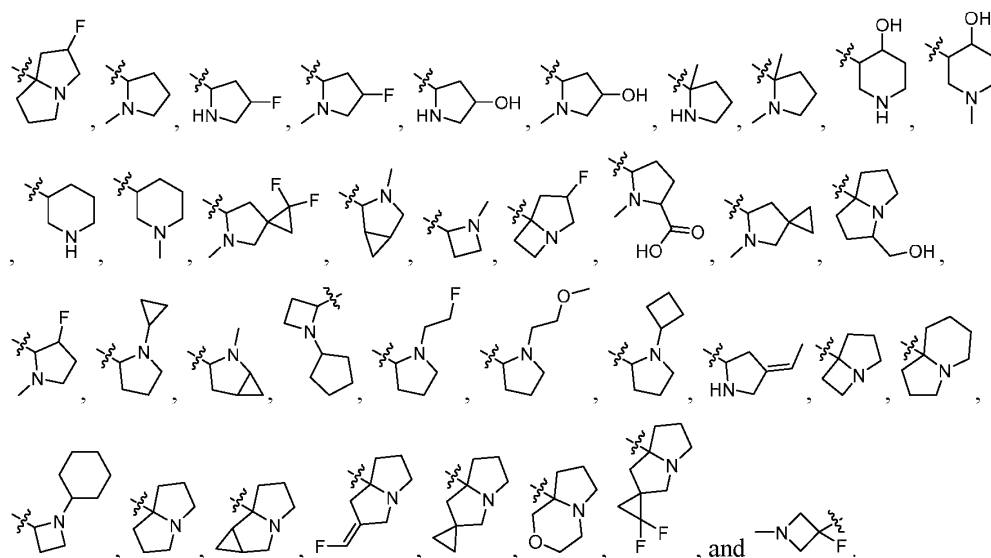
[0053] In some embodiments, R¹ is hydrogen and R² is hydrogen. In other embodiments,
 5 ring A is selected from the group consisting of, for example,



[0054] In further embodiments, R³ is selected from the group consisting of, for example, -
 NH₂, chloro, and -CHF₂. In certain embodiments, R³ is -NH₂. In additional embodiments, for
 10 example, R⁴ is hydrogen and R⁵ is -CH₃. In some embodiments, R⁶ is fluoro. In other
 embodiments, for example, R⁷ is hydrogen or -CH₃. In still other embodiments, R⁸ and R⁹ are
 each independently selected from the group consisting of, for example, hydrogen, deuterium,
 and -CH₃

[0055] In certain other embodiments, R^B is independently selected for each occurrence from
 the group consisting of halogen, hydroxyl, -COOH, =CHCH₃, =CHF, cyclopropyl, cyclobutyl,
 15 cyclopentyl, cyclohexyl, and C₁-C₃alkyl optionally substituted with hydroxyl, halogen, or -
 OCH₃. In some embodiments, R^B is independently selected for each occurrence from the group
 consisting of halogen, hydroxyl, -CH₃, =CHCH₃, =CHF, -COOH, -CH₂OH, -CH₂CH₂F,
 CH₂CH₂OCH₃, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

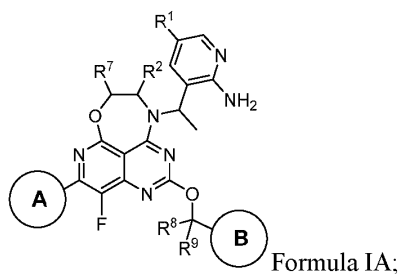
[0056] In some embodiments, ring B is selected from the group consisting of, for example:



- 5 [0057] In other embodiments, ring B and R^B are absent and replaced with -CH₂OH or cyclopropyl; wherein cyclopropyl is substituted with -CH₂OH or -CH₂NR^aR^b. In still other embodiments, ring B and R^B are absent and replaced with a substituent selected from the group

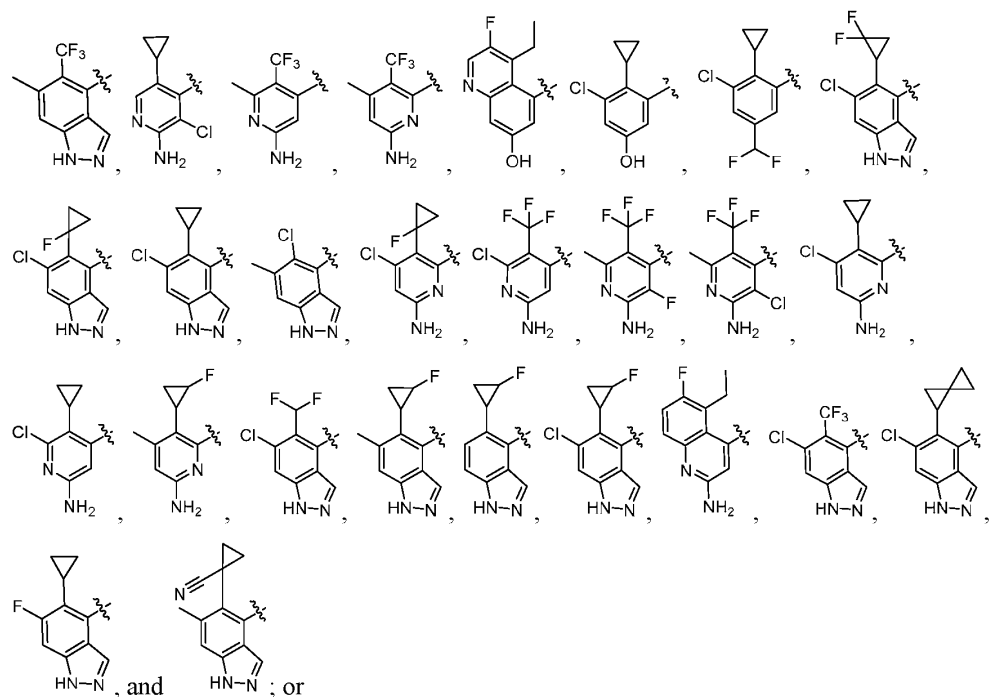
consisting of, for example, -CH₂OH, , , , and .

- 10 [0058] In some embodiments, for example, a compound of the present disclosure is represented by Formula IA:

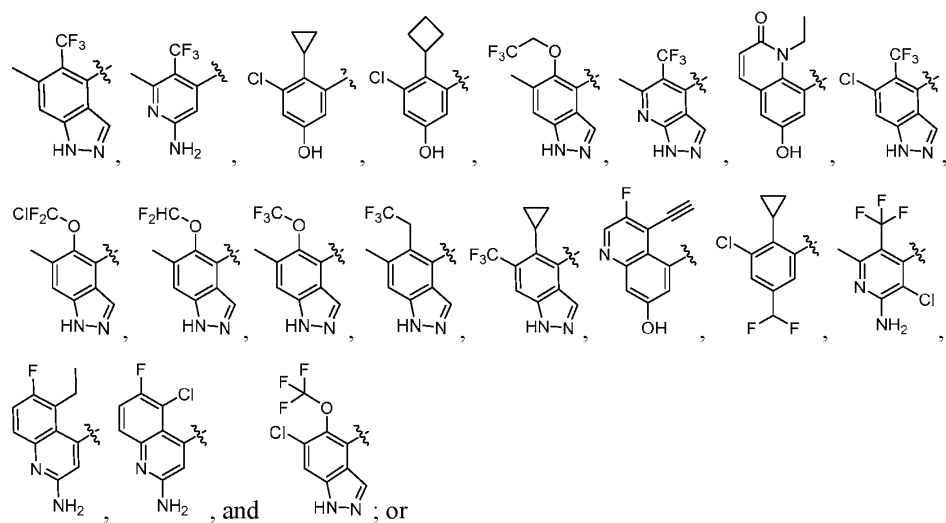


or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

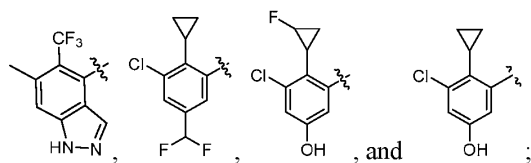
R¹ is halogen, R² is hydrogen or -CH₃, and ring A is selected from the group consisting of



5 R¹ is hydrogen, R² is -CH₃, and ring A is selected from the group consisting of:



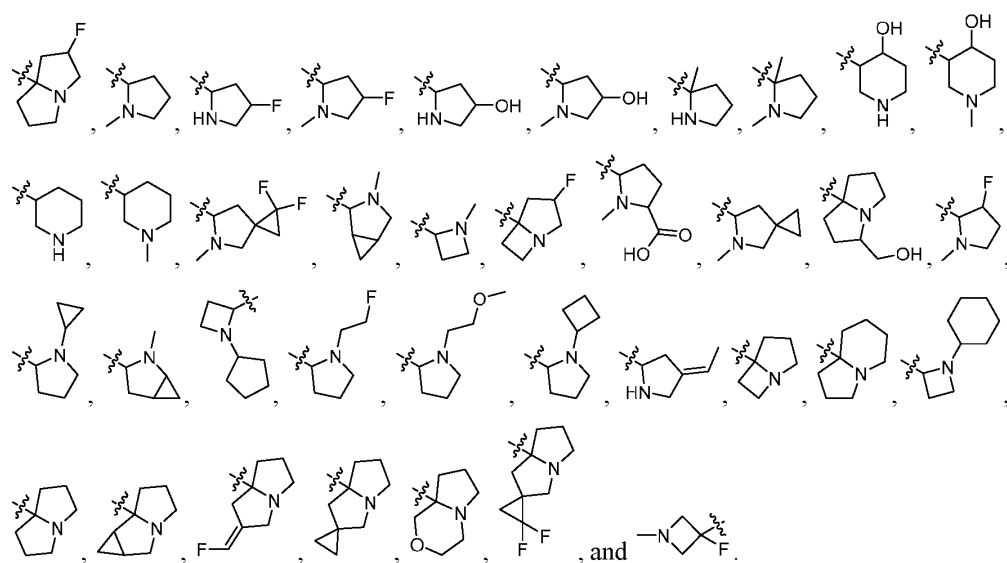
R¹ is hydrogen, R² is hydrogen, and ring A is selected from the group consisting of:



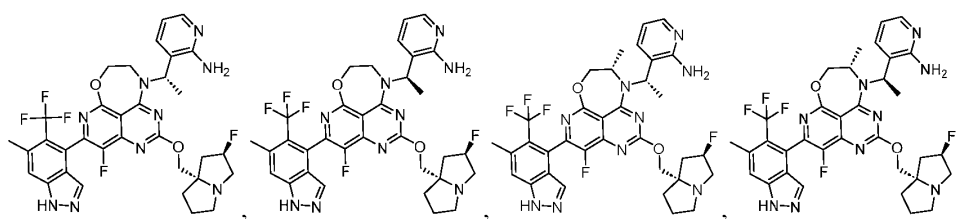
R⁷ is selected from the group consisting of hydrogen and -CH₃;

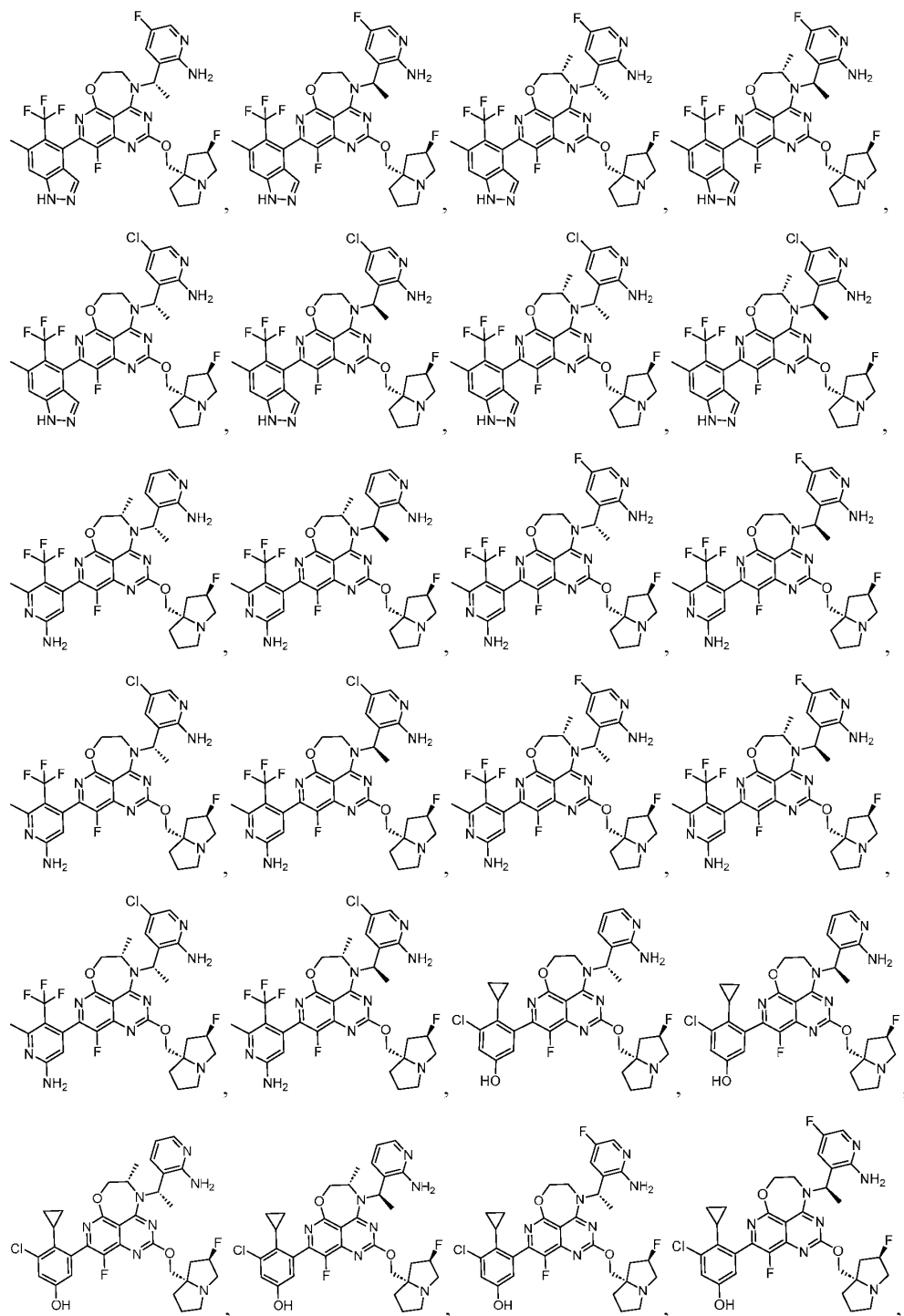
R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, deuterium, and -CH₃; and

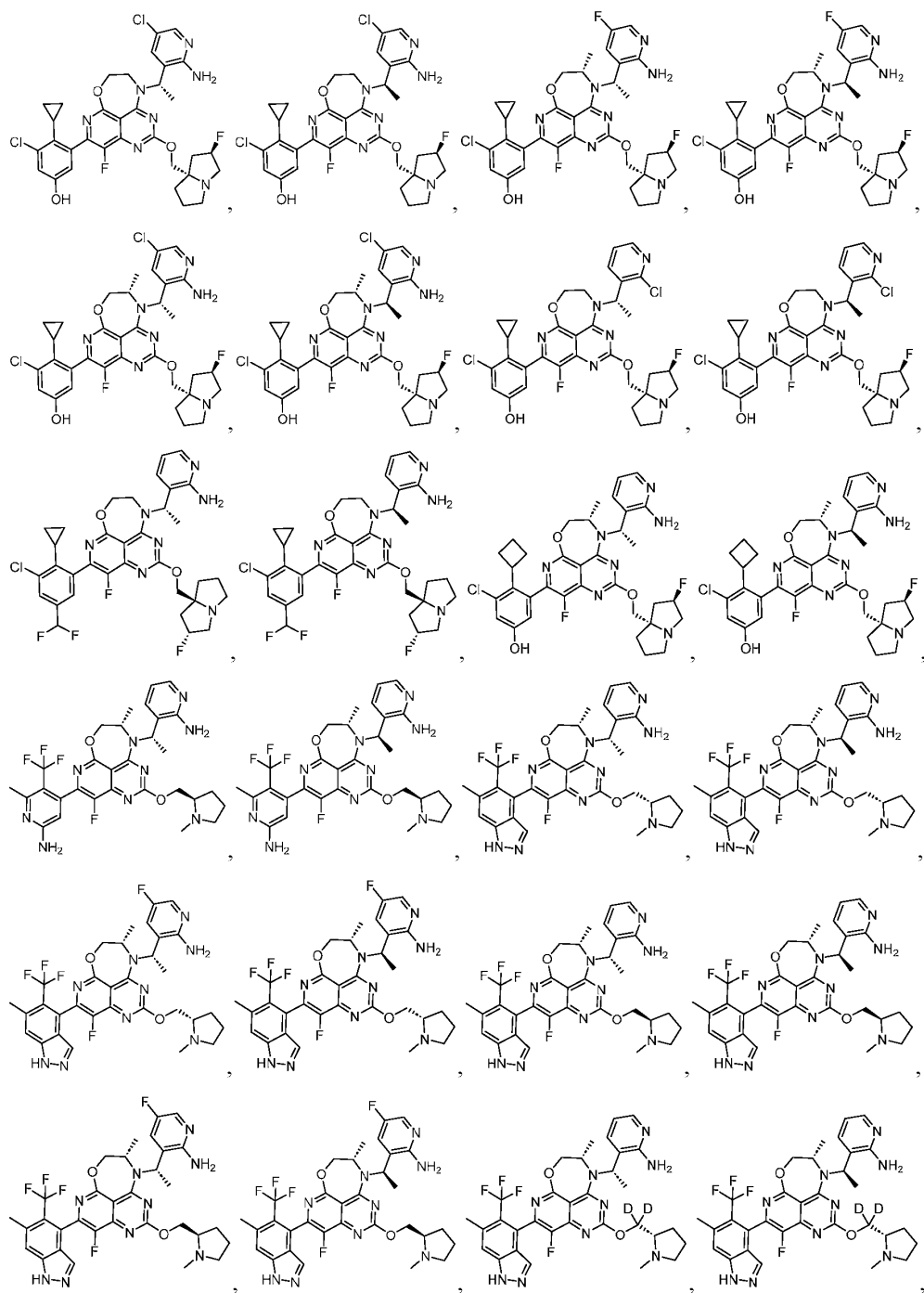
5 B is selected from the group consisting of

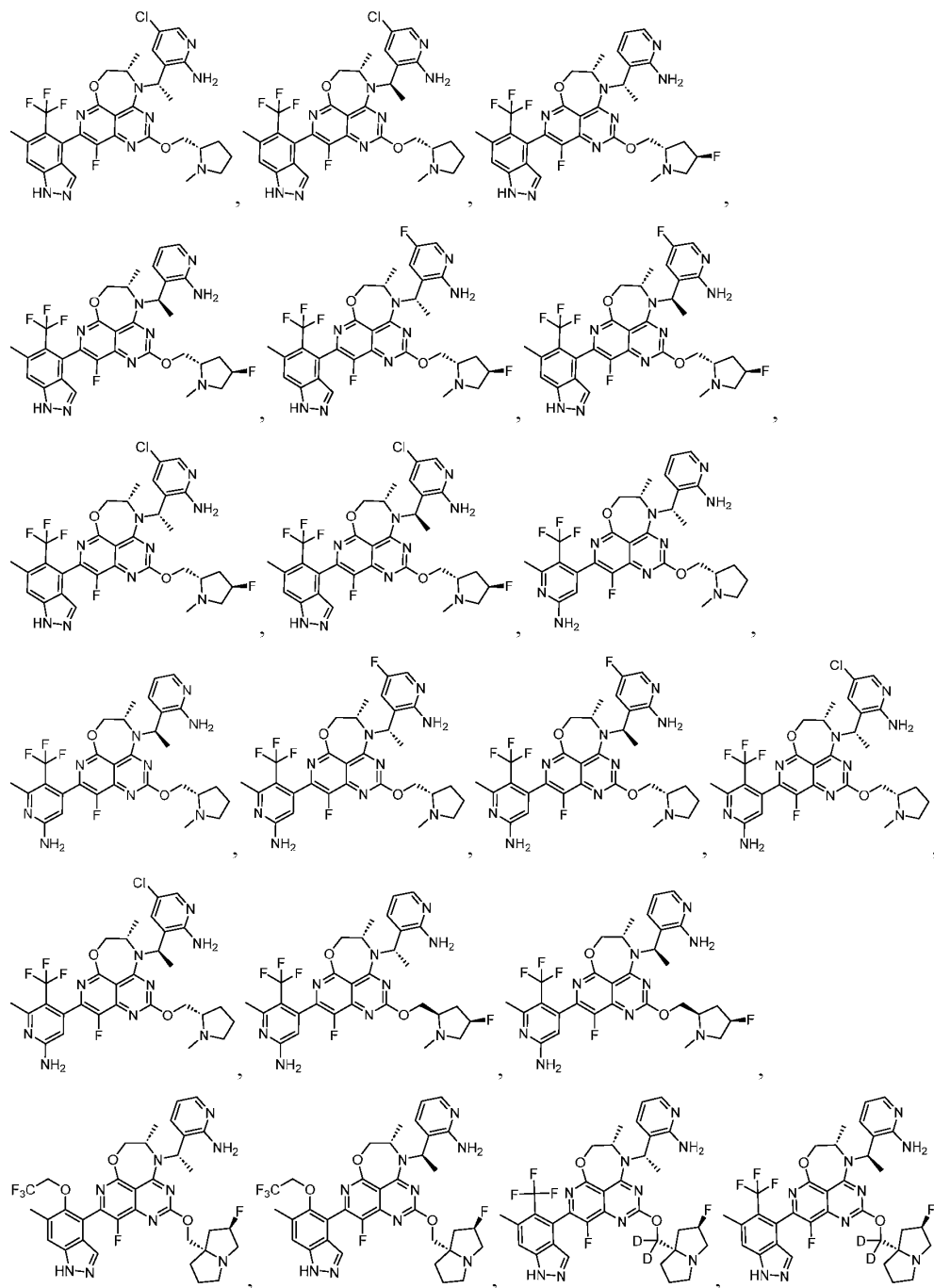


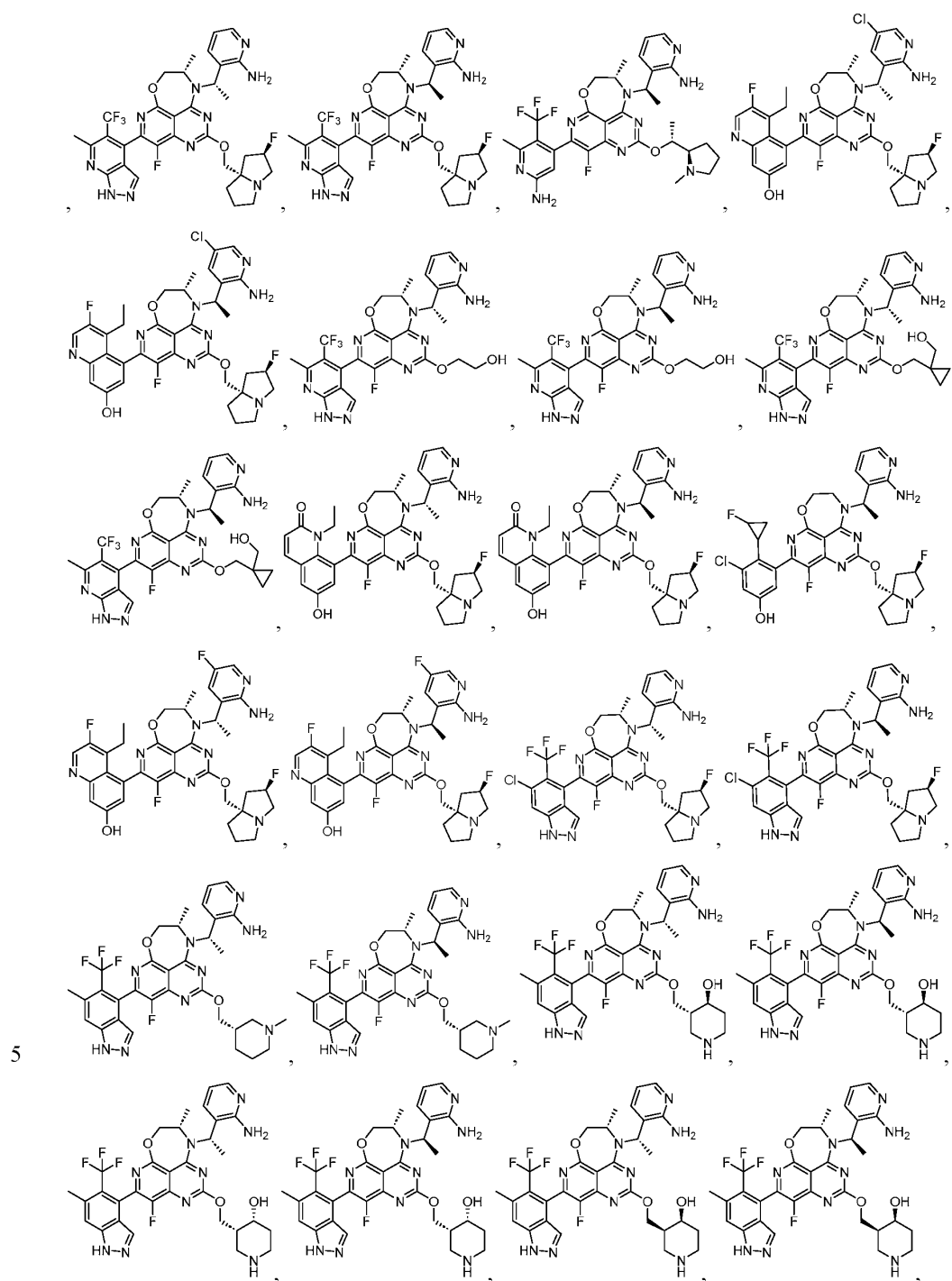
10 [0059] In other embodiments, for example, a compound of the present disclosure is selected from the group consisting of

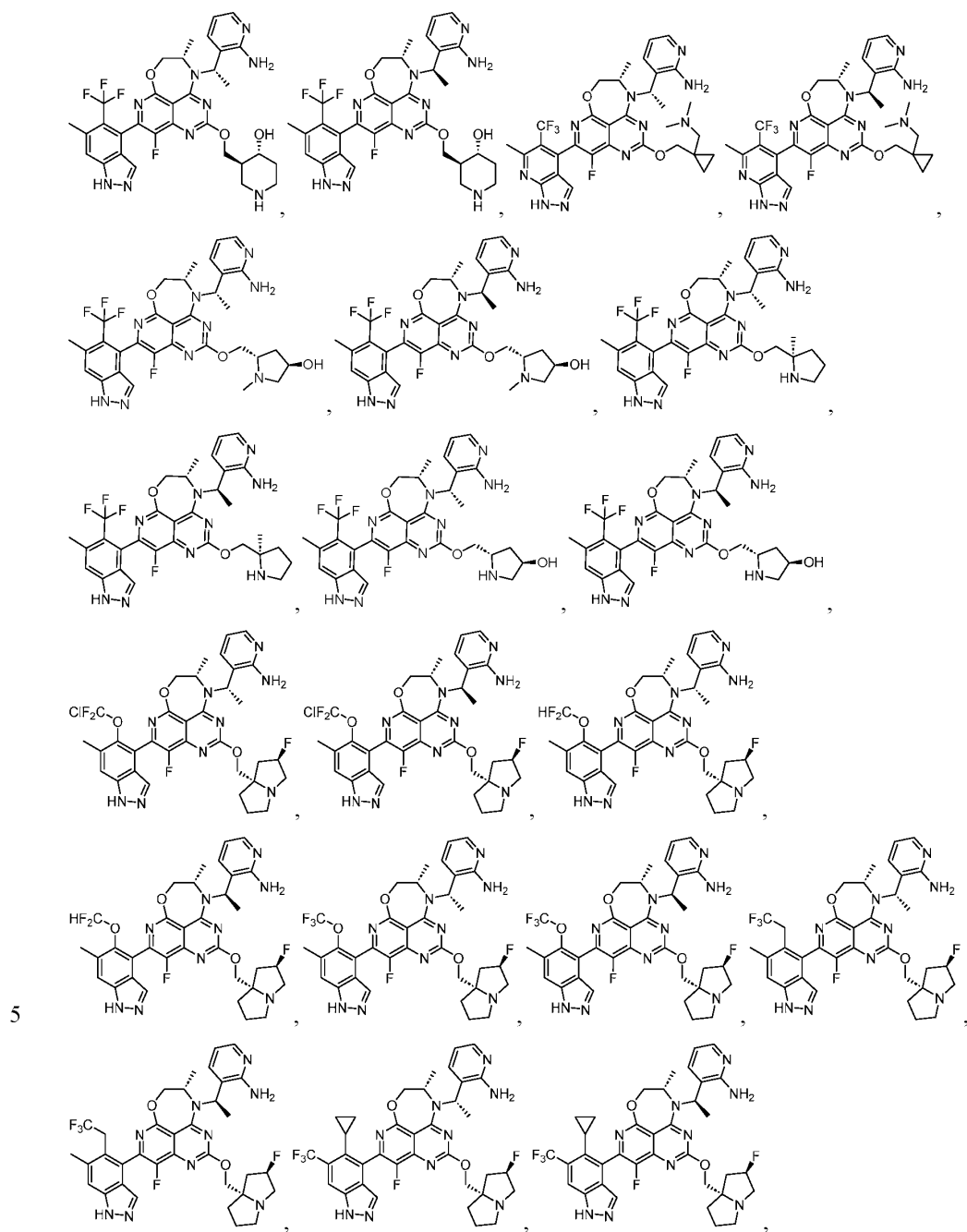


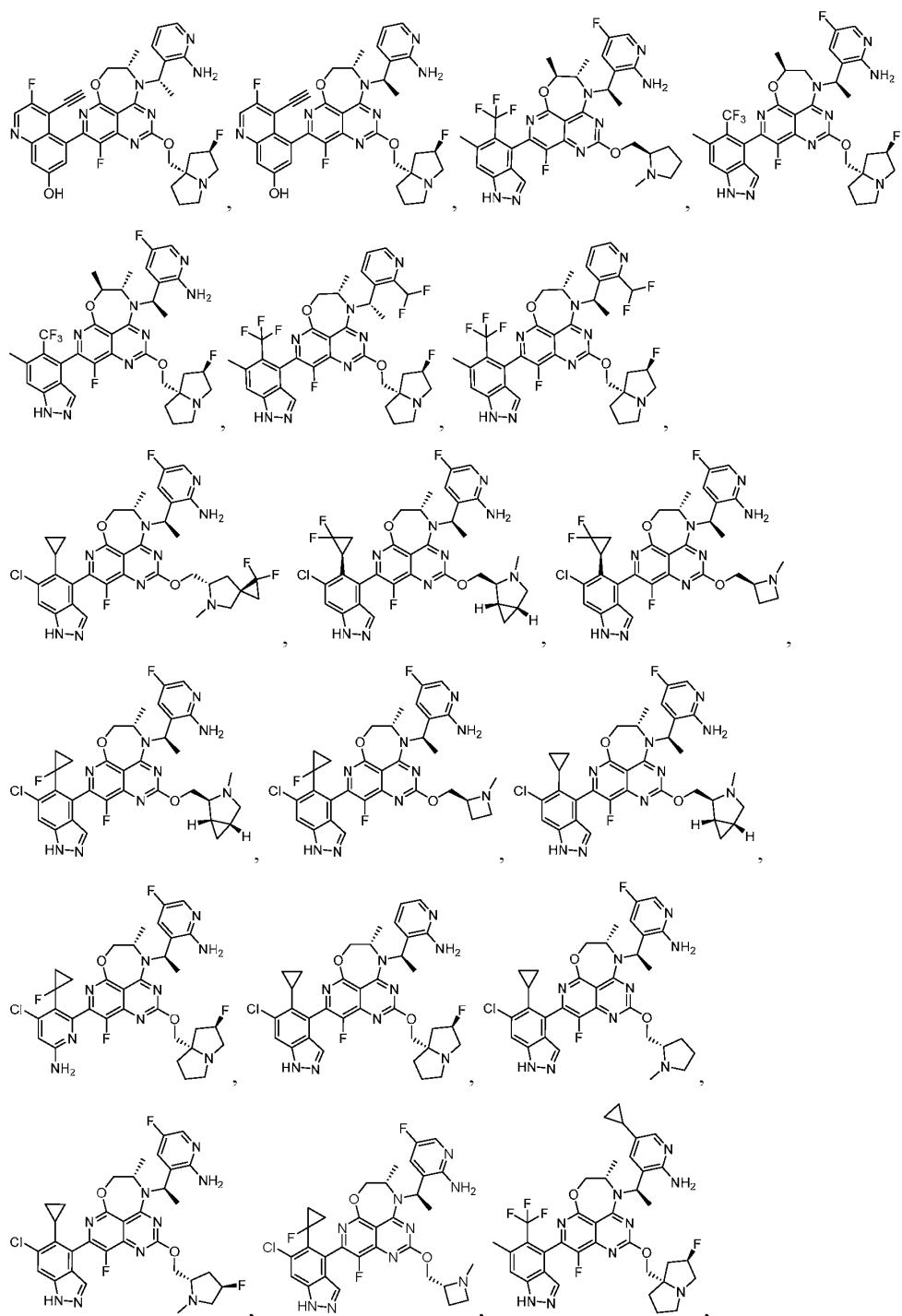


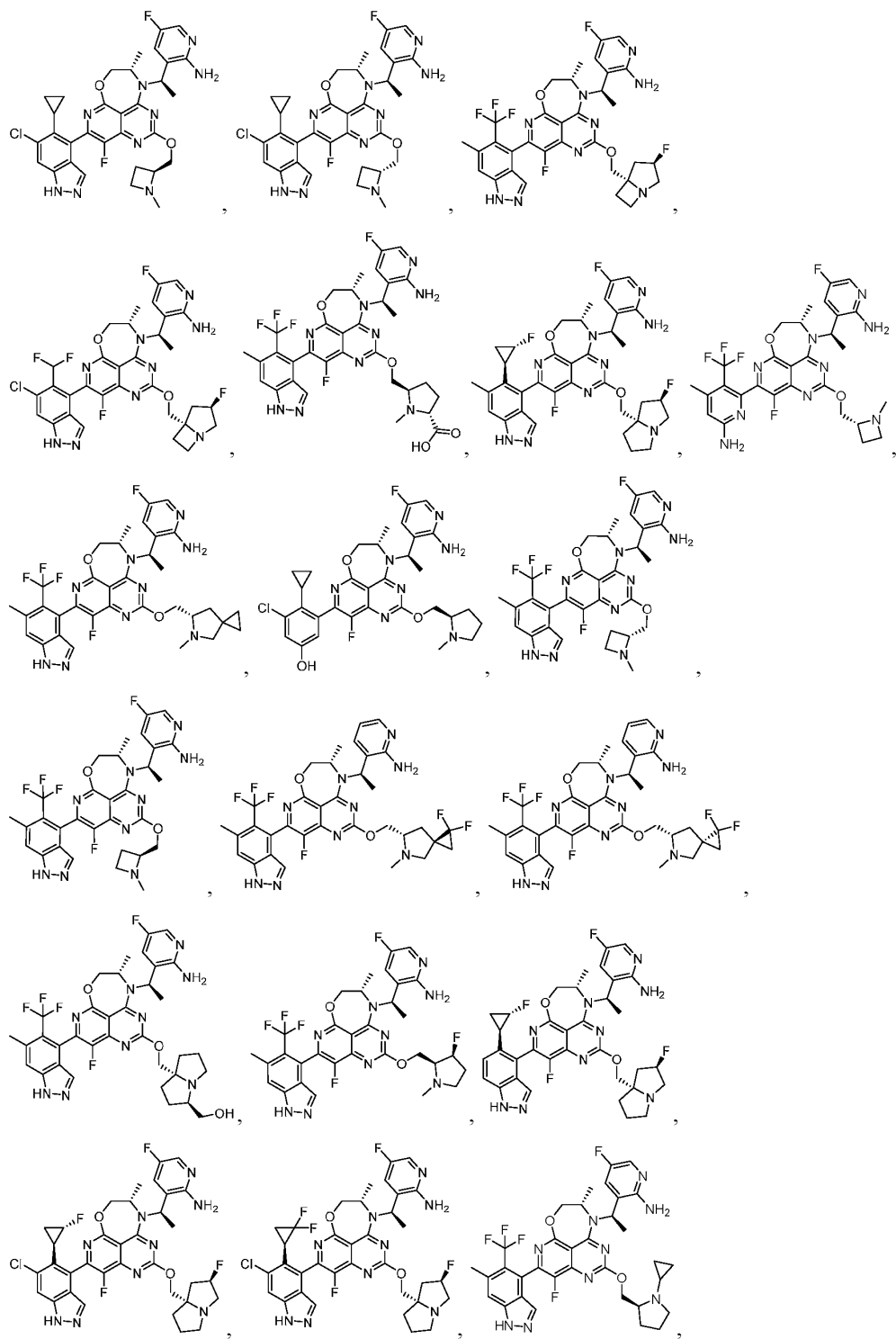


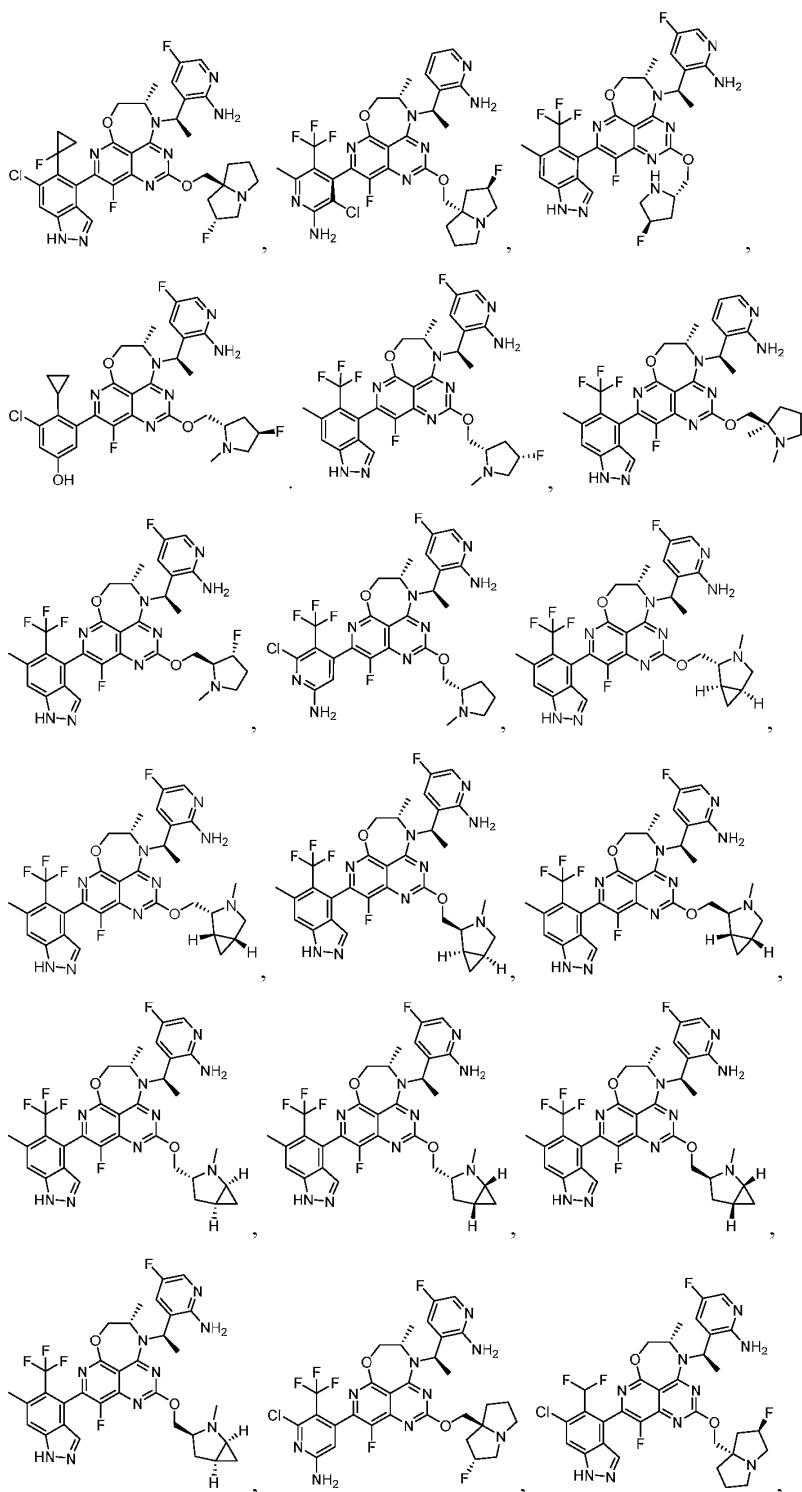


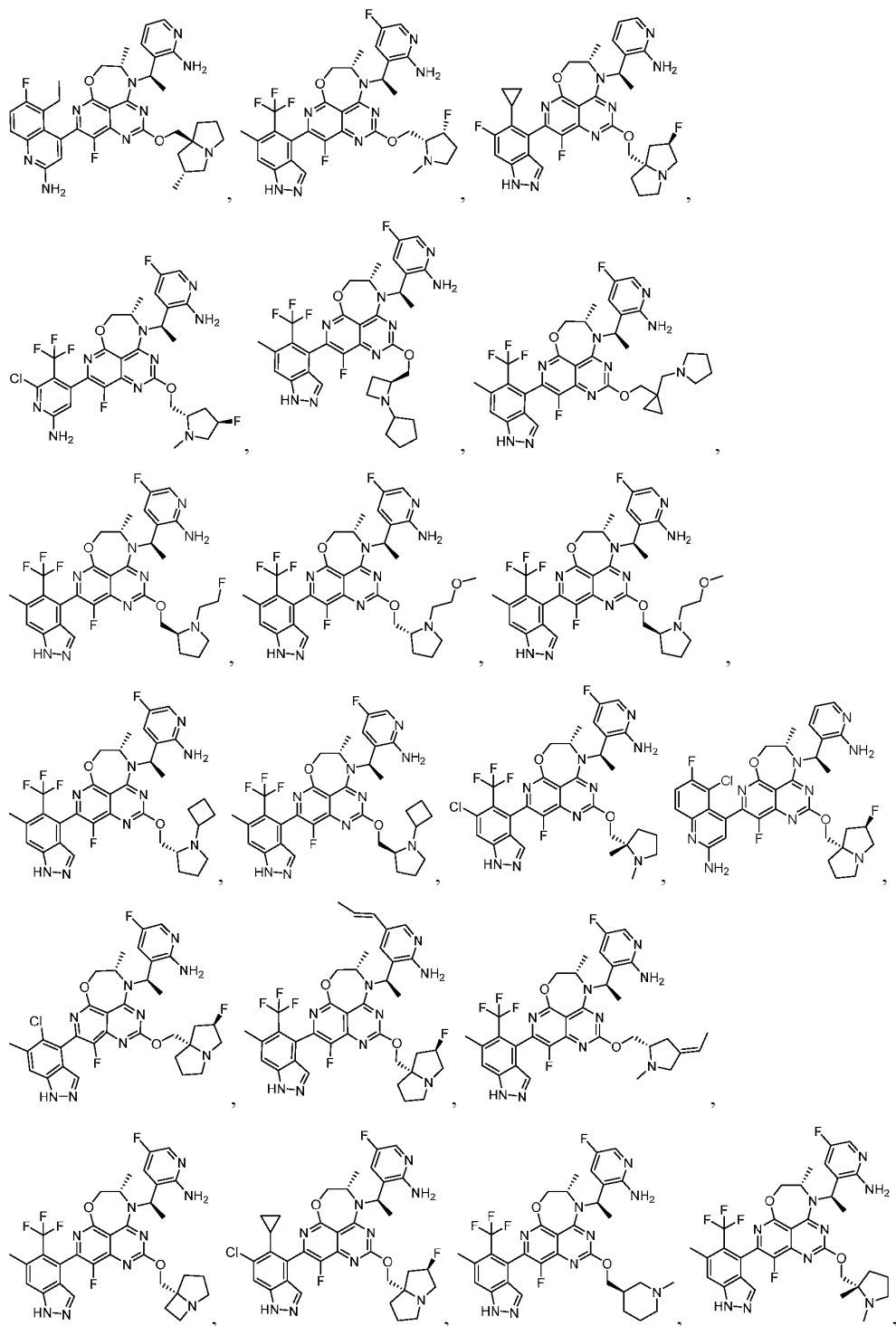




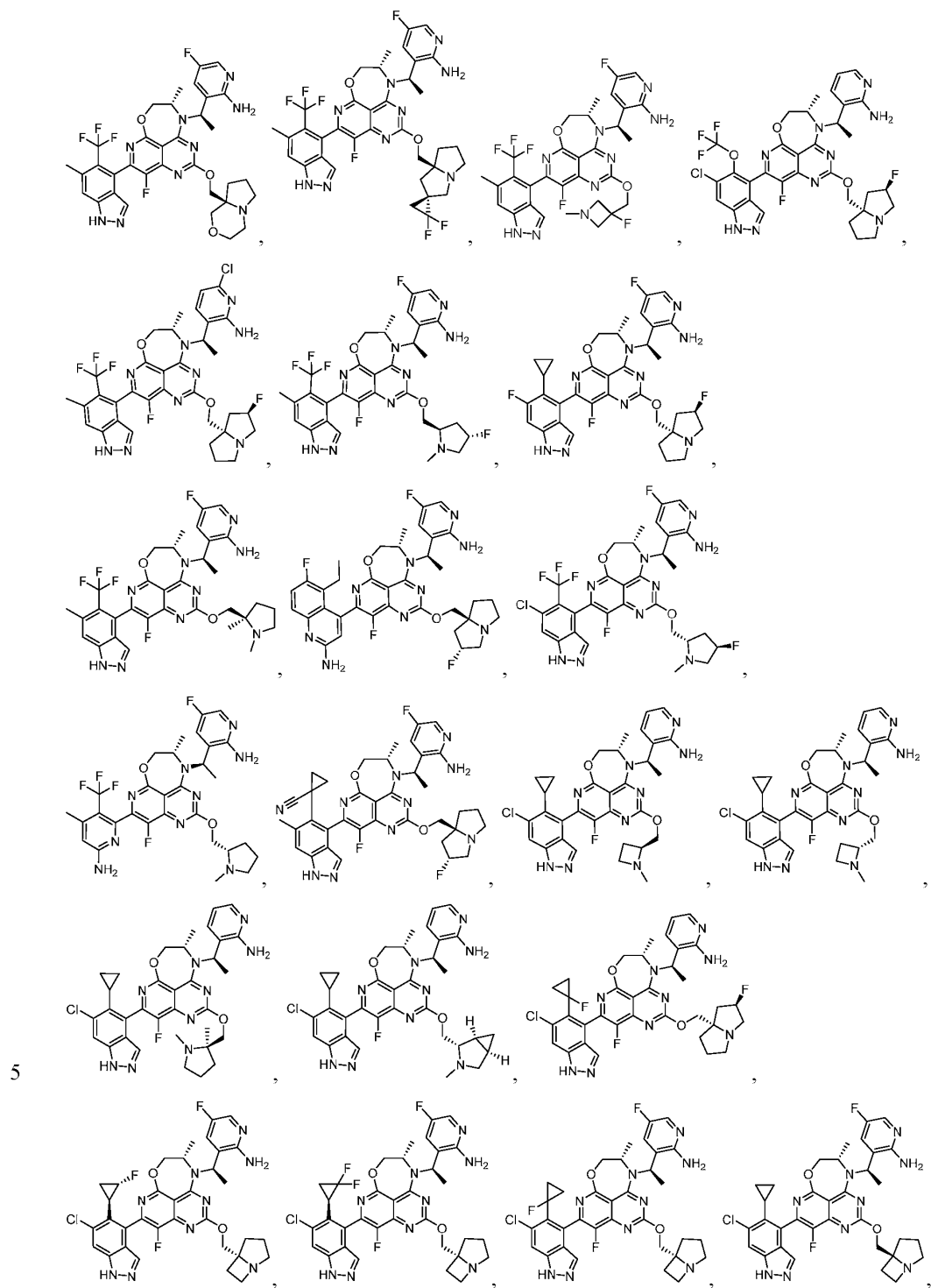


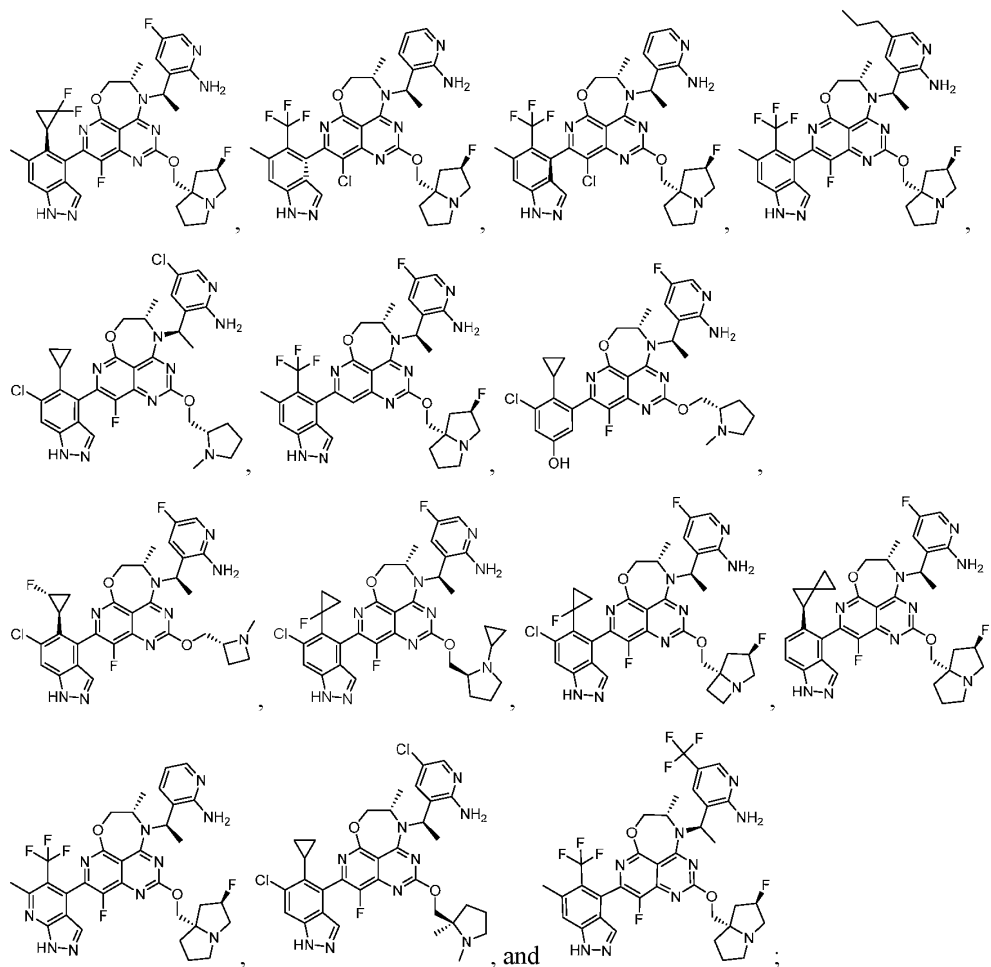






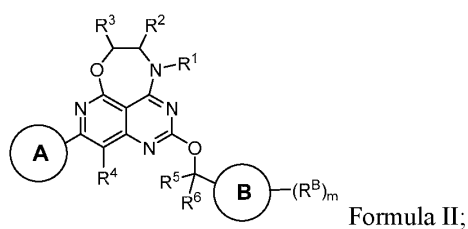






5 or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

[0060] Also disclosed herein is a compound represented by Formula II:



or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

ring A is selected from the group consisting of indazolyl, quinolinyl, quinolinonyl,
 10 benzothiophenyl, benzothiazolyl, pyridinyl, pyrimidinyl, and phenyl; wherein ring A is
 substituted with one, two, or three substituents each independently selected from R^A ;

R^A is independently selected for each occurrence from the group consisting of hydrogen, halogen, deuterium, hydroxyl, -CN, -NO₂, -NR^aR^b, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, and phenyl may optionally be substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, oxo, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;

R^1 is selected from the group consisting of C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, -CH(CH₃)-(C₃-C₆cycloalkyl), -CH₂-(C₃-C₆cycloalkyl), phenyl, 5-membered heteroaryl, and -CR^cR^d-(5-membered heteroaryl); wherein alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, and heteroaryl may optionally be substituted with one, two, three, or four substituents each independently selected from R^{11} ;

R^2 is selected from the group consisting of hydrogen, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, -CH(CH₃)-(C₃-C₆cycloalkyl), -CH₂-(C₃-C₆cycloalkyl), phenyl, 5-membered heteroaryl, and -CR^cR^d-(5-membered heteroaryl); wherein alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, and heteroaryl may optionally be substituted with one, two, three, or four substituents each independently selected from R^{22} ;

R^{11} and R^{22} are independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, -CN, -NO₂, -NR^aR^b, oxo, C₁-C₆alkyl, C₁-C₆alkoxy, phenyl, -COOH, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl;

R^3 is selected from the group consisting of hydrogen and C₁-C₆alkyl optionally substituted with one or more halogens or hydroxyl;

R^4 is selected from the group consisting of halogen, hydrogen, deuterium, and C₁-C₃alkyl;

R^5 and R^6 are each independently selected from the group consisting of hydrogen, deuterium, and C₁-C₃alkyl;

Ring B is selected from the group consisting of 5-10 membered heterocyclyl containing at least one ring nitrogen;

R^B is independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, -CN, $-NR^aR^b$, C₁-C₆alkyl, and C₁-C₆alkoxy;

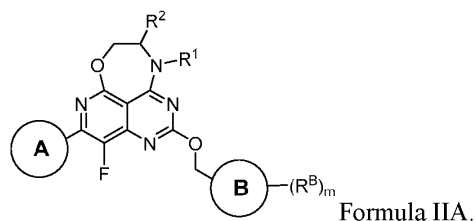
R^a and R^b are each independently selected from the group consisting of hydrogen and C₁-C₆alkyl, wherein C₁-C₆alkyl optionally substituted with one or more substituents each
 5 independently selected from the group consisting of halogen, deuterium, hydroxyl, and C₁-C₆alkoxy; or

R^a and R^b , together with the nitrogen to which they are attached, may be joined together to form a 4-7 membered heterocyclyl optionally substituted by one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, $-NR^aR^b$, C₁-
 10 C₆alkyl, and C₁-C₆alkoxy; and

m is 0, 1, 2, 3, or 4;

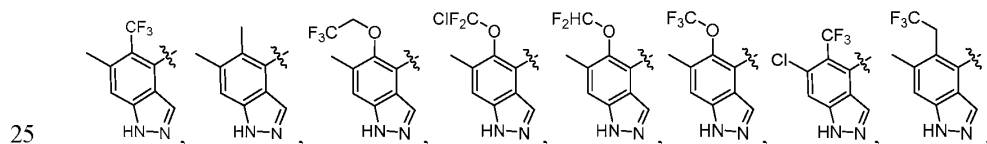
wherein if ring A is benzothiophenyl, then R^1 is CH₃ or substituted C₁-C₆alkyl.

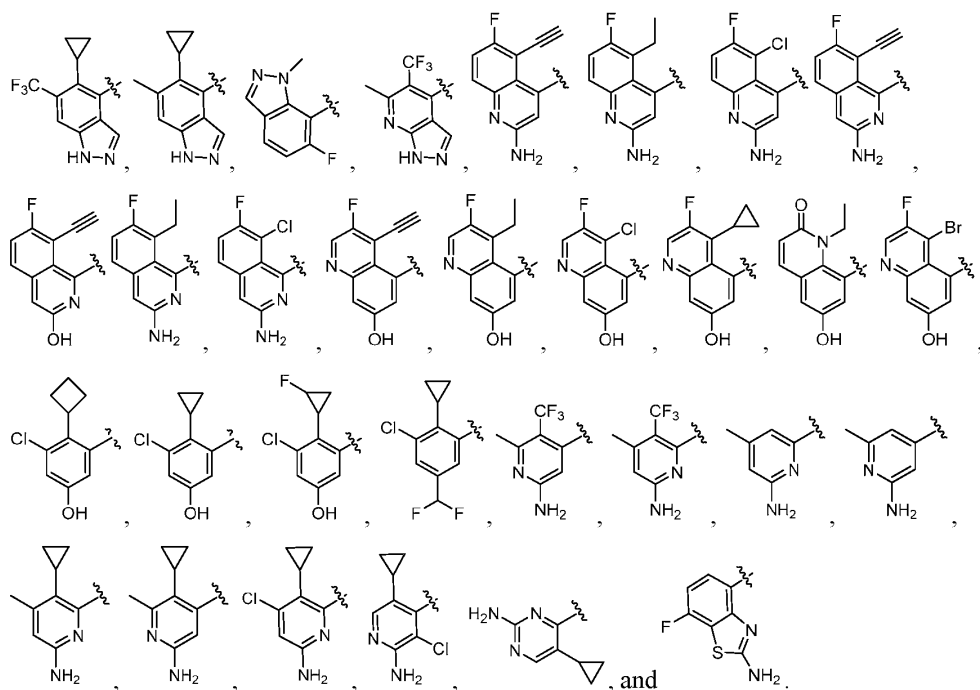
[0061] For example, in some embodiments R^3 is hydrogen or CH₃. In other embodiments, R^4 is fluoro. In still other embodiments, R^5 and R^6 are each hydrogen. In certain embodiments,
 15 for example, a compound of the present disclosure is represented by Formula IIA:



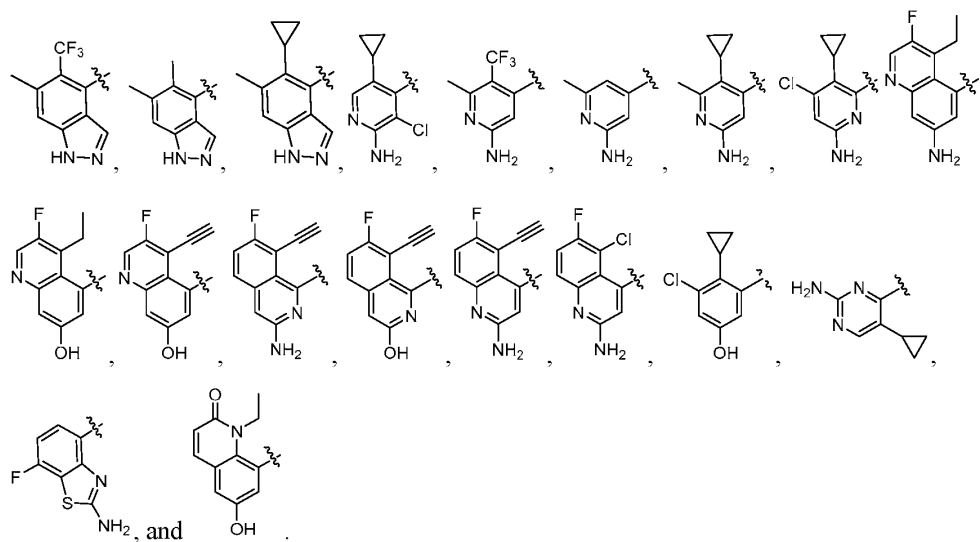
[0062] In some embodiments, ring A is selected from the group consisting of, for example, indazolyl, quinolinyl, quinolinonyl, benzothiazolyl, pyridinyl, pyrimidinyl, and phenyl; wherein ring A is substituted with one, two, or three substituents each independently selected from R^A .
 20 In other embodiments, R^A is independently selected for each occurrence from the group consisting of, for example, halogen, hydroxyl, -NH₂, C₁-C₄alkyl, and C₂-C₄alkynyl, C₁-C₄alkoxy, and C₃-C₄cycloalkyl, wherein alkyl, alkynyl, alkoxy, and cycloalkyl may optionally be substituted with one, two, or three halogens.

[0063] For example, in certain embodiments ring A is selected from the group consisting of:



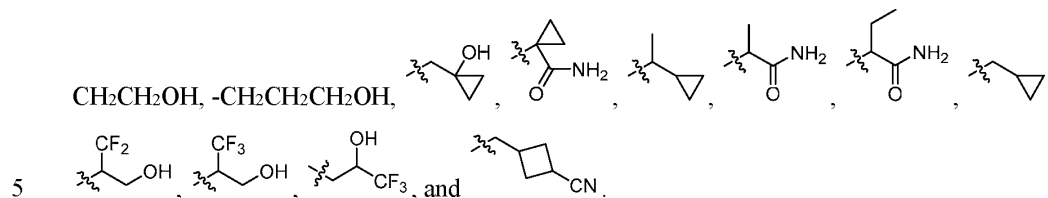


- 5 [0064] In further embodiments, ring A is selected from the group consisting of, for example,

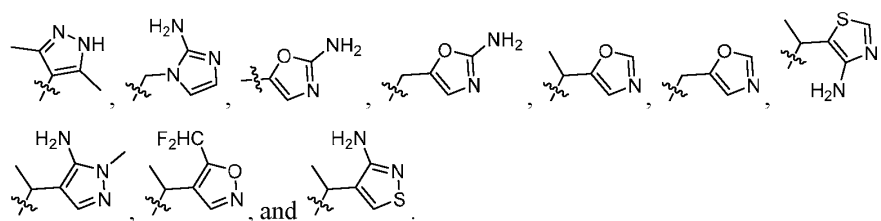


- 10 [0065] In some embodiments, R¹ is selected from the group consisting of, for example, C₁-C₆alkyl, C₃-C₄cycloalkyl, -CH(CH₃)-(C₃-C₄cycloalkyl), and -CH₂-(C₃-C₄cycloalkyl), wherein alkyl and cycloalkyl may optionally be substituted by one, two, three, or four groups each

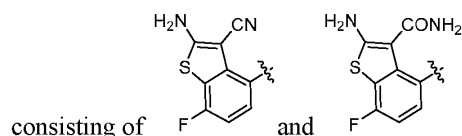
independently selected from the group consisting of halogen, hydroxyl, cyano, and -C(=O)NR^aR^b. In other embodiments, R¹ is selected from the group consisting of -CH₃, -CH₂CH₃, -CH₂CN, -CH₂CHF₂, -CH₂F₂Cl, -CH₂CF₃, -CH₂CH₂CHF₂, -CH(CH₃)CHF₂, -



[0066] In further embodiments, R¹ is selected from the group consisting of, for example, 5-membered heteroaryl, -CH₂-(5-membered heteroaryl), and -CH(CH₃)-(5-membered heteroaryl), wherein heteroaryl may optionally be substituted with one or two substituents each independently selected from the group consisting of -NR^aR^b and C₁-C₃alkyl, and wherein alkyl may optionally be substituted with one, two or three halogens. For example, in certain

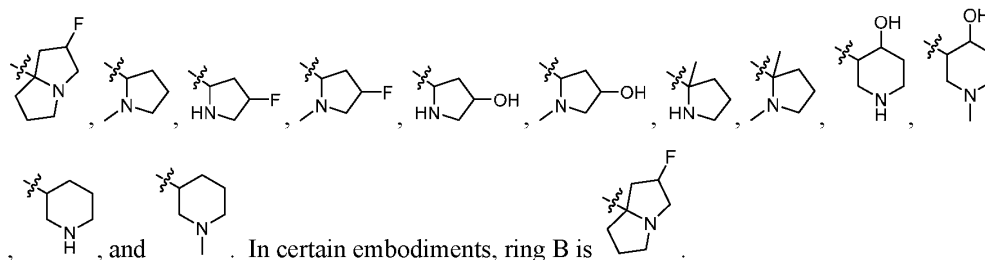


[0067] In some embodiments, ring A is benzothiophenyl substituted with one, two or three substituents each independently selected from the group consisting of halogen, cyano, -NH₂, and -C(O)NH₂. For example, in some embodiments ring A is selected from the group



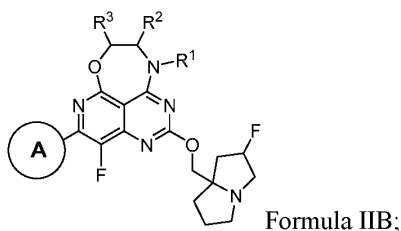
[0068] In other embodiments, R¹ is selected from the group consisting of, for example, -CH₃,-CH₂CHF₂, and -CH₂CH₂OH. In still other embodiments, R² is selected from the group consisting of hydrogen and C₁-C₆alkyl, wherein alkyl may optionally be substituted with one, two, or three substituents each independently selected from the group consisting of halogen and hydroxyl. In certain embodiments, R² is selected from the group consisting of hydrogen, -CH₃, and -CH₂CH₂OH. In further embodiments, R^B is selected from the group consisting of, for example, halogen, hydroxyl, and C₁-C₃alkyl. In additional embodiments, R^B is selected from the group consisting of halogen, hydroxyl, and -CH₃.

[0069] In some embodiments, ring B is selected from the group consisting of, for example:



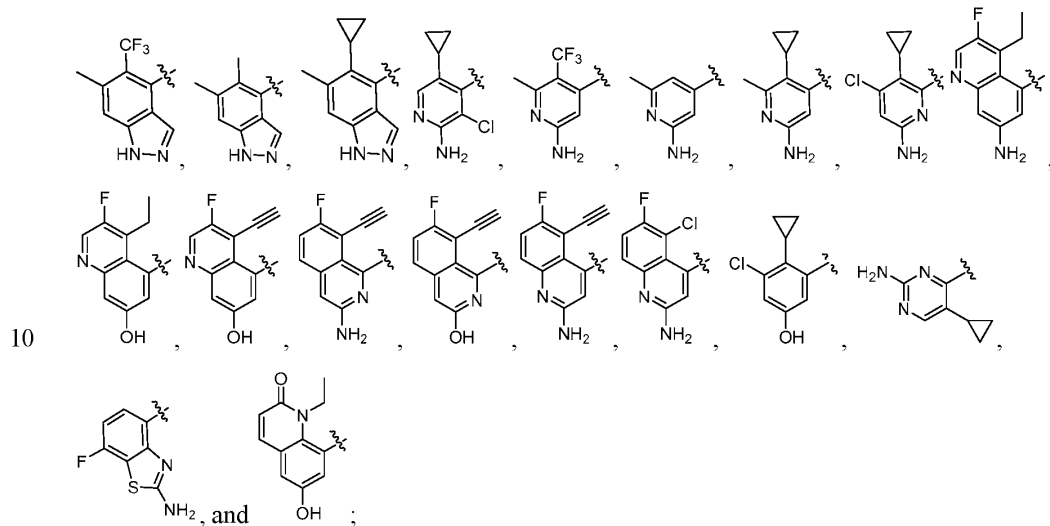
[0070] In some embodiments, a compound of the present disclosure is represented by

5 Formula IIB:

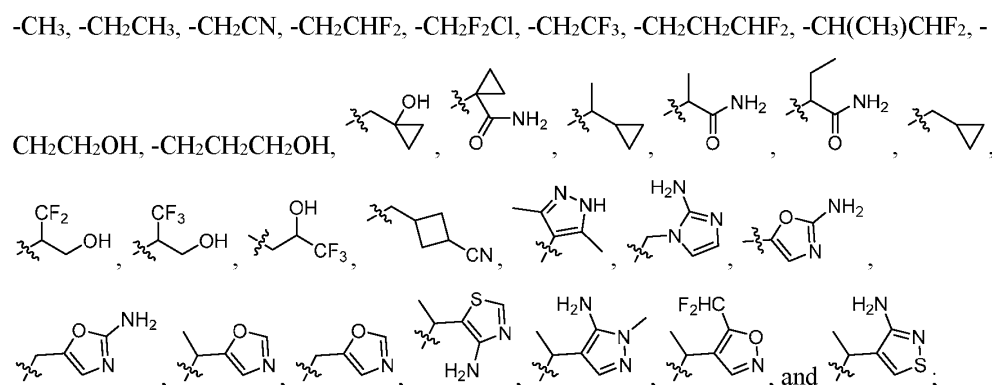


or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

Ring A is selected from the group consisting of

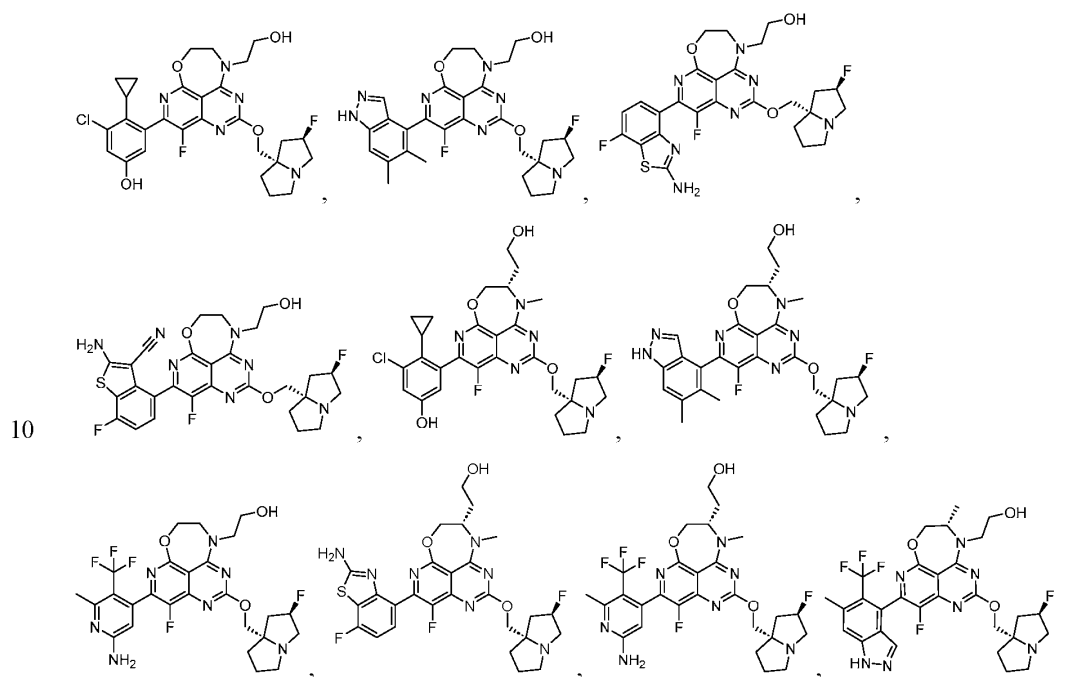


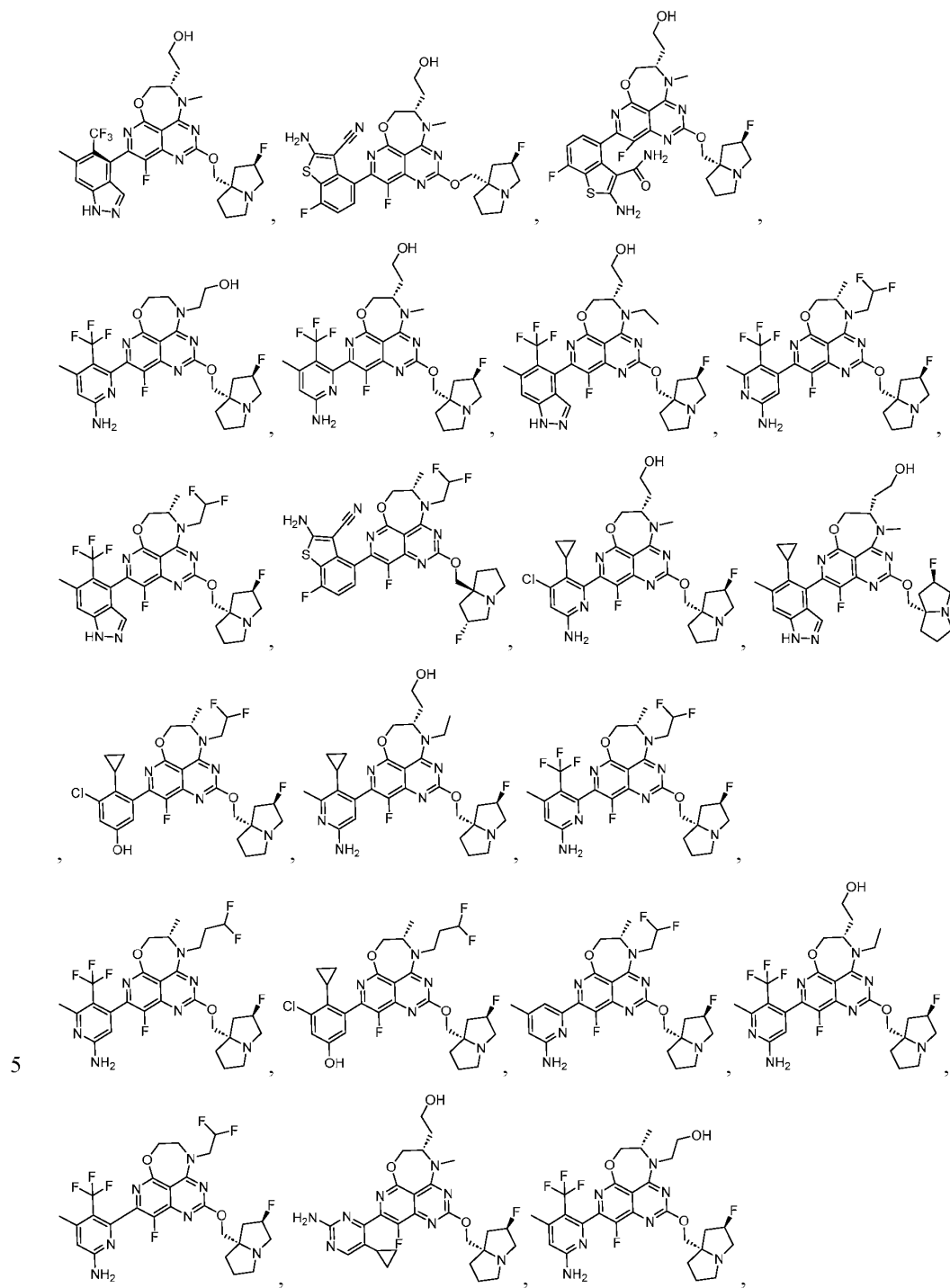
R¹ is selected from the group consisting of -CH₃, -CH₂CH₃, -CH₂CN, -CH₂CHF₂, -CH₂F₂Cl, -CH₂CF₃, -CH₂CH₂CHF₂, -CH(CH₃)CHF₂, -CH₂CH₂OH, -CH₂CH₂CH₂OH,

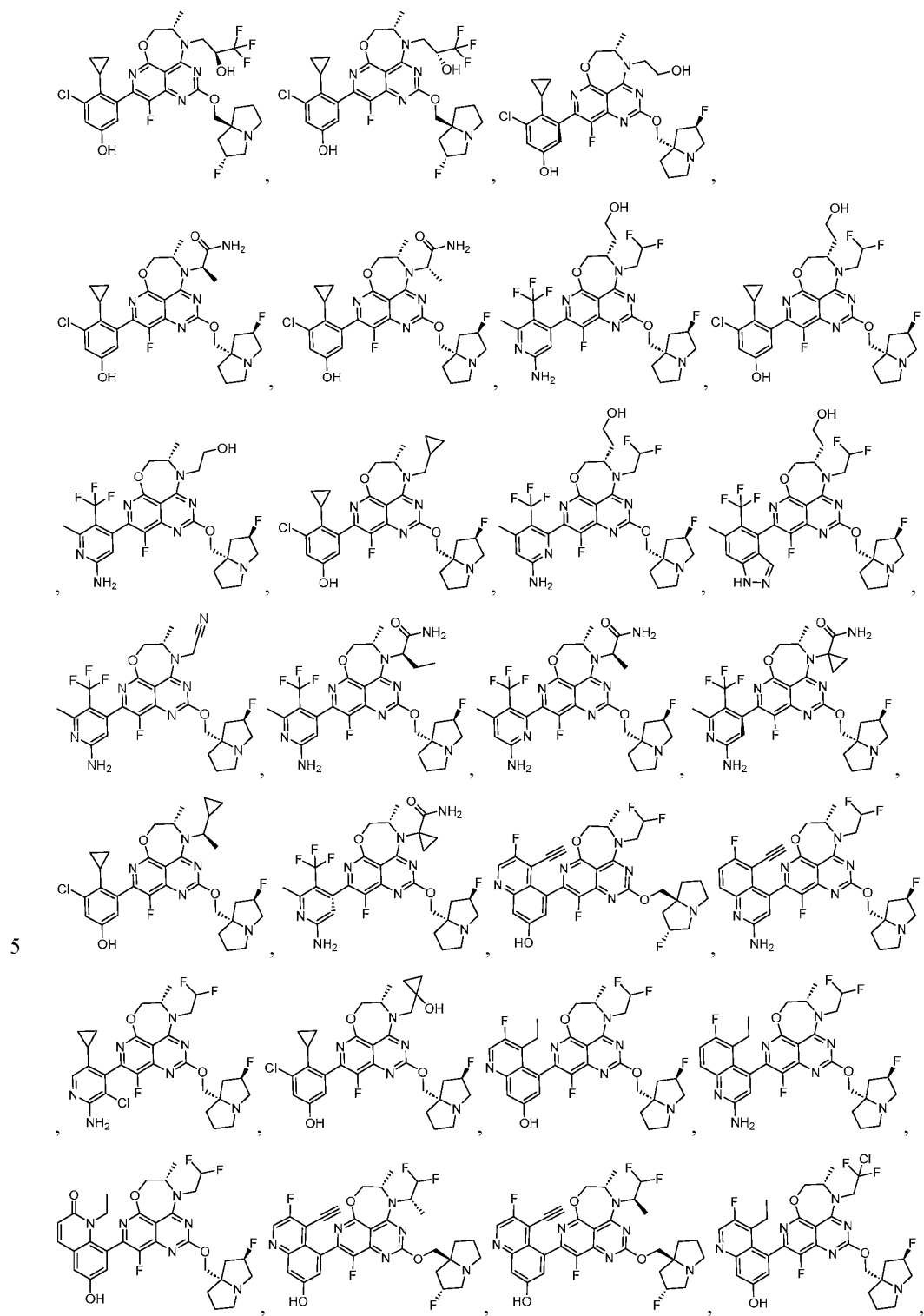


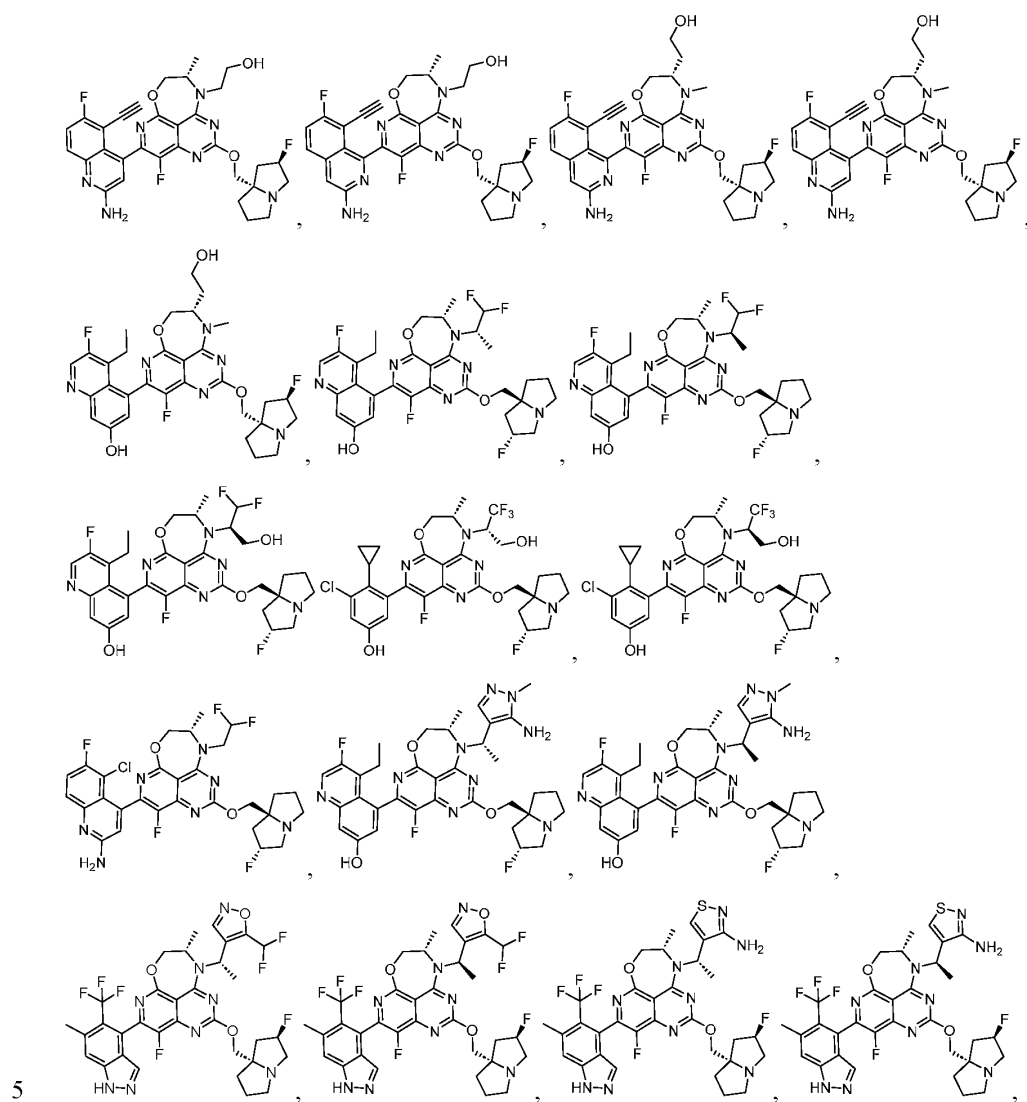
- 5 R² is selected from the group consisting of hydrogen, -CH₃, and -CH₂CH₂OH; and
 R³ is hydrogen or CH₃.

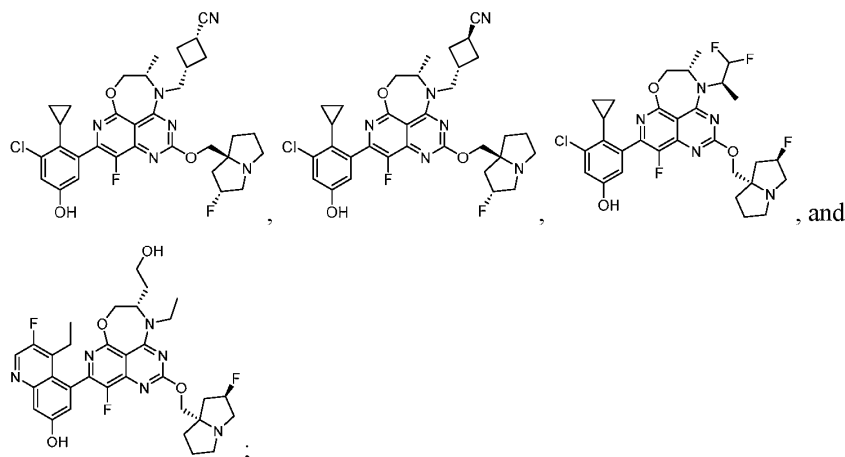
[0071] In other embodiments, for example, a compound of the present disclosure is selected from the group consisting of





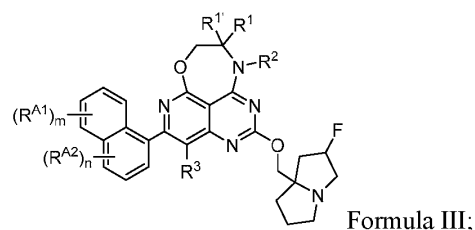






or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

[0072] Also disclosed is a compound represented by Formula III:



Formula III;

or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

- R^{A1} and R^{A2} are independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, -CN, -NO₂, -NR^aR^b, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, and phenyl may optionally be substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, oxo, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;
- R^{11} is hydrogen and R^1 is selected from the group consisting of hydrogen, -CH₃, -CF₃, -CH₂CH₂OH, -CH₂C(CH₃)₂OH, C₂-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, phenyl, 5-membered heteroaryl, and -CR^cR^d-(5-membered heteroaryl); wherein alkyl is substituted with one, two, three, or four substituents each independently selected from R^{11} ; and wherein alkenyl, alkynyl, cycloalkyl, phenyl, and heteroaryl may optionally be substituted with one, two, three, or four substituents each independently selected from R^{22} ; and

R^2 is selected from the group consisting of hydrogen, $-CH_3$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH_2CH(CH_3)OH$, $-CH_2C(CH_3)_2OH$, C_2 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 cycloalkyl, C_5 - C_6 cycloalkyl, phenyl, 5-membered heteroaryl, and $-CR^eR^d$ -(5-membered heteroaryl); wherein alkyl is substituted with one, two, three, or four substituents each independently selected from R^{11} ; and wherein alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, and heteroaryl may optionally be substituted with one, two, three, or four substituents each independently selected from R^{22} ;

or:

R^1 and $R^{1'}$, together with the carbon atom to which they are attached, may be joined together to form C_3 -cycloalkyl optionally substituted with one, two or three halogens or hydroxyl; and R^2 is C_1 - C_6 alkyl substituted with one, two, or three substituents each independently selected from the group consisting of halogen, hydroxyl, cyano, $-COOH$, and $C(=O)NR^aR^b$; or

R^1 and $R^{1'}$, together with the carbon atom to which they are attached, may be joined together to form C_4 -cycloalkyl optionally substituted with one, two or three halogens or hydroxyl; and R^2 is C_1 - C_6 alkyl optionally substituted with one, two, or three substituents each independently selected from the group consisting of halogen, hydroxyl, cyano, $-COOH$, and $C(=O)NR^aR^b$;

R^{11} is independently selected for each occurrence from the group consisting of halogen, deuterium, $-CN$, $-NO_2$, $-NR^aR^b$, oxo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, phenyl, $-COOH$, $-C(=O)NR^aR^b$, $-NR^a(C=O)R^b$, $-O(C=O)NR^aR^b$, $-NR^a(C=O)OR^b$, $-NR^a(C=O)NR^aR^b$, $-(C=O)C_1$ - C_6 alkyl, $-(C=O)OC_1$ - C_6 alkyl, $-O(C=O)C_1$ - C_6 alkyl, $-O(C=O)OC_1$ - C_6 alkyl, $-SH$, $-SC_1$ - C_6 alkyl, $-S(O)C_1$ - C_6 alkyl, $-S(O)_2C_1$ - C_6 alkyl, $-S(O)_2NR^aR^b$, and $-NR^aS(O)_2C_1$ - C_6 alkyl;

R^{22} is independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, $-CN$, $-NO_2$, $-NR^aR^b$, oxo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkyl, phenyl, $-COOH$, $-C(=O)NR^aR^b$, $-NR^a(C=O)R^b$, $-O(C=O)NR^aR^b$, $-NR^a(C=O)OR^b$, $-NR^a(C=O)NR^aR^b$, $-(C=O)C_1$ - C_6 alkyl, $-(C=O)OC_1$ - C_6 alkyl, $-O(C=O)C_1$ - C_6 alkyl, $-O(C=O)OC_1$ - C_6 alkyl, $-SH$, $-SC_1$ - C_6 alkyl, $-S(O)C_1$ - C_6 alkyl, $-S(O)_2C_1$ - C_6 alkyl, $-S(O)_2NR^aR^b$, and $-NR^aS(O)_2C_1$ - C_6 alkyl;

R^3 is selected from the group consisting of halogen, hydrogen, deuterium, and C_1 - C_3 alkyl;

R^a and R^b are each independently selected from the group consisting of hydrogen and C_1 - C_6 alkyl, wherein C_1 - C_6 alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, and C_1 - C_6 alkoxy; or

- 5 R^a and R^b , together with the nitrogen to which they are attached, may be joined together to form a 4-7 membered heterocyclyl optionally substituted by one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, $-NR^aR^b$, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy;

- 10 R^c and R^d are each independently selected from the group consisting of hydrogen and C_1 - C_6 alkyl;

m is 0, 1, 2, 3, or 4; and

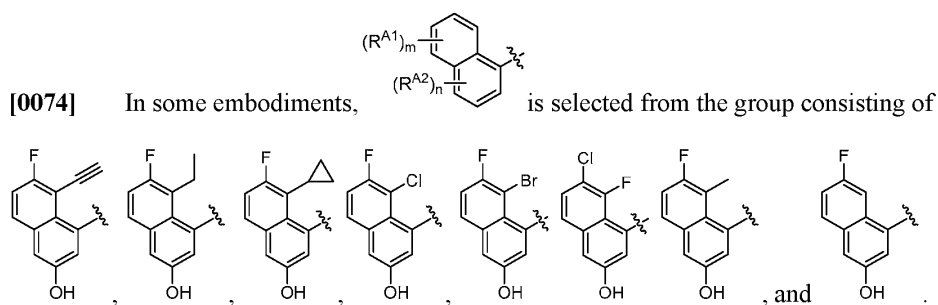
n is 0, 1, or 2;

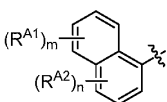
wherein:

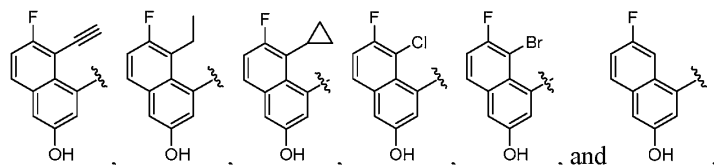
if R^1 is hydrogen, then R^2 is not hydrogen, $-CH_3$, or CH_2CH_2OH ; and

- 15 if R^1 is $-CH_3$, then R^2 is not hydrogen, $-CH_3$, $-CH_2CF_2$, $-CH_2CF_3$, or $-CH_2CH(CH_3)OH$.

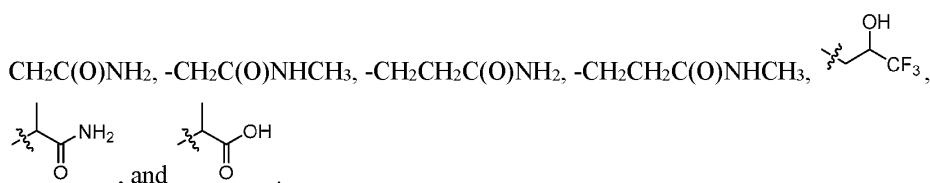
- [0073] For example, in some embodiments R^{A1} and R^{A2} are independently selected for each occurrence from the group consisting of, for example, halogen, hydroxyl, cyano, $-NH_2$, C_1 - C_4 alkyl, and C_2 - C_4 alkynyl, C_1 - C_4 alkoxy, and C_3 - C_4 cycloalkyl, wherein alkyl, alkynyl, alkoxy, and cycloalkyl may optionally be substituted with one, two, or three halogens. In other
- 20 embodiments, m is 1 or 2 and R^{A1} is independently selected for each occurrence from the group consisting of halogen, C_1 - C_4 alkyl, C_2 - C_4 alkynyl, and C_3 - C_4 cycloalkyl. In still other embodiments, n is 1 and R^{A2} is hydroxyl or $-NH_2$.



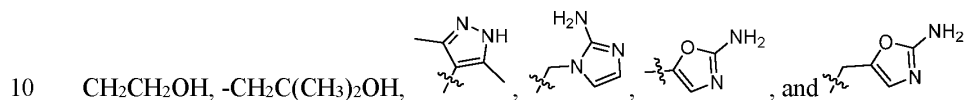
- 25 [0075] In other embodiments,  is selected from the group consisting of



[0076] In some embodiments, R¹ is hydrogen. In other embodiments, R¹ is hydrogen. In further embodiments, R² is selected from the group consisting of, for example, -CH₂CN, -CH₂CH(OH)CH₃, -CH₂CH₂CH₂OH, -CH₂C(O)NH₂, -CH₂C(O)NHCH₃, -CH₂CH₂C(O)NH₂, and -CH₂CH₂C(O)NHCH₃. In certain embodiments, R¹ is -CH₃. In additional embodiments, R² is selected from the group consisting of, for example, -CH₂CH₂OH, -CH₂CH₂CH₂OH, -



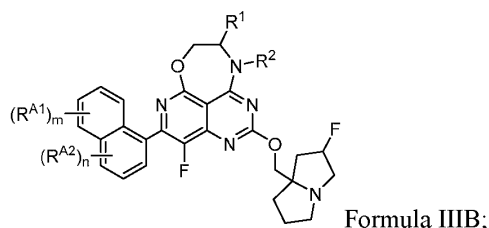
[0077] In some embodiments, R¹ is selected from the group consisting of -CF₃, -CH₂CF₃, -



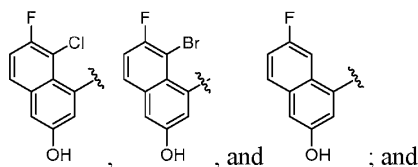
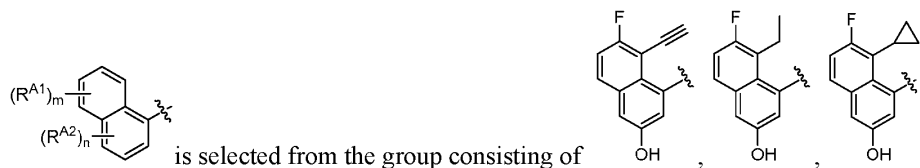
[0078] In other embodiments, R² is selected from the group consisting of hydrogen, -CH₃, -CH₂CHF₂, -CH₂CF₃, -CH₂CH₂OH, -CH₂CH₂C(O)NH₂, and -CH₂CH₂C(O)NHCH₃.

[0079] In some embodiments, R^{1'} and R¹, together with the carbon atom to which they are attached, are joined together to form C₃-cycloalkyl optionally substituted with hydroxyl; and R² is -CH₂CH₂OH. For example, in certain embodiments R^{1'} and R¹, together with the carbon atom to which they are attached, are joined together to form C₄-cycloalkyl optionally substituted with hydroxyl; and R² is -CH₃. In other embodiments, R³ is hydrogen.

[0080] In some embodiments, a compound of the present disclosure is represented by Formula IIIB:

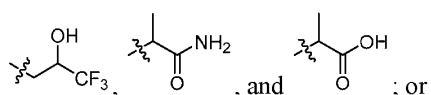


or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:



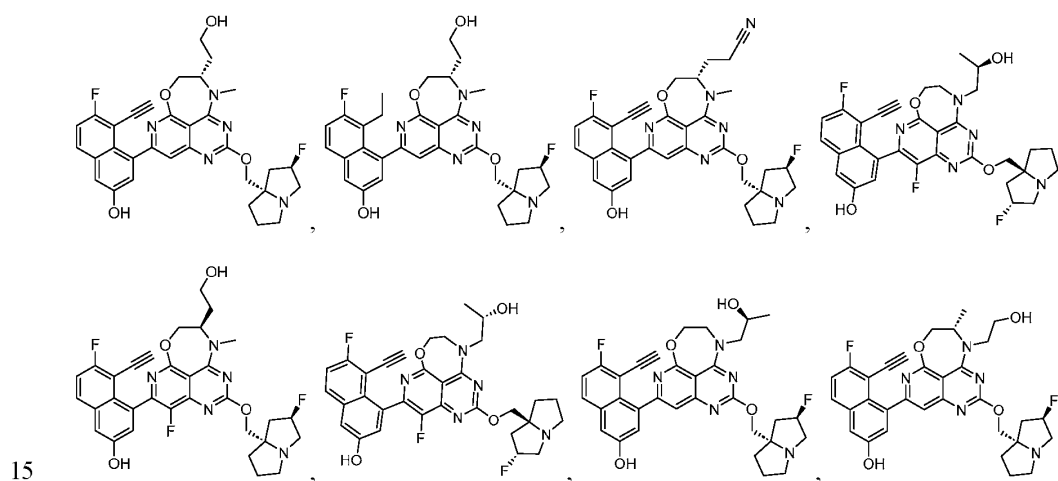
R^1 is hydrogen; and R^2 is selected from the group consisting of $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, and
 5 $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$; or

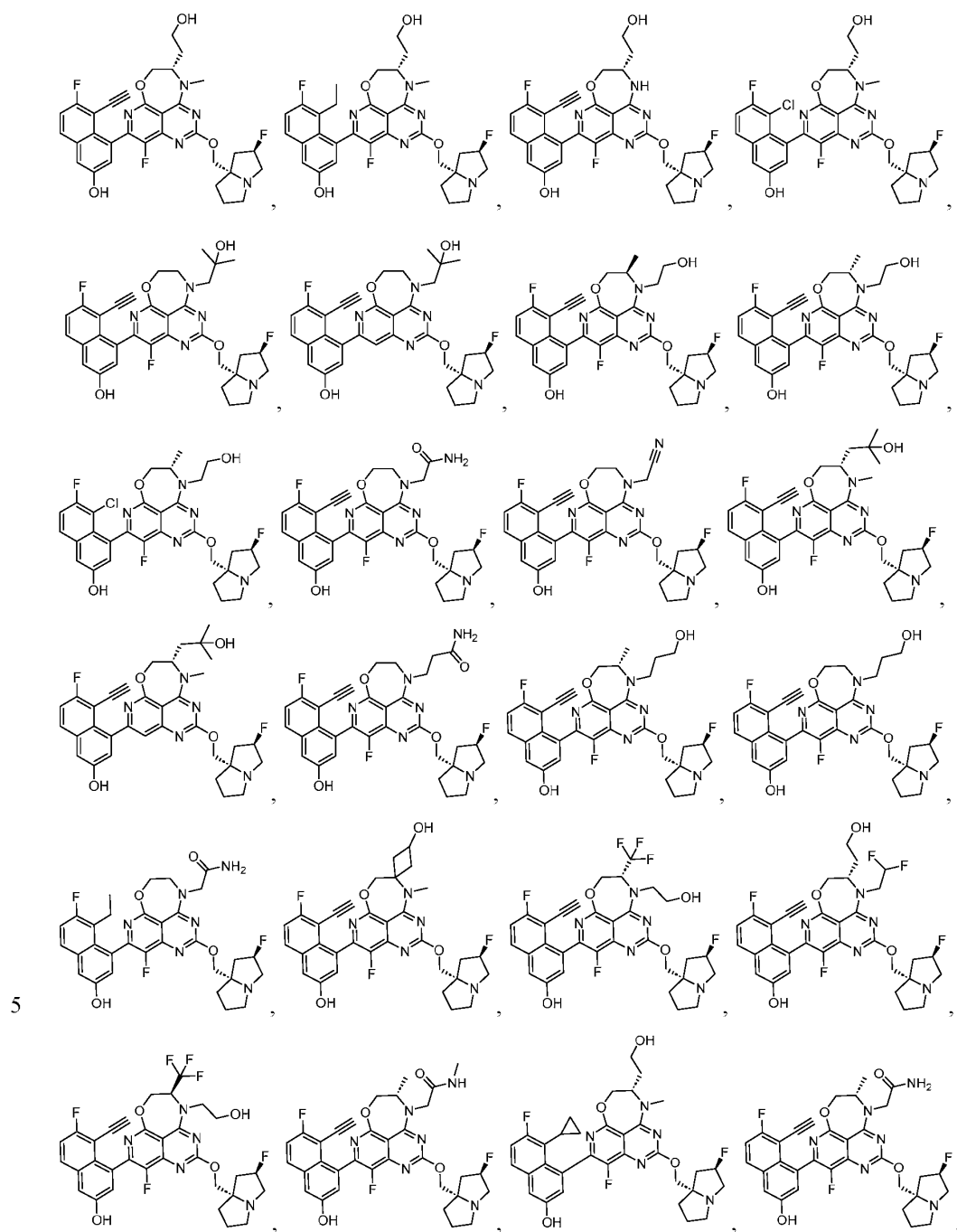
R^1 is $-\text{CH}_3$; and R^2 is selected from the group consisting of $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$,

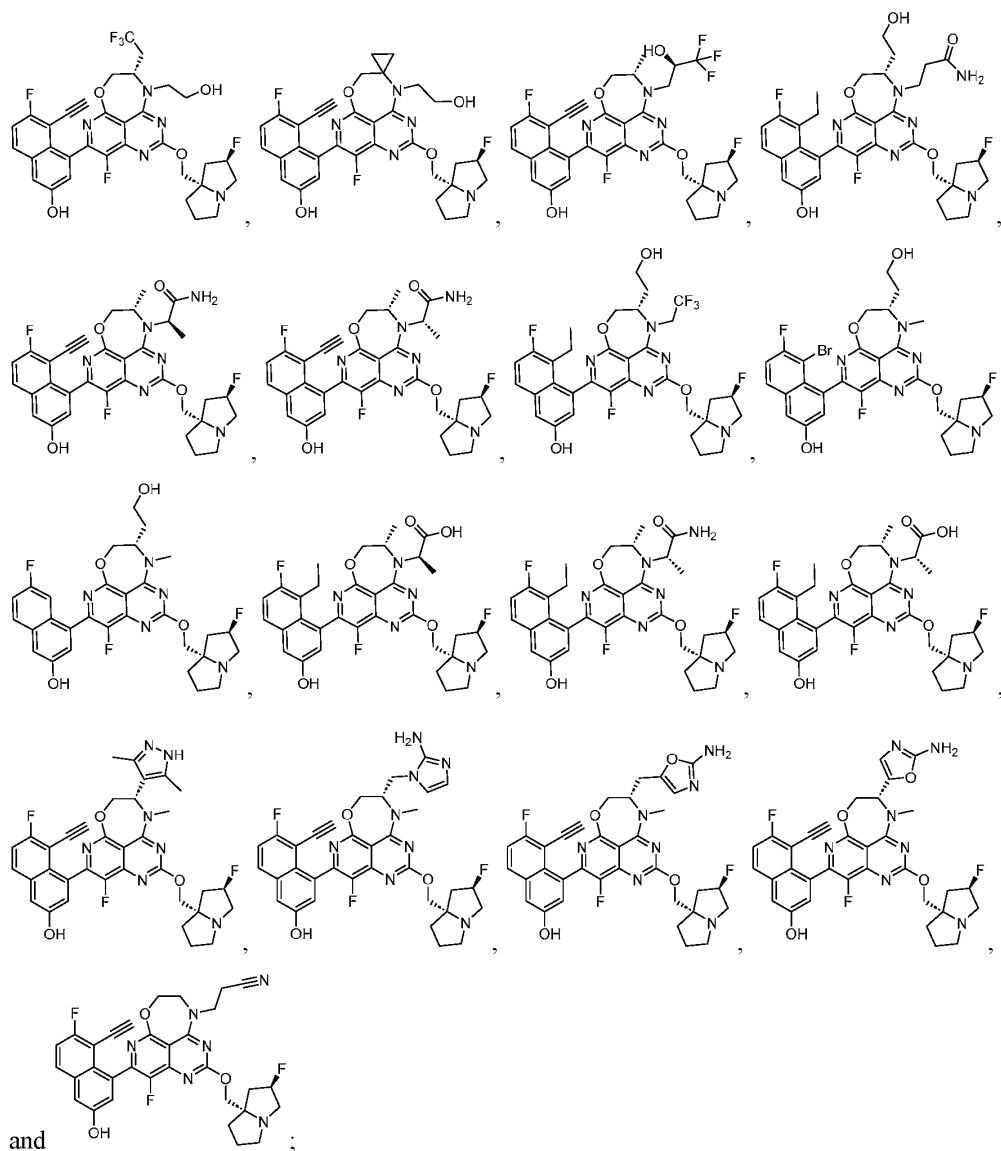


R^1 is selected from the group consisting of $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$; and R^2 is selected from the group consisting of hydrogen, $-\text{CH}_3$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, and $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$.
 10

[0081] In other embodiments, a compound of the present disclosure is selected from the group consisting of, for example:

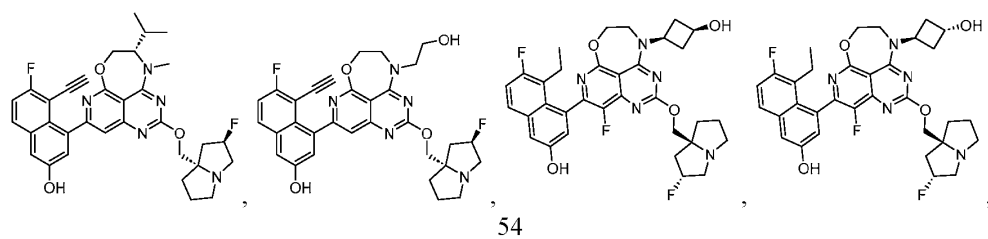


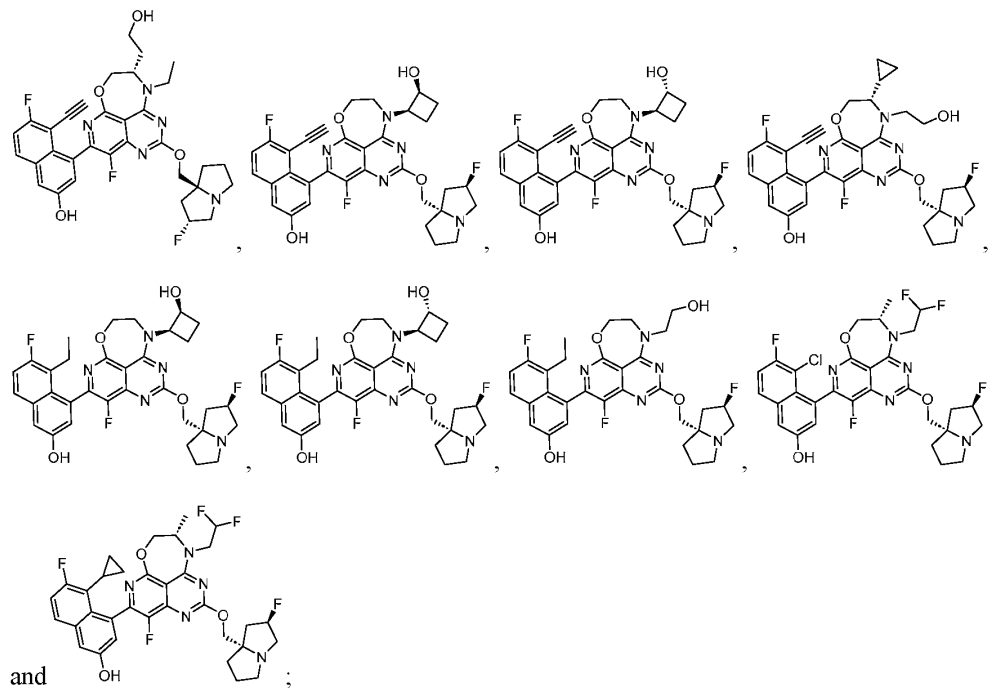




or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

[0082] In further embodiments, a compound of the present disclosure is selected from the group consisting of, for example:



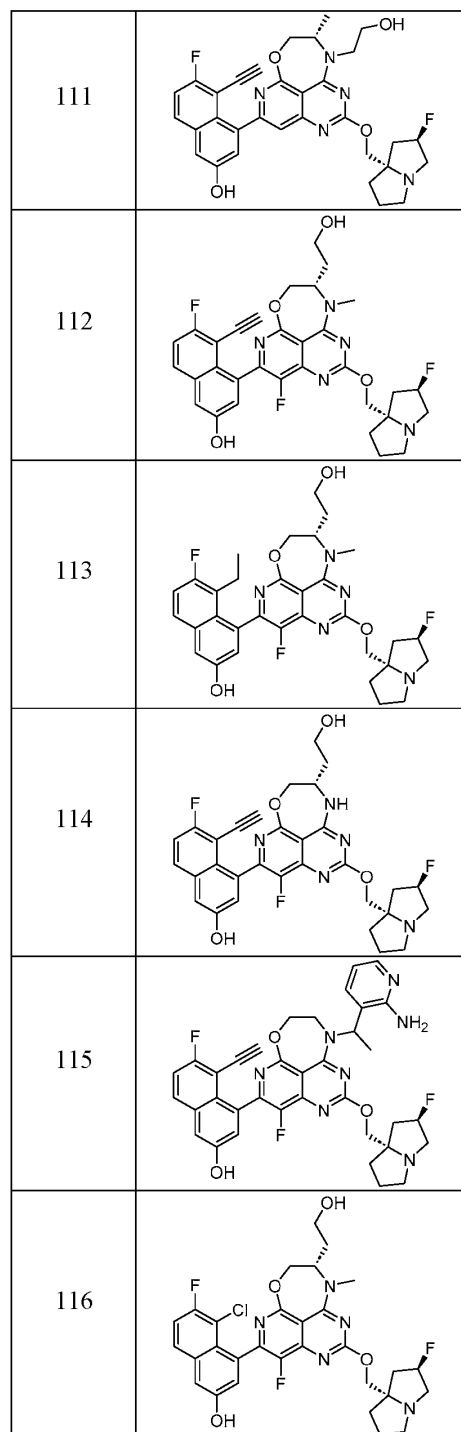
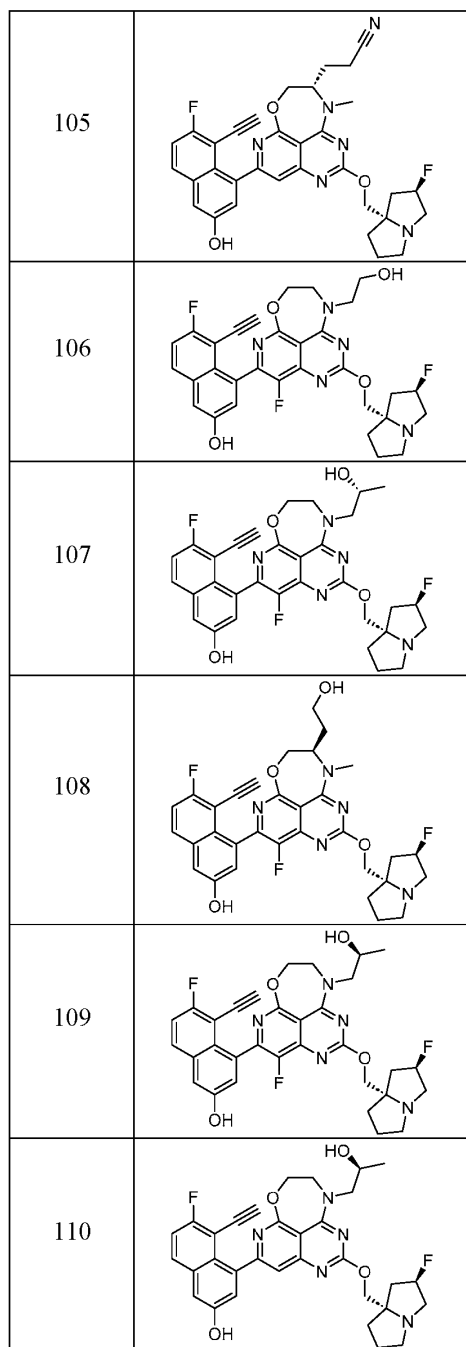


or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

- 5 [0083] In some embodiments, the compound is a compound identified in Table 1 below or a pharmaceutically acceptable salt thereof.

Table 1. Exemplary compounds.

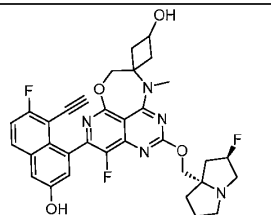
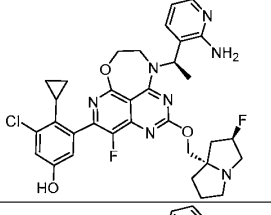
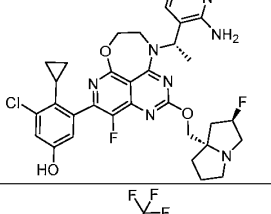
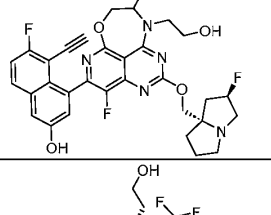
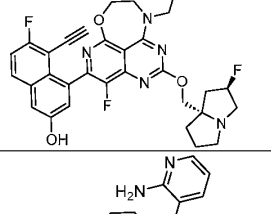
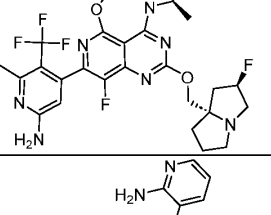
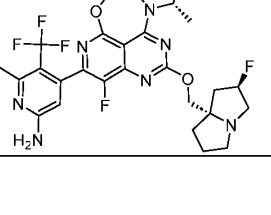
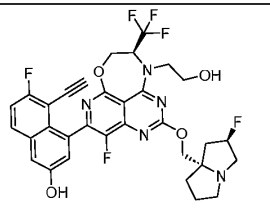
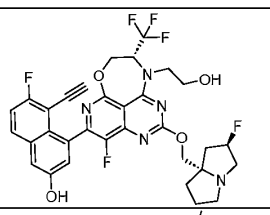
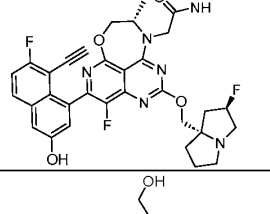
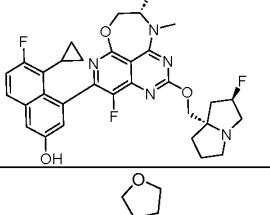
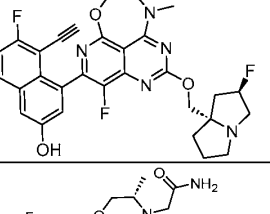
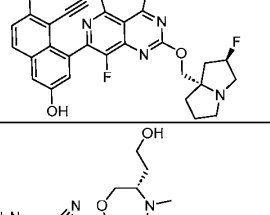
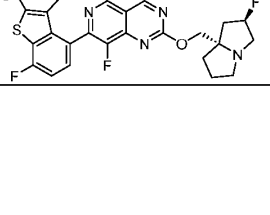
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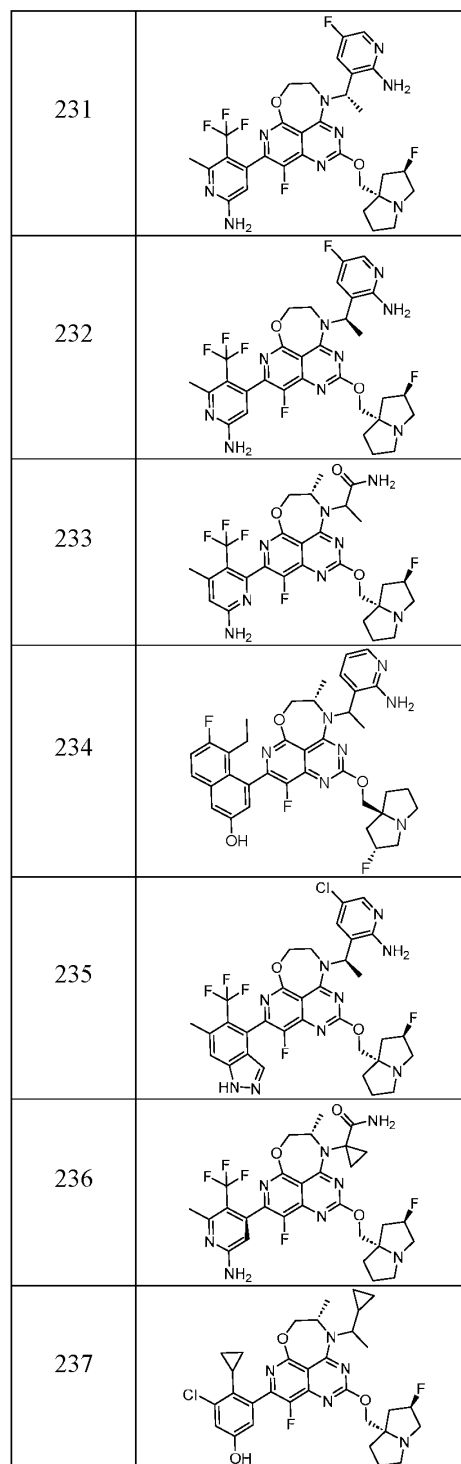
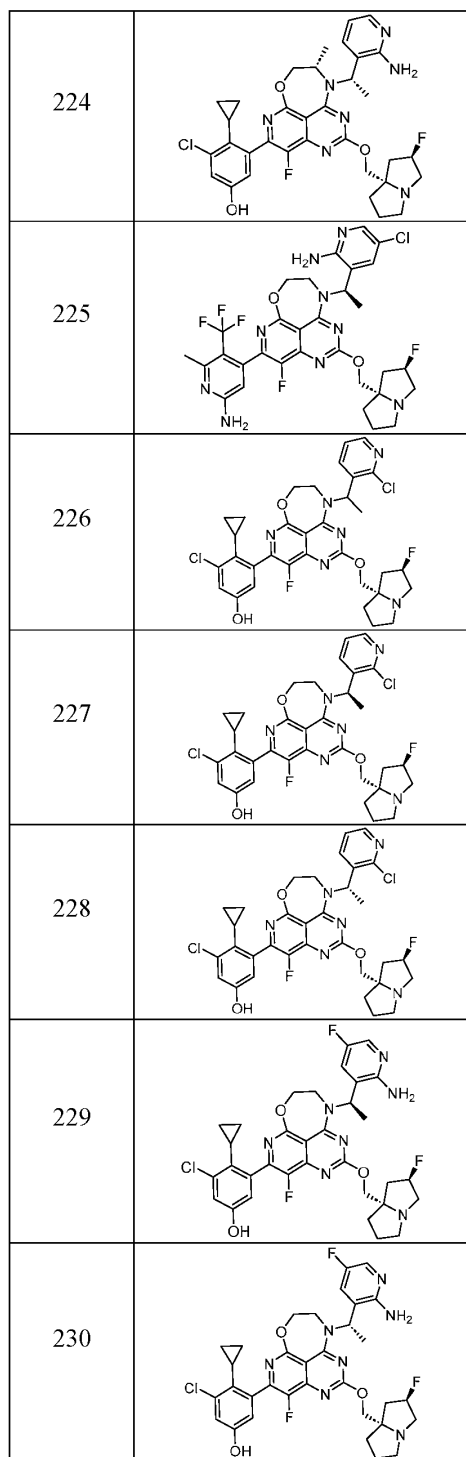
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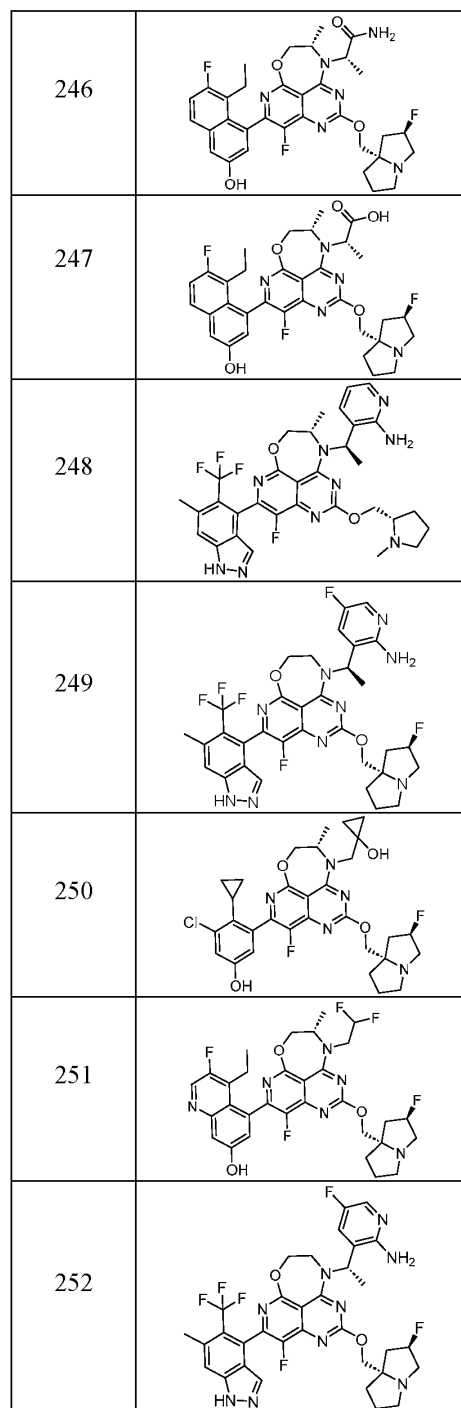
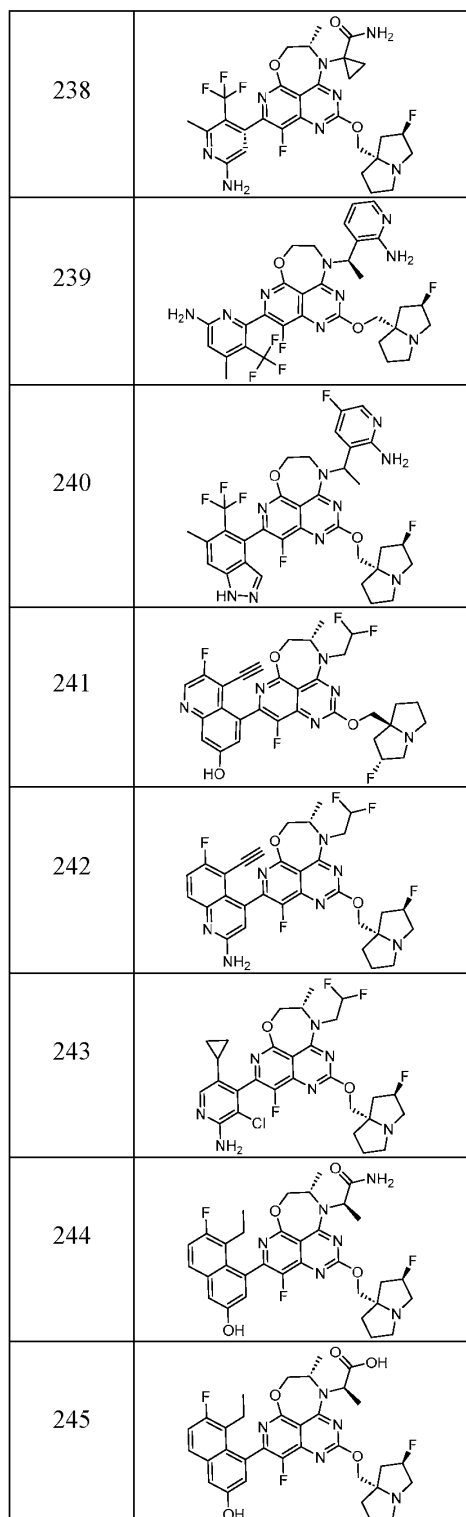
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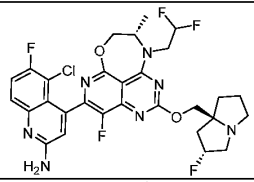
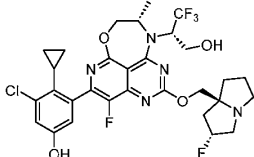
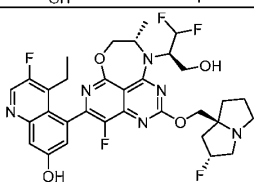
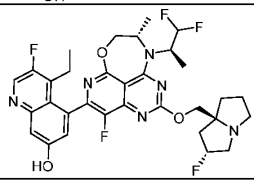
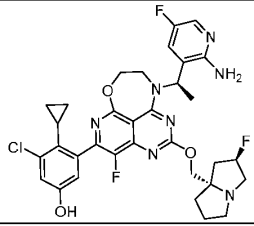
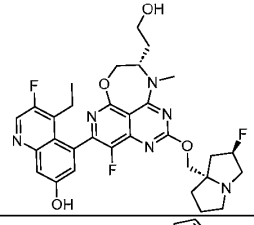
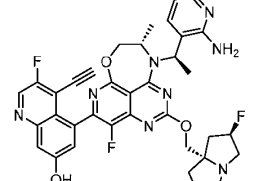
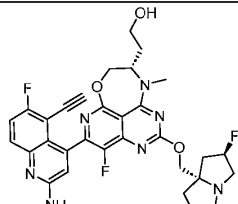
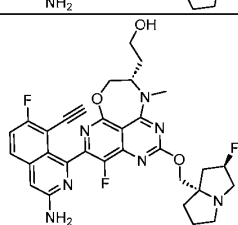
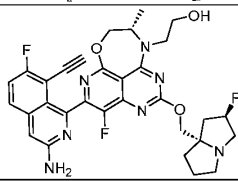
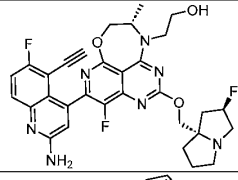
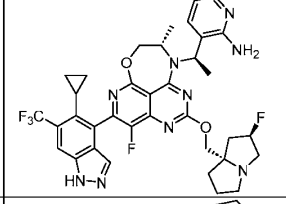
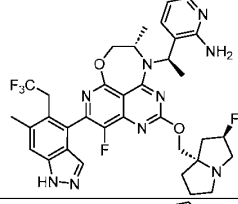
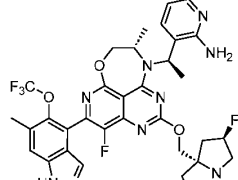
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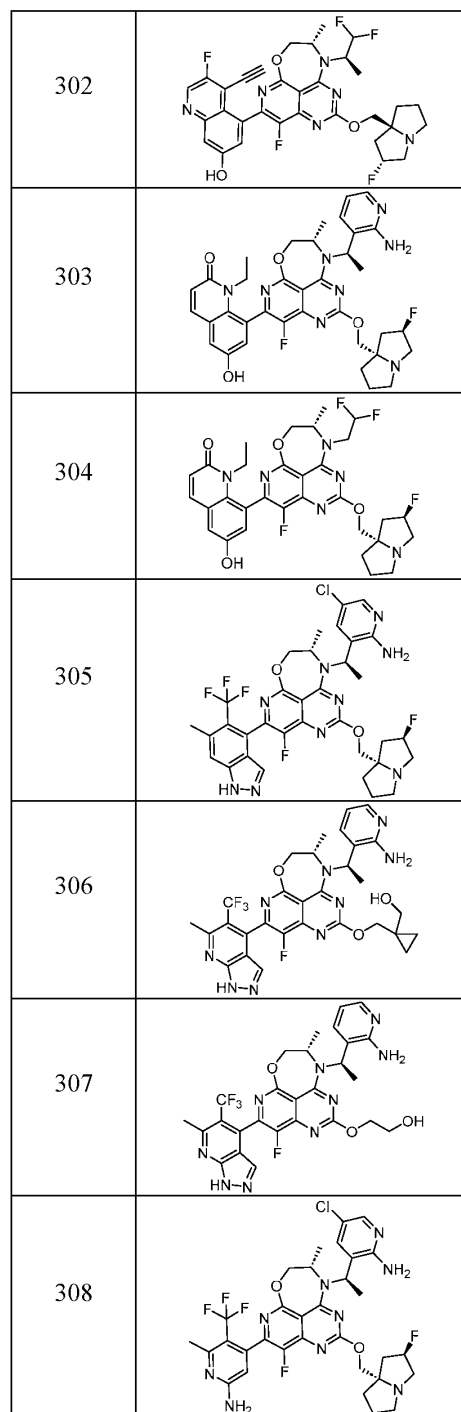
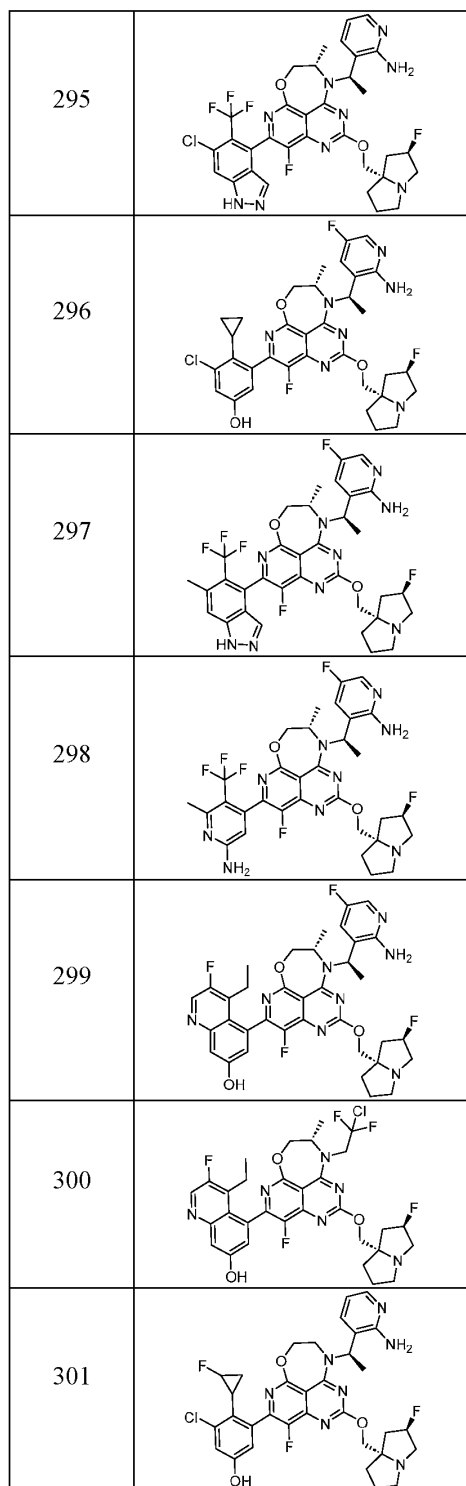




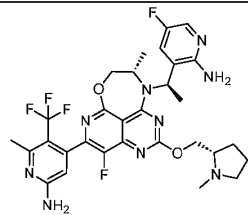
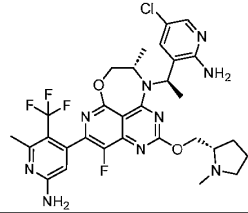
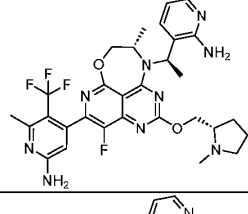
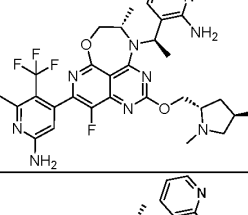
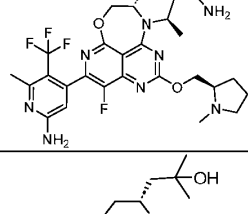
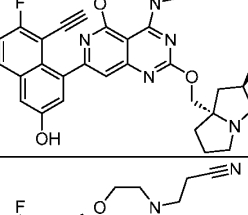
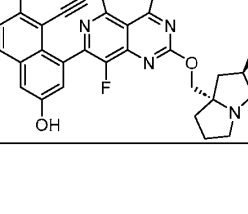
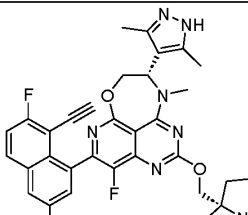
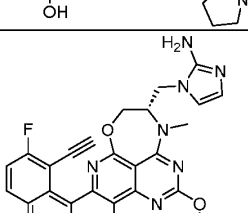
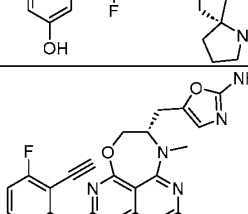
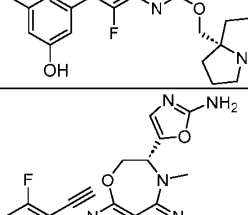
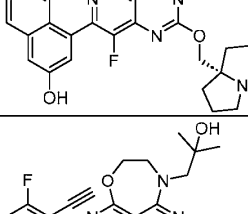
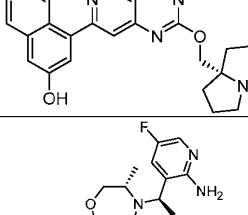
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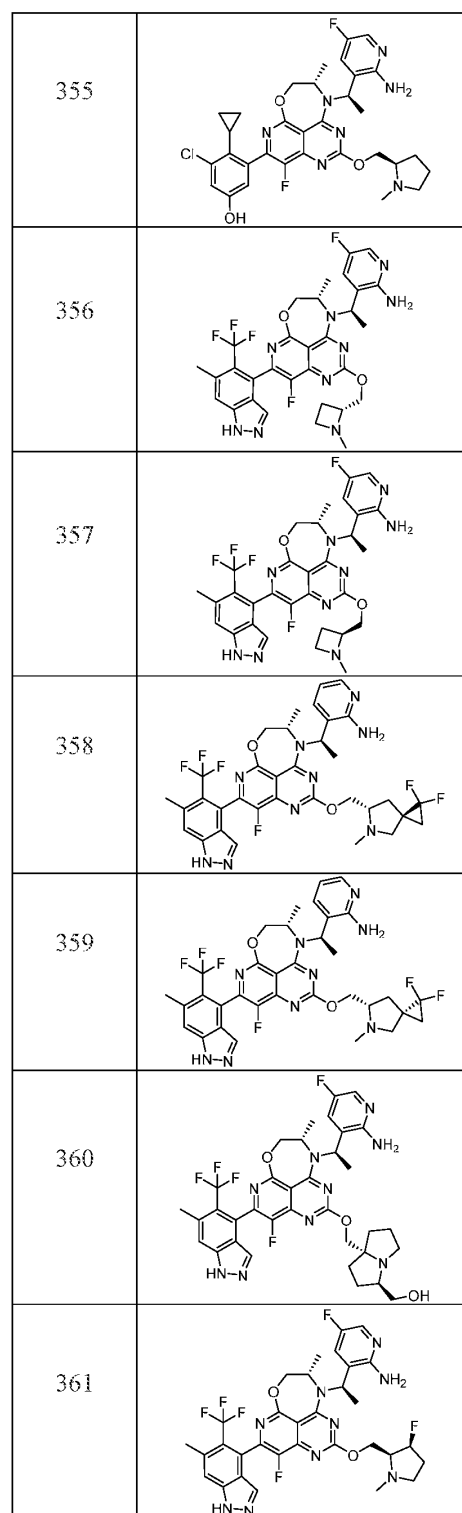
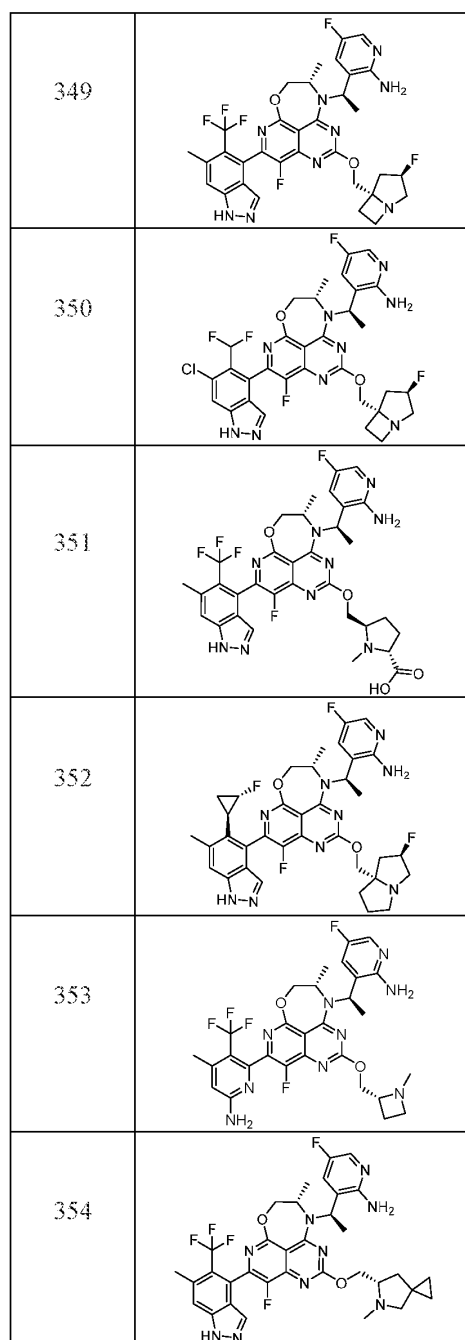
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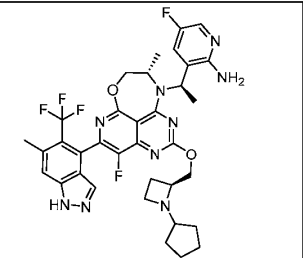
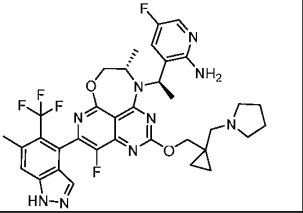
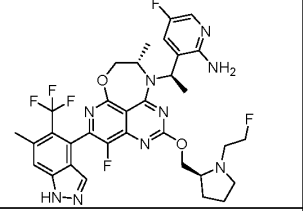
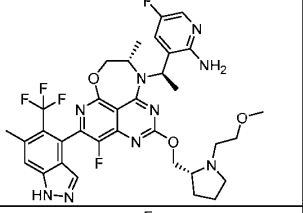
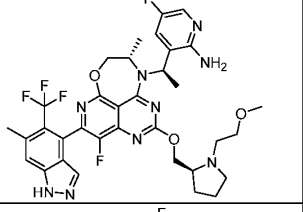
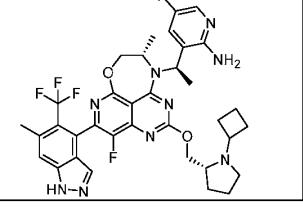
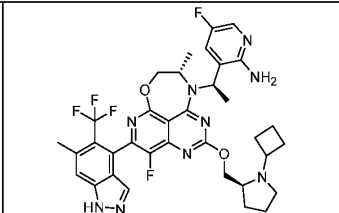
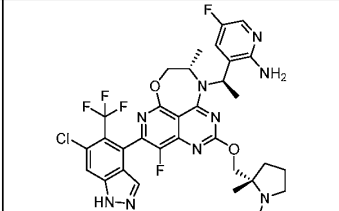
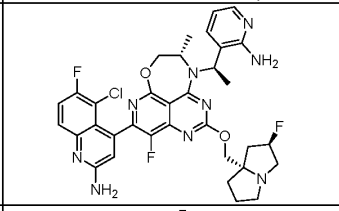
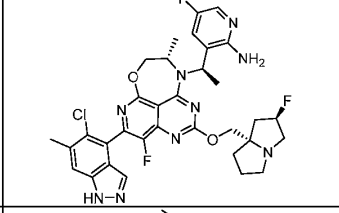
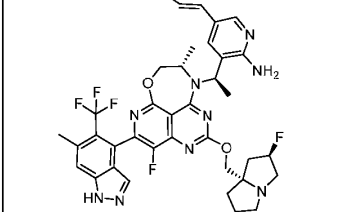
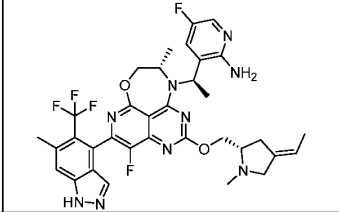
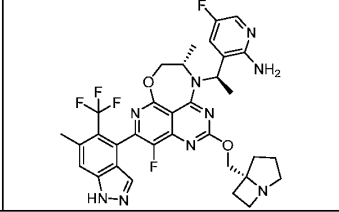
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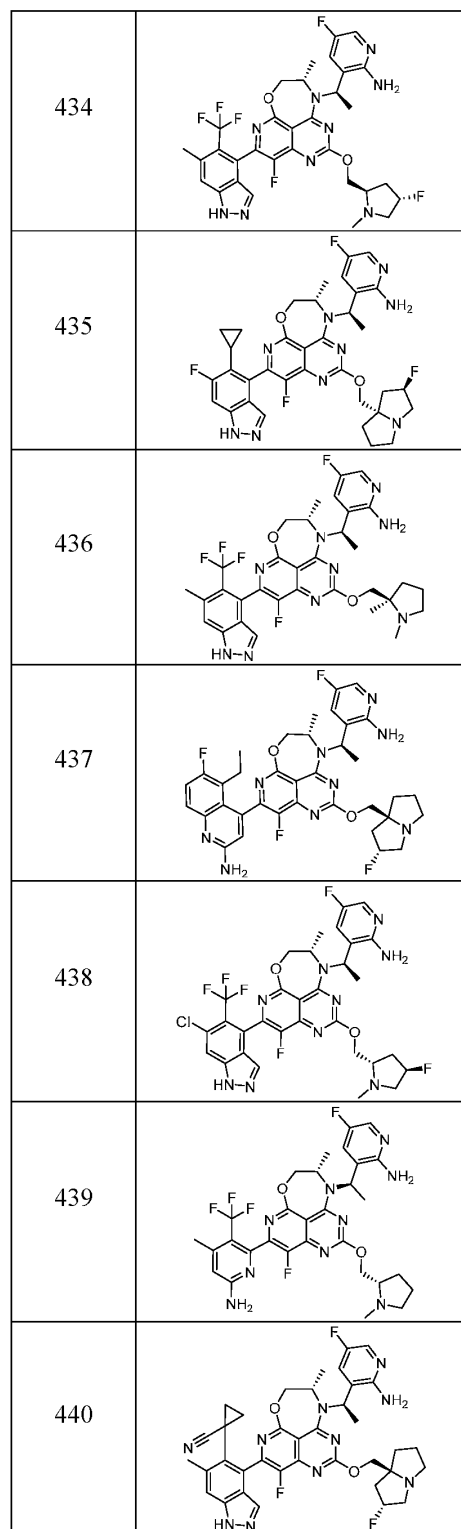
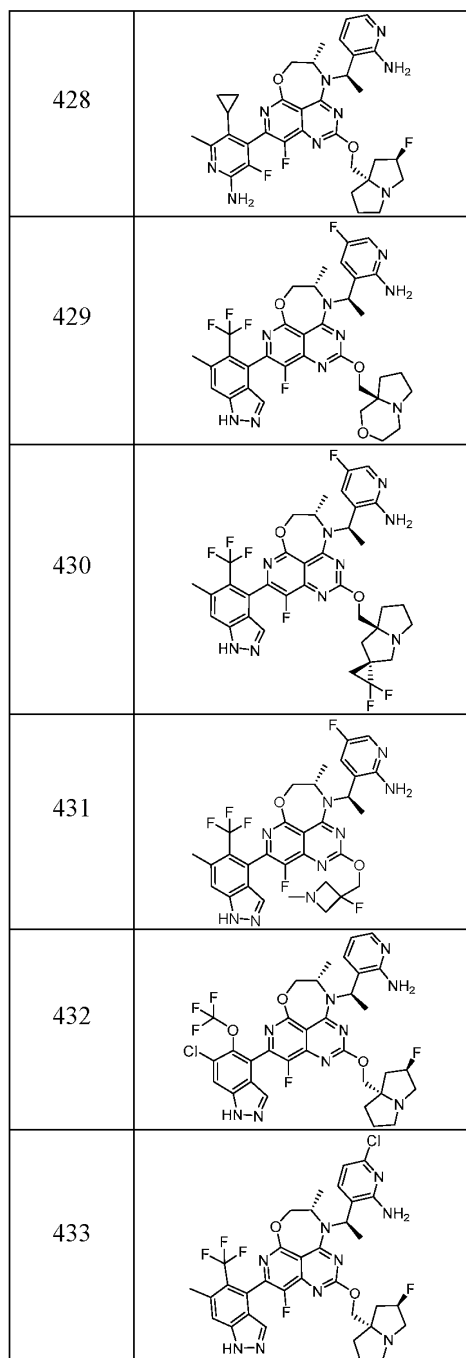
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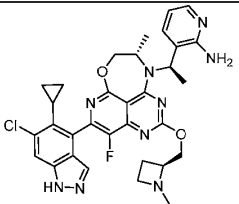
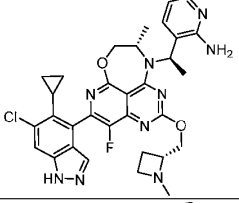
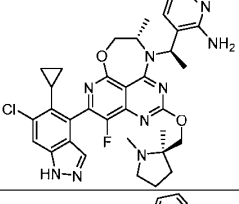
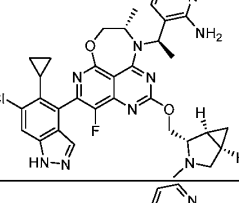
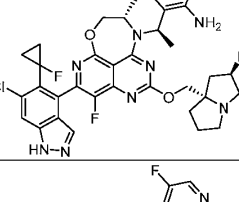
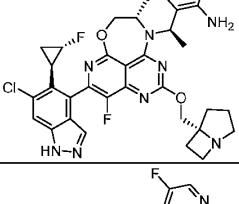
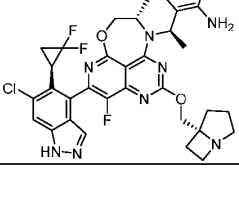
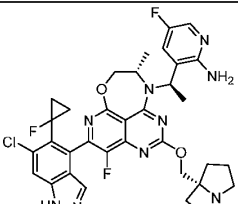
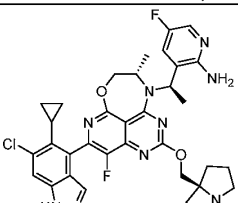
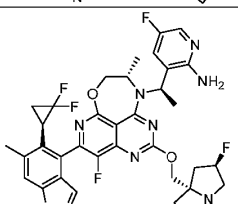
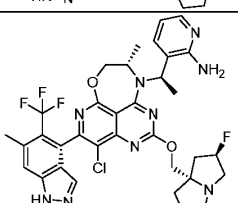
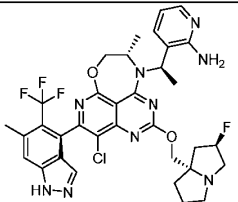
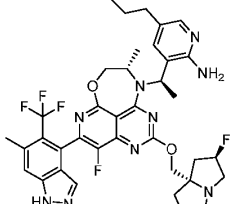
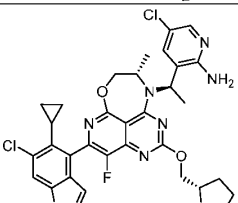
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[0084] Procedures for making compounds described herein are provided in the examples below. In the reactions described below, it may be necessary to protect reactive functional groups (such as hydroxyl, amino, thio or carboxyl groups) to avoid their unwanted participation in the reactions. The incorporation of such groups, and the methods required to introduce and remove them are known to those skilled in the art (for example, see Greene, Wuts, *Protective Groups in Organic Synthesis*. 2nd Ed. (1999)). The deprotection step may be the final step in the synthesis such that the removal of protecting groups affords compounds as disclosed herein.

Starting materials used in the following scheme can be purchased or prepared by methods described in the chemical literature, or by adaptations thereof, using methods known by those

skilled in the art. The order in which the steps are performed can vary depending on the groups introduced and the reagents used, but would be apparent to those skilled in the art.

[0085] Compounds disclosed herein, or any of the intermediates described in the schemes above, can be further derivatised by using one or more standard synthetic methods known to those skilled in the art. Such methods can involve substitution, oxidation or reduction reactions. These methods can also be used to obtain or modify disclosed compounds or any preceding intermediates by modifying, introducing or removing appropriate functional groups.

[0086] Where it is desired to obtain a particular enantiomer of a disclosed compound, this may be produced from a corresponding mixture of enantiomers by employing any suitable conventional procedure for resolving enantiomers known to those skilled in the art. For example, diastereomeric derivatives (such as salts) can be produced by reaction of a mixture of enantiomers of a disclosed compound (such a racemate) and an appropriate chiral compound (such as a chiral base). The diastereomers can then be separated by any conventional means such as crystallization or chromatography, and the desired enantiomer recovered (such as by treatment with an acid in the instance where the diastereomer is a salt). Alternatively, a racemic mixture of esters can be resolved by kinetic hydrolysis using a variety of biocatalysts (for example, see Patel *Stereoselective Biocatalysts*, Marcel Decker, New York 2000).

[0087] In another resolution process a racemate of disclosed compounds can be separated using chiral High Performance Liquid Chromatography. Alternatively, a particular enantiomer can be obtained by using an appropriate chiral intermediate in one of the processes described above. Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the disclosure.

[0088] In an alternative embodiment, disclosed compounds may also comprise one or more isotopic substitutions. For example, hydrogen may be ^2H (D or deuterium) or ^3H (T or tritium); carbon may be, for example, ^{13}C or ^{14}C ; oxygen may be, for example, ^{18}O ; nitrogen may be, for example, ^{15}N , and the like. In other embodiments, a particular isotope (e.g., ^3H , ^{13}C , ^{14}C , ^{18}O , or ^{15}N) can represent at least 1%, at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99%, or at least 99.9% of the total isotopic abundance of an element that occupies a specific site of the compound.

II. Methods

[0089] Further disclosed herein are methods of treating a patient suffering from a condition, disease, or disorder that is affected by, associated with, or would benefit from inhibition of Ras (e.g., K-Ras), comprising administering to the patient a therapeutically effective amount of a compound disclosed herein, or a pharmaceutical composition thereof. For example, disclosed herein are methods of treating a Ras protein-related (e.g., a K-Ras protein-related) disease or disorder in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound disclosed herein, or a pharmaceutical composition thereof.

[0090] In some embodiments, the present disclosure provides a method of treating a disease or disorder characterized by aberrant Ras activity due to a Ras mutant (e.g., aberrant K-Ras activity due to a K-Ras mutation). In some embodiments, for example, the compounds and compositions disclosed herein may be used to treat a cancer having one or more Ras mutations (e.g., a K-Ras mutation).

[0091] For example, the methods described herein may be useful to treat cancers including, but not limited to, lung, prostate, breast, brain, skin, cervical carcinomas, and testicular carcinomas. For example, in some embodiments, the cancers that may be treated by the compounds, compositions and methods disclosed herein are, but are not limited to, tumor types such as astrocytic, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatocellular, laryngeal, lung, oral, ovarian, prostate and thyroid carcinomas and sarcomas.

[0092] In certain embodiments, the compounds, compositions and methods disclosed herein can be used to treat cancers, including tumors, related to the cardiovascular system. Non-limiting examples contemplated herein include, e.g., angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma, myxoma, rhabdomyoma, fibroma, lipoma and teratoma.

[0093] In further embodiments, the compounds, compositions and methods disclosed herein can be used to treat cancers, including tumors, of the lung. Non-limiting examples contemplated herein include, e.g., bronchogenic carcinoma (for example, squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (for example, bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, and mesothelioma.

[0094] In some embodiments, the compounds, compositions and methods disclosed herein can be used to treat cancers, including tumors, of the gastrointestinal system. Non-limiting examples contemplated herein include, e.g., esophageal cancer (for example, squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach cancer (for example,

carcinoma, lymphoma, and leiomyosarcoma), pancreatic cancer (for example, ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel cancer (for example, adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), and large bowel cancer (for example, adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma).

[0095] In other embodiments, the compounds, compositions and methods disclosed herein can be used to treat cancers, including tumors, of the genitourinary tract. Non-limiting examples contemplated herein include, e.g., kidney cancer (for example, adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethral cancer (for example, squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate cancer (for example, adenocarcinoma, sarcoma), and testicular cancer (for example, seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma).

[0096] In still other embodiments, the compounds, compositions and methods disclosed herein can be used to treat cancers, including tumors, of the liver. Non-limiting examples contemplated herein include, e.g., hepatoma (for example, hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma and hemangioma.

[0097] In further embodiments, the compounds, compositions and methods disclosed herein can be used to treat cancers, including tumors, of the biliary tract. Non-limiting examples contemplated herein include, e.g., gall bladder carcinoma, ampullary carcinoma, and cholangiocarcinoma.

[0098] In certain embodiments, the compounds, compositions and methods disclosed herein can be used to treat cancers, including tumors, of the bone. Non-limiting examples contemplated herein include, e.g., osteogenic sarcoma (for example, osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (for example, reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (for example, osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors.

[0099] In some embodiments, the compounds, compositions and methods disclosed herein can be used to treat cancers, including tumors, of the nervous system. Non-limiting examples contemplated herein include, e.g., cancer and/or tumors of the skull (for example, osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), cancer and/or tumors of the meninges (for example, meningioma, meningiosarcoma, gliomatosis), brain cancer (for example,

astrocytoma, medulloblastoma, glioma, ependymoma, germinoma, pinealoma, glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), and cancer and/or tumors of the spinal cord (for example, neurofibroma, meningioma, glioma, sarcoma).

[00100] In other embodiments, the compounds, compositions and methods disclosed herein can be used to treat cancers, including tumors, of the gynecological system. Non-limiting examples contemplated herein include, e.g., cancers and/or tumors of the uterus (for example, endometrial carcinoma), cancers and/or tumors of the cervix (for example, cervical carcinoma, pre-tumor cervical dysplasia), cancers and/or tumors of the ovaries (for example, ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), cancers and/or tumors of the vulva (for example, squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), cancers and/or tumors of the vagina (for example, clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), and cancers and/or tumors of the fallopian tubes (carcinoma).

[00101] In further embodiments, the compounds, compositions and methods disclosed herein can be used to treat hematologic cancers, including tumors. Non-limiting examples contemplated herein include, e.g., cancers and/or tumors of the blood (for example, myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, and non-Hodgkin's lymphoma (malignant lymphoma).

[00102] In certain embodiments, the compounds, compositions and methods disclosed herein can be used to treat cancers, including tumors, of the skin. Non-limiting examples contemplated herein include, e.g., malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, and psoriasis. In some embodiments, the compounds, compositions and methods disclosed herein can be used to treat cancers, including tumors, of the adrenal glands, e.g., neuroblastoma.

[00103] In some embodiments, the methods described herein may be useful to treat cancers including, but not limited to, pancreatic cancer, colorectal cancer, multiple myeloma, lung adenocarcinoma, melanoma, endometrial cancer, uterine cancer, thyroid, acute myelocytic leukemia, bladder carcinoma, gastric cancer, cervical cancer, and head and neck squamous cell carcinoma.

[00104] In particular, in certain embodiments, the disclosure provides a method of treating the medical indications contemplated herein comprising administering to a patient in need thereof a therapeutically effective amount of a compound described herein.

5 [00105] In some embodiments, the Ras protein is wild-type (Ras^{wt}). Accordingly, in some embodiments, a compound of the present invention is employed in a method of treating a patient having a cancer comprising a Ras^{wt} (e.g., K-Ras^{wt}, H-Ras^{wt} or N-Ras^{wt}). In some embodiments, the Ras protein is Ras amplification (e.g., K-Ras^{amp}). Accordingly, in some embodiments, a compound of the present invention is employed in a method of treating a patient having a cancer comprising a Ras^{amp} (K-Ras^{amp}, H-Ras^{amp} or N-Ras^{amp}).

10 [00106] In some embodiments, the cancer comprises a Ras mutation, such as a Ras mutation described herein. In some embodiments, the mutation is selected from a K-Ras mutation (for example, G12D, G12V, G12C, G13D, G12R, G12A, Q61H, G12S, A146T, G13C, Q61L, Q61R, K117N, A146V, G12F, Q61K, L19F, Q22K, V14I, A59T, A146P, G13R, G12L, or G13V, and combinations thereof); a H-Ras mutation (for example, Q61 R, G13R, Q61K, G12S, 15 Q61L, G12D, G13V, G13D, G12C, K117N, A59T, G12V, G13C, Q61H, G13S, A18V, D119N, G13N, A146T, A66T, G12A, A146V, G12N, or G12R, and combinations thereof); and a N-Ras mutation (for example, Q61R, Q61K, G12D, Q61L, Q61H, G13R, G13D, G12S, G12C, G12V, G12A, G13V, G12R, P185S, G13C, A146T, G60E, Q61P, A59D, E132K, E49K, T50I, A146V, or A59T, and combinations thereof); or a combination of any thereof.

20 [00107] In some embodiments, the cancer comprises a K-Ras mutation selected from the group consisting of, for example, G12C, G12D, G13C, G12V, G13D, G12R, G12S, Q61H, Q61K and Q61L. In other embodiments, the cancer comprises an N-Ras mutation selected from the group consisting of, for example, G12C, Q61H, Q61K, Q61L, Q61P and Q61R. In still other embodiments, the cancer comprises an H-Ras mutation selected from the group 25 consisting of, for example, Q61H and Q61L. In further embodiments, the cancer comprises a Ras mutation selected from the group consisting of, for example, G12C, G13C, G12A, G12D, G13D, G12S, G13S, G12V and G13V. In certain embodiments, the cancer comprises at least two Ras mutations selected from the group consisting of, for example, G12C, G13C, G12A, G12D, G13D, G12S, G13S, G12V and G13V.

30 [00108] In some embodiments, a compound disclosed herein may inhibit more than one Ras mutant. For example, in some embodiments a disclosed compound may inhibit both K-Ras G12C and K-Ras G13C. In other embodiments, disclosed compound may inhibit both N-Ras G12C and K-Ras G12C. In still other embodiments, a disclosed compound may inhibit both N-

Ras G12C and K-Ras G12C. In further embodiments, a disclosed compound may inhibit both K-Ras G12C and K-Ras G12D. In certain embodiments, a disclosed compound may inhibit both K-Ras G12V and K-Ras G12C. In some embodiments, a disclosed compound may inhibit both K-Ras G12V and K-Ras G12S.

- 5 [00109] In some embodiments, a compound disclosed herein inhibits Ras^{wt} in addition to one or more additional Ras mutations (e.g., K, H or N-Ras^{wt} and K-Ras G12D, G12V, G12C, G13D, G12R, G12A, Q61H, G12S, A146T, G13C, Q61L, Q61R, K117N, A146V, G12F, Q61 K, L 19F, Q22K, V14I, A59T, A146P, G13R, G12L, or G13V; K, H, or N-Ras^{wt} and H-Ras Q61R, G13R, Q61K, G12S, Q61L, G12D, G13V, G13D, G12C, K117N, A59T, G12V, G13C, 10 Q61 H, G13S, A18V, D119N, G13N, A146T, A66T, G12A, A146V, G12N, or G12R; or K, H, or N-Ras^{wt} and N-Ras Q61R, Q61K, G12D, Q61L, Q61H, G13R, G13D, G12S, G12C, G12V, G12A, G13V, G12R, P185S, G13C, A146T, G60E, Q61P, A59D, E132K, E49K, T50I, A146V, or A59T).

- [00110] In some embodiments, a compound disclosed herein inhibits Ras^{amp} in addition to 15 one or more additional Ras mutations (e.g., K-, H- or N-Ras^{amp} and K-Ras G12D, G12V, G12C, G13D, G12R, G12A, Q61H, G12S, A146T, G13C, Q61L, Q61R, K117N, A146V, G12F, Q61K, L19F, Q22K, V14I, A59T, A146P, G13R, G12L, or G13V; K-, H- or N-Ras^{amp} and H-Ras Q61R, G13R, Q61K, G12S, Q61L, G12D, G13V, G13D, G12C, K117N, A59T, G12V, G13C, Q61H, G13S, A18V, D119N, G13N, A146T, A66T, G12A, A146V, G12N, or G12R; or 20 K-, H- or N-Ras^{amp} and N-Ras Q61R, Q61K, G12D, Q61L, Q61H, G13R, G13D, G12S, G12C, G12V, G12A, G13V, G12R, P185S, G13C, A146T, G60E, Q61P, A59D, E132K, E49K, T50I, A146V, or A59T).

- [00111] In some embodiments, a cancer comprises a Ras mutation and an STK11^{LOF}, a 25 KEAP1, an EPHA5 or an NF1 mutation. In some embodiments, the cancer is non-small cell lung cancer and comprises a K-Ras G12C mutation. In other embodiments, the cancer is non-small cell lung cancer and comprises a K-Ras G12C mutation and an STK11^{LOF} mutation. In other embodiments, the cancer is non-small cell lung cancer and comprises a K-Ras G12C mutation and an STK11^{LOF} mutation. In further embodiments, a cancer comprises a K-Ras G13C Ras mutation and an STK11^{LOF}, a KEAP1, an EPHA5 or an NF1 mutation. In certain 30 embodiments, the cancer is non-small cell lung cancer and comprises a K-Ras G12D mutation. In some embodiments, the cancer is non-small cell lung cancer and comprises a K-Ras G12V mutation. In further embodiments, the cancer is colorectal cancer and comprises a K-Ras G12C mutation. In some embodiments, the cancer is pancreatic cancer and comprises a K-Ras G12D

mutation. In other embodiments, the cancer is pancreatic cancer and comprises a K-Ras G12V mutation. In still other embodiments, the cancer is endometrial cancer and comprises a K-Ras G12C mutation. In certain embodiments, the cancer is lung cancer, colorectal cancer, or pancreatic cancer and comprises a K-Ras G12D mutation. In further embodiments, the cancer is lung cancer or pancreatic cancer and comprises a K-Ras G12D mutation. In some embodiments, the cancer is lung cancer and comprises a K-Ras G12D mutation. In some embodiments, the cancer is colorectal cancer and comprises a K-Ras G12D mutation. In some embodiments, the cancer is gastric cancer and comprises a K-Ras G12C mutation. In addition, a disclosed compound may inhibit Ras^{wt} (e.g., K-, H- or N-Ras^{wt}) or Ras^{amp} (e.g., K-, H- or N-Ras^{amp}).

[00112] Also disclosed herein are methods of inhibiting a Ras protein (e.g., a K-Ras protein) in a cell or tissue, comprising contacting the cell or tissue with a therapeutically effective amount of a compound disclosed herein, or a pharmaceutical composition thereof. In some embodiments, the Ras protein is a mutated Ras protein. Further disclosed herein are methods of inhibiting a Ras protein (e.g., a K-Ras protein) in a patient, comprising administering to the patient a therapeutically effective amount of a compound disclosed herein, or a pharmaceutical composition thereof.

[00113] The compounds described herein can be administered in combination with one or more additional therapeutic agents to treat a disorder described herein. For clarity, contemplated herein are both a fixed composition comprising a disclosed compound and another therapeutic agent such as disclosed herein, and methods of administering, separately a disclosed compound and a disclosed therapeutic. For example, provided in the present disclosure is a pharmaceutical composition comprising a compound described herein, one or more additional therapeutic agents, and a pharmaceutically acceptable excipient. In some embodiments, a disclosed compound and one additional therapeutic agent is administered. In some embodiments, a disclosed compound as defined herein and two additional therapeutic agents are administered. In some embodiments, a disclosed compound as defined herein and three additional therapeutic agents are administered. Combination therapy can be achieved by administering two or more therapeutic agents, each of which is formulated and administered separately. For example, a disclosed compound and an additional therapeutic agent can be formulated and administered separately. Combination therapy can also be achieved by administering two or more therapeutic agents in a single formulation, for example a pharmaceutical composition comprising a disclosed compound as one therapeutic agent and one or more additional therapeutic agents. For example, a disclosed compound and an additional

therapeutic agent can be administered in a single formulation. Other combinations are also encompassed by combination therapy. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or weeks of each other. In some cases, even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

[00114] Combination therapy can also include two or more administrations of one or more of the agents used in the combination using different sequencing of the component agents. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

[00115] In some embodiments, the additional therapy is the administration of side-effect limiting agents (e.g., agents intended to lessen the occurrence or severity of side effects of treatment). For example, in some embodiments, the compounds of the present invention can also be used in combination with a therapeutic agent that treats nausea. Examples of agents that can be used to treat nausea include: dronabinol, granisetron, metoclopramide, ondansetron, and prochlorperazine, or pharmaceutically acceptable salts thereof.

[00116] In some embodiments, the one or more additional therapies includes a non-drug treatment (e.g., surgery or radiation therapy). In some embodiments, the one or more additional therapies includes a therapeutic agent (e.g., a compound or biologic that is an anti-angiogenic agent, signal transduction inhibitor, antiproliferative agent, glycolysis inhibitor, or autophagy inhibitor). In some embodiments, the one or more additional therapies includes a non-drug treatment (e.g., surgery or radiation therapy) and a therapeutic agent (e.g., a compound or biologic that is an anti-angiogenic agent, signal transduction inhibitor, antiproliferative agent, glycolysis inhibitor, or autophagy inhibitor). In other embodiments, the one or more additional therapies includes two therapeutic agents. In still other embodiments, the one or more additional therapies includes three therapeutic agents. In some embodiments, the one or more additional therapies includes four or more therapeutic agents.

[00117] Examples of non-drug treatments include, but are not limited to, radiation therapy, cryotherapy, hyperthermia, surgery (e.g., surgical excision of tumor tissue), and T cell adoptive transfer (ACT) therapy. In some embodiments, the compounds of the invention may be used as an adjuvant therapy after surgery. In some embodiments, the compounds of the invention may be used as a neo-adjuvant therapy prior to surgery.

[00118] A therapeutic agent may be a compound used in the treatment of cancer or symptoms associated with cancer. For example, a therapeutic agent may be a steroid. Non-limiting examples contemplated herein include, but are not limited to, 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difuprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetate, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortol, halcinonide, halobetasol propionate, halometasone, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylaminoacetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetate, triamcinolone benetonide, triamcinolone hexacetonide, and salts or derivatives thereof.

[00119] In further embodiments, a therapeutic agent contemplated herein may be a biologic (e.g., cytokine (e.g., interferon or an interleukin such as IL-2)) used in treatment of cancer or symptoms associated therewith. In some embodiments, the biologic is an immunoglobulin-based biologic, e.g., a monoclonal antibody (e.g., a humanized antibody, a fully human antibody, an Fe fusion protein, or a functional fragment thereof) that agonizes a target to stimulate an anti-cancer response or antagonizes an antigen important for cancer. Also contemplated herein are antibody-drug conjugates.

[00120] In other embodiments, a therapeutic agent contemplated herein may be a T-cell checkpoint inhibitor. In one embodiment, the checkpoint inhibitor is an inhibitory antibody (e.g., a monospecific antibody such as a monoclonal antibody). The antibody may be, e.g., humanized or fully human. In some embodiments, the checkpoint inhibitor is a fusion protein, e.g., an Fe-receptor fusion protein. In some embodiments, the checkpoint inhibitor is an agent, such as an antibody, which interacts with a checkpoint protein. In some embodiments, the

checkpoint inhibitor is an agent, such as an antibody, which interacts with the ligand of a checkpoint protein. In some embodiments, the checkpoint inhibitor is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of CTLA-4 (e.g., an anti-CTLA-4 antibody or fusion a protein). In some embodiments, the checkpoint inhibitor is an inhibitor or antagonist (e.g., an inhibitory antibody or small molecule inhibitor) of PD-1. In some embodiments, the checkpoint inhibitor is an inhibitor or antagonist (e.g., an inhibitory antibody or small molecule inhibitor) of PD-L 1. In some embodiments, the checkpoint inhibitor is an inhibitor or antagonist (e.g., an inhibitory antibody or Fe fusion or small molecule inhibitor) of PD-L2 (e.g., a PD-L2/Ig fusion protein). In some embodiments, the checkpoint inhibitor is an inhibitor or antagonist (e.g., an inhibitory antibody or small molecule inhibitor) of B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands, or a combination thereof. In some embodiments, the checkpoint inhibitor is pembrolizumab, nivolumab, ipilimumab, tremelimumab, or lirilumab. In other embodiments, a therapeutic agent may be an anti-TIGIT antibody, such as etigilimab.

[00121] In some embodiments, a therapeutic agent contemplated herein may be an anti-cancer agent. Non-limiting examples contemplated herein include, but are not limited to, mitotic inhibitors, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, alkylating agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodopyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitors, interferons, platinum coordination complexes, anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroides, progestins, estrogens, antiestrogen, androgens, antiandrogen, and gonadotropin-releasing hormone analog. Further anti-cancer agents include leucovorin (LV), irinotecan, oxaliplatin, capecitabine, paclitaxel, and doxorubicin. In some embodiments, the one or more additional therapies includes two or more anti-cancer agents, for example, to be administered in combination or administered separately.

[00122] Other non-limiting examples of anti-cancer agents include, e.g., imatinib mesylate, carfilzomib, bortezomib, bicalutamide, gefitinib, alkylating agents such as thiotepa and cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, and meturedopa; uredopaethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide and trimethylolomelamine; acetogenins (e.g., bullatacin and bullatacinone); camptothecin and synthetic analogues (e.g., topotecan); bryostatin; calyculin; adozelesin; carzelesin; bizelesin; cryptophycins (e.g., cryptophycin 1 and cryptophycin 8);

- dolastatin; duocarmycin and synthetic analogues; eleutherobin; pancratistatin; sarcodictyin A; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as
- 5 carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, such as calicheamicin gammall and calicheamicin omegall; dynemicin such as dynemicin A; bisphosphonates such as clodronate; an esperamicin; neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores, aclacinomysins, actinomycin, authramycin, azaserine, bleomycins,
- 10 cactinomycin, calicheamicin, carabycin, caminomycin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo- 5-oxo-L-norleucine, adriamycin (doxorubicin), morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin,
- 15 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, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine,
- 20 floxuridine; androgens such as calusterone, dromostanolone propionate, epitioestanol, mepitioestane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenishers such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone such as epothilone B; etoglucid;
- 25 gallium nitrate; hydroxyurea; lentinan; lonidamine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes such as T-2 toxin, verracurin A, roridin A and anguidine;
- 30 urethane; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside; cyclophosphamide; thiotepa; toxoids (e.g., paclitaxel and doxetaxel; chlorambucil; tamoxifen; raloxifene; aromatase inhibiting 4(5)-imidazoles; 4-tiandroxytamoxifen; trioxifene; keoxifene; onapristone; torernifene; flutamide, nilutamide, bicalutamide, leuprolide, goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine;

platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide; ifosfamide; mitoxantrone; vincristine; vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; ibandronate; irinotecan; topoisomerase inhibitors; difluoromethylornithine; retinoids such as retinoic acid; esperamicins; capecitabine; and
 5 pharmaceutically acceptable salts of any of the aforementioned agents.

[00123] Additional non-limiting examples of anti-cancer agents include trastuzumab, bevacizumab, cetuximab, rituximab, avicine, abagovomab, acridine carboxamide, adecatumumab, 17-N-allylamino-17-demethoxygeldanamycin, alpharadin, alvocidib, 3-aminopyridine-2-carboxaldehyde thiosemicarbazone, amonafide, anthracenedione, anti-CD22
 10 immunotoxins, antineoplastics (e.g., cell-cycle nonspecific antineoplastic agents, and other antineoplastics described herein), antitumorigenic herbs, apaziquone, atiprimod, azathioprine, belotecan, bendamustine, biricodar, brostallicin, bryostatin, buthionine sulfoximine, calyculin, dichloroacetic acid, discodermolide, elsamitucin, enocitabine, eribulin, exatecan, exisulind, ferruginol, forodesine, fosfestrol, imexon, imiquimod, indolocarbazole, irofulven, laniquidar,
 15 larotaxel, lenalidomide, luranthone, lurtotecan, mafosfamide, mitozolomide, nafoxidine, nedaplatin, olaparib, ortataxel, pawpaw, pixantrone, proteasome inhibitors, rebeccamycin, resiquimod, rubitecan, SN-38, salinosporamide A, sapacitabine, swainsonine, talaporfin, tariquidar, tegafur-uracil, temodar, tesetaxel, triplatin tetranitrate, tris(2-chloroethyl)amine, troxacitabine, uramustine, vadimezan, vinflunine, and zosuquidar.

[00124] Further non-limiting examples of anti-cancer agents include natural products such as vinca alkaloids (e.g., vinblastine, vincristine, and vinorelbine), epidipodophyllotoxins (e.g., etoposide and teniposide), antibiotics (e.g., dactinomycin (actinomycin D), daunorubicin, and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin), mitomycin, antiplatelet agents, antiproliferative/antimitotic alkylating agents such as nitrogen mustards
 25 (e.g., mechlorethamine, cyclophosphamide and analogs, melphalan, and chlorambucil), ethylenimines and methylmelamines (e.g., hexaamethylmelaamine and thiotepa), CDK inhibitors (e.g., abemaciclib, ribociclib, palbociclib; seliciclib, dinaciclib), alkyl sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine and analogs, and streptozocin), trazenes-dacarbazine, antiproliferative/antimitotic antimetabolites such as folic acid analogs, pyrimidine analogs (e.g.,
 30 fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors (e.g., mercaptopurine, thioguanine, pentostatin, and 2-chlorodeoxyadenosine), aromatase inhibitors (e.g., anastrozole, exemestane, and letrozole), and platinum coordination complexes (e.g., cisplatin and carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide, histone deacetylase (HDAC) inhibitors (e.g., trichostatin, sodium butyrate, apicidan, suberoyl anilide

hydroamic acid, vorinostat, romidepsin, and panobinostat), mTOR inhibitors (e.g., vistusertib, temsirolimus, everolimus, ridaforolimus, and sirolimus), KSP(Eg5) inhibitors, DNA binding agents, PI3K delta and gamma inhibitors, copanlisib, alpelisib and idelalisib; multi-kinase inhibitors (e.g., sorafenib), hormones (e.g., estrogen), goserelin, leuprolide, triptorelin, IKK inhibitors, p38MAPK inhibitors, anti-IL-6, telomerase inhibitors, aurora kinase inhibitors, cell surface monoclonal antibodies, elotuzumab, HSP90 inhibitors, PI3K /Akt inhibitors, Akt inhibitors, PKC inhibitors (e.g., enzastaurin), Torc1/2 specific kinase inhibitors, ER/UPR targeting agents, cFMS inhibitors, JAK1/2 inhibitors, PARP inhibitors (e.g., olaparib and veliparib), and BCL-2 antagonists. In some embodiments, a contemplated anti-cancer agent is selected from, for example, mechlorethamine, camptothecin, ifosfamide, tamoxifen, raloxifene, gemcitabine, sorafenib, or any analog or derivative variant of the foregoing.

[00125] In some embodiments, the anti-cancer agent is a HER2 inhibitor, for example, monoclonal antibody such as trastuzumab and pertuzumab; or a small molecule tyrosine kinase inhibitor such as gefitinib, erlotinib, pilitinib, canertinib, or lapatinib. In other embodiments, a contemplated anti-cancer agent is an ALK inhibitor, for example, ceritinib, crizotinib, alectinib, brigatinib, entrectinib, ensartinib, or lorlatinib. In other embodiments, a contemplated anti-cancer agent is a SHP2 inhibitor, an SOS1 inhibitor, a Raf inhibitor, a MEK inhibitor, an ERK inhibitor, a PI3K inhibitor, a PTEN inhibitor, an AKT inhibitor, or an mTOR inhibitor (e.g., mTORC1 inhibitor or mTORC2 inhibitor).

[00126] In some embodiments, a contemplated anti-cancer agent is an additional Ras inhibitor or a Ras vaccine, or another therapeutic modality designed to directly or indirectly decrease the oncogenic activity of Ras. For example, in some embodiments a contemplated anti-cancer agent is an additional Ras inhibitor. In some embodiments, the Ras inhibitor targets Ras in its active, or GTP-bound state (Ras(ON)). In some embodiments, the Ras inhibitor targets Ras in its inactive, or GDP-bound state. In some embodiments, the Ras inhibitor is an inhibitor of K-Ras G12C. In other embodiments, the Ras inhibitor is an inhibitor of K-Ras G12C. In other embodiments, the Ras inhibitor is a K-Ras G12V inhibitor.

[00127] In certain embodiments, the methods described herein further comprises administering to the patient one or more additional therapeutic agents that treats a disease or disorder that is affected by, associated with, or would benefit from inhibition of Ras protein (e.g., K-Ras).

[00128] The methods described herein include administering to the patient a therapeutically effective amount of at least one compound as described herein, which is optionally formulated

in a pharmaceutical composition. In various embodiments, a therapeutically effective amount of at least one compound described herein present in a pharmaceutical composition is the only therapeutically active compound in a pharmaceutical composition. In certain embodiments, the method further comprises administering to the patient an additional therapeutic agent that treats a cancer, or that treats a disease or disorder that is affected by, associated with, or would benefit from inhibition of Ras, e.g., K-Ras.

[00129] In some embodiments, administering the compound(s) described herein to the patient allows for administering a lower dose of the additional therapeutic agent as compared to the dose of the additional therapeutic agent alone that is required to achieve similar results in treating, ameliorating, and/or preventing cancer, or in treating, ameliorating, and/or preventing a disease or disorder that is affected by, associated with, or would benefit from inhibition of Ras (e.g., K-Ras) in the patient. For example, in certain embodiments, the compound(s) described herein enhance(s) the activity of the additional therapeutic compound, thereby allowing for a lower dose of the additional therapeutic compound to provide the same effect.

[00130] In particular, in certain embodiments, the disclosure provides a method of treating the above medical indications comprising administering a subject in need thereof a therapeutically effective amount of a compound described herein.

III. Pharmaceutical Compositions and Kits

[00131] Another aspect of the disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with a pharmaceutically acceptable carrier. In particular, the present disclosure provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with one or more pharmaceutically acceptable carriers. These formulations include those suitable for oral, rectal, topical, intranasal, buccal, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions may be formulated as a unit dose, and/or may be formulated for oral or subcutaneous administration.

[00132] Exemplary pharmaceutical compositions of this disclosure may be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains one or more of the compounds of the disclosure, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic,

pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

- 5 **[00133]** For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical carrier, *e.g.*, conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.*, water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the disclosure, or a non-toxic
10 pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

- [00134]** In solid dosage forms for oral administration (capsules, tablets, pills, dragees,
15 powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4)
20 disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid
25 polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

- 30 **[00135]** A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-

active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

[00136] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[00137] Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[00138] Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

[00139] Dosage forms for transdermal administration of a subject composition include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[00140] The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

5 [00141] Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

10 [00142] Compositions and compounds of the present disclosure may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, 15 or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

20 [00143] Pharmaceutical compositions of this disclosure suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

25 [00144] Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the disclosure include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, 30 such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00145] In another aspect, the disclosure provides enteral pharmaceutical formulations including a disclosed compound and an enteric material; and a pharmaceutically acceptable

carrier or excipient thereof. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5. Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about 8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleate, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal colophonium, and several commercially available enteric dispersion systems (e. g. , Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either known or is readily determinable *in vitro*. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure would recognize that it is not comprehensive and that there are other enteric materials that would meet the objectives of the present disclosure.

[00146] The disclosure also provides kits for use by a e.g., a consumer in need of treatment of a disease or disorder described herein. Such kits include a suitable dosage form such as those described above and instructions describing the method of using such dosage form to mediate, reduce or prevent inflammation. The instructions would direct the consumer or medical personnel to administer the dosage form according to administration modes known to those skilled in the art. Such kits could advantageously be packaged and sold in single or multiple kit units. An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage

forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[00147] It may be desirable to provide a memory aid on the kit, *e.g.*, in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, *e.g.*, as follows “First Week, Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . . “etc. Other variations of memory aids will be readily apparent. A “daily dose” can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a first compound can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

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EXAMPLES

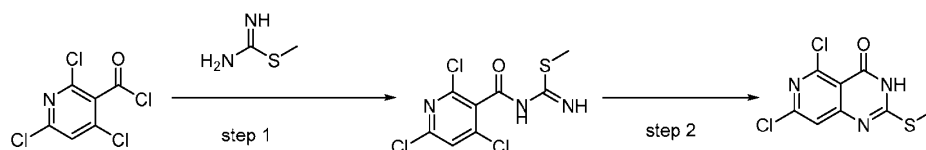
[00148] The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art. In the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, can be chosen to be the conditions standard for that reaction, unless otherwise indicated. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule should be compatible with the reagents and reactions proposed. Substituents not compatible with the reaction conditions will be apparent to one skilled in the art, and alternate methods are therefore indicated. The starting materials for the examples are either commercially available or are readily prepared by standard methods from known materials.

[00149] HPLC conditions: Method A A: Column: XBridge Prep OBD C18 Column, 30*150 mm, 5 μ m; Mobile Phase A: water (10mmol/L NH₄HCO₃+0.05% NH₃H₂O), Mobile Phase B:

- MeCN; Flow rate: 60 mL/min; Method B: Column: Xselect CSH C18 OBD Column 30*150mm 5µm; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: MeCN; Flow rate: 60 mL/min; Method C: Column: Xselect CSH C18 OBD Column 19*250mm 5µm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: MeCN; Flow rate: 30 mL/min; Method PL: Phenomenex Luna C18 150*25mm*10µm; Mobile phase: (water (0.225%FA)-MeCN).

Synthesis of Intermediates:

Synthesis of 5,7-dichloro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one (Intermediate 1)



- 10 *Step 1: Synthesis of methyl (2,4,6-trichloronicotinoyl)carbamimidothioate*

- [00150] A mixture of methyl carbamimidothioate (33.4 g, 179.2 mmol) and NaHCO₃ (37.8g, 448 mmol) in THF/H₂O (90 mL, 1:2) was stirred at rt for 10 min then 2,4,6-trichloronicotinoyl chloride (11g, 44 mmol) in THF (50 mL) was added and the reaction mixture stirred at rt for 1 h. The reaction was quenched with H₂O (300 mL) and extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure to give the title compound as a yellow oil, (10.1 g, 75.3%) as a yellow oil. LCMS m/z = 300 [M+H]⁺

Step 2: Synthesis of 5,7-dichloro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

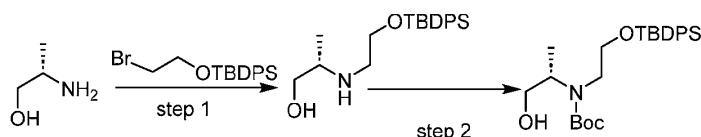
- [00151] DIPEA (10.93 g, 84.6 mmol) was added to a solution of methyl (2,4,6-trichloronicotinoyl)carbamimidothioate (10.1 g, 33.8 mmol) in dioxane (100 mL) and the reaction mixture was stirred at 100°C for 16 h under N₂. The cooled mixture was concentrated *in vacuo*, the residue diluted with water and acidified to pH 4 with 2N HCl (aq). The precipitated solids were collected by filtration, washed with water (3x50 mL) and dried to give the title compound (6.1 g, 68.8%) as a yellow solid. LCMS m/z = 262 [M+H]⁺

- 25 **Synthesis of tert-butyl (2-((tert-butyldiphenylsilyl)oxy)ethyl)(2-hydroxyethyl)carbamate (Intermediate 2)**



[00152] Imidazole (1.99 g, 29.2 mmol) and tert-butyl(chloro)diphenylsilane (4.42 g, 16.08 mmol) was added to a solution of tert-butyl N,N-bis(2-hydroxyethyl)carbamate (3 g, 14.62 mmol) in anhydrous DMF (10 mL) and the reaction mixture was stirred for 2 h at rt under N₂. The reaction was quenched with water (10 mL) and the mixture was extracted with EtOAc (25 mL x 3). The combined organic layer was washed with brine (10 mL x 3), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (0.1% TFA), 10% to 50% gradient in 10 min, to give the title compound (2 g, 30.8%) as a colorless oil. LCMS m/z = 444 [M+H]⁺

Synthesis of tert-butyl (S)-2-((tert-butyldiphenylsilyl)oxy)ethyl(1-hydroxypropan-2-yl)carbamate (Intermediate 3)



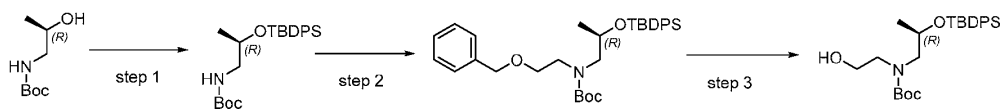
Step 1: Synthesis of (S)-2-((2-((tert-butyldiphenylsilyl)oxy)ethyl)amino)propan-1-ol

[00153] (2-Bromoethoxy)(tert-butyl)diphenylsilane (5.8 g, 15.96 mmol) was added to a solution of (2S)-2-aminopropan-1-ol (1.80 g, 23.94 mmol) in MeCN (20 mL) and the reaction mixture stirred for 3 h at 80°C under N₂. The resulting mixture was cooled to rt and evaporated under reduced pressure to give the title compound (2.34 g, crude) as a white solid. LCMS m/z = 358 [M+H]⁺

Step 2: Synthesis of tert-butyl (S)-2-((tert-butyldiphenylsilyl)oxy)ethyl(1-hydroxypropan-2-yl)carbamate

[00154] (Boc)₂O (1.71 g, 7.85 mmol) was added in portions to a solution of (S)-2-((2-((tert-butyldiphenylsilyl)oxy)ethyl)amino)propan-1-ol (2.34 g, 6.54 mmol) and TEA (1.36 mL, 9.82 mmol) in DCM (15 mL) and the reaction mixture was stirred for 3 h at rt under N₂. The reaction was diluted with water (100 mL) and the mixture extracted with DCM (10 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate concentrated *in vacuo*. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (10:1) to afford the title compound (1.7 g, 39.7%) as a colorless oil. LCMS m/z = 458 [M+H]⁺

Synthesis of tert-butyl (R)-2-((tert-butyldiphenylsilyl)oxy)propyl(2-hydroxyethyl)carbamate (Intermediate 4)



Step 1: Synthesis of tert-butyl (R)-(2-((tert-butyldiphenylsilyl)oxy)propyl)carbamate

[00155] TBDPS-Cl (17.25 g, 62.78 mmol) was added to a solution of tert-butyl (R)-(2-hydroxypropyl)carbamate (10 g, 57.07 mmol) and imidazole (7.77 g, 114.1 mmol) in DMF (100 mL) at 0°C and the reaction mixture was stirred overnight at rt under N₂. The reaction was quenched with water and the resulting mixture was extracted with EtOAc (3x100 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE / EtOAc (5:1)) to afford the title compound (23 g, 97.4%) as colorless oil. LCMS m/z = 414 [M+H]⁺

Step 2: Synthesis of tert-butyl (R)-(2-((tert-butyldiphenylsilyl)oxy)propyl)(2-((benzyloxy)ethyl)carbamate

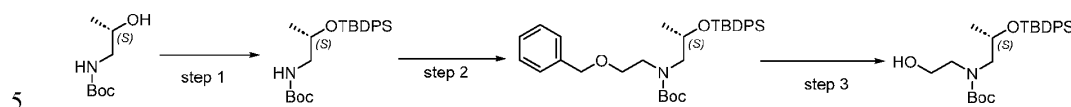
[00156] A solution of tert-butyl (R)-(2-((tert-butyldiphenylsilyl)oxy)propyl)carbamate (10 g, 24.18 mmol) in anhydrous DMF (100 mL) was treated with NaH (2.90 g, 72.5 mmol, 60%) at 0°C under N₂ and the mixture was stirred at 0°C for 10 min. ((2-Bromoethoxy)methyl)benzene (7.80 g, 36.26 mmol) was added and the reaction mixture was stirred for 16 h at rt. The reaction was quenched by water (100 mL) at 0°C and the resulting mixture extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine (3x200 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate concentrated *in vacuo*. The residue was purified by reverse-phase column chromatography using C18 gel, eluting with MeCN in water (0.1% FA), 10% to 50% gradient in 10 min to afford the title compound (4.5 g, 34.0%) as a white oil. LCMS m/z = 548 [M+H]⁺

Step 3: Synthesis of tert-butyl (R)-(2-((tert-butyldiphenylsilyl)oxy)propyl)(2-hydroxyethyl)carbamate

[00157] Pd/C (4.71 g, 12.53 mmol) was added carefully to a solution of tert-butyl (R)-(2-((benzyloxy)ethyl)(2-((tert-butyldiphenylsilyl)oxy)propyl)carbamate (4.5 g, 8.58 mmol) in MeOH (50 mL) and the reaction mixture was stirred for 16 h at 20°C under H₂. The mixture was filtered and the filter cake was washed with MeOH (3x40 mL). The filtrate was concentrated under reduced pressure and the residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (0.1% TFA), 80% to 90%

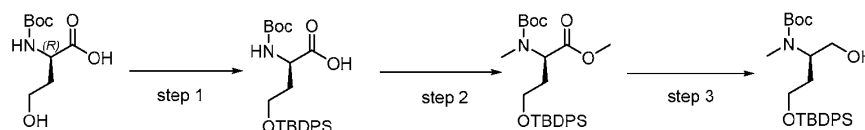
gradient in 10 min, to give the title compound (2.6 g, 66.2%) as a colorless oil. LCMS m/z = 458 $[M+H]^+$

Synthesis of tert-butyl (S)-(2-((tert-butyldiphenylsilyl)oxy)propyl)(2-hydroxyethyl)carbamate (Intermediate 5)



[00158] The title compound was obtained as a colorless oil, from tert-butyl (S)-(2-hydroxypropyl)carbamate, following the 3-step procedure described in Intermediate 4. LCMS m/z = 458 $[M+H]^+$

10 **Synthesis of tert-butyl (R)-(4-((tert-butyldiphenylsilyl)oxy)-1-hydroxybutan-2-yl)(methyl)carbamate (Intermediate 6)**



Step 1: Synthesis of N-(tert-butoxycarbonyl)-O-(tert-butyldiphenylsilyl)-D-homoserine

[00159] Imidazole (24.84 g, 364.9 mmol) was added in portions to a solution of (tert-butoxycarbonyl)-D-homoserine (10 g, 45.6 mmol) in DCM (500 mL). TBDPSCl (18.81 g, 68.42 mmol) was then added portion-wise and the reaction mixture was stirred for 16 h at rt. The resulting mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (3x100mL), dried over anhydrous Na_2SO_4 , filtered and the filtrate was evaporated under reduced pressure to afford the title compound, crude as a colorless oil. LCMS m/z = 480 $[M+H]^+$

20 *Step 2: Synthesis of methyl N-(tert-butoxycarbonyl)-O-(tert-butyldiphenylsilyl)-N-methyl-D-homoserinate*

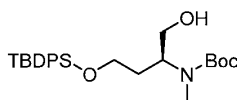
[00160] CH_3I (178.7 g, 1.26 mol) was added dropwise to a solution of N-(tert-butoxycarbonyl)-O-(tert-butyldiphenylsilyl)-D-homoserine (28.8 g, 62.93 mmol) and Ag_2O (72.92 g, 314.7 mmol) in DMF (500 mL) at 0°C under N_2 . The reaction mixture was slowly warmed to rt and stirred for 16 h. The reaction mixture was filtered, washing through with EtOAc and the filtrate washed with sat. brine. The brine was extracted with additional EtOAc (3 x 250 mL). The combined organic layers were washed with fresh brine (3x200mL), dried over

anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc: PE, 1:5) to afford the title compound (25.8 g, 84.4%) as a colorless oil. LCMS *m/z* = 486 [M+H]⁺

Step 3: Synthesis of tert-butyl (R)-4-((tert-butyldiphenylsilyl)oxy)-1-hydroxybutan-2-yl(methyl)carbamate

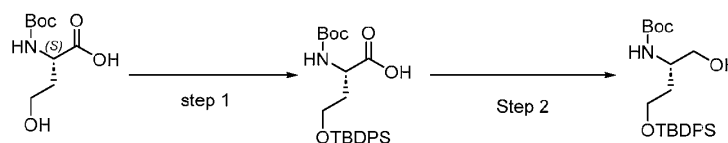
[00161] NaBH₄ (30.14 g, 797 mmol) was added in portions to a solution of methyl N-(tert-butoxycarbonyl)-O-(tert-butyldiphenylsilyl)-N-methyl-D-homoserinate (10 g, 20.5 mmol) in MeOH (150 mL) and THF (150 mL) at 0°C under N₂. The reaction mixture was slowly warmed to rt and stirred for 1h. The reaction was quenched with water (20 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 100mL), the combined organic layers were washed with brine (3x100mL), dried over anhydrous Na₂SO₄, filtered and the filtrate concentrated *in vacuo*. The residue was purified by silica gel column chromatography, eluting with EtOAc: PE (1:2) to afford the title compound (7g, 74.3%) as a colorless oil. LCMS *m/z* = 458 [M+H]⁺

Synthesis of tert-butyl (S)-4-((tert-butyldiphenylsilyl)oxy)-1-hydroxybutan-2-yl(methyl)carbamate (Intermediate 7)



[00162] The title compound was obtained as a colorless oil, from (tert-butoxycarbonyl)-L-homoserine following the same 3 step procedure described in Intermediate 6.

Synthesis of tert-butyl (S)-4-((tert-butyldiphenylsilyl)oxy)-1-hydroxybutan-2-yl(methyl)carbamate (Intermediate 8)



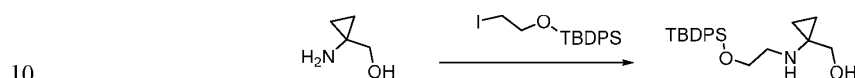
Step 1: Synthesis of N-(tert-butoxycarbonyl)-O-(tert-butyldiphenylsilyl)-L-homoserine

[00163] The title compound was obtained, 12.5 g, 60%, as a colorless oil, from (tert-butoxycarbonyl)-L-homoserine, following a similar procedure to that described in Intermediate 6, step 1. LCMS *m/z* = 458 [M+H]⁺

Step 2: Synthesis of tert-butyl (S)-4-((tert-butyldiphenylsilyl)oxy)-1-hydroxybutan-2-yl(methyl)carbamate

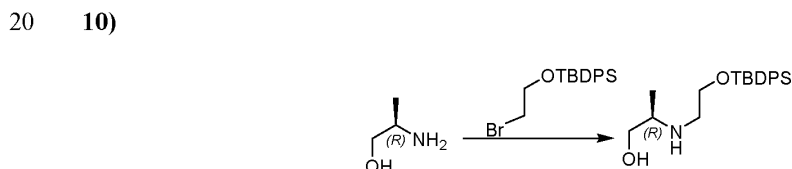
[00164] LiAlH_4 (1.85 g, 48.8 mmol) was added dropwise to an ice-cooled solution of the compound from step 1 (7.44 g, 16.3 mmol) in THF (80 mL) and the reaction mixture stirred at rt under N_2 for 1 h. The reaction was quenched with water at 0°C and the mixture extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (3x100 mL), dried over Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with EtOAc: PE (1:3) to afford the title compound (3.5 g, 48.5%) as a colorless oil. LCMS $m/z = 444$ $[\text{M}+\text{H}]^+$

Synthesis of (1-((2-((tert-butyldiphenylsilyl)oxy)ethyl)amino)cyclopropyl)methanol (Intermediate 9)



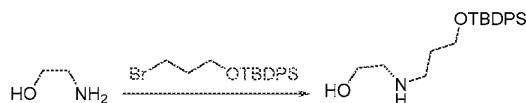
[00165] tert-Butyl(2-iodoethoxy)diphenylsilane (4.38 g, 10.7 mmol) in DMSO (1.5 mL) was added dropwise to a solution of (1-aminocyclopropyl)methanol (1.5 g, 10.7 mmol) in DMSO (1.5 mL) and DIPEA (5.58 mL, 32.0 mmol) and the reaction mixture was stirred overnight at 60°C . The mixture was extracted with EtOAc (2 x 250 mL), the combined organic layers were washed with brine (3x500 mL), dried over Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (5:1) to afford the title compound (880 mg, 22.3%) as a yellow oil. LCMS $m/z = 370$ $[\text{M}+\text{H}]^+$

Synthesis of (R)-2-((2-((tert-butyldiphenylsilyl)oxy)ethyl)amino)propan-1-ol (Intermediate 10)



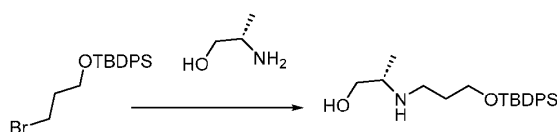
[00166] A mixture of (R)-(-)-2-amino-1-propanol (6.20 g, 82.6 mmol) and (2-bromoethoxy)(tert-butyl)diphenylsilane (20 g, 55.0 mmol) in MeCN (200 mL) was stirred for 3h at 80°C . The cooled reaction was quenched with water at rt, the layers separated and the aqueous phase extracted with DCM (3x200 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN in Water (0.1% NH_4HCO_3), 15% to 35% gradient in 10 min, to afford the title compound (7.1 g, 36.1%) as a white solid. LCMS $m/z = 358$ $[\text{M}+\text{H}]^+$

Synthesis of 2-((3-((tert-butyldiphenylsilyl)oxy)propyl)amino)ethan-1-ol (Intermediate 11)



[00167] The title compound was obtained as a yellow solid, 2.63 g, 55.5%, from ethanolamine and (3-bromopropoxy)(tert-butyl)diphenylsilane, following a similar procedure to that described in Intermediate 10. LCMS $m/z = 358$ $[M+H]^+$

Synthesis of (S)-2-((3-((tert-butyldiphenylsilyl)oxy)propyl)amino)propan-1-ol trifluoroacetate (Intermediate 12)



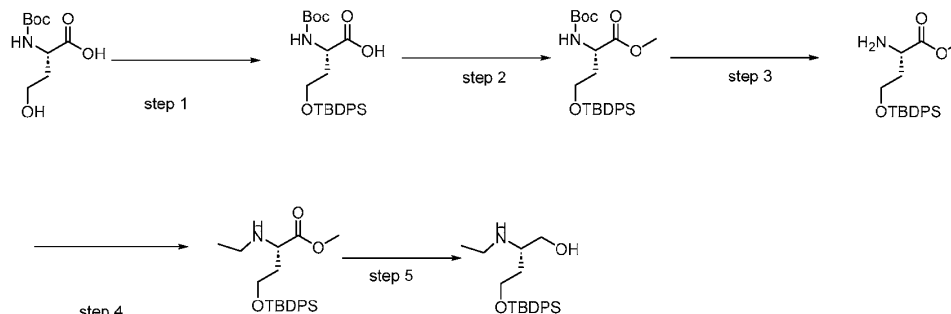
[00168] (2S)-2-Aminopropan-1-ol (1.49 g, 19.9 mmol) was added to a solution of (3-bromopropoxy)(tert-butyl)diphenylsilane (5 g, 13.2 mmol) in MeCN (100 mL) and the resulting mixture was stirred overnight at 80°C. The mixture was concentrated under reduced pressure and the residue was purified by reverse-phase column chromatography on C18 silica gel eluting with MeCN in Water (0.1% TFA), 10% to 100% gradient in 20 min, to give the title compound (2 g, 40.6%) as a yellow oil. LCMS $m/z = 372$ $[M+H]^+$

Synthesis of (S)-2-((2-((tert-butyldiphenylsilyl)oxy)ethyl)amino)-2-cyclopropylethan-1-ol (Intermediate 13)



[00169] To a stirred solution of (S)-2-amino-2-cyclopropylethan-1-ol hydrochloride (1 g, 9.9 mmol), KI (0.82 g, 4.94 mmol) and Cs_2CO_3 (9.66 g, 29.7 mmol) in DMF (10 mL) was added (2-bromoethoxy)(tert-butyl)diphenylsilane (4.67 g, 12.9 mmol) in portions at 60 °C under N_2 . The resulting mixture was extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (2x20 mL), dried over Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC eluting with EtOAc to afford the title compound (570 mg, 15%) as a yellow solid. LCMS $m/z = 384$ $[M+H+Na]^+$

Synthesis of (S)-4-((tert-butyldiphenylsilyl)oxy)-2-(ethylamino)butan-1-ol (Intermediate 14)



Step 1: Synthesis of *N*-(tert-butoxycarbonyl)-*O*-(tert-butyldiphenylsilyl)-*L*-homoserine

- 5 **[00170]** The title compound was obtained as a colorless oil, 12.5 g, 60%, from (tert-butoxycarbonyl)-*L*-homoserine, following a similar procedure to that described in Intermediate 6, step 1. LCMS m/z = 458 $[M+H]^+$

Step 2: Synthesis of methyl *N*-(tert-butoxycarbonyl)-*O*-(tert-butyldiphenylsilyl)-*L*-homoserinate

- 10 **[00171]** To a stirred solution of the compound from step 1 (12.5 g, 27.3 mmol) and Ag₂O (19.0 g, 81.9 mmol) in DMF (300 mL) was added CH₃I (4.65 g, 32.8 mmol) and the reaction mixture was stirred for 16 h at rt under N₂. The resulting mixture was filtered, the filter cake was washed with EtOAc and the filtrate diluted with saturated brine. The aqueous layer was separated and extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (3x100mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under
- 15 reduced pressure. The residue was purified by silica gel column chromatography, eluting with EtOAc: PE (1:10) to afford the title compound (11.5 g, 89.3%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.73 – 7.61 (m, 4H), 7.47 – 7.32 (m, 6H), 4.46 (td, 1H), 3.71 (d, 5H), 2.18 – 1.85 (m, 2H), 1.45 (s, 9H), 1.07 (s, 9H).

Step 3: Synthesis of methyl *N*-(tert-butoxycarbonyl)-*O*-(tert-butyldiphenylsilyl)-*L*-homoserinate

- 20 **[00172]** The title compound was obtained as a yellow oil, 3.12 g, crude, from the compound from step 2, following a similar procedure to that described in Example 2, step 2. LCMS m/z = 372 $[M+H]^+$

Step 4: Synthesis of methyl *O*-(tert-butyldiphenylsilyl)-*N*-ethyl-*L*-homoserinate

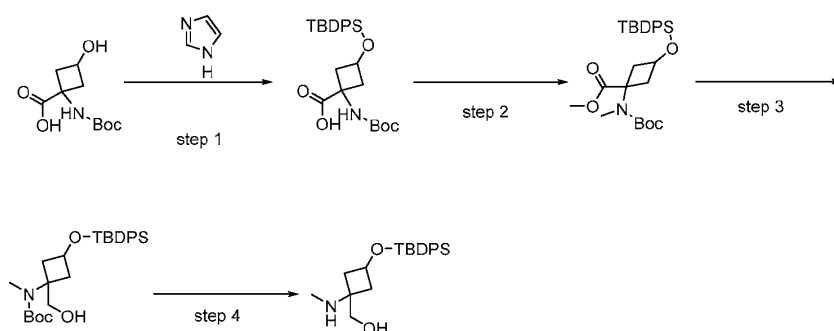
- 25 **[00173]** To a stirred solution of the compound from step 3 (2.46 g, 6.6 mmol) and acetaldehyde (0.88 g, 7.9 mmol, 40%) in DCM (20 mL) was added TEA (2.01 g, 19.86 mmol)

at 0°C and the reaction mixture was stirred at rt for 1.5 h under N₂. NaBH(OAc)₃ (2.81 g, 13.2 mmol) was added and the reaction mixture stirred for an additional 1.5 h at rt. The mixture was cooled to 0°C, diluted with brine (10 mL) and extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (3 x 50mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (10 mmol NH₄CO₃), 80% to 90% gradient in 10 min to afford the title compound (1.55 g, 58.6%) as a colorless oil. LCMS m/z = 400 [M+H]⁺

Step 5: Synthesis of (S)-4-((tert-butyldiphenylsilyl)oxy)-2-(ethylamino)butan-1-ol

[00174] The title compound was obtained as a yellow oil, 0.55 g, 39.4%, from the compound from step 4, following a similar procedure to that described in Intermediate 8, step 2. LCMS m/z = 372 [M+H]⁺

Synthesis of (3-((tert-butyldiphenylsilyl)oxy)-1-(methylamino)cyclobutyl)methanol (Intermediate 15)



Step 1: Synthesis of 1-((tert-butoxycarbonyl)amino)-3-((tert-butyldiphenylsilyl)oxy)cyclobutane-1-carboxylic acid

[00175] TBDPSCl (8.9 g, 32.4 mmol) was added to a solution of 1-((tert-butoxycarbonyl)amino)-3-hydroxycyclobutane-1-carboxylic acid (5 g, 21.6 mmol) in DMF (50 mL) at 0°C under N₂. Imidazole (4.4 g, 64.9 mmol) and DMAP (0.5 g, 4.32 mmol) were added in portions at 0°C and the reaction mixture was stirred overnight at 50°C under N₂. The mixture was extracted with EtOAc, the combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (10 mmol NH₄CO₃), 10% to 40% gradient in 10 min. The combined

column fractions were extracted with EtOAc (3 x 10 mL), the combined organic layers were washed with citric acid (3x10 mL), dried over Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure to afford the title compound (6.5 g, 64.0%) as a colorless oil. LCMS m/z = 471 [M+H]⁺

- 5 *Step 2 : Synthesis of methyl 1-((tert-butoxycarbonyl)(methyl)amino)-3-((tert-butyl)diphenylsilyl)oxy)cyclobutane-1-carboxylate*

[00176] To a stirred mixture of the compound from step 2 (6 g, 12.78 mmol) and NaH (919 mg, 38.3 mmol) in DMF (60 mL) was added MeI (5.4 g, 38.3 mmol) dropwise at 0°C under N₂ and the reaction mixture was stirred for 1h at rt. The mixture was extracted with EtOAc, the
10 combined organic layers were washed with brine and Na₂S₂O₃ (3x10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure to afford the title compound (6 g, 94.4%) as a yellow oil. LCMS m/z = 498 [M+H]⁺

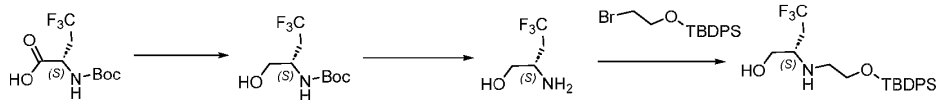
Step 3: Synthesis of tert-butyl (3-((tert-butyl)diphenylsilyl)oxy)-1-(hydroxymethyl)cyclobutyl (methyl)carbamate

15 [00177] To a solution of the compound from step 2 (1.0 g, 2.0 mmol) in Et₂O (20 mL) was added BF₃.Et₂O (427.7 mg, 3.0 mmol) dropwise at 0°C, followed by NH₃.BH₃ (155 mg, 5.0 mmol) in portions at 0°C. The reaction mixture was stirred for 1h at rt. The reaction was quenched with HCl (1M, 10mL) at 0°C and extracted with EtOAc. The combined organic layers were washed with brine (3x10 mL), dried over Na₂SO₄, filtered and the filtrate was
20 concentrated under reduced pressure. The residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (0.1% TFA), 10% to 85% gradient in 10 min, to afford the title compound (0.8 g, 84.8%) as a colorless oil. LCMS m/z = 470 [M+H]⁺

Step 4: Synthesis of (3-((tert-butyl)diphenylsilyl)oxy)-1-(methylamino)cyclobutyl methanol

25 [00178] A solution of the compound from step 3 (2.5 g, 5.32 mmol) and ZnBr₂ (11.99 g, 53.2 mmol) in DCM (20 mL) was stirred for 1h at rt under N₂. The resulting mixture was filtered and the filter cake was washed with DCM (20 mL). The filtrate was evaporated under reduced pressure to afford the title compound (740 mg, 37.6%) as a colorless oil. LCMS m/z = 370 [M+H]⁺

- 30 **Synthesis of (S)-2-((2-((tert-butyl)diphenylsilyl)oxy)ethyl)amino)-4,4,4-trifluorobutan-1-ol (Intermediate 16)**



Step 1: Synthesis of tert-butyl (S)-(4,4,4-trifluoro-1-hydroxybutan-2-yl)carbamate

- [00179] A solution of (S)-2-((tert-butoxycarbonyl)amino)-4,4,4-trifluorobutanoic acid (1.0 g, 3.9 mmol) in THF (1.5 mL) was treated with borane THF complex (19.44 mL, 1M, 19.44 mmol) at 0°C and the reaction mixture was stirred for 2 h at rt. The reaction was quenched with MeOH (10 mL) at 0°C and the mixture was stirred for 1 h at rt. The mixture was evaporated under reduced pressure to give the title compound (530 mg, 56.1%) as a yellow oil. LCMS m/z = 244 [M+H]⁺

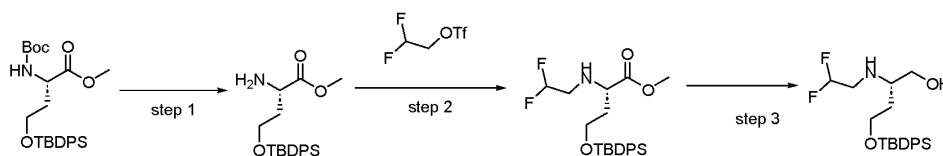
Step 2: Synthesis of (2S)-2-amino-4,4,4-trifluorobutan-1-ol hydrochloride

- [00180] A solution of the compound from step 1 (1.03 g, 4.2 mmol) and HCl in dioxane (2 mL, 4M, 8 mmol) in dioxane (2 mL) was stirred for 2 h at rt. The resulting mixture was evaporated under reduced pressure to afford the title compound (600 mg, crude) as a yellow oil. LCMS m/z = 144 [M+H]⁺

Step 3: Synthesis of (S)-2-((2-((tert-butyldiphenylsilyl)oxy)ethyl)amino)-4,4,4-trifluorobutan-1-ol

- [00181] The title compound was obtained as a yellow oil, 375 mg, 25%, from the compound from step 2, following a similar procedure to that described in Intermediate 9. LCMS m/z = 426 [M+H]⁺

Synthesis of (S)-4-((tert-butyldiphenylsilyl)oxy)-2-((2,2-difluoroethyl)amino)butan-1-ol (Intermediate 17)



Step 1: Synthesis of methyl O-(tert-butyldiphenylsilyl)-L-homoserinate

- [00182] TFA (5 mL) was added to a solution of methyl N-(tert-butoxycarbonyl)-O-(tert-butyldiphenylsilyl)-L-homoserinate (5 g, 10.6 mmol) in DCM (10 mL) and the reaction mixture was stirred overnight at rt. The mixture was concentrated under reduced pressure, the residue was washed with water (5x5 mL). The resulting mixture was extracted with EtOAc (3 x 200mL). The combined organic layers were washed with brine (400 mL), dried over Na₂SO₄,

filtered and the filtrate was evaporated under reduced pressure to give the title compound (3.5 g, 88.9%) as a yellow oil. LCMS $m/z = 372$ $[M+H]^+$

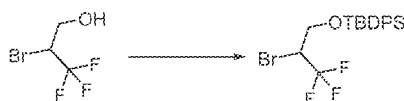
Step 2: Synthesis of methyl O-(tert-butyl diphenylsilyl)-N-(2,2-difluoroethyl)-L-homoserinate

[00183] A solution of 2,2-difluoroethyl trifluoromethanesulfonate (5.19 g, 24.2 mmol) in MeCN (5 mL) was added to a solution of the compound from step 1 (3 g, 8.1 mmol) in MeCN (5 mL). DIPEA (28.13 mL, 161.5 mmol) was then added dropwise and the reaction mixture was stirred overnight at rt. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluting with PE / EtOAc (3:1) to afford the title compound (1.98 g, 56.3%) as a colorless oil. LCMS $m/z = 436$ $[M+H]^+$

10 *Step 3: Synthesis of (S)-4-((tert-butyl diphenylsilyl)oxy)-2-((2,2-difluoroethyl)amino)butan-1-ol*

[00184] The title compound was obtained as a colorless oil, 1.33 g, 90.3%, from the compound from step 2, following a similar procedure to that described in Intermediate 15, step 3. LCMS $m/z = 408$ $[M+H]^+$

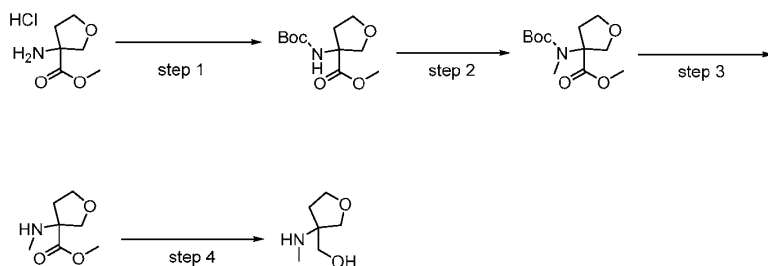
Synthesis of (2-bromo-3,3,3-trifluoropropoxy)(tert-butyl)diphenylsilane (Intermediate 18)



15

[00185] The title compound was obtained as a white oil, 2.05 g, 36%, from 2-bromo-1,1,1-trifluorobutane and TBDPSCl, following a similar procedure to that described in Intermediate 6, step 1. ^1H NMR (400 MHz, DMSO- d_6) δ 1.02 (s, 9H), 3.95 (s, 1H), 4.05 (s, 1H), 5.02 – 5.15 (m, 1H), 7.42 – 7.55 (m, 6H), 7.65 (m, 4H).

20 **Synthesis of (3-(methylamino)tetrahydrofuran-3-yl)methanol (Intermediate 19)**



Step 1: Synthesis of methyl 3-((tert-butoxycarbonyl)amino)tetrahydrofuran-3-carboxylate

[00186] (Boc) $_2$ O (1 g, 4.59 mmol) and Na $_2$ CO $_3$ (2.43 g, 22.9 mmol) were added to a solution of methyl 3-aminotetrahydrofuran-3-carboxylate hydrochloride (500 mg, 2.29 mmol) in

dioxane (2 mL) and H₂O (2 mL) and the reaction mixture was stirred at rt overnight. The reaction was diluted with H₂O, extracted with EtOAc, the combined organic extracts dried and evaporated under reduced pressure to afford the title compound (500 mg, 88.9%) as colorless oil. LCMS m/z = 246 [M+H]⁺

5 *Step 2: Synthesis of methyl 3-((tert-butoxycarbonyl)(methyl)amino)tetrahydrofuran-3-carboxylate*

[00187] The title compound was obtained as a colorless oil, 3 g, 63.9%, from the compound from step 1 and MeI, following a similar procedure to that described in Intermediate 14, step 2. LCMS m/z = 260 [M+H]⁺

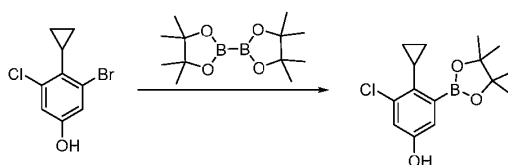
10 *Step 3: Synthesis of methyl 3-(methylamino)tetrahydrofuran-3-carboxylate*

[00188] A mixture of the compound from step 2 (2.5 g, 9.64 mmol) and TFA (5.50 g, 48.2 mmol) in DCM (50 mL) was stirred at rt under N₂. The mixture was basified to pH=8 with saturated NaHCO₃ (aq.) and the mixture was evaporated under reduced pressure, to give the title compound, crude as a white solid. LCMS m/z = 160 [M+H]⁺

15 *Step 4: Synthesis of (3-(methylamino)tetrahydrofuran-3-yl)methanol*

[00189] To a stirred mixture of the compound from step 3 (1.55 g, 9.74 mmol) and BF₃.Et₂O (2.76 g, 19.47 mmol) in Et₂O (30 mL) was added NH₃.BH₃ (901.8 mg, 29.21 mmol) at 0 °C under N₂. The mixture was acidified to pH=4 with conc. HCl. The aqueous layer was extracted with EtOAc (3x30 mL) and the combined organic extracts were evaporated under reduced pressure to afford the title compound, crude, 1 g, as a colorless oil. LCMS m/z = 131 [M+H]⁺

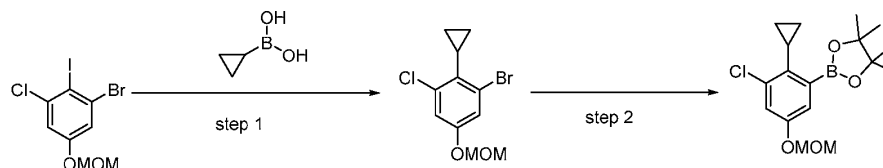
Synthesis of 3-chloro-4-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (Intermediate 20)



[00190] A mixture of 3-bromo-5-chloro-4-cyclopropylphenol (630 mg, 2.55 mmol), bis(pinacolato)diboron (975 mg, 3.84 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (228 mg, 0.28 mmol) and KOAc (750 mg, 7.65 mmol) in dioxane (10 mL) was stirred for 2 h at 100 °C under N₂. The reaction was quenched with water at rt and the resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by

silica gel column chromatography, eluting with PE / EtOAc (5:1) to afford the title compound (330 mg, 41.8%) as a white solid. ¹H NMR (300 MHz, CDCl₃) δ 6.97 – 6.86 (m, 2H), 3.50 (s, 3H), 1.95 (m, 1H), 1.37 (s, 12H), 1.31 (s, 1H), 1.26 (s, 5H), 1.08 – 0.85 (m, 3H), 0.59 – 0.42 (m, 2H).

5 **Synthesis of 2-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate 21)**



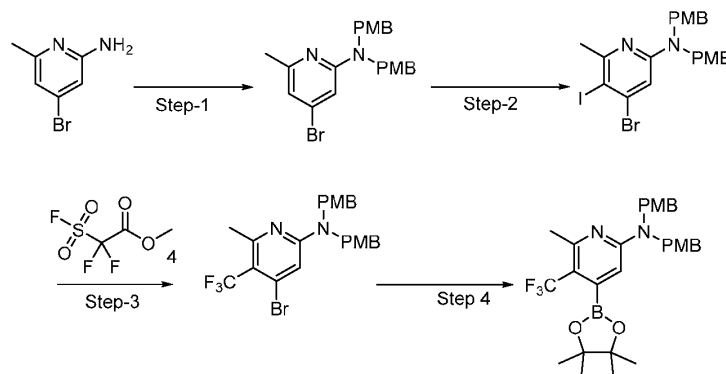
Step 1: Synthesis of 1-bromo-3-chloro-2-cyclopropyl-5-(methoxymethoxy)benzene

[00191] A solution of 1-bromo-3-chloro-2-iodo-5-(methoxymethoxy)benzene (2.20 g, 5.83 mmol), K₃PO₄ (3.71 g, 17.49 mmol), cyclopropylboronic acid (0.74 g, 8.74 mmol) and Pd(dppf)Cl₂ (0.41 g, 0.58 mmol) in dioxane (20 mL) and H₂O (4 mL) was stirred for 8 h at 100 °C under N₂. The cooled mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water, 0% to 100% gradient in 20 min to afford the title compound (220 mg, 12.9%) as a brown oil. ¹H NMR (400 MHz, DMSO-d₆) δ 7.19 (d, 1H), 7.03 (d, 1H), 5.11 (s, 2H), 3.46 (s, 3H), 1.69 – 1.64 (m, 1H), 1.19 – 1.07 (m, 2H), 0.78 – 0.62 (m, 2H).

20 *Step 2: Synthesis of 2-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane*

[00192] The title compound was obtained as a yellow solid, 120 mg, 46.9%, from the compound from step 1, following a similar procedure to that described in Intermediate 20. LCMS: m/z = 339 [M+H]⁺

25 **Synthesis of N,N-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)pyridin-2-amine (Intermediate 22)**



Step 1: Synthesis of 4-bromo-N,N-bis(4-methoxybenzyl)-6-methylpyridin-2-amine

[00193] NaH (1.60 g, 40.1 mmol) was added to a solution 4-bromo-6-methylpyridin-2-amine (3 g, 16.0 mmol) in DMF (30 mL) at 0 °C and the mixture stirred at rt for 30 min. 1-(Chloromethyl)-4-methoxybenzene (5.53 g, 35.3 mmol) was added and the reaction mixture was stirred for 4 h at 25 °C. The reaction was diluted with DCM (50 mL), quenched with sat. aq NH₄Cl solution and extracted with DCM (2 x 50 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography eluting with 0-30% EtOAc in hexane, to afford the title compound (6 g, 82%) as a white solid. LCMS m/z = 427 [M+H]⁺

Step 2: Synthesis of 4-bromo-5-iodo-N,N-bis(4-methoxybenzyl)-6-methylpyridin-2-amine

[00194] N-Iodosuccinimide (2.06 g, 9.17 mmol) was added to a solution of the compound from step 1 (4 g, 9.17 mmol) in AcOH (50 mL) at 0 °C and the reaction mixture was stirred for 2 h at 25 °C. The reaction was quenched with saturated Na₂SO₃ soln. and extracted with DCM (2 x 100 mL). The combined organic layer was washed with saturated NaHCO₃ solution, washed with water, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography using a gradient of 0-100% EtOAc in hexane, to afford the title compound (5 g, 88%) as a white solid. LCMS m/z = 553 [M+H]⁺

Step 3: Synthesis of 4-bromo-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

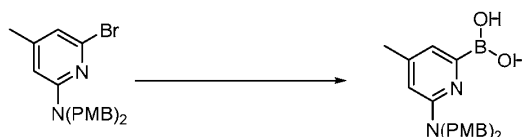
[00195] Methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.33 mL, 1.80 mmol), copper(I) iodide (430 mg, 2.25 mmol) and HPMA (800 mg, 4.52 mmol) were added to a solution of the compound from step 2 (500 mg, 0.90 mmol) in NMP (10 mL) and the reaction mixture was stirred at 90 °C for 2 h. The reaction mixture was diluted with water and extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated

under reduced pressure. The crude was purified by silica gel column chromatography using a gradient of 0-100% EtOAc in hexane, to afford the title compound (300 mg, 51.6%) as a white solid. LCMS $m/z = 497$ $[M]^+ +$

Step 4: Synthesis of *N,N*-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)pyridin-2-amine

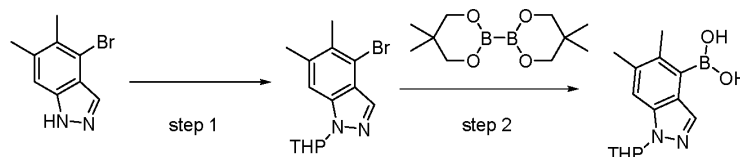
[00196] The title compound was obtained, 200 mg, 29.1%, from the compound from step 3, following a similar procedure to that described in Intermediate 20. LCMS $m/z = 543$ $[M+H]^+$

Synthesis of (6-(bis(4-methoxybenzyl)amino)-4-methylpyridin-2-yl)boronic acid (Intermediate 23)



[00197] A solution of 6-bromo-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine (1 g, 2.34 mmol), bis(pinacolato)diboron (1.19 g, 4.68 mmol), Pd(dppf)Cl₂ (0.17 g, 0.23 mmol) and KOAc (0.46 g, 1.63 mmol) in dioxane (10mL) was stirred for 2 h at 80 °C. The cooled mixture was filtered and the filtrate evaporated under reduced pressure to afford the title compound, crude, as a yellow oil. LCMS $m/z = 393$ $[M+H]^+$

Synthesis of (5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)boronic acid (Intermediate 24)



Step 1: Synthesis of 4-bromo-5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

[00198] A mixture of 4-bromo-5,6-dimethyl-1H-indazole (1 g, 4.44 mmol), DHP (0.81 mL, 8.88 mmol) and TsOH.H₂O (0.08 g, 0.44 mmol) in DCM (15 mL) was stirred for 3 h at rt under N₂. The reaction was quenched by the addition of sat. NaHCO₃ (aq.) (25 mL) at 0 °C and the resulting mixture was extracted with DCM (3 x 150 mL). The combined organic layers were washed with brine (2x30 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting

with PE / EtOAc (1: 2) to afford the title compound (1.3 g, 94.6%) as a yellow oil. LCMS m/z = 309 $[M+H]^+$

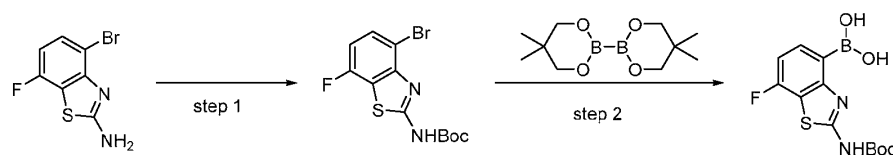
Step 2: (5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)boronic acid

[00199] A mixture of the compound from step 1 (500 mg, 1.62 mmol),

- 5 bis(pinacolato)diboron (1.1 g, 4.85 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (131 mg, 0.16 mmol) and KOAc (476 mg, 4.85 mmol) in dioxane (20 mL) was stirred for 4 h at 100°C under N₂. The reaction was quenched with water (100 mL) at rt and the resulting mixture was extracted with DCM (3 x 150 mL). The combined organic layers were washed with brine (2x50 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was
- 10 purified by prep-TLC (PE / EtOAc 2:1) and the product further purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (10 mmol NH₄CO₃), 0% to 42% gradient in 30 min to give the title compound (426 mg, 76.9%) as a white solid. LCMS m/z = 275 $[M+H]^+$

Synthesis of (2-((tert-butoxycarbonyl)amino)-7-fluorobenzo[d]thiazol-4-yl)boronic acid

- 15 **(Intermediate 25)**



Step 1: Synthesis of tert-butyl (4-bromo-7-fluorobenzo[d]thiazol-2-yl)carbamate

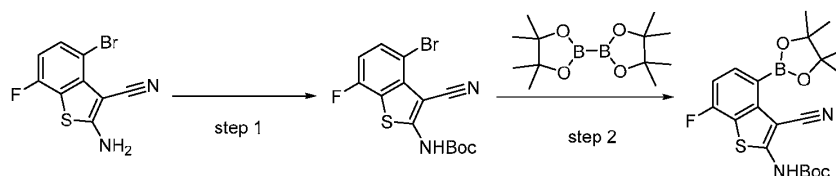
[00200] A mixture of 4-bromo-7-fluoro-1,3-benzothiazol-2-amine (2.0 g, 8.09 mmol), Boc₂O (2.6 g, 12.14 mmol), TEA (2.5 g, 24.3 mmol) and DMAP (99 mg, 0.81 mmol) in DCM (30 mL)

20 was stirred for 2 h at rt in air. The reaction was diluted with water (100 mL) and extracted with DCM (2 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (PE / EtOAc 20:1) to afford the title compound (1.7 g, 57.5%) as a white solid. LCMS m/z = 347 $[M+H]^+$

- 25 *Step 2: Synthesis of (2-((tert-butoxycarbonyl)amino)-7-fluorobenzo[d]thiazol-4-yl)boronic acid*

[00201] The title compound was obtained as a solid, 384 mg, 85%, from the compound from step 1, following a similar procedure to that described in Intermediate 24, step 2. LCMS m/z = 313 $[M+H]^+$

Synthesis of tert-butyl (3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)carbamate (Intermediate 26)



Step 1: Synthesis of tert-butyl (4-bromo-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate

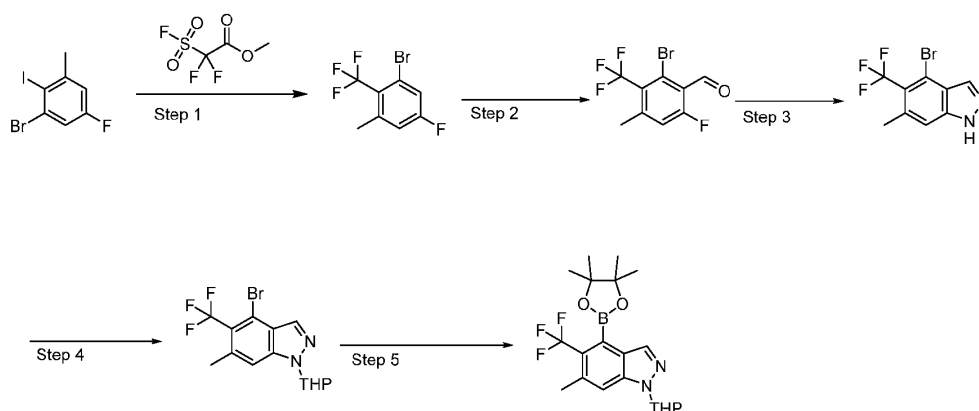
- 5 **[00202]** The title compound was obtained as a solid, 2.7 g, 98.5%, from 2-amino-4-bromo-7-fluorobenzo[b]thiophene-3-carbonitrile and (Boc)₂O, following a similar procedure to that described in Intermediate 25, step 1. LCMS *m/z* = 368 [M+H]⁺

Step 2: Synthesis of tert-butyl (3-cyano-7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophen-2-yl)carbamate

- 10 **[00203]** A mixture of the compound from step 1 (2.8 g, 7.54 mmol), bis(pinacolato)diboron (15.7 g, 61.9 mmol), Pd(PPh₃)₄ (1.0 g, 0.90 mmol) and KOAc (2.9 g, 30.2 mmol) in dioxane (80 mL) was stirred for 4 h at 95°C under N₂. The reaction was quenched with water (100 mL) at 0°C and the mixture was extracted with DCM (3 × 150 mL). The combined organic layers were washed with brine (3×50 mL), dried over Na₂SO₄, filtered the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (10 mmol NH₄CO₃), 0% to 48% gradient in 30 min to give the title compound (2.0 g, 63.3%) as a white solid. LCMS *m/z* = 417 [M-H]⁻
- 15

Synthesis of 6-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1H-indazole (Intermediate 27)

20



Step 1: Synthesis of 1-bromo-5-fluoro-3-methyl-2-(trifluoromethyl)benzene

[00204] To a solution of 1-bromo-5-fluoro-2-iodo-3-methylbenzene (14 g, 44.5 mmol) in DMF (140 mL) was added CuI (72.0 g, 377.9 mmol) and methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (72.6 g, 377.9 mmol) and the reaction mixture was stirred at 70 °C for 12 h under N₂. The reaction mixture was filtered and the filtrate was diluted with H₂O (200 mL) and extracted with PE (200 mL x 2). The combined organic layers were washed with brine (50 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (9 g, 78.8%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 7.33 - 7.31 (m, 1H), 6.95 (dd, 1H), 2.56 - 2.53 (m, 3H).

Step 2: Synthesis of 2-bromo-6-fluoro-4-methyl-3-(trifluoromethyl)benzaldehyde

[00205] To a solution of the compound from step 1 (5 g, 19.5 mmol) in THF (85 mL) was added LDA (2 M in THF, 19.45 mL) under N₂ at -65 °C and the mixture was stirred for 0.5 h. DMF (4.27 g, 58.4 mmol) was added dropwise at -65 °C and the reaction mixture was stirred for 1 h. The reaction was quenched with NH₄Cl (50 mL) at 0 °C, and then extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 0 to 50% EtOAc/PE gradient, to give the title compound (3.3 g, 59.5%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 10.35 (s, 1H), 7.08 (d, 1H), 2.64 - 2.60 (m, 3H).

Step 3: Synthesis of 4-bromo-6-methyl-5-(trifluoromethyl)-1H-indazole

[00206] To a solution of the compound from step 2 (5 g, 17.5 mmol) in DMSO (50 mL) was added NH₂NH₂·H₂O (17.56 g, 17.0 mL) and the reaction mixture was stirred at 60 °C for 2 h. The pH of the reaction mixture was adjusted to 7 using 1M HCl, the mixture diluted with H₂O

(100 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (50 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (4.6 g, crude) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 10.99 (br s, 1H), 8.19 (s, 1H), 7.31 (s, 1H), 2.66 - 2.63 (m, 3H).

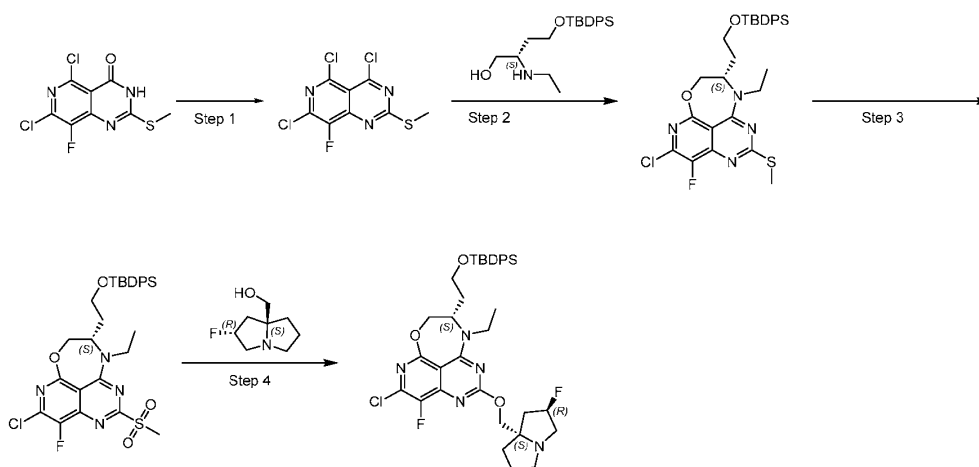
5 *Step 4: Synthesis of 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazole*

[00207] To a solution of the compound from step 3 (4.6 g, 16.48 mmol) in DCM (100 mL) was added TsOH (567.7 mg, 3.30 mmol), followed by DHP (5.55 g, 65.94 mmol) in MeCN (20 mL) and the reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 0 to 50% EtOAc/PE gradient @ 100 mL/min to give the title compound (5 g, 83.5%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ: 8.11 (s, 1H), 7.43 (s, 1H), 5.69 (dd, 1H), 4.03 - 3.99 (m, 1H), 3.79 - 3.72 (m, 1H), 2.71 - 2.65 (m, 3H), 2.56 - 2.47 (m, 1H), 2.19 - 2.07 (m, 2H), 1.81 - 1.67 (m, 3H).

15 *Step 5: Synthesis of 6-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-1H-indazole*

[00208] To a solution of the compound from step 4 (4.5 g, 12.4 mmol) and bis(pinacolato)diboron (18.88 g, 74.3 mmol) in dioxane (45 mL) was added Pd(dppf)Cl₂.CH₂Cl₂ (1.01 g, 1.24 mmol) and KOAc (4.86 g, 49.6 mmol) and the reaction mixture was stirred at 100 °C for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 0~60% EtOAc/PE gradient @ 100mL/min to give the title compound (1.9 g, 36.7%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ: 8.06 (s, 1H), 7.49 (s, 1H), 5.72 (dd, 1H), 3.98 (d, 1H), 3.77 - 3.71 (m, 1H), 2.62 (s, 3H), 2.57 - 2.48 (m, 1H), 2.18 - 2.15 (m, 1H), 2.08 - 2.04 (m, 1H), 1.80 - 1.66 (m, 3H), 1.45 (s, 12H), 1.27 (s, 1H).

Synthesis of (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-10-ethyl-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (Intermediate 28)



Step 1: Synthesis of 4,5,7-trichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidine

- [00209]** A solution of 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one (4 g, 14.3 mmol), POCl₃ (17.52 g, 114.2 mmol) and DIPEA (5.54 g, 42.8 mmol) in anhydrous MeCN (15 mL) was stirred for 0.5 h at 80 °C under N₂. The cooled mixture was evaporated under reduced pressure to afford the title compound, crude as a yellow solid. LCMS $m/z = 299$ [M+H]⁺

Step 2: Synthesis of (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-10-ethyl-4-fluoro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- [00210]** To a stirred solution of Intermediate 14, 3.73 g, 10.0 mmol) and the compound from step 1 (3.00 g, 10.0 mmol) in THF (30 mL) was added DIPEA (3.90 g, 30.1 mmol) and the resulting yellow suspension stirred at 25°C for 1 h. LiOtBu (2.2 M, 13.7 mL) was added and the reaction mixture stirred at 25°C for 1 h. The mixture was quenched with sat. NH₄Cl (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over MgSO₄ and concentrated. The residue was purified by silica gel chromatography eluting with 0~30%EtOAc/PE gradient @ 100 mL/min to give the title compound (2.50 g, 41.6%) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ : 7.65 - 7.56 (m, 4H), 7.51 - 7.36 (m, 6H), 4.62 (dd, 1H), 4.37 (d, 1H), 4.29 - 4.15 (m, 2H), 3.77 (br t, 2H), 3.39 (qd, 1H), 2.53 (s, 3H), 1.97 - 1.83 (m, 1H), 1.80 - 1.72 (m, 1H), 1.25 (t, 3H), 1.00 (s, 9H)

- Step 3: Synthesis of (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-10-ethyl-4-fluoro-2-(methylsulfonyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

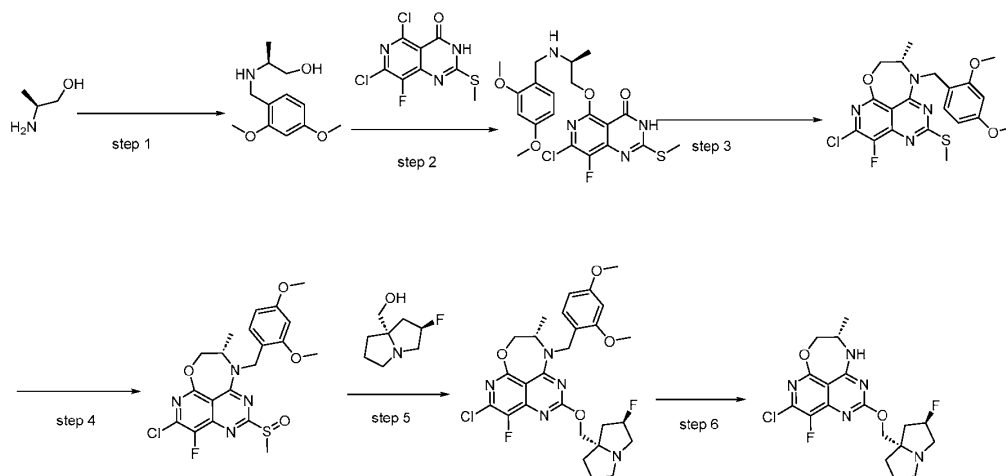
[00211] To a solution of the compound from step 2 (2.50 g, 4.19 mmol) in THF (20 mL) and H₂O (4 mL) was added m-CPBA (2.12 g, 10.4 mmol, 85% purity) and the reaction mixture was

stirred at 30 °C for 1h. The reaction was quenched with aq. 10% Na₂SO₃ (100 mL) and stirred for 10 mins. The mixture was extracted with EtOAc (100 mL x 2), washed with aq. 10% Na₂SO₃ (100 mL x 2), brine (20 mL), dried over MgSO₄, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography eluting with 0~40% EtOAc/PE gradient @ 80 mL/min to give the title compound (1.70 g, 64.5%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 7.62 (ddd, 4H), 7.49 - 7.39 (m, 6H), 4.70 (dd, 1H), 4.47 (d, 1H), 4.39 - 4.31 (m, 1H), 4.23 (qd, 1H), 3.83 - 3.73 (m, 2H), 3.51 (qd, 1H), 3.38 (s, 3H), 1.95 (qd, 1H), 1.81 - 1.77 (m, 1H), 1.28 (t, , 3H), 1.01 (s, 9H)

Step 4: Synthesis of (S)-9-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-5-chloro-10-ethyl-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00212] To a stirred solution of the compound from step 3 (1.70 g, 2.70 mmol) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (516 mg, 3.24 mmol) in THF (20 mL) at 0 °C was added LiOtBu (2.2 M, 2.46 mL, 5.4 mmol) and the resulting yellow suspension stirred at 25 °C for 1 h. The reaction mixture was added to water (50 mL), the mixture extracted with EtOAc (50 mL x 2) and the combined organic layers were dried over MgSO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography, eluting with 0-40% EtOAc/PE to give the title compound (1.1 g, 57.5%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 7.61 (ddd, 4H), 7.52 - 7.31 (m, 6H), 5.38 - 5.14 (m, 1H), 4.61 (dd, 1H), 4.34 (d, 1H), 4.21 (td, 2H), 4.14 - 4.07 (m, 1H), 4.06 - 3.98 (m, 1H), 3.77 (br t, 2H), 3.44 - 3.33 (m, 2H), 3.14 - 2.98 (m, 3H), 2.88 - 2.78 (m, 1H), 2.16 - 2.02 (m, 2H), 1.99 (s, 1H), 1.96 - 1.63 (m, 5H), 1.28 - 1.19 (m, 3H), 1.00 (s, 9H)

Synthesis of (S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (Intermediate 29)



Step 1: Synthesis of (S)-2-((2,4-dimethoxybenzyl)amino)propan-1-ol

[00213] To a stirred solution of (2S)-2-aminopropan-1-ol (10 g, 133.1 mmol) and 2,4-dimethoxybenzaldehyde (22.12 g, 133.1 mmol) in MeOH (500 mL) was added Na₂SO₄ (9.46 g, 66.6 mmol) and the resulting mixture was stirred for 24h at rt under N₂. The mixture was cooled to 0°C, NaBH₄ (2.52 g, 66.6 mmol) was added in portions and the mixture stirred for 30 min. AcOH (4.00 g, 66.6 mmol) was added dropwise and the reaction mixture was stirred for 15 min. The reaction was quenched with water at 0°C and the resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (3x100mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to afford the title compound (33 g, crude) as a white solid. LCMS m/z = 226 [M+H]⁺

Step 2: Synthesis of (S)-7-chloro-5-(2-((2,4-dimethoxybenzyl)amino)propoxy)-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

[00214] To a solution of the compound from step 1 (5 g, 22.2 mmol, crude) in THF (50 mL) was added NaH (60% in oil, 2.66 g, 66.6 mmol) at 0 °C and the mixture was stirred for 10 min. 5,7-Dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one (6.22 g, 22.2 mmol) was added and the reaction stirred at 60°C for 2h. The cooled reaction mixture was quenched with water, and the resulting mixture was extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (3x100mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water, 30% to 40% gradient in 10 min to afford the title compound (10.2 g, 98.0%) as a yellow solid. LCMS m/z = 469 [M+H]⁺

Step 3: Synthesis of ((S)-5-chloro-10-(2,4-dimethoxybenzyl)-4-fluoro-9-methyl-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00215] To a stirred solution of the compound from step 2 (10.2 g, 21.8 mmol) in DCM (100 mL) was added TEA (6.60 g, 65.3 mmol) and PyBOP® (16.98 g, 32.6 mmol) at rt and the reaction was stirred for 5h at rt under N₂. The resulting mixture was diluted with brine and extracted with EtOAc (3 x 100mL). The combined organic layers were washed with brine (3x100mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water, 40% to 50% gradient in 10 min to afford the title compound (5.1 g, 52.%) as a yellow solid. LCMS m/z = 451 [M+H]⁺

Step 4: Synthesis of (9S)-5-chloro-10-(2,4-dimethoxybenzyl)-4-fluoro-9-methyl-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00216] To a solution of the compound from step 3 (5.1 g, 11.3 mmol) in DCM (50 mL) was added a solution of m-CPBA (2.15 g, 12.4 mmol) in DCM dropwise at -15°C under N₂ and the reaction was stirred for 1 h at -15°C under N₂. The reaction was quenched by the addition of saturated NaHSO₃ soln. at -15°C. The resulting mixture was extracted with EtOAc (3 x 50mL), the combined organic layers were washed with brine (3x50mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to afford the title compound (5.28 g, crude) as a yellow solid. LCMS m/z = 467 [M+H]⁺

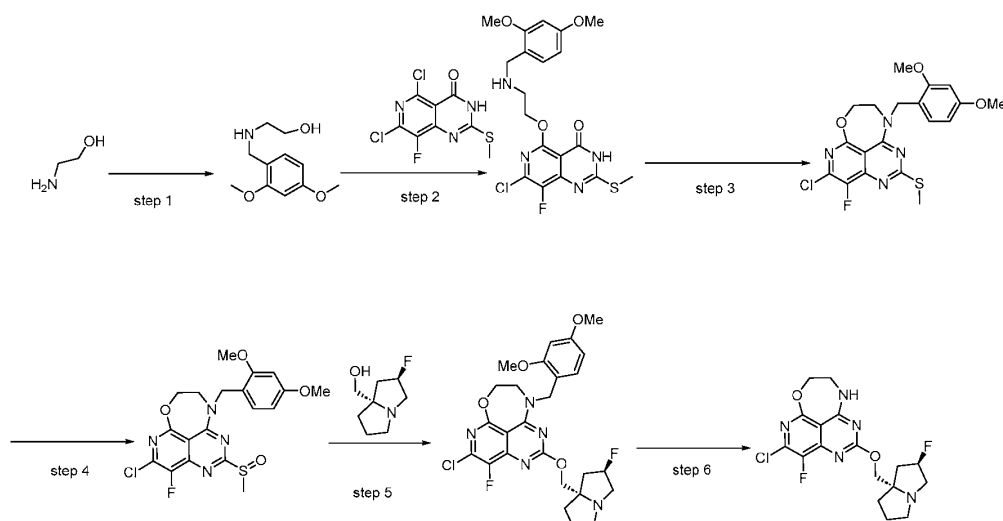
Step 5: Synthesis of (S)-5-chloro-10-(2,4-dimethoxybenzyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00217] To a stirred solution of the compound from step 4 (5.28 g, 11.3 mmol) in toluene (50 mL) was added ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (5.40 g, 33.9 mmol) and the mixture was stirred for 30 min at rt under N₂, then cooled to 0°C. NaOtBu (2.17 g, 22.6 mmol) was added and the reaction stirred for 30 min at 0°C. The mixture was diluted with brine, extracted with EtOAc (3 x 50mL), the combined organic layers were washed with brine (3x50mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water, 40% to 50% gradient in 10 min, to afford the title compound (4 g, 62.9%) as a white solid. LCMS m/z = 562 [M+H]⁺

Step 6: Synthesis of (S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00218] TFA (20 mL) was added to a solution of the compound from step 5 (4 g, 7.1 mmol) in DCE (20 mL) and the reaction mixture stirred for 16 h at 80°C under N₂. The cooled mixture was concentrated under reduced pressure and the residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water, 60% to 70% gradient in 10 min to afford the title compound (1.6 g, 54.6%) as an off-white solid. LCMS m/z = 412 [M+H]⁺

Synthesis of 5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (Intermediate 30)



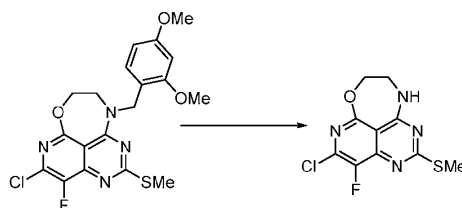
Steps 1 to 3: Synthesis of 5-chloro-10-(2,4-dimethoxybenzyl)-4-fluoro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00219] The title compound was obtained as a white solid, from ethanolamine, 2,4-dimethoxybenzaldehyde and 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one, following a similar 3 step procedure to that described in Intermediate 29, steps 1 to 3. LCMS m/z = 437 [M+H]⁺

Steps 4 to 6: Synthesis of (S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

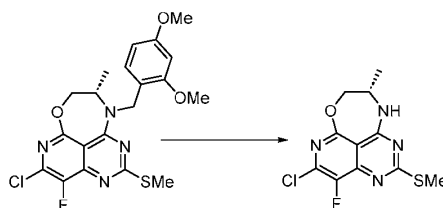
[00220] The title compound was obtained as a white solid, from the compound from steps 1 to 3 and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar 3 step procedure to that described in Intermediate 29, steps 4 to 6. LCMS m/z = 398 $[M+H]^+$

[00221] Synthesis of 5-chloro-4-fluoro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (Intermediate 31)



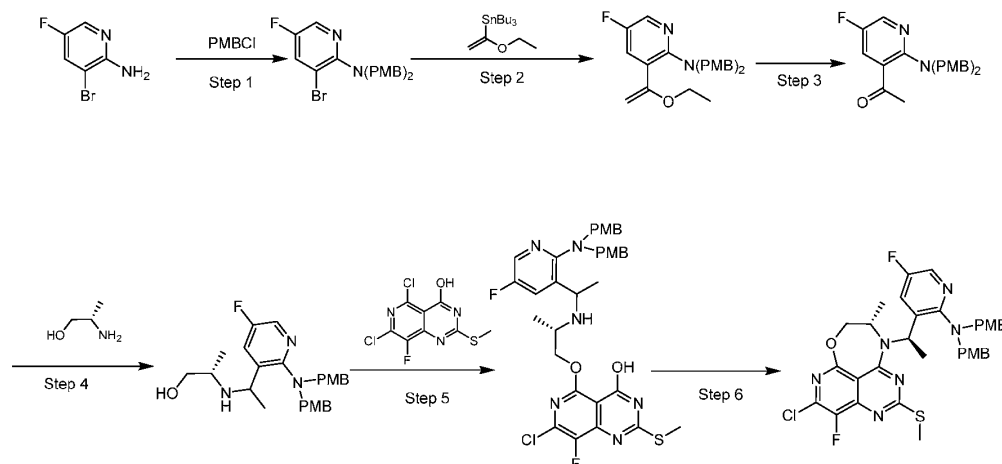
[00222] TFA (5 mL) was added to a solution of Intermediate 30, step 3 (500 mg, 1.24 mmol) in DCE (5 mL) and the reaction mixture was stirred at 80°C for 16 h under N₂. The cooled mixture was evaporated under reduced pressure to afford the title compound, crude. LCMS m/z = 287 $[M+H]^+$

Synthesis of (S)-5-chloro-4-fluoro-9-methyl-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (Intermediate 32)



[00223] The title compound was obtained from Intermediate 29, step 3, following the procedure described in Intermediate 31.

Synthesis of 3-((R)-1-((S)-5-chloro-4-fluoro-9-methyl-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine (Intermediate 33)



Step 1: Synthesis of 3-bromo-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00224] To a solution of 3-bromo-5-fluoropyridin-2-amine (150 g, 0.77 mol) in DMF (2 L) was added NaH (77.3 g, 1.93 mol, 60% purity) in portions at 0 °C under N₂ and the mixture was stirred at 0 °C for 1 h. PMBCl (266 g, 1.70 mol) was added dropwise at 0 °C under N₂ and the reaction mixture was stirred at rt for 18 h. The mixture was cooled and quenched with sat. NH₄Cl (2 L) dropwise and extracted with EtOAc (2 L x 2). The combined organic layers were washed with brine (500 mL x 3), dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was purified by silica gel chromatography, eluting with 0~25% EtOAc/PE to give the title compound (240 g, 72.0%) as a yellow oil. LCMS m/z = 431/433 [M+H]⁺

Step 2: Synthesis of 3-(1-ethoxyvinyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00225] To a solution of the compound from step 1 (120 g, 278 mmol) in DMF (1.5 L) was added tributyl(1-ethoxyvinyl)tin (151 g, 417 mmol), TEA (84.2 g, 834 mmol) and Pd(PPh₃)₂Cl₂ (8.7 g, 11.2 mmol) and the reaction mixture was stirred at 80 °C for 18 h under N₂. The mixture was poured into water (2 L) and extracted with EtOAc (2 L x 2). The combined organic layers were washed with brine (500 mL x 3), dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was purified by silica gel chromatography, eluting with 0~20% THF/PE to give the title compound (151 g, 64.2%) as a yellow gum. LCMS m/z = 423 [M+H]⁺

Step 3: Synthesis of 1-(2-(bis(4-methoxybenzyl)amino)-5-fluoropyridin-3-yl)ethan-1-one

[00226] To a solution of the compound from step 2 (150 g, 355 mmol) in dioxane (1.5 L) was added HCl/dioxane (200 mL, 4 M) and the reaction was stirred at rt for 1 h. The mixture was concentrated and the residue was diluted with sat. NaHCO₃ (300 mL) and EtOAc (2 L). The EtOAc layer was washed with brine (500 mL), dried over Na₂SO₄, filtered and the filtrate

was evaporated to give the title compound (130 g, 92.8%) as yellow oil. LCMS m/z = 395 [M+H]⁺

Step 4: Synthesis of (2S)-2-((1-(2-(bis(4-methoxybenzyl)amino)-5-fluoropyridin-3-yl)ethyl)amino)propan-1-ol

- 5 [00227] To a solution of the compound from step 3 (150 g, 380.3 mmol) and (S)-2-aminopropan-1-ol (85.7 g, 1.14 mol) in dioxane (1.5 L) was added Ti(i-PrO)₄ (162 g, 570 mmol) and 4Å molecular sieves (100 g, 380.3 mmol) and the mixture was stirred at 110 °C for 18 h under N₂. The mixture was cooled to 0 °C and NaBH₄ (28.8 g, 760 mmol) was added in portions while keeping the internal temperature below 20 °C. After the addition, the mixture
10 was stirred at rt for 2 h. The mixture was cooled to 0 °C, sat. NaHCO₃ (200 mL) was added dropwise under N₂ and the mixture was stirred at rt for 1 h. The resulting mixture was poured into water (2 L) and filtered through a pad of Celite®. The filter cake was rinsed with EtOAc (1 L x 2). The separated organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was purified by silica gel
15 chromatography, eluting with 0~100% THF/PE to give the title compound (130 g, 75.4%) as a yellow gum. LCMS m/z = 454 [M+H]⁺

Step 5: Synthesis of 5-((2S)-2-((1-(2-(bis(4-methoxybenzyl)amino)-5-fluoropyridin-3-yl)ethyl)amino)propoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-ol

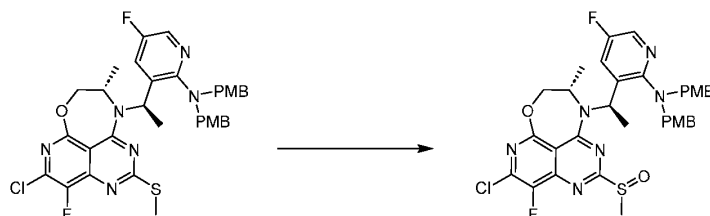
- [00228] To a solution of the compound from step 4 (80.9 g, 178 mmol) in THF (1.5 L) was
20 added NaH (25 g, 625 mmol, 60% purity) in portions at 0 °C under N₂. The mixture was stirred at 0 °C for 30 min. 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one (50 g, 178.5 mmol) was added in portions at 0 °C under N₂ and the reaction mixture was stirred at 60 °C for 2.5 h. The mixture was cooled to 0 °C and sat. NH₄Cl (500 mL) was added dropwise, while keeping the internal temperature below 15 °C. The mixture was extracted with EtOAc (1
25 L x 2). The combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with 0-40% of THF in PE to give the title compound (74 g, 59.4%) as a yellow solid.

- Step 6: Synthesis of 3-((R)-1-((S)-5-chloro-4-fluoro-9-methyl-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine*
30

[00229] To a solution of the compound from step 5 (70 g, 100.4 mmol) in DCE (1.5 L) was added DIPEA (38.9 g, 301 mmol) and BOP-Cl (38.3 g, 150 mmol) and the reaction mixture was

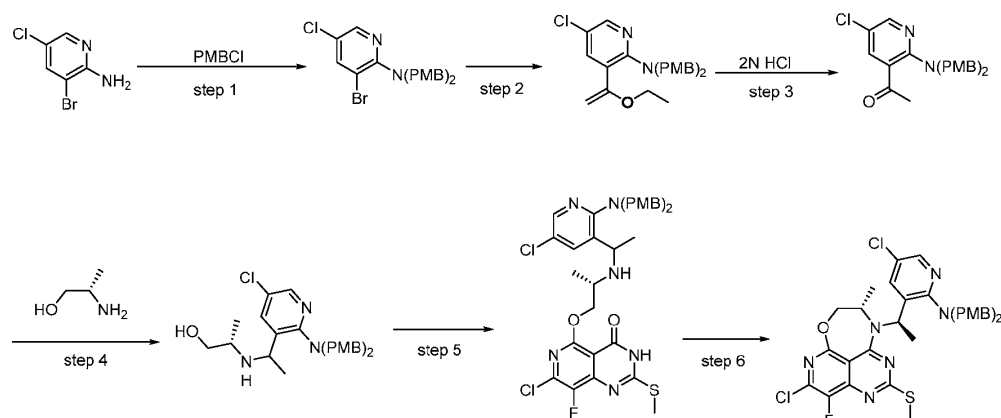
stirred at 90 °C for 18 h. The mixture was washed with sat. NaHCO₃ (1 L), brine (500 mL x 2), dried over Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Column, Eluent of 0~30% THF/PE gradient @ 100 mL/min) followed by prep-SFC (column: REGIS (s,s) WHELK-O1 (250mm*50mm,10um); mobile phase: CO₂ / EtOH (0.1%NH₃H₂O) (45:55) isocratic elution mode) to give the title compound (28 g, 41.1%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.41 (d, 1H), 7.97 (dd, 1H), 6.89 - 6.98 (m, 1 H), 6.70 (d, 4H), 6.54 (d, 4H), 4.38 - 4.49 (m, 1H), 4.21 - 4.32 (m, 1H), 4.09 (d, 2H), 3.96 - 4.03 (m, 1H), 3.83 (d, 2H), 3.64 (s, 6H), 2.66 (s, 3H), 1.39 (br d, 3H), -0.13 (d, 3H)

10 **Synthesis of 3-((1R)-1-((9S)-5-chloro-4-fluoro-9-methyl-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine (Intermediate 34)**



[00230] To a mixture of the compound from Intermediate 33 (26 g, 34.45 mmol) in DCM (250 mL) was added m-CPBA (7.69 g, 37.90 mmol, 85% purity) and the mixture was stirred at rt for 30 min. The reaction mixture was quenched with sat. NaHCO₃ (100 mL) and sat. Na₂SO₃ (50 mL), then extracted with DCM (200mL x 3). The combined organic phase was washed with brine (200 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound (24 g, 90.2%). LCMS m/z = 695 [M+H]⁺

20 **Synthesis of 5-chloro-3-((R)-1-((S)-5-chloro-4-fluoro-9-methyl-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine (Intermediate 35)**



Steps 1 and 2: Synthesis of 3-bromo-5-chloro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00231] The title compound was obtained as a yellow oil, from 3-bromo-5-chloropyridin-2-amine, PMBCl and tributyl(1-ethoxyethenyl)stannane, following a similar procedure to that described in Intermediate 33, steps 1 and 2. LCMS $m/z = 439$ $[M+H]^+$

Step 3: Synthesis of 1-(2-(bis(4-methoxybenzyl)amino)-5-chloropyridin-3-yl)ethan-1-one

[00232] A solution of the compound from steps 1 and 2 (21 g, 47.8 mmol) and 1M HCl (768.8 mL) in EtOAc (730 mL) was stirred at rt for 2h. The mixture was extracted with EtOAc (2 x 500 mL) and the combined organic layers were washed with NaHCO_3 (3 x 100 mL) and brine, dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (5:1) to afford the title compound (17 g, 86.5%) as a yellow oil. LCMS $m/z = 411$ $[M+H]^+$

Step 4: Synthesis of (2S)-2-((1-(2-(bis(4-methoxybenzyl)amino)-5-chloropyridin-3-yl)ethyl)amino)propan-1-ol

[00233] $\text{Ti}(\text{i-PrO})_4$ (47.04 g, 165.5 mmol) was added to a solution of the compound from step 3 (17 g, 41.4 mmol) and (2S)-2-aminopropan-1-ol (9.32 g, 124.1 mmol) in EtOH (300 mL) and the resulting mixture was stirred at 80°C overnight. NaBH_4 (4.70 g, 124.1 mmol) and HOAc (3.73 g, 62.1 mmol) were added at 0°C , and the reaction mixture was stirred at 0°C for 1h. The reaction was quenched with water/ice (100 mL) at 0°C , the resulting mixture was filtered and the filter cake was washed with EtOAc (4 x 500 mL). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluting with PE / EtOAc (1:8) to afford the title compound (16.85 g, 86.7%) as a yellow oil. LCMS $m/z = 470$ $[M+H]^+$

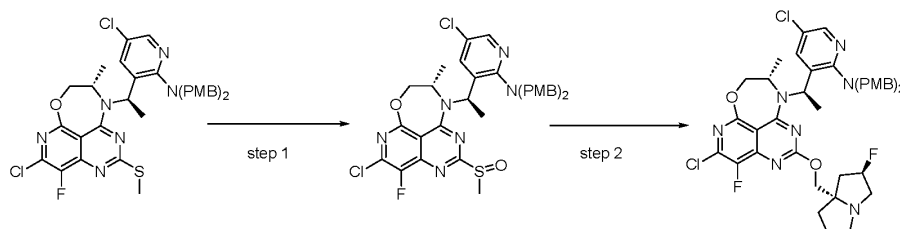
Step 5: Synthesis of 5-((2S)-2-((1-(2-(bis(4-methoxybenzyl)amino)-5-chloropyridin-3-yl)ethyl)amino)propoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

[00234] The title compound was obtained as a brown solid (6 g, 32.9%) from the compound from step 4, following a similar procedure to that described in Intermediate 33, step 5. LCMS $m/z = 713$ $[M+H]^+$

Step 6: Synthesis of 5-chloro-3-((R)-1-((S)-5-chloro-4-fluoro-9-methyl-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00235] DIPEA (3.80 g, 29.4 mmol) was added to a solution of the compound from step 5 (7 g, 9.81 mmol) and BOPCl (7.49 g, 29.4 mmol) in $CHCl_3$ (120 mL) and the resulting mixture was stirred at 80°C for 20 h. The reaction was quenched with ice-water at 0°C and the mixture was extracted with DCM (3 x 100 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (2:1) to afford the title compound (1.7 g, 22.4%) as a yellow solid. LCMS $m/z = 695$ $[M+H]^+$

Synthesis of 5-chloro-3-((R)-1-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine (Intermediate 36)



Step 1: Synthesis of 5-chloro-3-((1R)-1-((9S)-5-chloro-4-fluoro-9-methyl-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

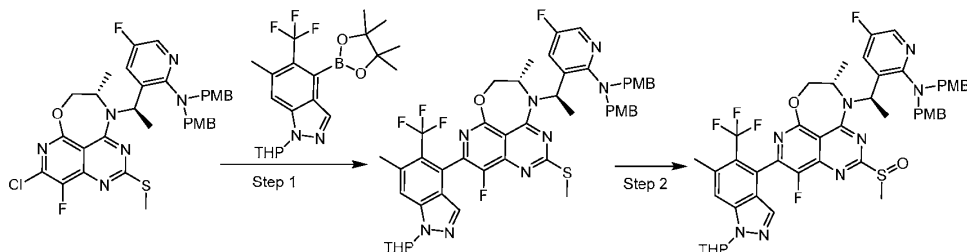
[00236] A solution of m-CPBA (526.5 mg, 2.59 mmol, 85%) in DCM (10 mL) was added dropwise at -15°C to a solution of Intermediate 35 (1.64 g, 2.36 mmol) in DCM (40 mL) and the reaction mixture was stirred at -15°C for 1 h. The reaction was quenched with $Na_2SO_3(aq)$ at 0 °C, the aqueous layer was extracted with DCM (3 x 10 mL), the combined

organic layers were washed with brine, dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure to afford the title compound (1.54 g, 91.9%) as a yellow solid. LCMS m/z = 711 [M+H]⁺

Step 2: Synthesis of 5-chloro-3-((R)-1-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00237] NaOtBu (243.1 mg, 2.53 mmol) was added at 0°C to a solution of the compound from step 1 (900 mg, 1.27 mmol) and ((2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl)methanol (604.0 mg, 3.80 mmol) in toluene (10 mL) and the mixture was stirred at 0°C for 30 min. The reaction was quenched with ice-water at 0°C. The aqueous layer was extracted with DCM (3 x 10 mL), the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM / MeOH (20:1) to afford the title compound (600 mg, 58.8%) as a white solid. LCMS m/z = 806 [M+H]⁺

Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine (Intermediate 37)



Step 1: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

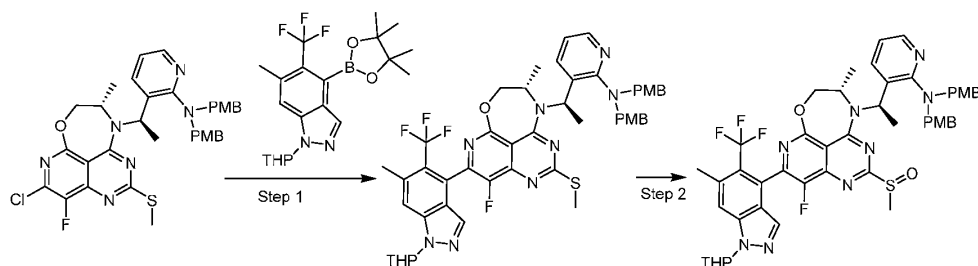
[00238] A mixture of Intermediate 27 (120.8 mg, 0.29 mmol), Intermediate 33 (200 mg, 0.99 mmol), CataCXium A Pd G3 (21.45 mg, 0.029 mmol) and K₃PO₄ (187.52 mg, 0.88 mmol) in dioxane (4 mL)/H₂O (1 mL) was stirred at 80°C for 1h under N₂. The mixture was cooled to rt, the reaction was quenched with ice-water and the mixture was extracted with DCM (3x10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered

and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EtOAc 1:1) to afford the title compound (110 mg, 40.3%) as a light brown solid. LCMS $m/z = 928$ $[M+H]^+$

Step 2: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00239] The title compound was obtained as a solid, 100 mg, crude, from the compound from step 1, following the procedure described in Intermediate 34. LCMS $m/z = 944$ $[M+H]^+$

Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Intermediate 38)



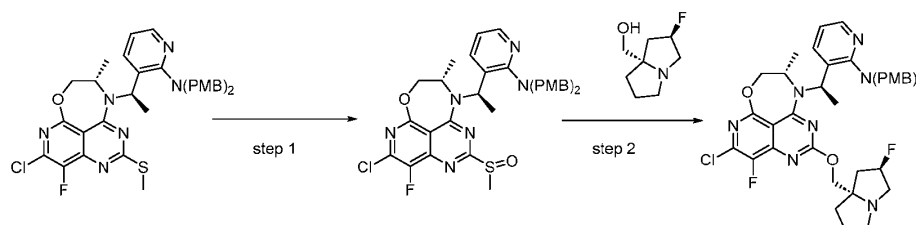
Step 1: Synthesis of 3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00240] The title compound was obtained as pale-yellow foam (450 mg, 64.3%) from the compounds of Example 93, step 4 and Intermediate 27 following the procedure described in Step 1 of Example 101. LCMS $m/z = 909$ $[M+H]^+$.

Step 2: Synthesis of 3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00241] The title compound was obtained as pale-brown foam (200 mg, 91%) from the compound from Step 1, following a similar procedure to that described in Step 4 of Intermediate 34. LCMS $m/z = 925$ $[M+H]^+$.

Synthesis of 3-((R)-1-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine (Intermediate 39)



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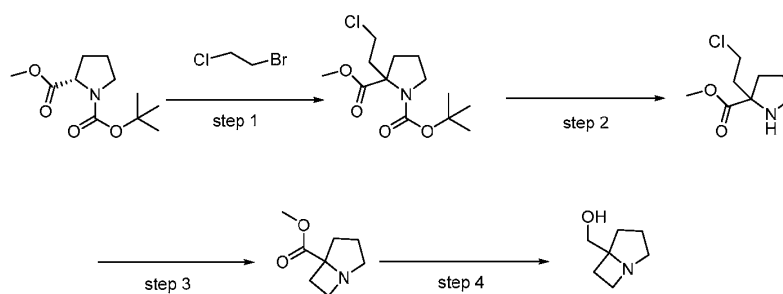
Step 1: Synthesis of 3-((1R)-1-((9S)-5-chloro-4-fluoro-9-methyl-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00242] The title compound was obtained as a yellow oil, 500 mg, crude, from the compound from step 4 of Example 93, following a similar procedure to that described in Example 1, step 3. LCMS $m/z = 677$ $[M+H]^+$

Step 2: Synthesis of 3-((R)-1-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00243] The title compound was obtained as a white solid, 455 mg, 79.7%, from the compound from step 1 and ((2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl)methanol, following a similar procedure to that described in Example 40, step 5. LCMS $m/z = 772$ $[M+H]^+$

Synthesis of (1-azabicyclo[3.2.0]heptan-5-yl)methanol (Intermediate 40)



Step 1: 1-tert-butyl 2-methyl (2R)-2-(2-chloroethyl)pyrrolidine-1,2-dicarboxylate

[00244] LDA (1.0M in THF, 10.5 mL, 34.9 mmol) was added dropwise at -78°C to a solution of 1-tert-butyl 2-methyl (2S)-pyrrolidine-1,2-dicarboxylate (4 g, 17.45 mmol) in THF

(40 mL) under N₂. The mixture was stirred at -78°C for 2 h, then, 1-bromo-2-chloroethane (5.00 g, 34.9 mmol) was added dropwise. The resulting mixture was stirred at rt overnight. The reaction was quenched with sat. NH₄Cl (aq.), the layers separated and the aqueous layer extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to give the title compound (4 g, 78.6%) as a yellow oil. LCMS m/z = 236 [M+H]⁺

Step 2: methyl (2R)-2-(2-chloroethyl)pyrrolidine-2-carboxylate hydrochloride

[00245] 4M HCl/dioxane (50 mL) was added to a solution of the compound from step 1 (4 g, 13.7 mmol) in dioxane (0.5 mL) and the reaction was stirred at rt for 1h under N₂. The resulting mixture was concentrated under reduced pressure to afford the title compound (3 g, 91.3%) as a yellow oil. LCMS m/z = 192 [M+H]⁺

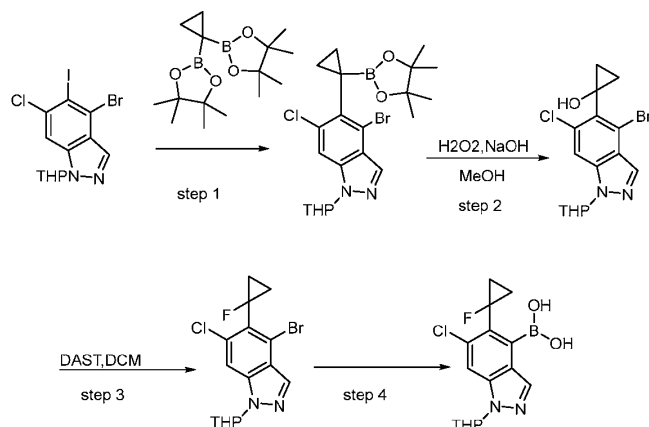
Step 3: methyl (5R)-1-azabicyclo[3.2.0]heptane-5-carboxylate

[00246] A mixture of the compound from step 2 (3g, 15.66 mmol) and TEA (9.01 mL, 64.80 mmol) in MeCN (45 mL) was stirred at 80°C for 2 h under N₂. The reaction was quenched with ice-water and the aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure to afford the title compound (1 g, 41.2%) as a brown oil. LCMS m/z = 156 [M+H]⁺

Step 4: 1-azabicyclo[3.2.0]heptan-5-ylmethanol

[00247] LiAlH₄ (20 mL, 0.042 mmol, 1.0 M in THF solution) was added dropwise at 0°C to a solution of the compound from step 3 (1 g, 6.44 mmol) in THF (10 mL) and the resulting mixture was stirred at 0°C for 1 h. The reaction was quenched with Na₂SO₄.H₂O, the mixture was filtered and the filter cake was washed with DCM (3x10 mL). The filtrate was evaporated under reduced pressure to afford the title compound (300 mg, 36.6%) as a yellow oil. LCMS m/z = 128 [M+H]⁺

Synthesis of (6-chloro-5-(1-fluorocyclopropyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)boronic acid (Intermediate 41)



Step 1: Synthesis of 4-bromo-6-chloro-1-(tetrahydro-2H-pyran-2-yl)-5-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)-1H-indazole

[00248] A solution of 4-bromo-6-chloro-5-iodo-1-(oxan-2-yl)indazole (1 g, 2.27 mmol), 2,2'-(cyclopropane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (998.9 mg, 3.40 mmol), Cs₂CO₃ (1.48 g, 4.53 mmol) and Pd(dppf)Cl₂ (165.7 mg, 0.23 mmol) in dioxane (8 mL) and H₂O (1 mL) was stirred at 100°C for 16 h under N₂. The mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by prep-TLC (DCM/ MeOH 12:1) to afford the title compound (524 mg, 48.0%) as a white solid. LCMS m/z = 482 [M+H]⁺

Step 2: Synthesis of 1-(4-bromo-6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-yl)cyclopropan-1-ol

[00249] A solution of the compound from step 1 (524 mg, 1.09 mmol), H₂O₂ (74.01 mg, 2.18 mmol) and NaOH (87.03 mg, 2.18 mmol) in MeOH (10 mL) was stirred at 0°C for 30 min. The reaction was quenched with NaHCO₃ (0.5 mL) at 0°C and the resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (DCM / MeOH 30:1) to afford the title compound (201 mg, 49.7%) as a white solid. LCMS m/z = 372 [M+H]⁺

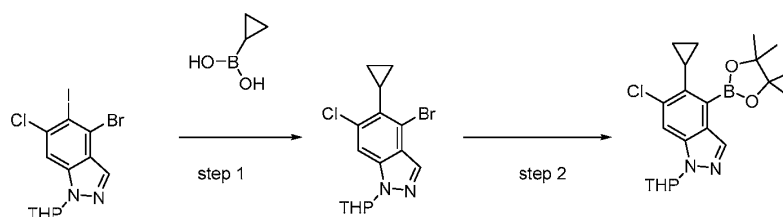
Step 3: Synthesis of 4-bromo-6-chloro-5-(1-fluorocyclopropyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

[00250] To a stirred solution of the compound from step 2 (110 mg, 0.30 mmol) in DCM (5 mL) was added DAST (95.41 mg, 0.59 mmol) in portions at -78°C under N₂ and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (PE / EtOAc 5:1) to afford the title compound (67 mg, 60.6%) as a yellow oil. LCMS m/z = 374 [M+H]⁺

Step 4: 6-chloro-5-(1-fluorocyclopropyl)-1-(oxan-2-yl)indazol-4-ylboronic acid

- [00251] A solution of the compound from step 3 (60 mg, 0.16 mmol), tetrahydroxydiborane (28.79 mg, 0.32 mmol) and TEA (65.0 mg, 0.64 mmol) and CataCXium A Pd G3 (11.69 mg, 0.016 mmol) in MeOH (5 mL) was stirred at rt for 4 h under N₂. The resulting mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (DCM / MeOH 30:1) to afford the title compound (32 mg, 58.9%) as a yellow solid. LCMS m/z = 339 [M+H]⁺

Synthesis of 6-chloro-5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (Intermediate 42)



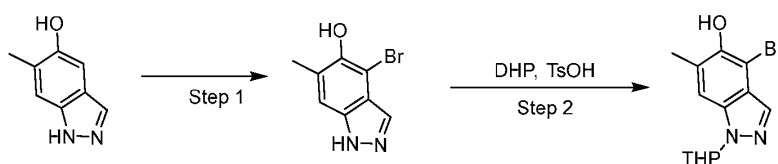
Step 1: Synthesis of 4-bromo-6-chloro-5-cyclopropyl-1-(oxan-2-yl)indazole

- [00252] A mixture of 4-bromo-6-chloro-5-iodo-1-(oxan-2-yl)indazole (2 g, 4.53 mmol), cyclopropylboronic acid (467 mg, 5.44 mmol), K₃PO₄ (2.88 g, 13.59 mmol) and Pd(dppf)Cl₂.CH₂Cl₂ (739.9 mg, 0.91 mmol) in dioxane (15 mL) and water (5 mL) was stirred at 100°C for 2 h under N₂. The mixture was cooled to rt and diluted with water. The resulting mixture was extracted with EtOAc (3 x 50 mL), the combined organic layers were washed with brine (3 x 50 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (1:5) to afford the title compound (0.52 g, 32.3%) as a white solid. LCMS m/z = 357 [M+H]⁺

Step 2: Synthesis of 6-chloro-5-cyclopropyl-1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole

[00253] The title compound was obtained as a colorless oil, 0.1 g, 23%, from the compound from step 1, following the procedure described in Intermediate 20. LCMS m/z = 403 [M+H]⁺

Synthesis of 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-ol (Intermediate 43)

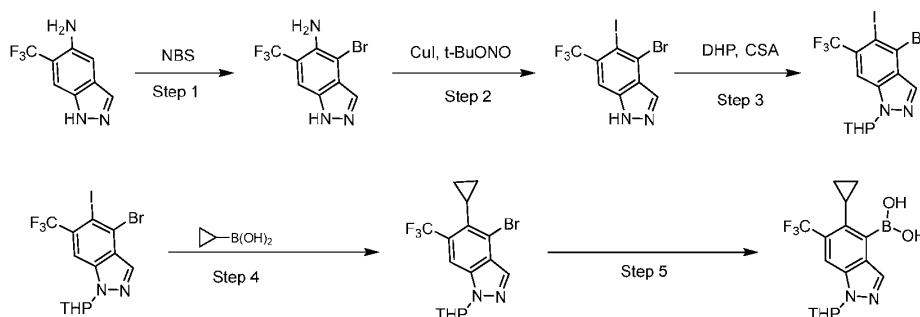


Step 1: Synthesis of 4-bromo-6-methyl-1H-indazol-5-ol

[00254] To a solution of 6-methyl-1H-indazol-5-ol (5.0 g, 33.7 mmol) in THF (100 mL) was added NBS (6.61 g, 37.1 mmol) portionwise at 0 °C and the reaction was stirred at 25 °C for 14 h. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (200 mL × 2). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, PE: EtOAc=1:0 to 1:1) to give the title compound (7.0 g, crude) as a brown solid. LCMS m/z = 227 [M+H]⁺

Step 2: Synthesis of 4-bromo-6-methyl-1-tetrahydropyran-2-yl-indazol-5-ol

[00255] To a solution of the compound from step 1 (7.00 g, 30.8 mmol) and TsOH (531 mg, 3.08 mmol) in DMF (50 mL) was added a solution of DHP (5.19 g, 61.7 mmol) in DMF (5 mL) at rt slowly. The resulting solution was stirred at rt for 14 h. The reaction mixture was poured into water (200 mL) and extracted with EtOAc (300 mL × 2). The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, PE: EtOAc=1:0 to 3:1) and further purified by reverse-phase HPLC to give the title compound (3.60 g, 38%) as a yellow solid. LCMS m/z = 313 [M+H]⁺

Synthesis of (5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-6-(trifluoromethyl)-1H-indazol-4-yl)boronic acid (Intermediate 44)*Step 1: Synthesis of 4-bromo-6-(trifluoromethyl)-1H-indazol-5-amine*

[00256] The title compound was obtained as a yellow solid, 5.0 g, 41%, from 6-(trifluoromethyl)-1H-indazol-5-amine, following a similar procedure to that described in Intermediate 43, step 1. LCMS m/z = 280 [M+H]⁺

Step 2: Synthesis of 4-bromo-5-iodo-6-(trifluoromethyl)-1H-indazole

[00257] To a solution of the compound from step 1 (500 mg, 1.79 mmol, 8 batches) in MeCN (10 mL) was added CuI (1.02 g, 5.36 mmol) and t-BuONO (570 mg, 5.53 mmol) and the

reaction mixture was stirred at 70°C for 2 h. The mixture was quenched with sat.aq NaHCO₃ (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, NH₃•H₂O (3 mL), PE: DCM/MeOH=1/0 to 0/1, PE: EtOAc=5:1) and then re-purified by reverse-phase flash column to give the title compound (1.10 g, 20%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 13.97 (s, 1H), 8.15 (s, 1H), 8.06 (s, 1H).

Step 3: Synthesis of 4-bromo-5-iodo-1-tetrahydropyran-2-yl-6-(trifluoromethyl)indazole

[00258] To a solution of the compound from step 2 (1.00 g, 2.56 mmol) and DHP (430 mg, 5.12 mmol) in THF (15 mL) was added camphor-10-sulfonic acid (89.1 mg, 0.38 mmol) and the reaction mixture was stirred at 70°C for 12 h. The mixture was quenched with sat.aq NaHCO₃ (10 mL) and then extracted with EtOAc (50 mL × 3). The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, PE/EtOAc=1/0 to 5/1) to give the title compound (700 mg, 52%) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 8.33 (s, 1H), 8.20 (s, 1H), 6.11 - 6.04 (m, 1H), 3.87 - 3.76 (m, 2H), 2.41 - 2.27 (m, 1H), 2.01 (s, 2H), 1.82 - 1.70 (m, 1H), 1.60 - 1.53 (m, 2H).

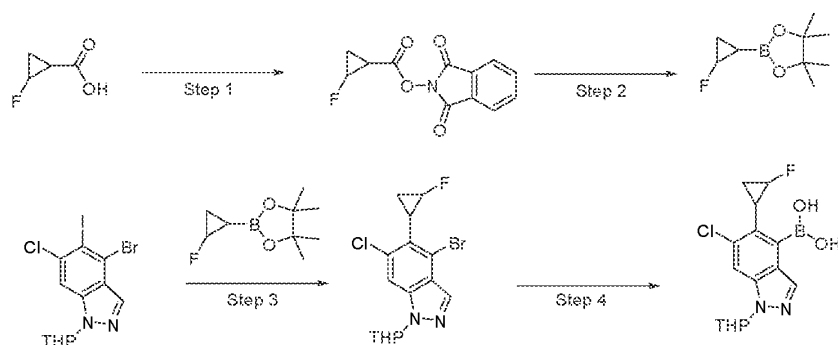
Step 4: Synthesis of 4-bromo-5-cyclopropyl-1-tetrahydropyran-2-yl-6-(trifluoromethyl)indazole

[00259] A mixture of the compound from step 3 (100 mg, 0.21 mmol), cyclopropyl boronic acid (27.1 mg, 0.32 mmol), Na₂CO₃ (33.4 mg, 0.32 mmol) and Pd(dppf)Cl₂ (15.4 mg, 21.0 μmol) in 2-MeTHF (1 mL) and H₂O (0.2 mL) was degassed and purged with N₂ and the reaction mixture was stirred at 100°C for 12 h under N₂. The mixture was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL × 3). The organic phase was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by prep-TLC (SiO₂, PE: EtOAc = 10:1) to give the title compound (30 mg, 34%) as a yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ 8.23 (s, 1H), 8.20 (s, 1H), 6.10 - 6.01 (m, 1H), 3.91 - 3.75 (m, 2H), 2.42 - 2.27 (m, 1H), 2.11 - 1.94 (m, 3H), 1.83 - 1.68 (m, 1H), 1.65 - 1.51 (m, 2H), 1.19 - 1.09 (m, 2H), 0.76 (d, 2H).

Step 5: Synthesis of (5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-6-(trifluoromethyl)-1H-indazol-4-yl)boronic acid

[00260] The title compound was obtained as a yellow solid, 40 mg, crude, from the compound from step 4 and tetrahydroxydiboron, following a similar procedure to that described in Intermediate 41, step 4. LCMS m/z = 355 [M+H]⁺

Synthesis of (6-chloro-5-(2-fluorocyclopropyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)boronic acid (Intermediate 45)



Step 1: Synthesis of 1,3-dioxoisindolin-2-yl 2-fluorocyclopropane-1-carboxylate

[00261] To a stirred mixture of 2-fluorocyclopropane-1-carboxylic acid (3.2 g, 30.75 mmol) and 2-hydroxy-2,3-dihydro-1H-isoindole-1,3-dione (5.52 g, 33.82 mmol) in DCM (20 mL) were added dicyclohexylcarbodiimide (0.46 g, 2.24 mmol) and DMAP (3.76 g, 30.75 mmol) and the reaction mixture was stirred at rt for 12 h. The resulting mixture was extracted with DCM (10 x mL). The combined organic layers were washed with NaHCO₃ (3x10 mL) and NaHSO₄ (10%), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to afford the title compound (7.6 g) as a yellow solid. LCMS m/z = 250 [M+H]⁺

Step 2: Synthesis of 2-(2-fluorocyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[00262] To a stirred solution of the compound from step 1 (7.61 g, 30.54 mmol) and bis(pinacolato)diboron (8.53 g, 33.59 mmol) in EtOAc (100 mL) was added tert-butyl pyridine-4-carboxylate (69.04 mg, 0.39 mmol) at rt under N₂. The resulting mixture was stirred at 80°C overnight under N₂. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (20:1) to afford the title compound (2.2 g, 38.7%) as a colorless oil. LCMS m/z = 205 [M+H]⁺

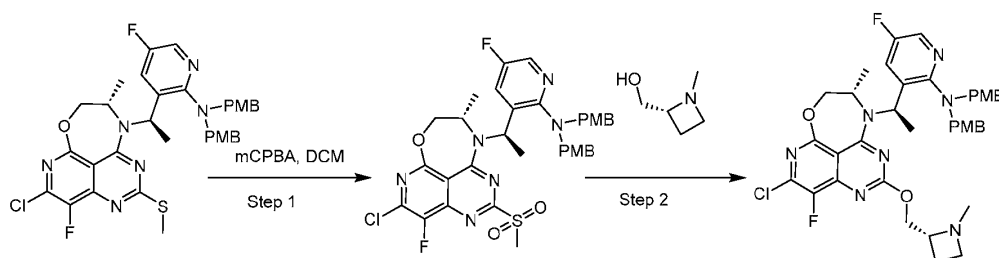
Step 3: Synthesis of 4-bromo-6-chloro-5-(2-fluorocyclopropyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

[00263] The title compound was obtained as a white solid, 120 mg, 23.6%, from the compound from step 2 and 4-bromo-6-chloro-5-iodo-1-(oxan-2-yl)indazole, following a similar procedure to that described in Intermediate 41, step 1. LCMS m/z = 373 [M+H]⁺

Step 4: Synthesis of (6-chloro-5-(2-fluorocyclopropyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)boronic acid

- [00264] To a stirred solution of the compound from step 3 (80 mg, 0.214 mmol) and tetrahydroxydiborane (76.78 mg, 0.86 mmol) in MeOH (1.6 mL) was added CataCXium A Pd G3 (15.59 mg, 0.02 mmol) and K₂CO₃ (59.18 mg, 0.43 mmol) and the reaction mixture was stirred at 40°C for 1h under N₂. The resulting mixture was concentrated *in vacuo* to give the title compound, crude. LCMS m/z = 339 [M+H]⁺

Synthesis of 3-((R)-1-((S)-5-chloro-4-fluoro-9-methyl-2-(((R)-1-methylazetidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine (Intermediate 46)



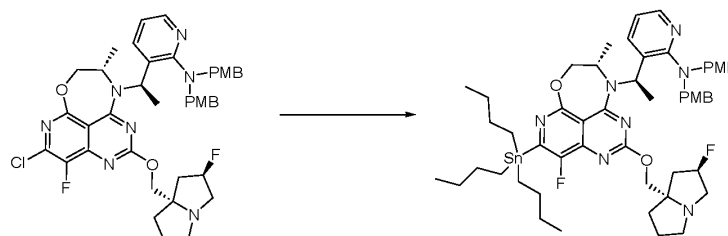
- 10 *Step 1: Synthesis of 3-((R)-1-((S)-5-chloro-4-fluoro-9-methyl-2-(methylsulfonyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine*

- [00265] A solution of Intermediate 33 (500 mg, 0.736 mmol) and m-CPBA (381.11 mg, 2.21 mmol) in DCM (5 mL) was stirred at rt for 2 h. The reaction was diluted with water (10 mL) and the resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE/EtOAc (3:1) to afford the title compound (500 mg, 95.5%) as a yellow solid. LCMS m/z = 711 [M+H]⁺

- 20 *Step 2: Synthesis of 3-((R)-1-((S)-5-chloro-4-fluoro-9-methyl-2-(((R)-1-methylazetidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine*

- [00266] To a stirred solution of the compound from step 1 (250 mg, 0.35 mmol) and ((2R)-1-methylazetidin-2-yl)methanol (42.67 mg, 0.42 mmol) in DCM (4 mL) was added LiOtBu (84.43 mg, 1.06 mmol) at 0°C and the reaction mixture was stirred at rt for 2 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (PE/EtOAc 1:1) to give the title compound (163 mg, 63.3%) as a yellow solid. LCMS m/z = 733 [M+H]⁺

Synthesis of 3-((R)-1-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(tributylstannyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine (Intermediate 47)

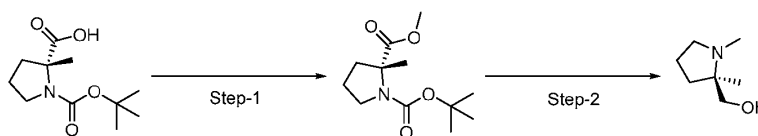


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[00267] A mixture of Intermediate 39 (260 mg, 0.12 mmol), bis(tributyltin) (587 mg, 0.39 mmol), $\text{Pd}_2(\text{dba})_3$ (31 mg, 0.01 mmol), tricyclohexylphosphane (21 mg, 0.02 mmol) and LiCl (72 mg, 0.66 mmol) in dioxane (3 mL) was stirred at 110°C for 16 h under N_2 . The resulting mixture was concentrated under reduced pressure and the residue was purified by Prep-TLC (PE/EtOAc 1:2) to afford the title compound (254 mg, 73.3%) as a light-yellow oil. LCMS m/z = 1028 $[\text{M}+\text{H}]^+$

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Synthesis of (R)-(1,2-dimethylpyrrolidin-2-yl)methanol (Intermediate 48)



Step 1: Synthesis of afford 1-(tert-butyl) 2-methyl (R)-2-methylpyrrolidine-1,2-dicarboxylate

[00268] To a solution of (R)-1-(tert-butoxycarbonyl)-2-methylpyrrolidine-2-carboxylic acid (500 mg, 2.18 mmol) in DMF (5 mL) was added K_2CO_3 (904 mg, 6.54 mmol) followed by MeI (0.18 mL, 2.84 mmol) at 0°C. The reaction mixture was stirred at rt for 16 h, then diluted with ice-cold water (5 mL) and extracted with EtOAc (3 x 20 mL). The organic phase was washed with sat. NaCl (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure, to yield the title compound (400 mg, 74.9%) as pale-yellow oil. LCMS m/z = 144 $[\text{M}+\text{H}-\text{Boc}]^+$.

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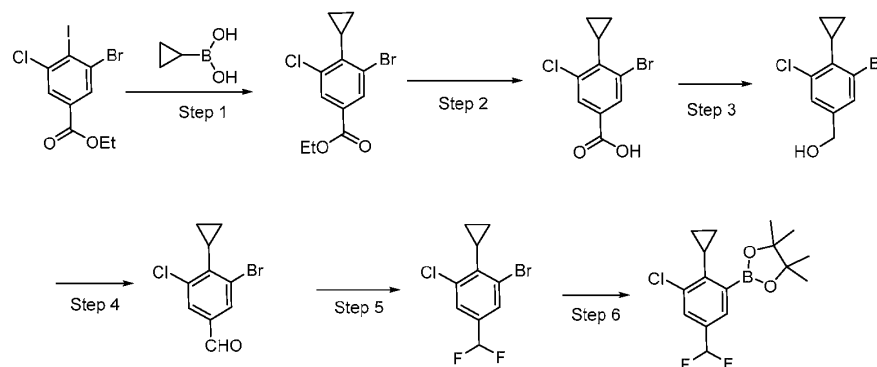
Step 2: Synthesis of (R)-(1,2-dimethylpyrrolidin-2-yl)methanol

[00269] To a solution of the compound of Step 1 (300 mg, 1.23 mmol) in THF (5 mL) was added LiAlH_4 (2M in THF) (3.08 mL, 6.17 mmol) at 0°C. The reaction mixture was stirred at rt for 16 h, then quenched with sat. Na_2SO_4 (3 mL) and diluted with 5% MeOH in DCM (20 mL). The mixture was filtered through Celite® and washed with 5% MeOH/DCM (2 x 20 mL). The

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filtrate was dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the title compound (155 mg, 82%) as a pale -yellow oil. LCMS $m/z = 130$ $[\text{M}+\text{H}]^+$.

Synthesis of 2-(3-chloro-2-cyclopropyl-5-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Intermediate 49)



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Step 1: Synthesis of 3-bromo-5-chloro-4-cyclopropylbenzoate

[00270] The title compound was obtained as a pale-yellow solid, 0.61 g, 18.9%, from ethyl 3-bromo-5-chloro-4-iodobenzoate and cyclopropylboronic acid, following a similar procedure to that described in Intermediate 42, step 1. LCMS $m/z = 305$ $[\text{M}+\text{H}]^+$.

10 *Step 2: Synthesis of 3-bromo-5-chloro-4-cyclopropylbenzoic acid*

[00271] To a solution of the title compound of Step 1 (2.32 g, 7.64 mmol) in a mixture of THF (17.5 mL) and water (7.5 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (0.96 g, 22.9 mmol) and the reaction mixture was stirred at rt for 16 h, then diluted with water (20 mL) and the pH adjusted to 2 ~3 with HCl (1.5 N). The mixture was extracted with EtOAc (3 x 30 mL). The organic phase was washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the title compound (2.1 g, 99%) as an off-white solid. LCMS $m/z = 274$ $[(\text{M}+\text{H})]^+$

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Step 3: Synthesis of (3-bromo-5-chloro-4-cyclopropylphenyl)methanol

[00272] To a solution of the title compound of Step 2 (2.1 g, 7.62 mmol) in THF (21 mL) was added borane THF complex (15.2 mL, 15.2 mmol) at 0°C under N_2 . The reaction mixture was stirred at rt for 16 h, then diluted with water (20 mL). The pH was adjusted to 2~3 with HCl (1.5N) and extracted with EtOAc (3 x 30mL). The organic layers were washed with brine (40 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the title compound (1.5 g, 74.8%) as pale yellow solid. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$): δ 7.52 (s, 1H),

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7.37 (s, 1H), 5.38 (t, 1H), 4.45 (d, 2H), 1.99-1.73 (m, 1H), 1.18-1.12 (m, 2H), 0.65-0.55 (m, 2H).

Step 4: Synthesis of 3-bromo-5-chloro-4-cyclopropylbenzaldehyde

[00273] To a solution of the title compound of Step 3 (400 mg, 1.53 mmol) in DCM (8 mL) was added pyridinium chlorochromate (494 mg, 2.29 mmol) and the reaction mixture was stirred at 0°C for 1 h. The mixture was diluted with DCM (10 mL) and filtered through Celite® and washed with DCM (3 x 20 mL). The organic phase was washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0-100% EtOAc in hexane) to afford the title compound (300 mg, 73.3%) as a pale yellow solid. ¹H-NMR (400 MHz, CDCl₃): δ 9.90 (s, 1H), 7.97 (d, 1H), 7.82 (d, 1H), 1.88-1.81 (m, 1H), 1.31-1.26 (m, 2H), 0.87-0.83 (m, 2H),

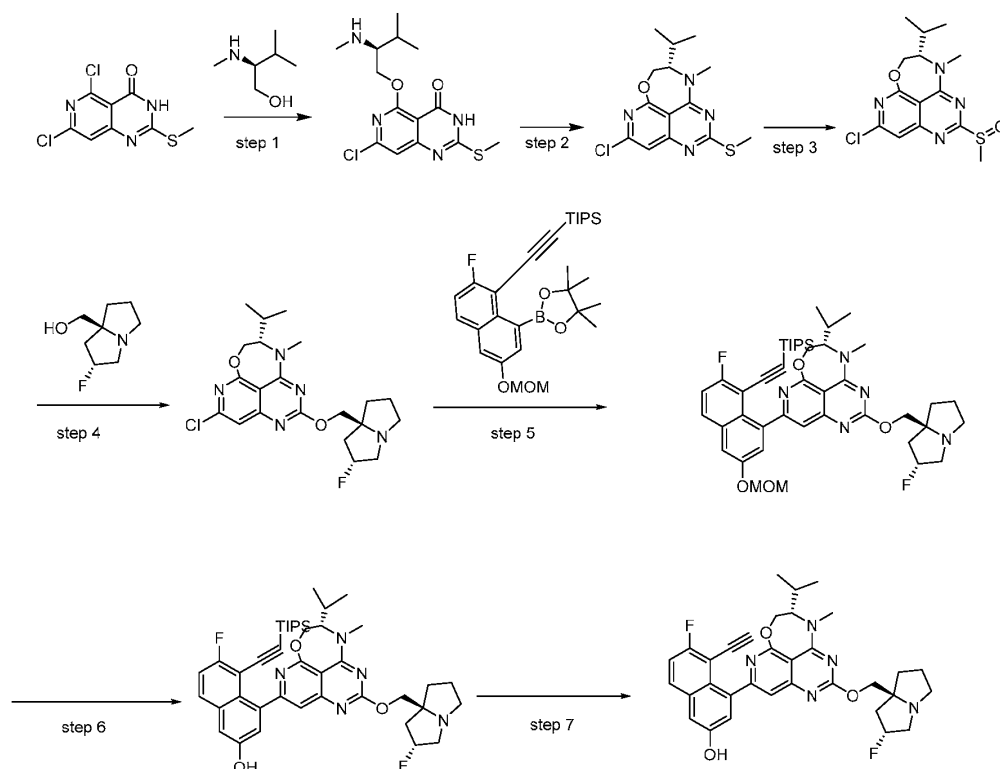
Step 5: Synthesis of 1-bromo-3-chloro-2-cyclopropyl-5-(difluoromethyl)benzene

[00274] To a solution of the title compound of Step 4 (300 mg, 1.16 mmol) in DCM (6 mL) was added DAST (0.46 mL, 3.47 mmol) at -78°C. The reaction mixture was stirred at rt for 16 h, then diluted with 10% NaHCO₃ solution (20 mL) and extracted with DCM (3 x 20 mL). The organic phase was washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound (270 mg, 83%) as a pale brown oil. ¹H-NMR (400 MHz, CDCl₃): δ 7.63 (d, 1H), 7.47 (d, 1H), 6.70-6.42 (m, 1H), 1.83-1.78 (m, 1H), 1.30-1.21 (m, 2H), 0.86-0.78 (m, 2H).

Step 6: Synthesis of 2-(3-chloro-2-cyclopropyl-5-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

[00275] The title compound was obtained as a pale-yellow oil (200 mg, 66.5%), from the compound from Step 5, following a similar procedure to that described in Intermediate 20. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 7.58-7.56 (m, 2H), 6.59 (t, 1H), 2.12-2.07 (m, 1H), 1.43 (s, 12H), 1.12-1.05 (m, 2H), 0.62-0.57 (m, 2H).

Example 1: Synthesis of 5-ethynyl-6-fluoro-4-((S)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-isopropyl-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 101)



Step 1: Synthesis of (S)-7-chloro-5-(3-methyl-2-(methylamino)butoxy)-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

[00276] (2S)-3-Methyl-2-(methylamino)butan-1-ol (536.5 mg, 4.58 mmol) was added to a suspension of NaH (534.1 mg, 13.35 mmol, 60%) in THF (10 mL) at 0°C under N₂ and the mixture was stirred for 10 min at 0°C. A solution of 5,7-dichloro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one (1 g, 3.82 mmol) in THF (10 mL) was added and the reaction mixture stirred for 1 h at 60°C. The reaction was cooled and quenched with ice-water (10 mL) at 0°C. The resulting mixture was extracted with EtOAc (3 x 30 mL), the combined organic layers were washed with brine (7 mL), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude product was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (0.1% TFA), 10% to 70% gradient in 10 min, to give the title compound (650 mg, 50%) as a brown solid. LCMS m/z = 343 [M+H]⁺

Step 2: Synthesis of (S)-5-chloro-9-isopropyl-10-methyl-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00277] PyBOP (1.14 g, 2.19 mmol) and TEA (1.18 g, 11.7 mmol) were added to a solution of (S)-7-chloro-5-(3-methyl-2-(methylamino)butoxy)-2-(methylthio)pyrido[4,3-d]pyrimidin-

4(3H)-one (500 mg, 1.46 mmol) in DCM (10 mL) and the reaction mixture was stirred at rt for 2 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (PE/EtOAc 1:1) to give the title compound (400 mg, 84.4%) as a white solid. LCMS m/z = 325 [M+H]⁺

5 *Step 3: Synthesis of (9S)-5-chloro-9-isopropyl-10-methyl-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

[00278] m-CPBA (106.3 mg, 0.62 mmol) was added to a solution of (S)-5-chloro-9-isopropyl-10-methyl-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (200 mg, 0.62 mmol) in DCM (6 mL) at -15°C under N₂ and the reaction mixture was stirred at -15°C for 1 h. The reaction was quenched with sat. NaHSO₃ (10 mL) at 0°C and the mixture extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (3x10mL), dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure to give the title compound (200 mg, crude). LCMS m/z = 341 [M+H]⁺

15 *Step 4: Synthesis of (S)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-isopropyl-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

[00279] NaH (88.4 mg, 2.21 mmol) was added to a solution of ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (117.3 mg, 0.74 mmol) in anhydrous THF (2 mL) at 0°C under N₂ and the mixture was stirred at 0°C for 10 min. A solution of (9S)-5-chloro-9-isopropyl-10-methyl-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (200 mg crude) in THF (5 mL) was added and the reaction mixture was stirred at rt for 1 h. The reaction was quenched with ice-water (5mL) and the mixture extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (3 x10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by reverse-phase column chromatography (C18 silica gel eluting with MeCN in water (10mmol/L NH₄HCO₃), 10% to 70% gradient in 10 min) to give the title compound (70 mg, 21.2%) as a white solid. LCMS m/z = 436 [M+H]⁺

25 *Step 5: Synthesis of (S)-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-isopropyl-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

[00280] A mixture of (S)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-isopropyl-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (70 mg, 0.16 mmol), cataCXium-A-Pd-G3 (23.4 mg, 0.032 mmol), K₃PO₄ (102.3 mg, 0.48 mmol) and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (164.6 mg, 0.32 mmol) in dioxane/H₂O (6 mL, v/v=5:1) was stirred for 2 h at 60°C under N₂. The cooled mixture was diluted with water (3mL), the mixture was extracted with DCM (10 x 5 mL), the combined organic layers were washed with brine (10 x 3 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The residue was purified by prep-TLC (DCM/MeOH 10:1) to afford the title compound (130 mg, 96.9%) as a yellow solid. LCMS m/z = 786 [M+H]⁺

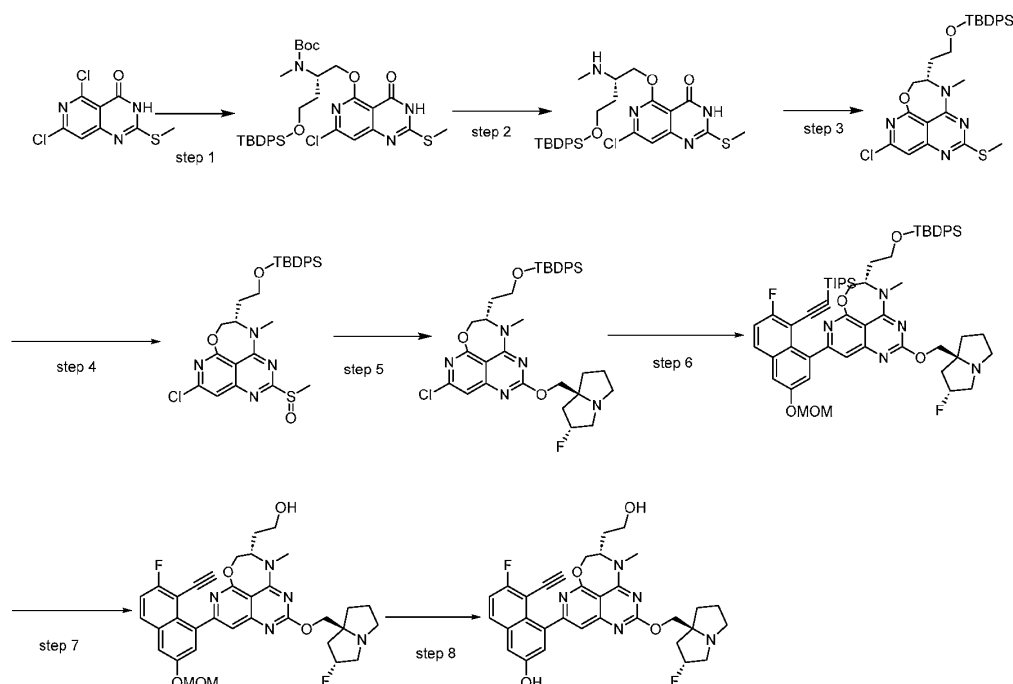
Step 6: Synthesis of 6-fluoro-4-((S)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-isopropyl-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol

[00281] A solution of (S)-5-(7-fluoro-3-(methoxymethoxy)-8-(((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-isopropyl-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (70 mg, 0.089 mmol) in 4N HCl in dioxane (2 mL) was stirred for 3h at rt under N₂. The resulting mixture was evaporated under reduced pressure to give the title compound (60 mg, crude). LCMS m/z = 742 [M+H]⁺

Step 7: Synthesis of 5-ethynyl-6-fluoro-4-((S)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-isopropyl-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol

[00282] CsF (194.5 mg, 1.28 mmol) was added to a solution of 6-fluoro-4-((S)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-isopropyl-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol (95 mg, 0.128 mmol) in anhydrous DMF (2 mL) and the reaction mixture was stirred for 2 h at rt under N₂. The reaction mixture was concentrated *in vacuo* and the residue purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (0.1% FA), 10% to 50% gradient in 10 min, to give the title compound (28.4 mg, 37.5%) as an off-white solid. LCMS m/z = 586 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.33 (s, 1H), 10.22 (d, 1H), 7.94 (dd, 1H), 7.45 (t, 1H), 7.34 (d, 1H), 7.20 (d, 1H), 7.13 (s, 1H), 4.81 (ddd, 1H), 4.63 (dq, 2H), 4.43 (dd, 1H), 3.81 (dt, 5H), 3.45 (s, 3H), 2.64 – 2.52 (m, 1H), 2.48 (s, 1H), 2.31 (dd, 1H), 2.26 – 2.00 (m, 4H), 1.01 (td, 6H).

Example 2: Synthesis of 5-ethynyl-6-fluoro-4-((S)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 103)



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Step 1: Synthesis of tert-butyl (S)-4-(((tert-butyldiphenylsilyl)oxy)-1-((7-chloro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)butan-2-yl)(methyl)carbamate

[00283] The title compound was obtained as a white solid, 209 mg, 7.7%, from 5,7-dichloro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one (Intermediate 1) and tert-butyl (S)-4-(((tert-butyldiphenylsilyl)oxy)-1-hydroxybutan-2-yl)(methyl)carbamate (Intermediate 7), following the procedure described in Example 1, step 1.

Step 2: Synthesis of (S)-5-(4-(((tert-butyldiphenylsilyl)oxy)-2-(methylamino)butoxy)-7-chloro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

[00284] TFA (5 mL) was added to a stirred solution of tert-butyl (S)-4-(((tert-butyldiphenylsilyl)oxy)-1-((7-chloro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)butan-2-yl)(methyl)carbamate (300 mg, 0.44 mmol) in DCM (20 mL) and the reaction mixture was stirred for 1 h at rt under N₂. The resulting mixture was evaporated under reduced pressure to afford the title compound (400 mg crude) as a yellow oil. LCMS m/z = 583 [M+H]⁺

Steps 3 to 5: Synthesis of (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00285] The title compound was obtained from (S)-5-(4-((tert-butyldiphenylsilyl)oxy)-2-(methylamino)butoxy)-7-chloro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following the same 3 step procedure described in Example 1, steps 2 to 4. LCMS m/z = 676 [M+H]⁺

Step 6: Synthesis of (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00286] The title compound was obtained as a yellow oil, 30 mg, 98.8%, from (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane, following a similar procedure to that described in Example 1, step 5. LCMS m/z = 1026 [M+H]⁺

Step 7: Synthesis of 2-((S)-5-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

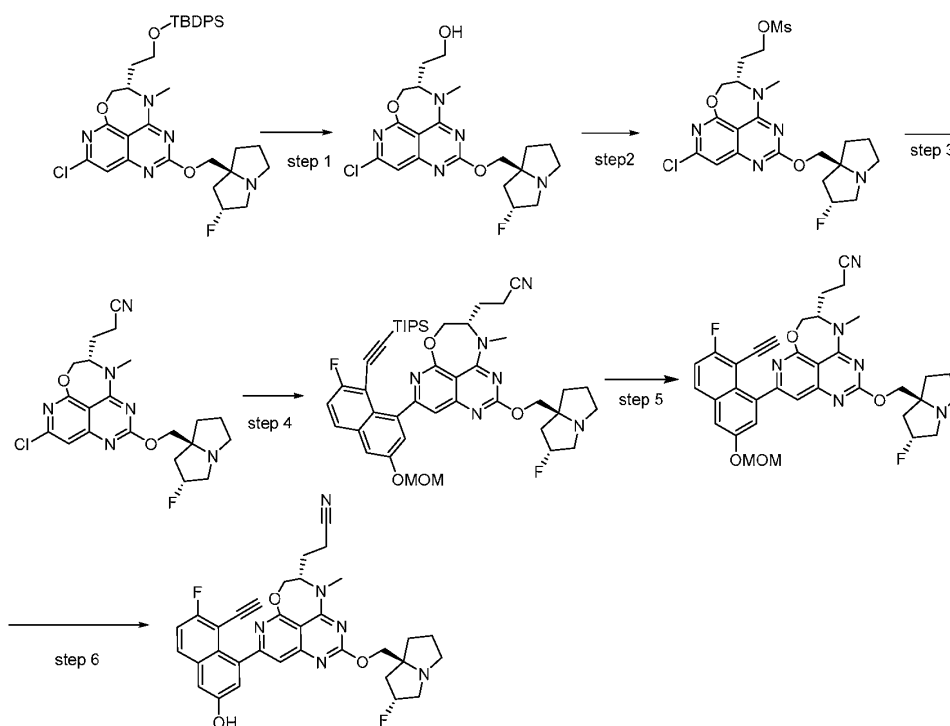
[00287] The title compound was obtained as a white solid, 15 mg, 81.3%, from (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene, following a similar procedure to that described in Example 1, step 7. LCMS m/z = 632 [M+H]⁺

Step 8: Synthesis of 5-ethynyl-6-fluoro-4-((S)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol

[00288] To a solution of 2-((S)-5-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (15 mg, 0.024 mmol) in

DCM (2 mL) was added 4 N HCl in dioxane (5 mL) dropwise and the reaction mixture was stirred for 1h at rt. The mixture was concentrated *in vacuo* at rt and the crude product was purified by Prep-HPLC (Method A, 23% to 48% B in 8 min), to afford the title compound (3.6 mg, 25.5%) as a white solid. LCMS m/z = 588 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.06 (s, 2H), 7.92 (dd, 2H), 7.43 (t, 1H), 7.30 (d, 1H), 7.21 – 7.04 (m, 1H), 7.02 (s, 1H), 5.28 (d, 2H), 4.74 (t, 1H), 4.72 – 4.53 (m, 1H), 4.43 (d, 1H), 4.20 – 3.88 (m, 4H), 3.56 (d, 2H), 3.17 – 3.05 (m, 2H), 3.02 (s, 1H), 2.83 (q, 1H), 2.12 (d, 1H), 2.02 (d, 2H), 1.92 – 1.64 (m, 5H).

Example 3: Synthesis of 3-((S)-5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)propanenitrile (Compound 105)



Step 1: Synthesis of 2-((S)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

[00289] To a solution of (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (Example 2, step 5) (150 mg, 0.22 mmol) in anhydrous DMF (7.50 mL) was added CsF (336.9 mg, 2.22 mmol) and the reaction

mixture was stirred for 1h at rt. The mixture was concentrated *in vacuo* and the residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (10 mmol/NH₄HCO₃), 10% to 50% gradient in 10 min, to afford the title compound (80 mg, 82.4%) as a white solid. LCMS m/z = 438 [M+H]⁺

- 5 *Step 2: Synthesis of 2-((S)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethyl methanesulfonate*

[00290] To a solution of 2-((S)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-
10 tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (40 mg, 0.09 mmol) and TEA (37.0 mg, 0.36 mmol) in DCM (4 mL) was added methanesulfonic anhydride (23.87 mg, 0.137 mmol) dropwise at 0°C under N₂ and the reaction mixture was stirred for 2h at 0°C. The reaction was quenched with water (2mL) and the mixture was extracted with DCM (3 x 10 mL). The combined organic layer was washed with brine (3 x 10 mL), dried over
15 anhydrous Na₂SO₄, filtered and evaporated under reduced pressure, to afford the title compound, 46 mg, crude. LCMS m/z = 516 [M+H]⁺

Step 3: Synthesis of 3-((S)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)propanenitrile

20 [00291] To a solution of 2-((S)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethyl methanesulfonate (46 mg, 0.09 mmol) and KI (119.6 mg, 0.72 mmol) in DMSO (4 mL) was added KCN (42.3 mg, 0.65 mmol) and the reaction mixture was stirred for 2 h at 100°C. The cooled reaction mixture was diluted with
25 water (10 mL) and the mixture extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with sat. FeSO₄ to remove excess KCN then washed with brine (3 x 10 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (10 mmol/L NH₄CO₃), 10% to 50% gradient in 10 min, to afford the title compound (23 mg, 57.7%) as a white solid. LCMS
30 m/z = 447 [M+H]⁺

Step 4: Synthesis of 3-((S)-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-

7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)propanenitrile

[00292] The title compound was obtained as a brown solid, 30 mg, 84.1%, from 3-((S)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)propanenitrile and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane, following a similar procedure to that described in Example 1, step 5. LCMS m/z = 797 [M+H]⁺

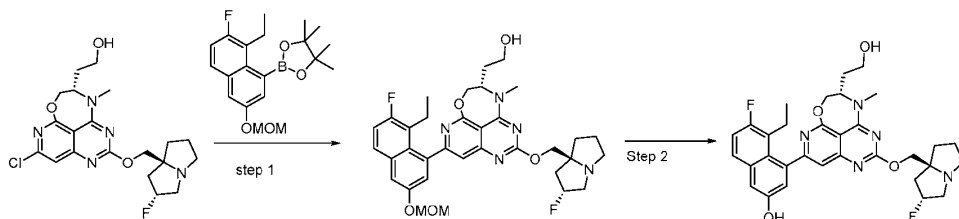
Step 5: Synthesis of 3-((S)-5-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)propanenitrile

[00293] The title compound was obtained as a white solid, from 3-((S)-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)propanenitrile, following the procedure described in step 1. LCMS m/z = 641 [M+H]⁺

Step 6: Synthesis of 3-((S)-5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)propanenitrile

[00294] To a solution of 3-((S)-5-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)propanenitrile (18 mg, 0.028 mmol) in DCM (5 mL) was added TFA (1 mL) dropwise at 0°C and the reaction mixture was stirred for 1.5 h at 0°C. The mixture was concentrated *in vacuo* and the crude product was purified by prep-HPLC (Method C, Gradient: 15% to 30% B in 8 min), to afford the title compound (4.5 mg, 26.3%) as a white solid. LCMS m/z = 596 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.77 (s, 1H), 10.13 (d, 1H), 7.94 (dd, 1H), 7.45 (t, 1H), 7.33 (d, 1H), 7.13 (d, 2H), 5.58 (d, 1H), 4.86 – 4.65 (m, 1H), 4.58 (q, 2H), 4.45 (dd, 1H), 4.15 – 4.04 (m, 1H), 4.06 – 3.88 (m, 2H), 3.81 (d, 3H), 2.74 (dd, 2H), 2.29 (s, 1H), 2.27 – 2.10 (m, 2H), 2.02 (q, 3H).

Example 4: Synthesis of 5-ethyl-6-fluoro-4-((S)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 104)



Step 1: Synthesis of 2-((S)-5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

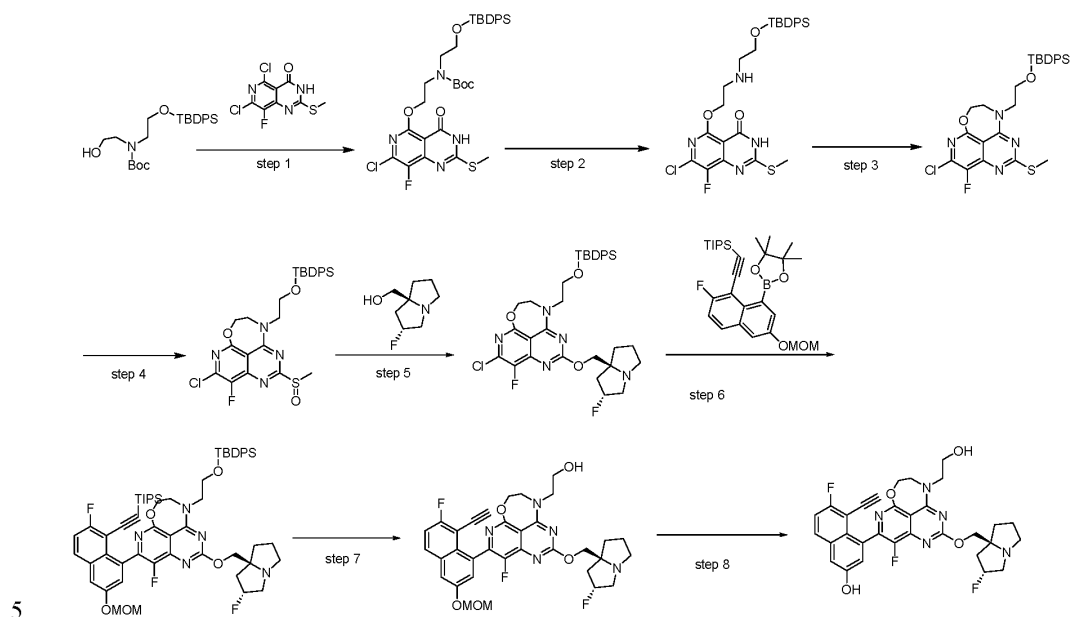
[00295] A mixture of 2-((S)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (Example 3, step 1) (20 mg, 0.046 mmol), cataCXium A Pd G3 (6.65 mg, 0.009 mmol), K_3PO_4 (38.78 mg, 0.184 mmol) and 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (24.7 mg, 0.069 mmol) in dioxane (3 mL) and H_2O (0.3 mL) was stirred for 1 h at $100^\circ C$ under N_2 . The cooled mixture was concentrated *in vacuo* and the residue was purified by reverse-phase column chromatography (C18 silica gel, eluting with MeCN in water (10mmol/L NH_4HCO_3), 10% to 50% gradient in 10 min), to afford the title compound (23 mg, 79.2%) as a white solid.

LCMS $m/z = 636 [M+H]^+$

Step 2: Synthesis of 5-ethyl-6-fluoro-4-((S)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol

[00296] To a solution of 2-((S)-5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (30 mg, 0.047 mmol) in DCM (1 mL) was added TFA (0.2 mL) dropwise and the reaction mixture was stirred for 0.5 h at $0^\circ C$. The mixture was concentrated under reduced pressure and the crude product was purified by prep-HPLC (Method A, Gradient: 27% to 52% B in 7 min), to give the title compound (6.5 mg, 22.7%) as a white solid. LCMS $m/z = 592 [M+H]^+$ 1H NMR (400 MHz, $DMSO-d_6$) δ 9.88 (s, 1H), 7.80 – 7.56 (m, 1H), 7.39 – 7.13 (m, 2H), 7.19 – 6.79 (m, 2H), 5.45 – 5.11 (m, 1H), 4.88 – 4.56 (m, 2H), 4.48 (d, 1H), 4.22 – 4.06 (m, 2H), 3.99 (d, 1H), 3.55 (s, 2H), 3.16 – 2.94 (m, 3H), 2.90 – 2.72 (m, 1H), 2.46 – 2.25 (m, 1H), 2.14 (ddd, 2H), 2.09 – 1.93 (m, 2H), 1.95 – 1.36 (m, 5H).

Example 5: Synthesis of 2-(5-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol (Compound 106)



Steps 1 and 2: Synthesis of 5-(2-((2-((tert-butyldiphenylsilyl)oxy)ethyl)amino)ethoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

[00297] The title compound was obtained from tert-butyl 2-((tert-butyldiphenylsilyl)oxy)ethyl(2-hydroxyethyl)carbamate (Intermediate 2) and 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one, following the same 2 step procedure described in Example 2, steps 1 and 2. LCMS $m/z = 587$ $[M+H]^+$

Step 3: Synthesis of 10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00298] TEA (499.8 mg, 4.94 mmol) and PyBOP® (771.1 mg, 1.48 mmol) were added to a solution of 5-(2-((2-((tert-butyldiphenylsilyl)oxy)ethyl)amino)ethoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one (580 mg, 0.99 mmol) in DCM (10 mL) and the reaction mixture was stirred at rt overnight under N_2 . The reaction mixture was concentrated *in vacuo* and the residue was purified by prep-TLC (DCM / MeOH 20:1) to afford the title compound (230 mg, 40.9 %) as a brown solid. LCMS $m/z = 569$ $[M+H]^+$

Steps 4 to 6: Synthesis of 10-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

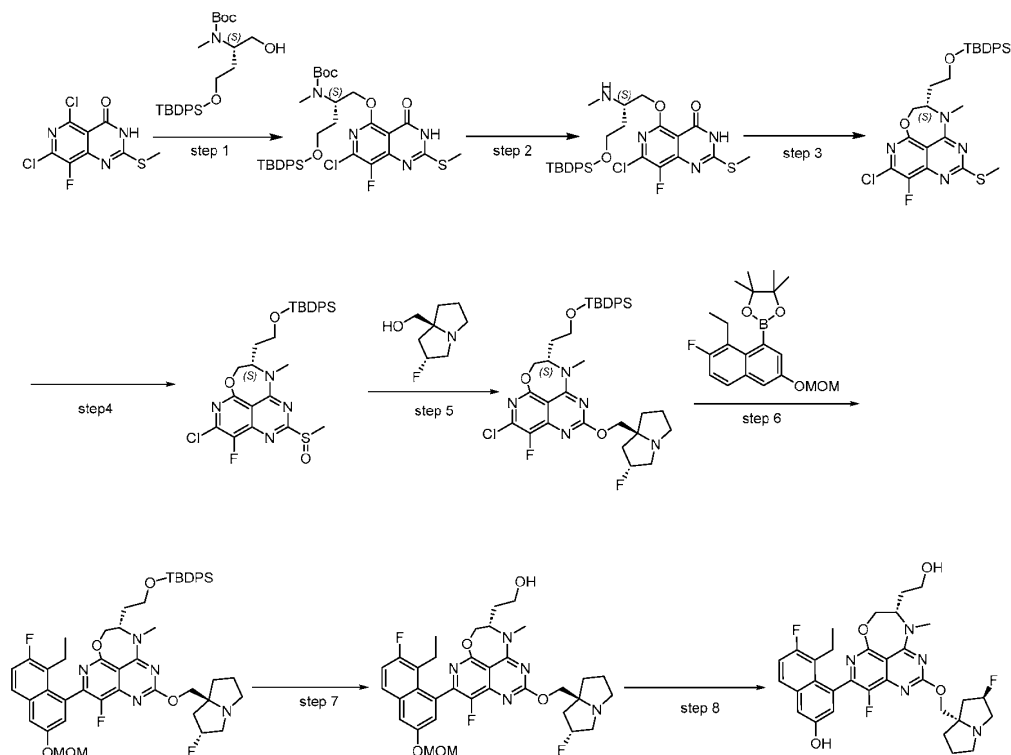
- 5 **[00299]** The title compound was obtained from 10-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene, ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane, following the same 3 step procedure described in
- 10 Example 1, steps 3 to 5. LCMS $m/z = 1030 [M+H]^+$

Steps 7 and 8: Synthesis of 2-(5-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol

- [00300]** The title compound was obtained as a white solid, from 10-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene,
- 15 following a similar 2 step procedure to that described in Example 3, steps 5 and 6. LCMS $m/z = 592 [M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 10.18 (s, 1H), 7.97 (dd, 1H), 7.46 (t, 1H), 7.38 (d, 1H), 7.15 (d, 1H), 5.55 (d, 1H), 4.90 (t, 1H), 4.57 (s, 3H), 4.15 – 3.98 (m, 4H), 3.88 – 3.66 (m, 5H), 2.30 (s, 2H), 2.09 (d, 4H), 1.35 – 1.12 (m, 1H).
- 20

Example 6: Synthesis of 5-ethyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 113)

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Steps 1 and 2: Synthesis of (S)-5-(4-((tert-butyldiphenylsilyl)oxy)-2-(methylamino)butoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one trifluoroacetate

- 5 **[00301]** The title compound was obtained from 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one and tert-butyl (S)-4-((tert-butyldiphenylsilyl)oxy)-1-hydroxybutan-2-yl(methyl)carbamate (Intermediate 7), following the same 2 step procedure as described in Example 2, step 1 and 2. LCMS $m/z = 601 [M+H]^+$

Step 3: Synthesis of (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-10-methyl-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- 10 **[00302]** PyBOP (233.7 mg, 0.45 mmol) was added to a solution of (S)-5-(4-((tert-butyldiphenylsilyl)oxy)-2-(methylamino)butoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one trifluoroacetate (180 mg, 0.30 mmol) and TEA (151.5 mg, 1.5 mmol) in DCM (2 mL) and the reaction mixture was stirred for 5 h at rt under N_2 . The reaction was quenched with water and the mixture extracted with DCM (3x10 mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column eluting

with PE / EtOAc (5:1) to afford the title compound (100 mg, 57.3%) as a white solid. LCMS $m/z = 583$ $[M+H]^+$

Step 4: Synthesis of (S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-10-methyl-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- 5 **[00303]** The title compound was obtained from (S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-10-methyl-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene, following the procedure described in Example 1, step 3. LCMS $m/z = 599$ $[M+H]^+$

- 10 *Step 5: Synthesis of (S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

- [00304]** A solution of (S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-10-methyl-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (50 mg, 0.083 mmol, and ((2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl)methanol (39.9 mg, 0.25 mmol) in toluene (1 mL) was stirred for 30 min at rt under N_2 , then cooled in an ice-bath. Sodium tert-butoxide (16.04 mg, 0.166 mmol) was added and the reaction mixture was stirred for 10 min at $0^\circ C$. The reaction was quenched with ice-water (5 mL) at $0^\circ C$ and the mixture extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4 , filtered and the filtrate concentrated *in vacuo*. The residue was purified by silica gel column chromatography, eluting with DCM/ MeOH (20:1) to afford the title compound (30 mg, 51.8%) as a white solid. LCMS $m/z = 694$ $[M+H]^+$

- 25 *Step 6: Synthesis of (S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

- [00305]** A mixture of (S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (25 mg, 0.036 mmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (25.94 mg, 0.072 mmol), K_3PO_4 (22.93 mg, 0.108 mmol) and cataCXium-A-Pd- G_3 (2.10 mg, 0.003 mmol) in dioxane/ H_2O (6 mL, v/v=5:1) was stirred for 1h at $100^\circ C$ under N_2 . The cooled reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column

chromatography, eluting with DCM / MeOH (15:1) to afford the title compound (20 mg, 62.3%) as a white solid. LCMS m/z = 892 [M+H]⁺

Step 7: Synthesis of 2-((S)-5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

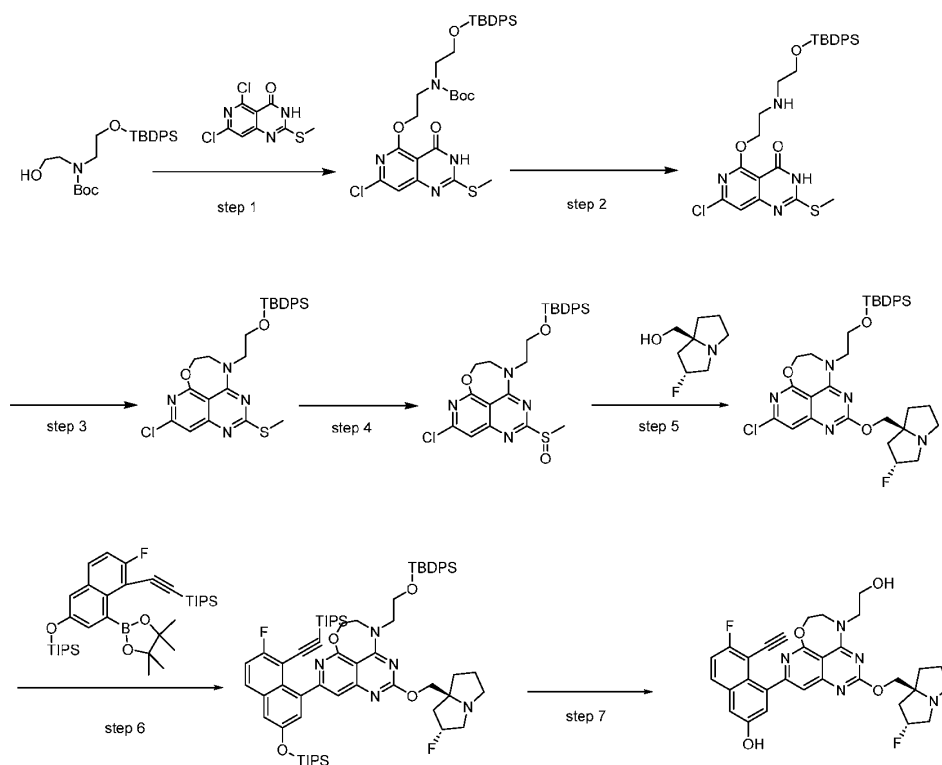
[00306] CsF (42.57 mg, 0.28 mmol) was added to a solution of (S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (25 mg, 0.028 mmol) in DMF (1 mL) and the reaction mixture was stirred for 30 min at 60°C under N₂. The cooled reaction mixture was purified directly by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (0.1% TFA), 60% to 70% gradient in 10 min, to give the title compound (10 mg, 54.%) as a white solid. LCMS m/z = 654 [M+H]⁺

Step 8: Synthesis of 5-ethyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol

[00307] TFA (0.2 mL) was added to a solution of 2-((S)-5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (10 mg, 0.015 mmol) in DCM (1 mL) and the reaction mixture was stirred for 30 min at rt under N₂. The mixture was concentrated *in vacuo* and the residue purified by prep-HPLC (Method B, Gradient: 20% B to 35% B in 7 min), to give the title compound (1.0 mg, 9.0%) as a yellow solid. LCMS m/z = 610 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.02 – 9.93 (m, 1H), 7.75 (dd, 1H), 7.39 – 7.29 (m, 1H), 4.75 – 4.52 (m, 2H), 4.52 – 4.43 (m, 1H), 2.19 (d, 2H), 2.05 (d, 1H), 1.80 (d, 1H), 1.24 (s, 1H), 0.80 (dt, 2H).

Example 7: Synthesis of 5-ethynyl-6-fluoro-4-(2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 102)

30



Step 1: Synthesis of tert-butyl (2-((tert-butyldiphenylsilyl)oxy)ethyl)(2-((7-chloro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)carbamate

- 5 **[00308]** tert-Butyl (2-((tert-butyldiphenylsilyl)oxy)ethyl)(2-hydroxyethyl)carbamate, Intermediate 2 (2 g, 4.51 mmol) was added to a suspension of NaH (378.6 mg, 15.78 mmol) in THF (10 mL) at 0°C and the mixture stirred for 15 mins. A solution of 5,7-dichloro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one, Intermediate 1 (1.18 g, 4.51 mmol) in THF (2 mL) was added dropwise at 0°C and the reaction mixture was stirred for 1 h at 60°C under
- 10 N₂. The cooled reaction was quenched with ice-water (10 mL) and the mixture extracted with EtOAc (25 mL x 3). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (0.1% TFA), 10% to 50% gradient in 10 min, to give the title compound (800 mg, 26.5%) as a white oil. LCMS m/z = 670 [M+H]⁺

- 15 Step 2: Synthesis of 5-(2-((tert-butyldiphenylsilyl)oxy)ethylamino)ethoxy-7-chloro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one trifluoroacetate

[00309] TFA (2.67 mL, 35.9 mmol) was added to a solution of tert-butyl (2-((tert-butyl)diphenylsilyl)oxy)ethyl(2-((7-chloro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)carbamate (800 mg, 1.2 mmol) in DCM (10 mL) and the reaction mixture was stirred for 0.5 h at rt under N₂. The mixture was evaporated under reduced pressure to give the title compound, crude, 600 mg. LCMS m/z = 570 [M+H]⁺

Step 3: Synthesis of 10-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-chloro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00310] TEA (231.1 mg, 2.29 mmol) and PyBOP® (356.6 mg, 0.69 mmol) were added to a solution of 5-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)amino)ethoxy)-7-chloro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one trifluoroacetate (260 mg, 0.457 mmol) in DCM (5 mL) and the reaction mixture was stirred overnight at rt under N₂. The solvent was removed under reduced pressure and the residue purified by prep-TLC (DCM / MeOH 20:1) to afford the title compound (170 mg, 67.5%) as a brown solid. LCMS m/z = 551 [M+H]⁺

Step 4: Synthesis of 10-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-chloro-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00311] m-CPBA (13.3 mg, 0.54 mmol) was added to a solution of 10-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-chloro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (300 mg, 0.544 mmol) in DCM (10 mL) at -15°C and the reaction mixture stirred at this temperature for 1 h. The reaction was quenched with Na₂SO₃ solution and extracted with DCM (3x10 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over Na₂SO₄ and evaporated under reduced pressure to give the title compound (200 mg, 64.8%) as a brown solid. LMS m/z = 267 [M+H]⁺

Step 5: Synthesis of 10-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00312] ((2R,7aS)-2-Fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (61.75 mg, 0.39 mmol) was added to a suspension of NaH (25.4 mg, 1.06 mmol) in anhydrous THF (5 mL) at 0°C and the mixture stirred for 15 min at 0°C under N₂. A solution of 10-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-chloro-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (200 mg, 0.35 mmol) in THF (2 mL) was added dropwise at 0°C and the reaction mixture was stirred for 1 h at rt. The reaction was quenched with water (5mL) at 0°C and then extracted with EtOAc (3 x 20mL). The combined organic layers were washed with brine (2x10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated *in*

vacuo. The residue was purified by prep-TLC (DCM / MeOH 20:1) to afford the title compound (100 mg, 77.9%) as a white solid. LCMS m/z = 662 [M+H]⁺

Step 6: Synthesis of 10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00313] A mixture of 10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (70 mg, 0.11 mmol), ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane (132.1 mg, 0.212 mmol), cataCXium-A-Pd-G3 (15.40 mg, 0.021 mmol) and K₃PO₄ (67.31 mg, 0.318 mmol) in dioxane/H₂O (5 mL, v/v=4:1) was stirred for 1h at 80°C under N₂. The cooled reaction was diluted with water (10 mL) and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (DCM / MeOH 20:1) to afford the title compound (75 mg, 63.1%) as a brown solid. LCMS m/z = 1124 [M+H]⁺

Step 7: Synthesis of 5-ethynyl-6-fluoro-4-(2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol

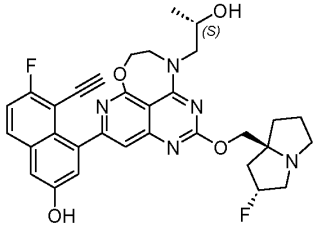
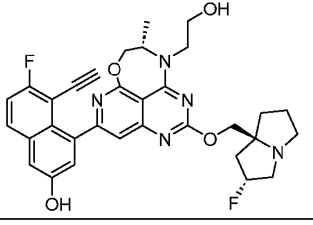
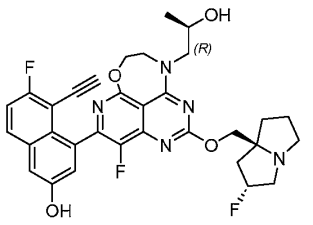
[00314] A mixture of 10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (70 mg, 0.062 mmol) and CsF (94.5 mg, 0.62 mmol) in anhydrous DMF (2 mL) was stirred for 1 h at 60°C under N₂. The reaction mixture was cooled to rt and purified by prep-HPLC (Method C, Gradient: 15% to 30% B in 7 min), to afford the title compound (12.6 mg, 24.0%) as a white solid. LCMS m/z = 574 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.36 – 10.59 (s, 1H), 8.15 (s, 1H), 7.92 (dd, 1H), 7.43 (t, 1H), 7.31 (d, 1H), 5.29 (d, 1H), 4.88 (s, 1H), 4.64 – 4.41 (m, 3H), 4.14 – 3.92 (m, 8H), 3.85 – 3.65 (m, 6H), 3.17 – 3.07 (m, 4H), 3.03 (s, 3H), 2.93 – 2.78 (m, 2H), 2.19 – 1.90 (m, 4H), 1.90 – 1.69 (m, 4H).

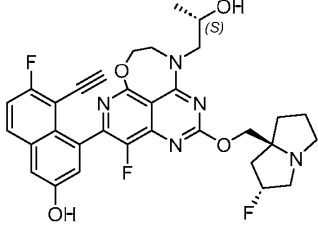
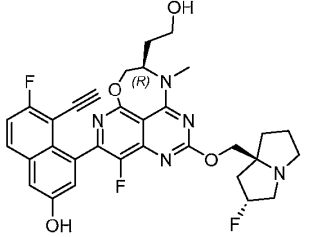
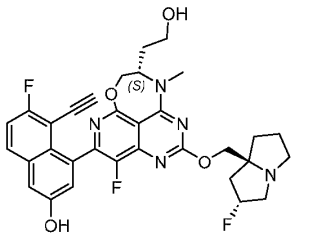
Examples 8 to 13

[00315] The compounds in Table 2 were obtained from the appropriate 5,7-dichloro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one, the appropriate alcohol, ((6-fluoro-4-(4,4,5,5-

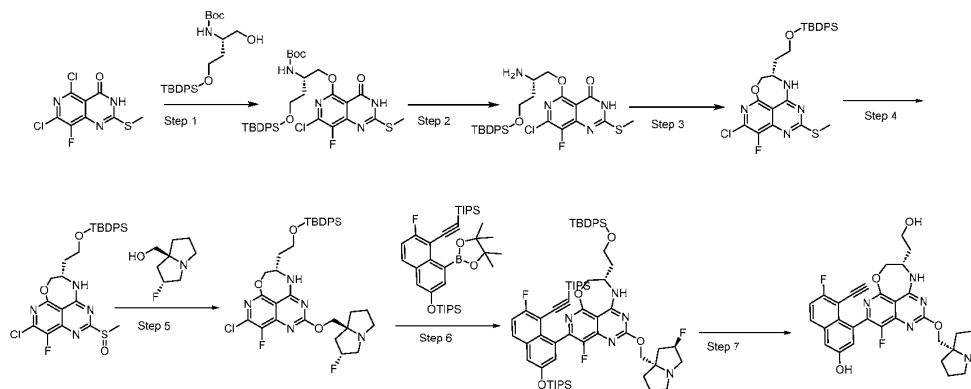
tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar 7 step procedure to that described in Example 7.

Table 2.

Example No	Name, Structure	Starting materials (SM) and Data
8 Compound 110	5-ethynyl-6-fluoro-4-((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((S)-2-hydroxypropyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol 	SM: Intermediate 1 and Intermediate 5. LCMS m/z = 588 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.15 (s, 1H), 7.92 (dd, 1H), 7.43 (t, 1H), 7.31 (d, 1H), 7.10 (d, 1H), 6.99 (s, 1H), 5.45 – 5.16 (m, 1H), 4.56 (q, 2H), 4.21 – 3.85 (m, 7H), 3.69 (d, 1H), 3.16 – 3.01 (m, 4H), 2.84 (td, 1H), 2.23 – 1.95 (m, 3H), 1.91 – 1.69 (m, 3H), 1.13 (d, 3H).
9 Compound 111	5-ethynyl-6-fluoro-4-((S)-2-((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol 	SM: Intermediate 1 and Intermediate 3. LCMS m/z = 588 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.09 (s, 1H), 7.92 (dd, 1H), 7.43 (t, 1H), 7.31 (d, 1H), 5.28 (d, 1H), 4.91 (s, 1H), 4.60 – 4.37 (m, 2H), 4.19 (dt, 1H), 4.10 – 3.92 (m, 3H), 3.80 (d, 2H), 3.18 – 3.00 (m, 4H), 2.12 – 1.94 (m, 3H), 1.90 – 1.65 (m, 3H), 1.27 (t, 3H).
10 Compound 107	5-ethynyl-6-fluoro-4-(4-fluoro-2-((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((R)-2-hydroxypropyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol 	SM: Intermediate 4 and 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one LCMS m/z = 606 $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 10.14 (s, 1H), 8.17 (s, 1H), 7.96 (dd, 1H), 7.46 (t, 1H), 7.37 (d, 1H), 7.14 (t, 1H), 5.47 – 5.16 (m, 2H), 4.64 – 4.48 (m, 2H), 4.26 – 3.95 (m, 7H), 3.91 (dd, 1H), 3.81 – 3.67 (m, 2H), 3.17 – 3.07 (m, 3H), 3.03 (d, 2H), 2.91 – 2.78 (m, 2H), 2.20 – 2.03 (m, 2H), 1.99 (tt, 1H), 1.92 – 1.70 (m, 3H), 1.14 (d, 3H).

11 Compound 109	5-ethynyl-6-fluoro-4-((4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((S)-2-hydroxypropyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol 	SM: Intermediate 5 and 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one LCMS m/z = 606 [M+H]⁺ ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.14 (s, 1H), 8.17 (s, 1H), 7.96 (dd, 1H), 7.46 (t, 1H), 7.37 (d, 1H), 7.14 (t, 1H), 5.47 – 5.16 (m, 2H), 4.64 – 4.48 (m, 2H), 4.26 – 3.95 (m, 7H), 3.91 (dd, 1H), 3.81 – 3.67 (m, 2H), 3.17 – 3.07 (m, 3H), 3.03 (d, 2H), 2.91 – 2.78 (m, 2H), 2.20 – 2.03 (m, 2H), 1.99 (tt, 1H), 1.92 – 1.70 (m, 3H), 1.14 (d, 3H).
12 Compound 108	5-ethynyl-6-fluoro-4-((R)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol 	SM: Intermediate 6 and 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one LCMS m/z = 606 [M+H]⁺ ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.15 (d, 1H), 7.96 (dd, 1H), 7.46 (td, 1H), 7.36 (t, 1H), 7.19 (d, 1H), 5.76 (s, 1H), 4.75 (s, 1H), 4.62 (ddd, 1H), 4.43 (dd, 1H), 4.19 – 3.93 (m, 4H), 3.56 (s, 2H), 3.38 (d, 3H), 3.15 – 3.04 (m, 2H), 3.02 (s, 1H), 2.83 (q, 1H), 2.13 (d, 1H), 2.07 – 1.95 (m, 2H), 1.90 – 1.70 (m, 4H).
13 Compound 112	5-ethynyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol 	SM: Intermediate 7 and 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one LCMS m/z = 606 [M+H]⁺ ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 8.19 (s, 1H), 7.95 (dd, 1H), 7.45 (td, 1H), 7.36 (d, 1H), 7.16 (dd, 1H), 5.28 (d, 1H), 4.62 (ddd, 1H), 4.43 (d, 1H), 4.13 (t, 2H), 4.08 – 3.92 (m, 2H), 3.56 (d, 3H), 3.14 – 3.08 (m, 2H), 3.02 (s, 2H), 2.83 (q, 1H), 2.14 (d, 1H), 2.10 – 1.96 (m, 2H), 1.82 (td, 5H).

Example 14: Synthesis of 5-ethynyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 114)



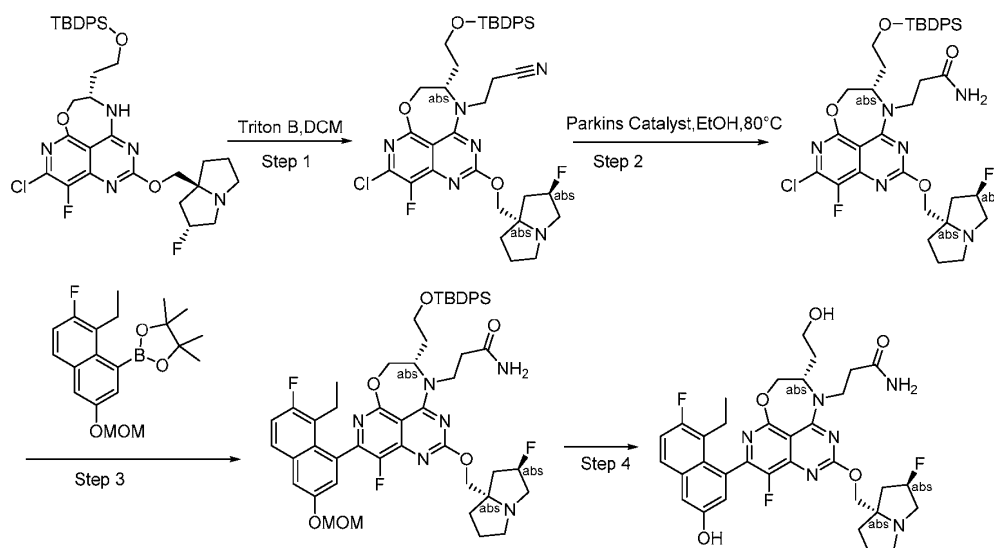
Steps 1 to 5: Synthesis of (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- 5 **[00316]** The title compound was obtained as a solid, from 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one, Intermediate 8 and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar 5 step procedure to that described in Example 7, steps 1 to 5. LCMS m/z = 680 $[M+H]^+$

- 10 Steps 6 and 7: Synthesis of 5-ethynyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol

- 15 **[00317]** The title compound was obtained as an off-white solid, from the compound from steps 1 to 5 and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane, following a similar 2 step procedure to that described in Example 7, steps 6 and 7. LCMS m/z = 592 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.22 (dd, 1H), 7.95 (dd, 1H), 7.45 (t, 1H), 7.36 (d, 1H), 7.16 (dd, 1H), 5.44 - 5.16 (m, 1H), 4.46 (d, 2H), 4.17 - 3.86 (m, 4H), 3.61 (d, 2H), 3.13 - 2.93 (m, 3H), 2.89 - 2.63 (m, 2H), 2.13 - 1.92 (m, 3H), 1.87 - 1.68 (m, 5H).

- 20 **Example 15: Synthesis of 3-((S)-5-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propenamide (Compound 178)**



Step 1: Synthesis of 3-((S)-9-(2-((tert-butyl)phenyl)silyl)oxy)ethyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanenitrile

- 5 **[00318]** To a stirred mixture of Example 14, steps 1 to 5, 230 mg, 0.34 mmol) and acrylonitrile (26.9 mg, 0.51 mmol) in DCM (5 mL) were added benzyltrimethylazanium oxidanide (11.31 mg, 0.07 mmol) and the reaction mixture was stirred for 2h at rt under N₂. The resulting mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (DCM / MeOH= 12:1) to afford the title compound (150 mg, 54.5%) as an off-white solid. LCMS m/z = 733 [M+H]⁺

Step 2: Synthesis of 3-((S)-9-(2-((tert-butyl)phenyl)silyl)oxy)ethyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide

- 15 **[00319]** A mixture of the compound from step 1 (30 mg, 0.041 mmol) and Parkin's catalyst (3.50 mg, 0.008 mmol) in EtOH (1 mL) was stirred for 2h at 80°C under N₂. The resulting mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (DCM / MeOH=10:1) to afford the title compound (20 mg, 59.9%) as a brown solid. LCMS m/z = 752 [M+H]⁺

- 20 Step 3: Synthesis of 3-((S)-9-(2-((tert-butyl)phenyl)silyl)oxy)ethyl)-5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-

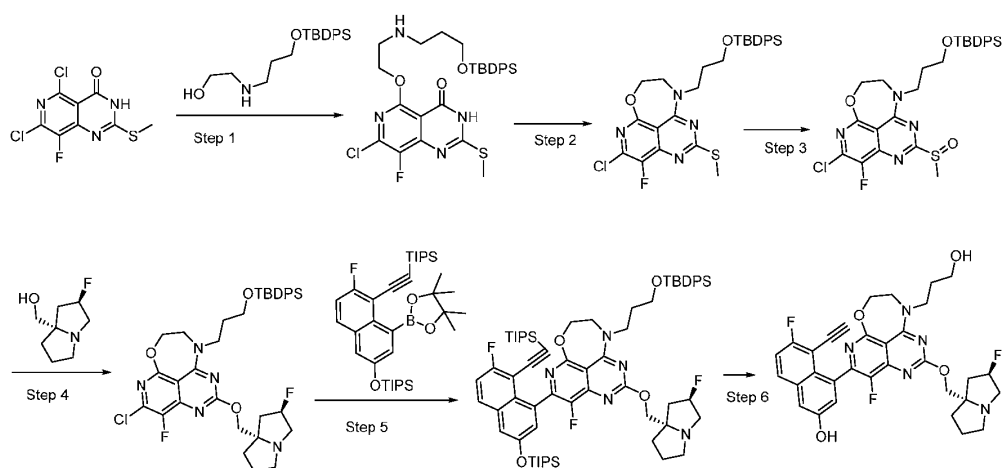
7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide

[00320] The title compound was obtained as a solid, 25 mg, 41.8%, from the compound from step 2 and 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, following a similar procedure to that described in Example 7, step 6.

Step 4: Synthesis of 3-((S)-5-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide

[00321] HCl in dioxane (1 mL) was added to a mixture of the compound from step 3 (30 mg, 0.032 mmol) in DCM (0.2 mL) and the reaction stirred for 1h at rt under N₂. The resulting mixture was concentrated under reduced pressure and the crude was purified by Prep-HPLC (Method D, Gradient: 11% B to 33% B in 7 min) to afford the title compound (3.1 mg, 11.8%) as an off-white solid. LCMS m/z = 713 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.76 (dd, 1H), 7.45 - 7.28 (m, 2H), 7.03 (dd, 1H), 5.66 - 5.23 (m, 2H), 4.69 - 4.65 (m, 1H), 4.39 - 4.35 (m, 2H), 4.33 - 4.22 (m, 3H), 3.76 - 3.57 (m, 3H), 3.46 - 3.17 (m, 3H), 2.98 - 2.93 (m, 1H), 2.87 - 2.71 (m, 1H), 2.63 - 2.60 (m, 1H), 2.45 - 2.41 (m, 2H), 2.35 - 2.27 (m, 1H), 2.24 - 2.18 (m, 2H), 2.11 - 2.02 (m, 2H), 2.98 - 2.02 (m, 3H), 1.85 - 1.72 (m, 2H), 1.51 - 1.40 (m, 1H).

Example 16: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(3-hydroxypropyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol formate (Compound 146)



Steps 1 to 3: Synthesis of 10-(3-((tert-butyl)di(phenyl)silyl)oxy)propyl)-5-chloro-4-fluoro-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00322] The title compound was obtained as a white solid, from Intermediate 11 and 5,7-dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one, following a similar 3 step procedure to that described in Example 1, steps 1 to 3. LCMS m/z = 599 [M+H]⁺

5 *Step 4: Synthesis of 10-(3-((tert-butyldiphenylsilyl)oxy)propyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

[00323] A solution of the compound from steps 1 to 3 (0.36 g, 0.60 mmol) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (0.29 g, 1.80 mmol) in toluene (5 mL) was stirred for 30 min at rt under N₂, then cooled to 0°C. NaOtBu (0.12 g, 1.20 mmol) was added
10 and the reaction mixture stirred for a further 30 min at 0°C. The resulting mixture was diluted with brine and extracted with EtOAc (3 x 10mL). The combined organic layers were washed with brine (3x10mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase column chromatography on C18 silica gel, eluting with MeCN : Water (10 mmol NH₄CO₃), 60% to 70% gradient in 10 min to
15 afford the title compound (0.176 g, 42.2%) as a white solid. LCMS m/z = 694 [M+H]⁺

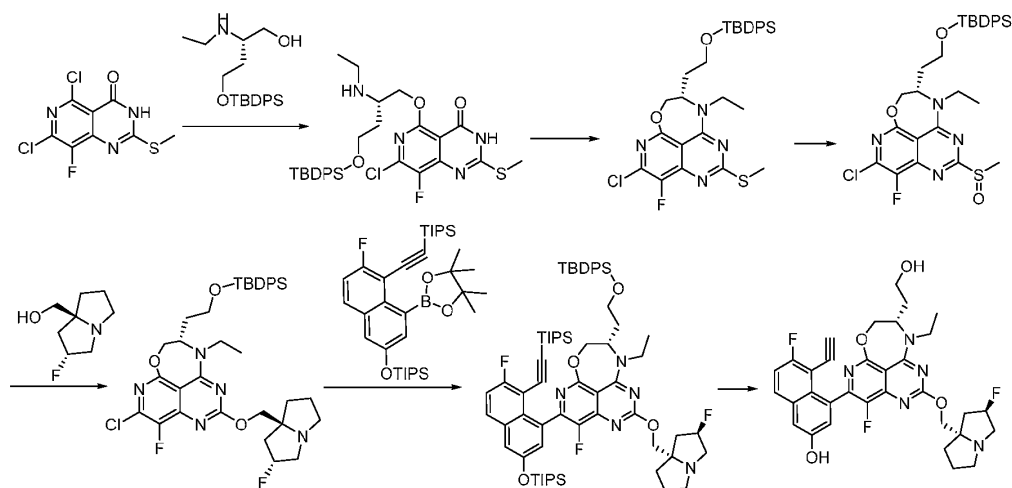
Step 5: Synthesis of 10-(3-((tert-butyldiphenylsilyl)oxy)propyl)-4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00324] To a stirred solution of the compound from step 4 (0.176 g, 0.25 mmol) and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane (237.6 mg, 0.38 mmol) in dioxane (4 mL) and H₂O (1 mL) were added K₃PO₄ (161.4 mg, 0.76 mmol) and cataCXium-A-Pd-G3 (18.46 mg, 0.025 mmol) and the reaction mixture was stirred for 1h at 80°C under N₂. The cooled mixture was diluted with brine
25 and extracted with EtOAc (3 x 20mL). The combined organic layers were washed with brine (3x20mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with MeOH: DCM (1:20) to afford the title compound (0.22 g, 74.7%) as an off-white solid. LCMS m/z = 615 [M+H]⁺

30 *Step 6: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(3-hydroxypropyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol formate*

[00325] To a stirred solution of the compound from step 5 (0.22 g, 0.19 mmol) in DMF (2 mL) was added CsF (0.43 g, 2.84 mmol) in portions at rt under N₂. The resulting mixture was stirred for 1h at 60°C under N₂, then cooled to rt. The resulting mixture was diluted with brine and extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (3x50mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by HPLC (Method D, Gradient: 15% B to 30% B in 7 min) to give the title compound (32.7 mg, 26.5%) as an off-white solid. LCMS m/z = 597 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 10.15 (br s, 1H), 8.15 (s, 1H), 7.96 (dd, 1H), 7.46 (t, 1H), 7.37 (d, 1H), 7.14 (d, 1H), 5.39 – 5.18 (m, 1H), 4.53 (t, 2H), 4.18 – 3.74 (m, 7H), 3.51 (t, 2H), 3.17 – 2.98 (m, 3H), 2.89 – 2.78 (m, 1H), 2.18 – 1.94 (m, 3H), 1.92 – 1.70 (m, 5H).

Example 17: Synthesis of 4-((S)-10-ethyl-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (Compound 138)



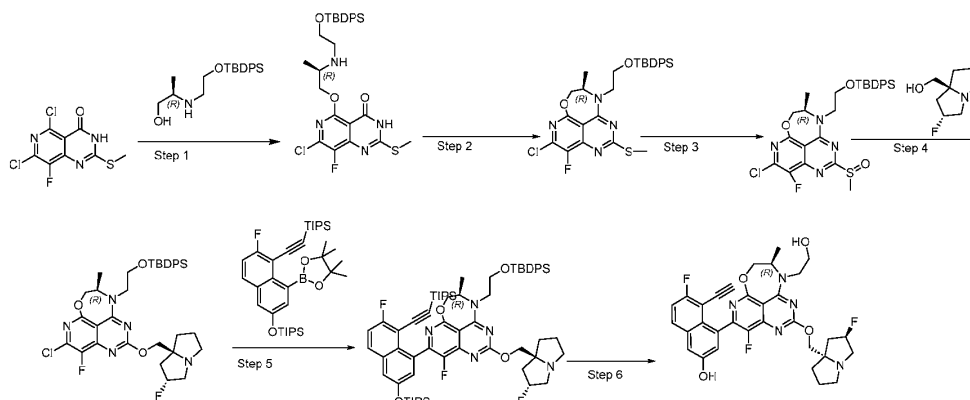
15

[00326] The title compound was obtained as a white solid, from Intermediate 14, 5,7-dichloro-8-fluoro-2-(methylsulfonyl)-3H-pyrido[4,3-d]pyrimidin-4-one, ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar 6 step process to that described in Example 16. LCMS m/z = 620 [M+H]⁺; 1H NMR (400 MHz, DMSO-d₆) δ 10.14 (s, 1H), 7.95 (dd, 1H), 7.46 (d, 1H), 7.36 (d, 1H), 7.19 (d, 1H), 5.39 – 5.17 (m, 1H), 4.84 – 4.57 (m, 2H), 4.38 – 4.19 (m, 2H), 4.19 – 3.92 (m, 4H),

20

3.55 (t, 3H), 3.16 – 2.96 (m, 3H), 2.84 (td, 1H), 2.19 – 1.93 (m, 3H), 1.91 – 1.68 (m, 5H), 1.36 – 1.19 (m, 3H).

Example 18: Synthesis of 5-ethynyl-6-fluoro-4-((R)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 119)



Steps 1 to 3: Synthesis of (9R)-10-(2-((tert-butyl(diphenyl)silyl)oxy)ethyl)-5-chloro-4-fluoro-9-methyl-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00327] The title compound was obtained as a white solid, from Intermediate 10 and 5,7-dichloro-8-fluoro-2-(methylsulfonyl)-3H-pyrido[4,3-d]pyrimidin-4-one, following a similar 3 step procedure to that described in Example 1, steps 1 to 3. LCMS $m/z = 599$ $[M+H]^+$

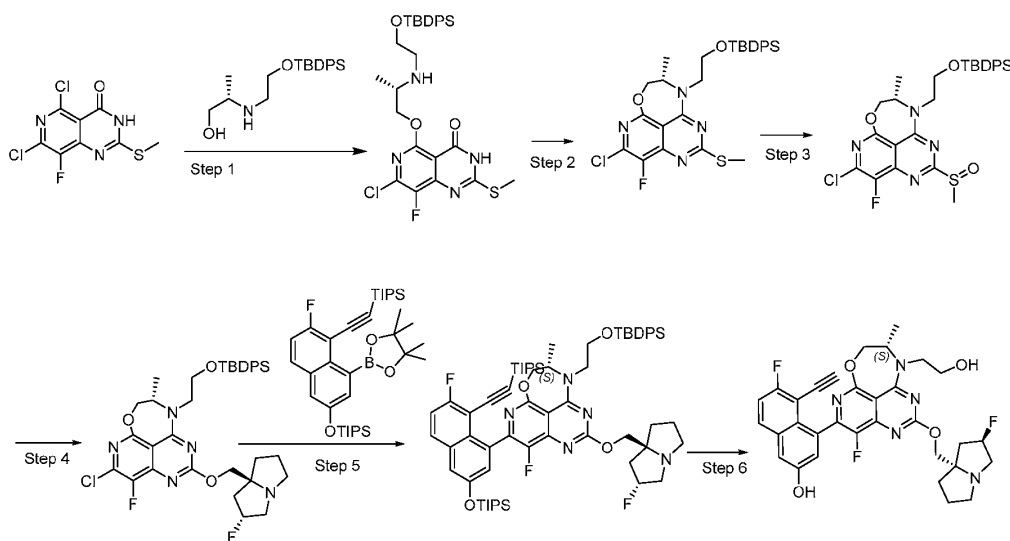
Step 4: Synthesis of (R)-10-(2-((tert-butyl(diphenyl)silyl)oxy)ethyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00328] A solution of the compound from steps 1 to 3 (1.36 g, 2.27 mmol) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (0.72 g, 4.54 mmol) in toluene (20 mL) was stirred for 30 min at rt under N₂. NaOtBu (0.65 g, 6.81 mmol) was added at 0°C and the resulting mixture was stirred for 10 min at 0°C under N₂. The reaction was quenched with water. The aqueous layer was extracted with DCM (3x30 mL), the combined organic layers were washed with brine (2x30 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH=15:1) to afford the title compound (400 mg, 25.4%) as a white solid. LCMS $m/z = 694$ $[M+H]^+$

Steps 5 to 6: Synthesis of 5-ethynyl-6-fluoro-4-((R)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol

[00329] The title compound was obtained as a yellow solid, from the compound from step 4 and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane, following a similar 2 step procedure to that described in Example 16, steps 5 and 6. LCMS $m/z = 668$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 10.10 (s, 1H), 7.95 (dd, 1H), 7.45 (td, 1H), 7.36 (d, 1H), 7.15 (dd, 1H), 5.21 (d, 1H), 4.88 (s, 1H), 4.55 (td, 1H), 4.41 (dd, 1H), 4.21 (dt, 3H), 4.12 - 3.95 (m, 4H), 3.91 - 3.73 (m, 2H), 3.13 - 2.99 (m, 3H), 2.84 (q, 1H), 2.17 - 1.94 (m, 3H), 1.80 (dt, 2H), 1.28 (d, 3H).

Example 19: Synthesis of 5-ethynyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 120)



Step 1: Synthesis of (S)-5-(2-((2-((tert-butyldiphenylsilyl)oxy)ethyl)amino)propoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

[00330] NaH (2.35 g, 58.7 mmol, 60%) was added slowly at 0°C to a solution of (S)-2-((2-((tert-butyldiphenylsilyl)oxy)ethyl)amino)propan-1-ol (Intermediate 3, step 1, 7 g, 19.6 mmol) in THF (100 mL) and the mixture was stirred for 10 min at 0°C under N_2 . 5,7-Dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one (10.97 g, 39.2 mmol)

in THF (20 mL) was added dropwise at 0°C and the reaction mixture was stirred for 1h at rt. The reaction was quenched with water at 0°C and the aqueous layer was extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase chromatography (column, C18 silica gel; mobile phase, MeOH in Water (0.1% TFA), 95% to 100% gradient in 10 min) to afford the title compound (4.6 g, 39.1%) as a white solid. LCMS m/z = 601 [M+H]⁺

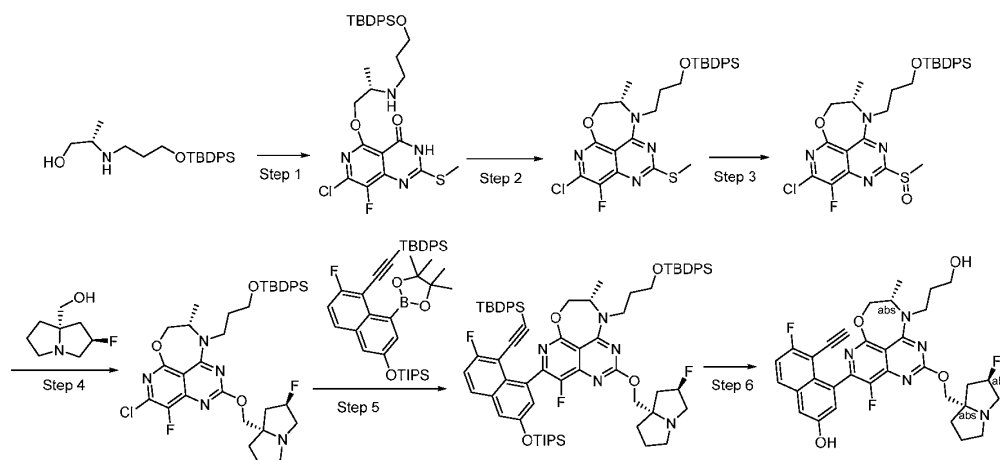
Steps 2 to 4: Synthesis of (S)-10-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00331] The title compound was obtained as a white solid, from the compound from step 1 and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar 2 step procedure to that described in Example 18, steps 2 to 4. LCMS m/z = 694 [M+H]⁺

Steps 5 to 6: Synthesis of 5-ethynyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol

[00332] The title compound was obtained as a white solid, from the compound from step 4 and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane, following a similar 2 step procedure to that described in Example 18, steps 5 to 6. LCMS m/z = 606 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 10.10 (s, 1H), 7.95 (dd, 1H), 7.52 – 7.31 (m, 2H), 7.15 (dd, 1H), 5.40 – 5.16 (m, 1H), 4.55 (td, 1H), 4.41 (dd, 1H), 4.28 – 4.16 (m, 2H), 4.11 (dd, 1H), 4.07 – 3.93 (m, 2H), 3.91 – 3.74 (m, 2H), 3.68 (dd, 1H), 3.58 (dt, 2H), 3.16 – 3.07 (m, 3H), 3.03 (s, 1H), 2.84 (q, 1H), 2.18 – 1.94 (m, 2H), 1.91 – 1.66 (m, 2H), 1.28 (d, 3H).

Example 20: Synthesis of 5-ethynyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(3-hydroxypropyl)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 145)



Step 1: Synthesis of (S)-5-(2-((3-((tert-butyldiphenylsilyl)oxy)propyl)amino)propoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

- [00333]** The title compound was obtained as a yellow solid, 3 g, 90.6%, from Intermediate 12 and 5,7-dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one, following a similar procedure to that described in Example 1, step 1. LCMS $m/z = 631$ [M+H]⁺

Step 2: Synthesis of (S)-10-(3-((tert-butyldiphenylsilyl)oxy)propyl)-5-chloro-4-fluoro-9-methyl-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- [00334]** The title compound was obtained as a white solid, 560 mg, 57.7%, from the compound from step 1, following a similar procedure to that described in Example 1, step 2, except the residue was purified by reverse-phase chromatography (column, C18; mobile phase, MeCN in Water (0.1% TFA), 10% to 100% gradient in 30 min. LCMS $m/z = 597$ [M+H]⁺

Step 3: Synthesis of (9S)-10-(3-((tert-butyldiphenylsilyl)oxy)propyl)-5-chloro-4-fluoro-9-methyl-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- [00335]** The title compound was obtained as a yellow solid, 830 mg, 89.8%, from the compound from step 2, following the procedure described in Example 7, step 4. LCMS $m/z = 613$ [M+H]⁺

- Step 4: Synthesis of (S)-10-(3-((tert-butyldiphenylsilyl)oxy)propyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

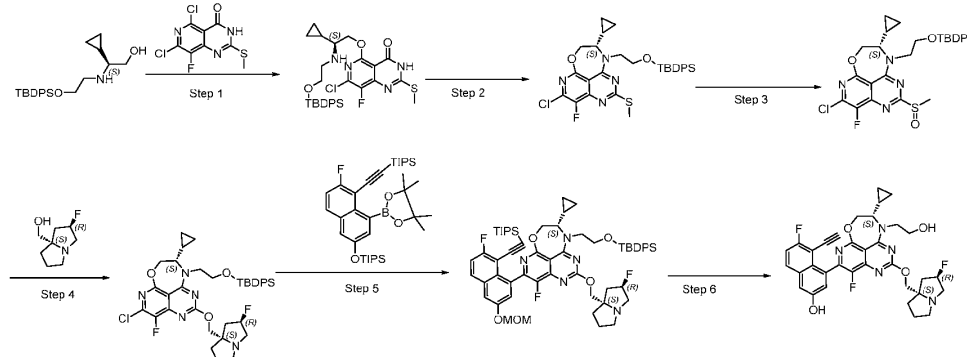
[00336] The title compound was obtained as a white solid, 135 mg, 14.3%, from ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol and the compound from step 3, following

a similar procedure to that described in Example 16, step 4, except reverse-phase chromatography (column, C18; mobile phase, MeCN in Water (0.1% TFA), 10% to 100% gradient in 10 min). LCMS $m/z = 708 [M+H]^+$

Steps 5 to 6: Synthesis of 5-ethynyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(3-hydroxypropyl)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol formate

[00337] The title compound was obtained as a white solid, from the compound from step 4 and tert-butyl((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-((triisopropylsilyl)oxy)naphthalen-1-yl)ethynyl)diphenylsilane, following a similar 2 step procedure to that described in Example 16, steps 5 and 6. LCMS $m/z = 620 [M+H]^+$. ¹H NMR (400 MHz, DMSO- d_6) δ 10.13 (s, 1H), 7.96 (dd, 1H), 7.46 (td, 1H), 7.37 (d, 1H), 7.15 (dd, 1H), 5.28 (d, 1H), 4.80 – 4.48 (m, 2H), 4.37 (dd, 1H), 4.29 – 3.93 (m, 5H), 3.50 (d, 3H), 3.19 – 2.94 (m, 3H), 2.83 (t, 1H), 2.19 – 1.62 (m, 8H), 1.37 – 1.09 (m, 3H).

Example 21: Synthesis of 4-((S)-9-cyclopropyl-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (Compound 144)



Step 1: Synthesis of (S)-5-(2-((2-((tert-butyldiphenylsilyl)oxy)ethyl)amino)-2-cyclopropylethoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

[00338] The title compound was obtained as a yellow solid, 100 mg, 30.6%, from Intermediate 13 and 5,7-dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one, following a similar procedure to that described in Example 19, step 1. LCMS $m/z = 627 [M+H]^+$

Step 2: Synthesis of (S)-10-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-5-chloro-9-cyclopropyl-4-fluoro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00339] To a stirred mixture of the compound from step 1 (250 mg, 0.4 mmol) and TEA (201.7 mg, 2.0 mmol) in DCM (3 mL) was added PyBOP® (311.1 mg, 0.6 mmol) dropwise 0 °C under N₂. The reaction mixture was irradiated with microwave radiation for 15 h at 0 °C. The resulting mixture was extracted with EtOAc (2 x 20 mL), the combined organic layers were washed with brine (2 x 20 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (1:1) to afford the title compound (210 mg) as an off-white solid. LCMS m/z = 609 [M+H]⁺

Step 3: Synthesis of (9S)-10-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-5-chloro-9-cyclopropyl-4-fluoro-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00340] The title compound was obtained from the compound from step 2, following the procedure described in Example 1, step 3. LCMS m/z = 625 [M+H]⁺

15 *Step 4: Synthesis of (S)-10-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-5-chloro-9-cyclopropyl-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

[00341] A solution of the compound from step 3 (190 mg, 0.3 mmol) in toluene (9.50 mL) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (193.5 mg, 1.22 mmol) was stirred for 30 min at rt under N₂. NaOtBu (58.4 mg, 0.61 mmol) was added portion wise at 0 °C and the reaction mixture was irradiated with microwave radiation for 10 min at 0 °C. The mixture was extracted with EtOAc (2 x 30 mL), the combined organic layers were washed with brine (2x20 mL) dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (PE / EtOAc 3:1) to afford the title compound (150 mg, 68.5%) as a white solid. LCMS m/z = 720 [M+H]⁺

Step 5: Synthesis of (S)-10-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-9-cyclopropyl-4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

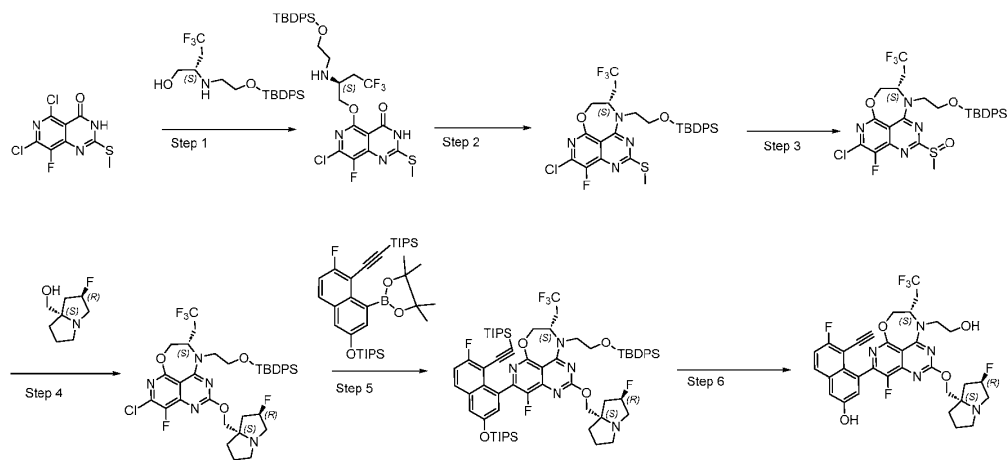
30 [00342] The title compound was obtained as a yellow solid, 95 mg, from the compound from step 4 and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-

((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane, following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 1070$ $[M+H]^+$

Step 6: Synthesis of 4-((S)-9-cyclopropyl-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol

[00343] The title compound was obtained as a white solid, 63.9 mg, 87.1%, from the compound from step 5, following a similar procedure to that described in Example 6, step 7. LCMS $m/z = 632$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 10.17 (d, 1H), 8.02 - 7.93 (m, 1H), 7.54 - 7.43 (m, 1H), 7.41 - 7.36 (m, 1H), 7.25 - 7.06 (m, 1H), 5.63 - 5.50 (m, 1H), 4.86 (s, 1H), 4.75 - 4.63 (m, 1H), 4.63 - 4.48 (m, 2H), 4.47 - 4.36 (m, 2H), 4.05 - 3.96 (m, 1H), 3.90 - 3.80 (m, 3H), 3.79 - 3.66 (m, 4H), 3.32 - 3.30 (m, 3H), 2.29 - 2.18 (s, 3H), 2.02 - 1.96 (m, 1H), 1.03 - 0.96 (m, 1H), 0.66 - 0.55 (m, 3H), 0.45 - 0.38 (m, 1H).

Example 22: Synthesis of 5-ethynyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-(2,2,2-trifluoroethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 169)



Steps 1 to 5: Synthesis of (S)-10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-fluoro-5-(7-fluoro-8-(((triisopropylsilyl)ethynyl)-3-(((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2,2,2-trifluoroethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00344] The title compound was obtained as a yellow solid, from Intermediate 16, 5,7-dichloro-8-fluoro-2-(methylsulfonyl)-3H-pyrido[4,3-d]pyrimidin-4-one, ((2R,7aS)-2-

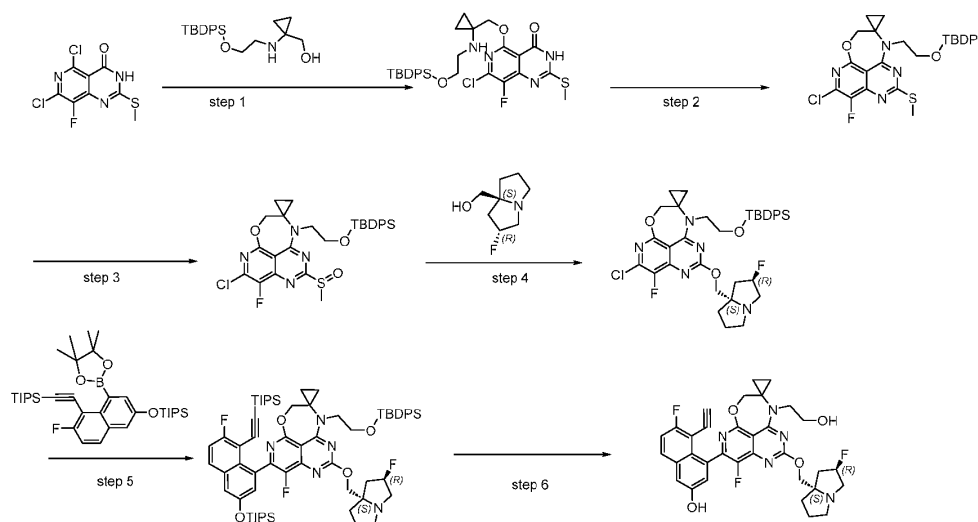
fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane, following a similar 5 step procedure to that described in Example 21, steps 1 to 5. LCMS m/z = 1224 $[M+H]^+$

- 5 *Step 6: Synthesis of 5-ethynyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-(2,2,2-trifluoroethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol*

[00345] The title compound was obtained as an off-white solid, 5.7 mg, 29.6%, from the product from steps 1 to 5, following a similar procedure to that described in Example 3, step 1.

- 10 LCMS m/z = 674 $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 10.76 (s, 1H), 10.18 (d, 1H), 7.98 (dd, 1H), 7.52 – 7.43 (m, 1H), 7.39 (t, 1H), 7.21 (d, 1H), 5.63 (s, 0.5H), 5.50 (s, 0.5H), 5.01 (s, 1H), 4.78 – 4.66 (m, 1H), 4.57 (dd, 3H), 4.50 (d, 1H), 4.38 (t, 1H), 4.03 (s, 1H), 3.87 (s, 1H), 3.78 (s, 5H), 2.83 (dd, 1H), 2.30 (d, 1H), 2.17 (s, 3H), 2.02 (s, 1H), 1.51 (d, 1H), 1.23 (s, 1H).

- Example 23: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-8H,10H-7-oxa-1,3,6,10-tetraazaspiro[cyclohepta[de]naphthalene-9,1'-cyclopropan]-1(10a),2,3a,3a1(6a),5-pentaen-5-yl)naphthalen-2-ol (Compound 170)**
- 15



- 20 *Step 1: Synthesis of 5-((1-((2-((tert-butyldiphenylsilyl)oxy)ethyl)amino)cyclopropyl)methoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one*

[00346] The title compound was obtained as a yellow solid, 170 mg, 38.1%, from Intermediate 9 and 5,7-dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one, following a similar procedure to that described in Example 1, step 4. LCMS m/z = 613 [M+H]⁺

5 *Step 2: Synthesis of 10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(methylthio)-8H,10H-7-oxa-1,3,6,10-tetraazaspiro[cyclohepta[de]naphthalene-9,1'-cyclopropan]-1(10a),2,3a,3a1(6a),5-pentaene*

[00347] The title compound was obtained as a white solid, 200 mg, 58.9%, from the compound from step 1, following the procedure described in Example 16, step 2. LCMS m/z = 595 [M+H]⁺

10 *Step 3: Synthesis of 10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(methylsulfinyl)-8H,10H-7-oxa-1,3,6,10-tetraazaspiro[cyclohepta[de]naphthalene-9,1'-cyclopropan]-1(10a),2,3a,3a1(6a),5-pentaene*

[00348] m-CPBA (126.1 mg, 0.73 mmol) was added to a solution of the compound from step 2 (290 mg, 0.49 mmol) in DCM (3 mL) at 0°C and the reaction mixture was stirred at rt for 15 min. The mixture was extracted with DCM (2 x 10mL), the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure to give the title compound (290 mg, crude) as a white solid. LCMS m/z = 985 [M+H]⁺

20 *Step 4: Synthesis of 10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8H,10H-7-oxa-1,3,6,10-tetraazaspiro[cyclohepta[de]naphthalene-9,1'-cyclopropan]-1(10a),2,3a,3a1(6a),5-pentaene*

[00349] ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (226.6 mg, 1.42 mmol) was added to a solution of the compound from step 3 (290 mg, 0.47 mmol) in toluene (5 mL) and the mixture was stirred at rt for 1h. NaOtBu (91.20 mg, 0.95 mmol) was added in portions and the reaction mixture was stirred at rt for 2h. The mixture was extracted with EtOAc (3 x 50mL), the combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (1:10) to afford the title compound (220 mg, 65.7%) as a colorless oil. LCMS m/z = 706 [M+H]⁺

30 *Step 5: Synthesis of 10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-*

fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8H,10H-7-oxa-1,3,6,10-tetraazaspiro[cyclohepta[de]naphthalene-9,1'-cyclopropan]-1(10a),2,3a,3a1(6a),5-pentaene

[00350] ((6-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-

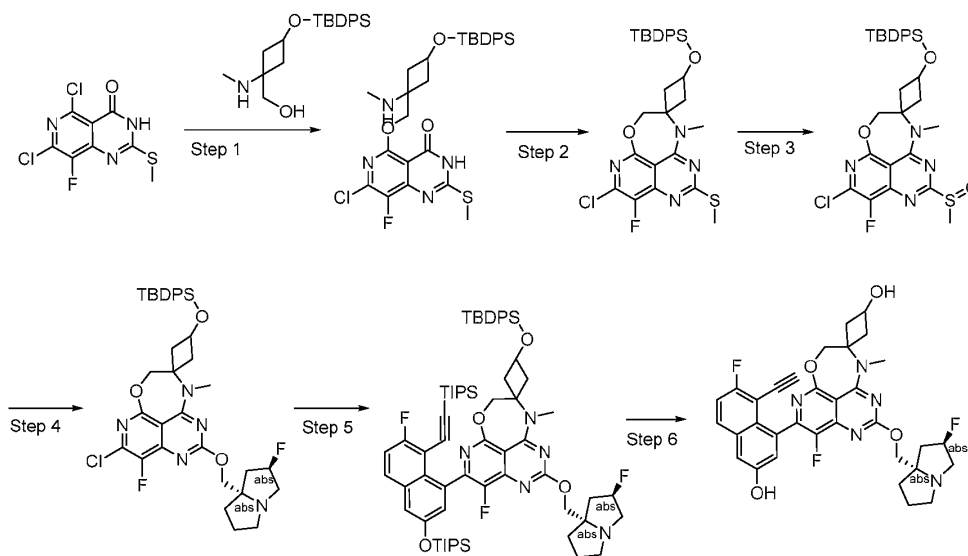
((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane (351.6 mg, 0.56 mmol) and cataCXium-A-Pd-G3 (20.62 mg, 0.03 mmol) were added to a solution of the compound from step 4 (200 mg, 0.28 mmol) in dioxane (1 mL). K₂CO₃ (117.4 mg, 0.85 mmol) and then H₂O (0.1 mL) were added and the reaction mixture was stirred at rt for 1h under N₂. The resulting mixture was extracted with EtOAc (3 x 10mL), the combined organic layers were washed with brine (15 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (1:1) to afford the title compound (320 mg, 96.7%) as a brown solid. LCMS m/z = 1169 [M+H]⁺

Step 6: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-8H,10H-7-oxa-1,3,6,10-

tetraazaspiro[cyclohepta[de]naphthalene-9,1'-cyclopropan]-1(10a),2,3a,3a1(6a),5-pentaen-5-yl)naphthalen-2-ol

[00351] CsF (415.9 mg, 2.74 mmol) was added to a solution of the compound from step 5 (160 mg, 0.137 mmol) in DMF (2 mL) and the reaction mixture was stirred at 60°C for 30 min. The resulting mixture was filtered, the filter cake was washed with DMF (2 mL). The crude product was purified by Prep-HPLC (Method D, Gradient: 5% B to 35% B in 7 min) to afford the title compound (44.0 mg, 51.9%) as a yellow solid. LCMS m/z = 618 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 10.14 (s, 1H), 8.04 – 7.86 (m, 1H), 7.46 (m, 1H), 7.37 (s, 1H), 7.18 (s, 1H), 5.41 – 5.18 (m, 1H), 5.09 – 4.91 (s, 1H), 4.88 – 4.61 (m, 1H), 4.32 – 4.05 (m, 4H), 4.05 – 3.95 (s, 1H), 3.81 – 3.49 (s, 4H), 3.19 – 2.89 (m, 2H), 2.32 – 2.01 (m, 3H), 2.01 – 1.71 (m, 3H), 1.62 – 1.40 (s, 1H), 1.34 – 1.21 (m, 2H), 1.21 – 1.13 (m, 1H), 1.13 – 0.95 (m, 1H).

Example 24: Synthesis of 5'-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4'-fluoro-2'-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10'-methyl-8'H,10'H-7'-oxa-1',3',6',10'-tetraazaspiro[cyclobutane-1,9'-cyclohepta[de]naphthalen]-1'(10a'),2',3a',3a1'(6a'),5'-pentaen-3-ol (Compound 154)



Steps 1 and 2: Synthesis of 3-((tert-butylidiphenylsilyl)oxy)-5'-chloro-4'-fluoro-10'-methyl-2'-(methylthio)-8'H,10'H-7'-oxa-1',3',6',10'-tetraazaspiro[cyclobutane-1,9'-cyclohepta[de]naphthalen]-1'(10a'),2',3a',3a1'(6a'),5'-pentaene

- 5 **[00352]** The title compound was obtained as a yellow solid, from Intermediate 15 and 5,7-dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one, following a similar procedure to that described in Example 1, steps 1 and 2. LCMS $m/z = 596$ $[M+H]^+$

Step 3: Synthesis of 3-((tert-butylidiphenylsilyl)oxy)-5'-chloro-4'-fluoro-10'-methyl-2'-(methylthio)-8'H,10'H-7'-oxa-1',3',6',10'-tetraazaspiro[cyclobutane-1,9'-cyclohepta[de]naphthalen]-1'(10a'),2',3a',3a1'(6a'),5'-pentaene

- 10 **[00353]** A solution of the compound from steps 1 and 2 (590 mg, 0.99 mmol) and m-CPBA (256.5 mg, 1.49 mmol) in DCM (10 mL) was stirred for 0.5h at rt. The resulting mixture was evaporated under reduced pressure to afford the title compound (600 mg, crude) as a white solid. LCMS $m/z = 612$ $[M+H]^+$

- 15 **Step 4:** Synthesis of 3-((tert-butylidiphenylsilyl)oxy)-5'-chloro-4'-fluoro-2'-((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10'-methyl-8'H,10'H-7'-oxa-1',3',6',10'-tetraazaspiro[cyclobutane-1,9'-cyclohepta[de]naphthalen]-1'(10a'),2',3a',3a1'(6a'),5'-pentaene

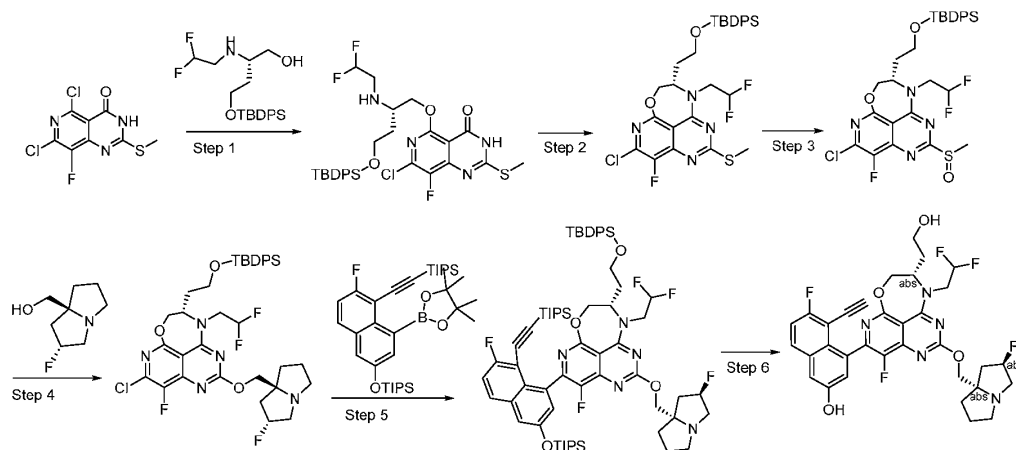
- [00354]** A solution of the compound from step 3 (570 mg, 0.93 mmol) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (222.7 mg, 1.40 mmol) in toluene (20 mL) was stirred for 1h at rt. NaOtBu (179.2 mg, 1.87 mmol) was added portion wise over 2 min at rt and the reaction mixture was stirred for 0.5h. The mixture was concentrated *in vacuo* and the

residue was purified by silica gel column chromatography, eluting with DCM / EtOAc (1:1) to afford the title compound (310 mg, 47.1%) as a white solid. LCMS m/z = 707 [M+H]⁺

Steps 5 to 6: Synthesis of 5'-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4'-fluoro-2'-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10'-methyl-8'H,10'H-7'-oxa-1',3',6',10'-tetraazaspiro[cyclobutane-1,9'-cyclohepta[de]naphthalen]-1'(10a'),2',3a',3a1'(6a'),5'-pentaen-3-ol formate.

[00355] The title compound was obtained as a yellow solid, from the compound from step 4 and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane, following a similar 2 step procedure to that described in Example 16, steps 5 and 6. LCMS m/z = 618 [M+H]⁺. ¹H NMR (400 MHz, DMSO- d_6) δ 7.96 (m, 1H), 7.46 (m, 1H), 7.37 - 7.31 (m 1H), 7.15 (m, 1H), 5.35 - 5.32 (m, 1H), 4.70 (s, 1H), 4.52 - 4.37 (m, 1H), 4.12 (m, 1H), 4.06 - 3.97 (m, 2H), 3.30 - 3.34 (m, 3H), 3.17 - 3.00 (m, 3H), 2.99 - 2.89 (m, 1H), 2.89 - 2.75 (m, 2H), 2.62 - 2.54 (m, 1H), 2.44 - 2.29 (m, 1H), 2.24 - 1.94 (m, 4H), 1.91 - 1.72 (m, 3H).

Example 25: Synthesis of 4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (Compound 158)



Step 1: Synthesis of (S)-5-(4-((tert-butylidiphenylsilyl)oxy)-2-((2,2-difluoroethyl)amino)butoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

[00356] A solution of Intermediate 17 (1 g, 2.45 mmol) in THF (5 mL) was added to a solution of NaH (294.4 mg, 7.36 mmol, 60%) in THF (5 mL) at 0°C under N₂ and the mixture

was stirred for 30 min at 0°C under N₂. 5,7-Dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one (687.2 mg, 2.45 mmol) in THF (5 mL) was added dropwise at 0°C and the reaction mixture was stirred for 1 day at 80°C. The reaction was quenched with HCl (1M) at 0°C and the mixture was extracted with EtOAc (2 x 50mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase flash chromatography column, C18 silica gel; mobile phase, MeCN in Water (0.1% TFA), 0% to 45% gradient in 20 min to give the title compound (523 mg, 19.6%) as a brown oil. LCMS m/z = 651 [M+H]⁺

Step 2: Synthesis of (S)-9-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-5-chloro-10-(2,2-difluoroethyl)-4-fluoro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00357] PyBOP® (958.9 mg, 1.84 mmol) was added in portions at 0°C to a solution of the compound from step 1 (800 mg, 1.23 mmol) and TEA (372.9 mg, 3.68 mmol) in THF (2 mL) and the reaction mixture was stirred overnight at 40°C. The mixture was extracted with EtOAc (3 x 80mL), the combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (5:1) to afford the title compound (240 mg, 24.7%) as a white oil. LCMS m/z = 633 [M+H]⁺

Step 3: Synthesis of (9S)-9-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-5-chloro-10-(2,2-difluoroethyl)-4-fluoro-2-(methylsulfanyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00358] The title compound was obtained as a white solid, 460 mg crude, from the compound from step 2, following a similar procedure to that described in Example 24, step 3. LCMS m/z = 649 [M+H]⁺

Step 4: Synthesis of (S)-9-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-5-chloro-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00359] ((2R,7aS)-2-Fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (176.6 mg, 1.11 mmol) was added to A solution of the compound from step 3 (240 mg, 0.37 mmol) in toluene (1.5 mL) and the mixture was stirred for 1h at rt under N₂. NaOtBu (71.1 mg, 0.74 mmol) was added in portions and the reaction mixture was stirred overnight at rt. The residue was purified

by prep-TLC (EtOAc) to afford the title compound (200 mg, 62.5%) as a white solid. LCMS $m/z = 744$ $[M+H]^+$

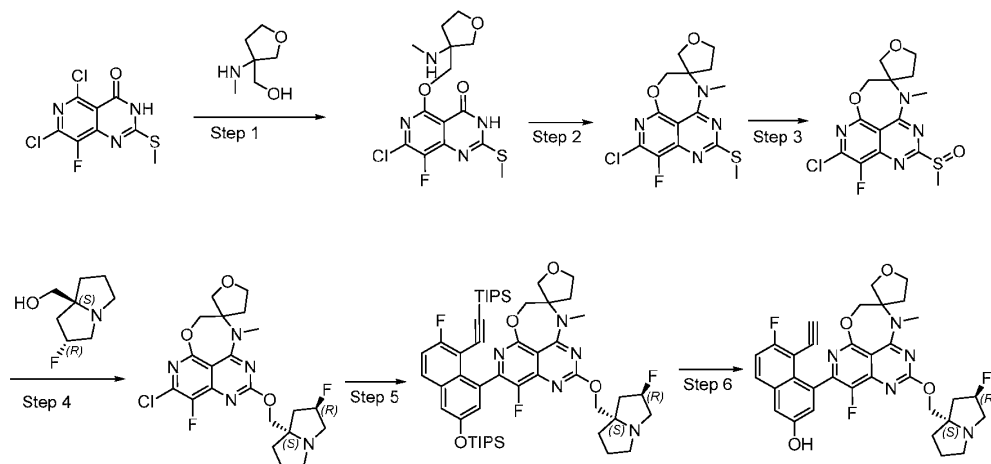
Step 5: Synthesis of (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-10-(2,2-difluoroethyl)-4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00360] The title compound was obtained as a yellow solid, 150 mg, 84.1%, from the compound from step 4 and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane, following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 1206$ $[M+H]^+$

Step 6: Synthesis of 4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol

[00361] The title compound was obtained as a yellow solid, 35 mg, 4%, from the compound from step 5, following a similar procedure to that described in Example 23, step 6, except the compound was purified by Prep-HPLC (Method A, 25% B to 52% B in 7 min). LCMS $m/z = 656$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 10.14 (m, 1H), 7.96 (m, 1H), 7.46 (m, 1H), 7.38 (m, 1H), 7.28 – 7.01 (m, 1H), 6.78 – 6.17 (m, 1H), 5.45 – 5.02 (m, 1H), 4.83 – 4.60 (m, 1H), 4.45 (m, 2H), 4.41 (m, 1H), 4.22 (m, 1H), 4.17 – 4.10 (m, 1H), 4.08 (m, 1H), 4.02 – 3.79 (m, 1H), 3.98 (m, 1H), 3.97 – 3.69 (s, 2H), 3.19 – 2.90 (m, 3H), 2.84 (m, 1H), 2.18 – 1.97 (m, 3H), 1.96 – 1.68 (m, 5H).

Example 26: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-4',5'-dihydro-2'H,8H,10H-7-oxa-1,3,6,10-tetraazaspiro[cyclohepta[de]naphthalene-9,3'-furan]-1(10a),2,3a,3a1(6a),5-pentaen-5-yl)naphthalen-2-ol (Compound 165)



Step 1: Synthesis of 7-chloro-8-fluoro-5-((3-(methylamino)tetrahydrofuran-3-yl)methoxy)-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

[00362] To a solution of Intermediate 19 (1 g, 7.62 mmol) in THF (20 mL) was added NaH (548.8 mg, 22.9 mmol) at 0°C and the mixture was stirred for 15 min. 5,7-Dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one (1.07 g, 3.81 mmol) was added and the reaction was warmed and stirred at rt for 1 h. The reaction was quenched with water and extracted with EtOAc (3 x 40 mL). The combined organic extracts were concentrated under reduced pressure to give the title compound (1 g, crude) as an off-white solid. LCMS $m/z = 375$ $[M+H]^+$

Step 2: Synthesis of 5-chloro-4-fluoro-10-methyl-2-(methylthio)-4',5'-dihydro-2'H,8H,10H-7-oxa-1,3,6,10-tetraazaspiro[cyclohepta[de]naphthalene-9,3'-furan]-1(10a),2,3a,3a1(6a),5-pentaene

[00363] The title compound was obtained as a light yellow solid, 400 mg, 47.3%, from the compound from step 1, following a similar procedure to that described in Example 1, step 2. LCMS $m/z = 357$ $[M+H]^+$.

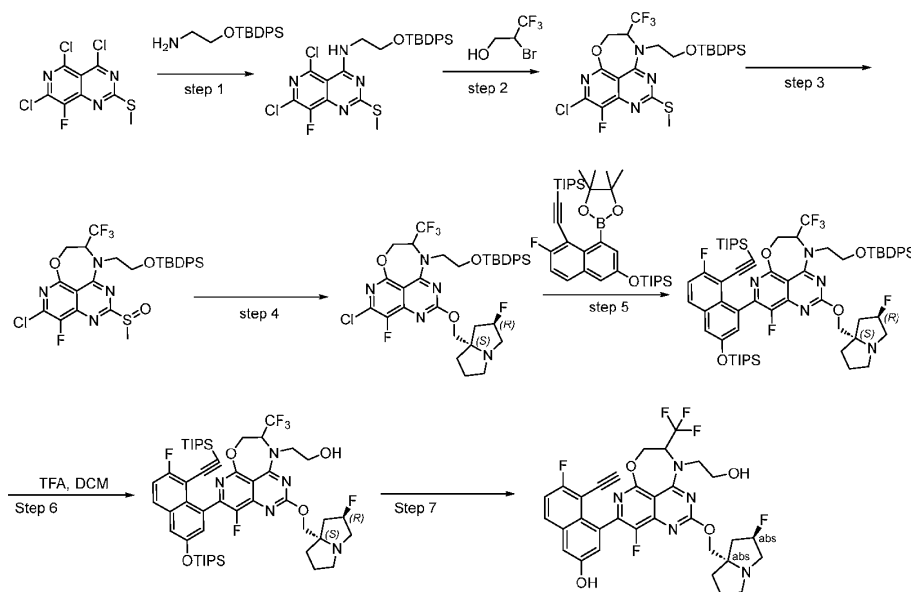
Steps 3 and 4: Synthesis of 5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-4',5'-dihydro-2'H,8H,10H-7-oxa-1,3,6,10-tetraazaspiro[cyclohepta[de]naphthalene-9,3'-furan]-1(10a),2,3a,3a1(6a),5-pentaene

[00364] The title compound was obtained as an off-white solid, from the compound from step 2, following a similar 2 step procedure to that described in Example 23, steps 3 and 4. LCMS $m/z = 468$ $[M+H]^+$

Steps 5 and 6: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-4',5'-dihydro-2'H,8H,10H-7-oxa-1,3,6,10-tetraazaspiro[cyclohepta[de]naphthalene-9,3'-furan]-1(10a),2,3a,3a1(6a),5-pentaen-5-yl)naphthalen-2-ol

- 5 [00365] The title compound was obtained as a white solid, from the compound from steps 3 and 4 and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane, following a similar 2 step procedure to that described in Example 16, steps 5 and 6. LCMS $m/z = 618$ $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 10.21 (s, 1H), 8.01-7.96 (m, 1H), 7.46 (t, 1H), 7.37 (d, 1H), 7.25 - 7.07 (m, 1H), 5.42 - 5.18 (m, 1H), 4.54 (s, 2H), 4.24 - 4.00 (m, 5H), 3.95 - 3.72 (m, 2H), 3.26 (s, 3H), 3.15 - 3.06 (m, 2H), 3.04 - 3.01 (m, 1H), 2.91 - 2.85 (m, 1H), 2.38 - 2.31 (m, 1H), 2.19 - 2.00 (m, 4H), 1.92 - 1.76 (m, 3H).

Example 27: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-(trifluoromethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol trifluoroacetate (Compound 157)



Step 1: Synthesis of N-(2-((tert-butyl dimethylsilyl)oxy)ethyl)-5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-amine

[00366] A solution of Intermediate 28, step 1 (4.8 g, 16.1 mmol), (2-aminoethoxy)(tert-butyl)dimethylsilane (5.64 g, 32.2 mmol) and DIPEA (6.23 g, 48.2 mmol) in anhydrous DCM (15 mL) was stirred for 0.5 h at rt. The reaction mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (MeOH/DCM 1:10) to give the title compound (2.4 g, 34.1%) as a yellow solid. LCMS m/z = 437 [M+H]⁺

Step 2: Synthesis of 10-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(methylthio)-9-(trifluoromethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00367] A solution of the compound from step 1 (1.87 g, 4.28 mmol), 2-bromo-3,3,3-trifluoropropan-1-ol (1.65 g, 8.55 mmol) and NaH (307.8 mg, 12.8 mmol) in anhydrous THF (10 mL) was stirred for 2 days at 60 °C. The mixture was allowed to cool to rt and the reaction was quenched with water (15 mL). The mixture was concentrated under reduced pressure, the residue was extracted with EtOAc (3x20 mL), the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with MeOH/DCM (1:10) to afford the title compound (190 mg, 8.7%) as a yellow solid. LCMS m/z = 513 [M+H]⁺

Step 3: Synthesis of 10-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(methylsulfinyl)-9-(trifluoromethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00368] A solution of the compound from step 2 (190 mg, 0.37 mmol) and m-CPBA (191.7 mg, 1.11 mmol) in anhydrous DCM (3 mL) was stirred for 1 h at rt. The resulting mixture was concentrated under reduced pressure and the residue was purified by Prep-TLC (MeOH/DCM 1:20) to give the title compound (110 mg, 54.5%) as a yellow solid. LCMS m/z = 529 [M+H]⁺

Step 4: Synthesis of 10-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(trifluoromethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00369] A mixture of the compound from step 3 (100 mg, 0.18 mmol), ((2R,7aS)-2-Fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (43.8 mg, 0.27 mmol) and LiOtBu (29.4 mg, 0.37 mmol) in anhydrous DCM (2 mL) was stirred for 1h at rt. The resulting mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (MeOH/DCM=1:10) to give the title compound (40 mg, 33.9%) as a yellow solid. LCMS m/z = 624 [M+H]⁺

Step 5: Synthesis of 10-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(trifluoromethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- 5 **[00370]** A mixture of the compound from step 4 (40 mg, 0.064 mmol), ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane (80.1 mg, 0.13 mmol), cataCXium-A-Pd-G3 (4.67 mg, 0.006 mmol) and K₃PO₄ (40.81 mg, 0.19 mmol) in anhydrous dioxane (2 mL) was stirred for 2 h at 80°C. The resulting mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (MeOH/DCM=1:10) to give the title compound (crude) as a yellow solid. LCMS m/z = 1087 [M+H]⁺
- 10

Step 6: Synthesis of 2-(4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(trifluoromethyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-

- 15 *tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol*

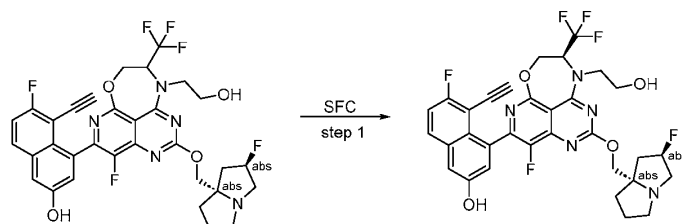
- [00371]** TFA (20.5 mg, 0.18 mmol) was added to a solution of the compound from step 5 (65 mg, 0.06 mmol) in anhydrous DCM (1 mL) and the reaction stirred for 1h at rt. The resulting mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (MeOH/DCM 1:10) to give the title compound (48 mg, 76.8%) as a yellow solid. LCMS m/z = 972 [M+H]⁺
- 20

Step 7: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-(trifluoromethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol trifluoroacetate

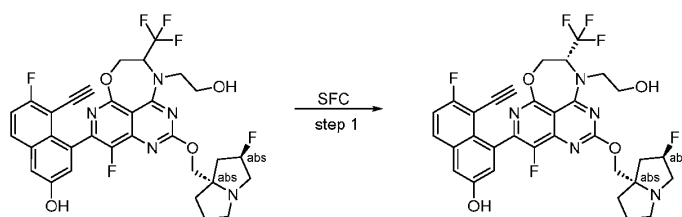
- [00372]** CsF (70.3 mg, 0.46 mmol) was added to a solution of the compound from step 6 (45 mg, 0.046 mmol) in DMF (1 mL) and the reaction mixture was stirred for 3h at rt. The residue was dissolved in water (5 mL), the mixture was extracted with EtOAc (3x10 mL) and the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The crude was purified by HPLC (Method E, Gradient: 22% B to 47% B in 9 min) to afford the title compound. (2 mg, 5.6%) as a yellow solid. LCMS m/z = 660 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 10.77 (s, 1H), 10.19 (s, 1H), 7.99 (s, 1H), 7.48 (s, 1H), 7.40 (d, 1H), 7.17 (dd, 1H), 5.72 – 5.42 (m, 2H), 5.09 – 4.60 (m, 1H), 4.66 – 4.50 (m, 2H), 4.38 (dd, 2H), 4.26 – 4.04 (m, 2H), 4.04 – 3.88 (m, 1H), 3.92 – 3.43
- 25
- 30

(m, 3H), 3.31 (s, 1H), 2.51 (s, 1H), 2.50 – 2.39 (m, 2H), 2.39 – 2.21 (m, 1H), 2.16 (m, 2H), 2.03 (s, 1H).

- Example 28: Synthesis of 5-ethynyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-(trifluoromethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 161)**



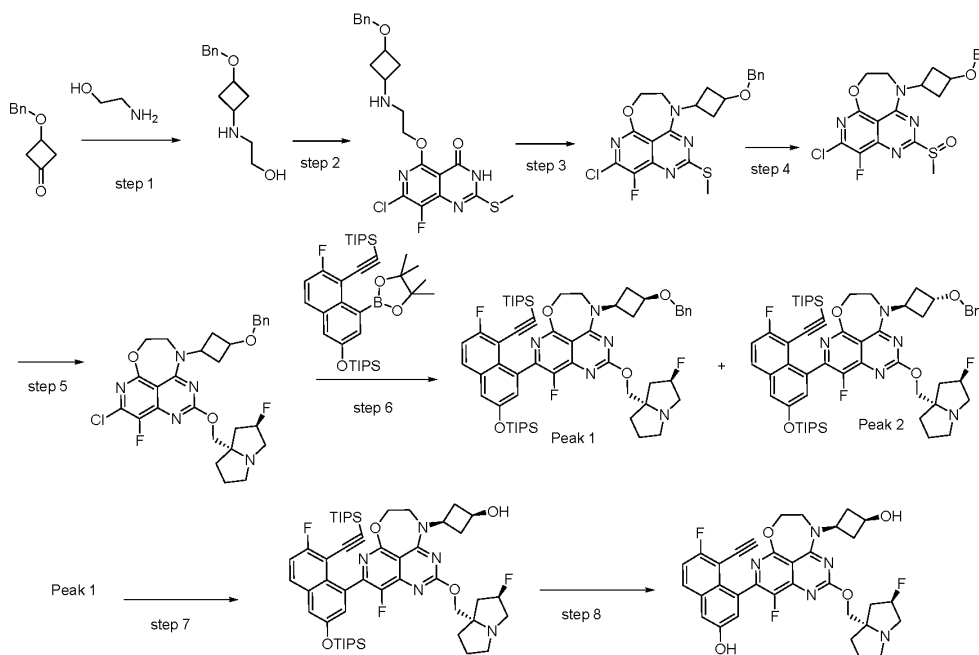
- Example 27 (10 mg, 0.015 mmol) was purified by Prep-chiral-HPLC: Column: (CHIRALPAK IE3; Mobile Phase A: MtBE: Hex (0.2%DEA): (EtOH: DCM=1:1) = 30: 70 at 1mL/min; Gradient: isocratic; to afford Peak 1 (1 mg, 8.5%) as a white solid: LCMS m/z = 660 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 10.17 (d, 1H), 8.05 – 7.90 (m, 1H), 7.47 (s, 1H), 7.39 (d, 1H), 7.17 (dd, 1H), 5.53 (s, 1H), 5.32 (d, 1H), 5.05 – 4.82 (m, 1H), 4.46 – 4.24 (m, 2H), 4.24 – 3.84 (m, 4H), 3.77 (s, 3H), 3.12 – 3.04 (m, 2H), 3.01 – 2.55 (m, 1H), 2.38 – 1.98 (m, 3H), 1.82 (s, 3H), 1.42 – 1.05 (m, 1H);
- Example 29: Synthesis of 5-ethynyl-6-fluoro-4-((R)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-(trifluoromethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 162)**



- [00373]** Example 27 (10 mg, 0.015 mmol) was purified by Prep-chiral-HPLC: Column: (CHIRALPAK IE3; Mobile Phase A: MtBE: Hex (0.2%DEA): (EtOH: DCM=1:1) = 30: 70 at 1mL/min; Gradient: isocratic; to afford Peak 2 (Example 29, 1.6 mg, 13.6%) as a white solid: LCMS m/z = 660 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 10.20 (d, 1H), 7.99 – 7.92 (m, 1H), 7.53 – 7.45 (m, 1H), 7.45 – 7.37 (m, 1H), 7.21–7.17 (m, 1H), 5.72 – 5.41 (m, 2H), 4.97 (d,

1H), 4.58 (s, 2H), 4.50 - 4.30 (m, 2H), 4.27 - 3.98 (m, 3H), 3.95 - 3.66 (m, 5H), 2.39 - 2.12 (m, 3H), 2.03 - 1.98 (m, 2H), 1.26 - 1.23 (m, 1H), 1.21 - 1.08 (m, 1H).

Example 30: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((1s,3R)-3-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 124)



Step 1: Synthesis of 2-((3-(benzyloxy)cyclobutyl)amino)ethan-1-ol

[00374] $\text{Ti}(\text{OPr})_4$ (4.84 g, 17.0 mmol) was added to a solution of 3-(benzyloxy)cyclobutan-1-one (3 g, 17.0 mmol) and ethanolamine (2.08 g, 34.2 mmol) in MeOH (20 mL) and the mixture was stirred for 2h at 80°C under N_2 , then cooled to rt. NaBH_3CN (2.14 g, 34.1 mmol) was added and the reaction mixture was stirred for 2h at 80°C under N_2 . The reaction was quenched with water at 0°C, the mixture was filtered and the filter cake was washed with MeOH (3x10 mL). The filtrate was concentrated under reduced pressure and the residue was purified by reverse-phase chromatography: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; to afford the title compound (2.5 g, 66.4%) as a white solid. LCMS m/z = 222 $[\text{M}+\text{H}]^+$

Step 2: Synthesis of 5-(2-((3-(benzyloxy)cyclobutyl)amino)ethoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

[00375] A solution of NaH (1.25 g, 31.2 mmol, 60%) in THF (60 mL) and the compound from step 1 (2.3 g, 10.4 mmol) was stirred for 10 min at 0°C under N₂. 5,7-Dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one (1.46 g, 5.2 mmol) was added at 0°C and the reaction mixture was stirred for 1h at 60°C under N₂. The reaction was quenched with water at 20°C and the mixture concentrated under vacuum. The residue was purified by reverse-phase chromatography: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; to afford the title compound (1.9 g, 39.3%) as a yellow oil. LCMS m/z = 465 [M+H]⁺

Step 3: Synthesis of 10-(3-(benzyloxy)cyclobutyl)-5-chloro-4-fluoro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00376] The title compound was obtained as a white solid, 1.2 g, 65.7%, from the compound from step 2, following a similar procedure to that described in Example 1, step 2. LCMS m/z = 447 [M+H]⁺

Step 4: Synthesis of 10-(3-(benzyloxy)cyclobutyl)-5-chloro-4-fluoro-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00377] A solution of the compound from step 3 (300 mg, 0.67 mmol) and m-CPBA (127.4 mg, 0.74 mmol) in DCM (4 mL) was stirred for 2h at 25°C under N₂. The resulting mixture was concentrated under vacuum. The residue was purified by reverse-phase chromatography: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; to afford the title compound (300 mg, 96.6%) as a white solid. LCMS m/z = 463 [M+H]⁺

Step 5: Synthesis of 10-(3-(benzyloxy)cyclobutyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00378] A solution of NaH (46.66 mg, 1.94 mmol, 60%) in THF (3 mL) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (113.5 mg, 0.71 mmol) was stirred for 20 min at 0°C under N₂. The compound from step 4 (300 mg, 0.65 mmol) was added at 0°C, and the reaction mixture was stirred for 2h at 25°C under N₂. The reaction was quenched with water (5 mL) at 0°C and the mixture was concentrated under reduced pressure. The residue was purified by reverse-phase chromatography: column, C18 silica gel; mobile phase, MeCN in Water (0.1% FA), 10% to 50% gradient in 10 min; to afford the title compound (100 mg, 27.7%) as a white solid. LCMS m/z = 558 [M+H]⁺

Step 6: Synthesis of 10-((1*s*,3*R*)-3-(benzyloxy)cyclobutyl)-4-fluoro-5-(7-fluoro-8-
 ((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-((2*R*,7*aS*)-2-
 fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-9,10-dihydro-8*H*-7-oxa-1,3,6,10-
 tetraazacyclohepta[*de*]naphthalene and 10-((1*r*,3*S*)-3-(benzyloxy)cyclobutyl)-4-fluoro-5-(7-
 5 fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-((2*R*,7*aS*)-2-
 fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-9,10-dihydro-8*H*-7-oxa-1,3,6,10-
 tetraazacyclohepta[*de*]naphthalene

[00379] A solution of the compound from step 5 (80 mg, 0.072 mmol) and ((6-fluoro-4-
 (4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-
 10 yl)oxy)triisopropylsilane (73.5 mg, 0.14 mmol), K₃PO₄ (45.7 mg, 0.22 mmol) and cataCXium-
 A-Pd-G3 (10.44 mg, 0.014 mmol) in dioxane (4 mL) and H₂O (0.8 mL) was stirred for 1 h at
 80°C under N₂. The cooled mixture was concentrated under reduced pressure and the residue
 was purified by Prep-TLC (PE / EtOAc 5:1) to afford Peak 1, 10-((1*s*,3*R*)-3-
 (benzyloxy)cyclobutyl)-4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-
 15 ((triisopropylsilyl)oxy)naphthalen-1-yl)-2-((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-
 yl)methoxy)-9,10-dihydro-8*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalene (80 mg,
 54.7%) and Peak 2, 10-((1*r*,3*S*)-3-(benzyloxy)cyclobutyl)-4-fluoro-5-(7-fluoro-8-
 ((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-((2*R*,7*aS*)-2-
 fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-9,10-dihydro-8*H*-7-oxa-1,3,6,10-
 20 tetraazacyclohepta[*de*]naphthalene (50 mg, 34.2%) as a yellow solid. LCMS *m/z* = 1020
 [M+H]⁺

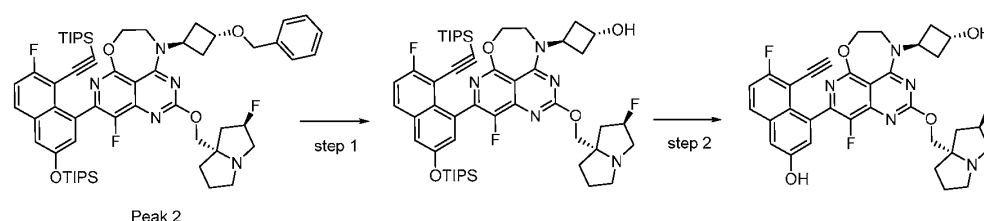
Step 7: Synthesis of (1*R*,3*s*)-3-(4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-
 ((triisopropylsilyl)oxy)naphthalen-1-yl)-2-((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-
 25 yl)methoxy)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-
 yl)cyclobutan-1-ol

[00380] A solution of step 6, Peak 1 (25 mg, 0.024 mmol) and Pd/C (7.82 mg, 0.07 mmol)
 in THF (3 mL) was stirred for 30 mins at 60°C under H₂. The reaction mixture was filtered
 through a Celite® pad and the filtrate concentrated under reduced pressure to give the title
 compound, crude as a light-yellow oil. LCMS *m/z* = 930 [M+H]⁺

Step 8: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-
 pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-((1*s*,3*R*)-3-hydroxycyclobutyl)-9,10-dihydro-8*H*-7-oxa-
 1,3,6,10-tetraazacyclohepta[*de*]naphthalen-5-yl)naphthalen-2-ol

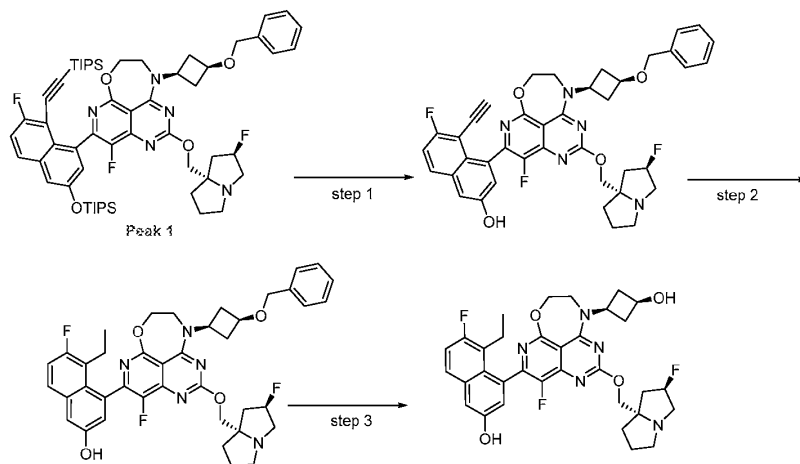
[00381] CsF (19.63 mg, 0.13 mmol) was added to a solution of the compound from step 7 (10 mg, 0.013 mmol) in DMF (1 mL) and the reaction mixture stirred until no starting material remained. The mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Method D, Gradient: 20% B to 44% B in 7 min) to afford the title compound (1 mg, 12.3%) as a white solid. LCMS m/z = 619 $[M+H]^+$; 1H NMR (400 MHz, DMSO- d_6) δ 10.15 (s, 1H), 7.96 (dd, 1H), 7.46 (t, 1H), 7.37 (d, 1H), 7.14 (d, 1H), 5.22 (d, 1H), 4.69 (t, 1H), 4.56 (dd, 2H), 4.09 (s, 1H), 4.02 (s, 4H), 3.07 (d, 2H), 2.56 (dd, 5H), 2.06 – 2.04 (m, 4H), 1.85 (s, 2H), 1.24 (s, 2H), 0.84 (s, 1H).

Example 31: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((1r,3S)-3-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 125)



[00382] The title compound was obtained as a white solid, from Peak 2, Example 30, step 6, following the 2 step procedure described in Example 30, steps 7 and 8. LCMS m/z = 619 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.16 (s, 1H), 7.95 (dd, 1H), 7.45 (t, 1H), 7.36 (d, 1H), 7.14 (d, 1H), 5.55 (t, 1H), 5.39 - 5.33 (m, 1H), 5.24 - 5.15 (m, 1H), 4.58 - 4.46 (m, 3H), 4.30 - 4.24 (m, 1H), 4.15 - 4.07 (m, 2H), 4.06 - 3.94 (m, 2H), 3.90 - 3.77 (m, 1H), 3.14 - 3.05 (m, 3H), 3.04 - 3.00 (m, 1H), 2.86 - 2.83 (m, 1H), 2.35 - 2.18 (m, 2H), 2.17 - 2.11 (m, 1H), 2.08 - 1.94 (m, 2H), 1.89 - 1.70 (m, 3H).

Example 32: Synthesis of 5-ethyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((1s,3R)-3-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 136)



*Step 1: Synthesis of 4-(10-((1*s*,3*R*)-3-(benzyloxy)cyclobutyl)-4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-9,10-dihydro-8*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol*

- 5 **[00383]** A mixture of Peak 1, Example 30, step 6, (22 mg, 0.022 mmol) and CsF (32.8 mg, 0.22 mmol) in DMF (2 mL) was stirred at rt for 2 h. The mixture was concentrated under reduced pressure, and the residue diluted with water (20mL). The aqueous layer was extracted with DCM (3 x 20mL), the combined organic layers were washed with brine, dried over Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure to give the title
 10 compound, 20 mg, 72%, as a yellow solid. LCMS *m/z* = 708 [M+H]⁺

*Step 2: Synthesis of 4-(10-((1*s*,3*R*)-3-(benzyloxy)cyclobutyl)-4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-9,10-dihydro-8*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-5-yl)-5-ethyl-6-fluoronaphthalen-2-ol*

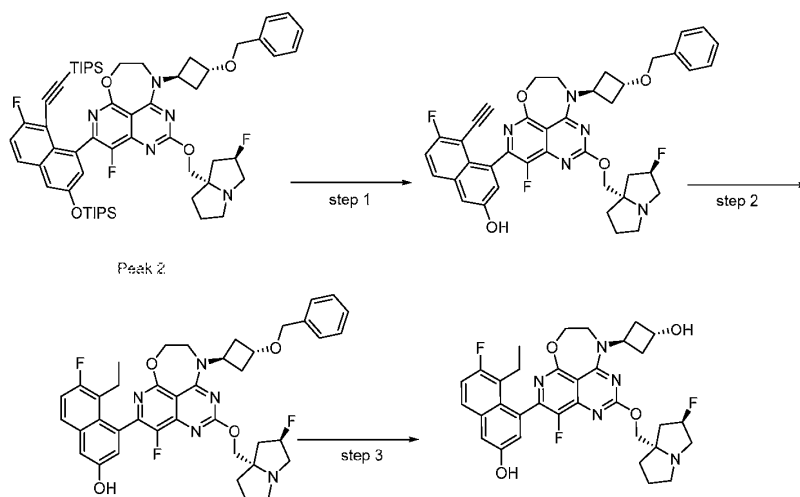
- [00384]** To a solution of the compound from step 1 (22 mg, 0.003 mmol) in MeOH (2 mL)
 15 was added Pd/C (10%, 25 mg) under N₂ and the reaction mixture was hydrogenated at rt for 15 min under an atmosphere of H₂. The mixture was filtered through Celite® and evaporated under reduced pressure to give the title compound as a yellow solid, 20 mg, crude. LCMS *m/z* = 712 [M+H]⁺

*Step 3: Synthesis of 5-ethyl-6-fluoro-4-(4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-10-((1*s*,3*R*)-3-hydroxycyclobutyl)-9,10-dihydro-8*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-5-yl)naphthalen-2-ol*

- 20 **[00385]** A mixture of the compound from step 2 (10 mg, 0.014 mmol) and Pd/C (3.0 mg, 0.03 mmol) and HCO₂NH₄ (6.20 mg, 0.1 mmol) in MeOH (2 mL) was stirred at 60°C for 30

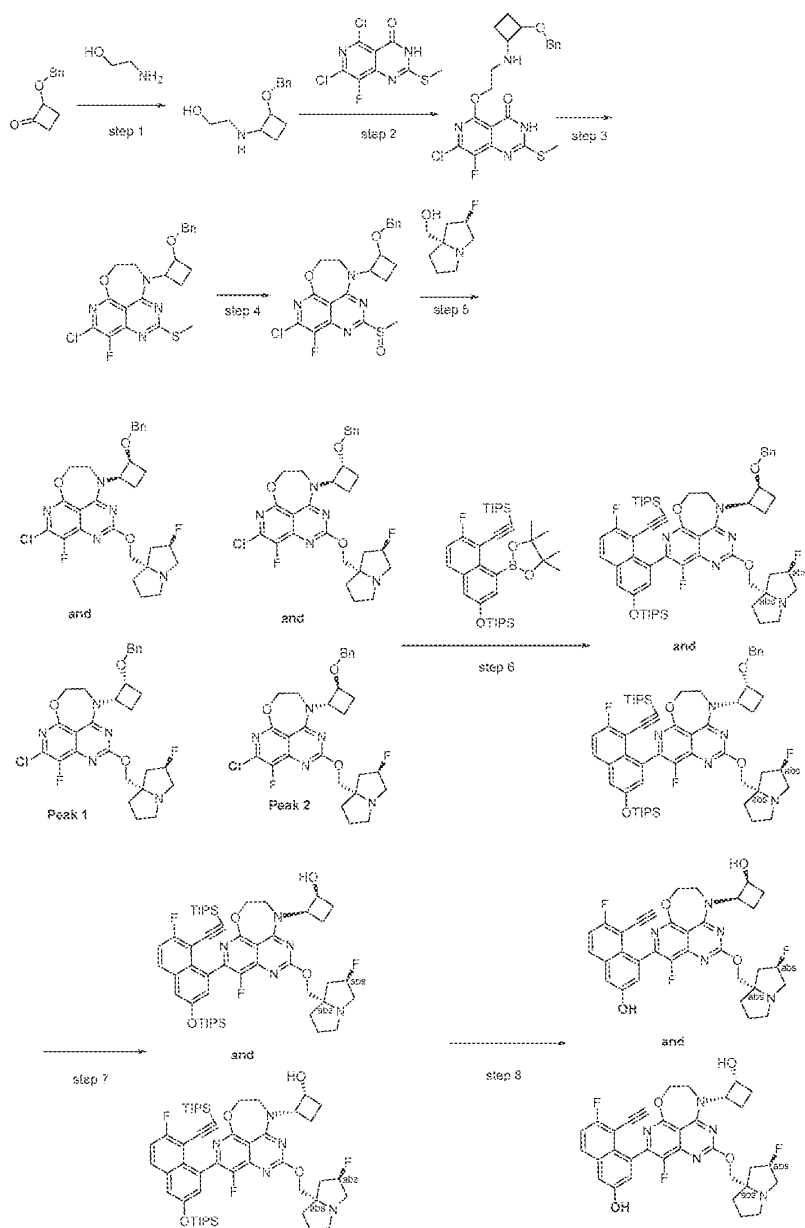
mins. The mixture was filtered through Celite® and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Method C, Gradient: 12% B to 35% B in 8 min) to afford the title compound (2 mg, 22.0%) as a white solid. LCMS m/z = 622 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6): δ 7.74 (dd, 1H), 7.35 - 7.30 (m, 2H), 7.00 (s, 1H), 5.35 - 5.21 (m, 1H), 4.57 - 4.53 (m, 3H), 4.22 - 4.13 (m, 2H), 4.14 - 3.84 (m, 3H), 3.10 - 3.08 (m, 3H), 3.06 - 3.01 (m, 1H), 2.90 - 2.82 (m, 2H), 2.26 - 2.18 (m, 2H), 2.09 - 2.03 (m, 4H), 1.85 - 1.78 (m, 4H), 1.42 - 1.35 (m, 1H), 1.24 (t, 3H).

Example 33: Synthesis of 5-ethyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((1r,3S)-3-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 137)



[00386] The title compound was obtained as a white solid, from Peak 2, Example 30, step 6, following the three-step procedure described in Example 32. LCMS m/z = 622 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.71 (br s, 1H), 7.74 - 7.30 (m, 2H), 7.23-7.01 (m, 2H), 5.65 - 5.61 (m, 1H), 5.35 - 5.21 (m, 1H), 4.55 - 4.53 (m, 2H), 4.51 - 4.27 (m, 2H), 4.15 - 4.13 (m, 1H), 4.07 - 3.94 (m, 4H), 3.88 - 3.82 (m, 3H), 2.89-2.67 (m, 2H), 2.50-2.24 (m, 2H), 2.14-2.00 (m, 2H), 1.86-1.82 (m, 2H), 1.57-1.54 (m, 2H), 1.45-1.37 (m, 2H), 1.25-1.21 (m, 3H).

Example 34: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((1R*,2S*)-2-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol formate and 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((1S*,2R*)-2-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 141)



Step 1 : Synthesis of 2-((2-(benzyloxy)cyclobutyl)amino)ethan-1-ol

[00387] The title compound was obtained as a yellow oil, 1 g, 79.6%, from 2-(benzyloxy)cyclobutan-1-one and ethanolamine, following a similar procedure to that described in Example 5 30, step 1. LCMS $m/z = 222$ [M+H]⁺

Step 2 : Synthesis of 5-(2-((2-(benzyloxy)cyclobutyl)amino)ethoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

[00388] To a solution of the compound from step 1 (1 g, 4.52 mmol) in THF (20 mL) was added NaH (0.54 g, 13.6 mmol, 60%) at 0°C and the mixture was stirred for 10 min. 5,7-Dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one (1.52 g, 5.4 mmol) was added and the reaction mixture was stirred for 1h at rt. The reaction was quenched with ice/water at 0 °C, the resulting mixture was filtered and the filter cake was washed with MeCN (3x10 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by reverse phase chromatography (MeCN/H₂O=65%) to afford the title compound (1.5 g, 71.4%) as a yellow solid. LCMS m/z = 465 [M+H]⁺

Step 3 : Synthesis of 10-(2-(benzyloxy)cyclobutyl)-5-chloro-4-fluoro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00389] The title compound was obtained as a white solid, 450 mg, 46.8%, from the compound from step 2, following a similar procedure to that described in Example 30, step 3. LCMS m/z = 447 [M+H]⁺

Step 4 : Synthesis of 10-(2-(benzyloxy)cyclobutyl)-5-chloro-4-fluoro-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00390] A solution of the compound from step 3 (200 mg, 0.45 mmol) in DCM (4 mL) was treated with m-CPBA (109.0 mg, 0.54 mmol) at -15°C under N₂ and the reaction mixture was stirred for 40 min at -15°C. The reaction was quenched with water/ice (10 mL) at rt, the aqueous layer was extracted with DCM (3x10 mL) and the combined organic extracts were concentrated under reduced pressure to afford the title compound (150 mg, 72.4%) as a yellow solid. LCMS m/z = 463 [M+H]⁺

Step 5 : Synthesis of 10-((1R,2S*)-2-(benzyloxy)cyclobutyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene and 10-((1S*,2R*)-2-(benzyloxy)cyclobutyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

[00391] A solution of the compound from step 4 (300 mg, 0.65 mmol) and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane (309.5 mg, 1.94 mmol) in toluene (8 mL) was stirred for 30 min at rt under N₂, then cooled to 0°C. NaOtBu (124.6 mg, 1.30 mmol) was added in portions and the

reaction mixture was stirred for 10 min at 0 °C under N₂. The resulting mixture was diluted with H₂O (10 mL), the aqueous layer was extracted with DCM (3 x 20 mL) and the combined organic extracts were concentrated under reduced pressure. The residue was purified by reverse-phase chromatography column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L

- 5 NH₄HCO₃), 40% to 80% gradient in 10 min; to afford Peak 1, 10-((1R*,2S*)-2-(benzyloxy)cyclobutyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene and 10-((1S*,2R*)-2-(benzyloxy)cyclobutyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-
- 10 tetraazacyclohepta[de]naphthalene (200 mg, 55.3%) as a white solid and Peak 2, 10-((1R*,2R*)-2-(benzyloxy)cyclobutyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene or 10-((1S*,2S*)-2-(benzyloxy)cyclobutyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-
- 15 oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (100 mg, 27.7%) as a white solid. LCMS m/z = 558 [M+H]⁺

Step 6 : Synthesis of 10-((1R,2S*)-2-(benzyloxy)cyclobutyl)-4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-*

20 *tetraazacyclohepta[de]naphthalene and 10-((1S*,2R*)-2-(benzyloxy)cyclobutyl)-4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

- [00392] The title compound was obtained as a brown solid, 300 mg, 82%, from Peak 1, step
- 25 5, and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane, following a similar procedure to that described in Example 30, step 6. LCMS m/z = 1021 [M+H]⁺

- Step 7 : Synthesis of (1R*,2S*)-2-(4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-*
- 30 *yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)cyclobutan-1-ol and (1S*,2R*)-2-(4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-*

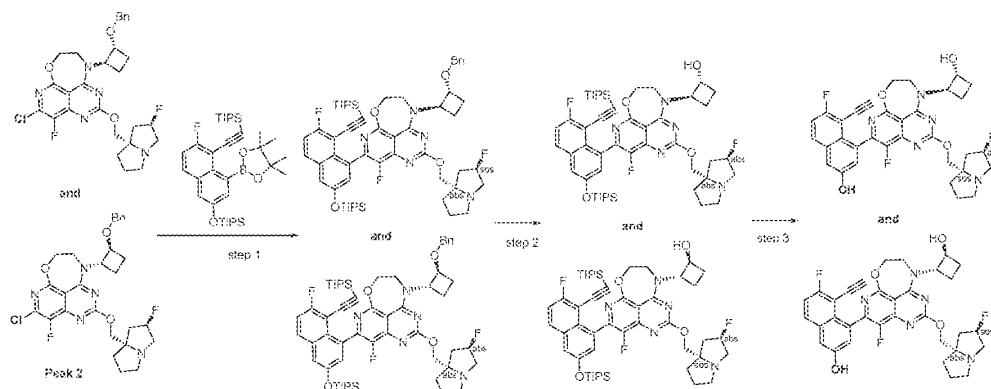
yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)cyclobutan-1-ol

[00393] A mixture of the compound from step 6 (150 mg, 0.15 mmol), ammonium formate (278.1 mg, 4.43 mmol) and Pd/C (312.9 mg, 2.95 mmol) in MeOH (5 mL) was stirred for 30 min at 70 °C in air. The resulting mixture was filtered, the filter cake was washed with MeOH (3x10 mL) and the filtrate was evaporated under reduced pressure to give the title compound (60 mg, crude) as a light yellow oil. LCMS m/z = 931 [M+H]⁺

Step 8 : Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((1R*,2S*)-2-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol formate and 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((1S*,2R*)-2-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol formate

[00394] The title compound was obtained as a white solid, 6.1 mg, 14.2%, from the compound from step 7, following a similar procedure to that described in Example 30, step 8. LCMS m/z = 618 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.15 (s, 1H), 8.14 (s, 1H), 7.96 - 7.92 (m, 1H), 7.46 - 7.42 (dd, 1H), 7.37 (d, 1H), 7.15 - 7.12 (dd, 1H), 5.35 (s, 1H), 5.22 (s, 1H), 4.57 (s, 4H), 4.18 - 4.06 (m, 2H), 4.01 (d, 2H), 3.81 (d, 1H), 3.13 - 3.07 (m, 2H), 3.03 (s, 1H), 2.89 - 2.80 (m, 1H), 2.13 (s, 1H), 2.05 (s, 2H), 2.01 (s, 2H), 1.89 - 1.75 (m, 3H), 1.67-1.62 (t, 1H).

Example 35: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((1R*,2R*)-2-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol formate and 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((1S*,2S*)-2-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol formate (Compound 142)



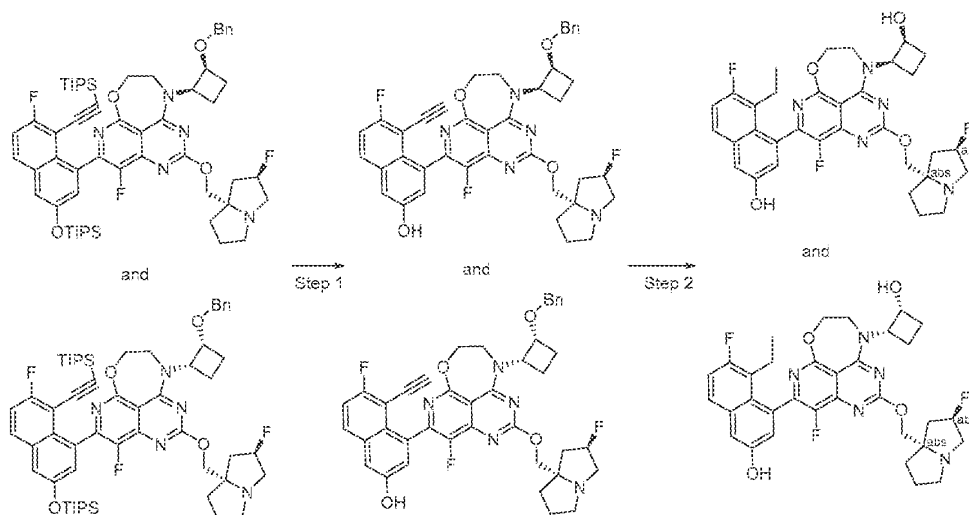
Step 1: Synthesis of 10-((1R*,2R*)-2-(benzyloxy)cyclobutyl)-4-fluoro-5-(7-fluoro-8-
 ((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-((2R,7aS)-2-
 5 fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-
 tetraazacyclohepta[de]naphthalene and 10-((1S*,2S*)-2-(benzyloxy)cyclobutyl)-4-fluoro-5-(7-
 fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-((2R,7aS)-2-
 fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-
 tetraazacyclohepta[de]naphthalene

10 **[00395]** The title compound was obtained as a white solid, from Peak 2, Example 34, step 5
 and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-
 ((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane, following the procedure
 described in Example 34, step 6. LCMS $m/z = 1021$ $[M+H]^+$

Steps 2 and 3: Synthesis of 5-ethynyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-
 15 pyrrolizin-7a(5H)-yl)methoxy)-10-((1R*,2R*)-2-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-
 1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol formate and 5-ethynyl-6-
 fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-
 ((1S*,2S*)-2-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-
 tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol formate

20 **[00396]** The title compound was obtained as a solid, from the compound of step 1, following
 a similar 2 step procedure to that described in Example 34, steps 7 to 8. LCMS $m/z = 618$
 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.20 (s, 1H), 7.96 (dd, 1H), 7.46 (t, 1H), 7.37 (d,
 1H), 7.17 - 7.11(m, 1H), 5.56 (s, 1H), 5.36 - 5.22 (m, 1H), 4.89 - 4.69 (m, 1H), 4.63 - 4.51 (m,
 2H), 4.31 - 4.22 (m, 1H), 4.17 - 4.09 (m, 2H), 4.08 - 3.94 (m, 2H), 3.92 - 3.78 (m, 1H), 3.15 -
 25 2.98 (m, 3H), 2.83 (d, 1H), 2.21 - 1.91 (m, 5H), 1.89 - 1.68 (m, 3H), 1.64 - 1.43 (m, 2H).

Example 36: Synthesis of 5-ethyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(((1R*,2S*)-2-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol and 5-ethyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(((1S*,2R*)-2-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 149)



Step 1: Synthesis of 4-(10-(((1R,2S*)-2-(benzyloxy)cyclobutyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol and 4-(10-(((1S*,2R*)-2-(benzyloxy)cyclobutyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol*

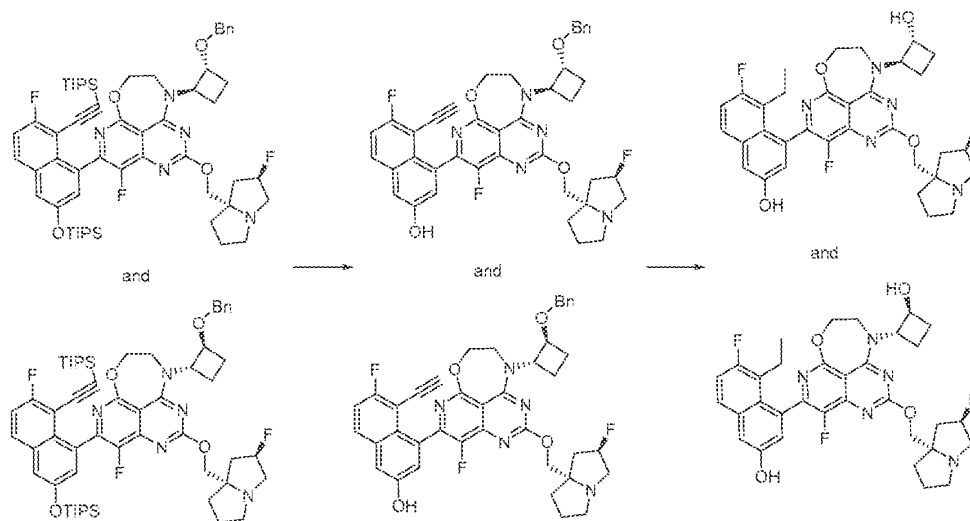
[00397] A solution of the compound of Example 34, step 6, (30 mg, 0.03 mmol) and CsF (22.3 mg, 0.145 mmol) in DMF (1 mL) was stirred for 30 min at rt. The resulting mixture was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM:MeOH=10:1) to afford the title compound (20 mg, 85%) as a yellow oil. LCMS m/z = 708 $[M+H]^+$

Step 2 : Synthesis of 5-ethyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(((1R,2S*)-2-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol and 5-ethyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(((1S*,2R*)-2-*

hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol

[00398] The title compound was obtained as a colorless oil, 5.3 mg, 19.7%, from the compound from step 1, following a similar procedure to that described in Example 32, step 3.

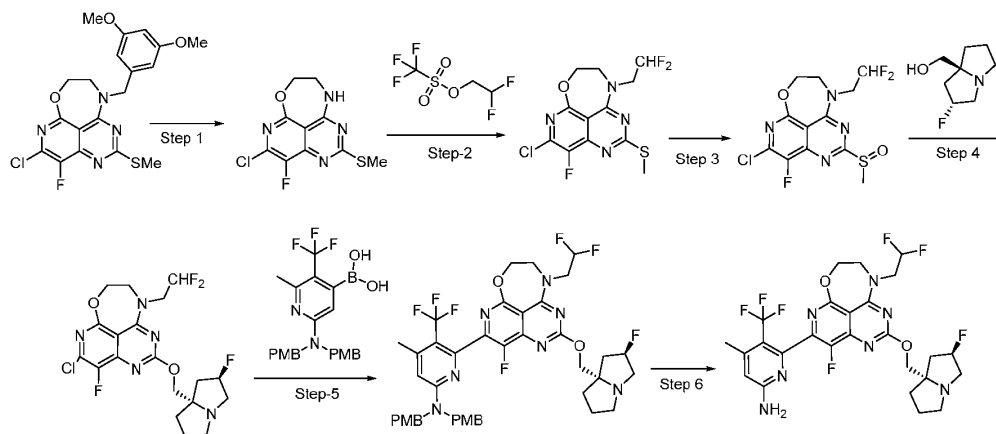
- 5 LCMS m/z = 622 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ : 7.75 (dd, 1H), 7.51 - 7.27 (m, 2H), 7.02 (d, 1H), 5.47 - 5.34 (m, 1H), 5.05 - 4.87 (m, 1H), 4.74 - 4.48 (m, 3H), 4.32 - 4.21 (m, 2H), 4.23 - 3.73 (m, 2H), 3.66 - 3.51 (m, 3H), 3.51 - 3.27 (m, 2H), 3.20 - 3.95 (m, 4H), 2.77 - 2.61 (m, 1H), 2.46 - 2.18 (m, 2H), 2.16 - 2.07 (m, 1H), 2.02 - 1.77 (m, 3H), 1.67 (t, 1H), 0.81 (t, 3H).
- 10 **Example 37: Synthesis of 5-ethyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((1R*,2R*)-2-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol and 5-ethyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((1S*,2S*)-2-hydroxycyclobutyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-**
- 15 **tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 150)**



[00399] The title compound was obtained as a white solid, 4 mg, 17.8%, from Example 35, step 1, following the same 2 step procedure described in Example 36. LCMS m/z = 622

- 20 $[M+H]^+$ 1H NMR (400 MHz, MeOH- d_4) 7.66 (dd, 1H), 7.53 - 7.16 (m, 2H), 7.05 (d, 1H), 5.65 - 5.28 (m, 1H), 5.03 - 4.93 (m, 1H), 4.78 - 4.43 (m, 4H), 4.36 (q, 1H), 4.14 - 3.94 (m, 2H), 3.70 - 3.52 (m, 3H), 3.28 - 3.20 (m, 1H), 2.62 - 2.39 (m, 3H), 2.39 - 2.14 (m, 6H), 2.04 (s, 1H), 1.83 - 1.62 (m, 2H), 0.86 (t, 3H).

Example 38: Synthesis of 6-(10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Compound 196)



5

Step 1: Synthesis of 5-chloro-10-(2,2-difluoroethyl)-4-fluoro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00400] Cs₂CO₃ (682 mg, 2.09 mmol), followed by 2,2-difluoroethyl trifluoromethanesulfonate (0.18 mL, 1.39 mmol) were added to a solution of Intermediate 31 (200 mg, 0.69 mmol) in DMF (6 mL) and the reaction mixture was stirred at 50 °C for 12 h. The reaction was quenched with ice-cold water (10 mL), extracted with EtOAc (2 x 25 mL), the organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography, using a gradient of 0-100% EtOAc in hexane, to afford the title compound (200 mg, 80%) as an off-white solid. LCMS m/z = 351 [M+H]⁺

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Step 2: Synthesis of 5-chloro-10-(2,2-difluoroethyl)-4-fluoro-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00401] m-CPBA (133 mg, 0.77 mmol) in DCM was added to a solution of the compound from step 1 (180 mg, 0.51 mmol) in DCM (3 mL) at 0 °C and the reaction mixture was stirred for 1 h at rt. The reaction mixture was quenched with sat. Na₂SO₃ solution (5 mL), extracted with DCM (3 x 10 mL) and washed with NaHCO₃ (10 mL) solution. The combined organic layer was dried over Na₂SO₄, filtered and evaporated under reduced pressure to give the title compound (150 mg, 80%) as a white solid. LCMS m/z = 367 [M+H]⁺

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[00402] Step 3: Synthesis of 5-chloro-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00403] The title compound was obtained, 100 mg, 49.8%, from the compound from step 2 and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar procedure to that described in Example 24, step 3. LCMS m/z = 462 [M+H]⁺.

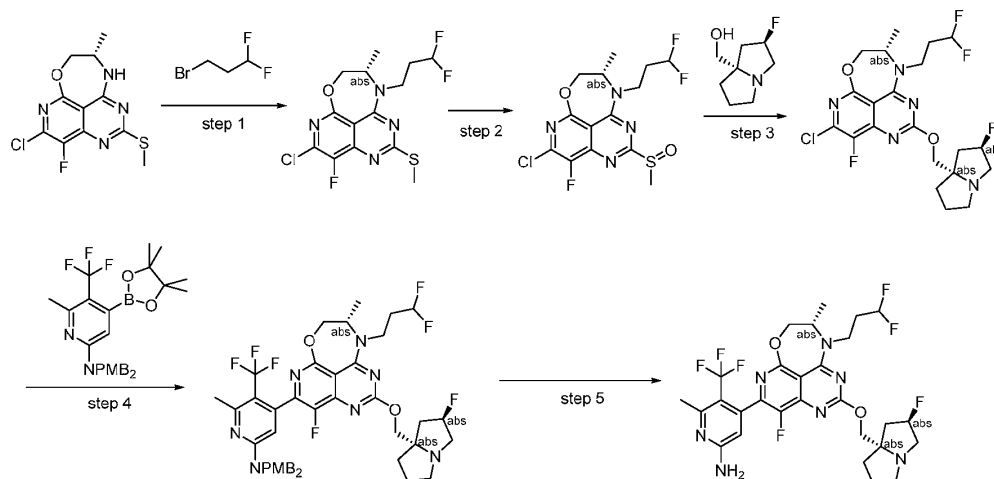
Step 4: Synthesis of 6-(10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

[00404] K₃PO₄ (138 mg, 0.65 mmol) and (6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)boronic acid (120 mg, 0.26 mmol) were added to a solution of the compound from step 3 (100 mg, 0.21 mmol) in dioxane (1 mL) and water (0.1 mL) and the mixture purged with N₂. CataCXium A Pd G3 (7.76 mg, 0.02 mmol) was added and the reaction mixture was irradiated in a microwave for 2 h at 110 °C. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography using a gradient of 0-100% EtOAc in hexane, to afford the title compound (100 mg, 52.2%) as a white solid. LCMS m/z = 842 [M+H]⁺.

Step 5: Synthesis of 6-(10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

[00405] Triflic acid (0.10 mL, 1.18 mmol) was added to a solution of the compound from step 4 (100 mg, 0.12 mmol) in TFA (4 mL) at 0 °C under N₂ and the reaction mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure and the crude compound was purified by prep-HPLC [column: X SELECT C18 (19*250) 5μ, Mobile Phase-A: 10mM NH₄CO₃ in water, Mobile Phase-B: MeCN, using gradient 0 to 100 % MeCN, at 15 mL/min, to afford the title compound (21 mg, 29.3%) as an off-white solid. LCMS m/z = 602 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 6.82 (s, 2H), 6.49-6.20 (m, 2H), 5.35-5.21 (m, 1H), 4.58-4.57 (m, 2H), 4.35-4.28 (m, 2H), 4.14-4.04 (m, 4H), 3.09-3.01 (m, 3H), 2.86-2.82 (m, 1H), 2.47 (d, 3H), 2.13-1.99 (m, 3H), 1.86-1.75 (m, 3H) ppm.

Example 39: Synthesis of 4-((S)-10-(3,3-difluoropropyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (Compound 192)



5

Step 1: Synthesis of (S)-5-chloro-10-(3,3-difluoropropyl)-4-fluoro-9-methyl-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00406] A mixture of Intermediate 32 (1.4 g, 4.66 mmol), 3-bromo-1,1-difluoropropane (0.89 g, 5.59 mmol) and Cs_2CO_3 (4.55 g, 14.0 mmol) in DMF (20 mL) was stirred at 60 °C for 2 h under N_2 . The reaction mixture was purified by reverse phase column chromatography with to afford the title compound (1.5 g, 85.1%) as a white solid. LCMS $m/z = 379$ $[\text{M}+\text{H}]^+$

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Step 2: Synthesis of (9S)-5-chloro-10-(3,3-difluoropropyl)-4-fluoro-9-methyl-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00407] The title compound was obtained as a yellow oil, 1.1g, crude, from the compound from step 1, following the procedure described in Example 16, step 3. LCMS $m/z = 395$ $[\text{M}+\text{H}]^+$

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Step 3: Synthesis of (S)-5-chloro-10-(3,3-difluoropropyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00408] ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (1.94 g, 12.2 mmol) was added to a solution of the compound from step 2 (1.6 g, 4.05 mmol) in toluene (40 mL) and the solution stirred at rt for 1 h under N_2 . NaOtBu (0.78 g, 8.1 mmol) was added in portions

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and the reaction mixture was stirred at rt for 1 h. The resulting mixture was concentrated under vacuum and the residue was purified by prep-TLC (DCM/ MeOH =10:1) to afford the title compound (1.2 g, 60.4%) as a white solid. LCMS m/z = 490 [M+H]⁺

5 Step 4: Synthesis of 4-((S)-10-(3,3-difluoropropyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

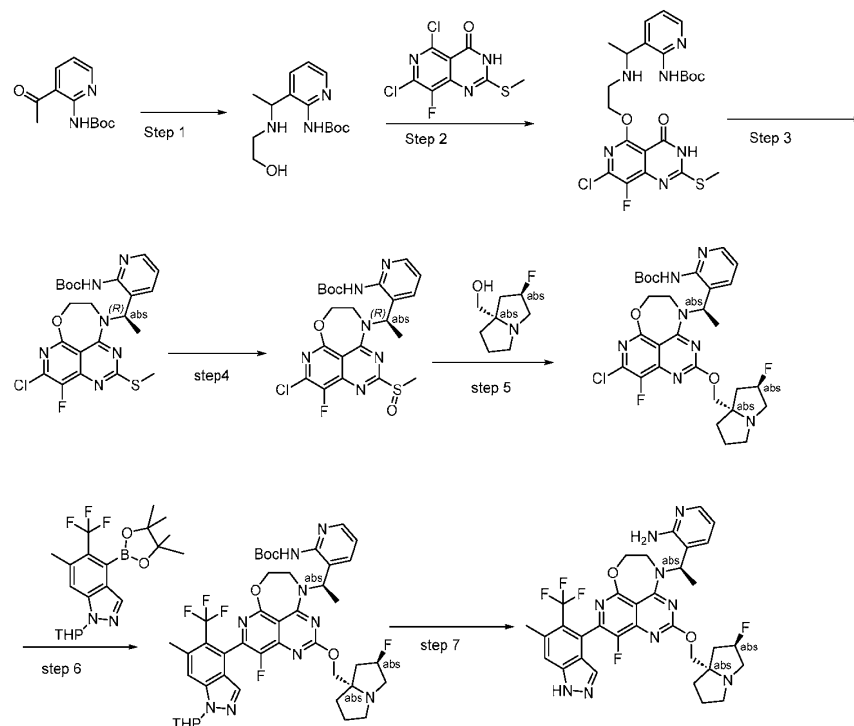
10 [00409] The title compound was obtained as a yellow solid, 75 mg, 21%, from the compound from step 3 and Intermediate 22, following a similar procedure to that described in Example 16, step 5. LCMS m/z = 870 [M+H]⁺

Step 5: Synthesis of 4-((S)-10-(3,3-difluoropropyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

15 [00410] A solution of the compound from step 4 (70 mg, 0.08 mmol) in TFA (2 mL) was stirred at 60 °C for 1 h under N₂. The reaction mixture was concentrated *in vacuo* and the crude product was purified by Prep-HPLC (Method D, Gradient: 5% B to 33% B in 7 min) to afford the title compound (31.8 mg, 62.6%) as a white solid. LCMS m/z = 630 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 6.78 (s, 2H), 6.37 – 6.03 (m, 2H), 5.37 (d, 1H), 4.49 (dd, 1H), 4.33 (d, 3H), 4.13 (dt, 2H), 3.64 – 3.50 (m, 2H), 3.02 (s, 3H), 2.40 (d, 3H), 2.28 (ddt, 4H), 2.11 – 1.79 (m, 4H), 1.19 (d, 3H).

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Example 40: Synthesis of 3-((1R)-1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 213)



Step 1: Synthesis of tert-butyl (3-((2-hydroxyethyl)amino)ethyl)pyridin-2-ylcarbamate

- [00411] To a solution of compound tert-butyl (3-acetylpyridin-2-yl)carbamate (250 g, 1.06 mol) in EtOH (1.5 L) was added 2-aminoethanol (96.9 g, 1.59 mol). Ti(i-PrO)₄ (300 g, 1.06 mol) was added dropwise and the reaction mixture stirred at 70 °C for 2 h. The mixture was cooled to 0 °C, sat. NaHCO₃ (200 mL) was added dropwise and the mixture was filtered through a pad of Celite®. The filter cake was washed with THF/MeOH (2 L/500 mL) and the filtrate was concentrated to give yellow residue. The residue was dissolved in THF (1.5 L), NaBH₄ (40.63 g, 1.07 mol) was added in portions and the reaction was stirred at 25 °C for 4 h. The mixture was cooled to 0 °C, 0.5 M of HCl aqueous (500 mL) was added dropwise at 0 °C and the mixture was filtered through a pad of Celite® and the filtrate was concentrated to give the title compound (180 g, crude) as a yellow solid. LCMS m/z = 182 [M-Boc+H]⁺

Step 2: Synthesis of tert-butyl (3-((1-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)amino)ethyl)pyridin-2-ylcarbamate

- [00412] To a solution of the compound from step 1 (166 g, 589 mmol) in THF (2.0 L) was added NaH (64.3 g, 1.61 mol, 60%) at 25 °C under N₂ and the mixture stirred for 5 min. 5,7-Dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one (150 g, 535.5 mmol) was added portionwise and the reaction was stirred at 70 °C for 30 min. The mixture was

cooled to 0 °C and quenched with sat.NH₄Cl (500 mL) and extracted with EtOAc (500 mL x 3). The combined organic layer was washed with brine (500 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated to give the title compound (240 g, crude) as a yellow solid. LCMS m/z = 525 [M+H]⁺

- 5 *Step 3: Synthesis of tert-butyl (R)-(3-(1-(5-chloro-4-fluoro-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-yl)carbamate*

[00413] To a solution of the compound from step 2 (240 g, 457.2 mmol) in DCM (2.0 L) was added BOP-Cl (233 g, 914 mmol) and DIPEA (295 g, 2.29 mol) and the reaction mixture was stirred at 25 °C for 16 h. The mixture was washed with sat.NaHCO₃ (500 mL), then brine (500 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by Combiflash® silica gel chromatography, eluting with 0-50% of THF in PE to give a yellow solid, 101 g, 43.6%. This was further purified by Chiral SFC (column: DAICEL CHIRALCEL OD (250mm*30mm,10um); mobile phase : CO₂-EtOH (0.1%NH₃H₂O); 45% B isocratic gradient) to give Peak 1, the title compound, 40 g, 37.9%, 100% ee. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.62 (s, 1H), 8.43 (dd, 1H), 8.02 (dd, 1H), 7.40 (dd, 1H), 6.64 (q, 1H), 4.26 - 4.40 (m, 2H), 3.33 - 3.58 (m, 1H), 3.22 - 3.29 (m, 1H), 2.59 (s, 3H), 1.59 (d, 3H), 1.12 (s, 9H) and Peak 2, tert-butyl (S)-(3-(1-(5-chloro-4-fluoro-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-yl)carbamate

- 20 *Step 4: Synthesis of tert-butyl (3-((1R)-1-(5-chloro-4-fluoro-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-yl)carbamate*

[00414] The title compound was obtained as a solid, 610 mg, 55%, from the title compound from step 3, following the procedure described in Example 1, step 3. LCMS m/z = 523 [M+H+Na]⁺

- 25 *Step 5: Synthesis of tert-butyl (3-((R)-1-(5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-yl)carbamate*

[00415] ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (456.6 mg, 2.9 mmol) was added to a solution of the compound from step 4 (500 mg, 0.9 mmol) in toluene (2 mL) and the mixture stirred at rt for 30 mins, then cooled to 0°C. LiOtBu (229.6 mg, 2.9 mmol) was added portion wise at 0°C and the reaction mixture stirred at 0°C for 10 mins. The reaction was quenched with water and the mixture was extracted with EtOAc (2 x 10mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column

chromatography, eluting with DCM / MeOH (8:1) to afford the title compound (370 mg, 65.0%) as an off-white solid. LCMS m/z = 618 [M+H]⁺

Step 6: Synthesis of tert-butyl (3-((1R)-1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-yl)carbamate

[00416] The title compound was obtained as a yellow solid, 85 mg, 65%, from the compound from step 5 and 6-methyl-1-(oxan-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)indazole, following a similar procedure to that described in Example 16, step 5. LCMS m/z = 866 [M+H+Na]⁺

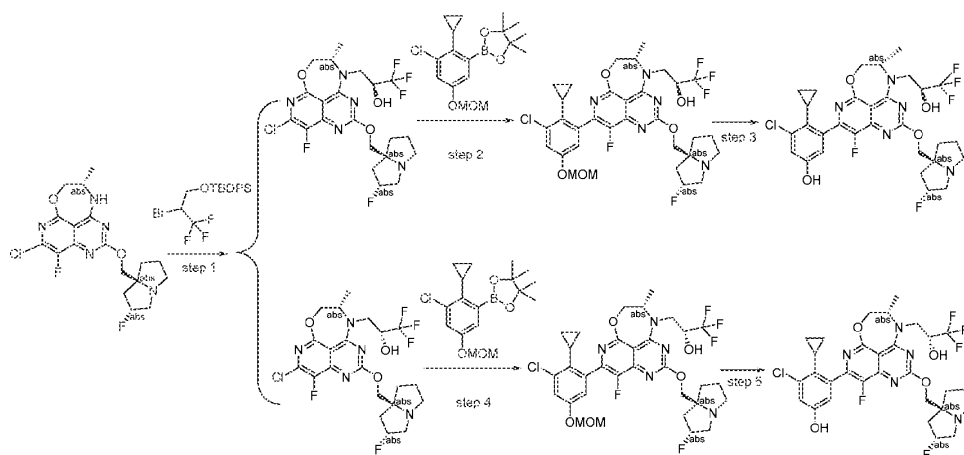
Step 7: Synthesis of 3-((1R)-1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00417] A solution of the compound from step 6 (100 mg, 0.115 mmol) and TFA (1 mL) in DCM (2 mL) was stirred for 1h at rt under N₂. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse phase column, C18 silica gel; mobile phase, MeCN in Water (10mmol/L NH₄HCO₃), 40% to 50% gradient in 10 min; The crude product (12mg) was purified by Prep-HPLC (Method D, Gradient: 7% B to 30% B in 8 min) to afford the title compound (48.4 mg, 63.1%) as a white solid. LCMS m/z = 682 [M+H+Na]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 13.50 (s, 1H), 7.98 (d, 1H), 7.71-7.65 (m, 3H), 6.68 – 6.65 (m, 1H), 6.42-6.35 (m, 1H), 5.83 – 5.71 (m, 2H), 5.44 – 5.40 (m, 1H), 4.47 – 4.21 (m, 1H), 4.32 – 4.28 (m, 3H), 3.79 – 3.71 (m, 1H), 3.46 – 3.38 (m, 1H), 3.27-2.81 (m, 2H), 2.64 – 2.52 (m, 3H), 2.39 – 2.31 (m, 1H), 2.28 – 2.11 (m, 3H), 1.89 – 1.80 (m, 3H), 1.58 – 1.50 (m, 4H).

Example 41: Synthesis of 3-chloro-4-cyclopropyl-5-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-10-((R)-3,3,3-trifluoro-2-hydroxypropyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol or 3-chloro-4-cyclopropyl-5-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-10-((S)-3,3,3-trifluoro-2-hydroxypropyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol (Compound 201)

and

Example 42: Synthesis of 3-chloro-4-cyclopropyl-5-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-10-((S)-3,3,3-trifluoro-2-hydroxypropyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol or 3-chloro-4-cyclopropyl-5-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-10-((R)-3,3,3-trifluoro-2-hydroxypropyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol (Compound 202)



Step 1: Synthesis of (R)-3-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)-1,1,1-trifluoropropan-2-ol and (S)-3-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)-1,1,1-trifluoropropan-2-ol

[00418] A mixture of Intermediate 29 (100 mg, 0.24 mmol), Intermediate 18 (314 mg, 0.72 mmol) and Cs₂CO₃ (397 mg, 1.21 mmol) in DMF (3 mL) was stirred at rt for 2h under N₂. The resulting mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 10:1) to afford Peak 1, (R)-3-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)-1,1,1-trifluoropropan-2-ol or (S)-3-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-

dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)-1,1,1-trifluoropropan-2-ol (35 mg, 27.5%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) 1.22 (m, 3H), 1.84 (s, 2H), 1.80 – 1.92 (m, 1H), 1.92 (s, 1H), 2.02 (s, 1H), 2.07 – 2.17 (m, 1H), 2.78 – 2.92 (m, 1H), 2.93 – 3.03 (m, 1H), 3.03 – 3.12 (m, 2H), 3.47 (s, 1H), 4.01 (s, 1H), 4.12 (s, 1H), 4.32 (m, 1H), 4.37 – 4.47 (m, 2H), 4.65 (m, 2H), 5.35 (m, 1H), 6.72 (s, 1H).

[00419] and Peak 2, (S)-3-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)-1,1,1-trifluoropropan-2-ol or (R)-3-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)-1,1,1-trifluoropropan-2-ol (35 mg, 27.5%) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ 1.25 (m, 4H), 1.84 (s, 1H), 1.70 – 1.98 (m, 2H), 2.03 (s, 1H), 2.07 – 2.18 (m, 1H), 2.82 (m, 1H), 3.00 (s, 1H), 3.09 (m, 2H), 3.79 (s, 1H), 4.08 (s, 2H), 4.13 – 4.24 (m, 1H), 4.32 (s, 1H), 4.40 (s, 1H), 4.49 (s, 1H), 4.58 (s, 1H), 5.35 (m, 1H), 6.60 (s, 1H).

Step 2: Synthesis of (R)-3-((S)-5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)-1,1,1-trifluoropropan-2-ol or (S)-3-((S)-5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)-1,1,1-trifluoropropan-2-ol

[00420] The title compound was obtained as a brown solid, 36 mg, 81.6%, from Peak 1, the compound from step 1, and Intermediate 21, following a similar procedure to that described in Example 16, step 5. LCMS m/z = 698 [M+H]⁺

Step 3: Synthesis of 3-chloro-4-cyclopropyl-5-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-10-((R)-3,3,3-trifluoro-2-hydroxypropyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol or 3-chloro-4-cyclopropyl-5-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-10-((S)-3,3,3-trifluoro-2-hydroxypropyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol

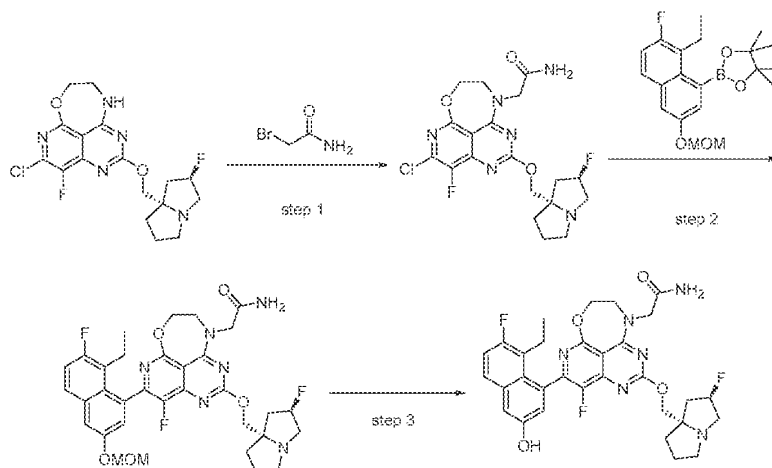
[00421] A solution of the compound from step 2 (49 mg, 0.07 mmol) and 4M HCl in dioxane (2 mL) was stirred at rt for 1h under N₂. The resulting mixture was concentrated under reduced pressure. The crude product (49 mg) was purified by Prep-HPLC (Method A, Gradient: 42% B to 67% B in 7min) to afford the title compound (20.6 mg, 44.9 %) as a white solid. LCMS m/z

= 656 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ -0.05 - 0.10 (m, 2H), 0.58-0.68 (m, 2H), 1.22 (m, 3H), 1.67 - 1.84 (m, 4H), 1.90 (s, 1H), 1.97 - 2.15 (m, 2H), 2.75 - 2.87 (m, 1H), 2.91 - 3.03 (m, 1H), 3.05 (s, 2H), 3.42 (s, 1H), 3.98 (s, 1H), 4.10 (s, 1H), 4.27 (s, 1H), 4.58 - 4.53 (m, 2H), 4.62 - 4.71 (m, 2H), 5.29 - 5.35 (m, 1H), 6.65 (s, 1H), 6.73 (s, 1H), 6.90 (s, 1H), 9.93 (s, 1H).

Steps 4 and 5: Synthesis of 3-chloro-4-cyclopropyl-5-((*S*)-4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-9-methyl-10-((*S*)-3,3,3-trifluoro-2-hydroxypropyl)-9,10-dihydro-8*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-5-yl)phenol or 3-chloro-4-cyclopropyl-5-((*S*)-4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-9-methyl-10-((*R*)-3,3,3-trifluoro-2-hydroxypropyl)-9,10-dihydro-8*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-5-yl)phenol,

[00422] The title compound was obtained as a white solid, from Peak 2, the compound from step 1, following the 2 step procedure described in steps 2 and 3. LCMS *m/z* = 656 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ -0.08-0.07 (m, 2H), 0.62 (s, 2H), 1.30 (m, 3H), 1.77 (m, 3H), 1.86 (s, 1H), 1.96 (s, 1H), 2.06 (s, 1H), 2.14 (s, 1H), 2.84 (s, 1H), 3.03 (s, 1H), 3.08 - 3.13 (m, 2H), 3.79-3.83 (m, 1H), 4.10 (s, 2H), 4.19 (t, 1H), 4.33 (dd, 1H), 4.40 (dd, 1H), 4.43 (dd, 1H), 4.56 (m, 2H), 5.22 - 5.36 (s, 1H), 6.61 (s, 1H), 6.76 (s, 1H), 6.94 (s, 1H), 9.97 (s, 1H).

Example 43: Synthesis of 2-(5-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)acetamide (Compound 148)



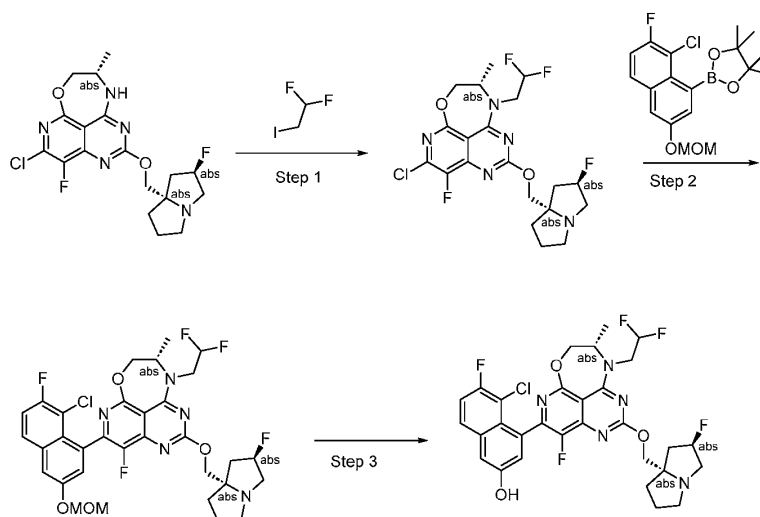
Steps 1 and 2: Synthesis of 2-(5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)acetamide

[00423] The title compound was obtained from Intermediate 30, bromoacetamide and 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, following a similar 2 step procedure to that described in Example 46, steps 1 and 2.

Step 3: Synthesis of 2-(5-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)acetamide formate

[00424] The title compound was obtained as a white solid, from the compound from steps 1 and 2, following a similar procedure to that described in Example 15, step 4. LCMS m/z = 609 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6): δ 0.81 (m, 3H), 1.72 – 2.09 (m, 6H), 2.27 (s, 1H), 2.41 (s, 1H), 2.78 – 2.88 (m, 1H), 3.03 (s, 1H), 3.10 (m, 2H), 3.96 – 4.01 (m, 2H), 4.09 (m, 2H), 4.45 (m, 2H), 4.61 (m, 2H), 5.35 (s, 1H), 7.01 (s, 1H), 7.22 (s, 1H), 7.31 (s, 1H), 7.35 (s, 1H), 7.60 (s, 1H), 7.75 (s, 1H), 8.18 (s, 1H).

Example 44: Synthesis of 5-chloro-4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-fluoronaphthalen-2-ol formate (Compound 199)



20

Step 1: Synthesis of (S)-5-chloro-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- [00425] To a stirred solution of Intermediate 29, 0.15 g, 0.36 mmol) and Cs₂CO₃ (356 mg, 1.09 mmol) in DMF (3 mL) was added 1,1-difluoro-2-iodoethane (105 mg, 0.55 mmol) and the reaction mixture was stirred at 80°C for 1h under N₂. The cooled mixture was diluted with brine and extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (3x50mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase chromatography, C18 silica gel; mobile phase, MeCN in water, 40% to 50% gradient in 10 min to afford the title compound (0.12 g, 69.2%) as an off-white solid. LCMS m/z = 476 [M+H]⁺

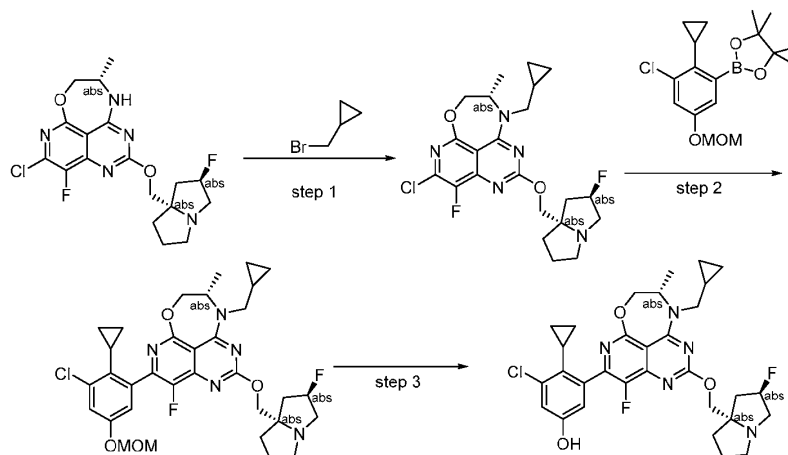
Step 2: Synthesis of (S)-5-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- [00426] The title compound was obtained as a white solid, 0.1 g, 39%, from the compound from step 1 and 2-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, following a similar procedure to that described in Example 16, step 5. LCMS m/z = 680 [M+H]⁺

Step 3: Synthesis of 5-chloro-4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-fluoronaphthalen-2-ol formate

- [00427] TFA (0.5 mL) was added to a solution of the compound from step 2 (68 mg, 0.1 mmol) in DCM (2.5 mL) and the reaction mixture was stirred at rt for 1h under N₂. The resulting mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (Method D, Gradient: 21% B to 32% B in 8 min) to afford the title compound (20.2 mg, 29.6%) as a white solid. LCMS m/z = 636 [M+H]⁺ + ¹H NMR (400 MHz, DMSO-d₆) δ 8.19 (s, 1H), 7.94 (ddd, 1H), 7.57 (td, 1H), 7.42 (t, 1H), 7.21, 7.15 (d, 1H), 6.46 (tdt, 1H), 5.42 – 5.13 (m, 1H), 4.60 (dt, 1H), 4.54 – 4.29 (m, 2H), 4.16 (ddd, 3H), 4.05 (dd, 1H), 3.16 – 3.05 (m, 2H), 3.01 (d, 1H), 2.90 – 2.74 (m, 1H), 2.19 – 1.91 (m, 3H), 1.80 (dtd, 3H), 1.28 (d, 3H).

- 30 **Example 45: Synthesis of 3-chloro-4-cyclopropyl-5-((S)-10-(cyclopropylmethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol (Compound 210)**



Step 1: Synthesis of (S)-5-chloro-10-(cyclopropylmethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- 5 **[00428]** A mixture of Intermediate 29 (80 mg, 0.19 mmol), (bromomethyl)cyclopropane (31.47 mg, 0.23 mmol) and Cs_2CO_3 (189.9 mg, 0.58 mmol) in DMF (2 mL) was stirred at rt for 2 h under N_2 . The resulting mixture was concentrated *in vacuo* and the residue was purified by prep-TLC (DCM / MeOH 10:1) to afford the title compound (70 mg, 77.3%) as a white solid. LCMS m/z = 466 $[\text{M}+\text{H}]^+$

- 10 *Step 2: Synthesis of (S)-5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-10-(cyclopropylmethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

[00429] The title compound was obtained as a white solid, 70 mg, 72.5%, from the compound from step 1 and Intermediate 21, following a similar procedure to that described in

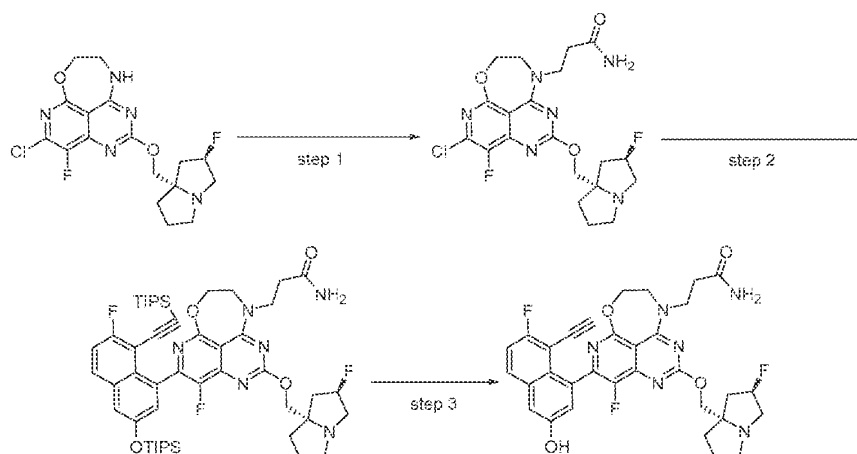
- 15 Example 16, step 5. LCMS m/z = 642 $[\text{M}+\text{H}]^+$.

Step 3: Synthesis of 3-chloro-4-cyclopropyl-5-((S)-10-(cyclopropylmethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol

- [00430]** A solution of the compound from step 2 (70 mg, 0.11 mmol) in DCM (2
20 mL) and TFA (0.8 mL) was stirred at rt for 1 h in air. The resulting mixture was concentrated *in vacuo* and the crude product was purified by prep-HPLC (Method B, Gradient: 25% B to 40% B in 7 min) to afford the title compound (36.2 mg, 55.2%) as a white solid. LCMS m/z = 598 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.98 (s, 1H), 6.94 (d, 1H), 6.77 (d, 1H), 5.53-5.21

(m, 1H), 4.65 - 4.52 (m, 1H), 4.46 - 4.36 (m, 2H), 4.34-4.19 (m, 2H), 3.98 - 3.91 (m, 1H), 3.58 - 3.51 (m, 1H), 3.15 - 3.10 (m, 1H), 2.55 - 2.51 (m, 2H), 2.41 - 2.20 (m, 2H), 2.17 - 1.83 (m, 4H), 1.76 - 1.71 (m, 1H), 1.38 - 1.18 (m, 5H), 0.69 - 0.58 (m, 2H), 0.57 - 0.49 (m, 2H), 0.48 - 0.37 (m, 2H), 0.11 - 0.05 (m, 1H), 0.04 - 0.01 (m, 1H).

- 5 **Example 46: Synthesis of 3-(5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide (Compound 143)**



- 10 *Step 1: Synthesis of 3-(5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide*

[00431] The title compound was obtained as a white solid, 18 mg, 15.5%, from Intermediate 30 and 3-bromopropanamide, following a similar procedure to that described in Example 44, step 1. LCMS $m/z = 467$ $[M+H]^+$

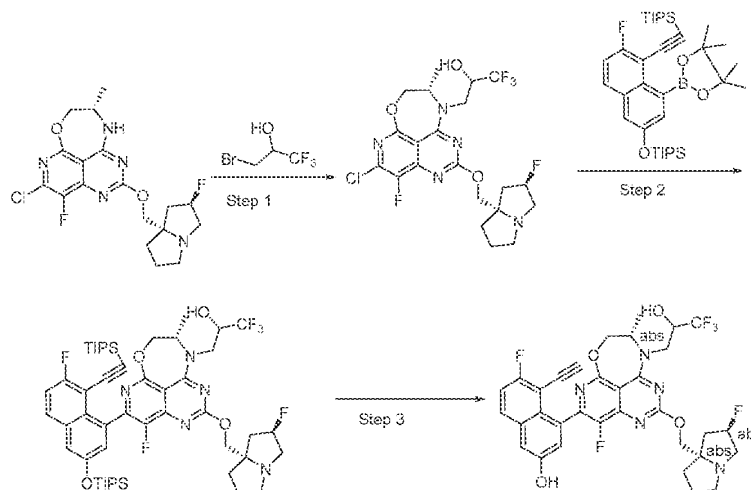
- 15 *Step 2: Synthesis of 3-(4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide*

- 20 **[00432]** The title compound was obtained as a yellow solid, 15 mg, 50.3%, from the compound from step 1 and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane, following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 930$ $[M+H]^+$

Step 3: Synthesis of 3-(5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy))-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide

[00433] The title compound was obtained as a white solid, 3.6 mg, 36.5%, from the compound from step 2, following a similar procedure to that described in Example 30, step 8, except the compound was purified by Prep-HPLC (Method D, Gradient: 14% B to 30% B in 7 min). LCMS m/z = 619 $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6): δ 10.23 (s, 1H), 8.15 - 7.87 (m, 1H), 7.64 - 7.31 (m, 3H), 7.21 - 6.89 (m, 2H), 5.72 - 5.41 (m, 1H), 4.81 - 4.41 (m, 4H), 4.19 - 3.98 (m, 4H), 3.93 - 3.65 (m, 3H), 2.40 - 1.97 (m, 8H), 1.59 - 1.33 (m, 2H).

Example 47: Synthesis of 5-ethynyl-6-fluoro-4-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy))-9-methyl-10-(3,3,3-trifluoro-2-hydroxypropyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 173)



Step 1: Synthesis of 3-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy))-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)-1,1,1-trifluoropropan-2-ol

[00434] The title compound was obtained as an off-white solid, 170 mg, 89%, from Intermediate 29 and 3-bromo-1,1,1-trifluoropropan-2-ol, following a similar procedure to that described in Example 44, step 1. LCMS m/z = 524 $[M+H]^+$

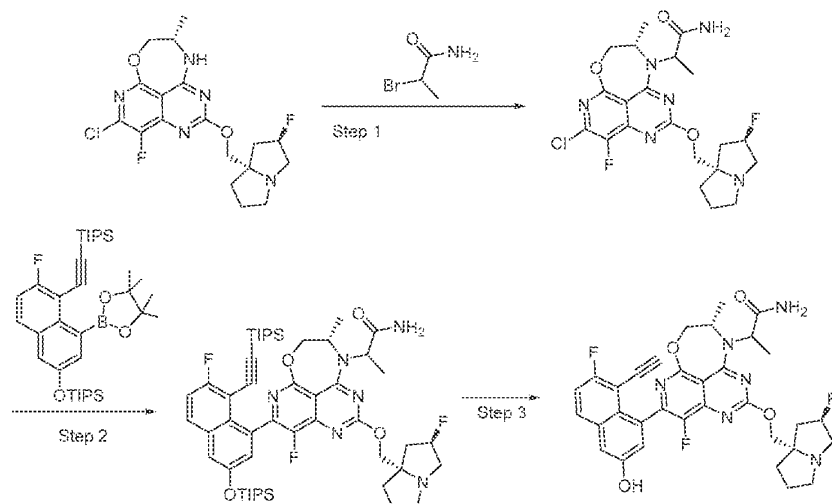
Steps 2 and 3: Synthesis of 5-ethynyl-6-fluoro-4-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy))-9-methyl-10-(3,3,3-trifluoro-2-

hydroxypropyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol formate

[00435] The title compound was obtained as an off-white solid, from the compound from step 1, following a similar 2 step procedure to that described in Example 16, steps 5 and 6.

- 5 LCMS $m/z = 626 [M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.07 (d, 1H), 8.15 (s, 1H), 7.96 (ddd, 1H), 7.46 (td, 1H), 7.38 (d, 1H), 7.21 (d, 1H), 7.12 (d, 1H), 6.67 (d, 1H), 5.44 – 5.09 (m, 1H), 4.77 – 4.22 (m, 4H), 4.22 – 3.83 (m, 4H), 3.17 – 2.95 (m, 3H), 2.85 (t, 1H), 2.19 – 2.01 (m, 2H), 2.01 – 1.66 (m, 3H), 1.41 – 1.20 (m, 3H).

Example 48: Synthesis of 2-((S)-5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide
 10 **(Compound 176)**



Step 1: Synthesis of 2-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide

- [00436]** A solution of Intermediate 29, (50 mg, 0.12 mmol), 2-bromopropanamide (18.5 mg, 0.12 mmol) and CS_2CO_3 (118.7 mg, 0.36 mmol) in DMF (5 mL, 0.605 mmol) was stirred at 25°C for 2 h. The resulting mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 10mL). The combined organic layers were washed with brine (10mL), dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was

purified by silica gel column chromatography, eluting with PE:EtOAc (3:1) to afford the title compound (46 mg, 73%) as a yellow solid. LCMS m/z = 483 $[M+H]^+$

Step 2: Synthesis of 2-((S)-4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide

[00437] The title compound was obtained as a yellow solid, 58 mg, 71%, from the compound from step 1 and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane, following a similar procedure to that described in Example 16, step 5. LCMS m/z = 473 $[M+H]^+$

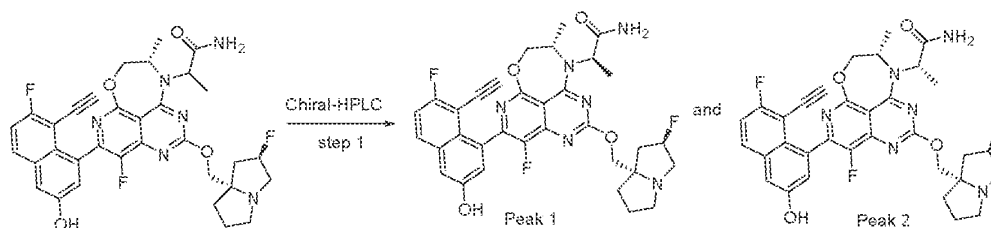
Step 3: Synthesis of 2-((S)-5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide formate

[00438] A solution of the compound from step 2 (50 mg, 0.053 mmol) and CsF (160.7 mg, 1.06 mmol) in DMF (6 mL) was stirred at 25°C for 4 h. The resulting mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10mL). The combined organic layers were washed with brine (10mL), dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE/EtOAc 2:1) to afford crude product (40 mg) as a light-yellow oil. The residue was purified by prep HPLC (Method D, Gradient: 15% B to 25% B in 8 min) to afford the title compound (23.2 mg, 60%) as a yellow solid. LCMS m/z = 633 $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.13 (d, 1H), 8.03 - 7.92 (m, 1H), 7.53 - 7.22 (m, 3H), 7.23 - 6.95 (m, 2H), 5.74 - 5.22 (m, 2H), 4.64 - 4.43 (m, 2H), 4.28 - 3.92 (m, 4H), 3.20 - 3.06 (m, 3H), 2.94 - 2.81 (m, 1H), 2.19 - 2.12 (m, 1H), 2.10 - 1.95 (m, 2H), 1.92 - 1.74 (m, 3H), 1.55 - 1.40 (m, 3H), 1.38 - 1.17 (m, 3H).

Example 49: Synthesis of (R)-2-((S)-5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide (Compound 179)

and

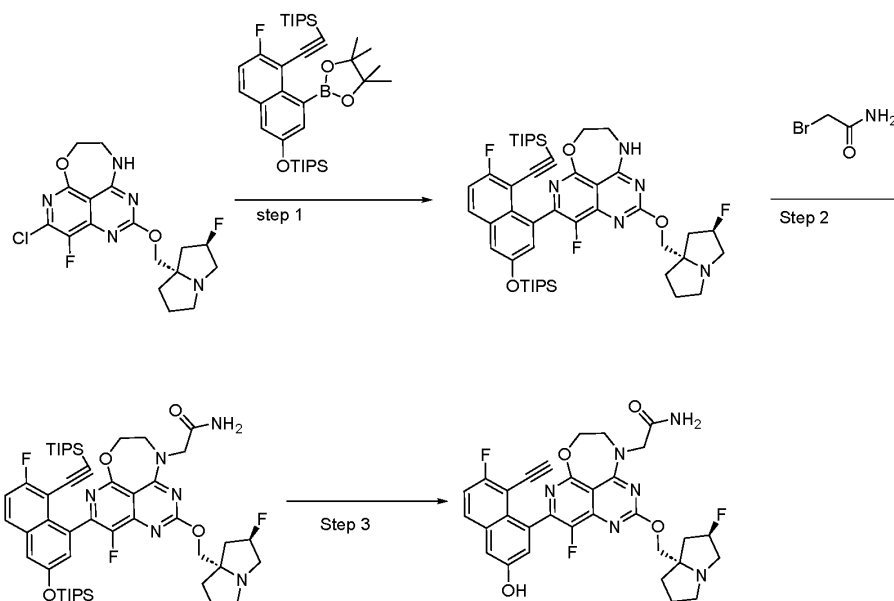
Example 50: Synthesis of (S)-2-((S)-5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide (Compound 183)



[00439] Example 48 (15 mg) was purified by Prep-HPLC (Column: CHIRALPAK IE, 2*25 cm, 5 μ m; Mobile Phase A: MTBE (0.2% IPA), Mobile Phase B: MeOH: DCM=1:1; Flow rate: 20 mL/min; Gradient: isocratic 15; to afford Peak 1, Example 49 (3.4 mg, 22.7%) as a white solid. LCMS m/z = 634 [M+H]⁺. ¹H NMR (400 MHz, DMSO- d_6) δ 1.23 (s, 1H), 1.27 – 1.42 (m, 4H), 1.51 (m, 3H), 1.89 (s, 3H), 2.24 (s, 3H), 2.98 (s, 2H), 3.87 (s, 1H), 4.27 (m, 3H), 4.46 – 4.62 (m, 2H), 5.32 (s, 1H), 5.45 (s, 1H), 7.17 (s, 2H), 7.38 (m, 2H), 7.46 (s, 1H), 7.97 (s, 1H), 10.18 (s, 1H).

[00440] Further elution provided Peak 2, Example 50, 6.1 mg, 40.7%. LCMS m/z = 634 [M+H]⁺. ¹H NMR (400 MHz, DMSO- d_6) δ 7.94 (dd, 1H), 7.50 – 7.32 (m, 3H), 7.25–7.21 (m, 1H), 7.19 – 7.08 (m, 1H), 5.68 – 5.62 (m, 1H), 5.43 – 5.09 (m, 1H), 4.67 – 4.42 (m, 2H), 4.22 – 4.18 (m, 1H), 4.13 – 3.92 (m, 3H), 3.25 – 3.20 (m, 1H), 3.18 – 3.08 (m, 2H), 3.05 – 2.95 (m, 1H), 2.85 – 2.80 (m, 1H), 2.16 – 1.96 (m, 2H), 1.92 – 1.73 (m, 2H), 1.61 – 1.58 (m, 2H), 1.28 – 1.20 (m, 2H), 1.17–1.14 (m, 2H), 1.12 – 1.08 (m, 1H).

Example 51: Synthesis of 2-(5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)acetamide (Compound 122)



Step 1: Synthesis of 4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

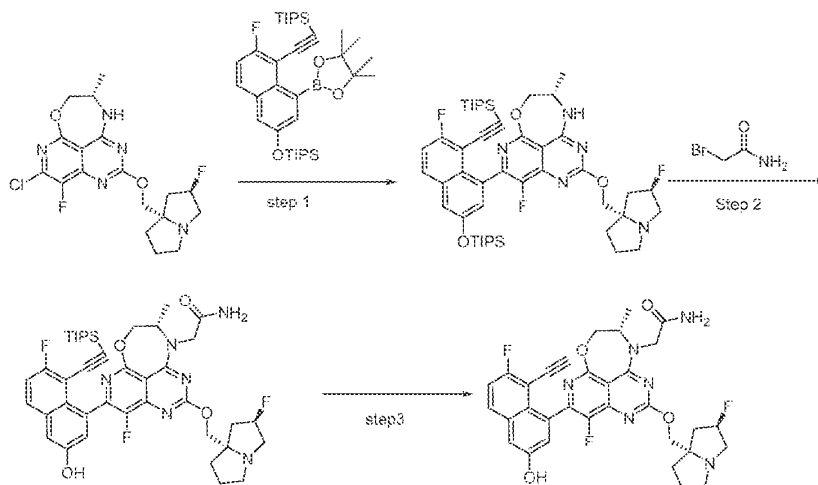
- 5 **[00441]** A mixture of Intermediate 30 (0.153 g, 0.39 mmol), ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane (0.36 g, 0.58 mmol), K₃PO₄ (0.24 g, 1.16 mmol) and cataCXium-A-Pd-G3 (28.0 mg, 0.04 mmol) in dioxane (5mL)/ H₂O (1 mL) was stirred for 2h at 80°C under N₂. The cooled mixture was diluted with saturated brine and extracted with EtOAc (3 x 25mL).
- 10 The combined organic layers were washed with brine (3x25mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase column chromatography (C18 silica gel; mobile phase, MeCN in water, 40% to 50% gradient in 10 min to give the title compound (0.248 g, 75%) as a white solid. LCMS m/z = 860 [M+H]⁺
- 15 *Step 2: Synthesis of 2-(4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)acetamide*

[00442] The title compound was obtained as a white solid, 130 mg, 49.2%, from bromoacetamide and the compound from step 1, following a similar procedure to that described in Example 44, step 1. LCMS $m/z = 918$ $[M+H]^+$

Step 3: Synthesis of 2-(5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)acetamide

[00443] The title compound was obtained as an off-white solid, 15.4 mg, 8.9%, from the compound from step 2, following a similar procedure to that described in Example 23, step 6. LCMS $m/z = 605$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.15 (s, 1H), 7.96 (dd, 1H), 7.58 (s, 1H), 7.46 (t, 1H), 7.37 (d, 1H), 7.22 (s, 1H), 7.15 (d, 1H), 5.30 (d, 1H), 4.67 – 4.46 (m, 3H), 4.33 (dd, 1H), 4.19 – 3.88 (m, 5H), 3.20 – 3.00 (m, 3H), 2.86 (q, 1H), 2.18 – 1.94 (m, 3H), 1.91 – 1.68 (m, 3H).

Example 52: Synthesis of 2-((S)-5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)acetamide (Compound 166)



Step 1: Synthesis of (S)-4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

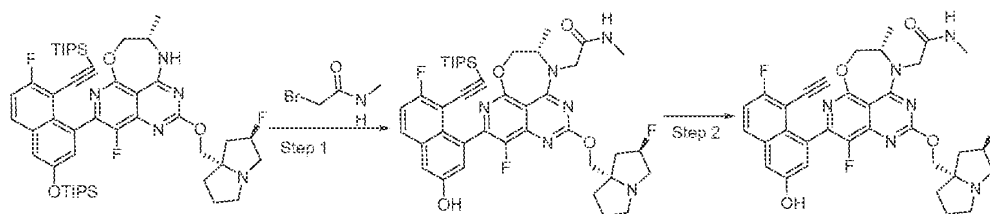
[00444] The title compound was obtained from Intermediate 29 and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-

yl)oxy)triisopropylsilane, following a similar procedure to that described in Example 51, step 1.
LCMS $m/z = 875$ $[M+H]^+$

Step 2 and 3: Synthesis of 2-((S)-5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-
(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-
5 oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)acetamide

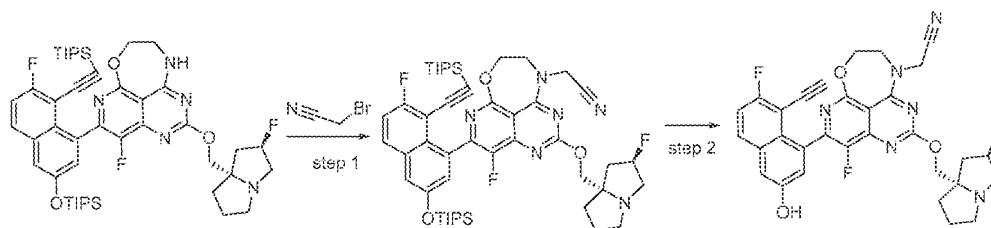
[00445] The title compound was obtained as a white solid, from the compound from step 1 and bromoacetamide, following a similar 2 step procedure to that described in Example 51.
LCMS $m/z = 619$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.14 (d, 1H), 7.96 (ddd, 1H),
7.57 (s, 1H), 7.46 (td, 1H), 7.37 (t, 1H), 7.26 – 7.06 (m, 2H), 5.30 (d, 1H), 4.67 – 4.41 (m, 3H),
10 4.21 – 4.01 (m, 4H), 3.97 (s, 1H), 3.20 – 3.00 (m, 3H), 2.86 (d, 1H), 2.18 – 1.92 (m, 3H), 1.92 –
1.69 (m, 3H), 1.29 (dd, 3H).

Example 53: Synthesis of 2-((S)-5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-
fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-
dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)-N-methylacetamide
15 (Compound 163)



[00446] The title compound was obtained from Example 52, step 1 and 2-bromo-N-methylacetamide, following a similar 2 step procedure to that described in Example 51, steps 2
and 3, except the compound was purified by prep-HPLC (Xcselect CSH F-phenyl OBD Column,
20 19*250 mm, 5 μ m; Mobile Phase A: Water (0.1% FA), Mobile Phase B: MeOH; Flow rate: 30
mL/min; Gradient: 17% to 47% B in 9 min). LCMS $m/z = 633$ $[M+H]^+$. 1H NMR (400 MHz,
DMSO- d_6) δ 10.14 (d, 1H), 8.11 – 7.89 (m, 2H), 7.52 – 7.31 (m, 2H), 7.16 (dd, 1H), 5.32 (d,
1H), 4.67 – 4.46 (m, 3H), 4.43 – 4.25 (m, 1H), 4.25 – 3.91 (m, 3H), 3.25 – 3.02 (m, 4H), 2.90
(s, 1H), 2.65 (d, 3H), 2.23 – 1.95 (m, 3H), 1.95 – 1.70 (m, 3H), 1.29 (d, 3H).

25 Example 54: Synthesis of 2-(5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-
(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-
1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)acetonitrile (Compound 123)



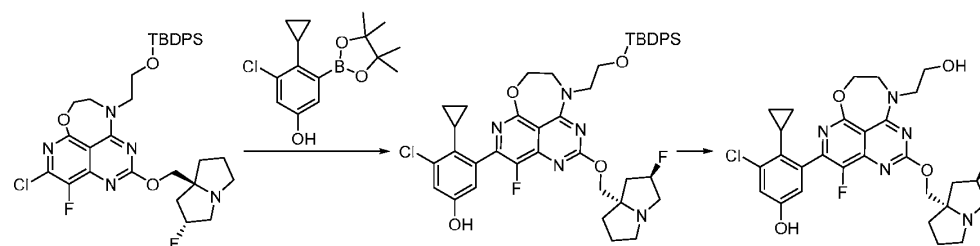
Step 1: Synthesis of 2-(4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy))-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)acetonitrile

[00447] The title compound was obtained as a yellow solid, 55 mg, 76%, from 2-bromoacetonitrile and Example 51, step 1, following a similar procedure to that described in Example 44, step 1. LCMS $m/z = 899$ $[M+H]^+$

Step 2: Synthesis of 2-(5-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy))-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)acetonitrile formate

[00448] The title compound was obtained as a white solid, 11.2 mg, 29.8%, from the compound from step 1, following a similar procedure to that described in Example 30, step 8. LCMS $m/z = 633$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 10.16 (s, 1H), 7.96 (dd, 1H), 7.47 (d, 1H), 7.44 – 7.27 (m, 1H), 7.15 (d, 1H), 5.30 (d, 1H), 4.86 (s, 2H), 4.68 – 4.51 (m, 2H), 4.27 – 3.93 (m, 5H), 3.05 (s, 3H), 2.86 (s, 1H), 2.22 – 1.97 (m, 3H), 1.84 (dd, 3H).

Example 55: Synthesis of 3-chloro-4-cyclopropyl-5-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy))-10-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol (Compound 126)



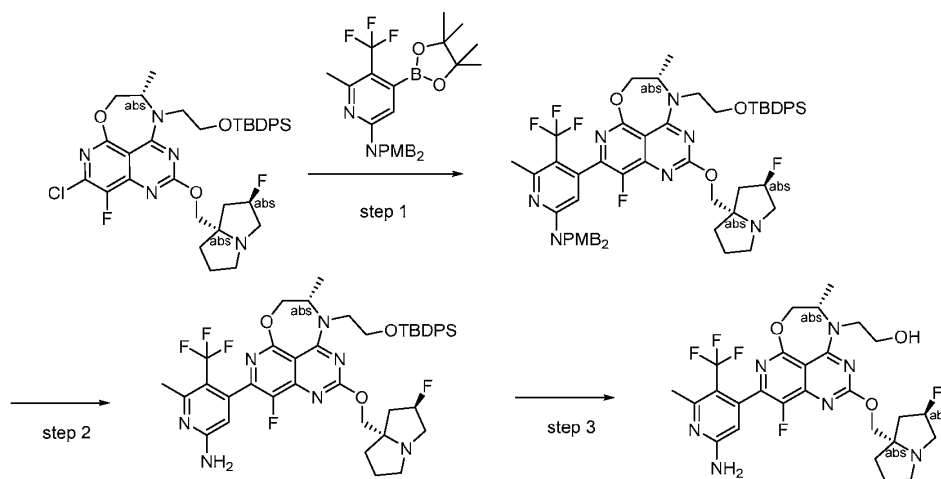
Step 1: Synthesis of 3-(10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy))-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol

[00449] The title compound was obtained as a white solid, 75 mg, 89.7%, from Intermediate 20 and the compound of Example 5, step 5, following the procedure described in Example 16, step 5. LCMS $m/z = 811$ $[M-H]^+$

Step 2: Synthesis of 3-chloro-4-cyclopropyl-5-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol

[00450] CsF (70 mg, 0.46 mmol) was added to a solution of the compound from step 1 (70 mg, 0.07 mmol) in DMF (5 mL) and the reaction mixture was stirred for 1 h at rt. The resulting mixture was filtered, the filter cake was washed with DCM (5 x 3 mL) and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC (Column: YMC-Actus Triart C18 ExRS 30*150 mm, 5 μ m; Mobile Phase A: Water (10mmol/L NH_4HCO_3), Mobile Phase B: MeCN; Flow rate: 60 mL/min; Gradient: 32% B to 46% B in 9 min to afford the title compound (20.9 mg, 40.3%) as a white solid. LCMS $m/z = 574$ $[M+H]^+$ 1H NMR (500 MHz, $DMSO-d_6$) δ 9.97 (s, 1H), 6.93 (m, 1H), 6.73 (m, 1H), 5.34 - 5.23 (m, 1H), 4.88 (m, 1H), 4.57 - 4.52 (m, 2H), 4.11 (m, 1H), 4.02 (m, 3H), 3.93 (m, 2H), 3.73 (m, 2H), 3.14 - 3.03 (m, 2H), 3.02 (m, 1H), 2.83 (m, 1H), 2.18 - 2.06 (m, 2H), 2.04 - 1.95 (m, 1H), 1.90 - 1.82 (m, 1H), 1.82 - 1.72 (m, 3H), 0.66 - 0.61 (m, 2H), 0.06 - 0.11 (m, 2H).

Example 56: Synthesis of 2-((S)-5-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol (Compound 209)



Step 1: 4-((S)-10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

- 5 [00451] The title compound was obtained as a brown oil, 130 mg 56%, from the compound of Example 19, steps 2 to 4 and Intermediate 22, following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 1075 [M+H]^+$

Step 2: Synthesis of 4-((S)-10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

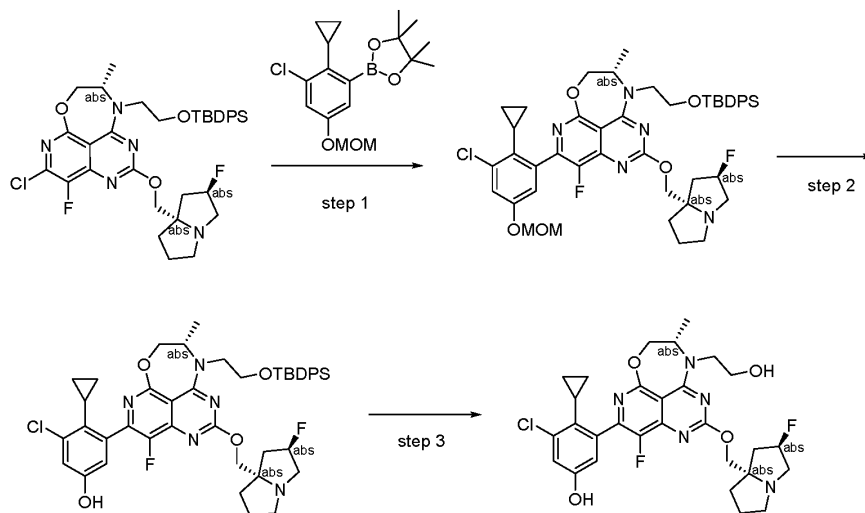
10

- [00452] A stirred solution of the compound from step 1 (58 mg, 0.054 mmol) and ammonium cerium(IV) nitrate (88.8 mg, 0.16 mmol) in MeCN (2 mL) and H₂O (2 mL) was stirred for 30 min at 0°C under N₂. The resulting mixture was concentrated *in vacuo* and the residue was purified by prep-TLC (DCM: MeOH=5:1) to afford the title compound (15 mg, 33.3%) as a yellow solid. LCMS $m/z = 835 [M+H]^+$
- 15

Step 3: Synthesis of 2-((S)-5-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol formate

- [00453] The title compound was obtained as a colorless oil, 1 mg, 9.6%, from the compound from step 2, following a similar procedure to that described in Example 30, step 8. LCMS $m/z = 596 [M+H]^+$ ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.24 (s, 6H), 1.95 – 2.27 (m, 7H), 3.59 (d, 8H), 4.19 (d, 1H), 4.51 (d, 3H), 5.26 (d, 2H), 6.27 (s, 1H), 6.88 (d, 2H).
- 20

- Example 57: Synthesis of 3-chloro-4-cyclopropyl-5-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol (Compound 203)**
- 25



Step 1: Synthesis of (S)-10-(2-((tert-butyl diphenylsilyl)oxy)ethyl)-5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- 5 **[00454]** The title compound was obtained as a yellow oil, 119 mg, 95%, from the compound of Example 19, steps 2 to 4 and Intermediate 21, following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 871$ $[M+H]^+$

Step 2: Synthesis of 3-((S)-10-(2-((tert-butyl diphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol

10

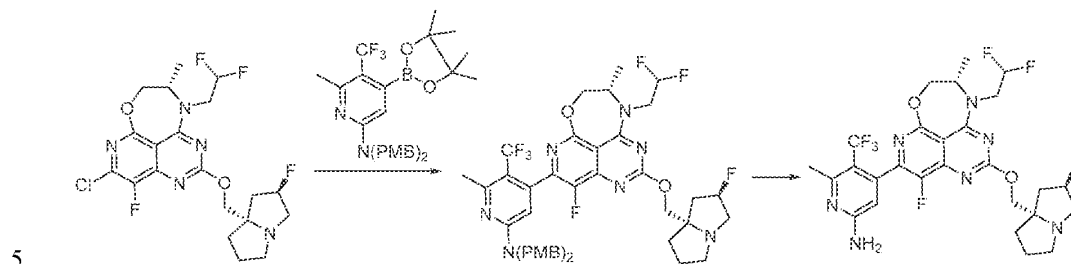
[00455] A solution of the compound from step 1 (86 mg, 0.01 mmol) in DCM (5 mL) and TFA (1.5 mL) was stirred for 1 h at 25°C under N_2 . The resulting mixture was filtered and the filtrate evaporated under reduced pressure to afford the title compound, crude as a yellow oil. LCMS $m/z = 827$ $[M+H]^+$

- 15 *Step 3: Synthesis of 3-chloro-4-cyclopropyl-5-((S)-10-(2-hydroxyethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol*

[00456] The title compound was obtained as a white solid, 3.6 mg, 10.1%, from the compound from step 2, following a similar procedure to that described in Example 16, step 6. LCMS $m/z = 588$ $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$): δ 0.61 (s, 2H), 1.25 (s, 4H), 1.86 (s, 4H), 2.93 (d, 10H), 3.74 (dd, 2H), 4.18 (d, 3H), 4.35 – 4.65 (m, 2H), 4.91 (s, 1H), 5.35 (d, 1H), 6.76 (s, 1H), 6.94 (s, 1H), 9.97 (s, 1H).

20

Example 58: Synthesis of 4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (Compound 180)



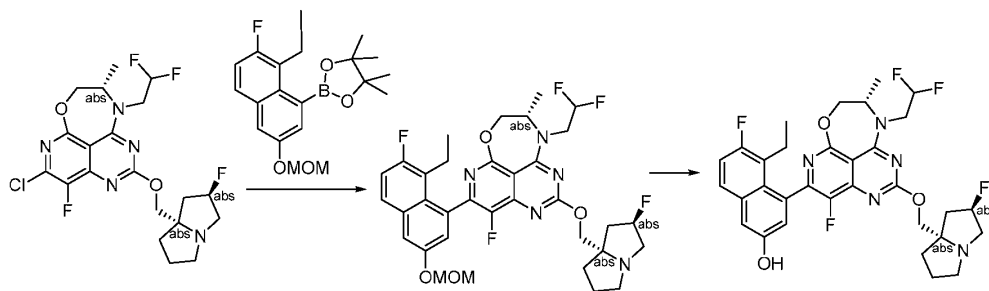
Step 1: Synthesis of 4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

10 **[00457]** The title compound was obtained as a white solid, 88 mg, 48.9%, from Intermediate 22 and Example 44, step 1, following a similar procedure to that described in Example 16, step 5. LCMS m/z = 856 $[M+H]^+$

Step 2: Synthesis of 4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

15 **[00458]** A solution of the compound from step 1 (75 mg, 0.09 mmol) in TFA (2 mL) was stirred at 50°C for 3h under N_2 . The mixture was allowed to cool down to rt and concentrated under reduced pressure. The residue was purified by prep-HPLC (Method D, Gradient: 5% B to 35% B in 8 min) to afford the title compound (11.6 mg, 21.5%) as a white solid. LCMS m/z = 616 $[M+H]^+$ 1H NMR (400 MHz, $MeOH-d_4$) δ 8.48 (s, 1H), 6.59 – 6.18 (m, 1H), 5.41 (dt, 1H), 4.67 (dd, 1H), 4.55 – 4.34 (m, 4H), 4.26 (qd, 1H), 4.08 (dtd, 1H), 3.64 – 3.38 (m, 3H), 3.25 – 3.11 (m, 1H), 2.57 – 2.44 (m, 3H), 2.44 – 2.27 (m, 2H), 2.16 (ddt, 3H), 2.07 – 1.90 (m, 1H), 1.37 (d, 3H).

25 **Example 59: Synthesis of 4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethyl-6-fluoronaphthalen-2-ol (Compound 200)**



Step 1: Synthesis of (S)-10-(2,2-difluoroethyl)-5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

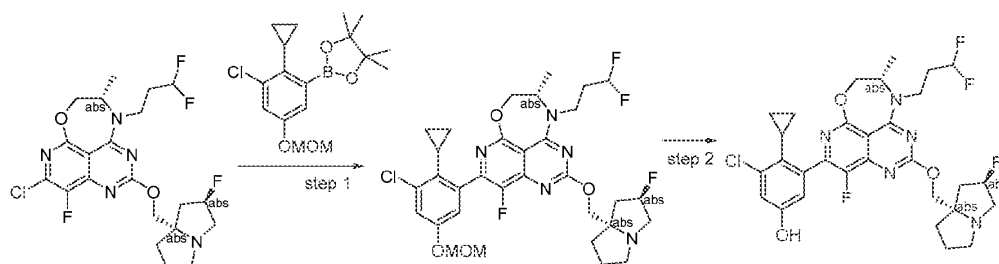
[00459] The title compound was obtained as a white solid, 0.1 g, 70.6%, from Example 44, step 1 and 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 674$ $[M+H]^+$.

Step 2: Synthesis of 4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethyl-6-fluoronaphthalen-2-ol

[00460] The title compound was obtained as a white solid, 26.2 mg, 26%, from the compound from step 1, following a similar procedure to that described in Example 45, step 3.

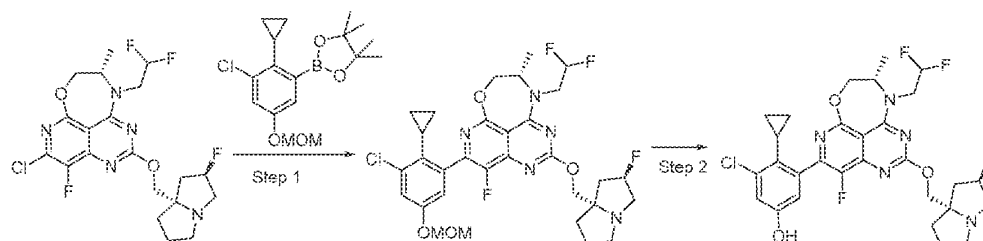
LCMS $m/z = 630$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.93 (d, 1H), 7.76 (dd, 1H), 7.41 – 7.25 (m, 2H), 7.02 (dd, 1H), 6.47 (dddd, 1H), 5.31 (d, 1H), 4.70 – 4.54 (m, 1H), 4.54 – 4.30 (m, 2H), 4.30 – 3.99 (m, 4H), 3.12 (d, 3H), 2.88 (d, 1H), 2.44 – 2.29 (m, 1H), 2.21 (ddd, 2H), 2.06 (d, 2H), 1.94 – 1.70 (m, 3H), 1.27 (d, 3H), 0.81 (dt, 3H).

Example 60: Synthesis of 3-chloro-4-cyclopropyl-5-((S)-10-(3,3-difluoropropyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol (Compound 193)



[00461] The title compound was obtained as a white solid, from Example 39, step 3 and Intermediate 21, following a similar 2 step procedure to that described in Example 59. LCMS $m/z = 622$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 10.00 (s, 1H), 6.91 (d, 1H), 6.72 (d, 1H), 6.25-6.21 (m, 1H), 5.54-5.51 (m, 1H), 4.54-4.51 (m, 3H), 4.35 (d, 1H), 4.26-4.12 (m, 2H), 3.92-3.65 (m, 6H), 3.29-3.21 (m, 4H), 2.44-2.27 (m, 3H), 2.25-2.08 (m, 3H), 2.01 (dd, 1H), 1.73-1.71 (m, 1H), 1.24 (d, 3H).

Example 61: Synthesis of 3-chloro-4-cyclopropyl-5-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol (Compound 187)



Step 1: Synthesis of (S)-5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00462] The title compound was obtained as a white solid, 54 mg, 75.8%, from Example 44, step 1 and Intermediate 21 following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 652$ $[M+H]^+$

Step 2: Synthesis of 3-chloro-4-cyclopropyl-5-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol

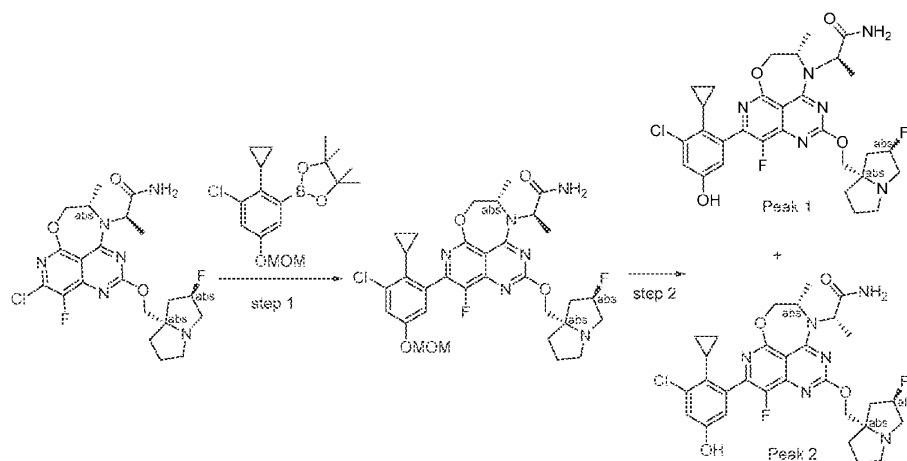
[00463] The title compound was obtained as a white solid, 3.5 mg, 7.7%, from the compound from step 1, following a similar procedure to that described in Example 44, step 3. LCMS $m/z =$

608 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 9.98 (s, 1H), 6.94 (d, 1H), 6.77 (d, 1H), 6.45 (tt, 1H), 5.34 (d, 1H), 4.61 (dd, 1H), 4.54 – 4.30 (m, 2H), 4.30 – 3.98 (m, 4H), 3.21 (s, 3H), 2.92 (s, 1H), 2.25 – 1.97 (m, 3H), 1.97 – 1.67 (m, 4H), 1.27 (d, 3H), 0.69 – 0.49 (m, 2H), 0.03 – 0.06 (m, 2H).

- 5 **Example 62: Synthesis of (R)-2-((S)-5-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide (Compound 205)**

and

- 10 **Example 63: Synthesis of (S)-2-((S)-5-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide (Compound 206)**



- 15 *Step 1: Synthesis of (R)-2-((S)-5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide*

[00464] A solution of (R)-2-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-

- 20 tetraazacyclohepta[de]naphthalen-10-yl)propanamide (100 mg, 0.21 mmol), Intermediate 21, (70.1 mg, 0.21 mmol), CataCXium A Pd G₃ and Cs₂CO₃ (202.4 mg, 0.62 mmol) in H₂O (5 mL) and dioxane (25 mL) was stirred at 100°C for 2h under N₂. The cooled mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3 x 10mL). The combined organic layers were washed

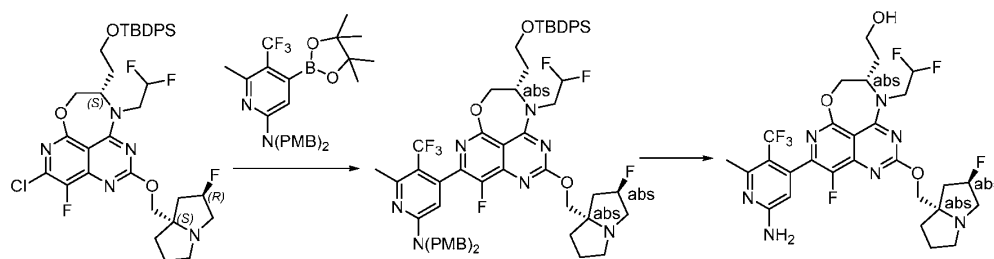
with brine (10mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE:EtOAc (5:1) to afford the title compound (50 mg, 36%) as a yellow solid. LCMS m/z = 659 [M+H]⁺

- 5 *Step 2: Synthesis of (R)-2-((S)-5-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide and (S)-2-((S)-5-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-*
 10 *tetraazacyclohepta[de]naphthalen-10-yl)propanamide*

- [00465] A solution of the compound from step 1 (50 mg, 0.076 mmol) in TFA (2 mL) and DCM (10 mL) was stirred at 25°C for 1 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by Prep-TLC (PE/EtOAc 2:1) to afford crude product (20 mg) as a yellow oil. This was purified by Prep-chiral-HPLC: column, C18 silica
 15 gel; Column: CHIRALPAK IE, 2*25 cm, 5 µm; Mobile Phase A: Hex (0.5% 2M NH₃-MeOH), Mobile Phase B: EtOH: DCM=1:1; Flow rate: 20 mL/min; Isocratic Gradient: 50% B in 14 min; to afford Peak 1, Compound 205 (1 mg, 0.2%) as a light yellow solid, LCMS m/z = 615 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 9.97 (s, 1H), 7.34 (s, 1H), 7.12 (s, 1H), 6.94 (s, 1H), 6.75 (s, 1H), 5.37 (s, 1H), 5.24 (s, 1H), 4.55 (s, 2H), 4.26 (s, 1H), 4.07 (s, 2H), 3.09 (s,
 20 2H), 2.95 (s, 2H), 2.13 – 2.08 (m, 4H), 2.01 – 1.85 (s, 5H), 1.79 (s, 3H), 1.30 – 1.21 (m, 5H).

- [00466] and Peak 2, Compound 206, (0.8 mg, 0.2%) as a light yellow solid. LCMS m/z = 615 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 9.97 (s, 1H), 7.34 (s, 1H), 7.12 (s, 1H), 6.94 (s, 1H), 6.75 (s, 1H), 5.37 (s, 1H), 5.24 (s, 1H), 4.55 (s, 2H), 4.26 (s, 1H), 4.07 (s, 2H), 3.09 (s, 2H), 3.01 (s, 1H), 2.95 (s, 1H), 2.13 – 2.12 (m, 1H), 2.12 – 2.08 (m, 3H) 2.01 – 1.85 (s, 5H),
 25 1.79 (s, 3H), 1.30 – 1.21 (m, 5H).

Example 64: Synthesis of 2-((S)-5-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (Compound 207)



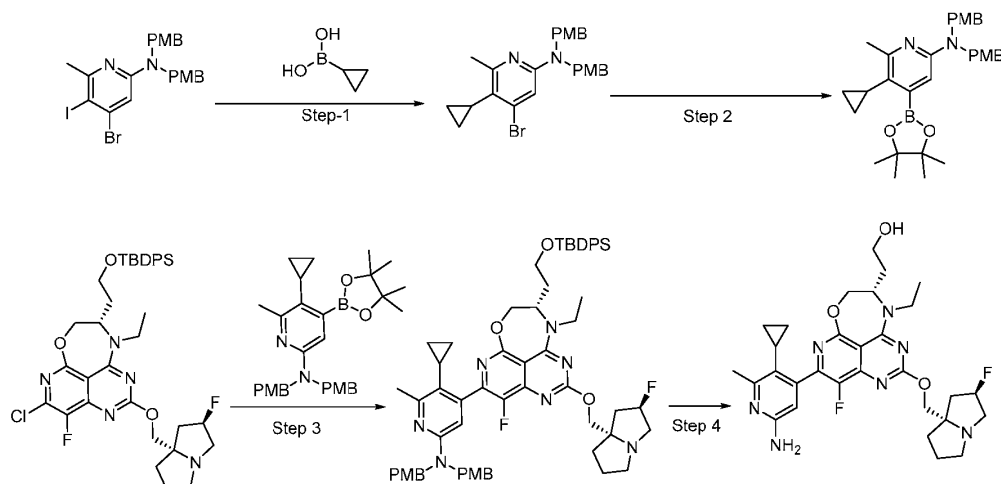
Step 1: Synthesis of 4-((S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[00467] The title compound was obtained as a white solid, 40 mg, 42.7%, from Example 25, step 4 and Intermediate 22, following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 1124$ $[M+H]^+$

Step 2: Synthesis of 2-((S)-5-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

[00468] A solution of the compound from step 1 (30 mg, 0.027 mmol) in TFA (0.5 mL) and DCE (0.5 mL) was stirred at 80°C for 16 h under N_2 . The mixture was allowed to cool to rt and concentrated under reduced pressure. The residue was purified by prep-HPLC (Method D, Gradient: 5% B to 30% B in 7 min) to afford the title compound (2.4 mg, 13.9%) as a white solid. LCMS $m/z = 646$ $[M+H]^+$ 1H NMR (400 MHz, $DMSO-d_6$) δ 10.80 (d, 1H), 6.90 (s, 2H), 6.55 (ddd, 1H), 6.38 – 6.19 (m, 1H), 5.57 (dt, 1H), 4.74 (dd, 1H), 4.64 (d, 1H), 4.55 (d, 1H), 4.46 (d, 1H), 4.24 (td, 1H), 3.87 (dd, 2H), 3.77 (dt, 1H), 3.53 (dp, 2H), 3.31 (tt, 1H), 2.57 – 2.53 (m, 1H), 2.49 – 2.43 (m, 4H), 2.35 – 2.24 (m, 1H), 2.18 (qt, 2H), 2.10 – 1.98 (m, 1H), 1.78 (q, 2H).

Example 65: Synthesis of 2-((S)-5-(6-amino-3-cyclopropyl-2-methylpyridin-4-yl)-10-ethyl-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (Compound 189)



Step 1: Synthesis of 4-bromo-5-cyclopropyl-N,N-bis(4-methoxybenzyl)-6-methylpyridin-2-amine

[00469] Cyclopropylboronic acid (149 mg, 1.73 mmol) and K_2CO_3 (600 mg, 4.34 mmol) were added to a solution of 4-bromo-5-iodo-N,N-bis(4-methoxybenzyl)-6-methylpyridin-2-amine (800 mg, 1.44 mmol) in toluene (15 mL) and water (3 mL) and the mixture purged with N_2 for 2 min. $Pd(dppf)Cl_2 \cdot DCM$ (118 mg, 0.14 mmol) was added and the reaction mixture was stirred at 80 °C for 16 h. The reaction mixture was filtered through Celite®, diluted with water (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography, using a gradient of 0-100% EtOAc in hexane, to give the title compound (430 mg, 50.9%). LCMS $m/z = 467 [M+H]^+$

Step 2: Synthesis of 5-cyclopropyl-N,N-bis(4-methoxybenzyl)-6-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine

[00470] Bis(pinacolato)diboron (79 mg, 0.31 mmol) and KOAc (46.0 mg, 0.46 mmol) were added to a solution of the compound from step 1 (100 mg, 0.15 mmol) in dioxane (2 mL) and the mixture purged with N_2 for 2 min. $PdCl_2(dppf)$ (10.29 mg, 0.014 mmol) was added and the reaction mixture was stirred at 100 °C for 16 h. The reaction mixture was diluted with EtOAc (3 x 20 mL), filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using a gradient of 0-100% EtOAc in hexane, to obtain the title compound (60 mg, 60.8%). LCMS $m/z = 515 [M+H]^+$

Step 3: Synthesis of 4-((S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-10-ethyl-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-

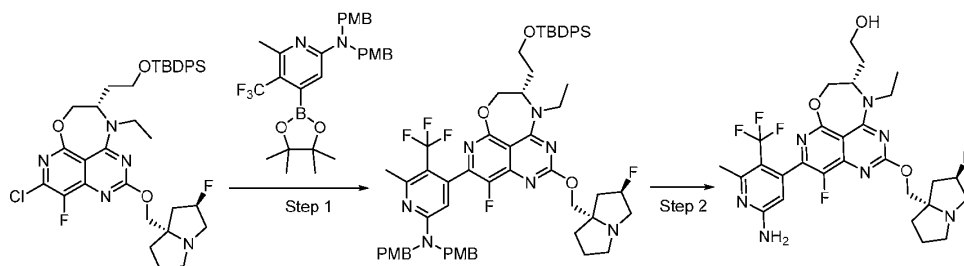
1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-cyclopropyl-N,N-bis(4-methoxybenzyl)-6-methylpyridin-2-amine

[00471] The compound from step 2 (87 mg, 0.17 mmol) and K₃PO₄ (53.9 mg, 0.25 mmol) were added to a solution of Intermediate 28, 60 mg, 0.08 mmol) in dioxane (3 mL) and water (0.6 mL) and the mixture purged with N₂ for 2 min. CataCXium A Pd G₃ (6.17 mg, 8.47 μmol) was added and the reaction mixture was purged with N₂ then irradiated in a microwave at 110 °C for 2 h. The cooled mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to obtain the title compound, crude (160 mg, 84%). LCMS m/z = 1061 [M+H]⁺

Step 4: Synthesis of 2-((S)-5-(6-amino-3-cyclopropyl-2-methylpyridin-4-yl)-10-ethyl-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

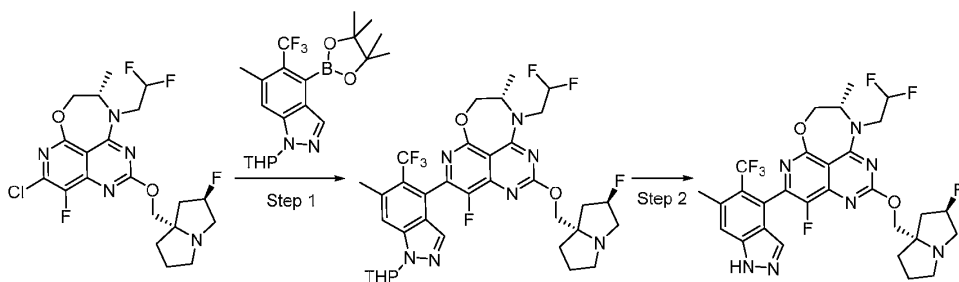
[00472] Triflic acid (0.16 mL, 1.88 mmol) was added to a solution of the compound from step 3 (200 mg, 0.18 mmol) in TFA (0.5 mL) at 0 °C and the reaction stirred for 1 h at 25 °C. The reaction was diluted with DCM (20 mL) and concentrated under reduced pressure. The crude compound was purified by prep-HPLC reverse phase purification [column: SHIMPACK C18(250X19mm)5u, Mobile Phase-A: 10mM NH₄CO₃ in water, Mobile Phase-B: MeCN, using gradient 0 to 100 % MeCN, Flow rate: 15 mL/min. The combined product containing fractions were lyophilized to afford the title compound (9.3 mg, 8.3 %) as an off-white solid. LCMS m/z = 582 [M+H]⁺ ¹H-NMR (400 MHz, DMSO-*d*₆): δ 6.28 (s, 1H), 5.82 (s, 2H), 5.39-5.25 (m, 1H), 4.77 (t, 1H), 4.65 (dd, 1H), 4.37 (d, 1H), 4.29-4.14 (m, 4H), 3.57-3.52 (m, 2H), 3.17-2.89 (m, 4H), 2.43 (s, 3H), 2.18-2.05 (m, 3H), 1.81-1.70 (m, 7H), 1.28 (t, 3H), 0.54-0.53 (m, 2H), 0.04-0.03 (m, 2H).

Example 66: Synthesis of 2-((S)-5-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-10-ethyl-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (Compound 195)



[00473] The title compound was obtained, from Intermediate 28 and Intermediate 22, following a similar 2 step procedure to that described in Example 38, steps 3 and 4. LCMS m/z = 610 $[M+H]^+$. 1H -NMR (400 MHz, $DMSO-d_6$): δ 6.80 (brs, 2H), 6.24 (brs, 1H), 5.35-5.22 (m, 1H), 4.77-4.73 (m, 1H), 4.66-4.63 (m, 1H), 4.37 (d, 1H), 4.25-4.23 (m, 1H), 4.14-4.11 (m, 2H), 4.04 (d, 1H), 3.56-3.51 (m, 3H), 3.43-3.39 (m, 3H), 3.10-3.02 (m, 3H), 2.84-2.83 (m, 1H), 2.14-2.13 (m, 1H), 2.05-2.00 (m, 2H), 1.86-1.72 (m, 5H), 1.27 (t, 3H)

Example 67: Synthesis of (9S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (Compound 181)



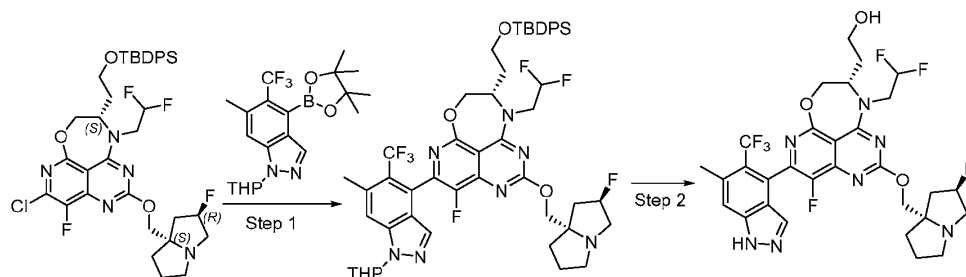
Step 1: Synthesis of (9S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00474] The title compound was obtained as a white solid, 69 mg, 45.4%, from the compound of Example 44, Step 1 and Intermediate 27 following a similar procedure to that described in Example 16, step 5. LCMS m/z = 724 $[M+H]^+$

Step 2: Synthesis of (9S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

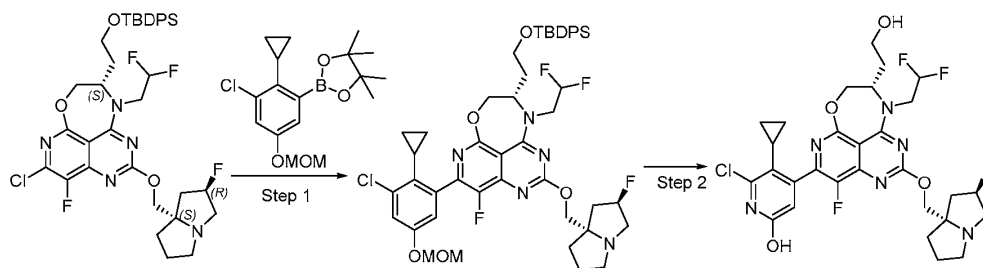
[00475] To a stirred solution of the compound from step 1 (50 mg, 0.07 mmol) in dioxane (1 mL) was added HCl (4.0 M in dioxane, 2 mL) and the reaction mixture was stirred at rt for 1h under N₂. The resulting mixture was concentrated under reduced pressure and the residue was purified by prep-HPLC (Method D, Gradient: 15% B to 42% B in 8 min); to afford the title compound (8.1 mg, 18.3 %) as a white solid. LCMS $m/z = 640$ [M+H]⁺ 128H NMR (400 MHz, MeOH-d₄) δ 7.78 – 7.59 (m, 2H), 6.63 – 6.19 (m, 1H), 5.57 (dt, 1H), 4.78 – 4.60 (m, 3H), 4.60 – 4.43 (m, 2H), 4.37 – 4.24 (m, 1H), 4.24 – 3.98 (m, 2H), 3.98 – 3.79 (m, 3H), 3.54 – 3.39 (m, 1H), 2.77 – 2.48 (m, 5H), 2.44 – 2.26 (m, 3H), 2.18 (d, 1H), 1.43 (dd, 3H).

Example 68: Synthesis of 2-((9S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (Compound 217)



[00476] The title compound was obtained as a white solid, from Example 25, step 4 and Intermediate 27, following a similar 2 step procedure to that described in Example 67. LCMS $m/z = 670$ [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 13.54 (d, 1H), 7.79 – 7.59 (m, 1H), 7.46 – 7.20 (m, 1H), 6.52 (t, 1H), 5.57 (d, 1H), 4.85 (s, 1H), 4.81 – 4.70 (m, 1H), 4.71 – 4.57 (m, 3H), 4.57 – 4.43 (m, 1H), 4.27 (q, 1H), 4.02 (d, 2H), 3.90 – 3.45 (m, 6H), 2.65 (m, 2H), 2.46 (s, 3H), 2.28 (d, 1H), 2.11 (d, 2H), 1.93 – 1.69 (m, 2H).

Example 69: Synthesis of 6-chloro-5-cyclopropyl-4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)pyridin-2-ol (Compound 208)



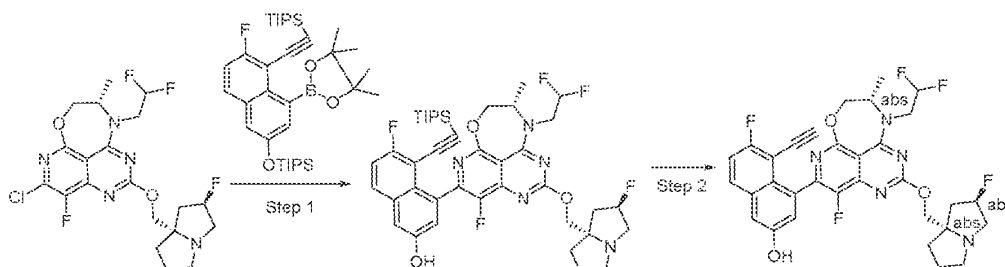
Step 1: Synthesis of (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00477] The title compound was obtained as a white solid, 37 mg, 50.7%, from Example 25, step 4 and Intermediate 21, following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 920$ $[M+H]^+$

Step 2: Synthesis of 6-chloro-5-cyclopropyl-4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)pyridin-2-ol

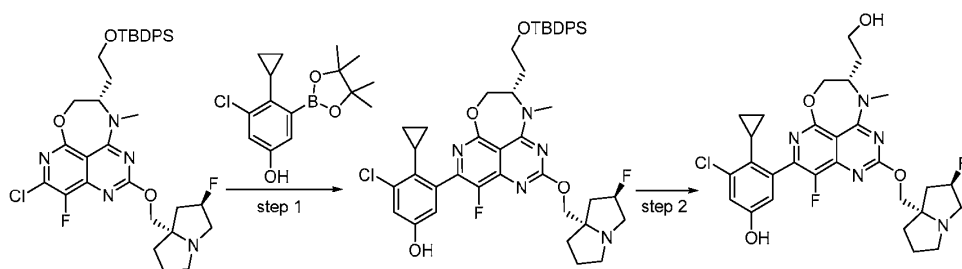
[00478] The title compound was obtained as a white solid, 3.8 mg, 18%, from the compound from step 1, following a similar procedure to that described in Example 41, step 3. LCMS $m/z = 638$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.97 (s, 1H), 6.94 (d, 1H), 6.76 (d, 1H), 6.65 – 6.27 (m, 1H), 5.40 – 5.13 (m, 1H), 4.80 (t, 1H), 4.75 – 4.56 (m, 2H), 4.48 (d, 1H), 4.21 (td, 1H), 4.13 (d, 1H), 4.03 (d, 1H), 3.89 (dtd, 1H), 3.53 (d, 2H), 3.14 – 2.93 (m, 3H), 2.89 – 2.77 (m, 1H), 2.13 (d, 1H), 2.08 – 1.92 (m, 2H), 1.92 – 1.70 (m, 6H), 0.61 (d, 2H), 0.05 – 0.03 (m, 2H).

Example 70: Synthesis of 4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (Compound 172)



[00479] The title compound was obtained as a white solid, from the compound of Example 44, step 1 and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane, following a similar 2 step procedure to that described in Example 16, steps 5 and 6. LCMS $m/z = 626$ $[M+H]^+$ ¹H NMR (400 MHz, DMSO- d_6) δ 10.15 (d, 1H), 7.97 (ddd, 1H), 7.46 (td, 1H), 7.38 (d, 1H), 7.21 (d, 1H), 6.45 (ddt, 1H), 5.42 – 5.14 (m, 1H), 4.61 (ddd, 1H), 4.53 – 4.28 (m, 2H), 4.25 – 3.91 (m, 5H), 3.09 (d, 3H), 2.86 (q, 1H), 2.21 – 1.94 (m, 3H), 1.82 (tdd, 3H), 1.29 (d, 3H).

Example 71: Synthesis of 3-chloro-4-cyclopropyl-5-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol (Compound 130)



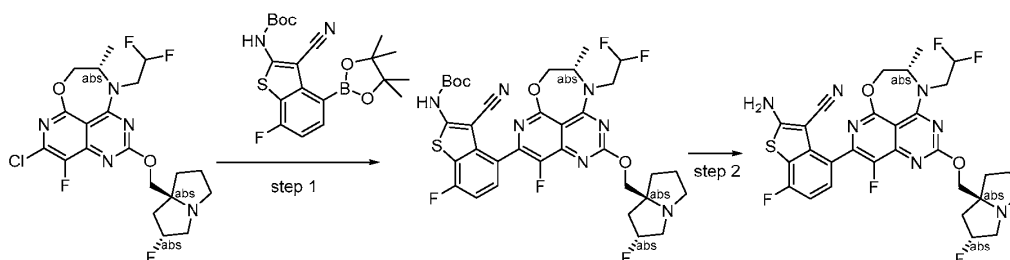
Step 1: Synthesis of 3-((S)-9-(2-((tert-butyl)di(phenyl)silyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol

[00480] A solution of Intermediate 20 (29.70 mg, 0.10 mmol), Example 6, step 5 (70 mg, 0.10 mmol), Na_2CO_3 (32.06 mg, 0.30 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (7.38 mg, 0.01 mmol) in H_2O (2 mL) and dioxane (10 mL) was stirred for 2h at 100°C under N_2 . The cooled reaction was concentrated under reduced pressure, the residue was diluted with H_2O (20 mL) and the mixture extracted with EtOAc (3 x 30mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (PE/EtOAc 2:1) to afford the title compound (50 mg, 60.0%) as a yellow solid. LCMS $m/z = 826$ $[M+H]^+$

Step 2 : Synthesis of 3-chloro-4-cyclopropyl-5-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol

[00481] The title compound was obtained as a white solid, 19.1 mg, 44.7%, from the compound from step 1, following a similar procedure to that described in Example 48, step 3. LCMS $m/z = 588$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.97 (s, 1H), 6.93 (d, 1H), 6.75 (d, 1H), 5.42 – 5.18 (m, 1H), 5.15 – 4.95 (m, 1H), 4.62 (dd, 1H), 4.45 (d, 1H), 4.18 – 4.09 (m, 2H), 4.02 (d, 1H), 3.54 – 3.45 (m, 2H), 3.36 (s, 3H), 3.17 – 3.04 (m, 2H), 3.03 (d, 1H), 2.89 – 2.78 (m, 1H), 2.17 – 2.11 (m, 1H), 2.06 (d, 1H), 2.01 (m, 1H), 1.80 – 1.69 (m, 6H), 0.72 – 0.46 (m, 2H), 0.05 (dd, 1H), -0.02 – -0.10 (m, 1H).

Example 72: Synthesis of 2-amino-4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile (Compound 182)



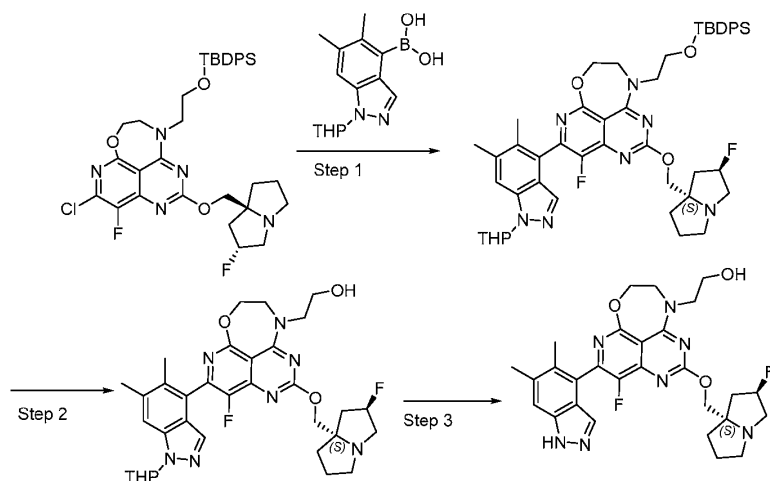
Step 1: Synthesis of tert-butyl (3-cyano-4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-7-fluorobenzo[b]thiophen-2-yl)carbamate

[00482] A mixture of Example 44, step 1 (100 mg, 0.20 mmol), Intermediate 26 (48 mg, 0.22 mmol), Pd(dtbpf)Cl₂ (70 mg, 0.20 mmol) and K₃PO₄ (128.4 mg, 0.606 mmol) in dioxane (2 mL) and H₂O (0.4 mL) was stirred at 100°C for 2 h under N₂. The reaction was quenched with water (10 mL) at rt. The aqueous layer was extracted with DCM (3 x 10mL), the combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH 10:1) to afford the title compound (30 mg, 19.6%) as a yellow solid. LCMS $m/z = 732$ $[M+H]^+$

Step 2: Synthesis of 2-amino-4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-7-fluorobenzo[b]thiophene-3-carbonitrile

[00483] TFA (0.6 mL) was added to a solution of the compound from step 1 (30 mg, 0.041 mmol) in DCM (3 mL) and the reaction was stirred at rt for 2 h under N₂. The mixture was concentrated *in vacuo* and the crude product purified by Prep-HPLC (Method A, Gradient: 22% B to 47% B in 8 min) to afford the title compound (5.1 mg, 19.7%) as a white solid. LCMS *m/z* = 632 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.10 (s, 2H), 7.41 (dd, 1H), 7.13 (t, 1H), 6.47 (tt, 1H), 5.31 (d, 1H), 4.62 (dd, 1H), 4.54 – 4.30 (m, 2H), 4.29 – 3.98 (m, 4H), 3.12 (d, 3H), 2.95 – 2.78 (m, 1H), 2.28 – 1.95 (m, 3H), 1.95 – 1.67 (m, 3H), 1.28 (d, 3H).

Example 73: Synthesis of 2-(5-(5,6-dimethyl-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol (Compound 127)



Step 1: Synthesis of 10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00484] A mixture of Intermediate 24 (125 mg, 0.36 mmol), 10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (Example 5, step 5, 100 mg, 0.14 mmol), Pd(dtbpf)Cl₂ (9 mg, 0.01 mmol) and DIPEA (57 mg, 0.44 mmol) in THF (5 mL) and H₂O (1 mL) was stirred for 2 h at 70°C under N₂. The reaction was quenched with water (50 mL) at rt and the mixture extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine (2x50 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by

Prep-TLC (DCM / MeOH 10:1) to afford the title compound (116 mg, 90.2%) as a solid. LCMS $m/z = 874$ [M+H]⁺

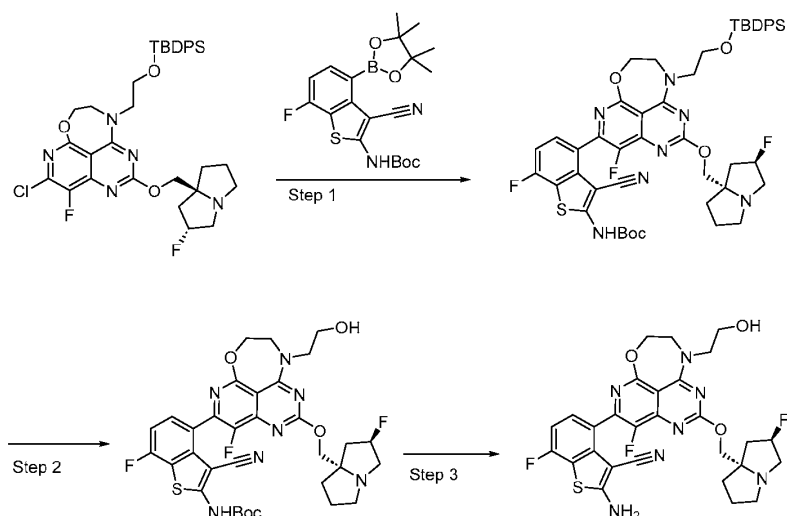
Step 2: Synthesis of 2-(5-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol

[00485] A mixture of the compound from step 1 (111 mg, 0.12 mmol) and CsF (57 mg, 0.38 mmol) in DMF (10 mL) was stirred for 2 h at 40°C under N₂. The reaction was quenched with water (100 mL) and the mixture extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (2x50 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure to give the title compound (75 mg, 92.9%) as a brown solid. LCMS $m/z = 636$ [M+H]⁺

Step 3: Synthesis of 2-(5-(5,6-dimethyl-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol

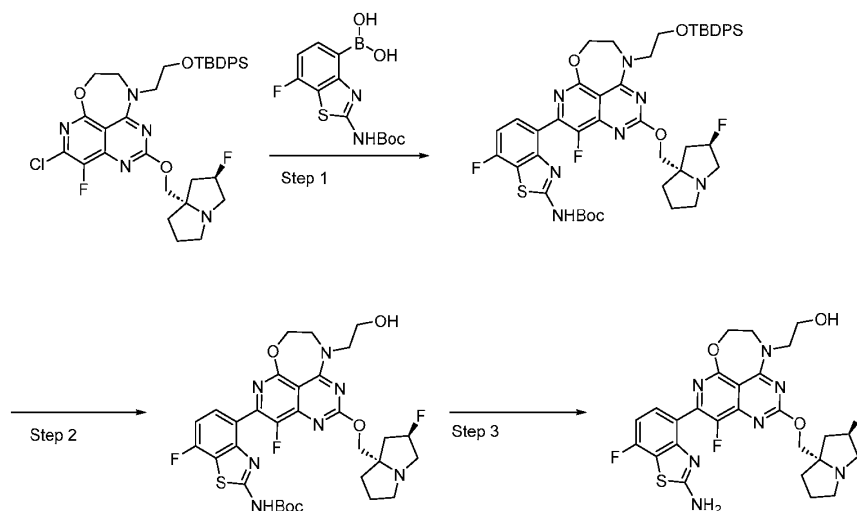
[00486] TFA (1 mL) was added to a solution of the compound from step 2 (72 mg, 0.11 mmol) in DCM (5 mL) and the reaction mixture was stirred for 1 h at rt. The resulting mixture was concentrated under reduced pressure and the residue was purified by reverse phase chromatography: C18 column; mobile phase, MeCN in water (10 mmol/L NH₄HCO₃), MeCN 0% to 48% gradient in 30 min to give the title compound (22 mg, 35.2%) as a white solid. LCMS $m/z = 552$ [M+H]⁺. ¹H NMR (500 MHz, DMSO-d₆) δ 12.95 (s, 1H), 7.58 (s, 1H), 7.46 (s, 1H), 5.34 (d, 1H), 4.88 (m, 1H), 4.57 (s, 2H), 4.13 (m, 1H), 4.04 (m, 3H), 3.96 (m, 2H), 3.73 (m, 2H), 3.14 – 3.04 (m, 2H), 3.02 (m, 1H), 2.83 (m, 1H), 2.43 (s, 3H), 2.21 – 2.08 (m, 3H), 2.06 (m, 1H), 2.04 – 1.95 (m, 1H), 1.85 – 1.73 (m, 3H), 1.24 (s, 1H).

Example 74: Synthesis of 2-amino-7-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)benzo[b]thiophene-3-carbonitrile (Compound 129)



[00487] The title compound was obtained as a white solid, from Intermediate 26 and Example 5, step 5 following a similar 3 step procedure to that described in Example 73. LCMS $m/z = 598$ $[M+H]^+$ 1H NMR (500 MHz, DMSO- d_6) δ 8.09 (s, 2H), 7.36 (s, 1H), 7.13 (s, 1H), 5.24 (m, 1H), 4.91 (m, 1H), 4.57 – 4.52 (m, 2H), 4.13 – 3.93 (m, 6H), 3.74 (m, 2H), 3.11 (s, 1H), 3.09 (s, 1H), 2.84 (m, 1H), 2.19 – 1.96 (m, 3H), 1.89 – 1.78 (s, 3H), 1.24 (s, 1H).

Example 75: Synthesis of 2-(5-(2-amino-7-fluorobenzo[d]thiazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol (Compound 128)



10

[00488] The title compound was obtained as a white solid, from Example 5, step 5 and Intermediate 25, following a similar 3 step procedure to that described in Example 73. LCMS

$m/z = 574 [M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ 7.91 (s, 2H), 7.36 (dd, 1H), 7.05 (t, 1H), 5.23 (t, 1H), 4.87 (t, 1H), 4.54 (dd, 2H), 4.12 (d, 1H), 4.06 – 3.97 (m, 3H), 3.93 (t, 2H), 3.71 (q, 2H), 3.13 – 2.97 (m, 3H), 2.83 (td, 1H), 2.17 – 2.03 (m, 2H), 2.00 (dt, 1H), 1.91 – 1.68 (m, 3H).

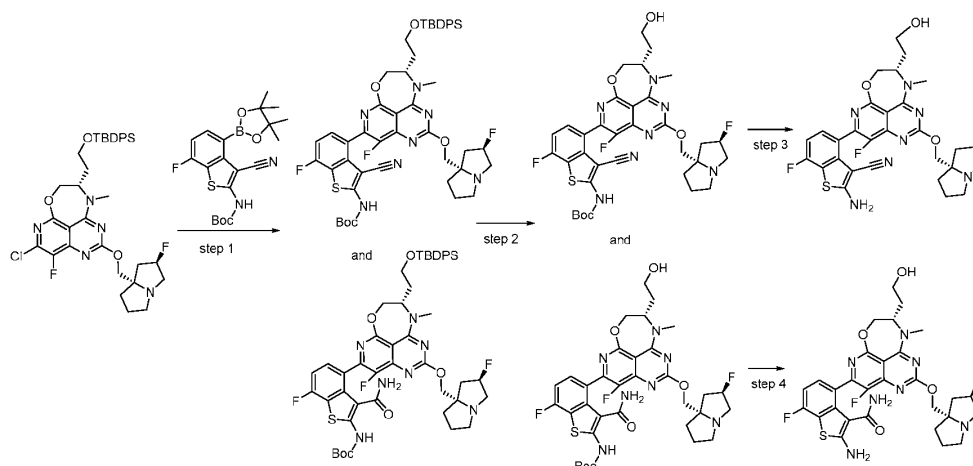
Example 76: Synthesis of 2-amino-7-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-

5 fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)benzo[b]thiophene-3-carbonitrile (Compound 167)

and

Example 77: Synthesis of 2-amino-7-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-

10 fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)benzo[b]thiophene-3-carboxamide (Compound 168)



Step 1: tert-butyl (4-((S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluoro
15 *tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-*
tetraaza cyclohepta[de]naphthalen-5-yl)-3-cyano-7-fluorobenzo[b]thiophen-2-yl)carbamate
and tert-butyl (4-((S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-
fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-
1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-3-carbamoyl-7-fluorobenzo[b]thiophen-2-
20 *yl)carbamate*

[00489] A solution of Example 6, step 5 (100 mg, 0.072 mmol), Intermediate 26 (36.2 mg, 0.09 mmol) and K_3PO_4 (61.15 mg, 0.29 mmol) and $Pd(dtbpf)Cl_2$ (46.94 mg, 0.072 mmol) in dioxane (5 mL) and H_2O (1 mL) was stirred at 100°C for 16 h under N_2 . The mixture was

cooled to rt and concentrated under reduced pressure. The residue was purified by prep-TLC (CHCl₃ / MeOH 10:1) to afford a mixture of the title compounds (10 mg, 7.3%) as a brown oil. LCMS m/z = 950 [M+H]⁺

Step 2: *tert*-butyl (3-cyano-7-fluoro-4-((*S*)-4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8*H*-7-oxa-1,3,6,10-tetraaza cyclohepta[de]naphthalen-5-yl)benzo[*b*]thiophen-2-yl)carbamate and *tert*-butyl (3-carbamoyl-7-fluoro-4-((*S*)-4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8*H*-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)benzo[*b*]thiophen-2-yl)carbamate

- 10 [00490] CsF (4.80 mg, 0.03 mmol) was added to a solution of the compounds from step 1 (6 mg, 0.006 mmol) in DMF (0.5 mL) and the reaction mixture stirred at rt for 2 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by Prep-TLC (DCM / MeOH 10:1) to afford *tert*-butyl (3-cyano-7-fluoro-4-((*S*)-4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-
- 15 dihydro-8*H*-7-oxa-1,3,6,10-tetraaza cyclohepta[de]naphthalen-5-yl)benzo[*b*]thiophen-2-yl)carbamate (4 mg) as a yellow solid. LCMS m/z = 713 [M+H]⁺ and *tert*-butyl (3-carbamoyl-7-fluoro-4-((*S*)-4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8*H*-7-oxa-1,3,6,10-
- 20 tetraazacyclohepta[de]naphthalen-5-yl)benzo[*b*]thiophen-2-yl)carbamate, 3 mg, as a yellow solid. LCMS m/z = 730 [M+H]⁺

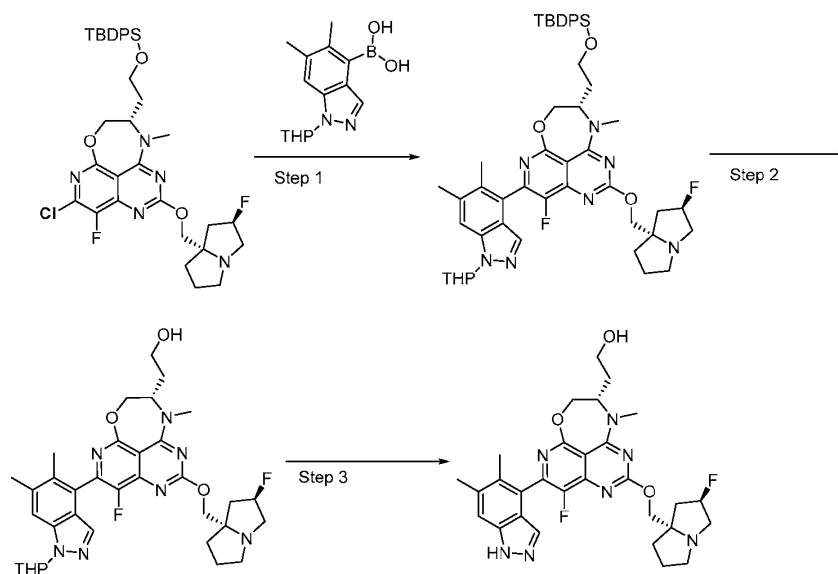
Step 3: 2-amino-7-fluoro-4-((*S*)-4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8*H*-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)benzo[*b*]thiophene-3-carbonitrile

- [00491] The title compound was obtained as a white solid, 1.2 mg, 46.1%, from *tert*-butyl (3-cyano-7-fluoro-4-((*S*)-4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8*H*-7-oxa-1,3,6,10-tetraaza
- 25 cyclohepta[de]naphthalen-5-yl)benzo[*b*]thiophen-2-yl)carbamate, following a similar procedure to that described in Example 41, step 3. LCMS m/z = 612 [M+H]⁺ + ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.08 (s, 2H), 7.40 (d, 1H), 7.12 (t, 1H), 5.39 - 5.20 (m, 1H), 4.86 - 4.70 (m, 1H),
- 30 4.71 - 4.56 (m, 1H), 4.48 - 4.35 (m, 1H), 4.23 - 4.09 (m, 2H), 4.06 - 3.97 (m, 1H), 3.60 - 3.47 (m, 2H), 3.18 - 3.05 (m, 2H), 3.02 - 2.97 (m, 1H), 2.87 - 2.77 (m, 1H), 2.14 - 2.09 (m, 1H), 2.06 - 2.03 (m, 1H), 2.01 - 1.85 (m, 1H), 1.79 - 1.69 (m, 4H), 1.56 - 1.32 (m, 2H), 1.27-1.16 (m, 2H).

Step 4: Synthesis of 2-amino-7-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)benzo[b]thiophene-3-carboxamide

[00492] The title compound was obtained as a white solid, from tert-butyl (3-carbamoyl-7-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)benzo[b]thiophen-2-yl)carbamate, following a similar procedure to that described in Example 67, step 2. LCMS m/z = 630 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 7.38 (t, 1H), 7.02 (t, 1H), 6.90 (s, 2H), 6.57 (s, 2H), 5.39 - 5.18 (m, 1H), 5.22 (s, 1H), 4.88 - 4.66 (m, 1H), 4.60 - 4.52 (m, 1H), 4.37 (d, 1H), 4.19 - 4.07 (m, 2H), 4.01 (d, 1H), 3.54 - 3.50 (m, 1H), 3.12 - 3.07 (m, 2H), 3.02 (s, 1H), 2.87 - 2.78 (m, 1H), 2.15 - 2.09 (m, 1H), 2.08 - 2.03 (m, 1H), 2.00 - 1.95 (m, 1H), 1.88 - 1.74 (m, 6H), 1.27 - 1.18 (m, 2H).

Example 78: Synthesis of 2-((9S)-5-(5,6-dimethyl-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (Compound 131)



Step 1: Synthesis of (9S)-9-(2-((tert-butyl(diphenyl)silyl)oxy)ethyl)-5-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00493] The title compound was obtained as a yellow solid, 80 mg, 24.7%, from Intermediate 24 and Example 6, step 5, following a similar procedure to that described in Example 16, step 5. LCMS m/z = 888 $[M+H]^+$

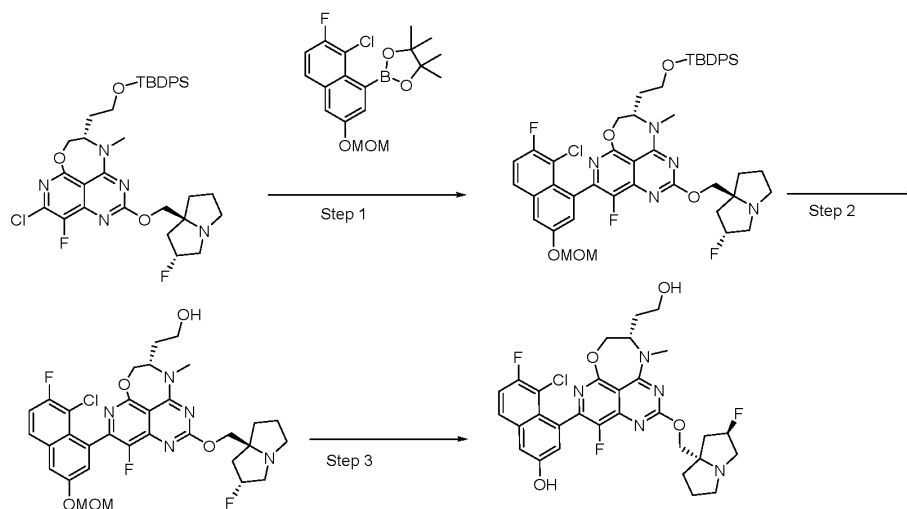
5 *Step 2: Synthesis of 2-((9S)-5-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol*

[00494] A mixture of the compound from step 1 (75 mg, 0.084 mmol) and CsF (128.28 mg, 0.840 mmol) in DMF (2 mL) was stirred for 1 h at 60 °C under N₂. The resulting mixture was evaporated under reduced pressure to afford the title compound, crude, as a white solid. LCMS
10 m/z = 650 $[M+H]^+$

Step 3: Synthesis of 2-((9S)-5-(5,6-dimethyl-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

[00495] The title compound was obtained as a white solid, 6.5 mg, 29.3%, from the
15 compound from step 2, following a similar procedure to that described in Example 44, step 3. LCMS m/z = 566 $[M+H]^+$ ¹H NMR (400 MHz, DMSO- d_6) δ 12.95 (s, 1H), 7.59 (d, 1H), 7.46 (s, 1H), 5.76 (s, 2H), 4.76 (s, 1H), 4.65 (d, 1H), 4.48 (d, 1H), 4.39 – 3.80 (s, 3H), 3.56 (s, 2H), 3.39 (s, 4H), 3.12 (s, 2H), 2.43 (s, 4H), 2.19 (s, 2H), 2.09 (s, 3H), 1.82 (s, 5H).

Example 79: Synthesis of 5-chloro-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol
20 **(Compound 116)**



Step 1: Synthesis of (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00496] The title compound was obtained as a brown solid, 15 mg, 77%, from Example 6, step 5 and 2-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, following a similar procedure to that described in Example 16, step. LCMS $m/z = 898$ $[M+H]^+$

Step 2: Synthesis of 2-((S)-5-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

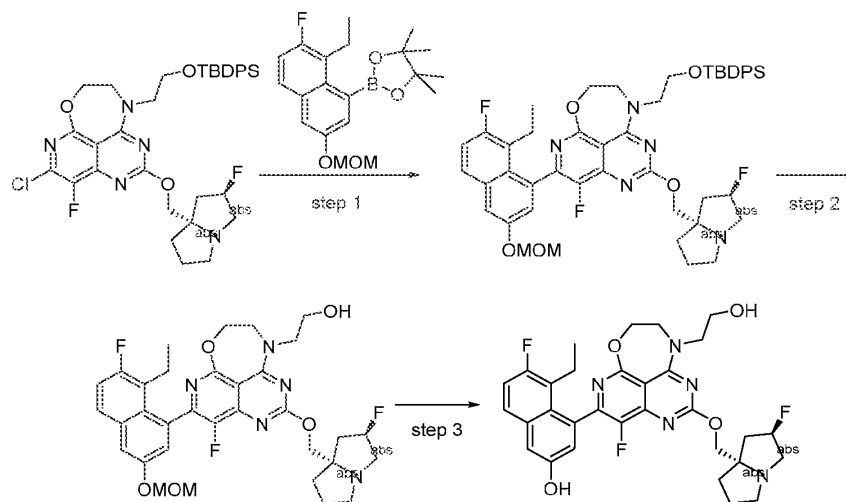
[00497] The title compound was obtained as a white solid, 8 mg, 77.8%, from the compound from step 1, following a similar procedure to that described in Example 7, step 7. LCMS $m/z = 660$ $[M+H]^+$

Step 3: Synthesis of 5-chloro-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol

[00498] The title compound was obtained as an off-white solid, 1 mg, 10.3%, from the compound from step 2, following a similar procedure to that described in Example 72, step 2. LCMS $m/z = 616$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 7.97 – 7.85 (m, 1H), 7.63 – 7.51 (m, 1H), 7.45 – 7.31 (m, 2H), 7.29 – 7.12 (m, 1H), 5.28 (d, 1H), 4.78 – 4.70 (m, 1H), 4.62 (d,

1H), 4.53 – 4.40 (m, 1H), 4.22 – 4.09 (m, 2H), 4.10 – 3.98 (m, 1H), 2.83 (d, 2H), 2.14 (d, 2H), 2.03 (d, 3H), 1.83 (d, 6H), 1.24 (s, 3H), 0.85 (d, 1H).

Example 80: Synthesis of 5-ethyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 153)



Step 1: Synthesis of 10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00499] The title compound was obtained as a white solid, 70 mg, 61%, from Example 5, step 5 and 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 879$ $[M+H]^+$

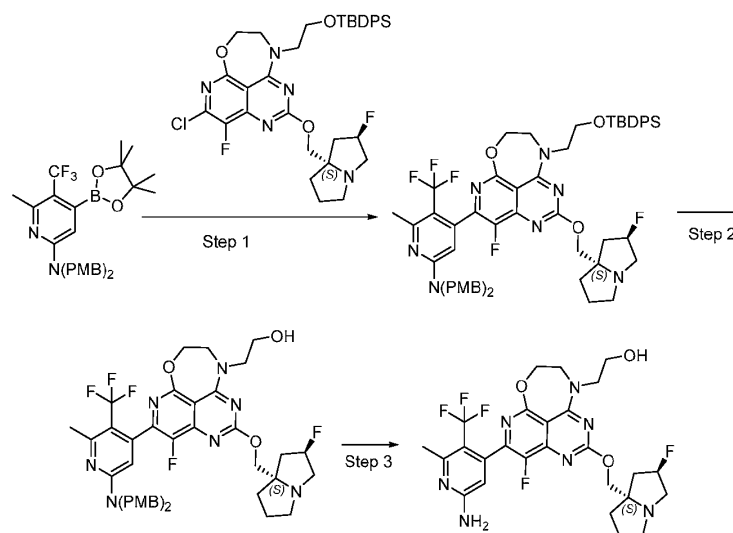
Step 2: Synthesis of 2-(5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol

[00500] CsF (224.9 mg, 1.48 mmol) was added to a solution of the compound from step 1 (65 mg, 0.074 mmol) in DMF (6 mL) and the reaction was stirred at 30°C for 2h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography to afford the title compound (40 mg, 84.5%) as light yellow solid. LCMS $m/z = 640$ $[M+H]^+$

Step 3: Synthesis of 5-ethyl-6-fluoro-4-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol

[00501] The title compound was obtained as a white solid, 3.1 mg, 7.5%, from the compound from step 2, following a similar procedure to that described in Example 44, step 3. LCMS m/z = 596 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.95 (s, 1H), 7.79 – 7.73 (m, 1H), 7.40 – 7.30 (m, 2H), 7.01 – 6.98 (m, 1H), 5.65 – 5.48 (m, 1H), 4.93 – 4.85 (m, 1H), 4.65 – 4.49 (m, 4H), 4.10 – 3.92 (m, 4H), 3.85 – 3.69 (m, 5H), 2.69 – 2.63 (m, 1H), 2.38 – 1.97 (m, 8H), 0.80 (t, 3H).

10 **Example 81: Synthesis of 2-(5-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol (Compound 132)**



Step 1: Synthesis of 4-(10-(2-(((tert-butyl)diphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[00502] The title compound was obtained as a yellow oil, 130 mg, 83%, from Example 5, step 5 and Intermediate 22, following a similar procedure to that described in Example 16, step

20 5. LCMS m/z = 1060 $[M+H]^+$

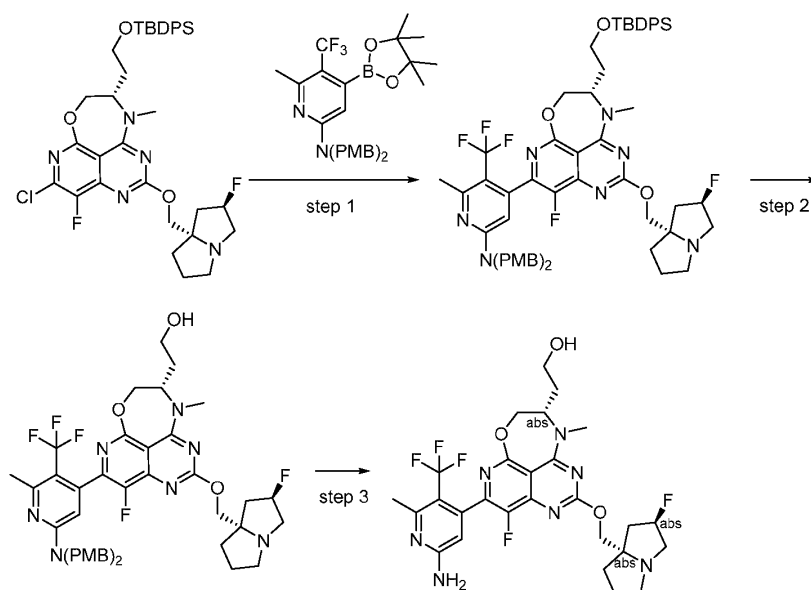
Step 2: Synthesis of 2-(5-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol

5 **[00503]** The title compound was obtained as a yellow solid, 80 mg, 86%, from the compound from step 1, following a similar procedure to that described in Example 27, step 6. LCMS m/z =821 [M+H]⁺

Step 3: Synthesis of 2-(5-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol

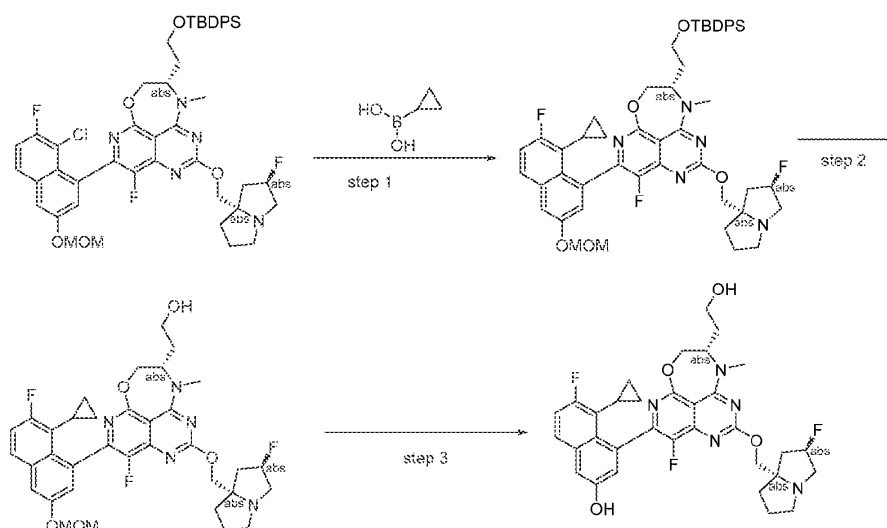
10 **[00504]** A solution of the compound from step 2 (40 mg, 0.050 mmol) in TFA (0.5 mL) was stirred for 1h at 50°C under N₂. The resulting mixture was concentrated under vacuum, the residue suspended in MeCN (0.5 mL) and H₂O (0.5 mL) and stirred for 30 min at 50°C. The residue was purified by Prep-HPLC (Method A, Gradient: 22% B to 45% B in 7 min) to afford the title compound (4.1 mg, 13.5%) as a white solid. LCMS m/z = 582 [M+H]⁺. ¹H NMR (400
15 MHz, DMSO-d₆) δ 7.30 – 6.94 (m, 2H), 6.83 (s, 3H), 5.48 (d, 1H), 4.86 (t, 2H), 4.55 (s, 2H), 4.42 (s, 4H), 3.98 (d, 4H), 3.72 (q, 3H), 2.48 – 2.45 (m, 3H), 2.25 – 1.90 (m, 4H).

**Example 82: Synthesis of 2-((S)-5-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (Compound
20 134)**



[00505] The title compound was obtained as a white solid, from Example 6, step 5 and Intermediate 22, following a similar 3 step process to that described in Example 81. LCMS m/z = 596 $[M+H]^+$ ¹H NMR (400 MHz, DMSO- d_6) δ 6.81 (s, 1H), 6.27 (d, 1H), 5.28 (d, 1H), 4.75 (t, 1H), 4.62 (dd, 1H), 4.44 (d, 1H), 4.13 (q, 2H), 4.01 (d, 1H), 3.54 (p, 2H), 3.33 (s, 3H), 3.17 - 2.92 (m, 3H), 2.83 (q, 1H), 2.48 - 2.39 (m, 3H), 2.12 - 1.91 (m, 3H), 1.90 - 1.62 (m, 6H).

Example 83: Synthesis of 5-cyclopropyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 164)



Step 1: Synthesis of (S)-9-(2-((tert-butyl diphenylsilyl)oxy)ethyl)-5-(8-cyclopropyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00506] To a solution of Example 79, step 1 (70 mg, 0.08 mmol) and cyclopropylboronic acid (20.08 mg, 0.23 mmol) in dioxane (2 mL) and H₂O (0.4 mL) were added K₂CO₃ (32.3 mg, 0.23 mmol) and Pd(dtbpf)Cl₂ (10.16 mg, 0.016 mmol) and the reaction mixture stirred for 8 h at 100°C under N₂. The cooled mixture was concentrated under reduced pressure and the residue was purified by prep-TLC (DCM:MeOH=10:1) to afford the title compound (40 mg, 56.8%) as a yellow solid. LCMS m/z = 904 [M+H]⁺

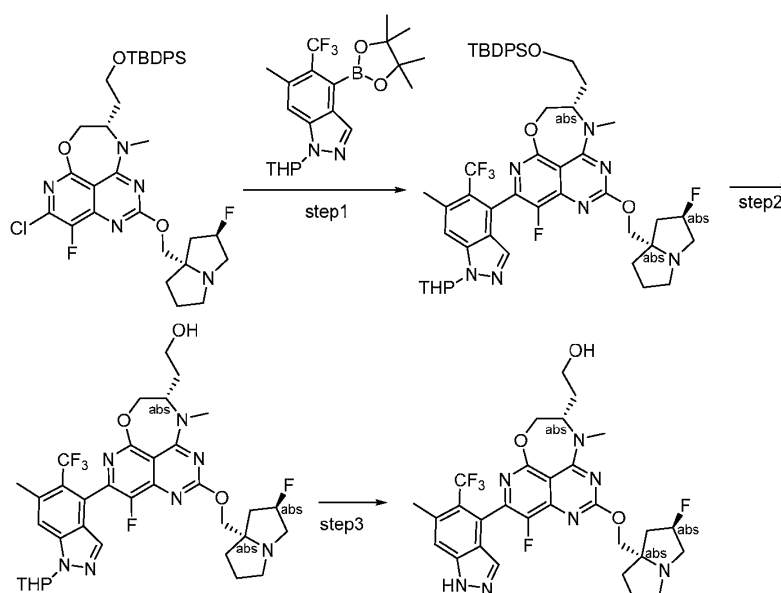
Step 2: Synthesis of 2-((S)-5-(8-cyclopropyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

[00507] The title compound was obtained as an oil, 25 mg, crude, from the compound from step 1, following a similar procedure to that described in Example 36, step 1. LCMS m/z = 666 [M+H]⁺

Step 3: Synthesis of 5-cyclopropyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol

[00508] The title compound was obtained as a white solid, 8.4 mg, 33.9%, from the compound from step 2, following a similar procedure to that described in Example 41, step 3. LCMS $m/z = 622$ $[M+H+Na]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 9.89 (d, 1H), 7.76 (d, 1H), 7.37 - 7.06 (m, 3H), 5.36-5.21 (m, 1H), 4.77 - 4.71 (m, 1H), 4.65 - 4.60 (m, 1H), 4.48 - 4.42 (m, 1H), 4.21 - 4.14 (d, 3H), 4.63 - 4.47 (m, 2H), 3.40 - 3.28 (m, 3H), 3.23 - 2.94 (m, 3H), 2.86 - 2.81 (m, 1H), 2.14 - 2.07 (m, 3H), 2.02 - 1.77 (m, 5H), 1.31 - 1.21 (m, 1H), 0.53 - 0.21 (m, 2H), 0.19 - 0.05 (m, 2H).

Example 84: Synthesis of 2-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (Compound 140)



Step 1: Synthesis of (9S)-9-(2-((tert-butyl diphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00509] The title compound was obtained as a yellow solid, 23 mg, 39.4%, from (S)-9-(2-((tert-butyl diphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (Example 6, step 5) and Intermediate 27, following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 943$ $[M+H]^+$

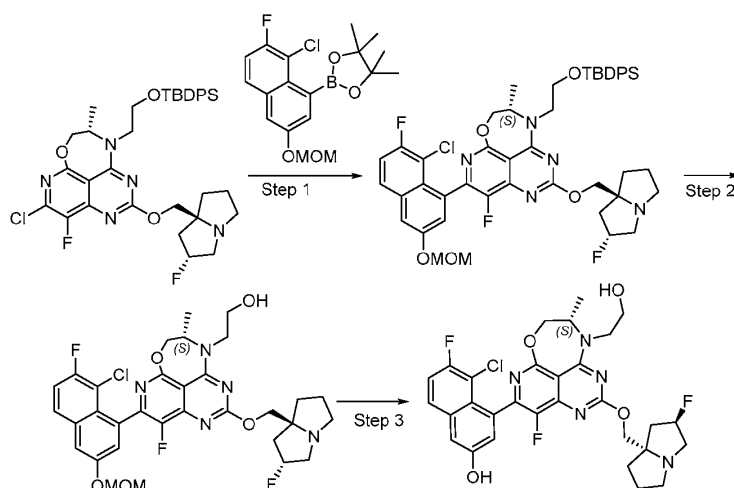
Step 2: Synthesis of 2-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

- 5 **[00510]** The title compound was obtained as a yellow oil, 10 mg, 66.9%, from the compound from step 1, following a similar procedure to that described in Example 36, step 1. LCMS $m/z = 704$ $[M+H]^+$

Step 3: Synthesis of 2-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

- [00511]** To a stirred solution of the compound from step 2 (2 mg, 0.003 mmol) in HCl in dioxane (1.5 mL) was stirred for 1 h at 25°C under N₂. The resulting mixture was concentrated under vacuum and the residue was purified by Prep-HPLC (Method C, Gradient: 22% B to 35% B in 8 min) to give the title compound as a white solid, 0.8 mg, 31%. LCMS $m/z = 620$ $[M+H]^+$. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 13.53 (br s, 1H), 10.98 (d, 1H), 7.77-7.67 (m, 2H), 5.64-5.48 (m, 1H), 4.74-4.57 (m, 3H), 4.55-4.43 (m, 1H), 4.21 (q, 1H), 3.92-3.72 (m, 4H), 3.62-3.55 (m, 2H), 3.47-3.42 (m, 3H), 3.37-3.20 (m, 3H), 2.68-2.61 (m, 3H), 2.34-2.05 (m, 3H), 1.90-1.71 (m, 2H)

- Example 85: Synthesis of 5-chloro-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 121)**



Step 1: Synthesis of (S)-10-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-5-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- 5 **[00512]** A mixture of Example 19, steps 2 to 4, 5 mg, 7 μ mol), 2-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.28 mg, 14 μ mol), K_3PO_4 (4.59 mg, 21 μ mol) and XPhos Pd G3 (0.61 mg, 1 μ mol) in DMA (5 mL) and H_2O (1 mL) was stirred for 1h at 75°C under N_2 . The reaction was quenched with water at 0°C and the aqueous layer was extracted with DCM (3x50 mL). The combined organic layers were
10 washed with brine (100 mL), dried over Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse-phase chromatography (column, C18 silica gel; mobile phase, MeCN in Water (0.1% TFA), 50% to 60% gradient in 10 min) to afford the title compound as a white solid. LCMS m/z = 898 $[M+H]^+$

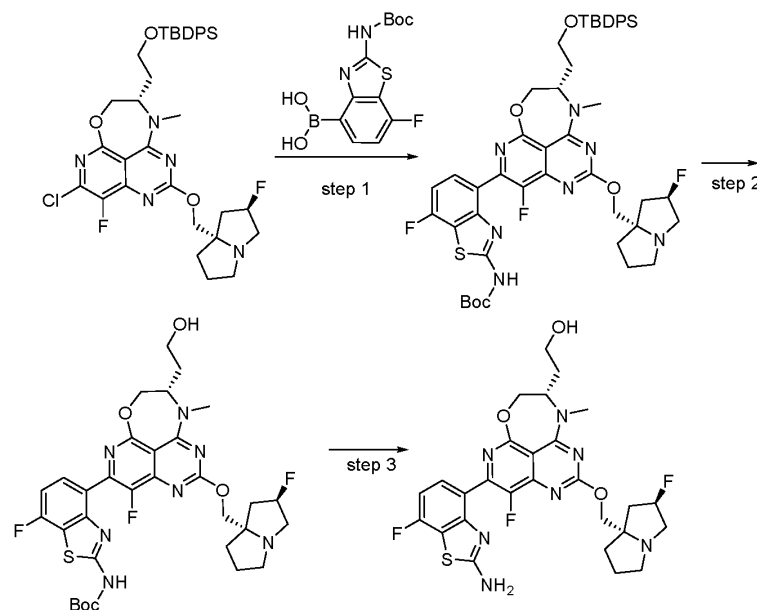
- Step 2: Synthesis of 2-((S)-5-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol*
- 15

[00513] The title compound was obtained as a white solid, 100 mg, 45%, from the compound from step 1, following the procedure described in Example 79, step 2. LCMS m/z = 660 $[M+H]^+$

- 20 *Step 3: Synthesis of 5-chloro-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2-hydroxyethyl)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol*

- [00514]** The title compound was obtained as a white solid, 10.4 mg, 10.2%, from the compound from step 2, following a similar procedure to that described in Example 44, step 3.
25 LCMS m/z = 616 $[M+H]^+$ 1H NMR (400 MHz, $DMSO-d_6$) δ 10.26 (d, 1H), 7.93 (dd, 1H), 7.56 (td, 1H), 7.41 (t, 1H), 7.19 (dd, 1H), 5.28 (d, 1H), 4.92 (s, 1H), 4.62 – 4.51 (m, 2H), 4.45 (dd, 1H), 4.34 – 4.18 (m, 1H), 4.12 (dd, 2H), 4.03 (dd, 1H), 3.80 (d, 2H), 3.10 (s, 3H), 3.02 (s, 1H), 2.83 (d, 1H), 2.13 (d, 1H), 2.10 – 1.93 (m, 2H), 1.92 – 1.69 (m, 2H), 1.25 (d, 3H).

- Example 86: Synthesis of 2-((S)-5-(2-amino-7-fluorobenzo[d]thiazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol formate (Compound 133)**
- 30



Step 1: Synthesis of tert-butyl (4-((S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-7-fluorobenzo[d]thiazol-2-yl)carbamate

[00515] A mixture of Example 6, step 5 (150 mg, 0.21 mmol), Intermediate 25 (102 mg, 0.32 mmol), Pd(PPh₃)₄ (25 mg, 0.02 mmol) and Cs₂CO₃ (353 mg, 1.08 mmol) in dioxane (5 mL) and H₂O (1 mL) was stirred for 6h at 100°C under N₂. The resulting mixture was diluted with H₂O (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (2x10 mL), dried over anhydrous Na₂SO₄, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 10:1) to afford the title compound (60 mg, 29.9%) as a light yellow solid. LCMS m/z = 925 [M+H]⁺

Step 2: Synthesis of tert-butyl (7-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)benzo[d]thiazol-2-yl)carbamate

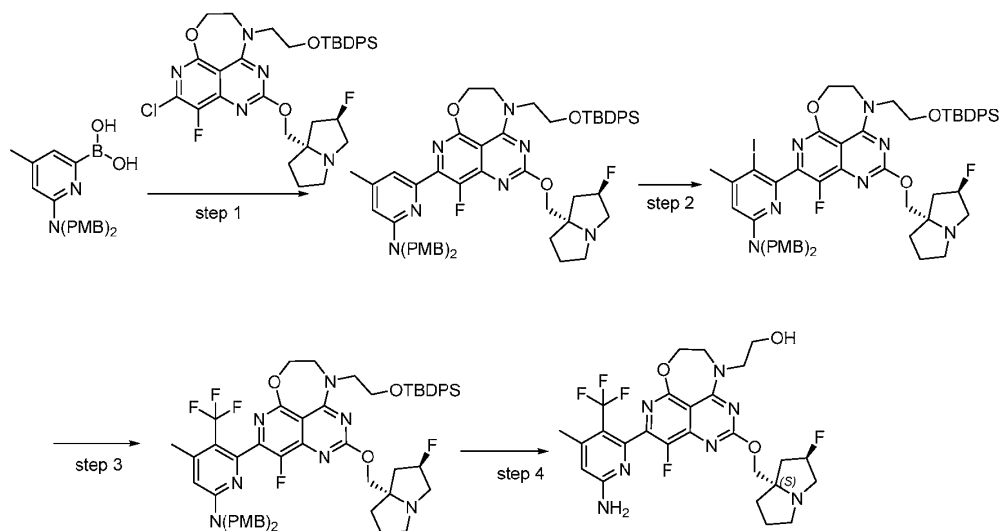
[00516] CsF (52 mg, 0.34 mmol) was added to a solution of the compound from step 1 (60 mg, 0.06 mmol) in DMF (2 mL) and the reaction mixture was stirred for 1h at 60°C. The mixture was diluted with H₂O (20 mL) extracted with EtOAc (3 x 20mL), the combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous Na₂SO₄, filtered and the

filtrate was evaporated under reduced pressure to give the title compound (44 mg, crude) as a yellow solid. LCMS m/z = 688 $[M+H]^+$

Step 3: Synthesis of 2-((S)-5-(2-amino-7-fluorobenzo[d]thiazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol formate

[00517] A solution of the compound from step 2 (20 mg, 0.02 mmol) and TFA (0.2 mL) in DCM (1 mL) was stirred for 2 h at rt. The resulting mixture was concentrated under reduced pressure and the crude was purified by Prep-HPLC (Method C, Gradient: 17% B to 30% B in 7 min) to afford the title compound (10.7 mg, 49.2%) as a light yellow solid. LCMS m/z = 588 $[M+H]^+$. ¹H NMR (400 MHz, DMSO- d_6 , ppm): δ 7.91 (s, 2H), 7.38 (t, 1H), 7.05 (t, 1H), 5.65 - 5.41 (m, 1H), 4.85 - 4.80 (m, 2H), 4.75 - 4.71 (m, 1H), 4.62 - 4.59 (m, 1H), 4.42 - 4.39 (m, 1H), 4.21 - 4.17 (m, 1H), 3.86 - 3.71 (m, 3H), 3.55 - 3.42 (m, 2H), 3.41 - 3.35 (m, 2H), 3.26 - 3.17 (m, 1H), 2.37 - 2.28 (m, 1H), 2.22 - 2.17 (m, 2H), 2.11 - 2.05 (m, 1H), 1.89 - 1.72 (m, 2H), 1.67 - 1.35 (m, 3H).

Example 87: Synthesis of 2-(5-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol (Compound 171)



Step 1: Synthesis of 6-(10-(2-((tert-butyl)di(phenyl)silyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine

[00518] The title compound was obtained as a yellow solid, 40 mg, 11%, from Example 5, step 5 and Intermediate 23, following a similar procedure to that described in Example 16, step 5. LCMS m/z = 993 $[M+H]^+$

Step 2: Synthesis of 6-(10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-iodo-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine

[00519] A solution of the compound from step 1 (35 mg, 0.035 mmol), NIS (11.90 mg, 0.053 mmol) and TsOH (1.21 mg, 0.007 mmol) in DMF (3 mL) was stirred for 2 h at 25°C under N₂. The resulting mixture was concentrated under reduced pressure, the residue was diluted with H₂O (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (DCM:MeOH=15:1) to afford the title compound (35 mg, 88.7%) as a red oil. LCMS m/z = 1119 $[M+H]^+$

Step 3: 6-(10-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

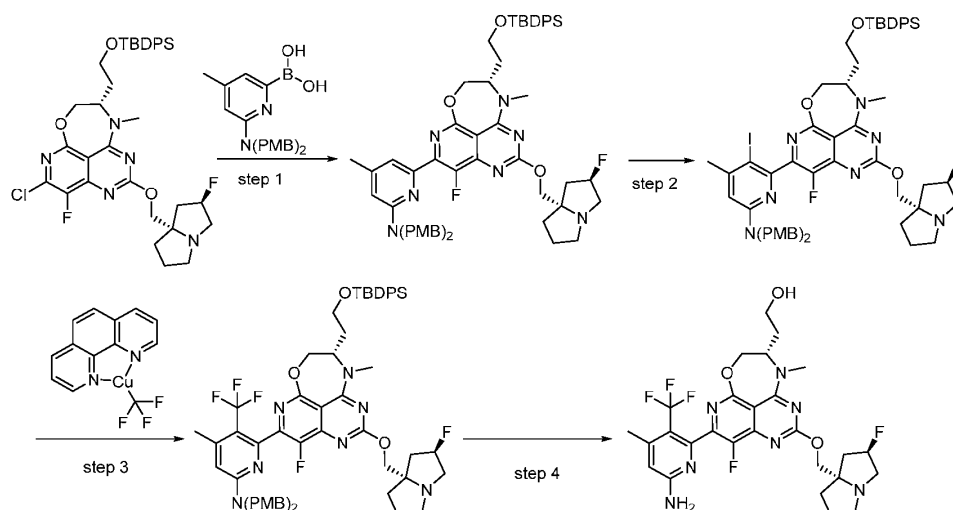
[00520] To a stirred solution of KF (11.95 mg, 0.205 mmol) and CuI (1.70 mg, 0.01 mmol) in DMF (5 mL) was added the compound from step 2 (46 mg, 0.041 mmol) and trifluoromethyl trimethylsilane (29.3 mg, 0.205 mmol) in DMF (5 mL) and the reaction mixture was stirred for 1 h at 70°C under N₂. The cooled mixture was concentrated *in vacuo* and the residue was purified by Prep-TLC (DCM:MeOH=10:1) to afford the title compound (17 mg, crude) as a yellow oil. LCMS m/z = 1061 $[M+H]^+$

Step 4: Synthesis of 2-(5-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol

[00521] Triflic acid (2 mL) was added to a solution of the compound from step 3 (14 mg, 0.013 mmol) and anisole (1.43 mg, 0.013 mmol) in DCM (5 mL) and the reaction mixture was stirred for 30 min at 25°C. The mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC (Method A, Gradient: 20% B to 47% B in 7 min) to give the title compound (2.0 mg, 25.7%) as an orange solid. LCMS m/z = 582 $[M+H]^+$ 1H NMR (400 MHz,

DMSO-d₄): δ 1.19 (d, 3H), 1.80 (s, 4H), 2.31 – 2.36 (m, 5H), 2.67 (p, 2H), 3.09 (s, 2H), 3.36 – 3.76 (m, 2H), 3.96 (d, 4H), 4.60 (d, 2H), 4.86 (t, 1H), 6.47 (s, 1H), 6.79 (s, 2H).

Example 88: Synthesis of 2-((S)-5-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (Compound 174)



Steps 1 and 2: Synthesis of 6-((S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-iodo-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine

[00522] The title compound was obtained as a yellow solid, from Example 6, step 5 and Intermediate 23, following a similar 2 step procedure to that described in Example 87, steps 1 and 2. LCMS m/z = 1132 $[M+H]^+$

Step 3: Synthesis of 6-((S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

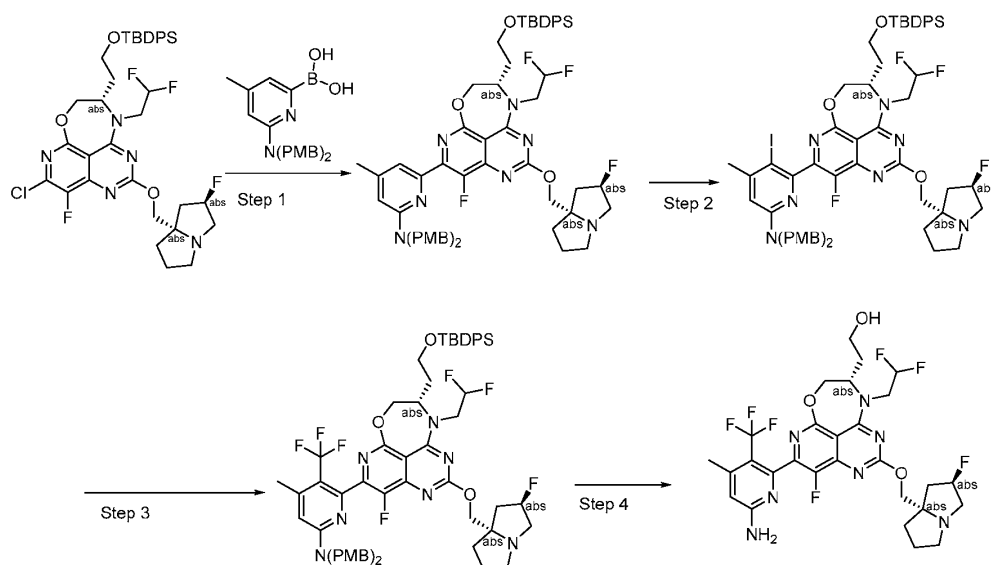
[00523] To a solution of 1,10-phenanthroline trifluoromethyl copper (40 mg, 0.13 mmol) and CuI (25 mg, 0.13 mmol) in DMF (2 mL) was added the compound from steps 1 and 2 (50 mg, 0.04 mmol), the mixture was purged N₂, and the reaction mixture was stirred at 60 °C for 1h. The reaction was diluted with EtOAc, washed with brine, dried and concentrated. The

crude product was purified by TLC (DCM:MeOH=20:1) to give the title compound (40 mg, 84.3%) as yellow solid. LCMS m/z = 1074 $[M+H]^+$

Step 4: Synthesis of 2-((S)-5-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol trifluoroacetate

[00524] To a solution of the compound from step 3 (30 mg, 0.028 mmol) in DCM (1 mL) was added CF_3SO_3H (0.2 mL) and anisole (10 μ L) and the reaction was stirred at rt for 1h. The reaction mixture was concentrated and the residue purified by prep-HPLC (Method B, Gradient: 18% B to 32% B in 7 min) to afford the title compound (11 mg, 55%) as white solid. LCMS m/z = 596 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 6.51 (s, 1H), 5.67 - 5.49 (m, 1H), 4.70 - 4.52 (m, 3H), 4.45 - 4.41 (m, 1H), 3.23 - 3.69 (m, 1H), 3.93 - 3.68 (m, 3H), 3.40 (s, 3H), 3.36 - 3.26 (m, 1H), 2.66 - 2.52 (m, 3H), 2.49 - 2.41 (m, 1H), 2.38 - 2.27 (m, 4H), 2.26 - 2.10 (m, 2H), 2.09 - 1.98 (m, 1H), 1.85 - 1.67 (m, 2H).

Example 89: Synthesis of 2-((S)-5-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-10-((2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (Compound 216)



Step 1: Synthesis of 6-((S)-9-(2-((tert-butyl)diphenylsilyl)oxy)ethyl)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-

oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine

[00525] The title compound was obtained as a yellow solid, 60 mg, 31.8%, from (S)-9-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-5-chloro-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene and Intermediate 23, following a similar procedure to that described in Example 16, step 5. LCMS m/z = 1057 [M+H]⁺

Step 2: Synthesis of 6-((S)-9-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-iodo-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine

[00526] The title compound was obtained as a yellow oil, 40 mg, 71.5%, from the compound from step 1, following a similar procedure to that described in Example 87, step 2. LCMS m/z = 1183 [M+H]⁺

Step 3: Synthesis of 6-((S)-9-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

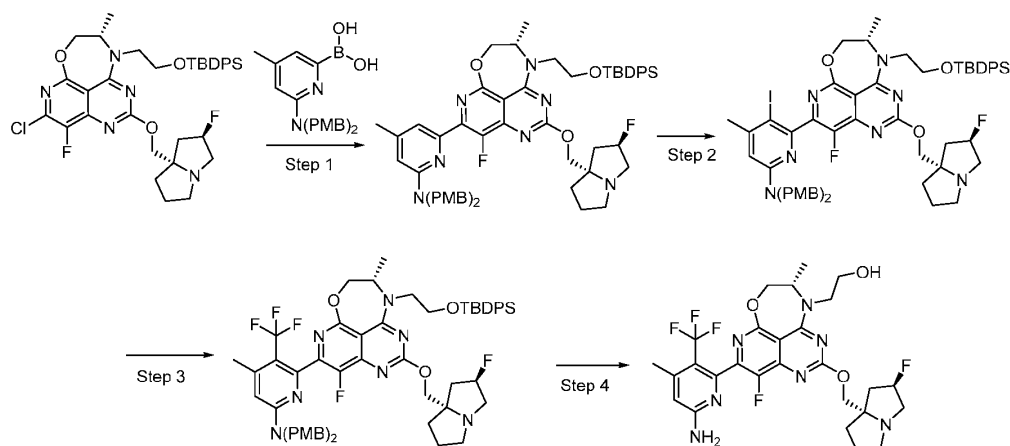
[00527] A solution of CuI (24.2 mg, 0.125 mmol) and KF (7.37 mg, 0.125 mmol) in DMF (1 mL) was stirred at rt for 25 min under N₂. The compound from step 2 (30 mg, 0.025 mmol) and trifluoromethyltrimethylsilane (18.0 mg, 0.125 mmol) were added and the reaction mixture was stirred at 60°C for 1h. The cooled mixture was quenched with water (20 mL) and extracted with EtOAc (3 x 10mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (1:1) to afford the title compound (20 mg, 70.1%) as a yellow solid. LCMS m/z = 1125 [M+H]⁺

Step 4: Synthesis of 2-((S)-5-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

[00528] The title compound was obtained as a brown solid, from the compound from step 3, following a similar procedure to that described in Example 64, step 2. LCMS m/z = 646 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.97 (d, 1H), 7.23 (s, 1H), 7.11 (s, 1H), 6.98 (s,

1H), 6.72 (d, 2H), 6.48 (s, 2H), 5.65 – 5.49 (m, 1H), 4.73 (dd, 1H), 4.69 – 4.51 (m, 2H), 4.45 (d, 1H), 4.23 (d, 3H), 2.38 – 2.25 (m, 4H), 2.24 – 2.10 (m, 3H), 2.04 (s, 2H), 1.76 (q, 2H), 1.20 (d, 3H).

Example 90: Synthesis of 2-((S)-5-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol (Compound 198)



Step 1: Synthesis of 6-((S)-10-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine

[00529] The title compound was obtained as an oil, 250 mg, 65%, from Example 19 steps 2 to 4 and Intermediate 23, following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 1007$ $[M+H]^+$

Step 2: Synthesis of 6-((S)-10-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-iodo-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine

[00530] The title compound was obtained as a yellow oil, 215 mg, 76%, from the compound from step 1, following a similar procedure to that described in Example 87, step 2. LCMS $m/z = 1133$ $[M+H]^+$

Step 3: Synthesis of 6-((S)-10-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-

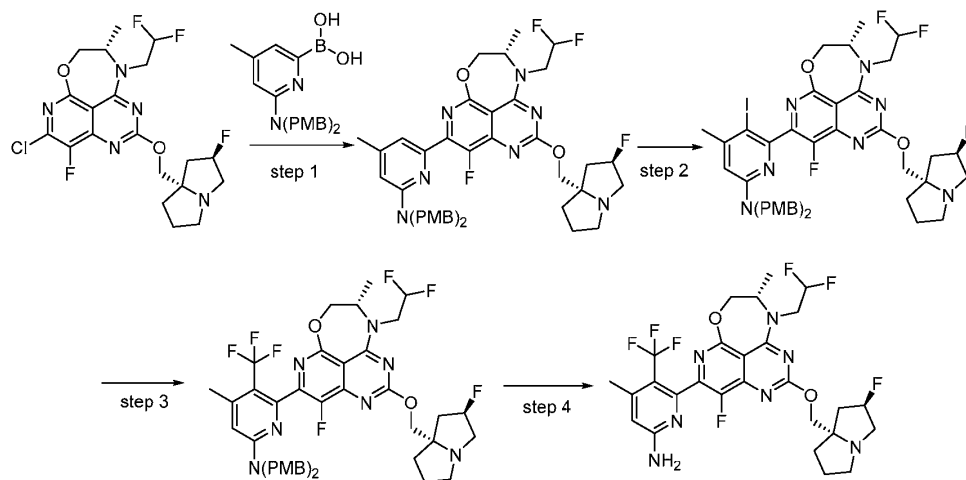
tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

[00531] The title compound was obtained as a yellow oil, 105 mg, 55%, from the compound from step 2, following a similar procedure to that described in Example 89, step 3. LCMS m/z = 1133 $[M+H]^+$

Step 4: Synthesis of 2-((S)-5-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethan-1-ol

[00532] The title compound was obtained as a white solid, 2.9 mg, 4.9%, from the compound from step 3, following a similar procedure to that described in Example 81, step 3. LCMS m/z = 596 $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6): δ 1.23 (d, 4H), 1.80 (s, 3H), 2.04 (s, 1H), 2.34 (dd, 4H), 2.65 – 3.13 (m, 6H), 3.62 (s, 1H), 3.68 – 3.95 (m, 1H), 4.17 (d, 3H), 4.41 (d, 1H), 4.55 (d, 1H), 4.90 – 4.85 (m, 1H), 5.30 (d, 1H), 6.47 (s, 1H), 6.82 (s, 2H).

Example 91: Synthesis of 6-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Compound 191)



Step 1: Synthesis of 6-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine

[00533] The title compound was obtained as a solid, 300 mg, 18%, from Example 44, step 1 and Intermediate 23, following a similar procedure to that described in Example 16, step 5.

LCMS m/z = 788 [M+H]⁺

5 *Step 2: Synthesis of 6-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-iodo-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine*

[00534] The title compound was obtained as a brown oil, 100 mg, crude, from the compound from step 1, following a similar procedure to that described in Example 87, step 2. LCMS m/z =

10 914 [M+H]⁺

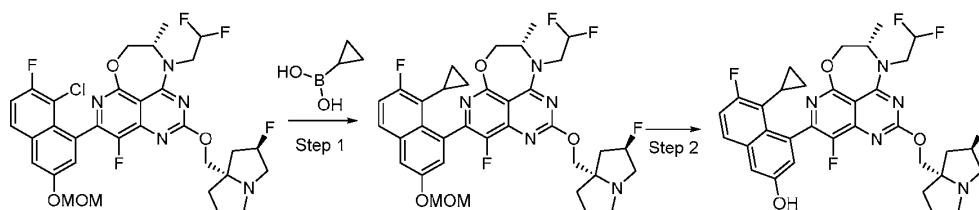
Step 2: Synthesis of 6-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

15 [00535] The title compound was obtained as a brown oil, from the compound from step 2, following a similar procedure to that described in Example 87, step 3. LCMS m/z = 856 [M+H]⁺

20 *Step 3: Synthesis of 6-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine*

[00536] The title compound was obtained as a white solid, 10.7 mg, 37.2%, from the compound from step 3, following a similar procedure to that described in Example 39, step 5. LCMS m/z = 616 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 6.83 (s, 2H), 6.63 – 6.20 (m, 2H), 5.38 (d, 1H), 4.61 (dd, 1H), 4.52 – 4.29 (m, 3H), 4.20 (dt, 3H), 3.34(m, 2H), 2.94 (d, 2H), 2.42 – 2.33 (m, 3H), 2.31 – 1.68 (m, 6H), 1.24 (d, 3H).

Example 92: Synthesis of 5-cyclopropyl-4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-fluoronaphthalen-2-ol formate (Compound 204)



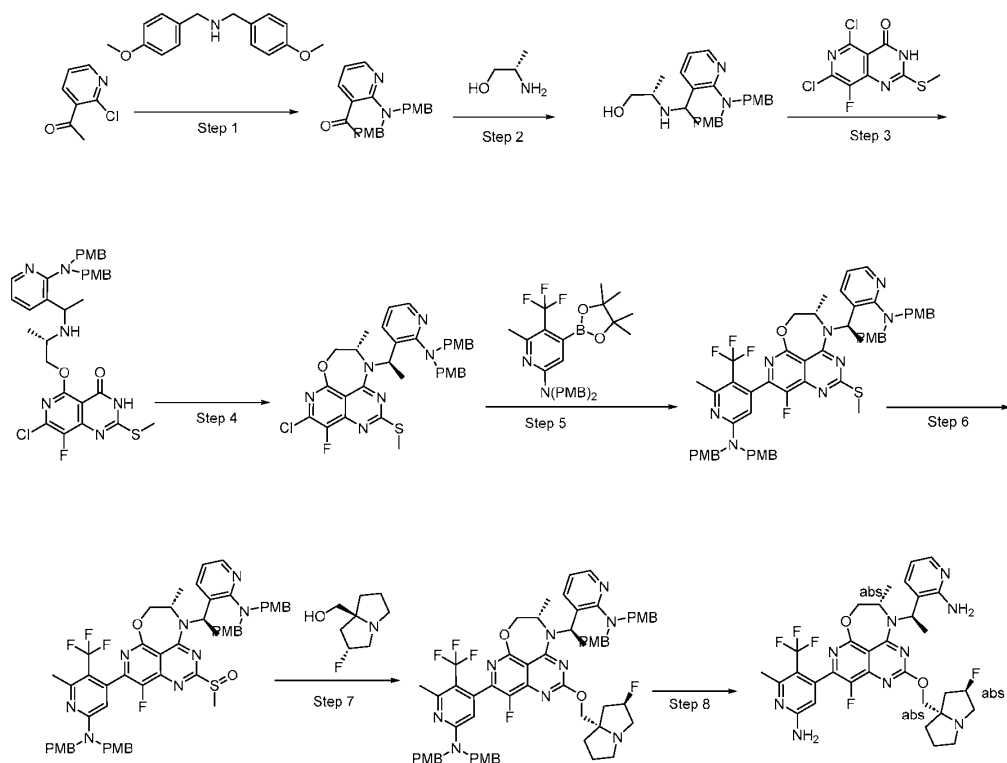
Step 1: Synthesis of (S)-5-(8-cyclopropyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- 5 **[00537]** The title compound was obtained as a white solid, 80 mg, 79.3%, from (S)-5-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene and cyclopropylboronic acid, following a similar procedure to that described in Example 83, step 1. LCMS m/z = 686 $[M+H]^+$

- 10 *Step 2: Synthesis of 5-cyclopropyl-4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-fluoronaphthalen-2-ol formate*

- [00538]** The title compound was obtained as a white solid, 26.2 mg, 26.1%, from the compound from step 1, following the procedure described in Example 44, step 3. LCMS m/z = 642 $[M+H]^+$ ¹H NMR (400 MHz, DMSO- d_6) δ 9.95 (s, 1H), 8.18 (s, 1H), 7.76 (ddd, 1H), 7.41 – 7.06 (m, 3H), 6.47 (ddt, 1H), 5.42 – 5.13 (m, 1H), 4.59 (ddd, 1H), 4.52 – 4.30 (m, 2H), 4.26 – 4.08 (m, 2H), 4.04 (dd, 1H), 3.16 – 3.05 (m, 2H), 3.02 (d, 1H), 2.83 (q, 1H), 2.20 – 2.09 (m, 1H), 2.09 – 1.93 (m, 2H), 1.90 – 1.71 (m, 3H), 1.33 – 1.18 (m, 4H), 0.53 – 0.03 (m, 4H).

- Example 93: Synthesis of 4-((9S)-10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (Compound 218)**



Step 1: Synthesis of 1-(2-(bis(4-methoxybenzyl)amino)pyridin-3-yl)ethan-1-one

- [00539]** DIPEA (16.8 mL, 96 mmol) and bis(4-methoxybenzyl)amine (12.41 g, 48.2 mmol) were added to a well-stirred solution 1-(2-chloropyridin-3-yl)ethan-1-one (5 g, 32.1 mmol) in DMSO (50 mL) and the reaction mixture was stirred at 120 °C for 24 h. The mixture was diluted with EtOAc (200 mL) and washed with water (3 x 100 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel, using a gradient of 0-100 % EtOAc in hexane, to afford the title compound (8 g, 62.0 %) as a pale-yellow liquid. LCMS m/z = 377 [M+H]⁺

- Step 2: Synthesis of (2S)-2-((1-(2-(bis(4-methoxybenzyl)amino)pyridin-3-yl)ethyl)amino)propan-1-ol*

- [00540]** (S)-2-Aminopropan-1-ol (4.94 mL, 63.8 mmol), titanium(IV)isopropoxide (9.44 mL, 31.9 mmol) and molecular sieves were added to a solution of the compound from step 1 (8 g, 21.25 mmol) in dioxane (80 mL) and the reaction mixture was heated to 100 °C and stirred for 16 h. NaBH₄ (2.41 g, 63.8 mmol) was added to the cooled reaction and the reaction mixture was stirred at rt for 2 h. The reaction was quenched with aq.NaHCO₃ solution (40 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over Na₂SO₄, filtered and

concentrated under reduced pressure. The crude was purified by silica gel column chromatography using a gradient of 0-15% MeOH in DCM, to afford the title compound (7.8 g, 82 %) as a pale-yellow liquid. LCMS m/z = 436 $[M+H]^+$

Step 3: Synthesis of 5-((2S)-2-((1-(2-(bis(4-methoxybenzyl)amino)pyridin-3-

5 *yl)ethyl)amino)propoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one*

[00541] NaHMDS (1M in THF, 21.42 mL, 21.42 mmol) was added dropwise to a stirred solution of 5,7-dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one, (3 g, 10.71 mmol) and the compound from step 2 (5.13 g, 11.8 mmol) in THF (30 mL) and DMF (6 mL) at 0 °C and the reaction mixture was stirred at rt for 12 h under N₂. The reaction was
10 quenched with ice-cold water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography, using a gradient of 0-15% MeOH in DCM, to afford the title compound (2.4 g, 33%) as a pale yellow solid. LCMS m/z = 679 $[M+H]^+$

15 *Step 4: Synthesis of 3-(1-((S)-5-chloro-4-fluoro-9-methyl-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine*

[00542] DIPEA (2.30 mL, 13.25 mmol) and BOP-Cl (1.34 g, 5.30 mmol) were added to a well-stirred solution the compound from step 3 (3 g, 4.42 mmol) in CHCl₃ (200 mL) and the
20 reaction mixture was stirred at 80 °C for 16 h. The mixture was concentrated under reduced pressure and the crude was purified by silica gel column chromatography using a gradient of 0-100 % EtOAc in hexane to afford the title compound (910 mg, 28.6 %, enriched for R isomer at alpha methyl pyridine with de 60%), as a pale yellow solid. LCMS m/z = 661 $[M+H]^+$

Step 5: Synthesis of 4-((9S)-10-(1-(2-(bis(4-methoxybenzyl)amino)pyridin-3-yl)ethyl)-4-fluoro-9-methyl-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[00543] K₃PO₄ (241 mg, 1.13 mmol) was added to a solution of the compound from step 4 (250 mg, 0.37 mmol) in dioxane (10 mL) and water (2 mL) and the mixture was degassed for 5 min with N₂. Intermediate 22 (348 mg, 0.75 mmol) followed by CataCXium® A Pd G3 (27.5
30 mg, 0.03 mmol) were added and the reaction mixture was irradiated in a microwave at 100 °C for 2 h. The cooled reaction mixture was diluted with EtOAc (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by silica gel column

chromatography using a gradient of 0-100 % EtOAc in hexane, to afford the title compound (260 mg, 62.3 %) as a pale yellow solid. LCMS m/z = 1042 [M+H]⁺

Step 6: Synthesis of 4-((9S)-10-(1-(2-(bis(4-methoxybenzyl)amino)pyridin-3-yl)ethyl)-4-fluoro-9-methyl-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-

5 *tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine*

[00544] m-CPBA (77 mg, 0.34 mmol) was added to a stirred solution of the compound from step 5 (240 mg, 0.23 mmol) in DCM (20 mL) at 0 °C and the reaction mixture was stirred at rt for 1 h. The reaction was quenched with aq. Na₂SO₃ solution (5 mL) and extracted with DCM
10 (2 x 20 mL). The combined organic layer was washed with aq. NaHCO₃ solution (10 mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure to provide the title compound, crude. LCMS m/z = 1057 [M+H]⁺

Step 7: Synthesis of 4-((9S)-10-(1-(2-(bis(4-methoxybenzyl)amino)pyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-
15 *(trifluoromethyl)pyridin-2-amine*

[00545] ((2R,7aS)-2-Fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (200 mg, 1.25 mmol) and NaOtBu (86 mg, 0.89 mmol) were added to a stirred solution the compound from step 6 (190 mg, 0.18 mmol) in toluene (25 mL) at 0 °C and the reaction mixture was stirred at
20 25 °C for 1 h. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over Na₂SO₄, filtered and evaporated under reduced pressure to give the title compound (190 mg, 75 %) as a pale-yellow gum. LCMS m/z = 1153 [M+H]⁺

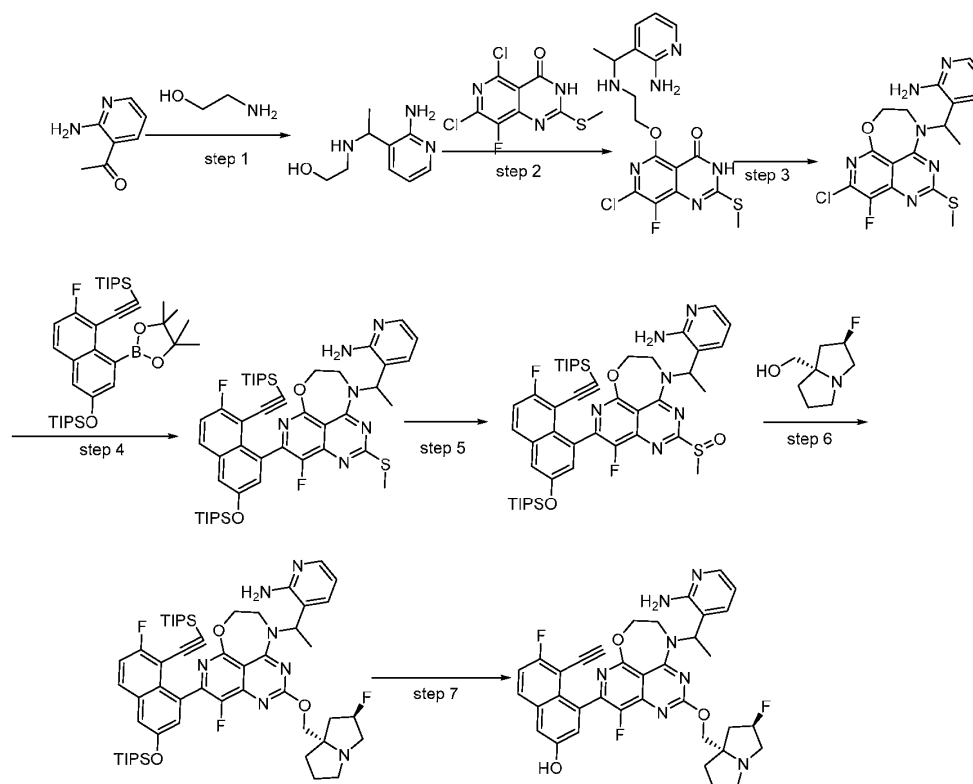
Step 8: Synthesis of 4-((9S)-10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-
25 *tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine*

[00546] Triflic acid (0.06 mL, 0.73 mmol) was added to a stirred solution of the compound from step 7 (230 mg, 0.2 mmol) in DCM (25 mL) and the reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with DCM (10 mL), the pH adjusted to 9 using saturated
30 NaHCO₃ solution and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layer was concentrated under reduced pressure and the crude compound was purified by prep-HPLC [column: ZORBAX C18 (20*50) 5 μ , Mobile Phase-A: 10 mM aqueous NH₄CO₃, Mobile Phase-B: MeCN, gradient 0 to 100 % MeCN, flow rate: 15 mL/min. The combined pure

fractions were lyophilized to afford the title compound (8.70 mg, 6.5 %) as an off white solid.

LCMS m/z = 672 $[M+H]^+$ 1H-NMR (400 MHz, DMSO- d_6): δ 8.00 (dd, 1H), 7.70 (d, 1H), 6.81 (s, 2H), 6.71-6.68 (m, 1H), 6.53-6.48 (m, 1H), 6.25 (brs, 1H), 5.60 (s, 2H), 5.36-5.23 (m, 1H), 4.53-4.50 (m, 1H), 4.31 (d, 1H), 4.14 (s, 2H), 4.04-4.03 (m, 1H), 3.11-3.02 (m, 3H), 2.84-2.83 (m, 1H), 2.48-2.47 (m, 3H), 2.17-2.14 (m, 2H), 2.08-2.03 (m, 2H), 1.87-1.79 (m, 3H), 1.63-1.59 (m, 3H), 0.54 (d, 2H) ppm.

Example 94: Synthesis of 4-(10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (Compound 115)



Step 1: Synthesis of 2-((1-(2-aminopyridin-3-yl)ethyl)amino)ethan-1-ol

[00547] The title compound was obtained as a brown oil, from ethanolamine and 1-(2-aminopyridin-3-yl)ethan-1-one, following a similar procedure to that described in Example 30, step 1. LCMS m/z = 182 $[M+H]^+$

Step 2: Synthesis of 5-(2-((1-(2-aminopyridin-3-yl)ethyl)amino)ethoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4(3H)-one

[00548] The title compound was obtained as a yellow oil, 4.2 g, 51.2%, from the compound from step 1 and 5,7-dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one, following a similar procedure to that described in Intermediate 29, step 2. LCMS m/z = 425 [M+H]⁺

Step 3: Synthesis of 3-(1-(5-chloro-4-fluoro-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00549] TEA (3.41 g, 33.9 mmol) was added to a solution of the compound from step 2 (4.8 g, 11.3 mmol) and PyBOP® (7.06 g, 13.56 mmol) in DMF (60 mL) and the reaction mixture was stirred for 2h at rt under N₂. The reaction was quenched with water and the aqueous layer was extracted with EtOAc (3x100 mL). The combined organic layers were washed with brine (2x100 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM / MeOH (20:1) to afford the title compound (2.7 g, 58.8%) as a yellow oil. LCMS m/z = 407 [M+H]⁺

Step 4: Synthesis of 3-(1-(4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00550] The title compound was obtained as a yellow oil, 640 mg, 49.9%, from the compound from step 3 and ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane following a similar procedure to that described in Example 16, step 5. LCMS m/z = 876 [M+H]⁺

Steps 5 and 6: Synthesis of 3-(1-(4-fluoro-5-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00551] The title compound was obtained as a yellow oil, from the compound from step 4 and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar procedure to that described in Example 18, steps 3 and 4. LCMS m/z = 518 [M+H]⁺

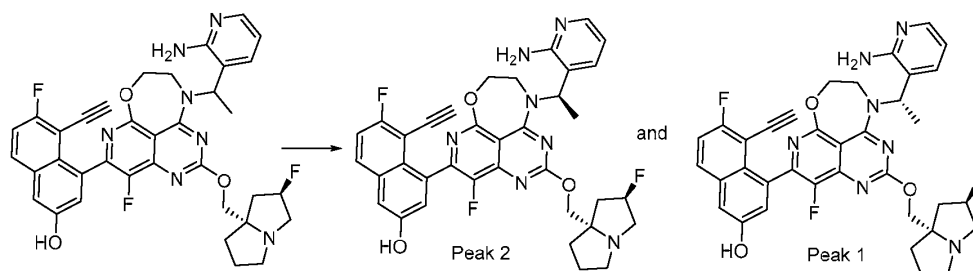
Step 7: Synthesis of 4-(10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol

[00552] CsF (278.9 mg, 1.80 mmol) was added to a solution of the compound from steps 5 and 6 (180 mg, 0.18 mmol) in DMF (3 mL) and the reaction mixture was stirred for 2h at rt under N₂. The reaction was quenched with water and the mixture extracted with EtOAc (3 x 5mL). The combined organic layers were washed with brine (2x5 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC (Method A, Gradient: 29% B to 54% B in 8 min) to afford the title compound (90 mg, 73.2%) as a white solid. LCMS m/z = 668 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.88 (dd, 1H), 7.63 – 7.43 (m, 2H), 7.38 (d, 1H), 7.16 (d, 1H), 4.76 – 4.52 (m, 2H), 4.40 – 3.99 (m, 4H), 3.72 (d, 1H), 3.08 (d, 3H), 2.93 (d, 3H), 2.33 (d, 2H), 2.22 – 2.07 (m, 3H), 1.98 – 1.85 (m, 2H), 1.73 – 1.52 (m, 3H), 1.25 (d, 3H), 0.84 (d, 1H).

Example 95: Synthesis of 4-(10-((S)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (Compound 117)

and

Example 96: Synthesis of 4-(10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (Compound 118)

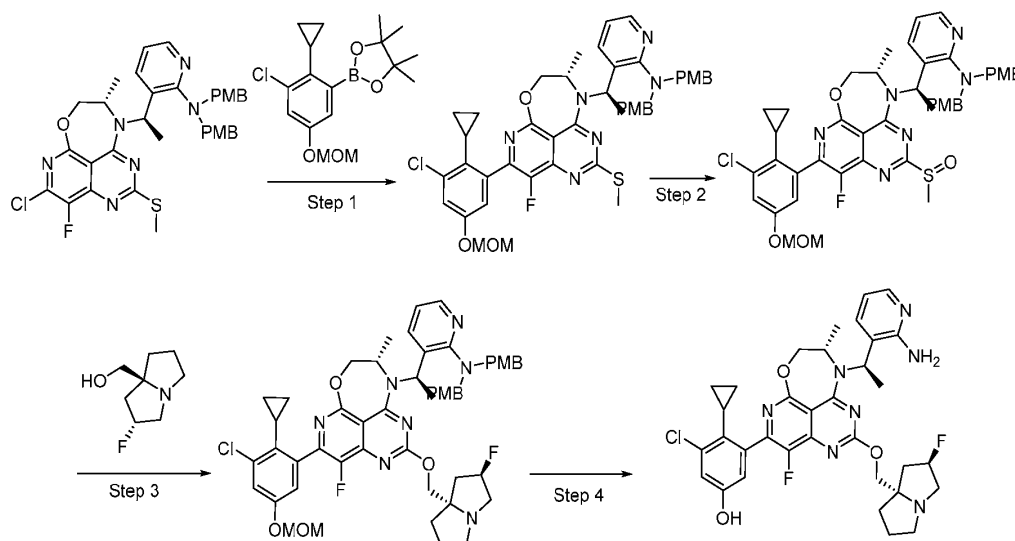


[00553] Example 94 (160 mg) was purified by Prep-HPLC (Column: CHIRALPAK IC3; Mobile Phase A: Hex (0.2%DEA): (MeOH: DCM=1:1) 65: 35; flow rate: 1mL/min; Gradient: isocratic to afford Peak 1, Example 95 (25.1 mg, 15.3%) as a white solid. LCMS m/z = 668 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 10.16 (s, 1H), 8.07 – 7.90 (m, 3H), 7.65 (d, 1H),

7.51 – 7.31 (m, 2H), 7.14 (d, 1H), 6.74 – 6.53 (m, 1H), 6.33 (dd, 1H), 5.78 (d, 4H), 5.30 (d, 2H), 4.41 (dd, 1H), 4.27 – 4.12 (m, 2H), 4.05 (d, 1H), 3.10 (d, 2H), 3.02 (s, 1H), 2.83 (s, 1H), 2.14 (s, 2H), 2.05 (d, 3H), 1.90 – 1.71 (m, 3H)

[00554] And Peak 2, Example 96. LCMS m/z = 668 $[M+H]^+$. 1H NMR (400 MHz, DMSO-
 5 d6) δ 10.16 (s, 1H), 8.02 – 7.87 (m, 2H), 7.65 (d, 2H), 7.54 – 7.31 (m, 1H), 7.14 (d, 1H), 6.68 (ddd, 1H), 6.34 (dt, 2H), 5.78 (d, 3H), 5.30 (d, 2H), 4.53 – 4.34 (m, 2H), 4.26 – 4.05 (m, 3H), 3.99 (d, 2H), 3.72 (ddd, 1H), 3.44 (dd, 1H), 3.17 – 2.98 (m, 4H), 1.38 – 1.17 (m, 3H), 0.96 – 0.77 (m, 1H).

Example 97: Synthesis of 3-((9S)-10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-
 10 2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol
 (Compound 212)



Step 1: Synthesis of 3-(1-((S)-5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4-fluoro-
 15 9-methyl-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00555] Intermediate 21 (164 mg, 0.48 mmol) and K_3PO_4 (154 mg, 0.72 mmol) were added to a solution of Example 93, step 4 (160 mg, 0.24 mmol) in dioxane (5 mL) and water (1.25 mL) and the mixture was purged with N_2 . CataCXium A Pd G3 (17.62 mg, 0.02 mmol) was
 20 added and the reaction mixture was irradiated in the microwave at 100 °C for 1.5 h. The reaction mixture was diluted with water (10 mL), extracted with EtOAc (3 x 20 mL) and the

combined organic extracts dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography using a gradient of 0-100 % EtOAc in hexane to afford the title compound (160 mg, 41.1 %) as an off-white solid. LCMS m/z = 837 [M+H]⁺

- 5 *Step 2: Synthesis of 3-(1-((9S)-5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4-fluoro-9-methyl-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine*

[00556] m-CPBA (96 mg, 0.43 mmol) was added to a stirred solution of the compound from step 1 (240 mg, 0.28 mmol) in DCM (10 mL) at 0 °C and the reaction mixture was stirred at rt
10 for 1 h. The reaction was quenched with Na₂SO₄ solution (10 mL) and extracted with DCM (2 x 10 mL). The combined organic layers were washed with NaHCO₃ solution (2 x 10 mL), dried over Na₂SO₄, filtered and evaporated under reduced pressure to give the title compound (240 mg, 53.0 %) as an off-white solid. LCMS m/z = 853 [M+H]⁺

- 15 *Step 3: Synthesis of 3-(1-((S)-5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine*

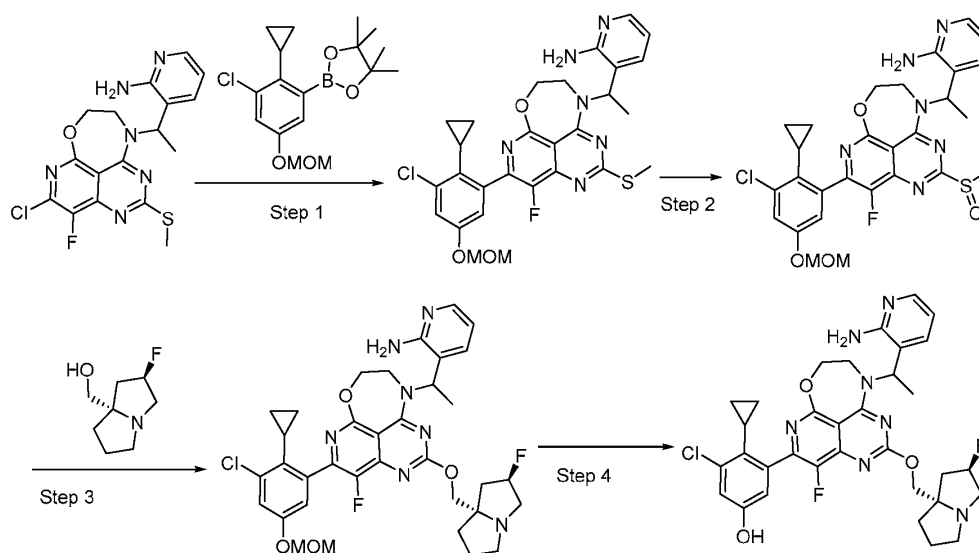
[00557] NaOtBu (61.9 mg, 0.64 mmol) was added to a stirred solution of the compound from step 2 (220 mg, 0.2 mmol) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol
20 (164 mg, 1.03 mmol) in toluene (10 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with water (10 mL), extracted with EtOAc (3 x 10 mL), the combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (220 mg, crude) as an off white solid. LCMS m/z = 948 [M+H]⁺

- 25 *Step 4: Synthesis of 3-((9S)-10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol*

[00558] Triflic acid (0.06 mL, 0.73 mmol) was added to a well-stirred solution of the compound from step 3 (70 mg, 0.07 mmol) in TFA (0.3 mL) and the reaction mixture was
30 stirred at rt for 1 h. The reaction mixture was diluted with DCM (10 mL), saturated NaHCO₃ solution was added to pH 9 and the organic layer was extracted with DCM (2 x 10 mL). The combined organic layer was concentrated under reduced pressure and the crude compound was purified by prep-HPLC [column: HPLC SHIMPACK C18 (19*250) 5μ, Mobile Phase-A: 10

mM aqueous NH_4CO_3 Mobile Phase-B: MeCN, using gradient 0 to 100 % MeCN, Flow rate: 15 mL/min. The combined pure fractions were lyophilized to afford the title compound (1.78 mg, 3.6 %) as an off-white solid. LCMS $m/z = 664$ $[\text{M}+\text{H}]^+$ $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 9.95 (s, 1H), 8.00 (d, 1H), 7.71 (d, 1H), 6.93 (d, 1H), 6.75-6.68 (m, 2H), 6.53 (d, 1H), 5.64 (s, 2H), 5.37-5.23 (m, 1H), 4.56-4.51 (m, 1H), 4.32 (d, 1H), 4.14 (s, 2H), 4.04 (t, 1H), 3.15-3.09 (m, 2H), 2.85-2.83 (m, 1H), 2.21-2.04 (m, 4H), 1.87-1.79 (m, 4H), 1.61 (d, 3H), 0.64-0.55 (m, 2H), 0.55 (d, 3H), 0.06-0.02 (m, 2H) ppm

Example 98: Synthesis of 3-(10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol (Compound 152)



Step 1: Synthesis of 3-(1-(5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4-fluoro-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00559] The title compound was obtained as a yellow solid, 95.5 mg, 39.6%, from Intermediate 21 and Example 94, Step 3, following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 581$ $[\text{M}+\text{H}]^+$

Step 2: Synthesis of 3-(1-(5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4-fluoro-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00560] The title compound was obtained as a yellow oil, 92 mg, 93.8%, from the compound from step 1, following a similar procedure to that described in Example 18, step 4. LCMS m/z = 599 [M+H]⁺

5 *Step 3: Synthesis of 3-(1-(5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine*

[00561] The title compound was obtained as a yellow solid, 35 mg, 32.8%, from the compound from step 2 and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar procedure to that described in Intermediate 29, step 5. LCMS m/z = 695
10 [M+H]⁺

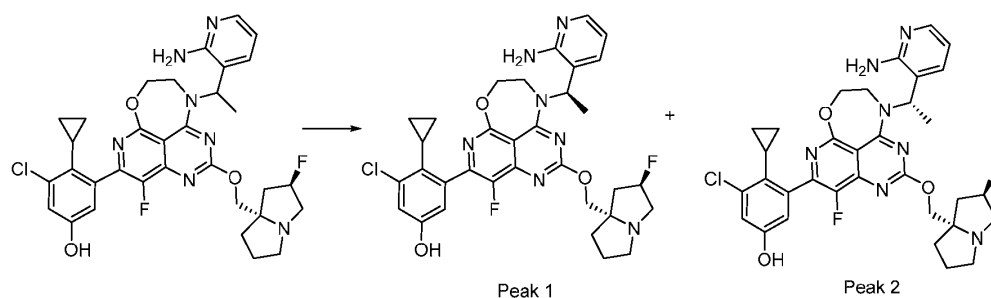
Step 4: Synthesis of 3-(10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol formate

[00562] A solution of the compound from step 3 (35mg, 0.05mmol) and TFA (1 mL) in
15 DCM (5 mL) was stirred for 1h at rt. The resulting mixture was concentrated under reduced pressure and the crude product was purified by Prep-HPLC (Method D, Gradient: 10% B to 23% B in 7min) to afford the title compound (27 mg, 82.3%) as a white solid. LCMS m/z = 650 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 9.96 (s, 1H), 7.98 (d, 1H), 7.63 (dd, 1H), 6.93 (d, 1H), 6.71 (d, 1H), 6.67-6.62 (m, 1H), 6.36 (d, 1H), 5.74 (s, 2H), 5.42 - 5.18 (m, 1H), 4.44
20 (dd, 1H), 4.37 - 4.03 (m, 3H), 3.85 - 3.69 (m, 1H), 3.41 - 3.38 (m, 1H), 3.21-3.09 (m, 3H), 2.95 - 2.81 (m, 1H), 2.27 - 2.00 (m, 3H), 1.98 - 1.74 (m, 4H), 1.57 (d, 3H), 0.71 - 0.54 (m, 2H), 0.08 - 0.02 (m, 2H).

Example 99: Synthesis of 3-(10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol formate
25 **(Compound 155)**

and

Example 100: Synthesis of 3-(10-((S)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol formate
30 **(Compound 156)**



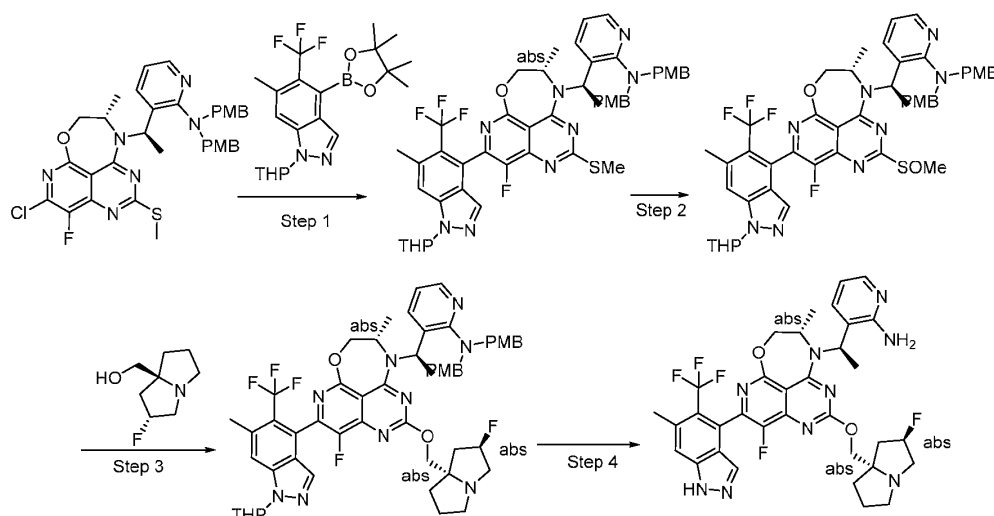
[00563] Example 98 (27 mg) was purified by Prep-chiral-HPLC (Column: CHIRALPAK IE, 2*25 cm, 5 μ m; Mobile Phase A: Hex (0.5% 2M NH_3 -MeOH), Mobile Phase B: EtOH:

DCM=1: 1; Flow rate: 20 mL/min; Gradient: 35% B isocratic in 16 min to afford Peak 1,

- 5 Example 99 (10.5 mg, 38.6%) as a white solid. LCMS m/z = 650 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.92 (s, 1H), 7.92 (dd, 1H), 7.59 (dd, 1H), 6.88 (d, 1H), 6.67 (d, 1H), 6.65 - 6.60 (m, 1H), 6.33 - 6.30 (m, 1H), 5.69 (s, 2H), 5.48 - 5.08 (m, 1H), 4.39 (dd, 1H), 4.36 - 4.08 (m, 3H), 3.69 (dd, 1H), 3.36 - 3.32 (m, 1H), 3.14 - 2.97 (m, 3H), 2.90 - 2.72 (m, 1H), 2.18 - 1.94 (m, 3H), 1.86 - 1.72 (m, 4H), 1.52 (d, 3H), 0.68 - 0.51 (m, 2H), 0.04 - 0.01 (m, 2H).

- 10 **[00564]** Peak 2, Example 100, (8.8 mg, 30.1%) as a white solid. LCMS m/z = 650 $[\text{M}+\text{H}]^+$ ^1H NMR (400 MHz, $\text{DMSO}-d_6$, ppm): δ 9.92 (s, 1H), 7.92 (dd, 1H), 7.59 (dd, 1H), 6.88 (d, 1H), 6.79 - 6.57 (m, 2H), 6.37 - 6.25 (m, 1H), 5.69 (s, 2H), 5.43 - 5.12 (m, 1H), 4.42-4.38 (m, 1H), 4.33 - 4.15 (m, 2H), 4.04 (d, 1H), 3.76-3.71 (m, 1H), 3.37-3.31 (m, 1H), 3.18 - 3.00 (m, 3H), 2.88 - 2.75 (m, 1H), 2.20 - 1.94 (m, 3H), 1.79 - 1.65 (m, 4H), 1.52 (d, 3H), 0.65 - 0.54 (m, 2H), 0.06 - 0.01 (m, 2H).
- 15

Example 101: Synthesis of 3-(1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 211)



Step 1: Synthesis of 3-(1-((9S)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl))-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

- 5 **[00565]** Intermediate 27 (248 mg, 0.60 mmol) and K_3PO_4 (193 mg, 0.90 mmol) were added to a solution of Example 93, step 4 (200 mg, 0.30 mmol) in dioxane (3.6 mL) and water (0.4 mL) and the mixture was degassed with N_2 . CataCXium Pd G3 (22.0 mg, 0.03 mmol) was added and the reaction mixture was irradiated in the microwave at 100 °C for 2 h. The cooled reaction mixture was diluted with water (10 mL), extracted with EtOAc (2 x 20 mL), the combined
10 organic extracts dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography, using a gradient of 0-100 % EtOAc in Hexane, to afford the title compound (220 mg, 60.2 %) as a pale yellow gum. LCMS m/z = 910 $[M+H]^+$.

Step 2: Synthesis of 3-(1-((9S)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl))-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

- 15 **[00566]** mCPBA (18.49 mg, 0.08 mmol) was added to a stirred solution of the compound from step 1 (50 mg, 0.05 mmol) in DCM (3 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with sat. Na_2SO_3 solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with 10% aqueous $NaHCO_3$
20 solution (10 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the title compound (50 mg, crude) as a pale yellow gum. LCMS m/z = 926 $[M+H]^+$

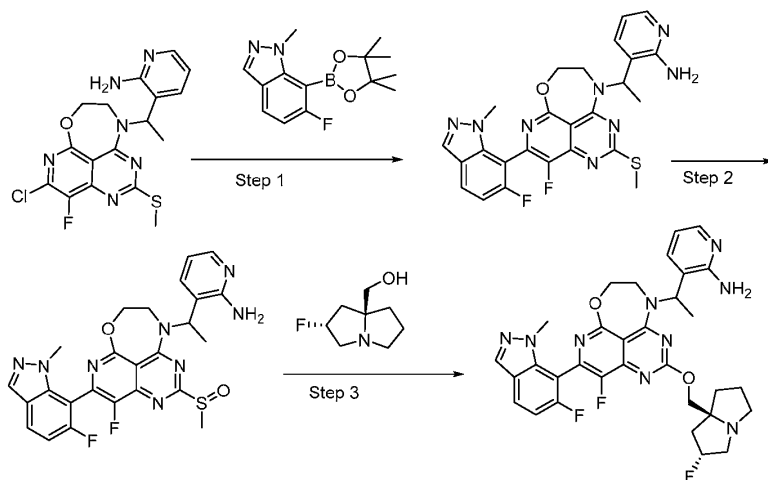
Step 3: Synthesis of 3-(1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

- 5 **[00567]** NaOtBu (15.58 mg, 0.16 mmol) was added to a stirred solution of the compound from step 2 (50 mg, 0.05 mmol) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (17.21 mg, 0.10 mmol) in toluene (3 mL) at 0 °C and the resulting mixture was stirred at 25 °C for 2 h. The reaction was quenched with water (5 mL), extracted with EtOAc (3 x 10 mL), the combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (70 mg, 77 %) as a pale-yellow gum. LCMS m/z = 1020 [M+H]⁺

Step 4: Synthesis of 3-(1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

- 15 **[00568]** TfOH (0.05 mL, 0.58 mmol) was added to a stirred solution of the compound from step 3 (60 mg, 0.05 mmol) in TFA (1 mL) and the reaction mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure and the crude compound was purified by prep-HPLC reverse phase purification [column: SHIMPACK c-18 (20x150), Mobile Phase-A: 10 mM in NH₄CO₃ in water, Mobile Phase-B: MeCN, using gradient 0 to 100 % MeCN, Flow rate: 15 mL/min]. The combined pure fractions were lyophilized to afford the title compound (6 mg, 14.2 %) as an off-white solid. LCMS m/z = 696 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ 13.52-13.46 (m, 1H), 8.01-8.00 (m, 1H), 7.79-7.71 (m, 3H), 6.73-6.69 (m, 1H), 6.55 (t, 1H), 5.71-5.63 (m, 2H), 5.37-5.23 (m, 1H), 4.55-4.53 (m, 1H), 4.38-4.33 (m, 1H), 4.15-4.04 (m, 3H), 3.11-3.09 (m, 2H), 3.02 (s, 1H), 2.84-2.83 (m, 1H), 2.65-2.64 (m, 3H), 2.17-2.15 (m, 1H), 2.08-2.04 (m, 2H), 1.87-1.79 (m, 3H), 1.65-1.61 (m, 3H), 0.64-0.56 (m, 3H) ppm.

Example 102: Synthesis of 3-(1-(4-fluoro-5-(6-fluoro-1-methyl-1H-indazol-7-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 190)



Step 1: Synthesis of 3-(1-(4-fluoro-5-(6-fluoro-1-methyl-1H-indazol-7-yl)-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00569] The title compound was obtained as a yellow solid, 50 mg, 39%, from Example 94, step 3 and 6-fluoro-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole following a similar procedure to that described in Example 16, step 5. LCMS m/z = 521 $[M+H]^+$

Step 2: Synthesis of 3-(1-(4-fluoro-5-(6-fluoro-1-methyl-1H-indazol-7-yl)-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

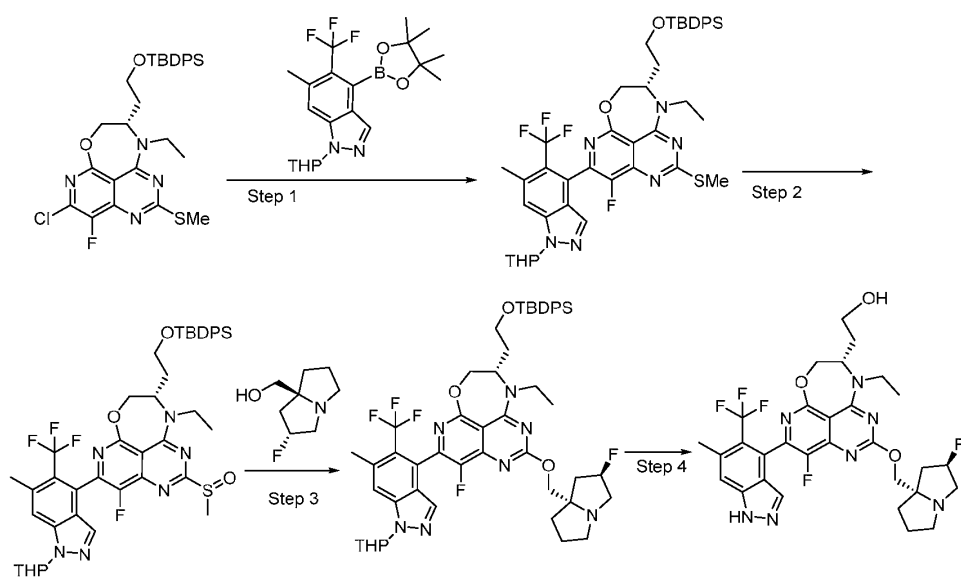
[00570] The title compound was obtained as a yellow solid, crude, from the compound from step 1, following a similar procedure to that described in Example 18, step 3. LCMS m/z = 537 $[M+H]^+$

Step 3: Synthesis of 3-(1-(4-fluoro-5-(6-fluoro-1-methyl-1H-indazol-7-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00571] A solution of the compound from step 2 (10 mg, 0.02 mmol) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (8.90 mg, 0.06 mmol) in toluene (1 mL) was stirred at rt for 30 min. NaOtBu (3.58 mg, 0.04 mmol) was added at 0°C and the reaction mixture was stirred at 0°C for 1h under N₂. The reaction was quenched with water at rt and the aqueous layer was extracted with DCM (3x10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The crude was purified by Prep-HPLC (Method D, Gradient: 2% B to 24% B in 7 min) to afford the title compound (1.6 mg, 13.6%) as an off-white solid. LCMS m/z

= 632 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.14 (d, 2H), 7.96 (dd, 2H), 7.64 (d, 1H), 7.18 (t, 1H), 6.68 (dd, 1H), 6.36 (dd, 1H), 5.74 (d, 2H), 5.36 (d, 1H), 4.57 – 4.13 (m, 6H), 3.82 – 3.75 (m, 3H), 3.64 (d, 4H), 2.93 (s, 1H), 2.26 – 2.06 (m, 4H), 1.89 (dd, 3H),

Example 103: Synthesis of 2-((9S)-10-ethyl-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (Compound 177)



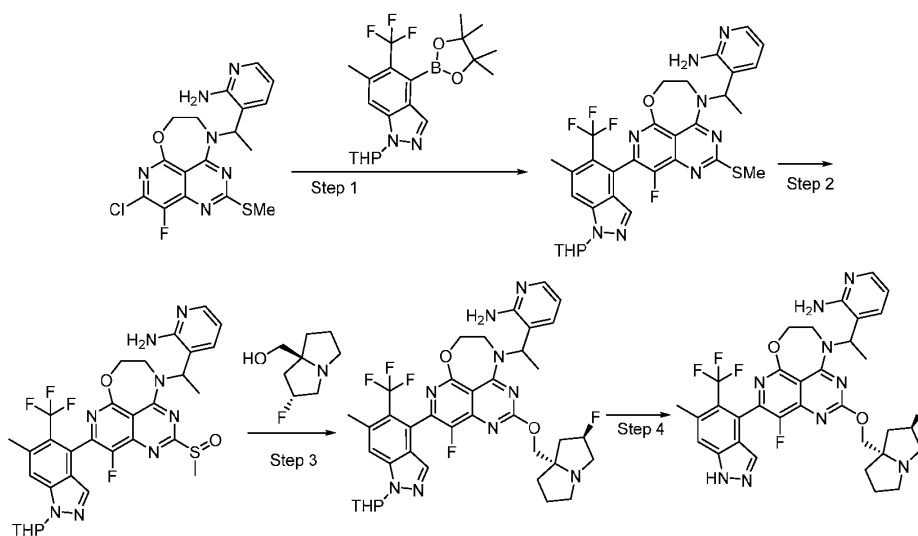
Steps 1 to 3: Synthesis of 3-(1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00572] The title compound was obtained as a pale yellow solid, from Intermediate 28, step 2, Intermediate 27 and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar 3 step procedure to that described in Example 101, steps 1 to 3. LCMS m/z = 957 [M+H]⁺

Step 4: Synthesis of 3-(1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00573] HCl in MeOH (1.25 M, 1.04 mL, 1.26 mmol) was added to a solution of the compound from steps 1 to 3 (40 mg, 0.04 mmol) in dioxane (2 mL) and the reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched with TEA (0.2 mL) and concentrated under reduced pressure. The crude compound was purified by prep-HPLC reverse phase purification [column: X SELECT C18 (19*250) 5 μ , Mobile Phase-A: 0.1% Formic acid in water, Mobile Phase-B: MeCN, using gradient 0 to 100 % MeCN, Flow rate: 15 mL/min. The combined pure fractions were lyophilized to afford the title compound (6.7 mg, 25.1%) as an off-white solid. LCMS m/z = 634 [M+H]⁺. ¹H-NMR (400 MHz, DMSO- d_6): δ 13.52 (d, 1H), 10.88 (brs, 1H), 7.75-7.67 (m, 2H), 5.64-5.51 (m, 1H), 4.74-4.59 (m, 4H), 4.43-4.21 (m, 3H), 3.86-3.71 (m, 3H), 3.59-3.49 (m, 4H), 2.68-2.67 (m, 4H), 2.50-2.33 (m, 1H), 2.18-2.04 (m, 3H), 1.89-1.82 (m, 2H), 1.31 (t, 3H) ppm.

Example 104: Synthesis of 3-(1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 151)



Step 1: Synthesis of 3-(1-(4-fluoro-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00574] The title compound was obtained as a yellow solid, 45 mg, 28%, from Example 94, step 3, following a similar procedure to that described in Example 16, step 5. LCMS m/z = 655 [M+H]⁺

Steps 2 and 3: Synthesis of 3-(1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

- 5 **[00575]** The title compound was obtained as a yellow solid, from the compound from step 1 and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar 2 step procedure to that described in Example 18, steps 2 and 3. LCMS m/z = 766 [M+H]⁺

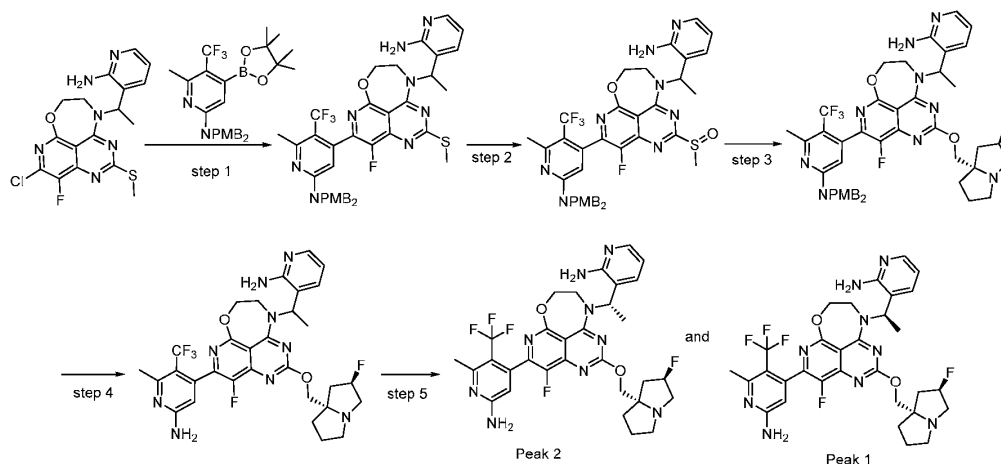
Step 4: Synthesis of 3-(1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

10

- [00576]** The title compound was obtained as a white solid, from the compound from steps 2 and 3, following the procedure described in Example 98, step 4. LCMS m/z = 682 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.51 (s, 1H), 7.98 (d, 1H), 7.72 (d, 2H), 7.64 (d, 1H), 6.68 (dd, 1H), 6.39 (dd, 1H), 5.76 (d, 2H), 5.41 - 5.29 (m, 1H), 4.45 (td, 1H), 4.31 (d, 1H), 4.14 (d, 1H), 15 4.07 (dd, 1H), 3.77 (dt, 2H), 3.09 (d, 2H), 3.02 (s, 2H), 2.64 (d, 3H), 2.16 - 1.95 (m, 3H), 1.82 (dd, 3H), 1.64 - 1.52 (m, 3H).

- Example 105: Synthesis of 4-(10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine**
- 20 **(Compound 159)**
- and

- Example 106: Synthesis of 4-(10-((S)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine**
- 25 **(Compound 160)**



Step 1: Synthesis of 4-(10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

- 5 **[00577]** The title compound was obtained as a yellow solid, 160 mg, 55%, from Example 94, step 3 and Intermediate 22, following a similar procedure to that described in Example 16, step 5. LCMS $m/z = 787$ $[M+H]^+$

Step 2: Synthesis of 4-(10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

10

[00578] The title compound was obtained as a yellow solid, 150 mg, 98%, from the compound from step 1, following a similar procedure to that described in Example 18, step 3. LCMS $m/z = 803$ $[M+H]^+$

Step 3: Synthesis of 4-(10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

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[00579] The compound from step 2 (150 mg, 0.187 mmol) was added to a solution of LiOtBu (29.9 mg, 0.37 mmol) and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, (38.7 mg, 0.24 mmol) in THF (15 mL) at 0°C under N₂ and the resulting mixture was stirred for 1h at rt. The reaction was quenched with water (20 mL) and the mixture extracted with DCM (3 x 20mL). The combined organic layers were washed with brine (2x20mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure.

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The residue was purified by Prep-TLC (DCM / MeOH 20:1) to afford the title compound (60 mg, 35.8%) as a white solid. LCMS m/z = 898 $[M+H]^+$

Step 4: Synthesis of 4-(10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

5

[00580] The title compound was obtained as a white solid, 16 mg, 39.%, from the compound from step 3, following a similar procedure to that described in Example 81, step 3. LCMS m/z = 658 $[M+H]^+$

Step 5: Synthesis of 4-(10-((S)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

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[00581] The compound from step 4 (16 mg, 0.024 mmol) was purified by Prep-chiral-HPLC (Column: CHIRALPAK IE, 2*25 cm, 5 μ m; Mobile Phase A: Hex (0.5% 2M NH_3 -MeOH), Mobile Phase B: EtOH: DCM=1:1; Flow rate: 20 mL/min; Gradient: isocratic 40%; to afford Peak 1, Example 105 (7.6 mg, 45.1%) as a white solid. LCMS m/z = 658 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 7.97 (dd, 1H), 7.65 – 7.51 (m, 1H), 6.83 (s, 2H), 6.67 (dd, 1H), 6.33 (q, 1H), 6.21 (s, 1H), 5.70 (s, 2H), 5.44 – 5.19 (m, 1H), 4.43 (dd, 1H), 4.29 (dd, 1H), 4.19 (d, 2H), 3.78 – 3.63 (m, 1H), 3.13 (s, 3H), 2.87 (s, 1H), 2.47 (q, 3H), 2.08 (q, 3H), 1.83 (s, 3H), 1.55 (d, 3H), 1.24 (s, 1H).

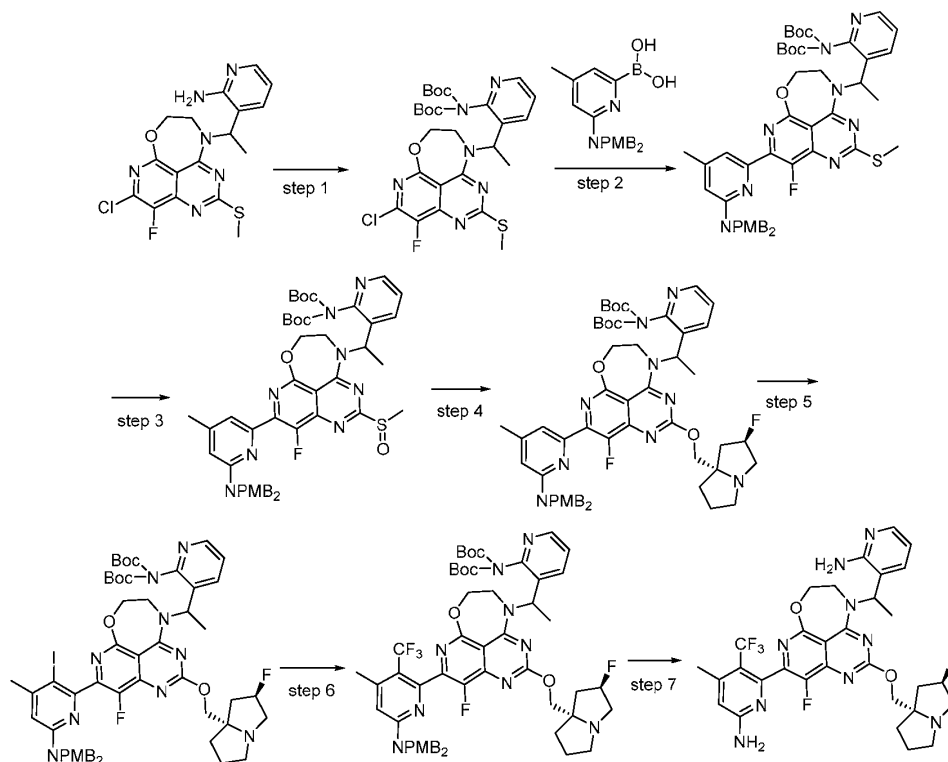
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[00582] Further elution provided Peak 2, Example 106, 5.4 mg, 33% as a white solid. LCMS m/z = 658 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 7.62 (dd, 1H), 6.83 (s, 2H), 6.67 (dd, 1H), 6.33 (q, 1H), 6.21 (s, 1H), 5.73 (d, 2H), 5.45 – 5.12 (m, 1H), 4.43 (dd, 1H), 4.38 – 4.16 (m, 2H), 4.09 (d, 1H), 3.73 (dd, 1H), 3.40 (d, 1H), 3.11 (d, 3H), 2.86 (s, 1H), 2.47 (d, 3H), 2.07 (m, 4H), 1.83 (dd, 3H), 1.56 (d, 3H).

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Example 107: Synthesis of 6-(10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine (Compound 175)

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Step 1: Synthesis of *tert*-butyl (tert-butoxycarbonyl)(3-(1-(5-chloro-4-fluoro-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-yl)carbamate

- 5 **[00583]** Boc₂O (7.51 g, 34.4 mmol) was added to a solution of Example 94, step 3 (1 g, 2.46 mmol), DMAP (174 mg, 1.43 mmol) and TEA (2.49 g, 24.58 mmol) in DCM (10 mL) at 0°C and the reaction mixture was stirred overnight at rt under N₂. The mixture was diluted with water and extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced
- 10 pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (1:3) to afford the title compound (700 mg, 46.9%) as a yellow solid. LCMS m/z = 607 [M+H]⁺

Step 2: Synthesis of *tert*-butyl (3-(1-(5-(6-(bis(4-methoxybenzyl)amino)-4-methylpyridin-2-yl)-4-fluoro-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-yl)(tert-butoxycarbonyl)carbamate

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[00584] The title compound was obtained as a yellow solid, 40 mg, 13.2%, from Intermediate 23, and the compound from step 1, following a similar procedure to that described in Example 16, step 5. LCMS m/z = 919 [M+H]⁺.

5 *Step 3: Synthesis of tert-butyl (3-(1-(5-(6-(bis(4-methoxybenzyl)amino)-4-methylpyridin-2-yl)-4-fluoro-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-yl)(tert-butoxycarbonyl)carbamate*

[00585] The title compound was obtained as a yellow solid, 70 mg, crude, from the compound from step 2, following a similar procedure to that described in Example 18, step 3. LCMS m/z = 935 [M+H]⁺

10 *Step 4: Synthesis of tert-butyl (3-(1-(5-(6-(bis(4-methoxybenzyl)amino)-4-methylpyridin-2-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-yl)(tert-butoxycarbonyl)carbamate*

[00586] A mixture of the compound from step 3 (70 mg, 0.075 mmol), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (14.30 mg, 0.09 mmol) and NaOtBu (8.63 mg, 0.09 mmol) in toluene (2 mL) was stirred at 0°C for 30 min under N₂. The reaction was quenched with water (10 mL) at rt and the mixture extracted with DCM (3 x 10mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford the title compound (50 mg, 64.8%) as a yellow solid. LCMS m/z = 1030 [M+H]⁺

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Steps 5 and 6: Synthesis of tert-butyl (3-(1-(5-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-yl)(tert-butoxycarbonyl)carbamate

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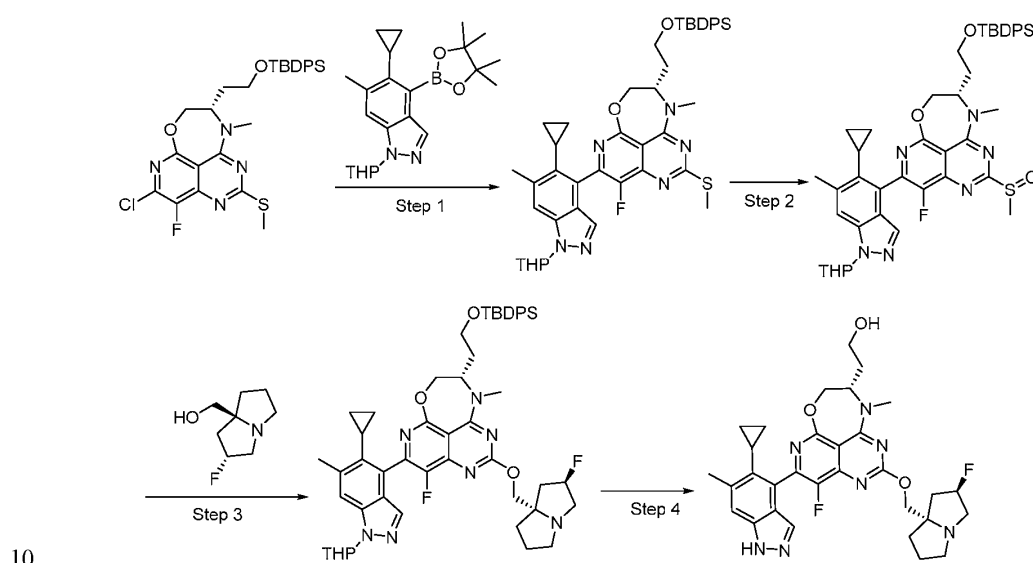
[00587] The title compound was obtained as a yellow solid, from the compound from step 4, following a similar 2 step procedure to that described in Example 87, steps 2 and 3. LCMS m/z = 1098 [M+H]⁺

Step 7: Synthesis of 6-(10-(1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine

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[00588] The title compound was obtained as a white solid, 0.5 mg, 66.8%, from the compound from steps 5 and 6, following a similar procedure to that described in Example 39, step 5, except Prep-HPLC (Method E, Gradient: 9% B to 31% B in 8 min) was used. LCMS $m/z = 658$ $[M+H]^+$. 1H NMR (400 MHz, MeOD- d_4) δ 8.07 (s, 2H), 6.98 (s, 1H), 6.59 (d, 1H), 5.63-5.52 (d, 1H), 4.88-4.47 (m, 4H), 4.11-3.91 (m, 4H), 3.65 (d, 2H), 2.35 (s, 3H), 2.18 (s, 1H), 2.03-1.98 (m, 3H), 1.70-1.70 (m, 3H), 1.29 (s, 3H).

Example 108: Synthesis of 2-((9S)-5-(5-cyclopropyl-6-methyl-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (Compound 185)



Steps 1 and 2: Synthesis of (9S)-9-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-5-(5-cyclopropyl-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-4-fluoro-10-methyl-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00589] The title compound was obtained as a gum, from the compound from Example 6, step 3 and 5-cyclopropyl-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole, following a similar 2 step procedure to that described in Example 93, steps 5 and 6. LCMS $m/z = 819$ $[M+H]^+$

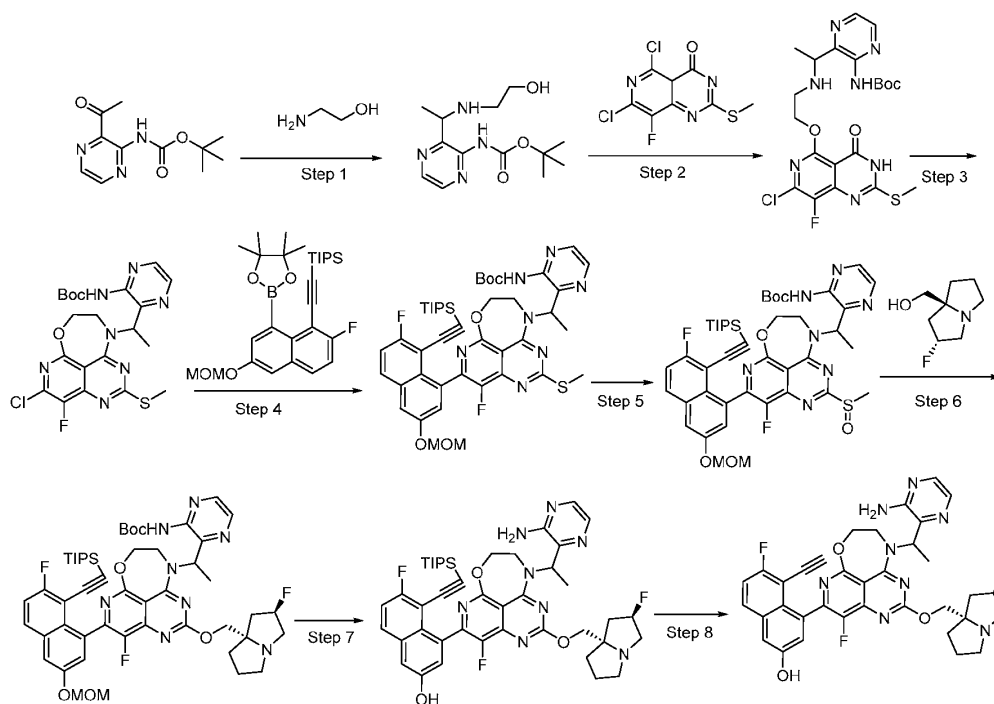
Step 3: Synthesis of (9S)-9-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-5-(5-cyclopropyl-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00590] The title compound was obtained as a pale yellow gum, from the compound from steps 1 and 2 and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar procedure to that described in Example 101, step 3. LCMS m/z = 915 $[M+H]^+$

Step 4: Synthesis of 2-((9S)-5-(5-cyclopropyl-6-methyl-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

[00591] The title compound was obtained as an off-white solid, 2.9 mg, 9%, from the compound from step 3, following a similar procedure to that described in Example 103, step 4. LCMS m/z = 592 $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6): δ 12.95 (d, 1H), 7.74-7.59 (m, 1H), 7.44 (s, 1H), 5.35-5.22 (m, 1H), 4.81-4.79 (m, 1H), 4.66-4.63 (m, 1H), 4.51-4.46 (m, 1H), 4.18-4.14 (m, 2H), 4.03 (t, 1H), 3.60-3.55 (m, 2H), 3.36-3.34 (m, 3H), 3.14-3.08 (m, 2H), 3.02 (s, 1H), 2.84-2.82 (m, 1H), 2.60-2.56 (m, 3H), 2.15-2.13 (m, 1H), 2.06-2.01 (m, 2H), 1.89-1.77 (m, 6H), 0.85-0.71 (m, 1H), 0.61-0.47 (m, 1H), 0.12-0.01 (m, 2H)

Example 109: Synthesis of 4-(10-(1-(3-aminopyrazin-2-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol (Compound 186)



Steps 1 and 2: Synthesis of tert-butyl (3-(1-((2-((7-chloro-8-fluoro-2-(methylthio)-4-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-5-yl)oxy)ethyl)amino)ethyl)pyrazin-2-yl)carbamate

[00592] The title compound was obtained as a solid, from 2-aminoethan-1-ol, tert-butyl (3-acetylpyrazin-2-yl)carbamate and 5,7-dichloro-8-fluoro-2-(methylsulfanyl)-3H-pyrido[4,3-d]pyrimidin-4-one, following a similar 2 step procedure to that described in Example 93, steps 2 and 3. LCMS m/z = 526 [M+H]⁺

Step 3: Synthesis of tert-butyl (3-(1-(5-chloro-4-fluoro-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyrazin-2-yl)carbamate

[00593] The title compound was obtained as a solid (160 mg, 66.3%) from the compound from steps 1 and 2, following a similar procedure to that described in Example 94, step 3. LCMS m/z = 508 [M+H]⁺

Step 4: Synthesis of tert-butyl (3-(1-(4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyrazin-2-yl)carbamate

[00594] K₃PO₄ (157 mg, 0.73 mmol), Xphos (28.2 mg, 0.06 mmol) and XPhos Pd G3 (25 mg, 0.03 mmol) were added to a stirred solution of the compound from step 3 (150 mg, 0.29 mmol) and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (227 mg, 0.44 mmol) in THF (1 mL) and water (0.2 mL) and the reaction mixture degassed for 2 min at 25 °C and stirred at 80 °C for 16 h. The reaction mixture was filtered through Celite®, the filtrate diluted with water, and extracted with EtOAc (3 x 20 mL). The organic layer was concentrated under reduced pressure and the crude was purified by silica gel column chromatography to afford the title compound (80 mg, 24.6 %) as a yellow solid. LCMS m/z = 858 [M+H]⁺

Step 5: Synthesis of tert-butyl (3-(1-(4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyrazin-2-yl)carbamate

[00595] The title compound was obtained as an off-white solid, 70 mg, crude, from the compound from step 4, following the procedure described in Example 93, step 6. LCMS m/z = 774 [M-Boc+H]⁺

Step 6: Synthesis of tert-butyl (3-(1-(4-fluoro-5-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-

7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyrazin-2-yl)carbamate

- [00596] The title compound was obtained as a yellow solid, 60 mg, 60.1%, from the compound from step 5 and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar procedure to that described in Example 101, step 3. LCMS m/z = 969 [M-Boc+H]⁺

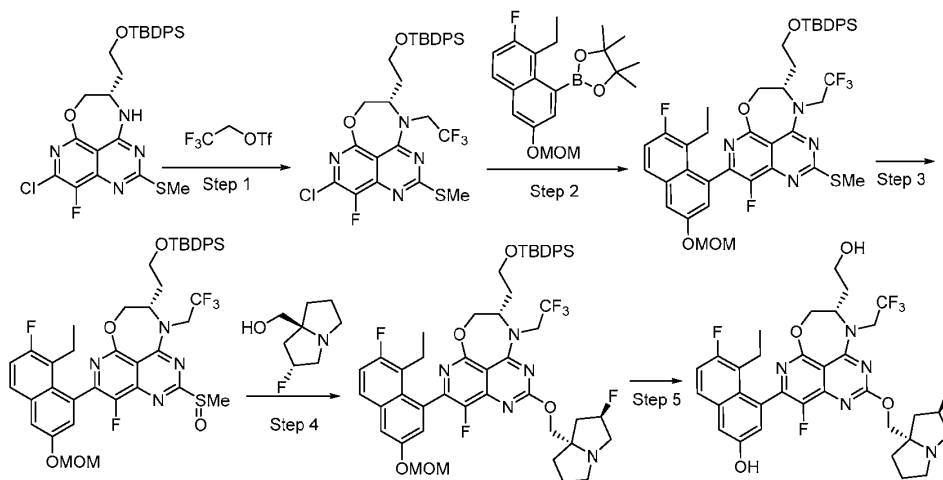
Step 7: Synthesis of 4-(10-(1-(3-aminopyrazin-2-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-fluoro-5-((triisopropylsilyl)ethynyl)naphthalen-2-ol

- [00597] 4M HCl in dioxane (0.12 mL, 4 mmol) was added to a solution of the compound from step 6 (60 mg, 0.06 mmol) in dioxane (1 mL) and the reaction mixture was stirred at rt for 3 h. The reaction mixture was concentrated under reduced pressure and the crude was washed with MTBE and hexane to give the title compound (40 mg, crude). LCMS m/z = 825 [M+H]⁺

- Step 8: Synthesis of 4-(10-(1-(3-aminopyrazin-2-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol*

- [00598] CsF (80 mg, 0.52 mmol) was added to a stirred solution of the compound from step 7 (80 mg, 0.097 mmol) in DMF (2 mL) and the reaction mixture was stirred at 70 °C for 4 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude compound was purified by prep-HPLC (Method C, gradient 0 to 100 % B) and the combined pure fractions were lyophilized to afford the title compound (2 mg, 3.0 %) as an off white solid. LCMS m/z = 669 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-d₆): δ 10.20 (s, 1H), 7.97-7.94 (m, 2H), 7.83-7.79 (m, 1H), 7.46 (t, 1H), 7.37 (d, 1H), 7.15-7.12 (m, 1H), 6.50-6.46 (m, 1H), 6.39-6.33 (m, 2H), 5.40-5.26 (m, 1H), 4.61-4.43 (m, 2H), 4.38-4.35 (m, 1H), 4.23-4.00 (m, 5H), 3.89-3.83 (m, 2H), 2.95-2.88 (m, 1H), 2.20-2.17 (m, 1H), 2.10-2.04 (m, 2H), 1.91-1.82 (m, 3H), 1.60 (t, 3H)

- Example 110: Synthesis of 5-ethyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-(2,2,2-trifluoroethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 188)**



Step 1: Synthesis of (S)-9-(2-((tert-butyl diphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(methylthio)-10-(2,2,2-trifluoroethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- 5 **[00599]** The title compound was obtained, 50 mg, 43.3%, from (S)-9-(2-((tert-butyl diphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene and 2,2,2-trifluoroethyl trifluoromethanesulfonate, following a similar procedure to that described in Example 48, step 1. LCMS m/z = 651 $[M+H]^+$

- 10 *Step 2: Synthesis of (S)-9-(2-((tert-butyl diphenylsilyl)oxy)ethyl)-5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(methylthio)-10-(2,2,2-trifluoroethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

- 15 **[00600]** The title compound was obtained, 60 mg, 89%, from the compound from step 1 and 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, following a similar procedure to that described in Example 93, step 5. LCMS m/z = 849 $[M+H]^+$

- 20 *Step 3: Synthesis of (9S)-9-(2-((tert-butyl diphenylsilyl)oxy)ethyl)-5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(methylsulfinyl)-10-(2,2,2-trifluoroethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

[00601] The title compound was obtained, 58 mg, crude, from the compound from step 2, following a similar procedure to that described in Example 93, step 6. LCMS m/z = 865 [M+H]⁺

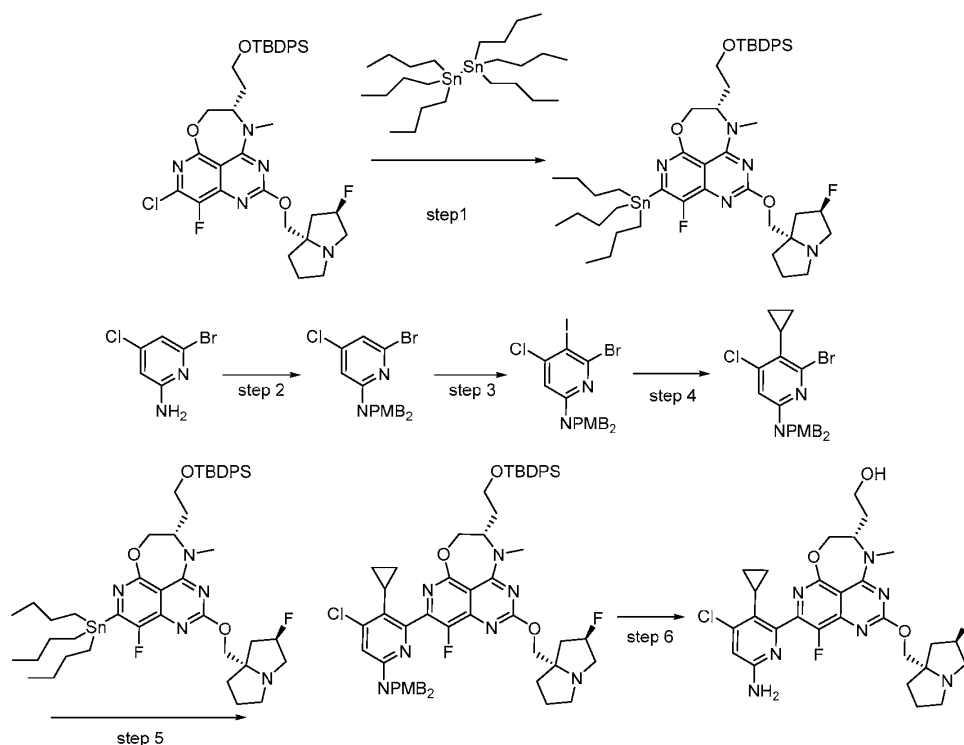
5 *Step 4: Synthesis of (S)-9-(2-((tert-butyl) diphenylsilyl)oxy)ethyl)-5-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-(2,2,2-trifluoroethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene*

[00602] The title compound was obtained, 60 mg, crude from the compound from step 3 and ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar procedure to that described in Example 101, step 3. LCMS m/z = 960 [M+H]⁺

10 *Step 5: Synthesis of 5-ethyl-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-(2,2,2-trifluoroethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol*

[00603] The title compound was obtained as an off-white solid, 4.1 mg, 9.7%, from the compound from step 4, following a similar procedure to that described in Example 103, step 4. LCMS m/z = 678 [M+H]⁺ 1H-NMR (400 MHz, DMSO-d₆): δ 9.95-9.89 (m, 1H), 7.76 (dd, 1H), 7.38-7.32 (m, 2H), 7.08-6.98 (m, 1H), 5.38-5.20 (m, 2H), 4.84-4.74 (m, 2H), 4.55-4.37 (m, 2H), 4.29-4.17 (m, 2H), 4.08-4.04 (m, 1H), 3.58-3.52 (m, 2H), 3.30-3.22 (m, 2H), 3.09 (s, 2H), 3.01 (s, 1H), 2.84-2.83 (m, 1H), 2.26-2.20 (m, 1H), 2.12 (s, 1H), 2.05-2.00 (m, 2H), 1.87-1.81 (m, 4H), 0.87-0.75 (m, 3H).

Example 111: Synthesis of 2-((S)-5-(6-amino-4-chloro-3-cyclopropylpyridin-2-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol (Compound 184)



Step 1: Synthesis of (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-5-(tributylstannyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

- 5 **[00604]** A mixture of (S)-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene (Example 6, step 5, 300 mg, 0.43 mmol), hexabutylstannane (752 mg, 1.3 mmol), LiCl (91.6 mg, 2.16 mmol), PPh₃ (22.7 mg, 0.086 mmol) and Pd₂(dba)₃ (39.57 mg, 0.043 mmol) in dioxane (12 mL) was stirred at 110 °C for 16 h
- 10 under N₂. The cooled reaction was diluted with H₂O (10 mL) and the mixture was extracted with EtOAc (3 x 30mL). The combined organic layers were washed with brine (20mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (DCM / MeOH 10:1) to afford the title compound (250 mg, 60.9%) as a white solid. LCMS m/z = 950 [M+H]⁺

- 15 *Step 2: Synthesis of 6-bromo-4-chloro-N,N-bis(4-methoxybenzyl)pyridin-2-amine*

[00605] To a stirred solution of 6-bromo-4-chloropyridin-2-amine (2.8 g, 13.5 mmol) in DMA (20 mL) was added NaH (971.6 mg, 40.5 mmol) in portions at 0°C under N₂ and the

mixture was stirred for 1h at rt under N₂. PMBCl (4.65 g, 29.7 mmol) was added dropwise over 2 min and the reaction mixture was stirred for 2h at rt. The mixture was extracted with EtOAc (10 x mL), the combined organic layers were washed with brine (3x10 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by trituration with PE (200 mL) to afford the title compound (3.9 g, 64.5%) as a yellow solid.

LCMS m/z = 447 [M+H]⁺

Step 3: Synthesis of 6-bromo-4-chloro-5-iodo-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00606] A mixture of the compound from step 2 (1 g, 2.23 mmol) and NIS (753.7 mg, 3.35 mmol) in HOAc (20 mL) was stirred overnight at rt. The resulting mixture was concentrated under vacuum and the residue was neutralized to pH 7 with saturated NaHCO₃ (aq.). The mixture was extracted with EtOAc (10 x mL), the combined organic layers were washed with brine (3x10 mL), dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (10:1) to afford the title compound (840 mg, 65.6%) as a white solid.

LCMS m/z = 573 [M+H]⁺

Step 3: Synthesis of 6-bromo-4-chloro-5-cyclopropyl-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00607] To a stirred solution of the compound from step 3 (800 mg, 1.4 mmol) and 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (468.6 mg, 2.79 mmol) in dioxane (25 mL) and H₂O (5 mL) were added K₂CO₃ (385.5 mg, 2.79 mmol) and Pd(dppf)Cl₂.DCM (113.6 mg, 0.14 mmol). The reaction mixture was stirred overnight at 80°C under N₂ and then concentrated under vacuum. The residue was purified by silica gel column chromatography, eluting with PE / EtOAc (10:1) to afford the title compound (270 mg, 39.7%) as a white solid.

LCMS m/z = 487 [M+H]⁺

Step 4: Synthesis of 6-((S)-9-(2-((tert-butyl)di(phenyl)silyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-chloro-5-cyclopropyl-N,N-bis(4-methoxybenzyl)pyridin-2-amine

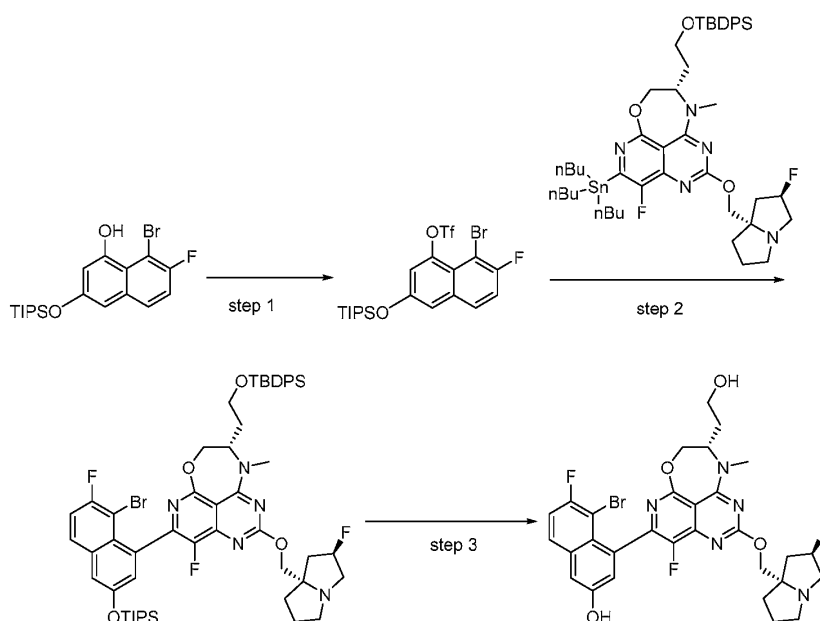
[00608] To a stirred mixture of the compound from step 1 (194.5 mg, 0.20 mmol) and the compound from step 4 (50 mg, 0.10 mmol) in aniline (1 mL) were added CuI (1.9 mg, 0.01 mmol), Pd(PPh₃)₄ (11.8 mg, 0.01 mmol) and LiCl (0.4 mg, 0.01 mmol) under N₂. The reaction mixture was stirred at 130°C overnight under N₂, then concentrated under vacuum. The residue was purified by prep-TLC (PE / DCM 1:1) to afford the title compound (40 mg, 36.6%) as a yellow solid.

LCMS m/z = 1067 [M+H]⁺

Step 5: Synthesis of 2-((S)-5-(6-amino-4-chloro-3-cyclopropylpyridin-2-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-9-yl)ethan-1-ol

[00609] A solution of the compound from step 5 (40 mg, 0.037 mmol) and TsOH (0.2 mL, 1
5 μmol) in DCM (1 mL) was stirred at rt for 1h under N_2 . The residue was purified by prep-
HPLC with the following conditions: Column: Xselect CSH C18 OBD Column 30*150mm
5 μm ; Mobile Phase A: Water (0.05% TFA), Mobile Phase B: MeCN; Flow rate: 60 mL/min;
Gradient: 10% B to 25% B in 7 min to afford the title compound, (8.6 mg, 44.6%) as a yellow
oil. LCMS m/z = 588 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.94 (dd, 1H), 7.50 - 7.32
10 (m, 3H), 7.25-7.21 (m, 1H), 7.19 - 7.08 (m, 1H), 5.68 - 5.62 (m, 1H), 5.43 - 5.09 (m, 1H), 4.67 -
4.42 (m, 2H), 4.22 - 4.18 (m, 1H), 4.13 - 3.92 (m, 3H), 3.25 - 3.20 (m, 1H), 3.18 - 3.08 (m, 2H),
3.05 - 2.95 (m, 1H), 2.85 - 2.80 (m, 1H), 2.16 - 1.96 (m, 2H), 1.92 - 1.73 (m, 2H), 1.61 - 1.58
(m, 2H), 1.28 - 1.20 (m, 2H), 1.17-1.14 (m, 2H), 1.12 - 1.08 (m, 1H).

Example 112: Synthesis of 5-bromo-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-
15 fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-
dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol
(Compound 214)



Step 1: Synthesis of 8-bromo-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl
20 trifluoromethanesulfonate

[00610] To a solution of 8-bromo-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-ol (650 mg, 1.57 mmol) in DCM (100 mL) was added DIEA (609 mg, 4.71 mmol), then the mixture was cooled to -40°C. (Trifluoromethane)sulfonyl trifluoromethanesulfonate (532 mg, 1.88 mmol) was added and the solution was stirred at -40°C for 0.5h. The mixture was concentrated *in vacuo* and the residue purified by silica gel column (PE:EtOAc=5:1) to afford the title compound (650 mg, 72.0%) as pink solid. ¹H NMR (400 MHz, CDCl₃) δ 7.71 – 7.66 (m, 1H), 7.36 – 7.25 (m, 3H), 1.40 – 1.24 (m, 3H), 1.13 (d, 18H).

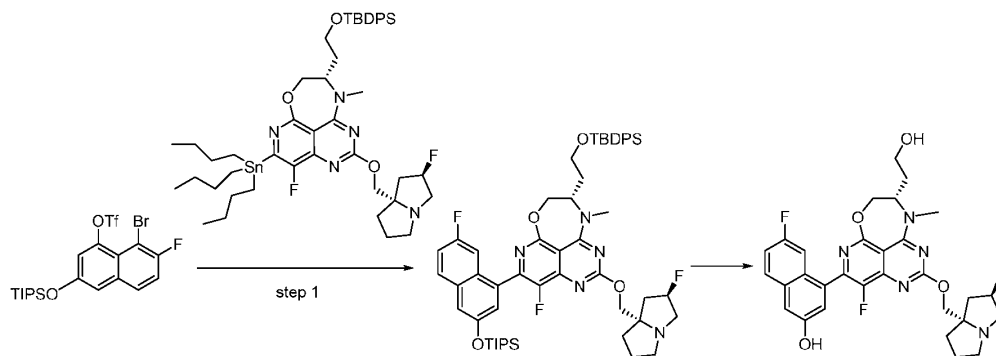
Step 2: Synthesis of (S)-5-(8-bromo-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-9-(2-((tert-butylidiphenylsilyl)oxy)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00611] To a solution of the compound from step 1 (50 mg, 0.092 mmol) and Example 111, step 1 (260 mg, 0.27 mmol) in dioxane (20 mL) was added CuI (17 mg, 0.09 mmol), Pd(PPh₃)₄ (11 mg, 9 μmol) and LiCl (12 mg, 0.28 mmol) and the reaction mixture was purged with N₂. The reaction was stirred at 80°C overnight, then cooled to rt and concentrated *in vacuo*. The residue was purified by silica gel (DCM:MeOH=20:1) and the product further purified by SFC (Column: GreenSep Naphthyl 3*25 cm, 5 μm; Mobile Phase A: CO₂, Mobile Phase B: MeCN: MeOH =4: 1(20 mM NH₃) at 75 mL/min; Gradient: isocratic 35% B to give the title compound. LCMS m/z = 1055 [M+H]⁺

Step 3: Synthesis of 5-bromo-6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol

[00612] To a solution of the compound from step 2 (40 mg, 0.04 mmol) in DMF (5 mL) was added CsF (115 mg, 0.76 mmol), and the reaction mixture was stirred at 30°C for 2h. The solid was filtered off and the filtrate purified by prep-HPLC (Method D, Gradient: 10% B to 33% B in 7 min) to afford the title compound (12.2 mg, 51.2%) as white solid. LCMS m/z = 660, 662 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.00 - 7.92 (m, 1H), 7.33 - 7.45 (m, 1H), 7.42 (d, 1H), 7.27 (d, 1H), 5.43 - 5.25 (m, 1H), 4.67 - 4.57 (m, 1H), 4.47 - 4.41 (m, 1H), 4.29 - 4.21 (m, 1H), 4.19 - 4.09 (m, 2H), 3.60 - 3.51 (m, 2H), 3.39 - 3.36 (m, 3H), 3.30 - 3.18 (m, 3H), 2.99 - 2.89 (m, 1H), 2.26 - 2.03 (m, 3H), 1.98 - 1.76 (m, 5H).

Example 113: Synthesis of 6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol (Compound 215)



Step 1: Synthesis of (S)-9-(2-((tert-butyl diphenylsilyl)oxy)ethyl)-4-fluoro-5-(7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

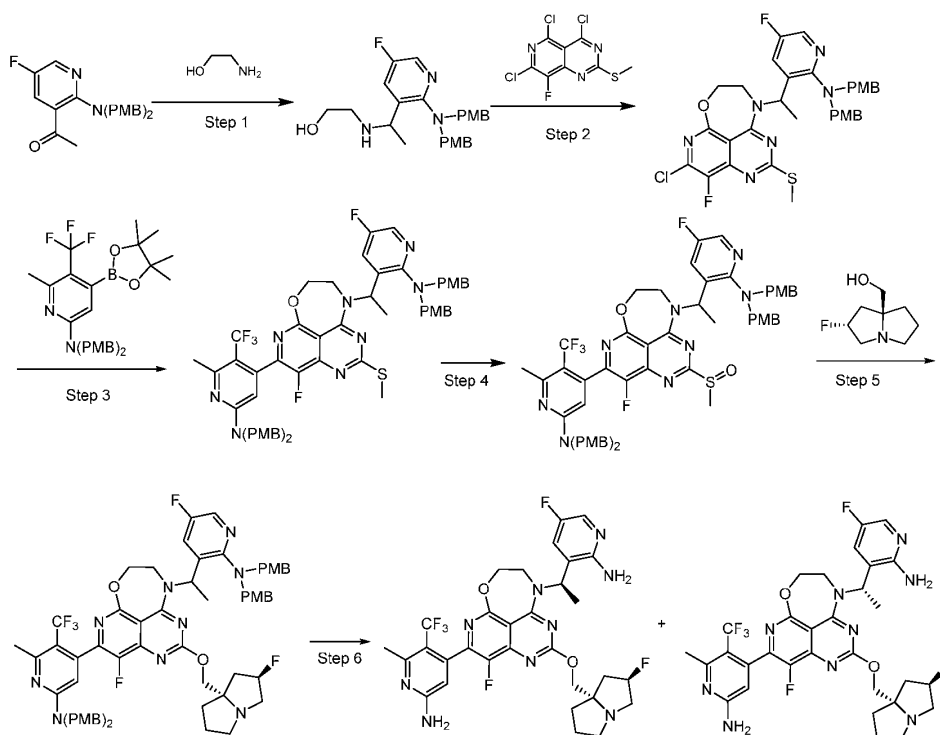
- 5 **[00613]** The title compound was obtained as a white solid, 10 mg, 10%, from Example 111, step 1 and 8-bromo-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl trifluoromethanesulfonate, following a similar procedure to that described in Example 112, step 2. LCMS $m/z = 997$ $[M+H]^+$

Step 2: Synthesis of 6-fluoro-4-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-10-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)naphthalen-2-ol formate

- 15 **[00614]** To a solution of the compound from step 1 (20 mg, 0.02 mmol) in DMF (5 mL) was added CsF (62 mg, 0.40 mmol) and the solution was stirred at 30°C for 2h. The solid was filtered off and the filtrate was purified by prep-HPLC (Method D, gradient: 10% B to 33% B) to afford the title compound (9.2 mg, 71.6%) as white solid. LCMS $m/z = 582$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 7.91 - 7.84 (m, 1H), 7.41 - 7.28 (m, 3H), 7.26 (s, 1H), 5.39 - 5.21 (m, 1H), 4.68 - 4.60 (m, 1H), 4.51 - 4.40 (m, 1H), 4.25 - 4.19 (m, 1H), 4.19 - 4.06 (m, 2H), 3.56 - 3.49 (m, 2H), 3.18 (s, 3H), 3.21 - 3.07 (m, 3H), 2.92 - 2.82 (m, 1H), 2.21 - 1.99 (m, 3H), 1.92 - 1.76 (m, 5H).

- 20 **Example 114: Synthesis of 4-(10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine or 4-(10-((S)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine**
 25 **(Compound 232)**

And Example 115: Synthesis of 4-(10-((S)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine or 4-(10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine (Compound 231)



Step 1: Synthesis of 2-((1-(2-(bis(4-methoxybenzyl)amino)-5-fluoropyridin-3-yl)ethyl)amino)ethan-1-ol

[00615] To a mixture solution of the compound from step 3 of the synthesis of intermediate 33 (15 g, 38.0 mmol) and ethanolamine (6.97 g, 114.1 mmol) in EtOH (10 mL) was added ZnCl₂ (217 mL, 152.1 mmol) and the mixture was warmed to 80 °C and stirred overnight. The solution was cooled to 60 °C, then NaCNBH₃ (9.6 g, 152.1 mmol) was added slowly. The mixture was dissolved in EtOAc, washed with brine, and concentrated *in vacuo*. The crude was purified by reverse phase chromatography (MeCN:H₂O(0.5%TFA)) to afford the title compound (4.5 g, 26.9%) as a yellow oil. LCMS m/z = 440 [M+H]⁺

Step 2: Synthesis of 3-(1-(5-chloro-4-fluoro-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00616] To a mixture of the compound from step 1 (500 mg, 1.14 mmol) and the compound
5 from step 1 of the synthesis of intermediate 28 (510 mg, 1.71 mmol) in THF (20 mL) was
added DIPEA (441 mg, 3.41 mmol) and the mixture was stirred at rt for 1 h. LiOtBu (1.55 mL,
3.41 mmol) was added dropwise at -5° C and the reaction was stirred at rt overnight. The
mixture was concentrated *in vacuo* and the residue purified by silica gel column
chromatography to afford the title compound (350 mg, 46.3%) as a yellow solid. LCMS m/z =
10 665 [M+H]⁺

Step 3: Synthesis of 4-(10-(1-(2-(bis(4-methoxybenzyl)amino)-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(methylthio)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[00617] To a mixture of the compound from step 2 (200 mg, 0.30 mmol) and intermediate 22
15 (179.9 mg, 0.39 mmol) in dioxane (18 mL) and water (3 mL) was added K₃PO₄ (191.5 mg,
0.903 mmol) and CataCXium A Pd G3 (21.90 mg, 0.030 mmol), the mixture was purged with
N₂ and stirred at 80°C for 4 h. The cooled mixture was concentrated *in vacuo* and the residue
purified by silica gel column (DCM: MeOH) to afford the title compound (300 mg, 95.5%) as a
light yellow solid. LCMS m/z = 1046 [M+H]⁺

20 *Step 4: Synthesis of 4-(10-(1-(2-(bis(4-methoxybenzyl)amino)-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(methylsulfinyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine*

[00618] To a solution of the compound from step 3 (400 mg, 0.383 mmol) in DCM (20
mL) was added m-CPBA (99.06 mg, 0.575 mmol) at 0°C and the reaction was stirred at rt for 2
25 h. The reaction was quenched by aq. Na₂SO₃, washed with brine, dried and evaporated under
reduced pressure to afford the title compound (400 mg, 98.5%) as an off white solid. LCMS
m/z = 1078 [M+H]⁺

30 *Step 5: Synthesis of 4-(10-(1-(2-(bis(4-methoxybenzyl)amino)-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine*

[00619] A mixture of the compound from step 4 (350 mg, 0.330 mmol) and ((2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl)methanol (158 mg, 0.99 mmol) in toluene (20 mL) was stirred at rt for 1h. NaOtBu (95 mg, 0.99 mmol) was added at -5°C and the reaction was stirred at -5°C for 15 min. The mixture was concentrated *in vacuo* and the residue purified by silica gel column (DCM:MeOH=20:1) to afford the title compound (200 mg, 52.4 %) as an off white solid.

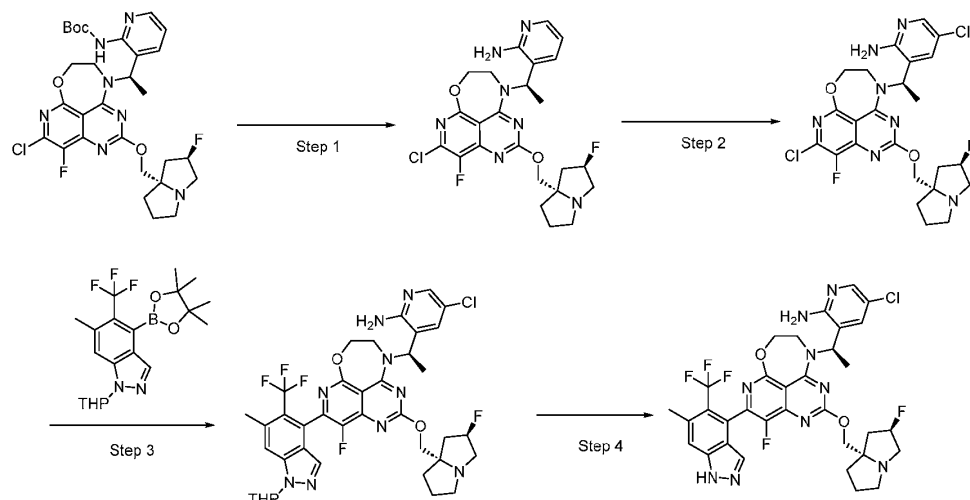
LCMS m/z = 1156 [M+H]⁺

Step 6: Synthesis of 4-(10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine and 4-(10-((S)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine

[00620] A mixture of the compound from step 5 (220 mg, 0.19 mmol) in TFA (20 mL) was stirred at 50°C for 3 h. The mixture was concentrated *in vacuo* to afford crude product as reddish solid. This was purified by HPLC (Column: CHIRALPAK IE, 2*25 cm, 5 µm; Mobile Phase A: Hex (0.5% 2M NH₃-MeOH), Mobile Phase B: EtOH: DCM=1:1; Flow rate: 20 mL/min; Gradient (B%): isocratic 35; to give Peak 1, Example 114 as a white solid, 41.4 mg, 70.8%. LCMS m/z = 676 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.98 – 7.93 (m, 1H), 7.64 – 7.56 (m, 1H), 6.88 – 6.79 (m, 2H), 6.35 – 6.25 (m, 1H), 6.24 – 6.19 (m, 1H), 5.72 – 5.65 (m, 2H), 5.43 – 5.22 (m, 1H), 4.56 – 4.40 (m, 1H), 4.38 – 4.27 (m, 1H), 4.21 – 4.08 (m, 2H), 3.83 – 3.70 (m, 1H), 3.50 – 3.39 (m, 1H), 3.26 – 2.81 (m, 4H), 2.49 – 2.45 (m, 3H), 2.22 – 1.98 (m, 3H), 1.95 – 1.73 (m, 3H), 1.60 – 1.50 (m, 3H).

[00621] And Peak 2, Example 115, (34.2 mg, 34.9%) as a white solid. LCMS m/z = 676 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.00 – 7.93 (m, 1H), 7.64 – 7.58 (m, 1H), 6.88 – 6.80 (m, 2H), 6.35 – 6.26 (m, 1H), 6.24 – 6.19 (m, 1H), 5.74 – 5.64 (m, 2H), 5.51 – 5.31 (m, 1H), 4.51 – 4.20 (m, 4H), 3.86 – 3.75 (m, 1H), 3.54 – 3.40 (m, 3H), 3.29 – 3.23 (m, 1H), 3.07 – 2.92 (m, 1H), 2.48 – 2.42 (m, 3H), 2.34 – 2.09 (m, 3H), 2.04 – 1.82 (m, 3H), 1.61 – 1.54 (m, 3H).

Example 116: Synthesis of 5-chloro-3-((1R)-1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 235)



Step 1: Synthesis of 3-((R)-1-(5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

- 5 **[00622]** TFA (0.2 mL, 0.002 mmol) was added at rt to a solution of the compound from step 5 of Example 40 (350 mg, 0.566 mmol) in DCM (1 mL) and the reaction was stirred at rt for 1 h under N₂. The resulting mixture was concentrated under reduced pressure. The residue was purified by reverse-phase chromatography (column, C18 silica gel; mobile phase, MeCN in water (0.1% NH₃·H₂O), 40% to 50% gradient in 10 min), to afford the title compound (200 mg, 68.2%) as a brown oil. LCMS m/z = 518 [M+H]⁺
- 10

Step 2: Synthesis of 5-chloro-3-((R)-1-(5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

- [00623]** CBMG reagent (66.77 mg, 0.319 mmol) was added to a solution of the compound from step 1 (150 mg, 0.290 mmol) in MeCN (3 mL) and the mixture was stirred at rt overnight under N₂. The reaction was quenched with ice-water at 0°C. The aqueous layer was extracted with DCM (3x20 mL), the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with DCM / MeOH (10:1) to afford the title compound (30 mg, 18.8%) as a yellow solid. LCMS m/z = 552 [M+H]⁺
- 15
- 20

Step 3: Synthesis of 5-chloro-3-((1R)-1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-pyrazol-4-yl)phenyl)pyridin-2-amine

1*H*-indazol-4-yl)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)pyridin-2-amine

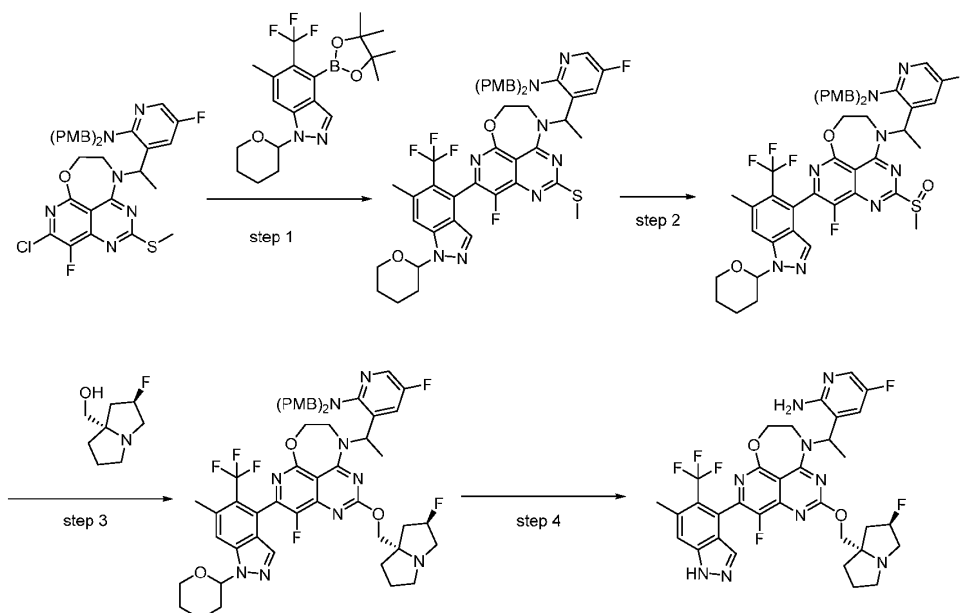
[00624] The title compound was obtained as a brown solid, 22 mg, 50.6%, from the compound from step 2, following a similar procedure to that described in Intermediate 37, step

5 1. LCMS $m/z = 800$ $[M+H]^+$

*Step 4: Synthesis of 5-chloro-3-((1*R*)-1-(4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1*H*-indazol-4-yl)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)pyridin-2-amine*

[00625] TFA (0.1 mL) was added at rt to a solution of the compound from step 3 (20 mg, 0.025 mmol) in DCM (1 mL) and the reaction was stirred at rt for 2 h under N_2 . The solvent was removed by reduced pressure. The crude product was purified by prep-HPLC (Method A, Gradient: 39% B to 65% B in 7 min) to afford the title compound (2.2 mg, 10.6%) as a white solid. LCMS $m/z = 716$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 7.99 (d, 1H), 7.74 (d, 2H), 7.69 (t, 1H), 6.34 (d, 1H), 5.41 (d, 2H), 4.54 – 4.26 (m, 3H), 3.84 (dd, 2H), 3.53 (ddd, 1H), 3.02 (s, 1H), 2.65 (s, 3H), 2.27 (d, 4H), 2.13 (d, 2H), 1.98 (s, 4H), 1.60 (d, 3H), 1.23 (s, 1H).

Example 117: Synthesis of 5-fluoro-3-(1-(4-fluoro-2-(((2*R*,7*aS*)-2-fluorotetrahydro-1*H*-pyrrolizin-7*a*(5*H*)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1*H*-indazol-4-yl)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 240)



Steps 1 and 2: Synthesis of 5-fluoro-3-(1-(4-fluoro-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00626] The title compound was obtained as a yellow oil, 200 mg, from step 2 of Example 114 and Intermediate 27, following a similar 2 step procedure to that described in Example 114, steps 3 and 4. LCMS m/z = 929 [M+H]⁺

Step 3: Synthesis of 5-fluoro-3-(1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00627] A solution of the compound from step 2 (200 mg, 0.215 mmol) and ((2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl)methanol (102.8 mg, 0.645 mmol) in toluene (10 mL) was stirred at rt for 1 h. t-BuOK (72.47 mg, 0.645 mmol) was added and the resulting mixture was stirred at rt for 1 h. The residue was purified by reverse-phase chromatography (column, C18 silica gel; mobile phase, MeCN in water (10mM NH₄HCO₃), 10% to 80% gradient in 10 min) to afford the title compound (200 mg, 90.7%) as a white solid. LCMS m/z = 1025 [M+H]⁺

Step 4: 5-fluoro-3-(1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

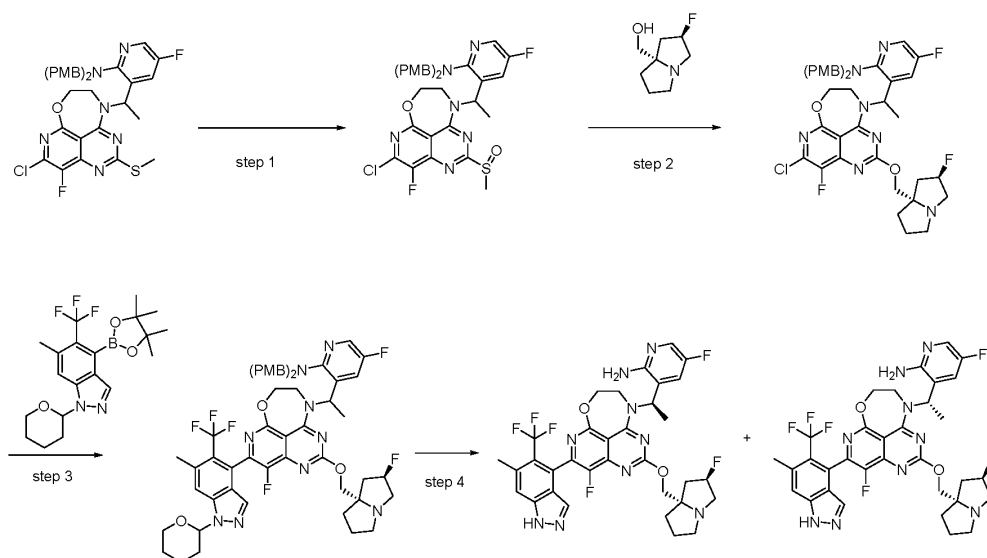
[00628] A solution of the compound from step 3 (80 mg, 0.078 mmol) in TFA (5 mL) was stirred at 50°C for 2 h. The crude product was purified by Prep-HPLC (Method A, Gradient: 37% B to 60% B in 7 min) to afford the title compound (17.4 mg, 31.8%) as a white solid. LCMS m/z = 700 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.90 (d, 1H), 7.71 – 7.61 (m, 3H), 6.61 (m, 1H), 4.51 (m, 1H), 5.33 (d, 1H), 4.45 – 4.37 (m, 2H), 4.37 – 4.28 (m, 2H), 3.90 – 3.77 (m, 1H), 3.60 (m, 1H), 3.24 (s, 2H), 3.05 (m, 1H), 2.68 (m, 3H), 2.31 – 2.17 (m, 3H), 2.08 – 1.88 (m, 3H), 1.66 (m, 3H), 1.48 (m, 2H), 1.29 (s, 1H).

Example 118: Synthesis of 5-fluoro-3-((1R)-1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine or 5-fluoro-3-((1S)-1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-

oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 249)

And

Example 119: Synthesis of 5-fluoro-3-((1S)-1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine or 5-fluoro-3-((1R)-1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 252)



Step 1: Synthesis of 3-(1-(5-chloro-4-fluoro-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00629] To a stirred solution of the compound from step 2 of Example 114 (300 mg, 0.451 mmol) in DCM (20 mL) was added m-CPBA (116.74 mg, 0.676 mmol) in portions at 0°C. The resulting mixture was stirred at 0°C for 1 h. The mixture was extracted with EtOAc (10 x mL). The combined organic layers were washed with brine (3x10 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure to afford the title compound (300 mg, 97.7%) as a yellow solid. LCMS m/z = 681 [M+H]⁺

Step 2: Synthesis of 3-(1-(5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00630] A solution of the compound from step 1 (200 mg, 0.294 mmol) and ((2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl)methanol (140.23 mg, 0.88 mmol) in toluene (5 mL) was stirred at rt for 1 h. NaOtBu (831.91 mg, 0.882 mmol) was added in portions over 2 min at 0°C and the resulting mixture was stirred at rt for 2 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluting with DCM / MeOH (10:1) to afford the title compound (90 mg, 39.5%) as a yellow solid. LCMS m/z = 776 [M+H]⁺

Step 3: Synthesis of 5-fluoro-3-(1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

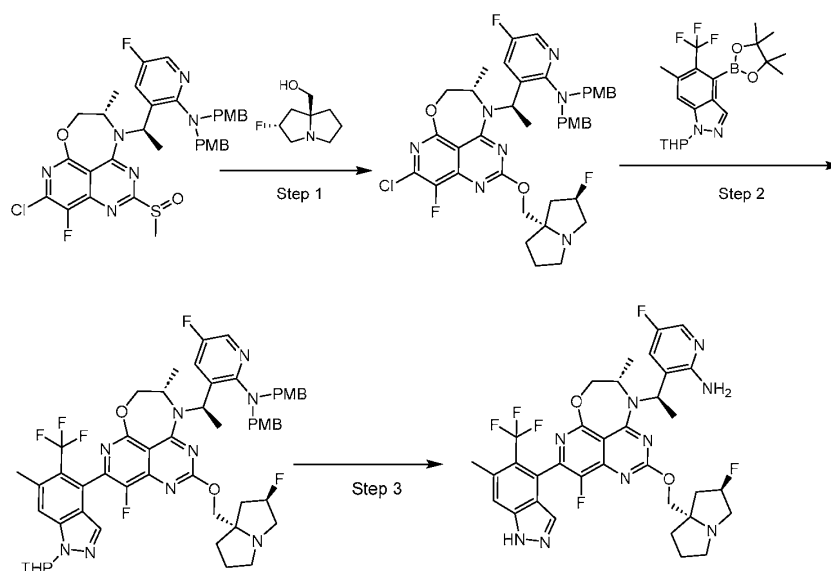
[00631] The title compound was obtained as a yellow solid, 90 mg, 85%, from the compound from step 2 and Intermediate 27, following a similar procedure to that described in Example 114, step 3. LCMS m/z = 1025 [M+H]⁺

Step 4: Synthesis of 5-fluoro-3-((1R)-1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine and 5-fluoro-3-((1S)-1-(4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00632] A solution of the compound from step 3 (80 mg, 0.078 mmol) in TFA (5 mL) was stirred at 50°C for 5 h. The reaction was concentrated *in vacuo* and the residue purified by Prep-HPLC (Method A, Gradient: 34% B to 59% B in 8 min) to afford Peak 1, Example 118 (22.1 mg, 40.4%) as a white solid. LCMS m/z = 700 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.49 (m, 1H), 7.97 (m, 1H), 7.71 (s, 2H), 7.62 (m, 1H), 6.35 (m, 1H), 5.77 (s, 1H), 5.70 (s, 1H), 5.23 (d, 1H), 4.47 (m, 1H), 4.34 (m, 1H), 4.15 (s, 2H), 3.82 (m, 1H), 3.49 (m, 1H), 3.12 (s, 2H), 3.05 (s, 1H), 2.88 – 2.82 (m, 1H), 2.64 (m, 3H), 2.16 (m, 1H), 2.08 (s, 1H), 2.03 (s, 1H), 1.89 – 1.73 (m, 3H), 1.59 (m, 3H).

[00633] And Peak 2, Example 119 (24.5 mg, 44.8%) as a white solid. LCMS m/z = 700
 [M+H]⁺ ¹H NMR (400 MHz, DMSO- d_6) δ 13.48 (s, 1H), 7.97 (m, 1H), 7.74 – 7.68 (m, 2H),
 7.62 (m, 1H), 6.36 (m, 1H), 5.77 (s, 1H), 5.69 (s, 1H), 5.22 (d, 1H), 4.47 (m, 1H), 4.35 (m, 1H),
 4.21 (m, 1H), 4.06 (m, 1H), 3.82 (m, 1H), 3.49 (m, 1H), 3.17 – 3.03 (m, 1H), 3.02 (s, 1H), 2.88
 5 – 2.78 (m, 1H), 2.64 (m, 3H), 2.18 – 2.08 (m, 1H), 2.08 – 1.95 (m, 2H), 1.89 – 1.80 (m, 1H),
 1.82 – 1.74 (m, 2H), 1.59 (m, 3H), 1.23 (s, 1H).

Example 120: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine trifluoroacetate (Compound 255)



Step 1: Synthesis of 3-((R)-1-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00634] A mixture of Intermediate 34 (260 mg, 0.374 mmol) and ((2R,7aS)-2-fluoro-hexahydropyrrolizin-7a-yl)methanol (178.6 mg, 1.12 mmol) in toluene (20 mL) was stirred at rt
 20 for 1 h, then cooled down to 0°C. NaOtBu (107.8 mg, 1.12 mmol) was added and the reaction was stirred at 0°C for 15 min. The mixture was concentrated *in vacuo* and the residue was

purified by silica gel column (DCM:MeOH=30:1) to afford the title compound (160 mg, 54.1%) as white solid. LCMS m/z = 790 [M+H]⁺

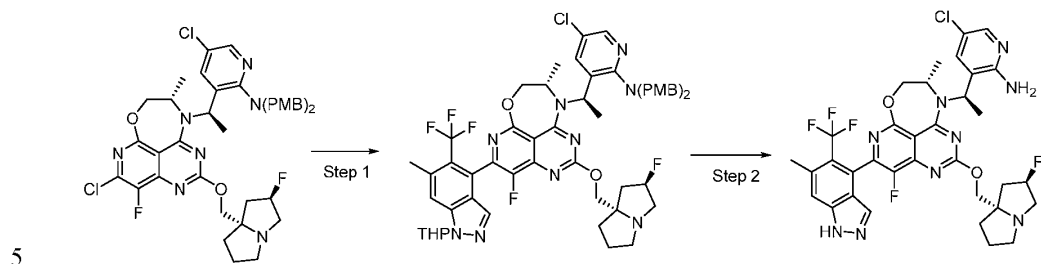
Step 2: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00635] To a solution of the compound from step 1 (120 mg, 0.152 mmol) and Intermediate 27 (186.9 mg, 0.456 mmol) in dioxane (8 mL) and H₂O (0.8 mL) was added CataCXium A Pd G3 (11.06 mg, 0.015 mmol) and K₃PO₄ (96.7 mg, 0.456 mmol) under N₂, the mixture purged with N₂ and the reaction was warmed to 80 °C and stirred for 6 h. The mixture was concentrated *in vacuo* and the residue purified by reverse-phase flash chromatography to afford the title compound (50 mg, 31.7%) as white solid. LCMS m/z = 1038 [M+H]⁺

Step 3: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine trifluoroacetate

[00636] To a solution of the compound from step 2 (69 mg, 0.066 mmol) in TFA (0.6 mL) was added trifluoromethanesulfonic acid (0.1 mL), then the mixture was stirred at rt for 0.5 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H₂O (1 mL), adjusted to pH=8 by careful addition of saturated NaHCO₃ solution, and extracted with EtOAc (3 mL * 3). The combined organic layers were washed with brine (5 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Xtimate C18 150*40mm*10um; mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN]; gradient: 40%-60% B over 11 min) to afford the title compound (18.2 mg, 41.5%) as a white solid. LCMS m/z = 714 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.35 - 13.72 (m, 1 H) 8.01 (d, J =2.64 Hz, 1 H) 7.58 - 7.81 (m, 3 H) 6.38 - 6.65 (m, 1 H) 5.56 - 5.83 (m, 2 H) 5.12 - 5.42 (m, 1 H) 4.48 - 4.59 (m, 1 H) 4.29 - 4.41 (m, 1 H) 4.05 - 4.20 (m, 3 H) 2.98 - 3.16 (m, 3 H) 2.79 - 2.89 (m, 1 H) 2.59 - 2.69 (m, 3 H) 2.01 - 2.20 (m, 3 H) 1.74 - 1.92 (m, 3 H) 1.62 (br d, J =6.60 Hz, 3 H) 0.54 - 0.74 (m, 3 H)

Example 121: Synthesis of 5-chloro-3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 305)



Step 1: Synthesis of 5-chloro-3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

10 **[00637]** A mixture of Intermediate 36 (100 mg, 0.124 mmol), Intermediate 27 (101.7 mg, 0.248 mmol), CataCXium A Pd G3 (9.03 mg, 0.012 mmol) and K_3PO_4 (78.93 mg, 0.372 mmol) in dioxane (2 mL) and H_2O (0.4 mL) was stirred at 80°C for 2 h. The reaction was quenched with ice-water at 0 °C, the layers separated and the aqueous phase was extracted with DCM (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous

15 Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure. The residue was purified by prep-TLC (DCM / MeOH 20:1) to afford the title compound (120 mg, 45.9%) as a yellow oil. LCMS m/z = 1054 $[M+H]^+$

Step 2: Synthesis of 5-chloro-3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate

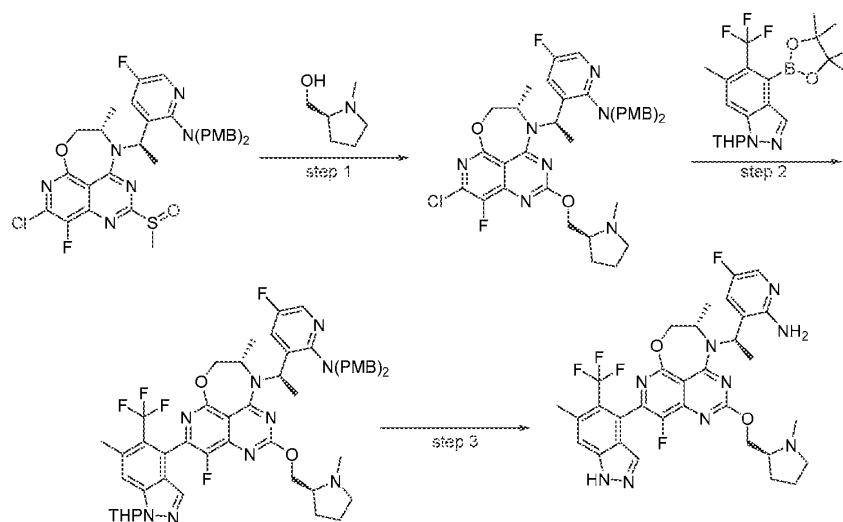
20

[00638] A solution of the compound from step 1 (100 mg, 0.102 mmol) in DCE (5 mL) and TFA (5 mL) was stirred at 80°C for 2 h. The cooled mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Method D, Gradient: 15% B to 38% B in 7 min) to afford the title compound (16.7 mg, 21.2%) as a white solid. LCMS m/z = 730 $[M+H]^+$ 1H NMR (400 MHz, $DMSO-d_6$) δ 13.54 (d, 1H), 10.92 (s, 1H), 8.04 (d, 1H), 7.79 (t, 1H), 7.76 – 7.66 (m, 2H), 6.53 (d, 1H), 5.95 (d, 2H), 5.54 (d, 1H), 4.79 – 4.43 (m, 3H), 4.34

25

(dd, 1H), 4.24 – 4.13 (m, 1H), 4.00-3.47 (m, 3H), 3.21-3.01 (m, 1H), 2.70 – 2.55 (m, 4H), 2.26 (s, 1H), 2.22 – 1.87 (m, 3H), 1.63 (d, 3H), 0.66 (dd, 3H).

Example 122: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 264)



Step 1: Synthesis of 3-((R)-1-((S)-5-chloro-4-fluoro-9-methyl-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00639] A mixture of Intermediate 34 (200 mg, 0.288 mmol) and (S)-(1-methylpyrrolidin-2-yl)methanol (66 mg, 0.576 mmol) in toluene (20 mL) was stirred at rt for 1 h, then the solution was cooled to 0°C and LiOtBu (70 mg, 0.864 mmol) was added. The reaction was stirred at rt for 15 min, then concentrated *in vacuo*. The reaction was filtered through a silica gel column eluting with DCM:MeOH (10/1) and the product further purified by reverse phase chromatography (C18 Column, Mobile Phase A: water (0.1% NH₄HCO₃); Mobile Phase B: MeCN; Flow rate: 60 mL/min) to afford the title compound (110 mg, 51.2%) as a light yellow solid. LCMS *m/z* = 746 [M+H]⁺

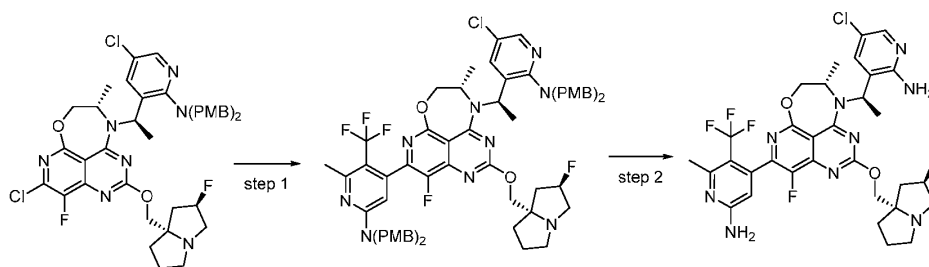
Step 2: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

- [00640] To a solution of the compound from step 1 (70 mg, 0.094 mmol) and Intermediate 27 (116 mg, 0.282 mmol) in dioxane (10 mL) and H₂O (1 mL) was added CataCXium A Pd G3 (7 mg, 0.009 mmol) and K₃PO₄ (60 mg, 0.282 mmol), the mixture purged with N₂ for 5 min, then stirred at 80°C for 4 h. The cooled mixture was concentrated *in vacuo* and purified by silica gel chromatography (DCM:MeOH=20:1) to afford the title compound (50 mg, 53.6%) as an off white solid. LCMS m/z = 994 [M+H]⁺

Step 3: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy))-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate

- [00641] A solution of the compound from step 2 (50 mg, 0.050 mmol) in TFA (3 mL) and DCE (3 mL) was stirred at 80°C for 2 h. The mixture was concentrated *in vacuo* and the residue purified by prep-HPLC (column: Xtimate C18 150*40mm*10um; mobile phase: [Water(FA)-MeCN]; gradient: 13%-33% B over 11 min) to afford the title compound (21.3 mg, 47.2%) as a white solid. LCMS m/z = 670 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.56 (s, 1H), 8.05 (s, 1H), 7.83 – 7.64 (m, 3H), 6.58 – 6.46 (m, 1H), 5.65 (brs, 2H), 4.92 – 4.81 (m, 1H), 4.67 – 4.53 (m, 2H), 4.43 – 4.27 (m, 1H), 4.20 – 4.07 (m, 1H), 3.93 – 3.80 (m, 1H), 3.45 – 3.50 (m, 1H), 3.20 – 3.03 (m, 1H), 3.02 – 2.90 (m, 3H), 2.72 – 2.57 (m, 3H), 2.34 – 2.17 (m, 1H), 2.17 – 1.86 (m, 3H), 1.71 – 1.53 (m, 3H), 0.73 – 0.57 (m, 3H).

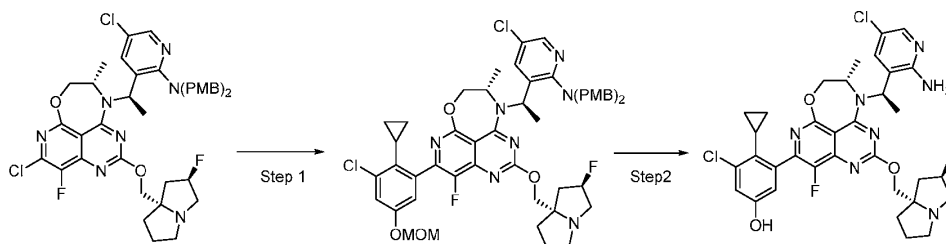
- Example 123: Synthesis of 4-((S)-10-((R)-1-(2-amino-5-chloropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate (Compound 308)**



- [00642] The title compound was obtained as a white solid, 13.6 mg, from Intermediate 36 and Intermediate 22, following a similar procedure to that described in Example 121. The crude product was purified by prep-HPLC (Method D, Gradient (B%): 5% B to 28% B in 7 min). LCMS m/z = 706 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.05 (d, 1H), 7.83 (d, 1H), 6.51

(d, 1H), 6.40 (s, 1H), 5.60 (d, 1H), 4.71 – 4.53 (m, 3H), 4.28 (d, 3H), 4.11 (d, 2H), 3.78 (dd, 3H), 3.32 (dd, 2H), 2.34 (d, 3H), 2.27 – 1.98 (m, 4H), 1.61 (d, 2H), 1.29 (d, 1H), 0.63 (d, 3H).

Example 124: Synthesis of 3-((S)-10-((R)-1-(2-amino-5-chloropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol (Compound 317)

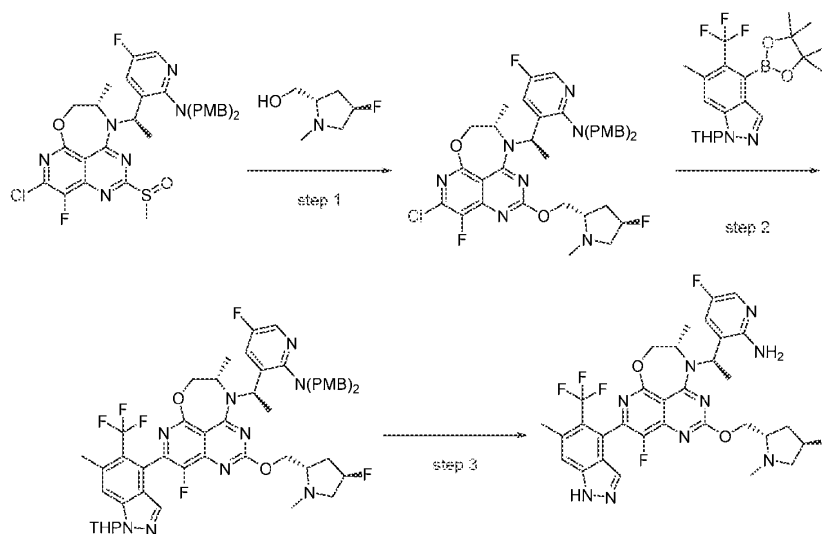


[00643] The title compound was obtained as a white solid, 10.2 mg, 14.7%, from

Intermediate 36 and Intermediate 21, following a similar procedure to that described in

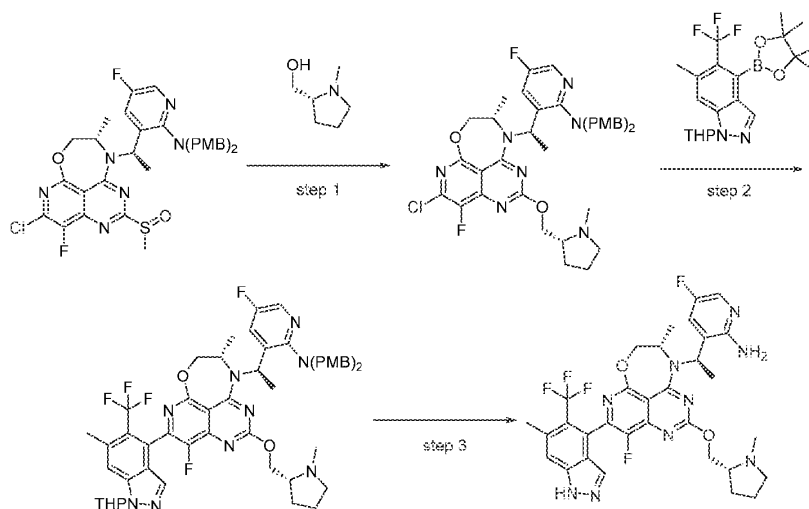
Example 121. The crude product was purified by Prep-HPLC (Method A, Gradient: 40% B to 67% B in 7) min. LCMS $m/z = 698$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 10.00 (s, 1H), 8.02 (d, 1H), 7.76 (d, 1H), 6.94 (d, 1H), 6.75 (d, 1H), 6.49 (d, 1H), 5.90 (s, 2H), 5.41 (d, 1H), 4.54 (dd, 1H), 4.32 (d, 3H), 4.13 (t, 1H), 3.51-3.45 (m, 1H), 3.20-2.80 (m, 2H), 2.41 – 2.07 (m, 3H), 1.92 (s, 3H), 1.76 (d, 2H), 1.61 (d, 3H), 0.61 (d, 5H), 0.06 (s, 2H).

Example 125: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-9-methyl-5-(6-methyl-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine trifluoroacetate (Compound 320)



[00644] The title compound was obtained as a white solid, 26.8 mg, from Intermediate 34, ((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methanol and Intermediate 27, following a similar 3 step procedure to that described in Example 122. The crude product was purified by prep-HPLC (Method B, Gradient (B%): 12% B to 38% B in 7 min). LCMS $m/z = 688$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.58 (brs, 1H), 10.34 (brs, 1H), 8.10 – 8.00 (m, 1H), 7.80 – 7.62 (m, 3H), 6.55 – 6.47 (m, 1H), 5.93 – 5.24 (m, 2H), 5.03 – 4.90 (m, 1H), 4.76 – 4.64 (m, 1H), 4.60 – 4.49 (m, 1H), 4.41 – 4.25 (m, 1H), 4.20 – 3.88 (m, 3H), 3.14 – 2.83 (m, 4H), 2.72 – 2.58 (m, 4H), 2.36 – 2.14 (m, 1H), 1.69 – 1.53 (m, 3H), 0.75 – 0.57 (m, 3H).

- 10 **Example 126: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((R)-1-methylpyrrolidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 265)**



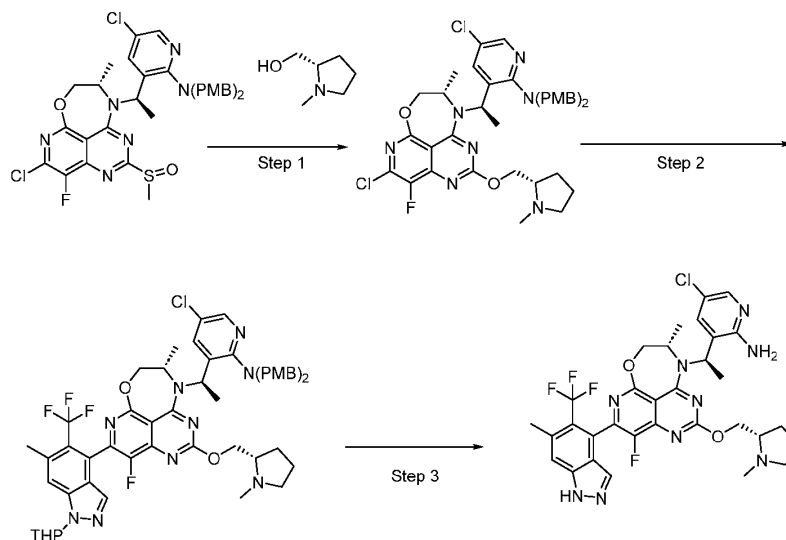
Step 1: Synthesis of 3-((R)-1-((S)-5-chloro-4-fluoro-9-methyl-2-(((R)-1-methylpyrrolidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

- 5 **[00645]** A solution of Intermediate 34 (80 mg, 0.115 mmol) and ((2R)-1-methylpyrrolidin-2-yl)methanol (40 mg, 0.345 mmol) in toluene (10 mL) was stirred at rt for 1 h, then the solution was cooled to 0°C. LiOtBu (27.64 mg, 0.345 mmol) was added and the mixture was concentrated *in vacuo*. The residue was purified by TLC (DCM:MeOH=20:1) to afford the title compound (55 mg, 64.0%) as an off white solid. LCMS m/z = 746 [M+H]⁺

- 10 *Steps 2 and 3: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((R)-1-methylpyrrolidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate*

- [00646]** The title compound was obtained as a white solid, 13.8 mg, 54.6%, from the compound from step 1 and Intermediate 27, following a similar 2 step procedure to that described in Example 122, steps 2 and 3. The crude product was purified by prep-HPLC (Method C, Gradient (B%): 12% B to 27% B in 7 min). LCMS m/z = 670 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.48 (brs, 1H), 7.99 (s, 1H), 7.75 – 7.57 (m, 3H), 6.53 – 6.41 (m, 1H), 5.50 (brs, 2H), 4.78 – 4.58 (m, 2H), 4.57 – 4.40 (m, 1H), 4.35 – 4.17 (m, 1H), 4.13 – 4.01 (m, 1H), 3.90 – 3.73 (m, 1H), 3.15 – 3.06 (m, 1H), 2.98 – 2.70 (m, 4H), 2.63 – 2.51 (m, 3H), 2.28 – 2.10 (m, 1H), 2.05 – 1.97 (m, 1H), 1.92 – 1.76 (m, 2H), 1.66 – 1.48 (m, 3H), 0.68 – 0.48 (m, 3H).
- 15
20

Example 127: Synthesis of 5-chloro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine trifluoroacetate (Compound 322)



5

Step 1: Synthesis of 5-chloro-3-((R)-1-((S)-5-chloro-4-fluoro-9-methyl-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

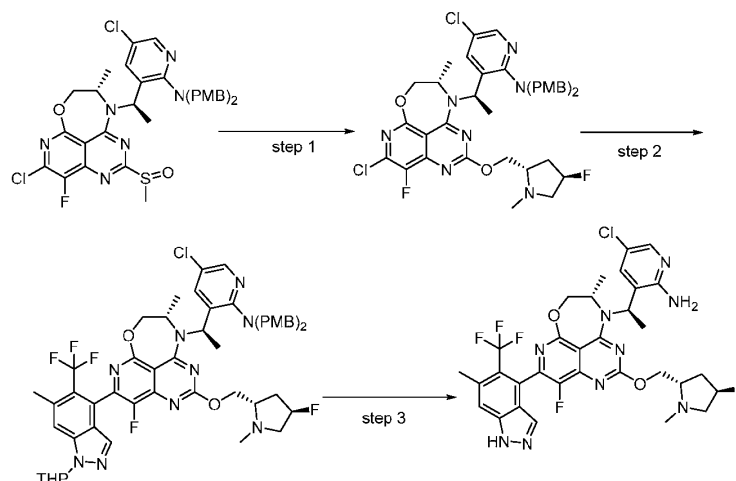
[00647] The title compound was obtained as a white solid, 210 mg, 49%, from the title compound of Intermediate 36, step 1 and ((2S)-1-methylpyrrolidin-2-yl)methanol, following a similar procedure to that described in Intermediate 36, step 2. LCMS $m/z = 762$ $[M+H]^+$

Steps 2 and 3: Synthesis of 5-chloro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine trifluoroacetate

[00648] The title compound was obtained as a white solid, 6.4 mg, from the compound from step 1 and Intermediate 27, following a similar procedure to that described in Example 121. The crude product was purified by HPLC Column (Method E, Gradient: 19% B to 51% B in 9 min). LCMS $m/z = 686$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.49 (d, 1H), 8.02 (d, 1H), 7.76 (t, 1H), 7.74 – 7.68 (m, 2H), 6.52 (m, 1H), 5.86 (d, 2H), 4.55 (ddd, 1H), 4.46 (ddd, 1H), 4.41 – 4.26 (m, 2H), 4.12 (m, 1H), 3.03 (dd, 1H), 2.79 (s, 1H), 2.64 (dd, 3H), 2.44 (s, 3H), 2.32 (q, 1H), 1.99 (qd, 1H), 1.73 (tt, 3H), 1.62 (d, 3H), 0.65 (dd, 3H).

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Example 128: Synthesis of 5-chloro-3-((1R)-1-((9S)-4-fluoro-2-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine trifluoroacetate (Compound 321)



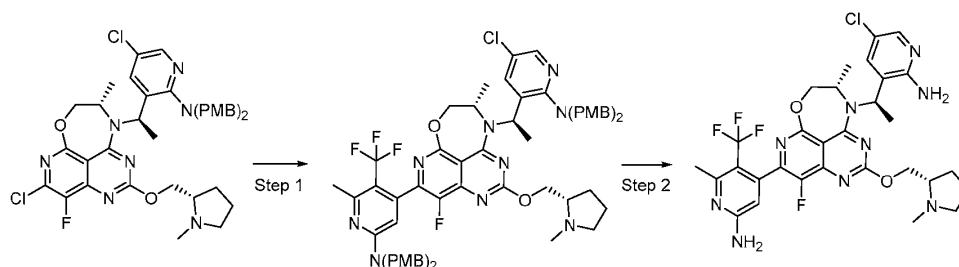
5

[00649] The title compound was obtained as a white solid, 11.8 mg, from the compound of step 1 of the synthesis of Intermediate 36, ((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methanol and Intermediate 27, following a similar 3 step procedure to that described in Example 127. The crude product was purified by Prep-HPLC (Method E, Gradient (B%): 20% B to 37% B in 7 min). LCMS $m/z = 704$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.54 (s, 1H), 8.06 (d, 1H), 7.81 (d, 1H), 7.76 – 7.63 (m, 2H), 6.49 (t, 1H), 5.91 (s, 2H), 5.48 (d, 2H), 4.95 (t, 1H), 4.68 (d, 1H), 4.58 (dt, 1H), 4.34 (dd, 2H), 4.17 (d, 2H), 4.08 – 3.95 (m, 1H), 3.54 (dd, 1H), 3.06 (s, 3H), 2.64 (dt, 3H), 1.63 (d, 3H), 0.67 (dd, 3H).

10

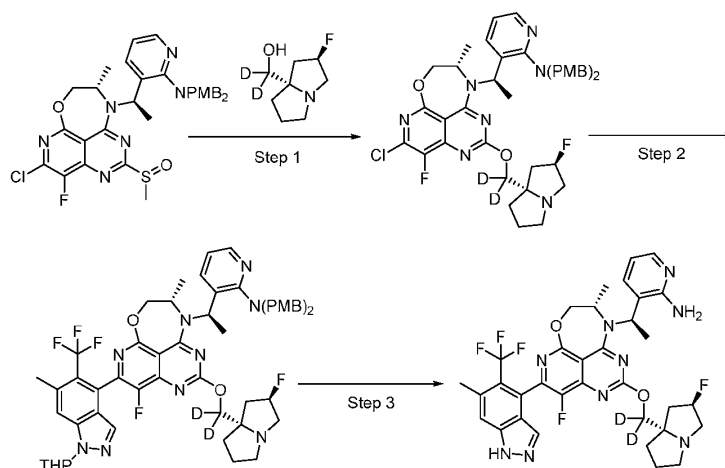
Example 129: Synthesis of 4-((S)-10-((R)-1-(2-amino-5-chloropyridin-3-yl)ethyl)-4-fluoro-9-methyl-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine formate (Compound 324)

15



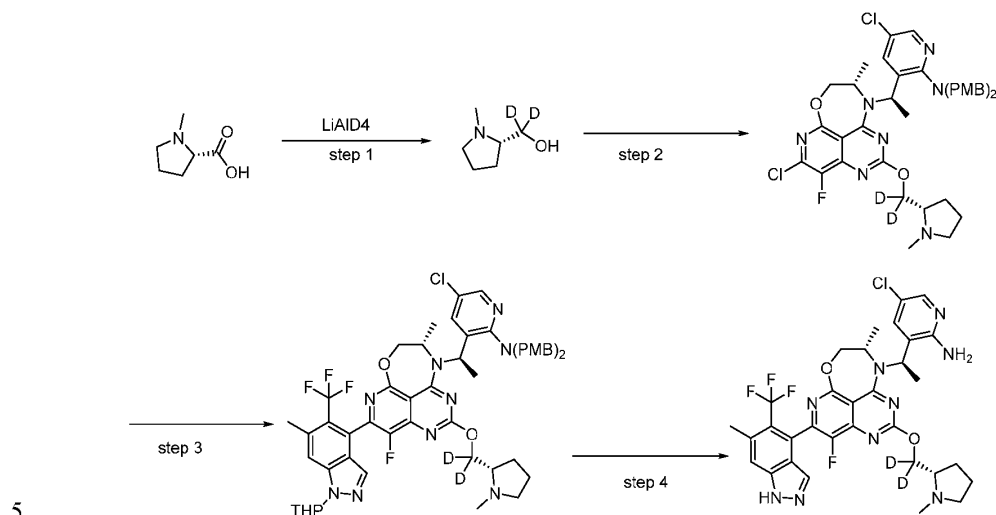
[00650] The title compound was obtained as a white solid, 10.9 mg, from the compound from step 1 of Example 127 and Intermediate 22, following a similar 2 step procedure to that described in Example 121. The crude product was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 19*250 mm, 5 μ m; Mobile Phase A: Water (0.05% FA), Mobile Phase B: MeCN; Flow rate: 30 mL/min; Gradient: 19% B to 51% B in 9 min). LCMS m/z = 662 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 8.02 (d, 1H), 7.75 (d, 1H), 6.80 (s, 2H), 6.46 (q, 1H), 6.24 (s, 1H), 5.78 (s, 2H), 4.63 (s, 1H), 4.59 – 4.46 (m, 2H), 4.30 (d, 1H), 4.11 (p, 1H), 2.75 (s, 4H), 2.47 (q, 4H), 2.11 (d, 2H), 2.01 – 1.73 (m, 3H), 1.60 (d, 3H), 0.60 (d, 3H).

Example 130: Synthesis of 3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy-d₂)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 314)



[00651] The title compound was obtained as a white solid, 17 mg, from the compound from step 1 of the synthesis of intermediate 39, ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methan-d₂-ol and Intermediate 27, following a similar 3 step procedure to that described in Example 127. The crude product was purified by Prep-HPLC (Method D, Gradient: 5% B to 28% B in 7 min). LCMS m/z = 698 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 13.58 (s, 1H), 8.11 (dd, 2H), 7.83 – 7.56 (m, 2H), 7.21 (d, 1H), 6.98 (t, 1H), 6.57 (q, 1H), 5.73 – 5.47 (m, 1H), 4.60 (ddd, 1H), 4.38 (dd, 1H), 4.17 (p, 1H), 3.93 – 3.76 (m, 3H), 3.76 – 3.56 (m, 2H), 3.30 (s, 3H), 2.64 (dt, 3H), 2.43 – 2.28 (m, 1H), 2.28 – 1.97 (m, 3H), 1.67 (dd, 2H), 0.70 (dd, 3H).

Example 131: Synthesis of 5-chloro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy-d₂))-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 416)



Step 1: (S)-1-methylpyrrolidin-2-yl)methan-d₂-ol

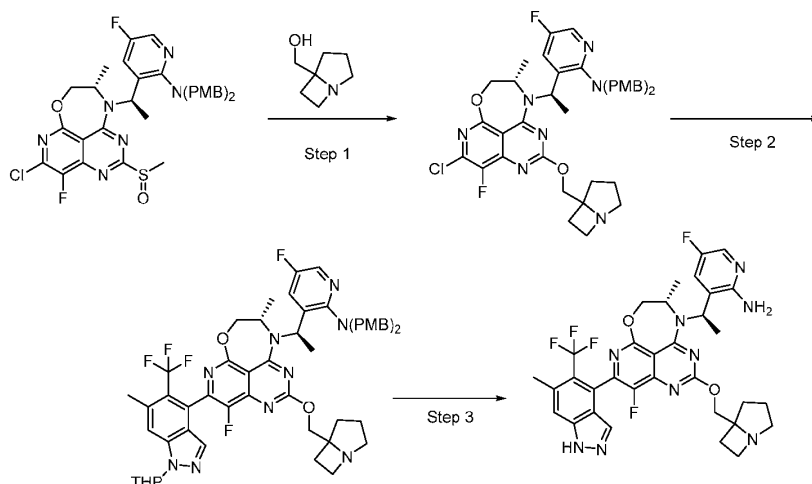
[00652] LiAlD₄ (325.0 mg, 7.74 mmol) was added carefully at 0°C to a solution of (2S)-1-methylpyrrolidine-2-carboxylic acid (500 mg, 3.87 mmol) in THF (5 mL) and the reaction was stirred at 0°C for 1 h under N₂. The reaction was quenched with D₂O at 0°C and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure to afford the title compound (300 mg, 66.1%) as a white oil. LCMS m/z = 118 [M+H]⁺

Steps 2 to 4: Synthesis of 5-chloro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((S)-1-methylpyrrolidin-2-yl)methoxy-d₂))-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00653] The title compound was obtained from the compounds from step 1, Intermediate 36 and Intermediate 27, following a similar 3 step procedure to that described in Example 127. The crude product was purified by Prep-HPLC (Method C, Gradient: 9% B to 39% B in 7 min). LCMS m/z = 688 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 13.54 (s, 1H), 9.78 (s, 1H), 8.05 (d, 1H), 7.80 (t, 1H), 7.76 – 7.63 (m, 2H), 6.48 (q, 1H), 5.90 (s, 2H), 4.61 – 4.54 (m, 1H), 4.33

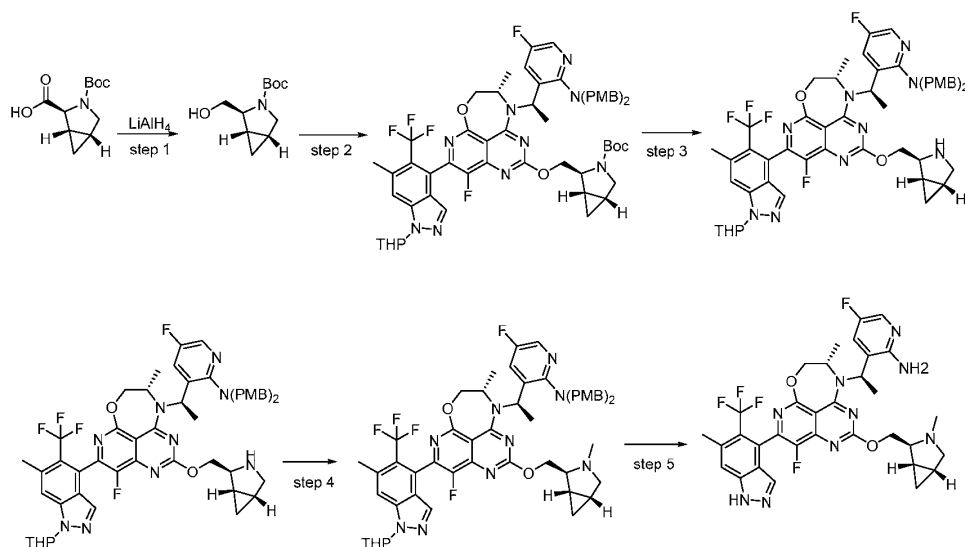
(dd, 1H), 4.20 – 4.13 (m, 1H), 3.89 – 3.78 (m, 1H), 3.17 – 3.10 (m, 2H), 3.01 – 2.94 (m, 3H), 2.64 (dd, 4H), 1.92 (tt, 2H), 1.63 (d, 3H), 0.67 (dd, 3H).

Example 132: Synthesis of 3-((1R)-1-((9S)-2-((1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine formate (Compound 400)



[00654] The title compound was obtained as a white solid, 2.7 mg, from Intermediate 34, Intermediate 40 and Intermediate 27, following a similar 3 step procedure to that described in Example 127. The crude product was purified by Prep-HPLC (Method D, Gradient: 10% B to 38% B in 7 min). LCMS $m/z = 682$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.53 (d, 1H), 10.13 (s, 1H), 8.03 (d, 1H), 7.74 (t, 2H), 7.69 (d, 1H), 6.55 (q, 1H), 5.71 (s, 2H), 4.93 (dd, 1H), 4.86 – 4.73 (m, 1H), 4.70 – 4.52 (m, 2H), 4.45 – 4.29 (m, 1H), 4.18 (q, 2H), 2.64 (dt, 2H), 2.59 (s, 1H), 2.39 – 2.21 (m, 3H), 2.10 (dd, 1H), 2.06 – 1.93 (m, 1H), 1.63 (d, 2H), 1.35 (s, 1H), 1.24 (s, 1H), 0.85 (t, 1H), 0.74 – 0.56 (m, 3H).

Example 133: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-2-(((1S,2S,5R)-3-methyl-3-azabicyclo[3.1.0]hexan-2-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 377)



Step 1: *tert*-butyl (1*S*,2*S*,5*R*)-2-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

[00655] LiAlH₄ (2 mL, 0.053 mmol, 1.0 M in THF solution) was added dropwise at 0°C to a solution of (1*S*,2*S*,5*R*)-3-(*tert*-butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (230 mg, 1.012 mmol) in THF (2 mL) and the reaction mixture was stirred at 0°C for 1 h. The reaction was quenched with Na₂SO₄·10H₂O at 0°C, the resulting mixture was filtered and the filter cake was washed with DCM (3×10 mL). The filtrate was dried over Na₂SO₄ and evaporated under reduced pressure to afford the title compound (130 mg, 60.2%) as a white oil. LCMS *m/z* = 158 [M+H]⁺

Step 2: Synthesis of *tert*-butyl (1*S*,2*S*,5*R*)-2-(((9*S*)-10-((*R*)-1-(2-(bis(4-methoxybenzyl)amino)-5-fluoropyridin-3-yl)ethyl)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-5-(trifluoromethyl)-1*H*-indazol-4-yl)-9,10-dihydro-8*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-2-yl)oxy)methyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate

[00656] The title compound was obtained as an oil, 170 mg, 73.4%, from Intermediate 37 and the compound from step 1, following a similar procedure to that described in Example 127, step 1. LCMS *m/z* = 1092 [M+H]⁺

Step 3: Synthesis of 3-((1*R*)-1-((9*S*)-2-(((1*S*,2*S*,5*R*)-3-azabicyclo[3.1.0]hexan-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-5-(trifluoromethyl)-1*H*-indazol-4-yl)-8,9-dihydro-10*H*-7-oxa-1,3,6,10-tetraazacyclohepta[*de*]naphthalen-10-yl)ethyl)-5-fluoro-*N,N*-bis(4-methoxybenzyl)pyridin-2-amine

[00657] 2,6-Dimethylpyridine (117.73 mg, 1.1 mmol) was added dropwise at 0°C to a solution of the compound from step 2 (183.1 mg, 0.82 mmol) in DCM (4 mL) and the resulting mixture was stirred at rt for 1 h. The reaction was concentrated under reduced pressure and the residue was purified by reverse-phase chromatography (column, C18; mobile phase, MeCN in Water (0.1% TFA), 50% to 55% gradient in 10 min) to give the title compound (60 mg, 44.0%) as a white solid. LCMS m/z = 992 [M+H]⁺

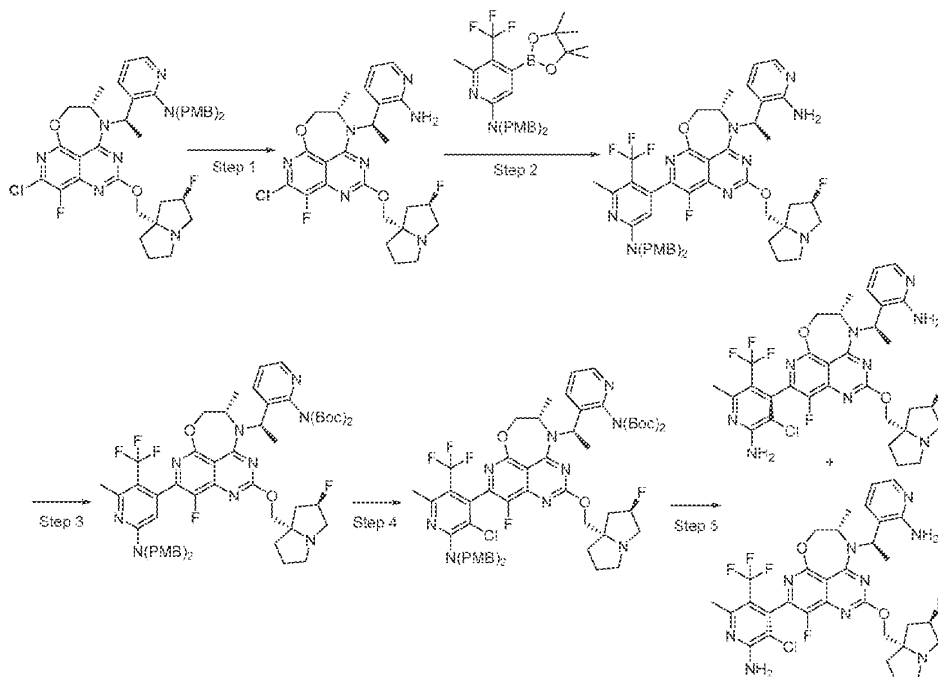
Step 4: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((1S,2S,5R)-3-methyl-3-azabicyclo[3.1.0]hexan-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00658] Formaldehyde solution (7.26 mg, 0.24 mmol) in MeOH (2 mL), NaCNBH₃ (6.84 mg, 0.108 mmol) and AcOH (18.16 mg, 0.30 mmol) were added to a solution of the compound from step 3 (60 mg, 0.060 mmol) and the reaction mixture was stirred at rt for 2 h under N₂. The resulting mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography, eluting with DCM / MeOH (12:1) to afford the title compound (50 mg, 82.2%) as a white solid. LCMS m/z = 1007 [M+H]⁺

Step 5: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-2-(((1S,2S,5R)-3-methyl-3-azabicyclo[3.1.0]hexan-2-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00659] The title compound was obtained as a white solid, 5 mg, 14.8%, from the compound from step 4, following a similar procedure to that described in Example 121, step 2. The crude product was purified by Prep-HPLC (Method A, Gradient (B%): 19% B to 34% B in 7 min). LCMS m/z = 682 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 13.50 (d, 1H), 8.00 (d, 1H), 7.82 – 7.61 (m, 3H), 6.56 (q, 1H), 5.65 (d, 2H), 4.60 – 4.45 (m, 2H), 4.42 – 4.31 (m, 2H), 4.12 (p, 1H), 3.17 (s, 1H), 2.94 (d, 1H), 2.70 – 2.61 (m, 3H), 2.38 (s, 3H), 1.63 (d, 3H), 1.53 – 1.42 (m, 2H), 0.66 (d, 2H), 0.59 (t, 3H), 0.45 (d, 1H).

Example 134: Synthesis of (R)-4-((S)-10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-3-chloro-6-methyl-5-(trifluoromethyl)pyridin-2-amine or (S)-4-((S)-10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-3-chloro-6-methyl-5-(trifluoromethyl)pyridin-2-amine (Compound 367)



Step 1: Synthesis of 3-((R)-1-((S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

- 5 **[00660]** A solution of Intermediate 39 (455 mg, 0.58 mmol) and TFA (4 mL) in DCE (4 mL) was stirred at 80°C for 1 h under N₂. The resulting mixture was evaporated under reduced pressure to give the title compound (310 mg, crude) as a colorless oil. LCMS m/z = 532 [M+H]⁺

- 10 *Step 2: Synthesis of 4-((S)-10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-N,N-bis(4-methoxybenzyl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine*

- 15 **[00661]** A mixture of the compounds from step 1 (310 mg, 0.58 mmol) and Intermediate 22 (540 mg, 0.99 mmol), CataCXium A Pd G3 (86 mg, 0.11 mmol) and K₃PO₄ (376 mg, 1.77 mmol) in dioxane (4 mL) and H₂O (0.4 mL) was stirred at 80°C for 1 h under N₂. The cooled mixture was concentrated under reduced pressure and the residue was purified by Prep-TLC (DCM / MeOH 10:1) to afford the title compound (402 mg, 75.6%) as a light yellow solid. LCMS m/z = 912 [M+H]⁺

Step 3: Synthesis of tert-butyl (3-((R)-1-((S)-5-(6-(bis(4-methoxybenzyl)amino)-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-yl)(tert-butoxycarbonyl)carbamate

- 5 **[00662]** A mixture of the compound from step 2 (402 mg, 0.44 mmol), Boc₂O (289 mg, 1.32 mmol), DIPEA (171 mg, 1.32 mmol) and DMAP (6 mg, 0.04 mmol) in DCM (5 mL) was stirred at rt for 16 h under N₂. The reaction was diluted with water (10 mL) and the mixture was extracted with DCM (3 x 10mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced
10 pressure to give the title compound (480 mg, 97.9%) as a brown solid. LCMS m/z = 1112 [M+H]⁺

Step 4: Synthesis of tert-butyl (3-((1R)-1-((9S)-5-(2-(bis(4-methoxybenzyl)amino)-3-chloro-6-methyl-5-(trifluoromethyl)pyridin-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-yl)(tert-butoxycarbonyl)carbamate

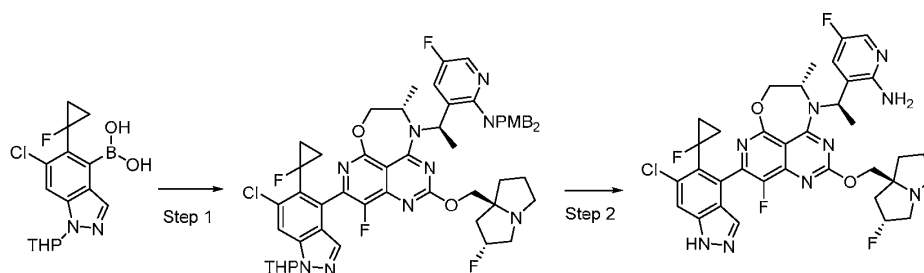
- 15 **[00663]** A mixture of the compound from step 3 (310 mg, 0.27 mmol) and 2-chloro-1,3-bis(methoxycarbonyl)guanidine (65 mg, 0.31 mmol) in MeCN (5 mL) was stirred at rt for 16 h under N₂. The resulting mixture was concentrated under reduced pressure and the residue was purified by Prep-TLC (DCM / MeOH 10:1) to afford the title compound (130 mg, 40.6%) as a
20 colorless oil. LCMS m/z = 1146 [M+H]⁺

Step 5: Synthesis of (R)-4-((S)-10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-3-chloro-6-methyl-5-(trifluoromethyl)pyridin-2-amine or (S)-4-((S)-10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-3-chloro-6-methyl-5-(trifluoromethyl)pyridin-2-amine

- 25 **[00664]** A solution of the compound from step 4 (130mg, 0.11 mmol), TFOH (1 mL) and TFA (10 mL) was stirred at rt for 30 min under N₂. The resulting mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Method A, Gradient:
30 36% B to 55% B in 7 min) to afford Peak 1, the title compound (23.7 mg, 29.6%) as a white solid. LCMS m/z = 706 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 7.99 - 7.97 (m, 1H), 7.70 - 7.68 (m, 1H), 7.28 (s, 2H), 6.69 - 6.67 (m, 1H), 6.50 - 6.47 (m, 1H), 5.60 (s, 2H), 5.25 (d, 1H), 4.53 - 4.50 (m, 1H), 4.35 - 4.32 (m, 1H), 4.16 - 4.10 (m, 2H), 4.03 - 4.01 (m, 1H), 3.12 - 3.09

(m, 3H), 2.86 - 2.81 (m, 1H), 2.47 (s, 3H), 2.18 - 2.06 (m, 3H), 1.83 - 1.75 (m, 3H), 1.60 (d, 3H), 0.63 - 0.52 (m, 3H).

Example 135: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(1-fluorocyclopropyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine trifluoroacetate (Compound 366)



Step 1: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(1-fluorocyclopropyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

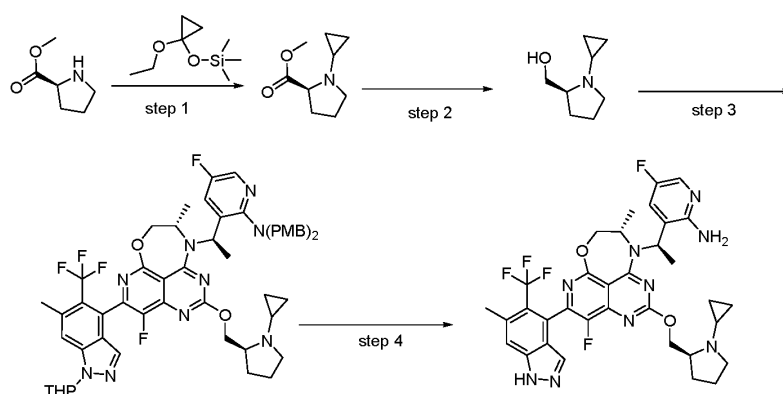
[00665] A solution of Intermediate 41 (27 mg, 0.08 mmol), the title compound of Example 120, step 1, (63.0 mg, 0.08 mmol), K_3PO_4 (50.8 mg, 0.24 mmol) and CataCXium A Pd G3 (11.62 mg, 0.016 mmol) in dioxane (3 mL) and H_2O (0.4 mL) was stirred at $80^\circ C$ for 16 h under N_2 . The cooled mixture was concentrated under reduced pressure and the residue was purified by Prep-TLC (PE / EtOAc 5:1) to afford the title compound (50 mg, 59.8%) as a white solid. LCMS m/z = 1048 $[M+H]^+$

Step 2: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(1-fluorocyclopropyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine trifluoroacetate

[00666] A solution of the compound from step 1 (20 mg, 0.019 mmol) in TFA (2 mL) was stirred at $60^\circ C$ for 2 h. The cooled mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Method D, Gradient (B%): 15% B to 33% B in 8 min) to afford the title compound (4.8 mg, 30.0%) as a white solid. LCMS m/z = 724 $[M+H]^+$ 1H NMR (400 MHz, $DMSO-d_6$) δ 13.54 - 13.51 (m, 1H), 8.04 (d, 1H), 7.94 - 7.89 (m, 1H), 7.85 (s, 1H), 7.81 - 7.71 (m, 1H), 6.54 (d, 1H), 5.66 - 5.53 (s, 3H), 4.81 - 4.78 (m, 1H), 4.76 - 4.66 (m,

2H), 4.64 - 4.55 (m, 1H), 4.36 (d, 1H), 3.87 - 3.83 (m, 3H), 2.67 - 2.65 (m, 1H), 2.31 - 2.28 (m, 1H), 2.17 - 2.12 (m, 2H), 2.10 - 2.01 (m, 1H), 1.67 - 1.60 (m, 3H), 1.28 - 1.24 (m, 1H), 1.22 - 1.19 (m, 1H), 1.18 - 1.09 (m, 1H), 0.98 - 0.57 (m, 6H).

Example 136: Synthesis of 3-((1R)-1-((9S)-2-(((S)-1-cyclopropylpyrrolidin-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine (Compound 365)



Step 1: Synthesis of methyl (2S)-1-cyclopropylpyrrolidine-2-carboxylate

[00667] NaCNBH₃ (1.46 g, 23.2 mmol) and AcOH (5.58 g, 92.9 mmol) were added to a solution of methyl (2S)-pyrrolidine-2-carboxylate (100 mg, 0.77 mmol) and (1-ethoxycyclopropoxy)trimethylsilane (4.05 g, 23.2 mmol) in THF (9 mL) and MeOH (1 mL) and the reaction mixture was stirred at 65°C overnight under N₂. The cooled reaction was quenched with sat. Na₂CO₃ (aq), the layers separated and the aqueous phase was extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure to afford the title compound (1 g, 76.3%) as a white oil. LCMS m/z = 170 [M+H]⁺

Step2: Synthesis of ((2S)-1-cyclopropylpyrrolidin-2-yl)methanol

[00668] LiAlH₄ (1.0 M in THF, 12 mL, 0.032 mmol) was added dropwise at 0°C to a solution of the compound from step 1 (1g, 5.91 mmol) in THF (10 mL) and the resulting mixture was stirred at 0°C for 1 h. The reaction was quenched with ice-water and the aqueous layer was extracted with EtOAc (3x30 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was evaporated under reduced pressure to afford the title compound (400 mg, 47.9%) as a white oil. LCMS m/z = 142 [M+H]⁺

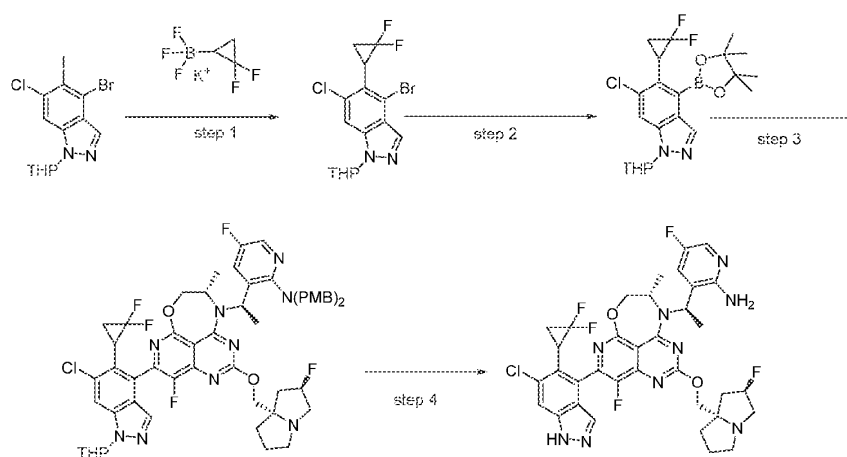
Step 3: Synthesis of 3-((1R)-1-((9S)-2-(((S)-1-cyclopropylpyrrolidin-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

- 5 **[00669]** The title compound was obtained as a yellow solid, 30 mg, 27.7%, from Intermediate 37 and the compound from step 2, following a similar procedure to that described in Example 127, step 1. LCMS m/z = 1021 $[M+H]^+$

Step 4: Synthesis of 3-((1R)-1-((9S)-2-(((S)-1-cyclopropylpyrrolidin-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine

- [00670]** The title compound was obtained as a white solid, 1.8 mg, 13.2%, from the compound from step 3, following a similar procedure to that described in Example 121, step 2. The crude product was purified by Prep-HPLC (Method A, Gradient: 45% B to 64% B in 7 min). LCMS m/z = 696 $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.53 (d, 1H), 8.00 (d, 1H),
15 7.71 (q, 3H), 6.62 – 6.50 (m, 1H), 5.60 (d, 2H), 4.75 – 4.50 (m, 2H), 4.35 (dd, 1H), 4.26 – 4.04 (m, 2H), 3.05 (s, 2H), 2.64 (dd, 3H), 2.22 – 1.93 (m, 1H), 1.81 (s, 1H), 1.73 (d, 2H), 1.62 (d, 3H), 1.24 (s, 3H), 0.63 (dd, 3H), 0.34 (d, 3H).

- Example 137: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(2,2-difluorocyclopropyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine (Compound 364)**



Step 1: Synthesis of 4-bromo-6-chloro-5-(2,2-difluorocyclopropyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

- [00671] A mixture of 4-bromo-6-chloro-5-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (1.5 g, 3.4 mmol), potassium (2,2-difluorocyclopropyl)trifluoroboranuide (0.75 g, 4.08 mmol),
 5 Pd(dppf)Cl₂.CH₂Cl₂ (0.55 g, 0.68 mmol) and K₂CO₃ (1.41 g, 10.2 mmol) in dioxane (16 mL) and H₂O (2 mL) was stirred at 100°C for 3 days under N₂. The reaction was quenched with ice-water at 0°C. The aqueous layer was extracted with EtOAc (3x20 mL), the combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase column
 10 chromatography C18 Column, Mobile Phase A: water (0.1% TFA); Mobile Phase B: MeCN; Flow rate: 60 mL/min to afford the title compound (100 mg, 7.5%) as a colorless oil. LCMS m/z = 391 [M+H]⁺

Step 2: Synthesis of 6-chloro-5-(2,2-difluorocyclopropyl)-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole

- 15 [00672] A mixture of the compound from step 1 (100 mg, 0.26 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (41.70 mg, 0.051 mmol) bis(pinacolato)diboron (97.26 mg, 0.38 mmol) and KOAc (75.18 mg, 0.77 mmol) in dioxane (1.5 mL) was stirred at 100°C for 4 h under N₂. The residue was purified directly by Prep-TLC (PE / EtOAc 10:1) to give the title compound (50 mg, 44.6%) as a brown oil. LCMS m/z = 439 [M+H]⁺

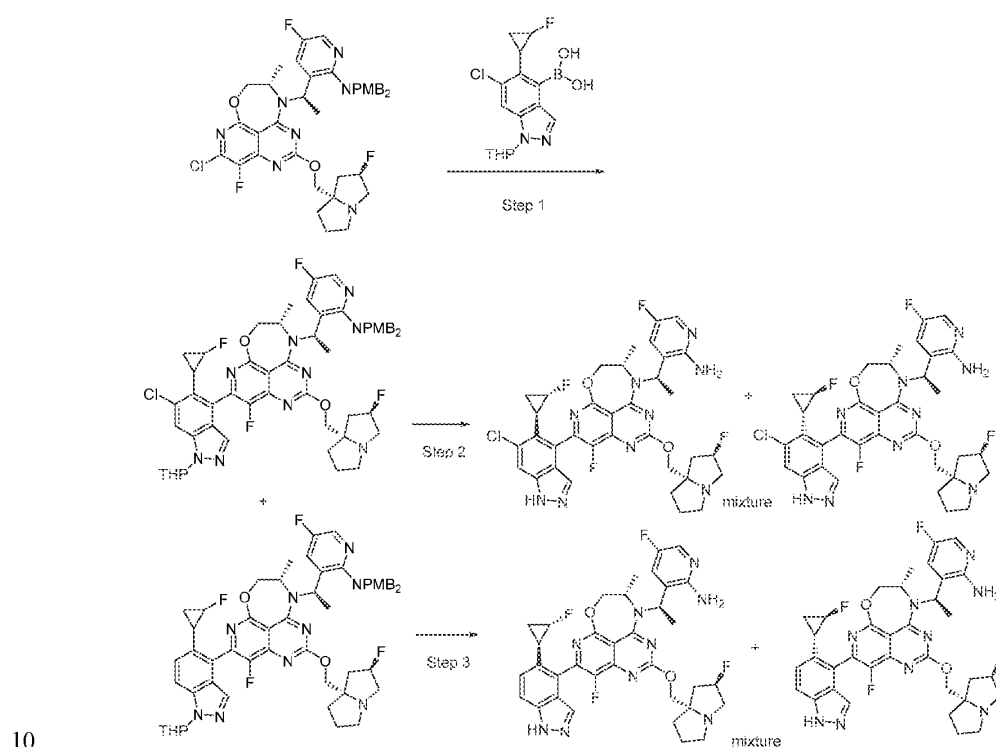
- 20 *Steps 3 to 4: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(2,2-difluorocyclopropyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine*

- [00673] The title compound was obtained as a white solid, 1.4 mg, from the compound from
 25 Example 120, step1 and the compound from step 2, following a similar 2 step procedure to that described in Example 121. The crude product was purified by Prep-HPLC (Method A, Gradient: 40% B to 61% B in 7 min). LCMS m/z = 742 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 8.01 (d, 1H), 7.96 – 7.77 (m, 2H), 7.70 (dd, 1H), 6.54 (d, 1H), 5.73 – 5.59 (m, 2H), 5.43 – 5.17 (m, 1H), 4.56 (dd, 1H), 4.34 (dd, 1H), 4.20 – 3.99 (m, 3H), 3.09 (s, 3H), 3.02 (s, 2H), 2.83
 30 (d, 1H), 2.20 – 2.11 (m, 1H), 2.10 – 2.00 (m, 2H), 1.63 (d, 4H), 1.23 (s, 2H), 1.06 – 0.94 (m, 1H), 0.90 – 0.76 (m, 1H), 0.64 (dd, 3H).

Example 138: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(2-fluorocyclopropyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine (Compound 363)

5 And

Example 139: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-5-(5-(2-fluorocyclopropyl)-1H-indazol-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 362)



Step 1 (i): Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(2-fluorocyclopropyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

15 *And Step 1 (ii): Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-5-(5-(2-fluorocyclopropyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine*

[00674] To a stirred solution of the compound of Example 120, step 1 (186.74 mg, 0.24 mmol) and Intermediate 45 (80 mg, 0.24 mmol) in MeOH (1.6 mL)/H₂O (0.2 mL) were added K₃PO₄ (150.5 mg, 0.71 mmol) and CataCXium A Pd G3 (17.21 mg, 0.024 mmol) and the reaction mixture was stirred at 80°C for 2 h under N₂. The resulting mixture was concentrated under vacuum and the residue was purified by silica gel column chromatography, eluting with DCM / MeOH (12:1) to afford the title compound (i) (120 mg, 48.4%) as a yellow solid. LCMS m/z = 1049 [M+H]⁺ and the title compound (ii) as a yellow solid. LCMS m/z = 1014 [M+H]⁺

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Step 2: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(2-fluorocyclopropyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine

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[00675] A solution of the compound from step 1(i) (150 mg, 0.143 mmol) in TFA (3 mL) was stirred at 50°C overnight. The crude product was purified by Prep-HPLC (Column: (S, S)WHELK-01 4.6*50 mm, 3.5 µm; Mobile Phase B: MeOH: MeCN=1: 1 (0.5% 2M NH₃-MeOH); Flow rate: 4 mL/min; Gradient: isocratic % B) to afford the title compound of Example 138 (24.9 mg, 24.0%) as a white solid. LCMS m/z = 724 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 13.33 (m, 1H), 8.01 (m, 1H), 7.87 – 7.74 (m, 2H), 7.70 (m, 1H), 6.54 (s, 1H), 5.66 (m, 2H), 5.37 (d, 1H), 4.55 (m, 1H), 4.43 – 4.31 (m, 2H), 4.15 (m, 3H), 3.11 (m, 2H), 3.03 (s, 1H), 2.84 (m, 1H), 2.36 (s, 1H), 2.14 (m, 1H), 2.06 (m, 2H), 1.89 – 1.73 (m, 3H), 1.63 (m, 3H), 1.23 (s, 1H), 0.64 (m, 4H).

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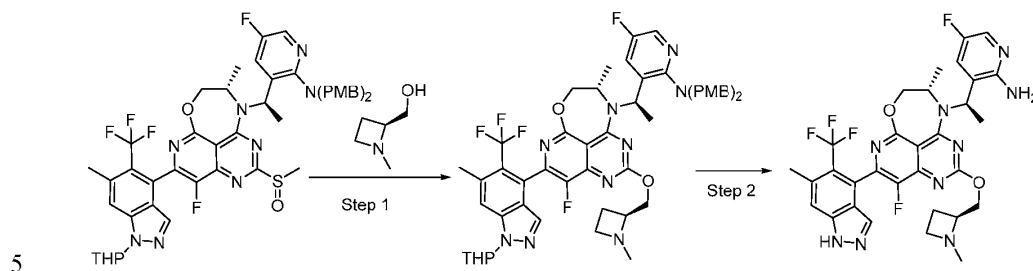
Step 3: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-5-(5-(2-fluorocyclopropyl)-1H-indazol-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate

[00676] A solution of the compound from step 1(ii) (30 mg, 0.030 mmol) in TFA (2 mL) was stirred at 50°C overnight. The crude product was purified by Prep-HPLC (Column: Xselect CSH C18 OBD column 30*150nm, 5 µm; Mobile Phase B: MeOH: MeCN=1: 1 (0.1% 2M FA) to afford the title compound of Example 139 (12.2 mg, 59.8%) as a white solid. LCMS m/z = 690 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 13.19 (s, 1H), 8.21 (s, 1H), 8.00 (m, 1H), 7.69 (m, 1H), 7.57 (m, 1H), 7.01 (m, 1H), 6.57 – 6.50 (m, 1H), 5.64 (m, 2H), 5.36 (m, 1H), 4.55 (m, 1H), 4.40 – 4.29 (m, 2H), 4.18 – 4.08 (m, 2H), 4.12 (s, 1H), 3.18 – 3.04 (m, 2H), 3.03 (s, 1H), 2.83 (m, 1H), 2.44 (s, 2H), 2.24 – 2.10 (m, 1H), 2.10 – 1.98 (m, 1H), 1.81 (m, 3H), 1.72 (s, 1H), 1.65 – 1.59 (m, 3H), 1.23 (s, 1H), 1.09 (t, 1H), 0.63 (s, 3H).

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Example 140: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((S)-1-methylazetidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 357)



Step 1: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((S)-1-methylazetidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

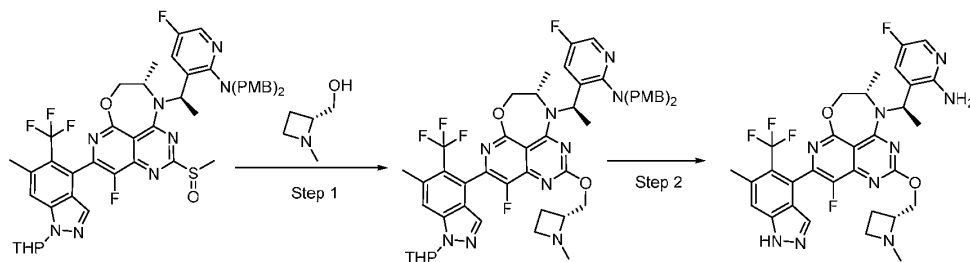
10 **[00677]** The title compound was obtained as a solid, 30 mg, 57.7%, from Intermediate 37 and (S)-(1-methylazetidin-2-yl)methanol, following a similar procedure to that described in Example 127, step 1. LCMS m/z = 981 $[M+H]^+$

Step 2: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((S)-1-methylazetidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate

15 **[00678]** The title compound was obtained as a white solid, 5.1 mg, 14%, from the compound from step 2, following a similar procedure to that described in Example 121, step 2. The crude product was purified by Prep-HPLC (Method D, Gradient: 7% B to 37% B in 7 min). LCMS m/z = 656 $[M+H]^+$ 1H NMR (400 MHz, $DMSO-d_6$): δ 13.52 (d, 1H), 8.27 (s, 1H), 7.71 (t, 3H), 6.38–6.67 (m, 1H), 5.60 (d, 2H), 4.08–4.57 (m, 5H), 3.29 (s, 2H), 2.78 (s, 1H), 2.64 (d, 3H), 2.27 (s, 3H), 1.98 (dt, 2H), 1.62 (d, 3H), 0.63 (dd, 3H).

Example 141: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((R)-1-methylazetidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 356)

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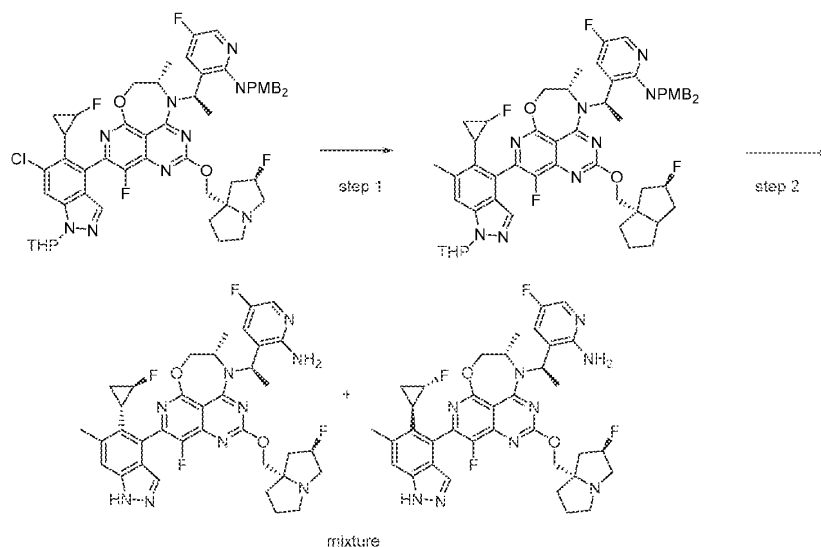
Step 1: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((R)-1-methylazetidin-2-yl)methoxy))-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00679] The title compound was obtained as a solid, 25 mg, 48.1%, from Intermediate 37 and ((2R)-1-methylazetidin-2-yl)methanol, following a similar procedure to that described in Example 127, step 1. LCMS m/z = 981 $[M+H]^+$

Step 2: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((R)-1-methylazetidin-2-yl)methoxy))-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate

[00680] The title compound was obtained as a white solid, 6.5 mg, 18%, from the compound from step 1, following a similar procedure to that described in Example 121, step 2. The crude product was purified by Prep-HPLC (Method D, Gradient: 7% B to 37% B in 7 min). LCMS m/z = 656 $[M+H]^+$ 1H NMR (400 MHz, $DMSO-d_6$): δ 13.52 (d, 1H), 8.00 (d, 1H), 7.70 – 7.76 (m, 2H), 5.63 (dd, 2H), 4.53 (dtd, 1H), 4.40 (dddd, 3H), 4.12-4.10 (m, 1H), 3.50 (s, 3H), 3.42-3.28 (m, 1H), 2.79-2.77 (m, 1H), 2.64 (dd, 3H), 2.28 (s, 3H), 2.04-1.95 (m, 2H), 1.62 (dd, 3H), 0.62 (dd, 3H).

Example 142: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-5-(5-(2-fluorocyclopropyl)-6-methyl-1H-indazol-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy))-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine trifluoroacetate (Compound 352)



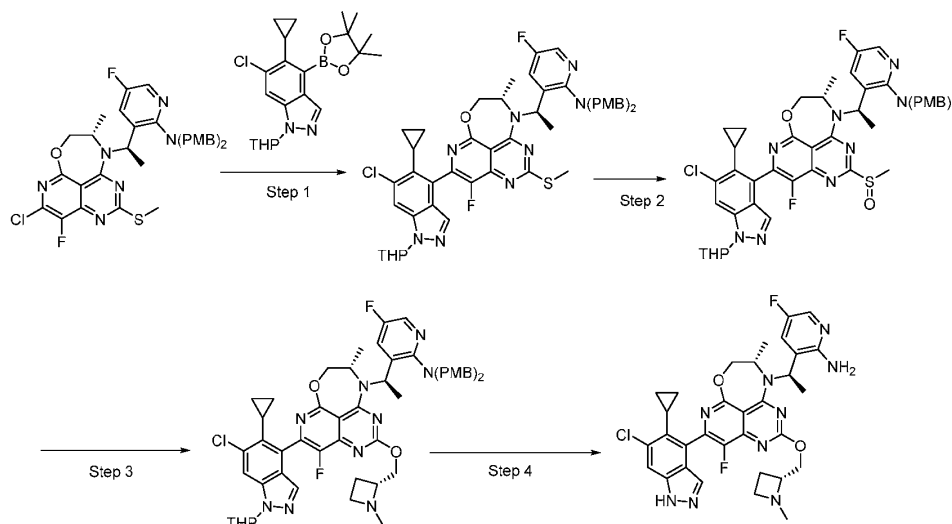
- Step 1: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-5-(5-(2-fluorocyclopropyl)-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00681] The title compound was obtained as a yellow solid, 160 mg, crude, from the compound from step 3 of Example 138 and methylboronic acid, following a similar procedure to that described in Example 83, step 1. LCMS $m/z = 1029$ $[M+H]^+$

- Step 2: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-5-(5-(2-fluorocyclopropyl)-6-methyl-1H-indazol-4-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine trifluoroacetate

- [00682]** A solution of the compound from step 1 (40 mg, 0.037 mmol) and TFA (0.2 mL) in DCM (1 mL) was stirred at rt for 1h under N_2 . The residue was purified by reverse-phase chromatography: column, C18 silica gel; mobile phase, MeCN in Water (0.1% TFA), 10% to 50% gradient in 10 min, to afford the title compound (8.6 mg, 44.6%) as a yellow oil. LCMS $m/z = 704$ $[M+H]^+$ 1H NMR (400 MHz, $DMSO-d_6$) δ 13.05 (s, 1H), 8.00 (m, 1H), 7.70 (m, 2H), 7.48 (m, 1H), 6.54 (m, 1H), 5.70 – 5.62 (m, 2H), 5.37 (d, 1H), 4.60 – 4.51 (m, 1H), 4.36 (m, 2H), 4.14 (m, 4H), 3.14 – 3.04 (m, 2H), 3.03 (s, 1H), 2.83 (m, 1H), 2.62 (s, 1H), 2.56 (m, 2H), 2.16 (m, 1H), 2.06 (m, 2H), 1.81 (s, 3H), 1.63 (m, 3H), 1.23 (s, 1H), 0.63 (m, 2H), 0.45 (m, 2H).

Example 143: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-cyclopropyl-1H-indazol-4-yl)-4-fluoro-9-methyl-2-(((R)-1-methylazetidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine formate (Compound 348)



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Steps 1 and 2: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-cyclopropyl-1H-indazol-4-yl)-4-fluoro-9-methyl-2-((R)-1-methylazetidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

10 **[00683]** The title compound was obtained crude, from Intermediate 27 and Intermediate 42, following a similar 2 step procedure to that described in the synthesis of Intermediate 37.

LCMS m/z = 935 $[M+H]^+$

Steps 3 and 4: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-cyclopropyl-1H-indazol-4-yl)-4-fluoro-9-methyl-2-((R)-1-methylazetidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine formate

15

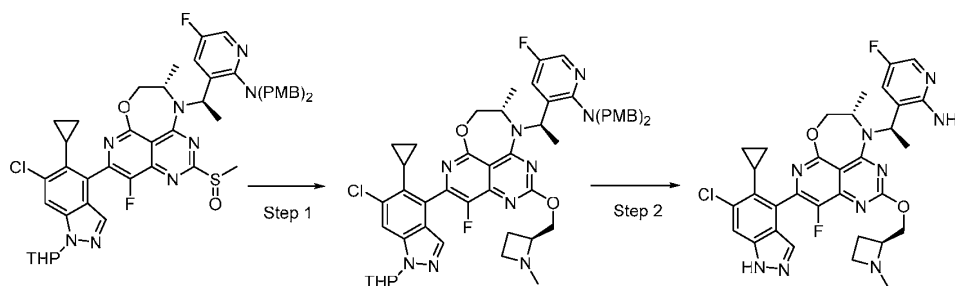
[00684] The title compound was obtained as a white solid, 1.8 mg, 16.9%, from the compound from step 2 and ((2R)-1-methylazetidin-2-yl)methanol, following a similar procedure to that described in Example 141. The crude product was purified by Prep-HPLC (Method D, Gradient: 7% B to 37% B in 7 min) to afford the title compound (1.8 mg, 16.9%) as

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a white solid. LCMS m/z = 648 $[M+H]^+$ 1H NMR (400 MHz, $DMSO-d_6$) δ 13.26 (d, 1H), 8.00 (d, 1H), 7.84 – 7.60 (m, 3H), 6.56 (dd, 1H), 5.64 (d, 2H), 4.56 (ddd, 1H), 4.51 – 4.43 (m, 2H),

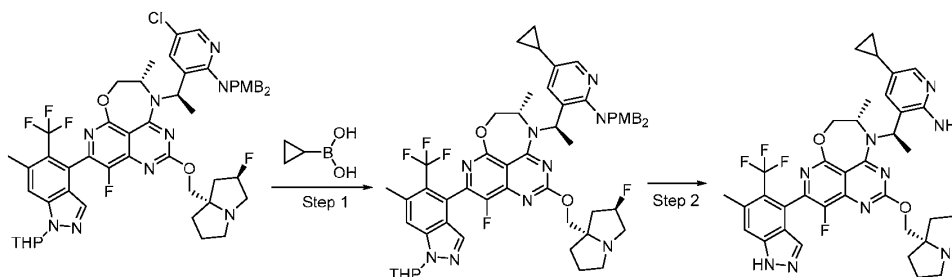
4.39 (td, 1H), 4.12 (d, 1H), 2.91 (d, 1H), 2.35 (s, 5H), 2.12 – 1.96 (m, 2H), 1.94 – 1.83 (m, 1H), 1.63 (dd, 3H), 0.95 – 0.74 (m, 2H), 0.64 (dd, 3H), 0.26 – 0.06 (m, 2H).

Example 144: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-cyclopropyl-1H-indazol-4-yl)-4-fluoro-9-methyl-2-(((S)-1-methylazetidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine formate (Compound 347)



[00685] The title compound was obtained as a white solid, 7.6 mg, from the compound from step 2 of Example 143 and ((2S)-1-methylazetidin-2-yl)methanol, following a similar procedure to that described in Example 141. The crude product was purified by HPLC (Method D, Gradient (B%): 12% B to 30% B in 8 min). LCMS m/z = 648 $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.25 (d, 1H), 8.00 (d, 1H), 7.86 – 7.57 (m, 3H), 6.64 – 6.40 (m, 1H), 5.61 (d, 2H), 4.47 (dddd, 4H), 4.10 (d, 1H), 2.83 – 2.62 (m, 1H), 2.28 (s, 3H), 1.96 (ddd, 4H), 1.68 – 1.55 (m, 3H), 0.95 – 0.72 (m, 2H), 0.64 (dd, 4H), 0.28 – 0.03 (m, 2H).

Example 145: Synthesis of 5-cyclopropyl-3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 346)



Step 1: 5-cyclopropyl-3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-

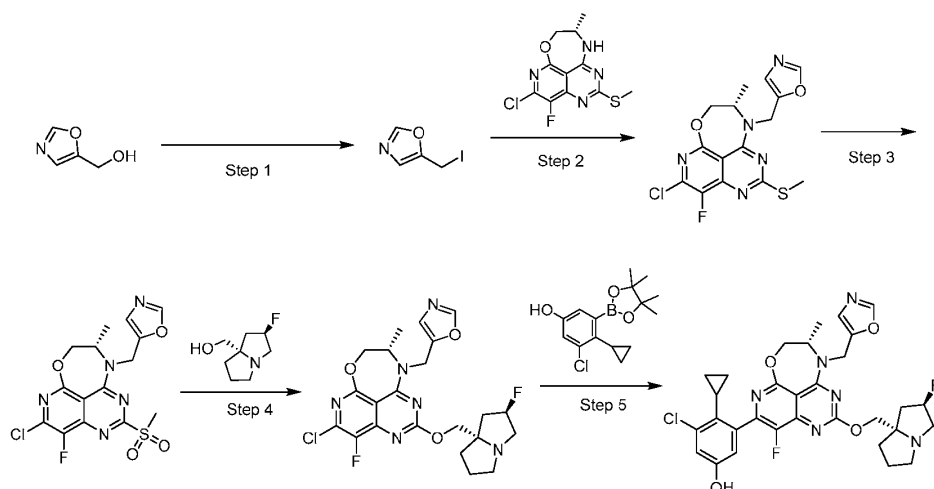
1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine trifluoroacetate

- 5 **[00686]** A mixture of the compound from step 1 of Example 121 (2 g, 1.9 mmol), cyclopropylboronic acid (1.6 g, 19 mmol), K₂CO₃ (790 mg, 5.7 mmol) and Pd(dtbpf)Cl₂ (248 mg, 0.38 mmol) in dioxane/H₂O (20 mL, V/V=5:1) was stirred at 100°C for 3 h under N₂. The reaction was quenched with ice-water at 0°C and the aqueous layer was extracted with DCM (3x100 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by reverse phase column chromatography (Column: C18 ; Mobile Phase A: Water (0.1% TFA), Mobile Phase B: ACN; Flow rate: 60 mL/min) to afford the title compound (1.3 g, 65%) as a yellow solid. LCMS m/z = 1060 [M+H]⁺
- 10

Step 2: 5-cyclopropyl-3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate

- 15 **[00687]** A solution of the compound from step 1 (300 mg, 0.28 mmol) in DCE (2 mL) and TFA (2 mL) was stirred at 80°C for 1 h under N₂. The cooled mixture was concentrated under reduced pressure and the crude product was purified by Prep-HPLC (Method D, Gradient (B%): 5% B to 27% B in 7 min) to afford the title compound (46.6 mg, 22.4%) as a white solid. LCMS m/z = 736 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.55 (d, 1H), 10.89 (s, 1H),
- 20 7.86 (d, 1H), 7.73 (d, 1H), 7.66 (s, 1H), 7.48 (s, 1H), 6.54 (q, 1H), 5.79 (s, 2H), 5.71 – 5.47 (m, 1H), 4.69 (d, 1H), 4.65 – 4.48 (m, 2H), 4.33 (dd, 1H), 4.14 (p, 1H), 3.91 – 3.65 (m, 3H), 2.64 (dt, 3H), 2.39 – 2.30 (m, 3H), 2.25 – 1.99 (m, 3H), 1.88 (tt, 1H), 1.71 – 1.55 (m, 3H), 0.92 (dd, 2H), 0.80 – 0.66 (m, 2H), 0.61 (dd, 3H).

- Example 146: Synthesis of 3-chloro-4-cyclopropyl-5-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-10-(oxazol-5-ylmethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol formate (Compound 311)**
- 25



Step 1: Synthesis of 5-(iodomethyl)oxazole

[00688] To a solution of oxazol-5-ylmethanol (1.00 g, 10.1 mmol), PPh₃ (3.97 g, 15.1 mmol) and imidazole (1.03 g, 15.1 mmol) in DCM (10 mL) was added I₂ (3.84 g, 15.1 mmol) at 0 °C under N₂ and the reaction was stirred at rt for 12 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (SiO₂, PE/EtOAc=1/0 to 1/1) to give the title compound (1.5 g, 67%) as a yellow oil. ¹H NMR (400 MHz, DMSO-d₆) δ = 8.40 (s, 1H), 7.20 (s, 1H), 4.66 (s, 2H).

Step 2: Synthesis of (S)-5-chloro-4-fluoro-9-methyl-2-(methylthio)-10-(oxazol-5-ylmethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00689] To a solution of Intermediate 32 (1.0 g, 3.33 mmol) in DMF (20 mL) was added Cs₂CO₃ (3.25 g, 9.98 mmol) and the compound from step 1 (1.04 g, 4.99 mmol) and the reaction mixture was stirred at 60°C for 2 h. The reaction mixture was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine (50 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (1.0 g, crude) as a yellow solid. LCMS m/z = 382 [M+H]⁺

Step 3: Synthesis of (S)-5-chloro-4-fluoro-9-methyl-2-(methylsulfonyl)-10-(oxazol-5-ylmethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00690] To a solution of the compound from step 2 (500 mg, 1.31 mmol) in THF (10 mL) and H₂O (5 mL) was added oxone (4.03 g, 6.55 mmol) and the reaction mixture was stirred at rt for 1 h. The reaction mixture was filtered and the filtrate was quenched with sat. Na₂SO₃ solution (20 mL) at 0°C. The solution was diluted with H₂O (20 mL) and extracted with EtOAc (40 mL x 2). The combined organic layers were washed with brine (40 mL x 2), dried over

Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (450 mg, crude) as a yellow solid. LCMS m/z = 414 [M+H]⁺

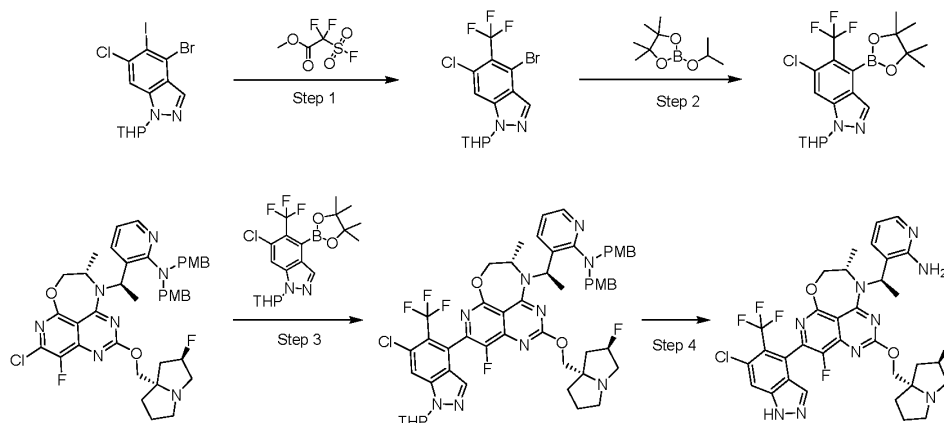
Step 4: Synthesis of (S)-5-chloro-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-10-(oxazol-5-ylmethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene

[00691] To a solution of the compound from step 3 (450 mg, 1.09 mmol) and [(2R,8S)-2-fluoro-1,2,3,5,6,7-hexahydropyrrolizin-8-yl]methanol (346 mg, 2.17 mmol) in THF (10 mL) was added 4Å molecular sieves (0.5 g) and LiOtBu (2.2 M in THF, 741 µL) under N₂ at 0 °C and the reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with H₂O (30 mL) and extracted with EtAOc (40 mL x 2). The combined organic layers were washed with brine (40 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reverse-phase HPLC and then re-purified by prep-HPLC (Method PL, gradient: 6%-36% B over 10 min) to give the title compound (180 mg, 33%) as a white solid. LCMS m/z = 493 [M+H]⁺

Step 5: Synthesis of 3-chloro-4-cyclopropyl-5-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-10-(oxazol-5-ylmethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol formate

[00692] A mixture of the compound from step 4 (50 mg, 101 µmol), Intermediate 20 (59.8 mg, 203 µmol), cataCXium A Pd G3 (7.39 mg, 10.1 µmol) and Cs₂CO₃ (66.1 mg, 203 µmol) in dioxane (2 mL) and H₂O (0.5 mL) was degassed and purged with N₂ for 5 min, and then the reaction was stirred at 100 °C for 1 h under N₂. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (20 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Method PL, gradient: 19%-49% B over 10 min) to give the title compound (4.85 mg, 7.5%) as an off-white solid. LCMS m/z = 625 [M+H]⁺ ¹H NMR (400 MHz, CD₃OD) δ = 8.20 (s, 1H), 7.26 (s, 1H), 6.95 (d, 1H), 6.77 (d, 1H), 5.45 - 5.26 (m, 2H), 5.06 (d, 1H), 4.66 (dd, 1H), 4.58 (s, 2H), 4.47 (d, 1H), 4.38 - 4.31 (m, 2H), 4.29 - 4.24 (m, 1H), 3.50 - 3.39 (m, 1H), 3.14 - 3.07 (m, 1H), 2.40 - 2.24 (m, 2H), 2.20 - 2.12 (m, 1H), 2.09 - 2.01 (m, 2H), 1.96 - 1.81 (m, 2H), 1.40 (d, 3H), 0.71 - 0.60 (m, 2H), 0.18 - 0.07 (m, 2H).

Example 147: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(trifluoromethyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 295)



Step 1: Synthesis of 4-bromo-6-chloro-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazole

[00693] A mixture of 4-bromo-6-chloro-5-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (1.37 g, 3.10 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (4.17 g, 21.7 mmol) and CuI (590 mg, 3.10 mmol) in DMF (15 mL) was degassed and purged with N₂ and the reaction mixture was stirred at 80°C for 16 h under N₂. The cooled mixture was poured into water (20 mL) and extracted with EtOAc (30 mL × 3). The organic layers were washed with brine (50 mL × 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by reverse-phase column chromatography and further purified by SFC (column: DAICEL Chiralcel OD (250mm×30mm,10um); mobile phase: [CO₂-i-PrOH(0.1%NH₃H₂O)];B%:10%, isocratic elution) to give the title compound (350 mg, 29%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1H), 7.70 (s, 1H), 5.69 - 5.52 (m, 1H), 3.93 - 3.90 (m, 1H), 3.76 - 3.55 (m, 1H), 2.47 - 2.28 (m, 1H), 2.13 - 1.92 (m, 2H), 1.79 - 1.59 (m, 3H)

Step 2: Synthesis of 6-chloro-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)indazole

[00694] To a solution of the compound from step 1 (350 mg, 0.91 mmol) in THF (5 mL) was added chloro(isopropyl)magnesium (2 M, 2.20 mL) dropwise at 0 °C and the mixture was stirred at rt for 0.5 h. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (848 mg, 4.56 mmol) was added at 0°C and the reaction mixture was stirred at rt for 13 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by reversed-phase column chromatography to give the title compound (160 mg, 40%) as a yellow solid. LCMS m/z = 431 [M+H]⁺

Step 3: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

- 5 **[00695]** A mixture of the compound from step 2 (140 mg, 0.325 mmol), Intermediate 39 (100 mg, 0.13 mmol), cataCXium® A Pd G3 (9.43 mg, 12.9 μ mol) and K₃PO₄ (82.4 mg, 0.388 mmol) in dioxane (1 mL) and H₂O (0.1 mL) was degassed and purged with N₂ and the reaction was stirred at 70 °C for 1 h under N₂. The reaction mixture was filtered and concentrated under reduced pressure. The crude product was purified by reverse-phase column chromatography to
10 give the title compound (25.0 mg, 18%) as a white solid. LCMS m/z = 1041 [M+H]⁺

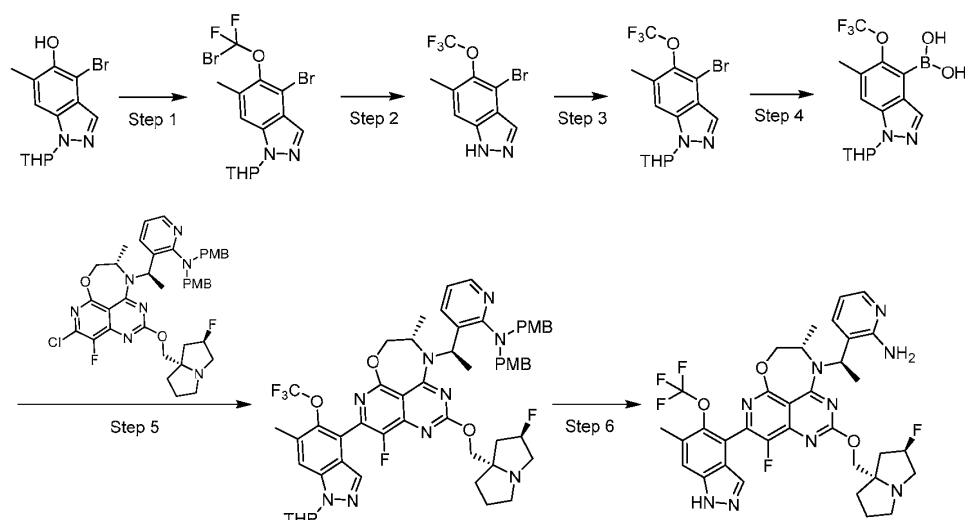
Step 4: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(trifluoromethyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate

- [00696]** A solution of the compound from step 3 (35.0 mg, 33.6 μ mol) in TFA (1 mL) and
15 TfOH (0.1 mL) was stirred at rt for 1 h. The reaction mixture was diluted with DCM (10 mL) and then poured into sat. NaHCO₃ solution (30 mL). The mixture was extracted with DCM (30 mL $\times$ 3), the combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (Method PL, gradient: 11%-41% B over 10 min) to give the title compound (16.86 mg, 65%) as an off-white gum. LCMS m/z =
20 716 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 13.82 (br s, 1H), 8.20 (s, 2H), 8.07 (d, 1H), 8.03 - 7.97 (m, 1H), 7.88 (s, 1H), 7.71 (d, 1H), 6.74 - 6.66 (m, 1H), 6.61 - 6.47 (m, 1H), 5.71 (s, 1H), 5.61 (s, 1H), 5.45 - 5.18 (m, 1H), 4.61 - 4.50 (m, 1H), 4.38 - 4.27 (m, 1H), 4.15 (s, 2H), 4.08 - 4.03 (m, 1H), 3.12 (d, 2H), 2.89 - 2.77 (m, 2H), 2.20 - 2.01 (m, 3H), 1.92 - 1.73 (m, 3H), 1.61 (d, 3H), 0.72 - 0.49 (m, 3H).

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Example 148: Synthesis of 3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethoxy)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 280)

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Step 1: Synthesis of 4-bromo-5-(bromodifluoromethoxy)-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

- [00697]** To a solution of Intermediate 43 (1.00 g, 3.21 mmol) in DMF (10 mL) was added NaH (257 mg, 6.43 mmol, 60% purity) in portions at 0°C and the mixture was stirred at 0°C for 0.5 h. Dibromo(difluoro)methane (2.02 g, 9.64 mmol) was added at 0°C and the reaction was stirred at rt for 2 h. The reaction mixture was quenched with saturated NH₄Cl solution (50 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL × 2), dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC (Method PL, gradient: 62%-92% B over 15 min) to give the title compound (500 mg, 35%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.04 (s, 1H), 7.44 (s, 1H), 5.70 (dd, 1H), 4.06 - 4.02 (m, 1H), 3.81 - 3.74 (m, 1H), 2.55 - 2.52 (m, 4H), 2.18 - 2.10 (m, 2H), 1.80 - 1.71 (m, 3H).

Step 2: Synthesis of 4-bromo-6-methyl-5-(trifluoromethoxy)-1H-indazole

- [00698]** To a solution of the compound from step 1 (350 mg, 0.80 mmol) in DCE (7 mL) was added AgBF₄ (774 mg, 3.98 mmol) at rt under N₂ and the mixture was stirred at 60°C for 2 h. The reaction mixture was quenched with ice water (20 mL), diluted with EtOAc (50 mL) and then filtered. The layers were separated and the aqueous layer was extracted with EtOAc (30 mL × 2). The combined organic layers were concentrated and the residue was purified by column chromatography (SiO₂, PE: EtOAc=1:0~4:1) to give the title compound (210 mg, 90%) as a yellow solid. LCMS m/z = 297 [M+H]⁺

Step 3: Synthesis of 4-bromo-6-methyl-1-(tetrahydropyran-2-yl)-5-(trifluoromethoxy)indazole

[00699] The title compound was obtained as a colorless oil, 280 mg, 73%, from the compound from step 2 and DHP, following a similar procedure to that described in Intermediate 43, step 2. LCMS m/z = 381 [M+H]⁺

Step 4: Synthesis of (6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethoxy)-1H-indazol-4-yl)boronic acid

[00700] A mixture of the compound from step 3 (50.0 mg, 0.132 mmol), tetrahydroxyboron (47.3 mg, 0.527 mmol), CataCXium A Pd G3 (9.60 mg, 13.2 μ mol) and TEA (40.0 mg, 0.396 mmol) in MeOH (1 mL) was degassed and purged with N₂, and the reaction mixture was stirred at rt for 1 h under N₂. The reaction mixture was evaporated under reduced pressure to give the title compound (50.0 mg, crude) as a brown solid. LCMS m/z = 345 [M+H]⁺

Step 5: Synthesis of 3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethoxy)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

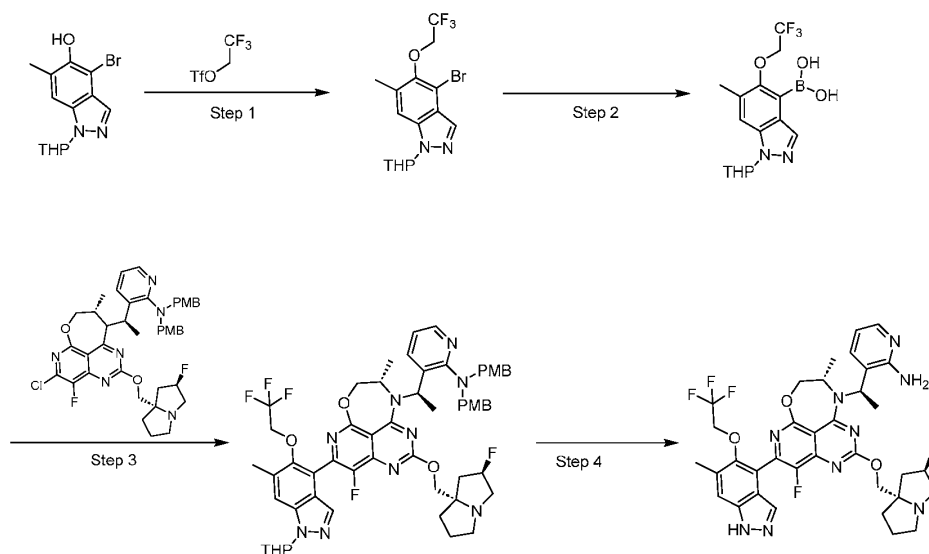
[00701] To a solution of the compound from step 4 (49.0 mg, 0.142 mmol), Intermediate 39 (100 mg, 0.129 mmol) and K₃PO₄ (82.5 mg, 0.388 mmol) in dioxane (2 mL) and H₂O (0.2 mL) was added CataCXium A Pd G3 (9.43 mg, 13.0 μ mol) and the reaction mixture was stirred at 70°C for 3 h under N₂. The reaction mixture was diluted with water (4 mL) and extracted with EtOAc (6 mL $\times$ 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC (Method PL, gradient:25%-55% B over 10 min) to give the title compound (30.0 mg, 22%) as a white solid. LCMS m/z = 1037 [M+H]⁺

Step 6: Synthesis of 3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethoxy)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate

[00702] A solution of the compound from step 5 (25.0 mg, 24.1 μ mol) in TfOH (84.8 mg, 565 μ mol) and TFA (0.5 mL) was stirred at rt for 1 h. The reaction mixture was diluted with DCM (10 mL) and then adjusted to pH 7~8 with saturated NaHCO₃ solution. The solution was extracted with DCM (10 mL $\times$ 2) and the combined organic layers were concentrated *in vacuo*. The residue was purified by prep-HPLC (Method PL, gradient:5%-35% B over 10 min) to give the title compound (11.61 mg, 63%) as an off-white solid. LCMS m/z = 712 [M+H]⁺ 1H NMR (400 MHz, DMSO-*d*₆) δ 13.37 (s, 1H), 8.15 (s, 1H), 8.01 - 7.99 (m, 1H), 7.89 (s, 1H), 7.73 - 7.69 (m, 2H), 6.72 - 6.69 (m, 1H), 6.57 - 6.52 (m, 1H), 5.64 (s, 2H), 5.37 - 5.24 (m, 1H), 4.59 -

4.54 (m, 1H), 4.36 (d, 1H), 4.18 (s, 2H), 4.09 - 4.03 (m, 1H), 3.15 - 3.05 (m, 3H), 2.88 - 2.85 (m, 1H), 2.49 (s, 3H), 2.20 - 2.06 (m, 3H), 1.89 - 1.81 (m, 3H), 1.62 (d, 3H), 0.58 (d, 3H).

Example 149: Synthesis of 3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(2,2,2-trifluoroethoxy)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 315)



Step 1: Synthesis of 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(2,2,2-trifluoroethoxy)-1H-indazole

[00703] To a solution of Intermediate 43 (250 mg, 0.803 mmol) and K_2CO_3 (222 mg, 1.61 mmol) in DMF (5 mL) was added 2,2,2-trifluoroethyl trifluoromethanesulfonate (280 mg, 1.21 mmol) and the reaction was stirred at rt for 2 h. The reaction mixture was poured into ice-water (20 mL), extracted with EtOAc (30 mL $\times$ 2) and the combined organic layers were concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2 , PE: EtOAc=1: 0 ~ 10: 1) to give the title compound (250 mg, 79%) as a pale yellow solid. LCMS m/z = 395 $[M+H]^+$

Step 2: Synthesis of (6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(2,2,2-trifluoroethoxy)-1H-indazol-4-yl)boronic acid

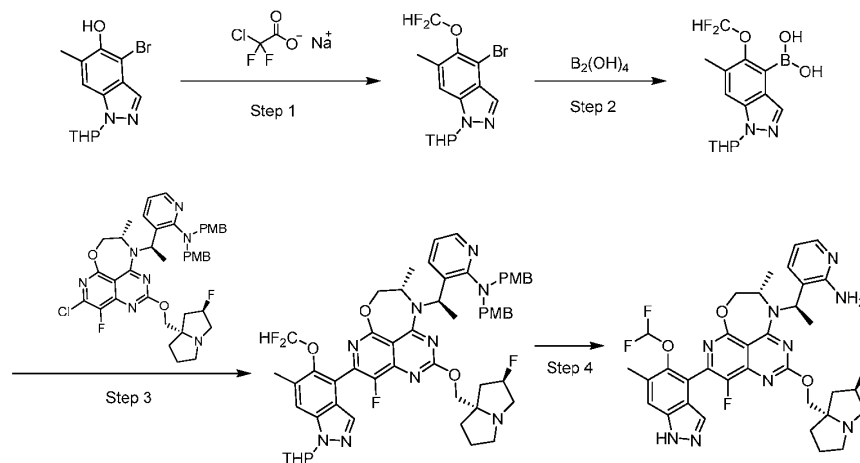
[00704] To a solution of the compound from step 1 (230 mg, 585 μ mol), TEA (237 mg, 2.34 mmol) and tetrahydroxydiboron (210 mg, 2.34 mmol) in MeOH (4 mL) was added CataCXium A Pd G3 (42.6 mg, 58.5 μ mol) under N_2 and the reaction was stirred at 50°C for 1 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was

purified by reverse-phase HPLC and then re-purified by Prep-HPLC (Method PL, gradient: 34%-64% B over 10 min) to give the title compound (150 mg, 72%) as a white solid. LCMS $m/z = 359$ $[M+H]^+$

Steps 3 and 4: Synthesis of 3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(2,2,2-trifluoroethoxy)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00705] The title compound was obtained as a white solid, 21.3 mg, 55%, from the compound from step 2 and Intermediate 39, following a similar procedure to that described in steps 5 and 6 of Example 148. LCMS $m/z = 726$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.14 (s, 1H), 8.19 (s, 1H), 8.00 (dd, 1H), 7.75 (s, 1H), 7.71 (d, 1H), 7.55 (s, 1H), 6.72 - 6.69 (m, 1H), 6.57 - 6.52 (m, 1H), 5.66 (s, 2H), 5.37 - 5.23 (m, 1H), 4.59 - 4.54 (m, 1H), 4.40 (q, 2H), 4.32 (d, 1H), 4.17 (s, 2H), 4.07 - 4.03 (m, 1H), 3.13 - 3.09 (m, 3H), 2.87 - 2.81 (m, 1H), 2.45 (s, 3H), 2.20 - 2.05 (m, 3H), 1.87 - 1.80 (m, 3H), 1.62 (d, 3H), 0.58 (d, 3H).

Example 150: Synthesis of 3-((1R)-1-((9S)-5-(5-(difluoromethoxy)-6-methyl-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 281)



Step 1: Synthesis of 4-bromo-5-(difluoromethoxy)-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

[00706] To a solution of Intermediate 43 (200 mg, 0.642 mmol) in DMF (10 mL) and H_2O (2 mL) was added Cs_2CO_3 (418 mg, 1.29 mmol) and sodium chlorodifluoroacetate (293 mg, 1.93

mmol) and the reaction mixture was stirred at 80°C for 2 h. The reaction was poured into saturated NH₄Cl solution (30 mL) and extracted with EtOAc (30 mL × 3). The organic layers were washed with brine (100 mL × 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE/EtOAc=1/0 to 10/1) to give the title compound (22.0 mg, 9.5%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.01 (s, 1H), 7.43 (s, 1H), 6.58 (t, 1H), 5.69 (dd, 1H), 4.09 - 3.94 (m, 1H), 3.87 - 3.63 (m, 1H), 2.66 - 2.44 (m, 4H), 2.24 - 2.02 (m, 2H), 1.88 - 1.66 (m, 3H)

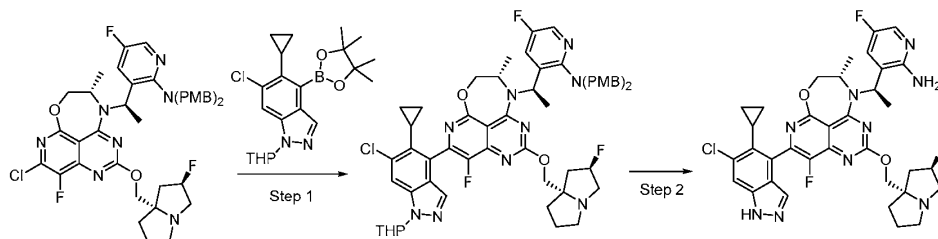
Step 2: Synthesis of (5-(difluoromethoxy)-6-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)boronic acid

- 10 **[00707]** The title compound was obtained as a solid, 90 mg, crude, from the compound from step 1 and tetrahydroxydiboron, following the procedure described in Example 148, step 4. LCMS m/z = 327 [M+H]⁺

Steps 3 and 4: Synthesis of 3-((1R)-1-((9S)-5-(5-(difluoromethoxy)-6-methyl-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate

- 15 **[00708]** The title compound was obtained as a solid, 31.8 mg, from the compounds from step 2 and Intermediate 39, following a similar procedure to that described in Example 147, steps 3 and 4. The crude was purified by prep-HPLC (Method PL, gradient: 7%-37% B over 10 min). LCMS m/z = 694 [M+H]⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 13.30 (s, 1H), 8.05 - 7.98 (m, 1H), 7.82 (s, 1H), 7.73 (d, 1H), 7.63 (s, 1H), 7.01 - 6.60 (m, 2H), 6.59 - 6.48 (m, 1H), 5.77 - 5.64 (m, 2H), 5.64 - 5.39 (m, 1H), 4.78 - 4.38 (m, 3H), 4.34 (d, 1H), 4.15 - 4.02 (m, 1H), 3.96 - 3.39 (m, 3H), 3.26 - 3.09 (m, 1H), 2.44 (s, 3H), 2.43 - 2.21 (m, 3H), 2.21 - 1.89 (m, 3H), 1.62 (d, 3H), 0.60 (d, 3H).

- 25 **Example 151: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-cyclopropyl-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine (Compound 401)**



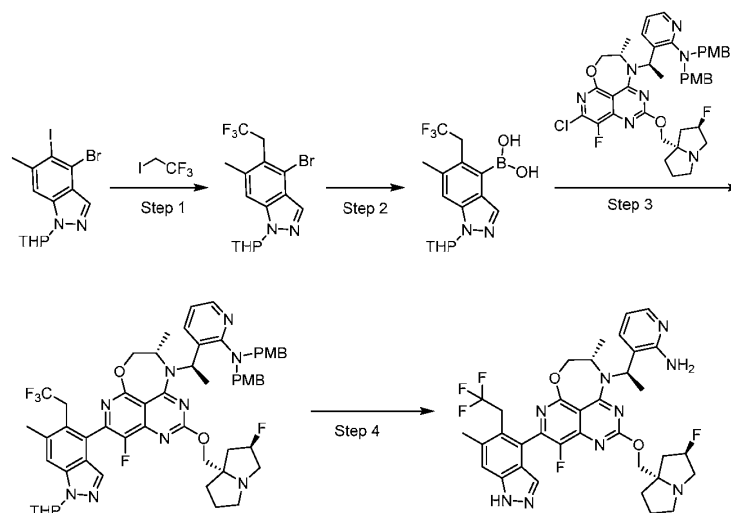
Step 1: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00709] To a mixture of the compound from Example 120, step 1 (0.1 g, 0.127 mmol) and Intermediate 42 (101.9 mg, 0.253 mmol) in dioxane (2.5 mL), H₂O (1 mL) was added XantPhos Pd G3 (6.00 mg, 6.33 μ mol), K₃PO₄ (80.58 mg, 0.38 mmol) under N₂ and the mixture was stirred at 100°C for 1 h. The reaction was filtered, the filtrate was diluted with water (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Column, Eluent of 0~20%THF/DCM @ 100 mL/min) to give the title compound (1.78 g, 35%) as a yellow solid. LCMS m/z = 1030 [M+H]⁺

Step 2: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-cyclopropyl-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine

[00710] To a solution of the compound from step 1 (1.75 g, 1.39 mmol) in TFA (17 mL) was added TFOH (5 mL) and the mixture was stirred at rt for 0.5 h. The reaction mixture was concentrated under reduced pressure, the residue was diluted with H₂O (50 mL), the pH adjusted to 8 using saturated NaHCO₃ solution, and the mixture extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: 55-Boston Prime C18 150×30mm, 5 μ m; mobile phase: [04-Water(0.05%NH₃H₂O)-01-MeCN]; gradient: 45%-65% B over 11.0 min) to give the title compound, 500.3 mg, 50.9% as a white solid. LCMS m/z = 706 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.25 (br d, 1 H) 8.01 (d, 1 H) 7.61 - 7.87 (m, 3 H) 6.54 (br t, 1 H) 5.66 (br d, 2 H) 5.15 - 5.45 (m, 1 H) 4.49 - 4.72 (m, 1 H) 4.38 (br dd, 1 H) 4.03 - 4.25 (m, 3 H) 2.97 - 3.20 (m, 3 H) 2.69 - 2.91 (m, 1 H) 1.76 - 2.25 (m, 7 H) 1.63 (br d, 3 H) 0.94 (s, 1H) 0.57 - 0.72 (m, 4 H) -0.06 - 0.29 (m, 2 H)

Example 152: Synthesis of 3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(2,2,2-trifluoroethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 279)



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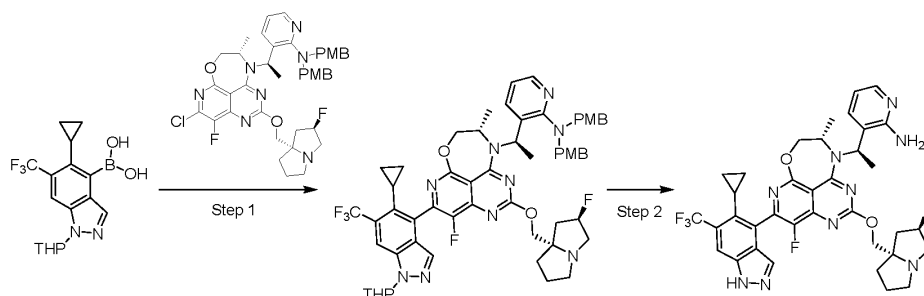
Step 1: Synthesis of 4-bromo-6-methyl-1-tetrahydropyran-2-yl-5-(2,2,2-trifluoroethyl)indazole

[00711] A mixture of 4-bromo-5-iodo-6-methyl-1-tetrahydropyran-2-yl-indazole (900 mg, 2.13 mmol), 1,1,1-trifluoro-2-iodoethane (1.34 g, 6.41 mmol), diiodonickel (66.7 mg, 0.213 mmol), dppf (118 mg, 0.213 mmol), manganese powder (411 mg, 74.8 mmol) and dtbbpy (57.3 mg, 0.213 mmol) in DMA (18 mL) was degassed and purged with N₂ and the reaction mixture was stirred at 80°C for 16 h under N₂. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (30 mL × 3). The organic layers were washed with brine (50 mL × 3), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Method PL, gradient: 52%-82% B over 18 min) and further purified by SFC (column: DAICEL CHIRALPAK AD (250mm*50mm, 10μm); mobile phase: [CO₂-i-PrOH(0.1% NH₃·H₂O)]; B%: 15%, isocratic elution) to give the title compound (120 mg, 14%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 8.08 (s, 1H), 7.50 (s, 1H), 5.75 (q, 1H), 4.10 (d, 1H), 3.95 - 3.79 (m, 3H), 2.77 - 2.49 (m, 4H), 2.32 - 2.20 (m, 1H), 2.20 - 2.11 (m, 1H), 1.91 - 1.80 (m, 2H), 1.80 - 1.71 (m, 1H).

Steps 2 to 4: Synthesis of 3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(2,2,2-trifluoroethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate

[00712] The title compound was obtained as a gray gum, 38.5 mg, from the compounds from step 1 and Intermediate 39, following a similar procedure to that described in Example 149, steps 2, 3 and 4. The crude was purified by prep-HPLC (Method PL, gradient: 8%-38% B over 10 min). LCMS m/z = 710 $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.35 - 13.11 (m, 1H), 11.71 - 11.20 (m, 1H), 8.23 - 7.95 (m, 2H), 7.65 (s, 1H), 7.58 (s, 1H), 7.52 - 7.04 (m, 1H), 7.03 - 6.86 (m, 1H), 6.67 - 6.52 (m, 1H), 5.73 - 5.49 (m, 1H), 4.83 - 4.51 (m, 3H), 4.49 - 4.29 (m, 1H), 4.26 - 3.95 (m, 2H), 3.92 - 3.60 (m, 5H), 2.77 - 2.60 (m, 1H), 2.55 (d, 4H), 2.42 - 2.30 (m, 1H), 2.28 - 2.12 (m, 2H), 2.11 - 1.99 (m, 1H), 1.67 (s, 3H), 0.66 (d, 3H).

Example 153: Synthesis of 3-((1R)-1-((9S)-5-(5-cyclopropyl-6-(trifluoromethyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 278)



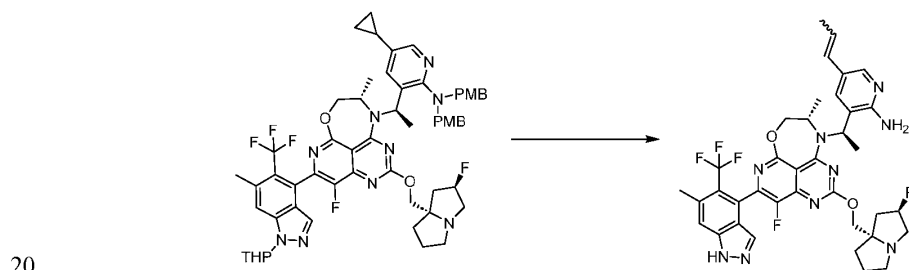
Step 1: Synthesis of 3-((1R)-1-((9S)-5-(5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-6-(trifluoromethyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00713] A mixture of Intermediate 44 (40.0 mg, 0.112 mmol), Intermediate 39 (87.2 mg, 0.112 mmol), K_3PO_4 (71.9 mg, 0.338 mmol) and CataCXium A Pd G3 (8.23 mg, 11.3 μ mol) in dioxane (1 mL) and H_2O (0.1 mL) was degassed and purged with N_2 and the reaction mixture was stirred at 70°C for 1 h under N_2 . The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL $\times$ 3). The combined organic phase was dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the title compound (100 mg, 85%) as a yellow solid. LCMS m/z = 1047 $[M+H]^+$

Step 2: Synthesis of 3-((1R)-1-((9S)-5-(5-cyclopropyl-6-(trifluoromethyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate

- 5 **[00714]** To a solution of the compound from step 1 (100 mg, 95.5 μ mol) in TFA (2 mL) was added TfOH (339 mg, 2.26 mmol) and the reaction mixture was stirred at rt for 1 h. The reaction was diluted with DCM (10 mL) and then adjusted to pH 8~9 with saturated NaHCO₃ solution at 0 °C. The mixture was extracted with DCM (10 mL $\times$ 2) and the combined organic layers were concentrated *in vacuo*. The residue was purified by prep-HPLC (Method PL, gradient: 10%-40% B over 10 min) to give the title compound (17.8 mg, 26%) as a white solid.
- 10 LCMS m/z = 722 [M+H]⁺ 1H NMR (400 MHz, DMSO- d_6) δ 13.60 (br s, 1H), 8.24 (s, 1H), 8.05 (d, 1H), 8.00 (d, 1H), 7.93 - 7.80 (m, 1H), 7.71 (d, 1H), 6.74 - 6.67 (m, 1H), 6.55 (t, 1H), 5.67 (s, 2H), 5.43 - 5.17 (m, 1H), 4.67 - 4.50 (m, 1H), 4.41 - 4.31 (m, 1H), 4.18 - 4.11 (m, 2H), 4.09 - 4.03 (m, 1H), 3.15 - 3.08 (m, 2H), 3.02 (s, 1H), 2.88 - 2.77 (m, 1H), 2.21 - 2.14 (m, 1H),
- 15 2.13 - 1.97 (m, 3H), 1.92 - 1.75 (m, 3H), 1.62 (d, 3H), 0.90 - 0.50 (m, 5H), 0.35 - 0.02 (m, 2H).

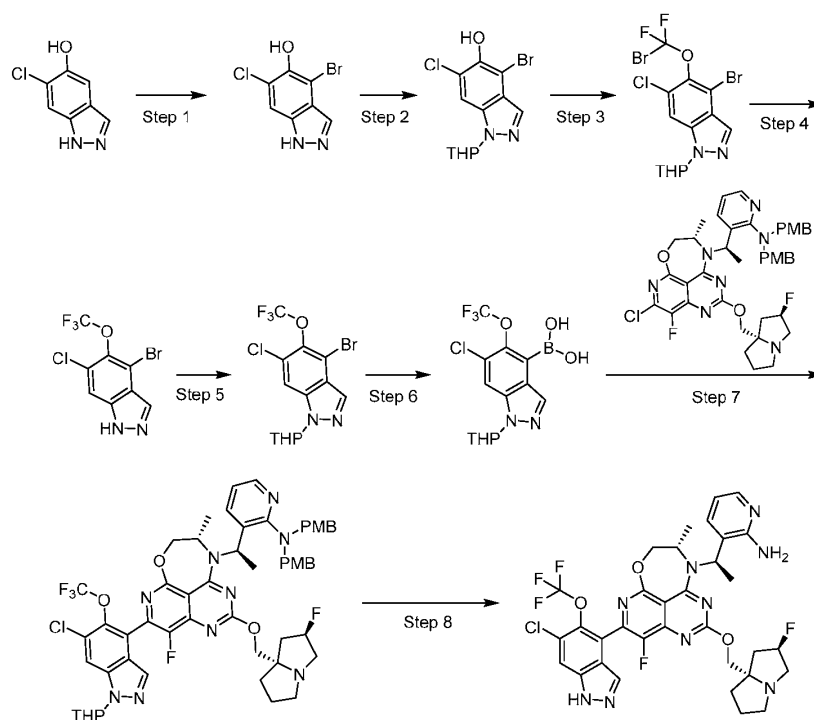
Example 154: Synthesis of 3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-(prop-1-en-1-yl)pyridin-2-amine formate (Compound 398)



- [00715]** The title compound was obtained as a gray solid, 12.2 mg, 53%, from the compound from step 1 of Example 145, following a similar procedure to that described in Example 153, step 2. The crude product was purified by prep-HPLC (Method PL, gradient: 12%-42% B over 10 min). LCMS m/z = 736 [M+H]⁺ 1H NMR (400 MHz, DMSO- d_6) δ 13.52 (br s, 1H), 8.27 (s, 2H), 7.96 (d, 1H), 7.79 (br s, 1H), 7.73 (s, 1H), 7.70 (br s, 1H), 6.60 - 6.48 (m, 1H), 6.37 - 6.29 (m, 1H), 6.27 - 6.14 (m, 1H), 5.74 (s, 1H), 5.66 (s, 1H), 5.39 - 5.18 (m, 1H), 4.60 - 4.49 (m, 1H), 4.39 - 4.26 (m, 1H), 4.12 - 4.05 (m, 1H), 3.96 - 3.80 (m, 1H), 3.12 - 3.04 (m, 3H), 2.87 -
- 25

2.79 (m, 1H), 2.64 (br d, 3H), 2.20 - 2.12 (m, 1H), 2.11 - 2.05 (m, 1H), 2.04 - 1.97 (m, 1H), 1.85 (br d, 4H), 1.81 - 1.71 (m, 2H), 1.64 (d, 3H), 0.66 - 0.51 (m, 3H).

Example 155: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(trifluoromethoxy)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate (Compound 432)



[00716] Step 1: Synthesis of 4-bromo-6-chloro-1H-indazol-5-ol

[00717] To a solution of 6-chloro-1H-indazol-5-ol (5.00 g, 29.6 mmol) in THF (50 mL) was added NBS (5.81 g, 32.6 mmol) slowly at 0°C and the reaction was stirred at rt for 14 h. The reaction mixture was poured into water (30 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (7.3 g, crude) as a red solid. LCMS m/z = 247, 249 [M+H]⁺

Step 2: Synthesis of 4-bromo-6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-ol

[00718] To a solution of the compound of step 1 (7.30 g, 29.5 mmol) in DMF (50 mL) was added DHP (4.96 g, 59.0 mmol) and TsOH (507 mg, 2.95 mmol) and the reaction mixture was stirred at rt for 16 h. The reaction mixture was poured into water (20 mL) and extracted with

EtOAc (20 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE/EtOAc=1/0 to 10/1) to give the title compound (9.70 g) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 7.92 (s, 1H), 7.66 (s, 1H), 5.65 (dd, 1H), 4.07 - 3.94 (m, 1H), 3.83 - 3.67 (m, 1H), 2.61 - 2.40 (m, 1H), 2.25 - 2.14 (m, 1H), 1.90 - 1.63 (m, 5H).

Step 3: Synthesis of 4-bromo-5-(bromodifluoromethoxy)-6-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

[00719] To a solution of the compound from step 2 (2.00 g, 6.03 mmol) in DMF (20 mL) was added NaH (482 mg, 12.0 mmol, 60% purity) in portions at 0°C. The resulting solution was stirred at 0°C for 0.5 h, then dibromo(difluoro)methane (3.80 g, 18.0 mmol) was added and the reaction was stirred at rt for 3 h. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (60 mL × 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, PE/EtOAc=1/0 to 10/1) to give the title compound (1.50 g, 54%) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.09 (s, 1H), 7.77 (s, 1H), 5.83 - 5.60 (m, 1H), 4.04 (d, 1H), 3.86 - 3.69 (m, 1H), 2.59 - 2.41 (m, 1H), 2.27 - 2.06 (m, 2H), 1.83 - 1.70 (m, 3H).

Step 4: Synthesis of 4-bromo-6-chloro-5-(trifluoromethoxy)-1H-indazole

[00720] To a solution of the compound from step 3 (1.50 g, 3.26 mmol) in DCE (15 mL) was added AgBF₄ (2.70 g, 13.8 mmol) and the reaction mixture was stirred at 60°C for 2 h. The reaction mixture was quenched with ice water (2 mL), diluted with EtOAc (5 mL), then filtered. The filtrate was separated, the aqueous layer was extracted with EtOAc (5 mL × 2) and the combined organic layers were concentrated. The residue was purified by reverse-phase flash column to give the title compound (780 mg, 76%) as a black solid. ¹H NMR (400 MHz, CDCl₃) δ 8.09 (s, 1H), 7.56 (s, 1H).

Step 5: Synthesis of 4-bromo-6-chloro-5-(trifluoromethoxy)-1H-indazole

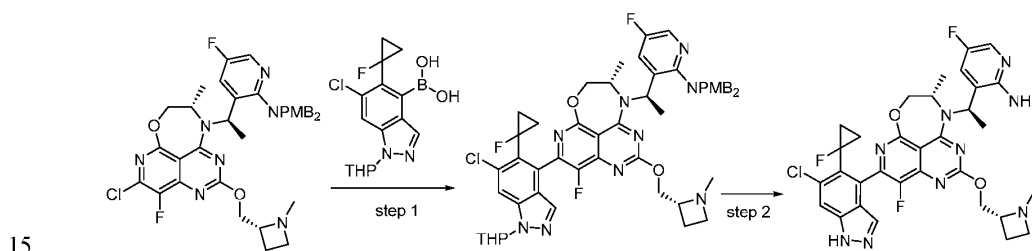
[00721] The title compound was obtained as a white solid, 250 mg, 28%, from the compound from step 4 and DHP following a similar procedure to that described in step 2. ¹H NMR (400 MHz, CDCl₃) δ 8.08 (s, 1H), 7.77 (s, 1H), 5.79 - 5.60 (m, 1H), 4.09 - 3.96 (m, 1H), 3.86 - 3.69 (m, 1H), 2.59 - 2.41 (m, 1H), 2.25 - 2.06 (m, 2H), 1.94 - 1.69 (m, 3H).

Steps 6 to 8: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(trifluoromethoxy)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-

dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine formate

[00722] The title compound was obtained as a yellow solid, 24.7 mg, from the compound from step 5 and Intermediate 39, following a similar procedure to that described in Example 149, steps 2, 3 and 4. The crude was purified by prep-HPLC (Method PL, gradient: 9%-39% B over 10.0 min). LCMS $m/z = 732$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.77 (br s, 1H), 8.26 (s, 2H), 8.06 (s, 1H), 8.02 - 7.95 (m, 2H), 7.71 (d, 1H), 6.73 - 6.67 (m, 1H), 6.58 - 6.46 (m, 1H), 5.61 (s, 2H), 5.29 (d, 1H), 4.64 - 4.52 (m, 1H), 4.36 (d, 1H), 4.17 (s, 2H), 4.07 - 4.00 (m, 1H), 3.13 - 3.07 (m, 2H), 3.03 (s, 1H), 2.87 - 2.80 (m, 1H), 2.22 - 2.13 (m, 1H), 2.10 - 2.00 (m, 2H), 1.87 - 1.71 (m, 3H), 1.62 (d, 3H), 0.58 (d, 3H).

Example 156: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(1-fluorocyclopropyl)-1H-indazol-4-yl)-4-fluoro-9-methyl-2-(((R)-1-methylazetidin-2-yl)methoxy))-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine formate (Compound 345)



Step 1: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(1-fluorocyclopropyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-4-fluoro-9-methyl-2-(((R)-1-methylazetidin-2-yl)methoxy))-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

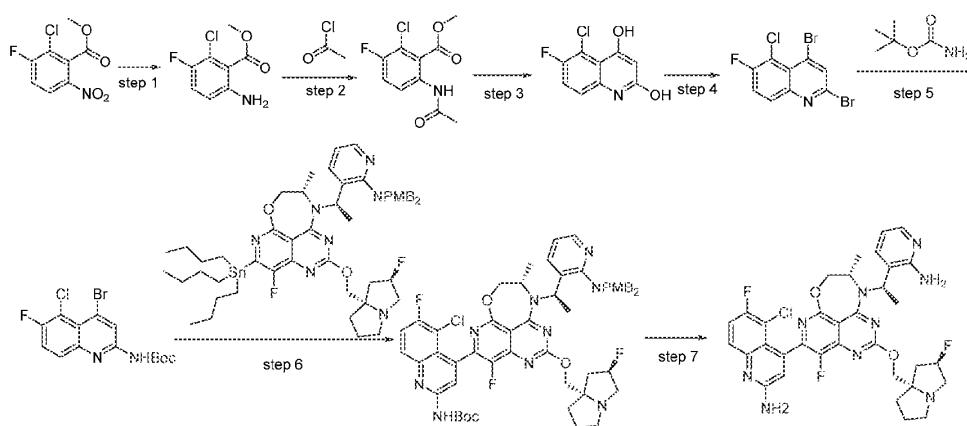
20 **[00723]** The title compound was obtained as a yellow solid, 10 mg, 22.8%, from Intermediate 41 and Intermediate 46, following a similar procedure to that described in Example 122, step 1. LCMS $m/z = 990$ $[M+H]^+$

Step 2: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(1-fluorocyclopropyl)-1H-indazol-4-yl)-4-fluoro-9-methyl-2-(((R)-1-methylazetidin-2-yl)methoxy))-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine formate

[00724] A solution of the compound from step 1 (10 mg, 0.010 mmol) in TFA (1 mL) was stirred at 60°C for 1 h. The mixture was allowed to cool to rt and concentrated under reduced pressure. The crude product was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD

Column 19*250 mm, 5 μ m; Mobile Phase A: Water (0.1%FA), Mobile Phase B: MeOH; Flow rate: 25 mL/min; Gradient (B%): 27% B to 50% B in 10min) to afford the title compound (1.5 mg, 20.9%) as a white solid. LCMS m/z = 666 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 13.49 - 13.41 (d, 1H), 8.00 (d, 1H), 7.90 (d, 1H), 7.84 (d, 1H), 7.70 - 7.65 (dd, 1H), 6.55 - 6.53 (m, 1H), 5.64 (d, 2H), 4.55 - 4.51 (m, 1H), 4.45 - 4.31 (m, 3H), 4.12 (t, 1H), 2.81 - 2.79 (m, 1H), 2.29 (s, 3H), 2.04 - 1.96 (m, 2H), 1.66 - 1.60 (m, 3H), 1.24 (s, 1H), 1.22 - 1.11 (m, 3H), 0.85 - 0.41 (m, 5H).

Example 157: Synthesis of 4-((S)-10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-6-fluoroquinolin-2-amine trifluoroacetate (Compound 396)



Step 1: Synthesis of methyl 6-amino-2-chloro-3-fluorobenzoate

[00725] A mixture of methyl 2-chloro-3-fluoro-6-nitrobenzoate (1 g, 4.28 mmol) and Pd/C (2.25 g, 21.40 mmol) in EtOAc (20 mL) was stirred at rt for 1 h under H₂. The resulting mixture was filtered and the filter cake was washed with EtOAc (3x10 mL). The filtrate was concentrated under reduced pressure to give the title compound, 700 mg, crude. LCMS m/z = 204 [M+H]⁺

Step 2: Synthesis of methyl 2-chloro-6-acetamido-3-fluorobenzoate

[00726] NaH (247.52 mg, 10.32 mmol) was added to a solution of the compound from step 1 (700 mg, 3.44 mmol) in THF (5 mL) at 0 °C and the mixture stirred for 30 min. Acetyl chloride (404.82 mg, 5.16 mmol) was added dropwise at 0 °C and the resulting mixture was stirred at rt for 1 h. The reaction was quenched with ice water and the mixture was concentrated under reduced pressure. The crude product was purified by reverse phase column chromatography

(C18 Column, 30*150 mm, 5 μ m; Mobile Phase A: Water(10mmol/L NH₄HCO₃+0.05%NH₃H₂O), Mobile Phase B: MeCN; Flow rate: 60 mL/min; Gradient (B%): 30% B to 50% B in 7 min) to afford the title compound (550 mg, 65.1%) as a yellow solid. LCMS m/z = 246 [M+H]⁺

5 *Step 3: Synthesis of 5-chloro-6-fluoroquinoline-2,4-diol*

[00727] To a stirred solution of the compound from step 2 (500 mg, 2.04 mmol) in THF (10 mL) was added LiHMDS (1.0 M in THF) (6.11 mL, 6.11 mmol) dropwise at -78 °C under N₂ and the reaction mixture was stirred at rt for 2 h. The reaction was quenched with ice water (10 mL) at 0 °C and the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined
10 organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure to give the title compound, crude, 100 mg, 23.0%. LCMS m/z = 214 [M+H]⁺

Step 4: Synthesis of 2,4-dibromo-5-chloro-6-fluoroquinoline

[00728] A mixture of the compound from step 3 (100 mg, 0.468 mmol) and phosphoryl
15 bromide (1.34 g, 4.68 mmol) in toluene (5 mL) was stirred at 100°C for 2 h under N₂. The reaction was quenched with water (10 mL) at rt and the aqueous layer was extracted with DCM (3 x 10mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (PE / EtOAc 5:1) to afford the title compound (90 mg, 56.9%) as a
20 yellow solid. LCMS m/z = 340 [M+H]⁺

Step 5: Synthesis of tert-butyl N-(4-bromo-5-chloro-6-fluoroquinolin-2-yl)carbamate

[00729] A mixture of the compound from step 4 (90 mg, 0.265 mmol), tert-butyl carbamate (15.53 mg, 0.133 mmol), Cs₂CO₃ (172.80 mg, 0.53 mmol), Xantphos (30.69 mg, 0.053 mmol) and Pd₂(dba)₃ (24.28 mg, 0.027 mmol) in dioxane (3 mL) was stirred at 60°C for 2 h under N₂.
25 The resulting mixture was concentrated under vacuum. The residue was purified by Prep-TLC (PE / EtOAc 3:1) to afford the title compound (45 mg, 45.1%) as a white solid. LCMS m/z = 375 [M+H]⁺

Step 6: Synthesis of 4-((S)-10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-6-fluoroquinolin-2-amine
30

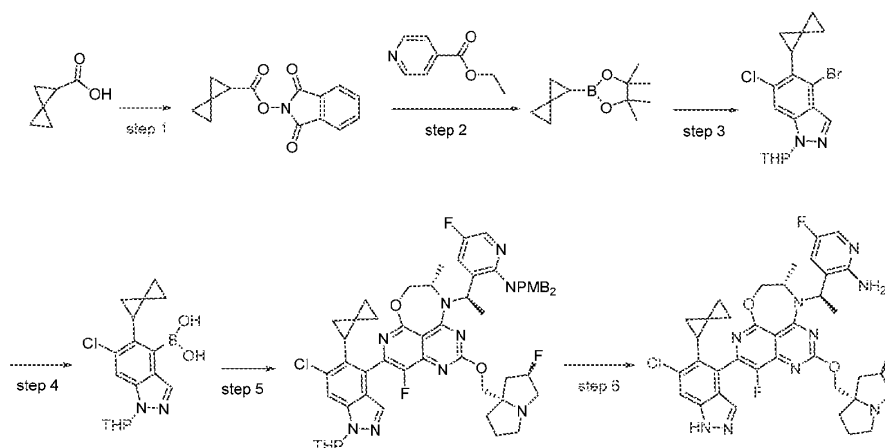
[00730] A mixture of the compound from step 5 (10 mg, 0.027 mmol) and Intermediate 47 (27.34 mg, 0.027 mmol), LiCl (5.64 mg, 0.135 mmol), CuI (25.35 mg, 0.135 mmol) and

$\text{Pd(PPh}_3)_4$ (3.08 mg, 0.003 mmol) in dioxane (5 mL) was stirred at 80°C for 16 h under N_2 . The resulting mixture was concentrated under vacuum and the residue was purified by Prep-TLC (DCM / MeOH 15:1) to afford the title compound (10 mg, 36.4%) as a white solid. LCMS m/z = 1033 $[\text{M}+\text{H}]^+$

- 5 *Step 7: Synthesis of 4-((S)-10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-6-fluoroquinolin-2-amine trifluoroacetate*

[00731] A solution of the compound from step 6 (10 mg, 0.010 mmol) in TFA (1 mL) and DCE (1 mL) was stirred at 80 °C for 2 h under N_2 . The resulting mixture was concentrated under vacuum. The mixture was purified by Prep-HPLC (Method E, Gradient: 10% B to 35% B in 7 min) to afford the title compound (1.5 mg, 19.2%) as a white solid. LCMS m/z = 692 $[\text{M}+\text{H}]^+$. $^1\text{H NMR}$ (400 MHz, DMSO-d_6) δ 8.08 - 8.03 (s, 1H), 7.70 - 7.60 (m, 1H), 7.27 (s, 1H), 7.14 - 6.83 (s, 3H), 6.67 - 6.62 (m, 1H), 5.66 - 5.53 (m, 1H), 5.32 (t, 1H), 4.67 - 4.28 (m, 2H), 4.20 - 4.10 (m, 1H), 3.89 - 3.77 (s, 3H), 2.36 (s, 1H), 2.09-1.90 (m, 2H), 1.75 - 1.59 (m, 2H), 1.46 (d, 1H), 1.35 - 1.23 (m, 4H), 1.21 (m, 3H), 0.85 (t, 2H), 0.65 (t, 2H).

Example 158: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(spiro[2.2]pentan-1-yl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-cyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine trifluoroacetate (Compound 425)



20

Step 1: Synthesis of 1,3-dioxoisindolin-2-yl spiro[2.2]pentane-1-carboxylate

[00732] The title compound was obtained as a yellow solid, 1.9 g, crude, from spiro[2.2]pentane-1-carboxylic acid and 2-hydroxy-2,3-dihydro-1H-isoindole-1,3-dione,

following a similar procedure to that described in Intermediate 45, step 1. LCMS m/z = 258 [M+H]⁺

Step 2: Synthesis of 4,4,5,5-tetramethyl-2-(spiro[2.2]pentan-1-yl)-1,3,2-dioxaborolane

- [00733] The title compound was obtained as a colorless oil, 300 mg, 20.9%, from the
5 compound from step 1 and ethyl isonicotinate, following a similar procedure to that described in Intermediate 45, step 2. ¹H NMR (400 MHz, CDCl₃) δ 1.16 (m, 12H), 1.02 (m, 1H), 0.97 (m, 1H), 0.85 – 0.63 (m, 4H), 0.29 (m, 1H).

Step 3: Synthesis of 4-bromo-6-chloro-5-(spiro[2.2]pentan-1-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole

- 10 [00734] To a stirred mixture of the compound from step 2 (351.7 mg, 1.81 mmol) and 4-bromo-6-chloro-5-iodo-1-(oxan-2-yl)indazole (400 mg, 0.906 mmol) in dioxane (4.8 mL) and water (1 mL) were added Pd(dppf)Cl₂.CH₂Cl₂ (74.0 mg, 0.091 mmol) and K₃PO₄ (577 mg, 2.72 mmol) and the reaction mixture was stirred at 100°C overnight under N₂. The cooled mixture was concentrated under reduced pressure. The crude product was purified by Prep-HPLC
15 (Method A, Gradient: 70% B to 95% B in 7 min) to give the title compound (100 mg, 28.9%) as a yellow solid. LCMS m/z = 381 [M+H]⁺

Step 4: Synthesis of (6-chloro-5-(spiro[2.2]pentan-1-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)boronic acid

- [00735] To a stirred mixture of the compound from step 3 (80 mg, 0.210 mmol) and B₂(OH)₄
20 (75.16 mg, 0.84 mmol) in MeOH (1.6 mL) were added CataCXium A Pd G3 (15.26 mg, 0.021 mmol) and TEA (63.63 mg, 0.630 mmol) and the reaction was stirred at 40°C for 1 h under N₂. The resulting mixture was used directly in the next step. LCMS m/z = 347 [M+H]⁺

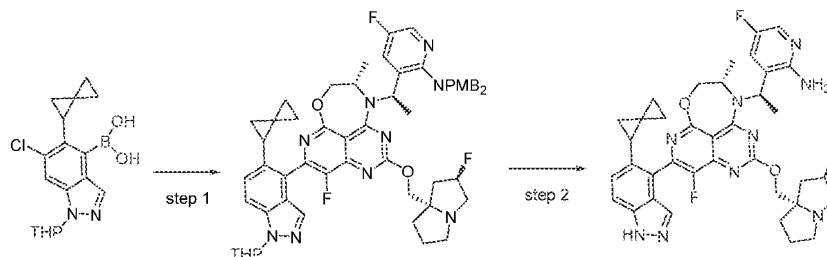
- Step 5: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(spiro[2.2]pentan-1-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-cyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine*
25

- [00736] To a stirred mixture of the compound from step 4 (80 mg, 0.231 mmol) and the
compound from Example 120, step 1, (145.9 mg, 0.185 mmol) in MeOH (1.6 mL) and water
(0.2 mL) was added CataCXium A Pd G3 (16.81 mg, 0.023 mmol) and K₃PO₄ (146.97 mg,
30 0.693 mmol) and the reaction mixture was stirred at 80°C for 2 h under N₂. The cooled mixture was concentrated under vacuum and the residue was purified by Prep-TLC (CH₂Cl₂ / MeOH = 10:1) to afford the title compound (90 mg) as a white solid. LCMS m/z = 1056 [M+H]⁺

Step 6: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(spiro[2.2]pentan-1-yl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-cyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine trifluoroacetate

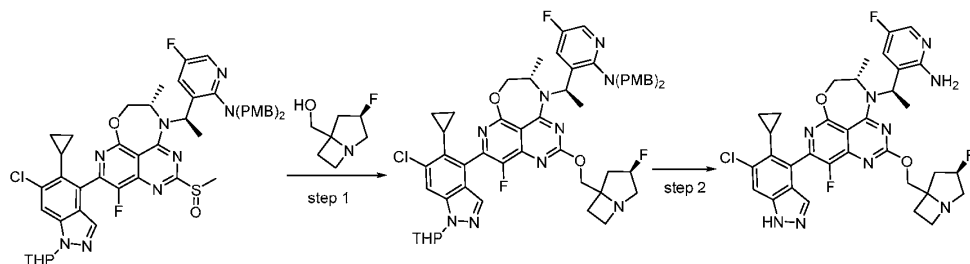
[00737] A solution of the compound from step 5 (90 mg, 0.085 mmol) in TFA (2 mL) was stirred at 50°C overnight. The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC (Method B, Gradient: 22% B to 35% B in 8 min) to afford the title compound (23.2 mg, 32.2%) as a yellow solid. LCMS $m/z = 732$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.27 (s, 1H), 8.04 - 8.01 (m, 1H), 7.86 - 7.71 (m, 2H), 6.53 (s, 1H), 5.66 (s, 2H), 5.53 (d, 1H), 4.71 - 4.68 (m, 1H), 4.64 - 4.56 (m, 4H), 4.37 - 4.32 (m, 2H), 4.19 - 4.10 (m, 2H), 3.81 - 3.73 (m, 2H), 3.61 - 3.58 (m, 1H), 3.31 (s, 1H), 2.63 - 2.58 (m, 2H), 2.41 - 2.39 (m, 1H), 2.25 - 2.11 (m, 2H), 2.07 (s, 1H), 1.63 - 1.60 (m, 3H), 1.06 - 0.91 (m, 2H), 0.82 - 0.69 (m, 2H), 0.64 - 0.61 (m, 3H).

Example 159 : Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(5-(spiro[2.2]pentan-1-yl)-1H-indazol-4-yl)-8,9-dihydro-10H-cyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine trifluoroacetate (Compound 460)



[00738] The title compound was obtained as a white solid, 2.7 mg, from the compound of Example 158, step 4 and Example 120, step 1, following a similar 2 step procedure to that described in Example 158, steps 5 and 6. LCMS $m/z = 698$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.16 (s, 1H), 8.01 (s, 1H), 7.74 - 7.56 (m, 3H), 7.20 (s, 1H), 6.54 (s, 1H), 5.66 (s, 2H), 5.23 (d, 1H), 4.55 - 4.51 (m, 1H), 4.34 (m, 1H), 4.15 (s, 3H), 3.10 - 3.05 (m, 2H), 3.03 (s, 1H), 2.83 (s, 1H), 2.20 - 2.13 (m, 2H), 2.06 - 2.01 (m, 2H), 1.78 - 1.72 (m, 3H), 1.62 - 1.58 (m, 3H), 1.36 (s, 1H), 1.23 (s, 1H), 1.17 (s, 1H), 0.82 - 0.78 (m, 1H), 0.62 (s, 4H), 0.47 (s, 1H).

Example 160: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-cyclopropyl-1H-indazol-4-yl)-4-fluoro-2-(((3R)-3-fluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine formate (Compound 423)



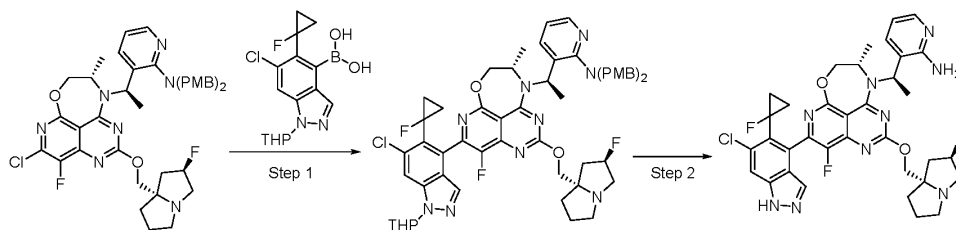
Step 1: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-cyclopropyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-4-fluoro-2-(((3R)-3-fluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoro-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00739] The title compound was obtained as a yellow solid, 30 mg, 27.6%, from Example 143, step 2 and ((3R,5S)-3-fluoro-1-azabicyclo[3.2.0]heptan-5-yl)methanol, following a similar procedure to that described in the synthesis of Intermediate 36, step 2. LCMS $m/z = 1016$ $[M+H]^+$

Step 2: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-cyclopropyl-1H-indazol-4-yl)-4-fluoro-2-(((3R)-3-fluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine formate

[00740] The title compound was obtained as a white solid, 3.2 mg 22%, from the compound of step 1, following a similar procedure to that described in Example 121, step 2. The crude product was purified by HPLC (Method C, Gradient (B%) 6% B to 35% B). LCMS $m/z = 692$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.25 (d, 1H), 8.00 (d, 1H), 7.84 – 7.66 (m, 3H), 6.54 (t, 1H), 5.56 (dd, 3H), 4.61 – 4.46 (m, 2H), 4.38 (dd, 1H), 4.27 – 4.18 (m, 1H), 4.11 (s, 1H), 3.06 (s, 2H), 3.00 (s, 1H), 2.92 (d, 1H), 2.29 – 2.20 (m, 1H), 2.18 – 2.07 (m, 1H), 1.99 (s, 1H), 1.94 – 1.85 (m, 1H), 1.63 (d, 2H), 1.23 (s, 2H), 0.96 – 0.74 (m, 2H), 0.64 (dd, 3H), 0.27 – 0.02 (m, 2H).

Example 161: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(1-fluorocyclopropyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 445)



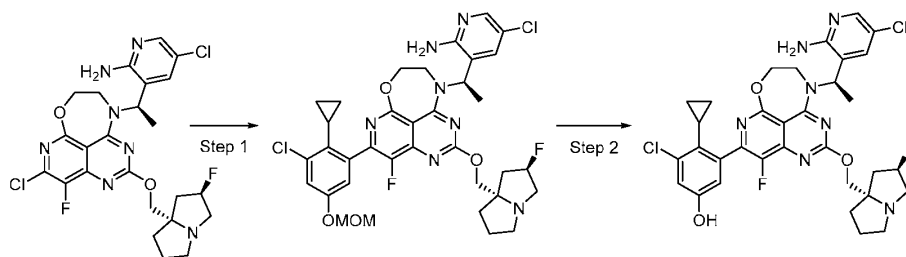
Step 1: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(1-fluorocyclopropyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00741] The title compound was obtained as a brown solid, 170 mg, 70.8%, from Intermediate 39 and Intermediate 41, following a similar procedure to that described in Intermediate 37, step 1. LCMS m/z = 1031 $[M+H]^+$

Step 2: Synthesis of 3-((1R)-1-((9S)-5-(6-chloro-5-(1-fluorocyclopropyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

[00742] A solution of the compound from step 1 (160 mg, 0.155 mmol) in TFA (5 mL) and TFOH (0.5 mL) was stirred at rt for 20 min under N_2 . The resulting mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC (Method A, Gradient (B%): 34% B to 53% B in 7 min) to afford the title compound (16.1 mg, 14.7%) as a white solid. LCMS m/z = 706 $[M+H]^+$ + 1H NMR (400 MHz, $DMSO-d_6$) δ 13.48 (d, 1H), 8.01 (dd, 1H), 7.89 (d, 1H), 7.83 (d, 1H), 7.72 (dd, 1H), 6.72 - 6.68 (m, 1H), 6.53 - 6.57 (m, 1H), 5.68 (d, 2H), 5.26 (d, 1H), 4.61 - 4.51 (m, 1H), 4.36 - 4.32 (m, 1H), 4.15 (d, 2H), 4.09 - 4.03 (m, 1H), 3.18 - 3.10 (m, 2H), 3.05 - 3.02 (m, 1H), 2.84 - 2.80 (m, 1H), 2.20 - 2.16 (m, 1H), 2.06 - 1.99 (m, 2H), 1.92 - 1.81 (m, 3H), 1.62 (d, 3H), 1.26 - 1.07 (m, 2H), 0.73 - 0.51 (m, 5H).

Example 162: Synthesis of 3-(10-((R)-1-(2-amino-5-chloropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol (Compound 219)



Step 1: Synthesis of 5-chloro-3-((R)-1-(5-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine

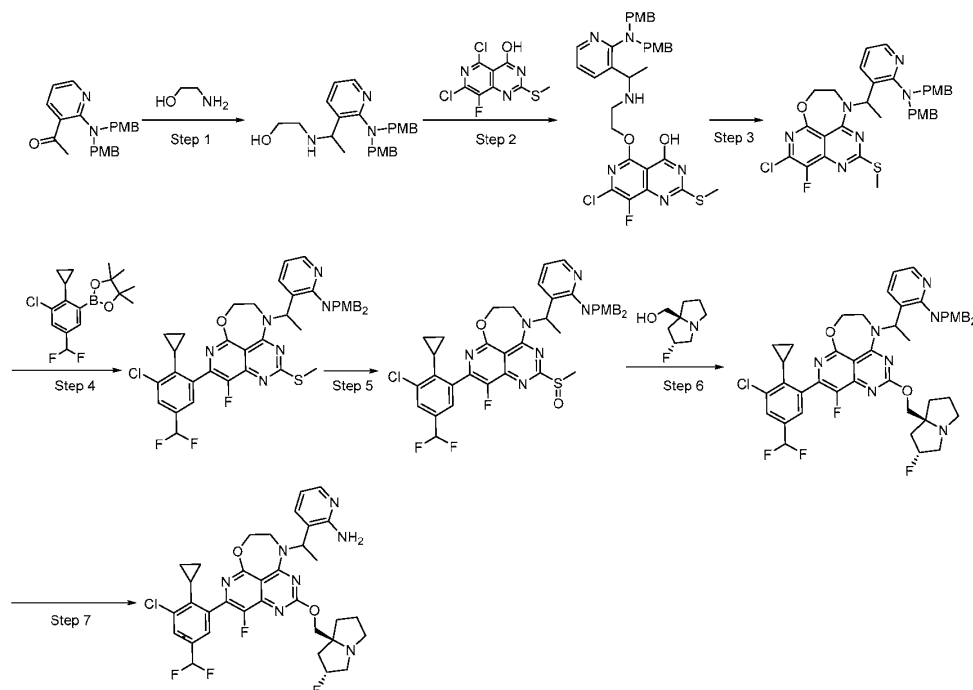
- 5 **[00743]** The title compound was obtained as a white solid, 20 mg, 50.5%, from Intermediate 21 and the compound from Example 116, step 2, following a similar procedure to that described in Example 116, step 3. LCMS $m/z = 728 [M+H]^+$

Step 2: Synthesis of 3-(1-((R)-1-(2-amino-5-chloropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol

10

- [00744]** A solution of the compound from step 1 (20 mg, 0.025 mmol) in DCE (1 mL) and TFA (0.1 mL) was stirred at rt for 2 h under N_2 . The crude product was purified by Prep-HPLC (Method A, Gradient: 39% B to 65% B in 7 min) to afford the title compound (2.2 mg, 10.6%) as a white solid. LCMS $m/z = 684 [M+H]^+$ 1H NMR (400 MHz, $DMSO-d_6$) δ 8.01 (d, 1H),
- 15 7.73 (d, 1H), 6.95 (d, 1H), 6.70 (d, 1H), 6.25 (q, 1H), 5.56 (d, 1H), 4.59 (d, 1H), 4.53 – 4.42 (m, 2H), 4.37 (dd, 1H), 3.83 – 3.65 (m, 5H), 3.56 (dd, 1H), 3.34 – 3.24 (m, 2H), 2.46 (s, 1H), 2.29 (d, 1H), 2.16 (dt, 3H), 2.02 (d, 1H), 1.76 (q, 1H), 1.56 (d, 3H), 0.70 – 0.53 (m, 2H), -0.09 (s, 2H).

- Example 163: Synthesis of 3-(1-(5-(3-chloro-2-cyclopropyl-5-(difluoromethyl)phenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 254)**
- 20



[00745] Step 1: Synthesis of 2-((1-(2-(bis(4-methoxybenzyl)amino)pyridin-3-yl)ethyl)amino)ethan-1-ol

[00746] The title compound was obtained as a pale-yellow oil, 3.5 g, 57%, from 1-(2-(bis(4-methoxybenzyl)amino)pyridin-3-yl)ethan-1-one and 2-aminoethan-1-ol, following a similar procedure to that described in Intermediate 33, step 4. LCMS $m/z = 422$ $[M+H]^+$.

Step 2: Synthesis of 5-(2-((1-(2-(bis(4-methoxybenzyl)amino)pyridin-3-yl)ethyl)amino)ethoxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-ol

[00747] To a solution of 5,7-dichloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-4-ol (500 mg, 1.79 mmol) and the title compound of Step 1 (715 mg, 1.70 mmol) in THF (10 mL) was added NaH (178 mg, 4.46 mmol) at 0°C. The reaction mixture was stirred at rt for 2 h, then quenched in ice water (30 mL) and extracted with EtOAc (3 x 20 mL). The organic phase was washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (0-100% EtOAc/PE followed by 0-5% MeOH/DCM) to afford the title compound (785 mg, 59.7%) as a pale-yellow foam. LCMS $m/z = 665$ $[M+H]^+$.

Step 3: Synthesis of 3-(1-(5-chloro-4-fluoro-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00748] The title compound was obtained as a pale-yellow foam (620 mg, 78%), from the compound from Step 2, following a similar procedure to that described in Step 4 of Example 93. LCMS m/z = 646 [M+H]⁺.

5 *Step 4: Synthesis of 3-(1-(5-(3-chloro-2-cyclopropyl-5-(difluoromethyl)phenyl)-4-fluoro-2-(methylthio)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine*

[00749] To a solution of the title compound of step 3 (250 mg, 0.386 mmol) and Intermediate 49 (190 mg, 0.58 mmol) in a mixture of dioxane (2 mL) and water (0.5 mL) was added K₃PO₄ (246 mg, 1.16 mmol) at 25°C, followed by PdCl₂(dppf).DCM (31.5 mg, 0.04 mmol) under N₂. The reaction mixture was stirred at 100°C for 16 h, then diluted with water (40 mL) and extracted with EtOAc (3 x 20 mL). The organic phase was washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (100% EtOAc/PE) to afford the title compound (180 mg, 50.7%) as a pale-yellow foam. LCMS m/z = 813 [M+H]⁺.

15 *Step 5: Synthesis of 3-(1-(5-(3-chloro-2-cyclopropyl-5-(difluoromethyl)phenyl)-4-fluoro-2-(methylsulfinyl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine*

[00750] The title compound was obtained as a pale brown oil (150 mg, 65.2%) from the compound from Step 4, following a similar procedure to that described in Step 4 of Example 114. LCMS m/z = 830 [M+H]⁺.

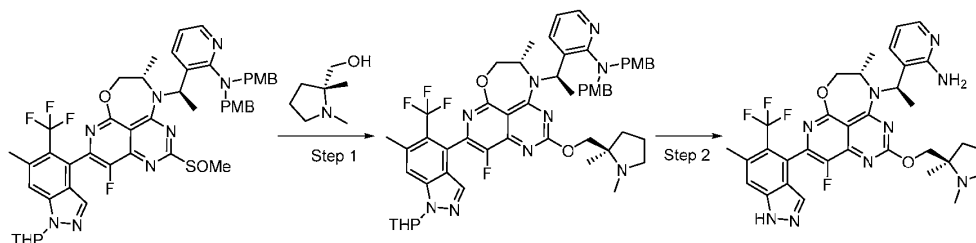
Step 6: Synthesis of 3-(1-(5-(3-chloro-2-cyclopropyl-5-(difluoromethyl)phenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

25 [00751] The title compound was obtained as a pale-yellow foam (110 mg, 49.6%) from the compound from step 5 and (2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, following a similar procedure to that described in step 5 of Example 114. LCMS m/z = 925 [M+H]⁺.

30 *Step 7: Synthesis of 3-(1-(5-(3-chloro-2-cyclopropyl-5-(difluoromethyl)phenyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine*

[00752] The title compound was prepared from the compound from step 6, following a similar procedure to that described in Step 8 of Example 93, and was purified by reverse phase Prep-HPLC (Column: X-Bridge C18 (250*19*5u), Mobile Phase: 10 mM in NH_4CO_3 in water, Mobile Phase-B: MeCN, using gradient 0 to 100 % MeCN, Flow rate: 16 mL/min) to afford an off white solid (31 mg, 37.7%) LCMS $m/z = 684$ $[\text{M}+\text{H}]^+$. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.98 (d, 1H), 7.78 (s, 1H), 7.64 (d, 1H), 7.55 (s, 1H), δ 7.10 (t, 1H), 6.68 (q, 1H), 6.36 (q, 1H), 5.74 (s, 2H), 5.39-5.26 (m, 1H), 4.49-4.44 (m, 1H), 4.35-4.30 (m, 1H), 4.25-3.95 (m, 2H), 3.83-3.71 (m, 1H), 3.51-3.43 (m, 1H), 3.20-2.72 (m, 4H), 2.35-1.75 (m, 7H), 1.61 (dd, 3H), 0.82-0.73 (m, 2H), 0.22-0.11 (m, 2H).

10 **Example 164: Synthesis of 3-((1R)-1-((9S)-2-(((R)-1,2-dimethylpyrrolidin-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 371)**



15 *Step 1: Synthesis of 3-((1R)-1-((9S)-2-(((S)-1,2-dimethylpyrrolidin-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine*

[00753] The title compound was prepared from Intermediate 38 and Intermediate 48, following a similar procedure to that described in Step 7 of Example 93, and was purified by reverse phase column chromatography (RediSep Gold® C18 Column (50 G), gradient 0-100% MeCN- H_2O (0.1M ammonium bicarbonate)) to afford a pale yellow foam (30 mg, 15.1%) LCMS $m/z = 990$ $[\text{M}+\text{H}]^+$.

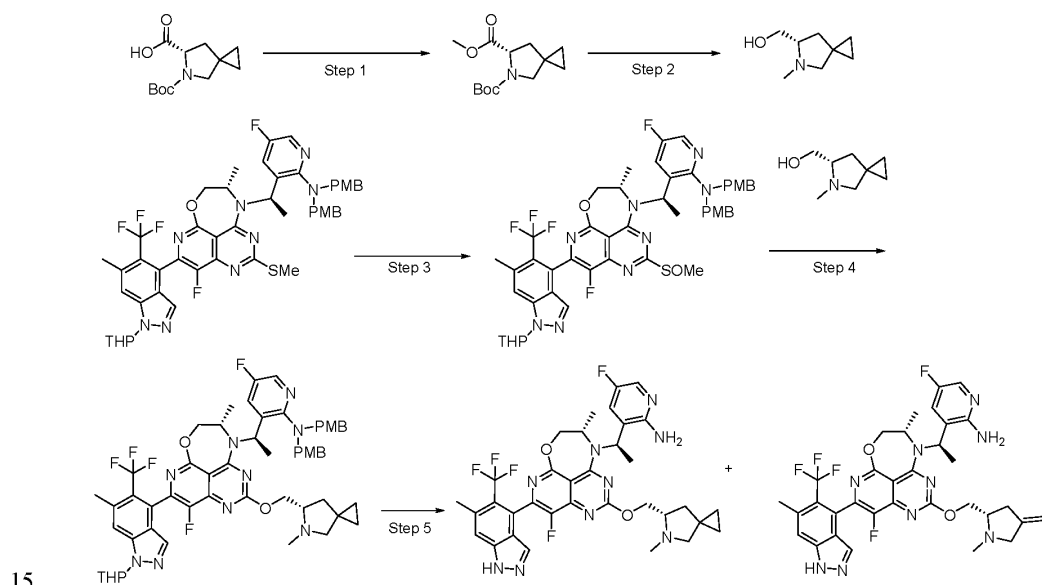
25 *Step 2: Synthesis of 3-((1R)-1-((9S)-2-(((R)-1,2-dimethylpyrrolidin-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine*

[00754] The title compound was prepared from the title compound of step 1 following a similar procedure to that described in Step 8 of Example 93. Purification by reverse phase Prep-HPLC (Column: X-SELECT C18 (150*19.2) 5 μM , Mobile phase: A: 10 mM NH_4CO_3 in water,

B: 100% MeCN, using gradient 0 to 100 % MeCN, Flow rate: 16 mL/min) provided an off-white solid (7.4 mg, 28.5%). LCMS $m/z = 666$ $[M+H]^+$. 1H -NMR (400 MHz, DMSO- d_6): δ 13.56-13.46 (m, 1H), 8.01 (dd, 1H), 7.74-7.71 (m, 3H), 6.72-6.68 (m, 1H), 6.56 (t, 1H), 5.72-5.64 (m, 2H), 4.39-4.31 (m, 1H), 4.30-4.28 (m, 2H), 4.21 (dd, 1H), 4.08-4.05 (m, 1H), 2.88-2.86 (m, 1H), 2.68-2.64 (m, 4H), 2.29 (s, 3H), 1.98-1.91 (m, 1H), 1.74-1.58 (m, 6H), 1.06 (s, 3H), 0.60 (dd, 3H),

Example 165: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((S)-5-methyl-5-azaspiro[2.4]heptan-6-yl)methoxy)-8,9-dihydro-10H-cyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Compound 2750)

And Example 166: Synthesis of 3-((1R)-1-((9S)-2-(((S,E)-4-ethylidene-1-methylpyrrolidin-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine (Compound 399)



Steps 1 and 2: Synthesis of (S)-5-(5-methyl-5-azaspiro[2.4]heptan-6-yl)methanol

[00755] The title compound (1.1 g, 73% over two steps, pale yellow oil) was prepared from (S)-5-(tert-butoxycarbonyl)-5-azaspiro[2.4]heptane-6-carboxylic acid following a similar procedure to that described in Steps 5 and 6 of Intermediate 48. LCMS $m/z = 142$ $[M+H]^+$.

Steps 3 and 4: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-1-(tetrahydro-2H-pyran-2-yl)-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((S)-5-methyl-5-

azaspiro[2.4]heptan-6-yl)methoxy)-8,9-dihydro-10H-cyclohepta[de]naphthalen-10-yl)ethyl)-N,N-bis(4-methoxybenzyl)pyridin-2-amine

[00756] The title compound (175 mg, 52.3%) was prepared from the compound of Intermediate 37, step 1 and the compound of Step 2 as a pale yellow solid following a similar 2
5 step procedure to that described in Steps 5 and 6 of Example 163. LCMS $m/z = 1020 [M+H]^+$.

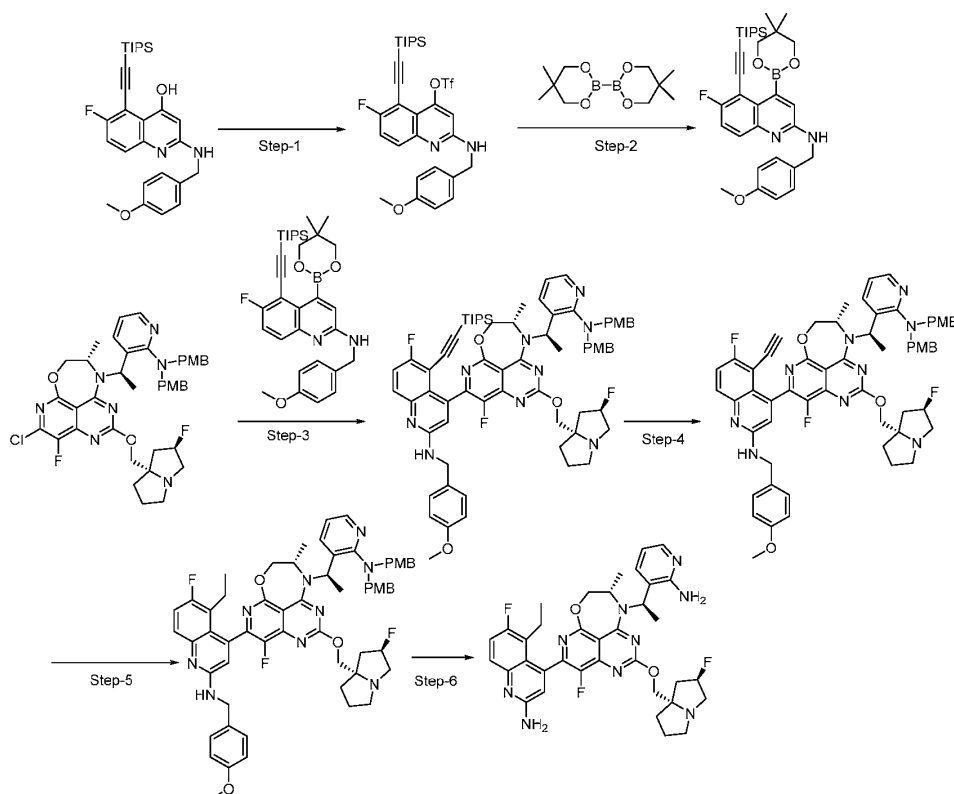
Step 5: Synthesis of 5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((S)-5-methyl-5-azaspiro[2.4]heptan-6-yl)methoxy)-8,9-dihydro-10H-cyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine (Example 165) and 3-((1R)-1-((9S)-2-(((S,E)-4-ethylidene-1-methylpyrrolidin-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-
10 *(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine (Example 166)*

[00757] The title compounds were prepared from the title compound of steps 3 and 4 following a similar procedure to that described in step 2 of Example 164 and were separated by reverse phase Prep-HPLC (Column : Xtimate C18 250*21mm, Mobile phase: A:10 mM
15 NH_4CO_3 in water with NH_4OH (pH:10), B:100% MeCN, using gradient 0 to 100 % MeCN, Flow rate: 15mL/min).

[00758] Peak 1, Example 165 (28 mg, 20.3%) as off white solid. LCMS $m/z = 696 [M+H]^+$. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 13.56-13.46 (m, 1H), 7.99 (d, 1H), 7.77-7.69 (m, 3H), 6.53 (t, 1H), 5.58 (m, 2H), 4.55-4.47 (m, 2H), 4.39-4.30 (m, 2H), 4.12 (t, 1H), 2.96-2.92 (m, 1H),
20 2.70-2.66 (m, 4H), 2.48-2.38 (m, 1H), 2.34 (s, 3H), 2.05-2.00 (m, 1H), 1.69-1.64 (m, 4H), 0.71-0.48 (m, 7H).

[00759] Peak 2, Example 166 (16 mg, 11.58%) as off white solid. LCMS $m/z = 696 [M+H]^+$. $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$): δ 13.52-13.46 (m, 1H), 8.01 (d, 1H), 7.73-7.69 (m, 3H), 6.56-6.52 (m, 1H), 5.63-5.56 (m, 2H), 5.30-5.29 (m, 1H), 4.55-4.48 (m, 2H), 4.45-4.35 (m, 2H),
25 4.15-4.05 (m, 1H), 3.70-3.58 (m, 1H), 2.79-2.68 (m, 2H), 2.67-2.54 (m, 4H), 2.47-2.33 (m, 3H), 2.28-2.15 (m, 1H), 1.63 (d, 3H), 1.54 (t, 3H), 0.63 (dd, 3H)

Example 167: Synthesis of 4-((S)-10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethyl-6-fluoroquinolin-2-
30 **amine (Compound 384)**



Step 1: Synthesis of 6-fluoro-2-((4-methoxybenzyl)amino)-5-((triisopropylsilyl)ethynyl)quinolin-4-yl trifluoromethanesulfonate

[00760] To a solution of 6-fluoro-2-((4-methoxybenzyl)amino)-5-((triisopropylsilyl)ethynyl)quinolin-4-ol (250 mg, 0.52 mmol) in DCM (10 mL) was added pyridine (0.21 mL, 2.6 mmol) followed by Tf₂O (0.44 mL, 2.6 mmol) at 0°C under N₂. The reaction mixture was stirred at 0°C for 1h, then quenched with water (10 mL) and extracted with DCM (3 x 10 mL). The organic phase was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-100% EtOAc/hexanes) to give the title compound (150 mg, 46.5%) as a brown gum. LCMS m/z = 611 [M+H]⁺.

Step 2: Synthesis of 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-6-fluoro-N-(4-methoxybenzyl)-5-((triisopropylsilyl)ethynyl)quinolin-2-amine

[00761] To a solution of the title compound of Step 1 (150 mg, 0.25 mmol) in dioxane (5 mL) were added 5,5,5',5'-tetramethyl-2,2'-bi(1,3,2-dioxaborinane) (83 mg, 0.37 mmol), KOAc (72.3 mg, 0.74 mmol) and PdCl₂(dppf)-DCM (20.06 mg, 0.02 mmol) at rt under N₂. The

reaction mixture was irradiated at 100°C for 1.5 h, then diluted with EtOAc (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-20% MeOH/DCM) to afford the title compound (150 mg, 49.7%) as an orange gum. LCMS m/z = 507 [M-68]⁺.

- 5 *Step 3: Synthesis of 4-((S)-10-((R)-1-(2-(bis(4-methoxybenzyl)amino)pyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-fluoro-N-(4-methoxybenzyl)-5-((triisopropylsilyl)ethynyl)quinolin-2-amine*

- 10 **[00762]** The title compound was obtained as pale-yellow foam (0.39 mmol, 64.3%) from the title compound of Step 2 and Intermediate 39 following a similar procedure to that described in Step 2 of Example 120. LCMS m/z = 1199 [M+H]⁺.

- 15 *Step 4: Synthesis of 4-((S)-10-((R)-1-(2-(bis(4-methoxybenzyl)amino)pyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoro-N-(4-methoxybenzyl)quinolin-2-amine*

- 20 **[00763]** To a solution of the title compound of step 3 (100 mg, 0.08 mmol) in DMF (3 mL) was added CsF (127 mg, 0.83 mmol) at rt under N₂. The reaction mixture was stirred at 80 °C for 3 h, then diluted with DCM (10 mL), filtered through Celite® and concentrated under reduced pressure to get the title compound (80 mg, 57.1%) as an orange gum. LCMS m/z = 1042 [M+H]⁺.

- Step 5: Synthesis of 4-((S)-10-((R)-1-(2-(bis(4-methoxybenzyl)amino)pyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethyl-6-fluoro-N-(4-methoxybenzyl)quinolin-2-amine*

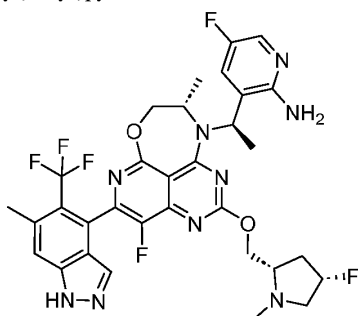
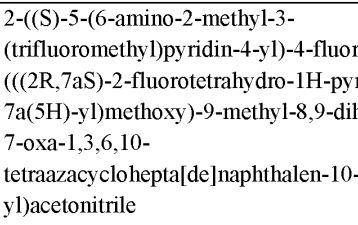
- 25 **[00764]** To a solution of the title compound of Step 4 (70 mg, 0.07 mmol) in MeOH (5 mL) was added Pd/C (10% loading, 50% wet, 71.5 mg, 0.07 mmol) at rt under N₂. The reaction mixture was stirred under H₂ for 32 h, then filtered through Celite® and washed with 20% MeOH in DCM (3 x 10 mL). The filtrate was concentrated under reduced pressure to afford the title compound (60 mg, 69.2%) as a brown gum. LCMS m/z = 1046 [M+H]⁺.

- 30 *Step 6: Synthesis of 4-((S)-10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethyl-6-fluoroquinolin-2-amine trifluoroacetate*

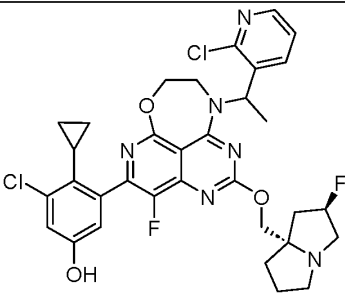
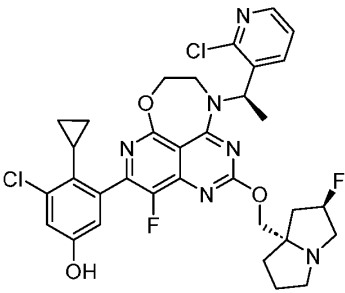
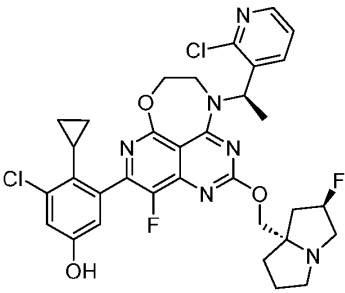
- [00765] To a solution of the title compound of Step 7 (50 mg, 0.05 mmol) in DCM (5 mL) was added triflic acid (144 mg, 0.96 mmol) at 0°C under N₂. The reaction mixture was stirred at rt for 1 h, then quenched with ice water (5 mL), basified with 10% NaHCO₃ (5 mL) (pH~10) and extracted with 5% MeOH in DCM (4 x 10 mL). The organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to get a residue which was purified by prep-HPLC (Column: XTIMATE C18(250*22)5μ, Mobile Phase-A: 10 mM in TFA in water, Mobile Phase-B: MeCN, gradient of 0 to 100 % MeCN, flow rate :18 mL/min) to afford the title compound (6.54 mg, 17.2%) as an off-white solid. LCMS m/z = 686 [M+H]⁺. ¹H-NMR (400 MHz, DMSO-*d*₆): δ 10.85 (br s, 1H), 8.17-7.92 (m, 3H), 7.74-7.59 (m, 2H), 7.12-6.88 (m, 2H), 6.54 (t, 2H), 5.68-5.55 (m, 1H), 4.75-4.56 (m, 3H), 4.38 (t, 1H), 4.21-4.11 (m, 1H), 3.91-3.78 (m, 4H), 3.39-3.20 (m, 3H), 2.45-2.32 (m, 2H), 2.28-2.01 (m, 4H), 1.72-1.61 (m, 3H), 0.92-0.74 (m, 3H), 0.69-0.59 (m, 3H).

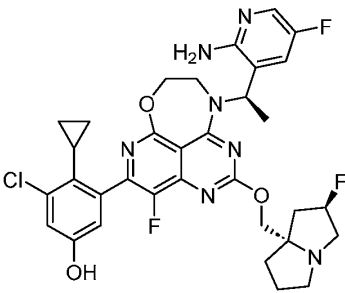
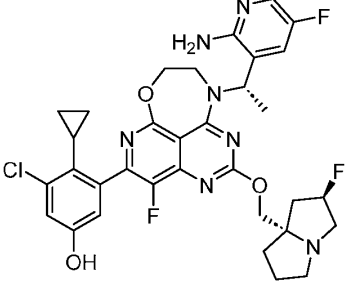
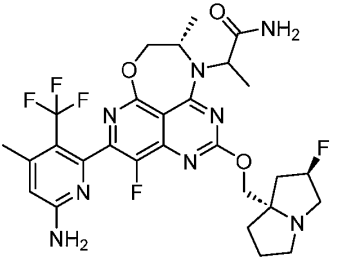
Examples 168 to 271

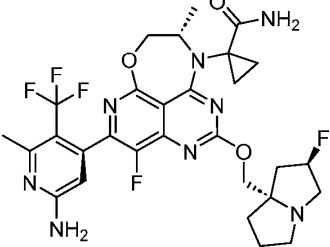
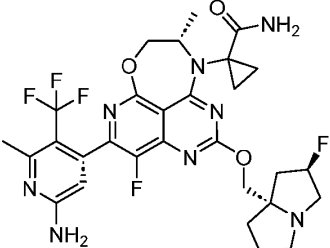
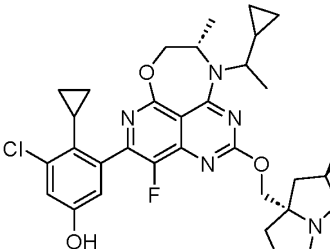
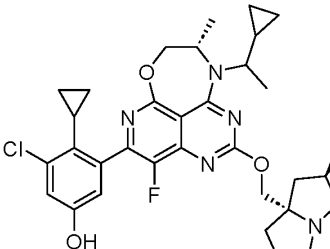
- [00766] Following synthetic protocols similar to those described in Examples 1-167 of the present disclosure, the following compounds were prepared:

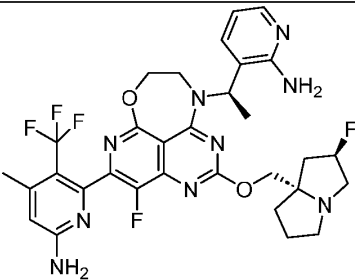
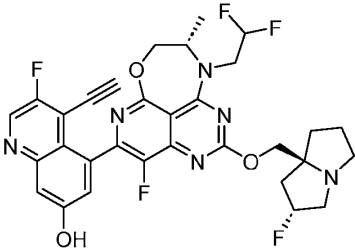
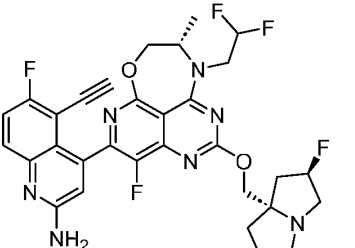
Exmpl No./ Compd No.	Compound structure and name	Data
168 Compound 370	5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-(((2S,4S)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 688 [M+H] ⁺ ¹ H NMR (300 MHz, DMSO- <i>d</i> ₆): 8.0 (s, 1H), 7.78-7.71 (m, 3H), 6.54 (m, 1H), 5.6 (d, 2H), 5.09-5.21 (m, 1H), 4.58-5.48 (m, 2H), 4.42-4.32 (m, 2H), 4.1 (m, 2H), 3.19-3.13 (m, 1H), 2.71-2.61 (m, 4H), 2.48-2.38 (m, 1H), 2.38 (s, 3H), 1.92-1.75 (m, 1H), 1.6 (d, 3H), 1.39 (m, 1H), 0.59-0.66 (m, 3H)
169 Compound 220	2-((S)-5-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)acetonitrile 	LCMS m/z = 591 [M+H] ⁺ ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 7.04 - 6.71 (m, 2H), 6.30 (s, 1H), 5.52 (d, 1H), 5.02 - 4.97 (m, 1H), 4.83 - 4.72 (m, 1H), 4.68 - 4.65 (s, 2H), 4.52 - 4.47 (m, 1H), 4.36 - 4.32 (m, 1H), 3.96 - 3.89 (m, 1H), 3.82 - 3.69 (m, 2H), 2.63 - 2.59 (m, 1H), 2.46 - 2.51 (m, 1H)

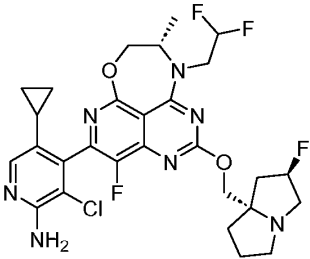
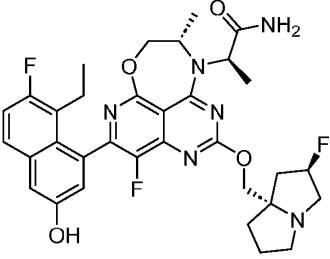
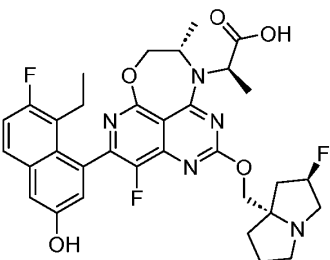
		6H), 2.26 - 2.35 (m, 1H), 2.12 - 2.22 (m, 2H), 2.11 - 1.98 (m, 1H), 1.43 - 1.28 (m, 3H).
170 Compound 221	2-((S)-5-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)butanamide 	LCMS m/z = 638 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆): δ 7.40 (s, 1H), 7.22 (s, 1H), 6.83 (s, 1H), 6.55 (s, 1H), 6.25 (s, 1H), 5.25 (d, 1H), 4.46 - 4.61 (m, 2H), 4.12 - 4.01 (m, 2H), 3.81 - 3.93 (m, 1H), 3.69 - 3.65 (m, 1H), 3.19 - 3.05 (m, 2H), 2.97 - 2.85 (m, 1H), 2.47 (s, 3H), 2.41 - 2.13 (m, 4H), 1.98 - 1.72 (m, 3H), 1.43 - 1.32 (m, 2H), 1.29 - 1.17 (m, 3H), 0.98 - 0.85 (m, 3H).
171 Compound 225	4-(10-((R)-1-(2-amino-5-chloropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine 	LCMS m/z = 692 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆) δ 8.05 (d, 1H), 7.79 (d, 1H), 6.45 (s, 1H), 6.27 (q, 1H), 5.69 - 5.49 (m, 2H), 4.62 (d, 1H), 4.53 (d, 2H), 4.47 (d, 1H), 4.41 (dd, 1H), 3.91 - 3.69 (m, 6H), 3.59 (dd, 1H), 3.33 (ddd, 1H), 2.50 (d, 2H), 2.37 - 2.28 (m, 1H), 2.26 - 2.12 (m, 3H), 2.13 - 2.00 (m, 2H), 1.60 (d, 4H).
172 Compound 226	3-chloro-5-(10-(1-(2-chloropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-cyclopropylphenol 	LCMS m/z = 669 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆) δ 10.02 (s, 1H), 8.38 - 8.36 (m, 1H), 8.02 (d, 1H), 7.51 (dd, 1H), 6.93 (d, 1H), 6.73 (d, 1H), 6.35 - 6.30 (m, 1H), 5.26 (d, 1H), 4.48 - 4.11 (m, 2H), 4.25 - 3.73 (m, 3H), 3.57 - 3.50 (m, 1H), 3.20 - 3.11 (m, 3H), 3.07 -

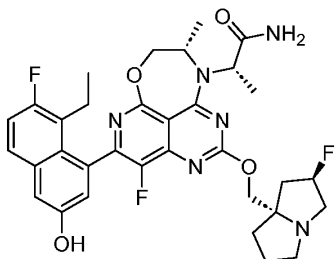
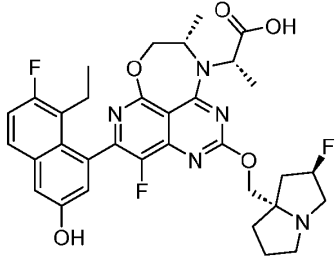
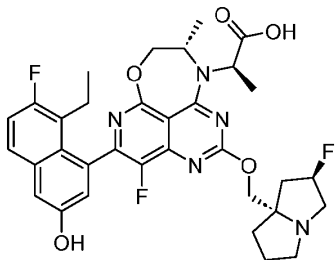
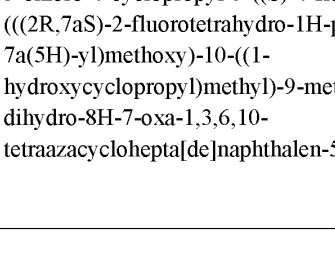
		2.92 (m, 1H), 2.75 - 2.71 (m, 1H), 2.15 - 2.11 (m, 1H), 2.10 - 2.05 (m, 1H), 2.05 - 2.02 (m, 1H), 1.86 - 1.75 (m, 3H), 1.66 (d, 3H), 0.76 - 0.73 (m, 2H), 0.05 - 0.01 (m, 2H).
173 Compound 227	3-chloro-5-(10-((S)-1-(2-chloropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-cyclopropylphenol 	Peak 2 LCMS m/z = 669 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 9.98 (s, 1H), 8.41 (dd, 1H), 8.05 (dd, 1H), 7.53 (dd, 1H), 6.94 (d, 1H), 6.73 (d, 1H), 6.32 (d, 1H), 5.53 (d, 1H), 4.60-4.57 (d, 1H), 4.56 - 4.42 (m, 3H), 3.95 - 3.81 (m, 2H), 3.77-3.71 (m, 3H), 3.63-3.51 (m, 1H), 3.33-3.21 (m, 2H), 2.72-2.63 (m, 1H), 2.61-2.45 (m, 1H), 2.37-2.31 (m, 1H), 2.18 -2.11 (m, 2H), 2.08-1.98 (m, 1H), 1.81 - 1.73 (m, 1H), 1.68-1.65 (m, 3H), 0.62-0.60 (m, 2H).
174 Compound 227	3-chloro-5-(10-((R)-1-(2-chloropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-cyclopropylphenol 	Peak 1 LCMS m/z = 669 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 9.98 (s, 1H), 8.41 (dd, 1H), 8.06 (dd, 1H), 7.54 (dd, 1H), 6.94 (d, 1H), 6.73 (d, 1H), 6.33 (d, 1H), 5.53 (d, 1H), 4.60-4.57 (d, 1H), 4.57 - 4.48 (m, 1H), 4.46 - 4.43 (m, 2H), 4.40 - 4.33 (m, 1H), 3.95 - 3.81 (m, 2H), 3.77 - 3.71 (m, 3H), 3.63 - 3.51 (m, 1H), 3.30 - 3.21 (m, 1H), 2.65 - 2.62 (m, 1H), 2.36 - 2.31 (m, 1H), 2.30 - 2.23 (m, 2H), 1.81 - 1.73 (m, 1H), 1.68 - 1.65 (m, 3H), 0.62 - 0.60 (m, 2H), 0.05 - 0.01 (m, 2H).
175 Compound 229	3-(10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-	Peak 2 LCMS m/z = 669 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 9.92 (s, 1H), 7.96 - 7.52 (m, 1H), 7.61 - 7.52 (m, 1H), 6.94 - 6.87 (m, 1H), 6.71 - 6.66 (m, 1H), 6.35 - 6.24 (m, 1H), 5.71 - 5.60 (m, 2H),

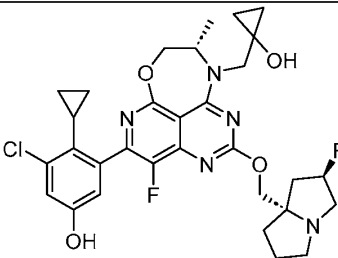
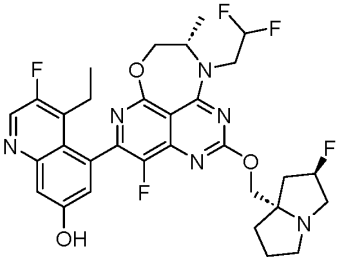
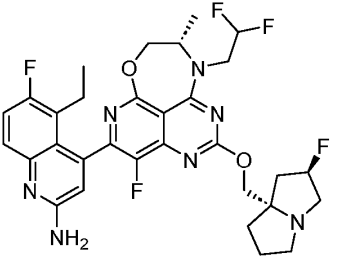
	4-cyclopropylphenol 	5.35 – 5.17 (m, 1H), 4.47 – 4.36 (m, 1H), 4.34 – 4.24 (m, 1H), 4.20 – 4.00 (m, 2H), 3.80 – 3.67 (m, 1H), 3.49 – 3.37 (m, 1H), 3.11 – 2.92 (m, 3H), 2.84 – 2.73 (m, 1H), 2.16 – 1.91 (m, 3H), 1.86 – 1.67 (m, 4H), 1.60 – 1.48 (m, 3H), 0.67 – 0.53 (m, 2H), 0.06 – -0.05 (m, 2H).
176 Compound 230	3-(10-((S)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol 	Peak 1 LCMS m/z = 668 [M+H]⁺ 1H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.92 (s, 1H), 7.96 – 7.52 (m, 1H), 7.61 – 7.52 (m, 1H), 6.94 – 6.87 (m, 1H), 6.71 – 6.66 (m, 1H), 6.35 – 6.24 (m, 1H), 5.71 – 5.60 (m, 2H), 5.35 – 5.17 (m, 1H), 4.47 – 4.36 (m, 1H), 4.34 – 4.24 (m, 1H), 4.20 – 4.12 (m, 1H), 4.05 – 3.97 (m, 1H), 3.82 – 3.72 (m, 1H), 3.49 – 3.37 (m, 1H), 3.11 – 2.92 (m, 3H), 2.84 – 2.73 (m, 1H), 2.16 – 1.92 (m, 3H), 1.86 – 1.67 (m, 4H), 1.60 – 1.48 (m, 3H), 0.67 – 0.53 (m, 2H), 0.03 – 0.03 (m, 2H).
177 Compound 233	2-((S)-5-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide 	LCMS m/z = 623 [M+H]⁺ 1H NMR (400 MHz, DMSO-<i>d</i>₆) : δ 7.42 – 7.35 (m, 1H), 7.18 – 7.10 (m, 1H), 6.81 (s, 2H), 6.48 (s, 1H), 5.29 (d, 1H), 4.39 – 4.64 (m, 2H), 4.27 – 4.21 (m, 1H), 4.18 – 4.09 (m, 2H), 3.13 – 3.09 (m, 2H), 3.08 – 3.03 (m, 1H), 2.91 – 2.83 (m, 1H), 2.39 – 2.32 (m, 4H), 2.14 – 2.11 (m, 1H), 2.05 – 1.98 (m, 2H), 1.75 – 1.84 (m, 3H), 1.56 – 1.52 (m, 3H), 1.25 – 1.17 (m, 3H).
178 Compound 236	1-((S)-5-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-	Peak 1 LCMS m/z = 635 [M+H]⁺ 1H NMR (400 MHz, DMSO-<i>d</i>₆) δ 7.67 – 7.58 (m, 1H), 7.28 – 6.74 (m, 3H), 6.29 (s, 1H), 5.53 (d, 1H), 4.61 – 4.52 (m, 3H), 4.45 – 4.36 (m, 1H),

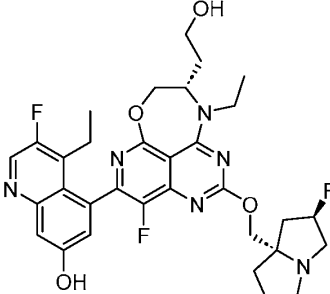
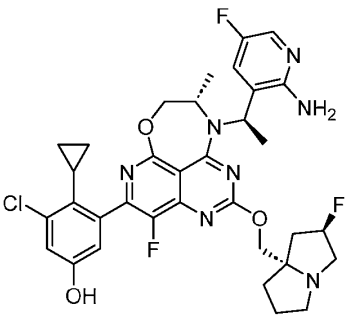
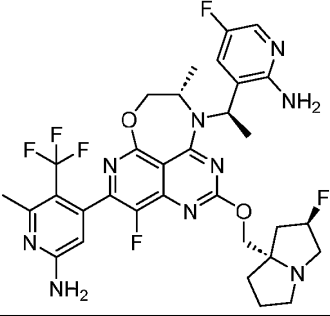
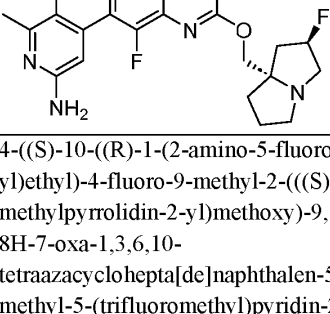
	tetraazacyclohepta[de]naphthalen-10-yl)cyclopropane-1-carboxamide 	4.31 - 4.23 (m, 2H), 3.86 - 3.48 (m, 4H), 2.65 - 2.60 (m, 1H), 2.49 - 2.46 (m, 3H), 2.31 - 2.25 (m, 1H), 2.21 - 2.15 (m, 2H), 2.12 - 2.09 (m, 1H), 1.80 - 1.74 (m, 1H), 1.61 - 1.58 (m, 1H), 1.43 - 1.28 (m, 1H), 1.26 - 1.17 (m, 2H), 1.16 - 1.14 (m, 2H).
179 Compound 238	1-((S)-5-(6-amino-2-methyl-3-(trifluoromethyl)pyridin-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)cyclopropane-1-carboxamide 	Peak 2 LCMS m/z = 635 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 7.72 (s, 1H), 7.29 - 7.04 (m, 3H), 6.29 (s, 1H), 5.59 (d, 1H), 4.63 - 4.58 (m, 1H), 4.57 - 4.49 (m, 2H), 4.48 - 4.45 (m, 2H), 4.34 - 4.30 (m, 3H), 4.22 - 4.19 (m, 2H), 2.50 - 2.46 (m, 4H), 2.36 - 2.30 (m, 1H), 2.27 - 2.17 (m, 2H), 2.13 - 2.09 (m, 1H), 1.86 - 1.74 (m, 1H), 1.58 - 1.51 (m, 1H), 1.36 - 1.31 (m, 1H), 1.25 - 1.14 (m, 4H).
180 Compound 237	3-chloro-4-cyclopropyl-5-((9S)-10-(1-cyclopropylethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol 	LCMS m/z = 612 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 9.95 (s, 1H), 6.93 (d, 1H), 6.80 - 6.66 (m, 1H), 5.41 - 5.11 (m, 1H), 4.71 - 4.40 (m, 5H), 4.34 (dd, 1H), 4.08 (t, 1H), 3.96 (dd, 1H), 3.13 - 2.93 (m, 3H), 2.87 - 2.72 (m, 1H), 2.19 - 1.91 (m, 3H), 1.88 - 1.63 (m, 4H), 1.40 - 1.09 (m, 7H), 0.72 - 0.54 (m, 3H), 0.53 - 0.16 (m, 2H), 0.07 (dq, 1H).
181 Compound 239	6-(10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine 	LCMS m/z = 658 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 8.12 - 8.02 (m, 2H), 7.03 - 6.96 (m, 1H), 6.50 (s, 1H), 6.28 - 6.20 (m, 1H), 5.69 - 5.50 (m, 1H), 4.65 - 4.41 (m, 4H), 4.00 - 3.60 (m, 5H), 3.37 - 3.27 (m, 1H), 2.45 - 2.42 (m,

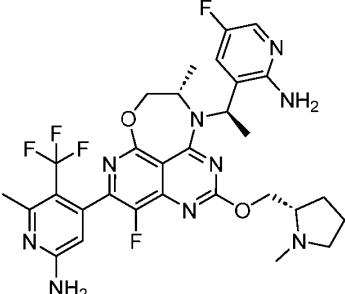
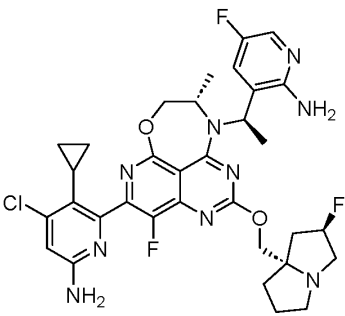
		2H), 2.39 – 2.28 (m, 4H), 2.27 – 2.03 (m, 3H), 1.62 (d, 3H)
182 Compound 241	5-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-ethynyl-3-fluoroquinolin-7-ol 	LCMS m/z = 627 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆) δ 10.71 (s, 1H), 8.95 (d, 1H), 7.46 (d, 1H), 7.28 (dd, 1H), 6.45 (tq, 1H), 5.42 – 5.13 (m, 1H), 4.61 (ddd, 1H), 4.55 – 4.35 (m, 4H), 4.21 (qd, 1H), 4.16 – 3.99 (m, 2H), 3.15 – 3.04 (m, 2H), 3.01 (d, 1H), 2.90 – 2.77 (m, 1H), 2.17 – 2.07 (m, 1H), 2.07 – 1.92 (m, 2H), 1.92 – 1.69 (m, 3H), 1.28 (t, 3H).
183 Compound 242	4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoroquinolin-2-amine 	LCMS m/z = 626 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆) δ 8.30 – 7.64 (m, 2H), 7.63 – 7.35 (m, 2H), 7.32 – 6.93 (m, 1H), 6.68 – 6.23 (m, 1H), 5.58 (d, 1H), 4.73 – 4.51 (m, 3H), 4.48 – 4.43 (m, 2H), 4.27 – 4.21 (m, 2H), 4.17 (d, 1H), 3.98 – 3.88 (m, 1H), 3.83 – 3.72 (m, 2H), 3.18 – 3.16 (m, 1H), 2.67 – 2.54 (m, 1H), 2.50 – 2.46 (m, 1H), 2.33 – 2.18 (m, 3H), 2.17 – 2.05 (s, 1H), 1.30 (dd, 3H).
184 Compound 243	3-chloro-5-cyclopropyl-4-((9S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)pyridin-2-amine 	LCMS m/z = 608 [M+H] ⁺ 1H NMR (400 MHz, MeOD-d ₄) δ 7.78 (s, 1H), 6.71 – 6.23 (m, 1H), 5.28 (m, 1H), 4.68 (m, 1H), 4.55 – 4.35 (m, 3H), 4.32 (m, 1H), 4.20 (m, 1H), 4.00 (m, 1H), 3.71 – 3.38 (m, 3H), 3.09 (m, 1H), 2.66 (s, 3H), 2.29 (m, 2H), 2.29 – 2.07 (m, 3H), 2.07 – 1.91 (m, 1H), 1.68 – 1.39 (m, 1H),

		1.28 (m, 3H), 1.18 (m, 1H), 0.71 – 0.42 (m, 2H).
185 Compound 244	(R)-2-((S)-5-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanamide 	Peak 1 LCMS m/z = 637 [M-H]⁺ 1H NMR (400 MHz, DMSO-d₆) 10.01-9.98 (m, 1H), 7.79-7.71 (m, 1H), 7.40-7.29 (m, 3H), 7.15-7.07 (m, 1H), 7.03-6.95 (m, 1H), 5.72-5.47 (m, 1H), 5.09-4.73 (m, 1H), 4.68-4.51 (m, 4H), 4.43-4.28 (m, 1H), 3.93-3.82 (m, 2H), 3.82-3.69 (m, 1H), 2.32-2.22 (m, 2H), 2.19-2.11 (m, 2H), 2.08-2.01 (m, 1H), 1.56-1.51 (m, 3H), 1.38-1.28 (m, 3H), 1.28-1.21 (m, 3H), 0.89-0.77 (m, 4H).
186 Compound 245	(R)-2-((S)-5-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanoic acid 	Peak 1 LCMS m/z = 638 [M-H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 12.89-12.58 (m, 1H), 10.02-9.98 (m, 1H), 7.79-7.76 (m, 1H), 7.40-7.29 (m, 2H), 7.03-6.95 (m, 1H), 5.67-5.49 (m, 1H), 5.09-4.83 (m, 1H), 4.69-4.61 (m, 1H), 4.59-4.41 (m, 3H), 3.26-4.19 (m, 1H), 3.93-3.82 (m, 2H), 3.79-3.75 (m, 2H), 3.71-3.66 (m, 1H), 3.34-3.27 (m, 1H), 2.53 (s, 1H), 2.32-2.17 (m, 4H), 2.08-2.01 (m, 1H), 1.64 -1.56 (m, 3H), 1.27-1.21 (m, 3H), 0.89-0.77 (m, 3H).
187 Compound 246	(S)-2-((S)-5-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-	Peak 2 LCMS m/z = 637 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 10.01 -9.89 (m, 1H), 7.79-7.71 (m, 1H), 7.50-7.28 (m, 3H), 7.15 -7.09 (m, 1H), 7.09-6.95 (m, 1H), 5.72-5.53 (m, 1H), 5.47-5.28 (m, 1H), 4.68-4.51 (m, 2H), 4.27-4.14 (m, 1H), 4.13-3.97 (m, 2H), 3.14 -3.06

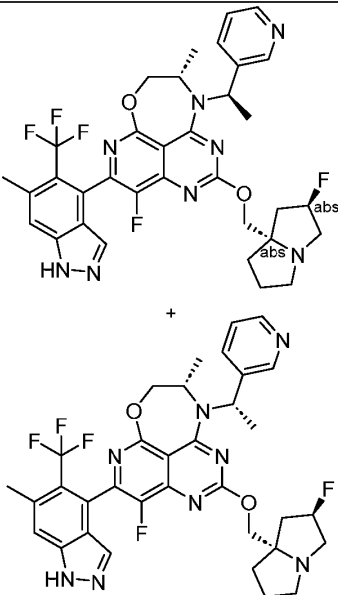
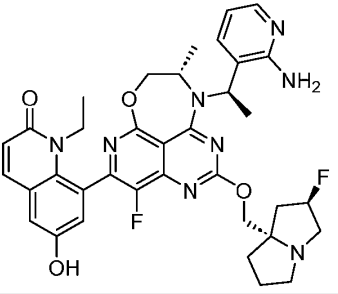
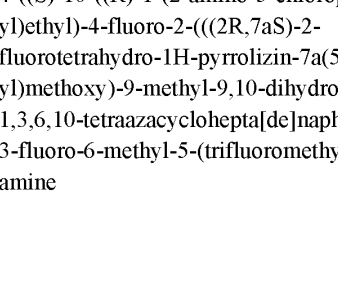
	yl)propanamide 	(m, 2H), 3.03-3.01 (m, 1H), 2.88-2.81 (m, 1H), 2.32-2.25 (m, 1H), 2.16-2.09 (m, 1H), 2.08-1.98 (m, 2H), 1.89-1.71 (m, 3H), 1.63-1.56 (m, 3H), 1.28-1.21 (m, 4H), 0.89-0.77 (m, 3H).
188 Compound 247	(S)-2-((S)-5-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanoic acid or (R)-2-((S)-5-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)propanoic acid  + 	Peak 2 LCMS m/z = 638 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 12.89-12.58 (m, 1H), 9.98-9.89 (m, 1H), 7.79-7.76 (m, 1H), 7.40-7.29 (m, 2H), 7.03-6.95 (m, 1H), 5.67-5.41 (m, 1H), 4.82-4.61 (m, 2H), 4.59-4.41 (m, 2H), 4.26-4.19 (m, 1H), 3.91-3.66 (m, 4H), 2.32-1.97 (m, 7H), 1.64-1.56 (m, 3H), 1.34-1.25 (m, 3H), 1.24-1.21 (m, 1H), 0.89-0.75 (m, 4H).
189 Compound 250	3-chloro-4-cyclopropyl-5-((S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-10-((1-hydroxycyclopropyl)methyl)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol 	LCMS m/z = 614 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 9.98 (s, 1H), 6.94 (d, 1H), 6.77 (d, 1H), 5.41-5.10 (m, 1H), 4.76-4.34 (m, 4H), 4.12-3.94 (m, 2H), 3.90 (d, 1H), 3.14-2.93 (m, 3H), 2.82 (td, 1H), 2.57 (q, 2H), 2.13-2.03 (m, 1H), 1.99 (d, 1H), 1.97-

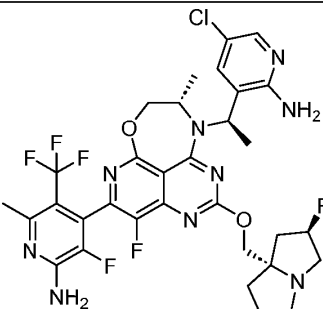
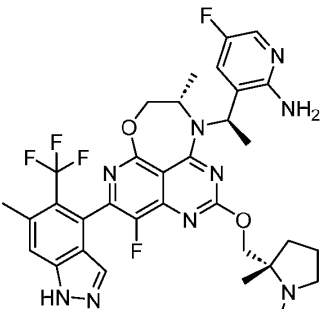
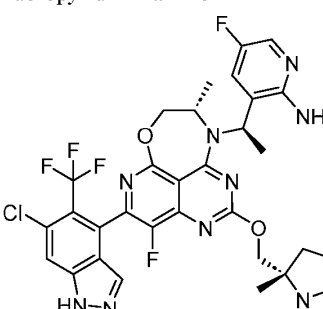
		1.88 (m, 1H), 1.87 – 1.79 (m, 1H), 1.79 – 1.69 (m, 4H), 1.27 (d, 3H), 1.01 (t, 3H), 0.63 (d, 2H), 0.06 (tt, 1H).
190 Compound 251	5-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-ethyl-3-fluoroquinolin-7-ol 	LCMS m/z = 631 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆) δ 10.38 (d, 1H), 8.79 (d, 1H), 7.42 (t, 1H), 7.14 (dd, 1H), 6.46 (t, 1H), 5.29 (d, 1H), 4.62 (dd, 1H), 4.53 – 4.29 (m, 2H), 4.27 – 4.10 (m, 3H), 4.06 (d, 1H), 3.16 – 2.93 (m, 3H), 2.84 (q, 1H), 2.35 – 2.18 (m, 2H), 2.14 (d, 1H), 2.08 – 1.94 (m, 2H), 1.81 (dt, 3H), 1.27 (d, 3H), 0.86 (dt, 3H).
191 Compound 253	4-((S)-10-(2,2-difluoroethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethyl-6-fluoroquinolin-2-amine 	LCMS m/z = 630 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆) δ 7.60 – 7.45 (m, 2H), 6.80 (d, 1H), 6.49 (t, 1H), 5.58 (d, 1H), 4.71 – 4.48 (m, 3H), 4.26 – 4.11 (m, 2H), 3.95 – 3.81 (m, 2H), 3.77 – 3.69 (m, 5H), 3.31 (dd, 2H), 2.49 – 2.35 (m, 1H), 2.33 – 2.29 (d, 1H), 2.25 – 2.12 (m, 4H), 2.09 – 2.06 (m, 1H), 1.29 (d, 3H), 0.85 – 0.81 (m, 1H), 0.79 – 0.76 (m, 2H).
192 Compound 422	4-ethyl-5-((S)-10-ethyl-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-(2-hydroxyethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-3-fluoroquinolin-7-ol	LCMS m/z = 625 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆) δ 8.78 (d, 1H), 7.69 – 7.30 (m, 1H), 7.26 – 6.96 (m, 1H), 5.28 (d, 1H), 4.78 (dd, 1H), 4.70 – 4.60 (m, 1H), 4.41 (dd, 1H), 4.35 – 4.21 (m, 1H), 4.15 (dd, 2H), 4.05 (d, 1H), 3.92 – 3.80 (m, 1H), 3.59 – 3.47 (m, 1H), 3.05 (d, 4H), 2.83 (q, 1H), 2.33 (p, 2H), 2.13 (s, 1H), 2.03 (d, 1H), 1.91

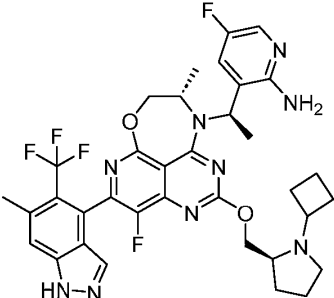
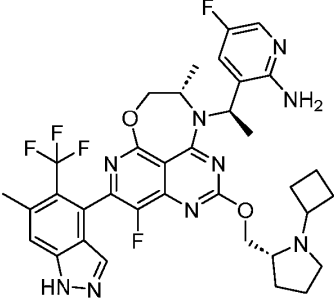
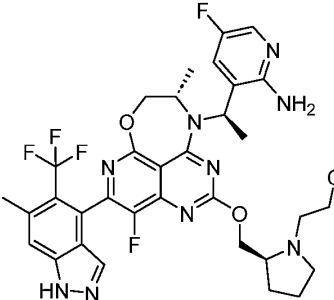
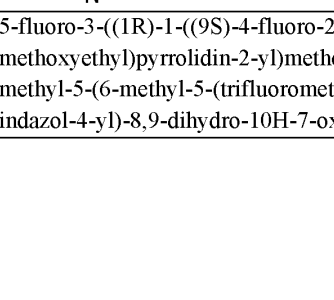
		– 1.65 (m, 5H), 1.34 – 1.16 (m, 4H), 0.85 (dq, 3H).
193 Compound 296	3-((S)-10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol 	LCMS m/z = 682 [M+H]⁺ ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 7.99 (d, 1H), 7.68 (dd, 1H), 6.93 (d, 1H), 6.74 (s, 1H), 6.51 (d, 1H), 5.62 (s, 2H), 5.36 (d, 1H), 4.52 – 4.49 (m, 1H), 4.35 – 4.31 (m, 1H), 4.13 – 4.09 (m, 3H), 3.15 – 3.09 (m, 2H), 3.05 – 3.02 (m, 1H), 2.89 – 2.83 (m, 1H), 2.19 – 2.12 (m, 1H), 2.09 – 2.03 (m, 1H), 1.89 – 1.80 (m, 1H), 1.79 – 1.71 (m, 4H), 1.61 – 1.52 (m, 3H), 0.61 – 0.59 (m, 2H), 0.59 – 0.58 (m, 3H), 0.10 – 0.09 (m, 2H).
194 Compound 298	4-((S)-10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine 	LCMS m/z = 690 [M+H]⁺ ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 10.79 (brs, 1H), 8.12 – 7.97 (m, 1H), 7.83 – 7.67 (m, 1H), 7.23 – 6.78 (m, 1H), 6.57 – 6.43 (m, 1H), 6.38 – 6.17 (m, 1H), 5.71 – 5.40 (m, 1H), 4.79 – 4.63 (m, 1H), 4.63 – 4.43 (m, 2H), 4.39 – 4.25 (m, 1H), 4.20 – 4.04 (m, 1H), 3.98 – 3.77 (m, 3H), 3.24 – 3.06 (m, 1H), 2.70 – 2.57 (m, 3H), 2.41 – 2.27 (m, 2H), 2.27 – 1.93 (m, 4H), 1.70 – 1.50 (m, 3H), 1.34 – 1.08 (m, 1H), 0.72 – 0.51 (m, 3H).
195 Compound 323	4-((S)-10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-9-methyl-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine 	LCMS m/z = 646 [M+H]⁺ ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ 9.93 (brs, 1H), 8.06 – 8.01 (m, 1H), 7.80 – 7.70 (m, 1H), 7.44 – 7.61 (m, 2H), 6.53 – 6.41 (m, 1H), 6.35 – 6.22 (m, 1H), 4.90 – 4.79 (m, 1H),

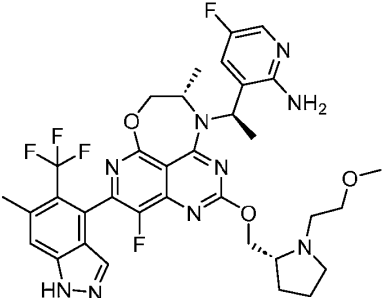
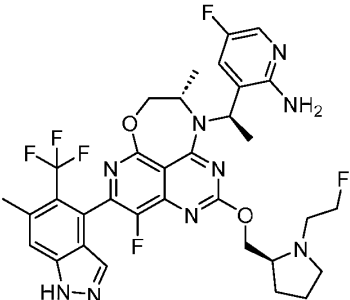
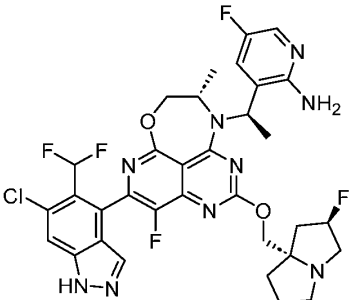
		4.68 – 4.49 (m, 2H), 4.37 – 4.28 (m, 1H), 4.16 – 4.09 (m, 1H), 3.92 – 3.81 (m, 1H), 3.36 – 3.27 (m, 1H), 3.22 – 3.06 (m, 1H), 3.04 – 2.90 (m, 3H), 2.48 – 2.44 (m, 3H), 2.35 – 2.21 (m, 1H), 2.14 – 2.02 (m, 1H), 2.00 – 1.83 (m, 2H), 1.66 – 1.33 (m, 3H), 0.64 – 0.55 (m, 3H).
196 Compound 418	6-((S)-10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-4-chloro-5-cyclopropylpyridin-2-amine 	LCMS m/z = 682 [M+H] ⁺ 1H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.76 (s, 1H), 7.95 (d, 1H), 7.67 – 7.65 (m, 1H), 7.17 – 6.92 (m, 1H), 6.61 (s, 1H), 6.44 – 6.43 (m, 1H), 5.67 – 5.45 (m, 1H), 4.58 (d, 1H), 4.52 – 4.45 (m, 2H), 4.25 (d, 1H), 4.21 – 4.04 (m, 2H), 3.79 – 3.75 (m, 1H), 3.70 – 3.64 (s, 2H), 2.43 – 2.42 (m, 2H), 2.29 – 2.27 (m, 3H), 2.25 – 2.16 (m, 2H), 2.13 – 2.11 (m, 2H), 1.98 (s, 1H), 1.58 – 1.56 (m, 4H), 0.53 – 0.55 (m, 4H).
197 Compound 417	3-chloro-4-cyclopropyl-5-((S)-10-((S)-1,1-difluoropropan-2-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol or 3-chloro-4-cyclopropyl-5-((S)-10-((R)-1,1-difluoropropan-2-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)phenol	Peak 2 LCMS m/z = 622 [M+H] ⁺

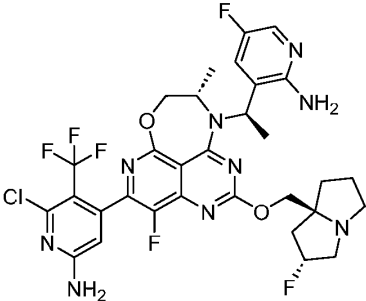
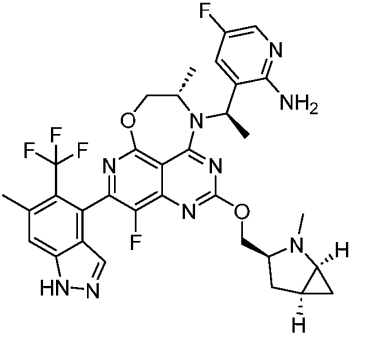
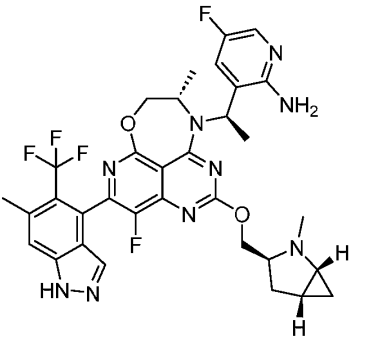
198 Compound 415	5-chloro-3-((1R)-1-((9S)-2-(((S)-1,2-dimethylpyrrolidin-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine	LCMS $m/z = 700$ $[M+H]^+$ 1H NMR (400 MHz, $DMSO-d_6$) δ 13.53 (s, 1H), 10.08 – 9.50 (m, 1H), 8.05 (d, 1H), 7.80 (t, 1H), 7.74 – 7.66 (m, 2H), 6.51 (p, 1H), 5.96 (s, 2H), 4.75 (d, 1H), 4.56 (tt, 2H), 4.35 (ddd, 1H), 4.24 – 4.12 (m, 1H), 3.37 – 3.11 (m, 1H), 2.85 (dd, 3H), 2.70 – 2.57 (m, 4H), 2.33 – 1.81 (m, 3H), 1.64 (d, 3H), 1.51 (s, 1H), 1.40 (s, 2H), 0.67 (dd, 3H).
199 Compound 414	(9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-10-((R)-1-(pyridin-3-yl)ethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene or (9S)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-10-((S)-1-(pyridin-3-yl)ethyl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalene	LCMS $m/z = 681$ $[M+H]^+$ 1H NMR (400 MHz, $DMSO-d_6$) δ 13.54 (s, 1H), 8.81 – 8.79 (d, 1H), 8.76 – 8.58 (d, 1H), 8.24 – 7.96 (m, 1H), 7.81 – 7.75 (m, 2H), 7.73 – 7.52 (m, 1H), 6.62 – 6.60 (m, 1H), 5.76 – 5.45 (m, 4H), 4.39 – 4.31 (m, 1H), 4.25 – 4.11 (m, 2H), 3.87 – 3.80 (m, 1H), 3.32 – 3.28 (m, 2H), 2.67 – 2.64 (m, 3H), 2.32 – 2.15 (m, 3H), 2.11 – 1.98 (m, 1H), 1.78 – 1.64 (m, 3H), 1.34 – 1.23 (m, 2H), 0.92 – 0.73 (m, 1H).

		
200 Compound 303	8-((S)-10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-1-ethyl-6-hydroxyquinolin-2(1H)-one 	LCMS $m/z = 685 [M+H]^+$ 1H NMR (400 MHz, DMSO-d_6) δ: 9.87 – 9.93 (m, 1H), 8.01 – 8.09 (m, 2H), 7.81 – 7.89 (m, 1H), 7.18 – 7.27 (m, 2H), 6.92 – 7.02 (m, 3H), 6.62 – 6.65 (m, 1H), 6.47 – 6.61 (m, 1H), 5.48 – 5.67 (m, 1H), 4.63 – 4.72 (m, 1H), 4.58 – 4.61 (m, 2H), 4.28 – 4.36 (m, 1H), 4.08 – 4.16 (m, 1H), 4.01 – 4.04 (m, 2H), 3.83 – 3.91 (m, 6H), 2.31 – 2.39 (m, 1H), 2.09 – 2.23 (m, 2H), 1.98 – 2.08 (m, 1H), 1.61 – 1.69 (m, 3H), 0.72 – 0.89 (m, 3H), 0.59 – 0.71 (m, 3H).
201 Compound 404	4-((S)-10-((R)-1-(2-amino-5-chloropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-3-fluoro-6-methyl-5-(trifluoromethyl)pyridin-2-amine 	LCMS $m/z = 724 [M+H]^+$ 1H NMR (400 MHz, DMSO-d_6) δ: 8.01 (t, 1H), 7.74 (d, 1H), 7.21 (d, 2H), 6.46 (d, 1H), 5.84 (d, 2H), 5.29 (d, 1H), 4.52 (dd, 1H), 4.34 (dd, 1H), 4.19 – 4.05 (m, 3H), 3.15 – 3.06 (m, 2H), 3.01 (s, 1H), 2.83 (q, 1H), 2.48 – 2.41 (m, 3H), 2.15 (d, 1H), 2.08 – 2.00 (m, 2H), 1.88 – 1.75 (m, 3H), 1.60 (d, 3H), 0.58 (d, 3H).

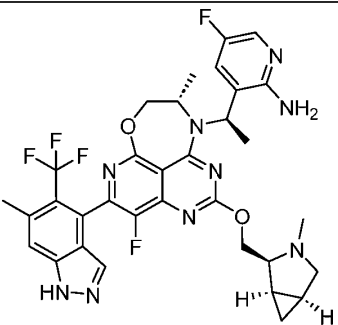
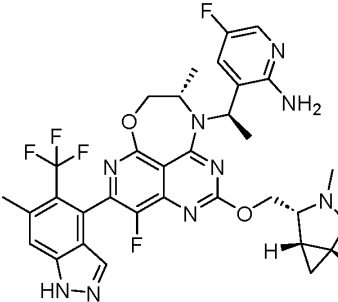
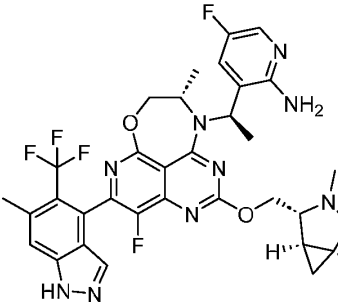
		
202 Compound 403		LCMS $m/z = 684$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.52 (s, 1H), 10.02 – 9.45 (m, 1H), 8.05 (dd, 1H), 7.85 – 7.58 (m, 3H), 6.67 – 6.41 (m, 1H), 4.79 – 4.63 (m, 2H), 4.57 (dddd, 2H), 4.36 (ddd, 1H), 4.24 – 4.10 (m, 1H), 3.63 (s, 1H), 3.28 (ddd, 1H), 2.85 (dd, 3H), 2.71 – 2.56 (m, 3H), 2.23 – 1.84 (m, 4H), 1.64 (d, 3H), 1.51 (s, 1H), 1.41 (s, 2H), 0.67 (dd, 3H).
203 Compound 395		LCMS $m/z = 704$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.84 (d, 1H), 8.09 (d, 1H), 8.03 (d, 1H), 7.86 (s, 1H), 7.73 (dd, 1H), 6.63 – 6.41 (m, 1H), 5.71 (d, 1H), 4.75 (d, 1H), 4.61 – 4.28 (m, 1H), 4.26 – 4.07 (m, 1H), 2.91 – 2.66 (m, 3H), 2.25 – 2.05 (m, 2H), 2.05 – 1.84 (m, 3H), 1.63 (d, 3H), 1.51 (s, 1H), 1.37 (d, 3H), 1.26 (d, 2H), 0.86 (q, 1H), 0.66 (dd, 3H).
204 Compound 394		LCMS $m/z = 710$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.49 (d, 1H), 8.00 (d, 1H), 7.71 (dt, 3H), 6.52 (dd, 1H), 5.60 (d, 2H), 4.60 – 4.41 (m, 2H), 4.35 (dd, 1H),

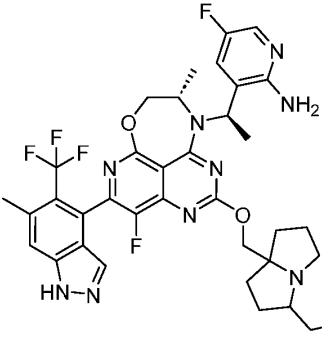
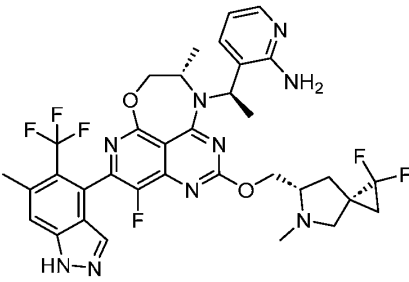
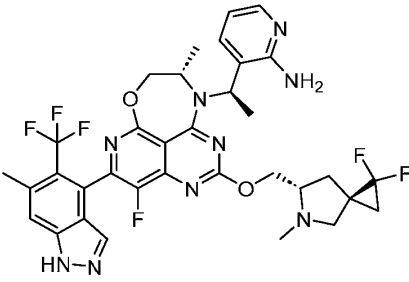
	tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine 	4.12 (q, 2H), 3.31-2.91 (m, 2H) 2.65 (ddt, 3H), 2.02 (d, 5H), 1.76 (s, 3H), 1.62 (d, 5H), 1.24 (s, 1H), 0.84 (q, 1H), 0.63 (dd, 3H).
205 Compound 393	3-((1R)-1-((9S)-2-(((R)-1-cyclobutylpyrrolidin-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine 	LCMS m/z = 710 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 8.01 (d, 1H), 7.82 – 7.71 (m, 3H), 7.67 (s, 1H), 6.63 – 6.50 (m, 1H), 4.62 (td, 2H), 4.50 (d, 1H), 4.05 (s, 2H), 4.33 (d, 1H), 3.80 (s, 2H), 3.40 (s, 1H), 3.06 (s, 1H), 2.74 – 2.61 (m, 3H), 2.37 – 2.18 (m, 5H), 1.98 (dt, 3H), 1.79 – 1.55 (m, 5H), 0.66 (dd, 3H).
206 Compound 392	5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-(((S)-1-(2-methoxyethyl)pyrrolidin-2-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 714 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 13.49 (d, 1H), 8.00 (d, 1H), 7.71 (q, 3H), 6.54 (q, 1H), 5.60 (d, 2H), 4.53 (ddd, 1H), 4.44 – 4.28 (m, 2H), 4.20 (ddd, 1H), 4.10 (dt, 1H), 3.41 (td, 3H), 3.18 (d, 3H), 3.10 – 2.98 (m, 2H), 2.91 (s, 1H), 2.70 – 2.58 (m, 3H), 2.38 – 2.20 (m, 1H), 1.97 – 1.83 (m, 1H), 1.70 (ddd, 3H), 1.61 (d, 3H), 0.62 (dd, 3H).
207 Compound 391	5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-(((R)-1-(2-methoxyethyl)pyrrolidin-2-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10- 	LCMS m/z = 714 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 8.01 (d, 1H), 7.89 – 7.63 (m, 3H), 6.56 (q, 1H), 4.74 – 4.50 (m, 4H),

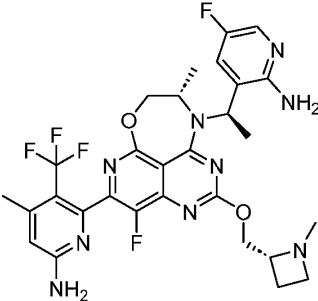
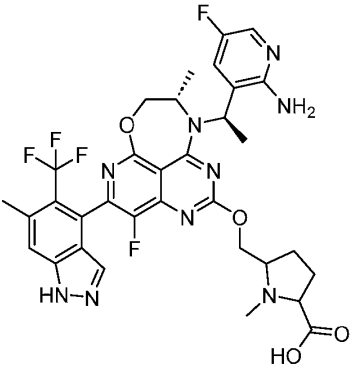
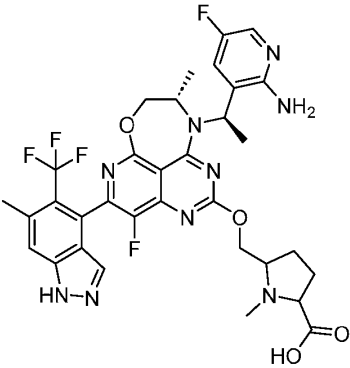
	tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	4.46 – 4.26 (m, 2H), 4.17 – 4.05 (m, 1H), 3.79 – 3.57 (m, 1H), 3.47 (s, 3H), 3.26 (d, 3H), 3.12 (s, 1H), 2.97 (s, 1H), 2.65 (dd, 3H), 2.28 – 2.11 (m, 1H), 2.03 – 1.75 (m, 3H), 1.63 (d, 4H), 0.66 (dd, 3H).
208 Compound 390	5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-(((S)-1-(2-fluoroethyl)pyrrolidin-2-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 702 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 13.51 (d, 1H), 9.97 (s, 1H), 8.02 (d, 1H), 7.82 – 7.56 (m, 3H), 6.51 (t, 1H), 5.60 (d, 2H), 4.98 – 4.70 (m, 4H), 4.56 (s, 1H), 4.33 (dd, 1H), 4.24 – 3.45 (m, 4H), 3.11–2.92 (m, 1H), 2.70 – 2.57 (m, 3H), 2.18 – 1.80 (m, 4H), 1.62 (d, 3H), 0.72 – 0.51 (m, 3H).
209 Compound 383	3-((1R)-1-((9S)-5-(6-chloro-5-(difluoromethyl)-1H-indazol-4-yl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine 	LCMS m/z = 716 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 13.70 (s, 1H), 10.83 (s, 1H), 8.03 (d, 1H), 7.97 (s, 1H), 7.87 (s, 1H), 7.73 (m, 1H), 7.00 (s, 1H), 6.55 (d, 1H), 5.68–5.53 (d, 3H), 4.73 (d, 1H), 4.60 (d, 1H), 4.31 (t, 1H), 4.19 (s, 1H), 3.89–3.72 (d, 3H), 2.67–2.52 (m, 1H), 2.32 (d, 2H), 2.25–2.06 (m, 3H), 1.63 (d, 3H), 1.23 (s, 1H), 0.67 (d, 3H).
210 Compound 382	4-(((S)-10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-	LCMS m/z = 710 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 7.99 (s, 1H), 7.68 (s, 1H), 7.27 (s, 2H), 6.77 (s, 1H), 6.48 (s, 1H), 5.56

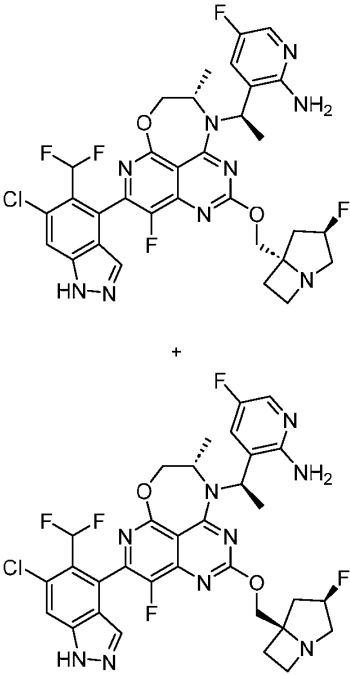
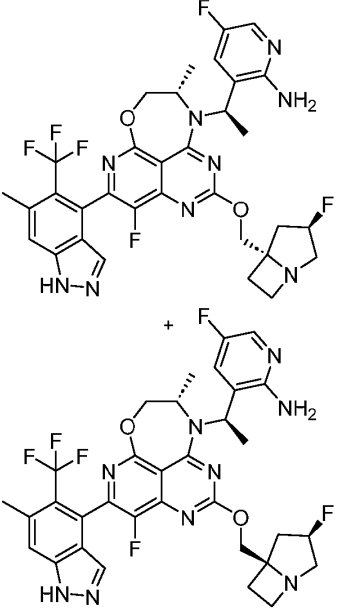
	1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-chloro-5-(trifluoromethyl)pyridin-2-amine 	(s, 2H), 5.22 (s, 1H), 4.51 (s, 1H), 4.31 (s, 1H), 4.10 (m, 3H), 3.11 (s, 1H), 2.98 (s, 1H), 2.81 (s, 1H), 2.15 (s, 1H), 2.05 (m, 2H), 1.86 (s, 1H), 1.80 (m, 2H), 1.60 (m, 3H) 1.24 (s, 1H), 0.55 (m, 3H).
211 Compound 381	5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-2-(((1S,3S,5S)-2-methyl-2-azabicyclo[3.1.0]hexan-3-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 682 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 13.50 (d, 1H), 8.00 (d, 1H), 7.71 (q, 3H), 6.52 (p, 1H), 5.60 (d, 2H), 4.53 (ddd, 1H), 4.44 – 4.23 (m, 2H), 4.13 (ddd, 2H), 3.44 (t, 3H), 2.64 (dd, 3H), 2.46 – 2.25 (m, 3H), 1.61 (d, 3H), 1.53 (dd, 1H), 1.43 (tdd, 1H), 0.69 – 0.49 (m, 4H), 0.31 (dt, 1H).
212 Compound 380	5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-2-(((1R,3S,5R)-2-methyl-2-azabicyclo[3.1.0]hexan-3-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS = 682 [M+H]⁺ ¹H NMR (400 MHz, DMSO-d₆) δ 8.00 (d, 1H), 7.78 – 7.62 (m, 3H), 6.50 (q, 1H), 6.08 (s, 1H), 5.58 (d, 2H), 4.53 (ddd, 1H), 4.45 – 4.31 (m, 2H), 4.26 (tt, 1H), 4.11 (q, 1H), 2.66 (ddd, 4H), 2.43 (d, 1H), 2.34 (d, 3H), 2.16 – 2.04 (m, 1H), 1.88 – 1.73 (m, 1H), 1.61 (d, 3H), 1.34 (ddd, 1H), 0.69 – 0.52 (m, 4H), 0.10 – 0.02 (m, 1H).

213 Compound 379	5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-2-(((1R,3R,5R)-2-methyl-2-azabicyclo[3.1.0]hexan-3-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine	LCMS $m/z = 682 [M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.53 (d, 1H), 8.02 (d, 1H), 7.78 – 7.61 (m, 3H), 6.59 – 6.41 (m, 1H), 5.62 (d, 2H), 4.66 – 4.27 (m, 4H), 4.14 (t, 1H), 3.30-2.72 (m, 4H), 2.64 (dd, 4H), 2.00 – 1.50 (m, 6H), 1.02-0.90 (d, 1H), 0.64 (dd, 4H).
214 Compound 378	5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-2-(((1S,3R,5S)-2-methyl-2-azabicyclo[3.1.0]hexan-3-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine	LCMS $m/z = 682 [M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.52 (d, 1H), 8.05 – 7.97 (m, 1H), 7.76 – 7.62 (m, 3H), 6.51 (dd, 1H), 5.62 (d, 2H), 4.77 – 4.25 (m, 4H), 4.13 (t, 1H), 2.81 (s, 4H), 2.64 (dd, 4H), 2.15 (d, 1H), 1.95 (d, 1H), 1.62 (d, 5H), 0.64 (dd, 4H)
215 Compound 376	5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-2-(((1R,2S,5S)-3-methyl-3-azabicyclo[3.1.0]hexan-2-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine	LCMS $m/z = 682 [M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 13.50 (d, 1H), 8.00 (d, 1H), 7.82 – 7.61 (m, 3H), 6.56 (q, 1H), 5.65 (d, 2H), 4.60 – 4.45 (m, 2H), 4.42 – 4.31 (m, 2H), 4.12 (m, 1H), 3.17 (s, 1H), 2.94 (d, 1H), 2.70 – 2.61 (m, 3H), 2.38 (s, 3H), 1.63 (d, 3H), 1.53 – 1.42 (m, 2H), 0.66 (d, 2H), 0.59 (t, 3H), 0.45 (d, 1H).

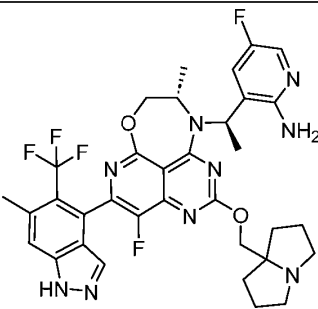
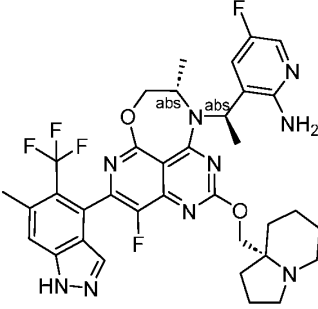
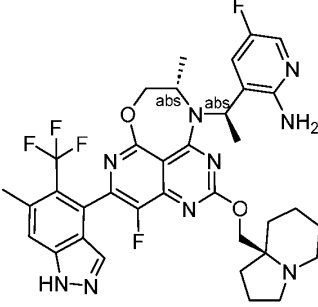
		
216 Compound 375	5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-2-(((1S,2R,5R)-3-methyl-3-azabicyclo[3.1.0]hexan-2-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 682 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆) δ 8.00 (d, 1H), 7.83 – 7.64 (m, 3H), 6.60 – 6.49 (m, 1H), 5.64 (d, 2H), 4.61 – 4.47 (m, 2H), 4.36 (dd, 1H), 4.26 – 4.07 (m, 2H), 2.98 (d, 1H), 2.83 (dt, 1H), 2.70 – 2.59 (m, 2H), 2.29 (s, 4H), 2.11 – 2.04 (m, 1H), 1.60 (dd, 3H), 1.45 – 1.33 (m, 1H), 1.24 (s, 3H), 0.87 (d, 1H), 0.69 – 0.52 (m, 2H), 0.30 (qd, 1H).
217 Compound 374	5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-2-(((1R,2R,5S)-3-methyl-3-azabicyclo[3.1.0]hexan-2-yl)methoxy)-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 682 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆) δ 8.00 (d, 1H), 7.83 – 7.64 (m, 3H), 6.60 – 6.49 (m, 1H), 5.64 (d, 2H), 4.61 – 4.47 (m, 2H), 4.36 (dd, 1H), 4.26 – 4.07 (m, 2H), 2.98 (d, 1H), 2.83 (dt, 1H), 2.70 – 2.59 (m, 2H), 2.29 (s, 4H), 2.11 – 2.04 (m, 1H), 1.60 (dd, 3H), 1.45 – 1.33 (m, 1H), 1.24 (s, 3H), 0.87 (dd, 1H), 0.69 – 0.52 (m, 2H), 0.30 (qd, 1H).
218 Compound 360	(7a-(((9S)-10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-9,10-dihydro-8H-7-oxa-1,3,6,10-	LCMS m/z = 726 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆) δ 13.54 (d, 1H), 8.02 (s, 1H), 7.87 – 7.56 (m, 3H), 6.55 (d, 1H), 5.65 (t,

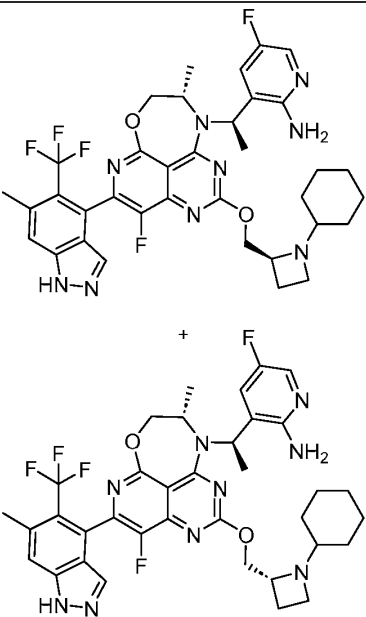
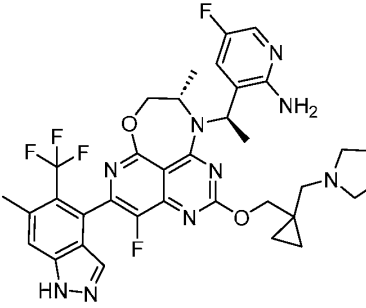
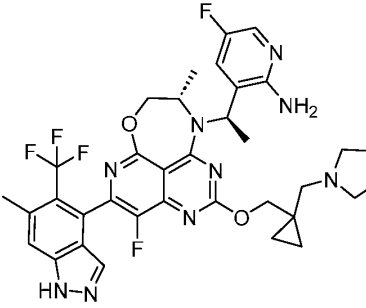
	tetraazacyclohepta[de]naphthalen-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methanol 	2H), 5.35 (s, 1H), 4.74 – 4.43 (m, 3H), 4.35 (dd, 1H), 4.15 (s, 1H), 3.72 (s, 3H), 2.70 – 2.61 (m, 4H), 2.31 (d, 2H), 2.03 (s, 7H), 1.68 – 1.56 (m, 3H), 0.78 – 0.49 (m, 3H).
219 Compound 359	3-((1R)-1-((9S)-2-(((3S,6S)-1,1-difluoro-5-methyl-5-azaspiro[2.4]heptan-6-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-cyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 714 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 0.60 (m, 2H), 0.84 (s, 1H), 1.24 (s, 2H), 1.47 (s, 2H), 1.61 (m, 3H), 1.87 – 1.96 (m, 1H), 2.03 – 2.09 (m, 1H), 2.38 (s, 2H), 2.64 (s, 2H), 2.96 (m, 2H), 4.05 (s, 1H), 4.31 (s, 1H), 4.36 (m, 2H), 4.49 – 4.57 (m, 2H), 5.57 (s, 1H), 5.64 (s, 1H), 6.54 (s, 1H), 6.71 (s, 1H), 7.72 (s, 3H), 8.00 (s, 1H), 13.53 (s, 1H).
220 Compound 358	3-((1R)-1-((9S)-2-(((3S,6S)-1,1-difluoro-5-methyl-5-azaspiro[2.4]heptan-6-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-cyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 714 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 13.50 (s, 1H), 8.00 (s, 1H), 7.72 (m, 3H), 6.70 (s, 1H), 6.54 (s, 1H), 5.66 (s, 1H), 5.58 (s, 1H), 4.40 – 4.60 (m, 3H), 4.34 (m, 2H), 4.01 – 4.09 (m, 1H), 2.89 (m, 2H), 2.64 (m, 2H), 2.57 (s, 1H), 2.37 (m, 3H), 2.20 – 2.33 (m, 1H), 1.73 – 1.84 (m, 1H), 1.61 (m, 2H), 1.57 (s, 1H), 1.45 (s, 1H), 1.23 (s, 1H), 0.84 (s, 1H), 0.60 (m, 2H).
221 Compound 353	6-((S)-10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-9-methyl-2-(((R)-1-methylazetidin-2-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-	LCMS m/z = 632 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆) δ 7.99 (d, 1H), 7.68 (dd, 1H), 6.80 (s, 2H), 6.50 (d, 2H), 5.56 (s, 2H), 4.52-

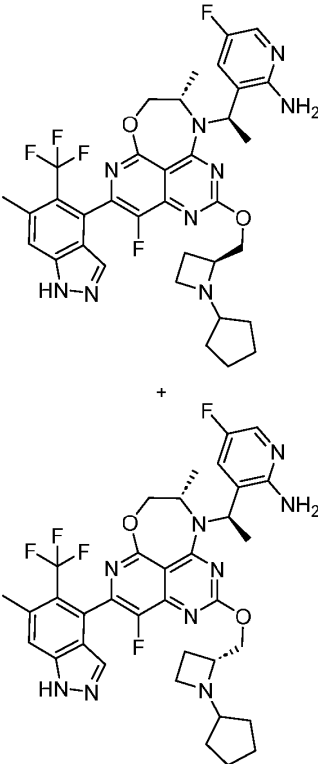
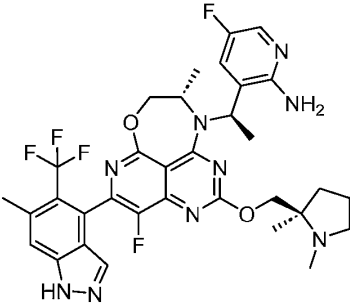
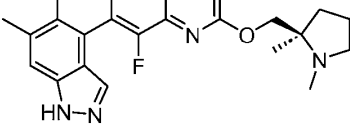
	tetraazacyclohepta[de]naphthalen-5-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine 	4.49 (m, 1H), 4.42 - 4.21 (m, 3H), 4.11 - 4.03 (m, 1H), 3.39 (s, 2H), 2.78-2.74 (m, 1H), 2.38 - 2.33 (m, 3H), 2.27 (s, 3H), 2.06 - 1.91 (m, 2H), 1.60 (d, 3H), 0.55 (d, 3H)
222 Compound 351	(2R,5R)-5-((((9S)-10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-2-yl)oxy)methyl)-1-methylpyrrolidine-2-carboxylic acid 	LCMC $m/z = 714 [M+H]^+$ 1H NMR (400 MHz, DMSO-d_6) δ 13.50 (d, 1H), 8.00 (d, 1H), 7.87 - 7.62 (m, 3H), 6.54 (d, 1H), 5.66 (d, 1H), 5.58 (d, 1H), 4.52 (ddt, 2H), 4.45 - 4.26 (m, 2H), 4.17 - 4.05 (m, 1H), 3.25 - 2.83 (m, 6H), 2.64 (dd, 3H), 2.05 (dq, 2H), 1.80 - 1.42 (m, 4H), 0.72 - 0.53 (m, 3H).
223 Compound 350	3-((1R)-1-((9S)-5-(6-chloro-5-(difluoromethyl)-1H-indazol-4-yl)-4-fluoro-2-(((3R,5S)-3-fluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine 	LCMS $m/z = 702 [M+H]^+$ 1H NMR (400 MHz, DMSO-d_6) δ 13.67 (s, 1H), 8.01 (d, 1H), 7.92 (d, 2H), 7.70 (d, 1H), 7.03 (td, 1H), 6.55 (d, 1H), 5.71 - 5.49 (m, 3H), 4.54 (dd, 2H), 4.38 - 4.19 (m, 2H), 4.12 (s, 1H), 3.06 (s, 2H), 2.99 (s, 1H), 2.92 (d, 2H), 2.25 (dd, 2H), 2.13 (td, 1H), 1.62 (d, 3H), 0.65 (d, 3H).

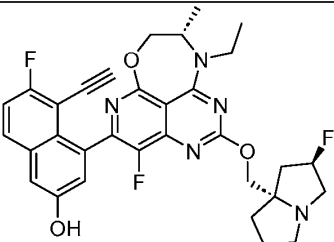
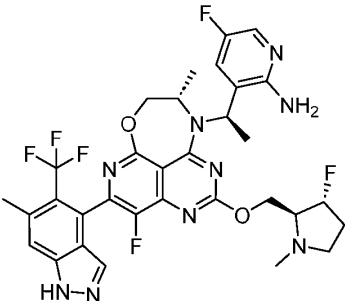
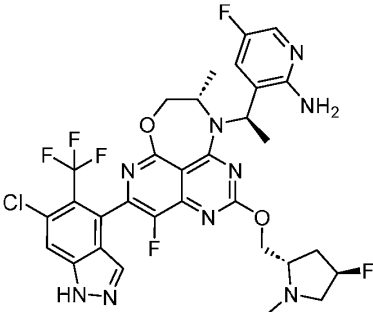
		
224 Compound 349	5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-(((3R,5S)-3-fluoro-1-azabicyclo[3.2.0]heptan-5-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS $m/z = 700$ $[M+H]^+$ 1H NMR (400 MHz, $DMSO-d_6$) δ 13.52 (d, 1H), 8.01 (d, 1H), 7.80 – 7.65 (m, 3H), 6.54 (m, 1H), 5.73 – 5.49 (m, 3H), 4.63 – 4.49 (m, 2H), 4.36 (dd, 1H), 4.24 (dd, 1H), 4.16 – 4.06 (m, 1H), 3.12 – 2.94 (m, 4H), 2.64 (d, 3H), 2.47 – 2.36 (m, 2H), 2.27– 2.16 (m, 2H), 1.62 (d, 3H), 0.63 (dd, 3H).

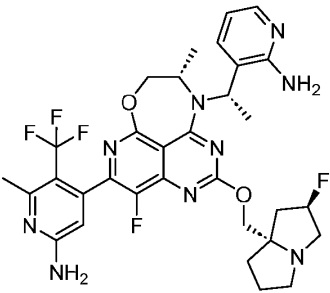
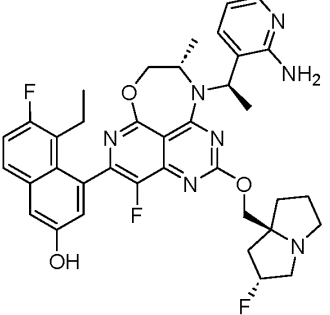
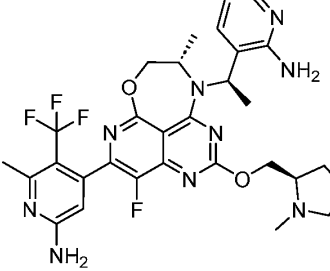
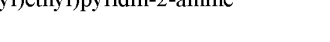
225 Compound 412	3-((1R)-1-((9S)-2-((dihydro-1H,3'H-spiro[cyclopropane-1,2'-pyrrolizin]-7a'(5'H)-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-cyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine	LCMS m/z = 722 [M+H] ⁺
226 Compound 368	5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-(((2S,4R)-4-fluoropyrrolidin-2-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine	LCMS m/z = 674 [M+H] ⁺
227 Compound 407	5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine	LCMS m/z = 696 [M+H] ⁺

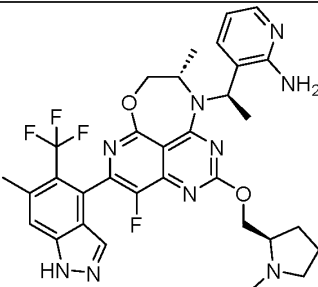
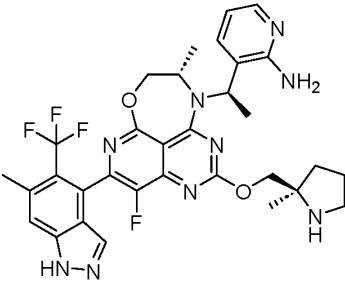
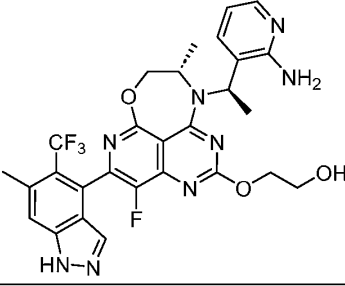
		
228 Compound 405	5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-((hexahydroindolizin-8a(1H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine  + 	LCMS m/z = 710 [M+H] ⁺
229 Compound 406	3-((1R)-1-((9S)-2-((1-cyclohexylazetidin-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine	LCMS m/z = 724 [M+H] ⁺

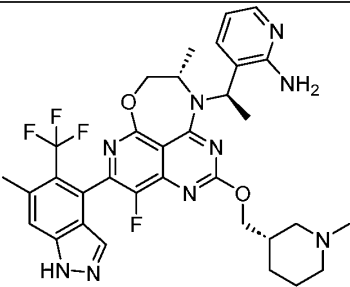
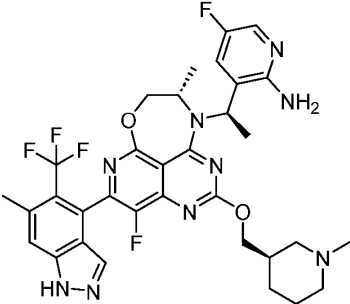
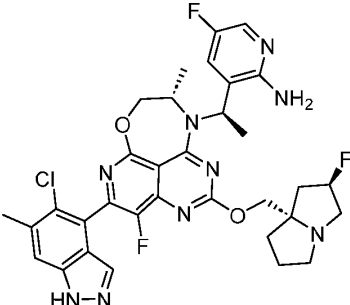
		
230 Compound 389	5-fluoro-3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine: 	LCMS m/z = 710 [M+H] ⁺
231 Compound 388	3-((1R)-1-((9S)-2-((1-cyclopentylazetidin-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine 	LCMS m/z = 710 [M+H] ⁺

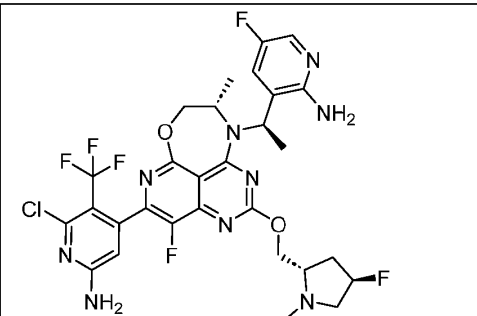
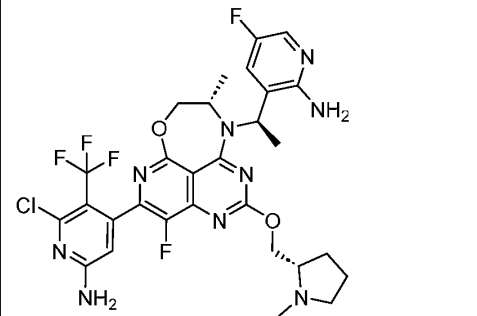
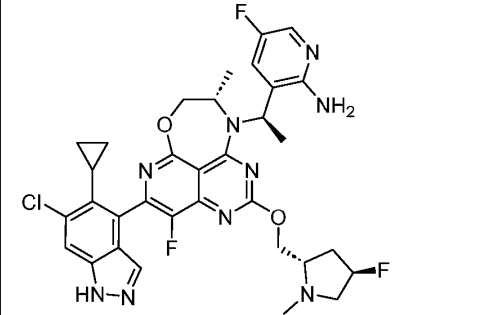
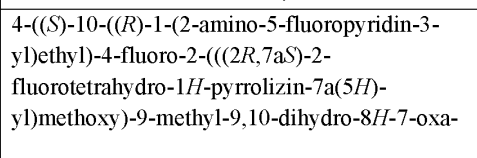
		
232 Compound 436	3-(((1<i>R</i>)-1-((9<i>S</i>)-2-(((<i>R</i>)-1,2-dimethylpyrrolidin-2-yl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1<i>H</i>-indazol-4-yl)-8,9-dihydro-10<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine 	LCMS m/z = 684 $[M+H]^+$ ¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ 13.50 (br s, 1H), 8.00 (d, 1H), 7.72-7.69 (m, 3H), 6.55 (t, 1H), 5.70-5.62 (m, 2H), 4.55-4.49 (m, 1H), 4.40-4.27 (m, 2H), 4.22-4.19 (m, 1H), 4.14-4.11 (m, 1H), 2.79-2.71 (m, 1H), 2.59-2.52 (m, 5H), 2.28 (s, 3H), 1.73-1.58 (m, 6H), 1.06 (s, 3H), 0.63 (dd, 3H),
233 Compound 222	4-((<i>S</i>)-10-ethyl-4-fluoro-2-(((2<i>R</i>,7<i>aS</i>)-2-fluorotetrahydro-1<i>H</i>-pyrrolizin-7<i>a</i>(5<i>H</i>)-yl)methoxy)-9-methyl-9,10-dihydro-8<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethynyl-6-fluoronaphthalen-2-ol 	LCMS m/z = 590 $[M+H]^+$ ¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ 10.14 (brs, 1H), 7.96 (dd, 1H), 7.49-7.43 (m, 1H), 7.37 (d, 1H), 7.20-7.11 (m, 1H), 5.36-5.22 (m, 1H), 4.56-4.51 (m, 1H), 4.35-4.32 (m, 1H), 4.17-4.02 (m, 5H), 3.54-3.49 (m, 1H), 3.15-3.02 (m, 3H), 2.87-2.81

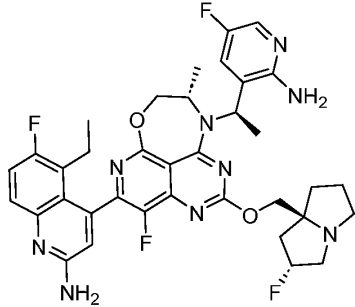
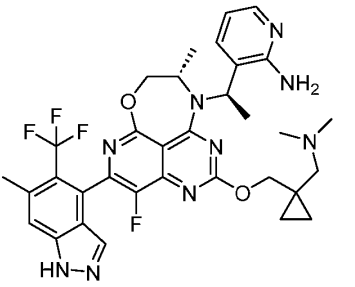
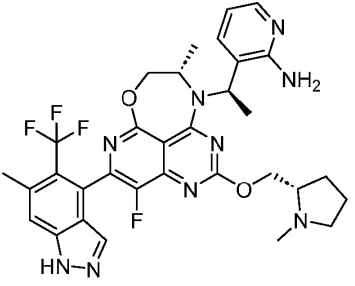
		(m, 1H), 2.14-2.02 (m, 3H), 1.87-1.75 (m, 3H), 1.31-1.27 (m, 6H).
234 Compound 372	5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-((2S,3R)-3-fluoro-1-methylpyrrolidin-2-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 688 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆): δ 13.51 (s, 1H), 8.01 (s, 1H), 7.73-7.69 (m, 3H), 6.54 (t, 1H), 5.64 (s, 1H), 5.57 (s, 1H), 5.20-5.06 (m, 1H), 4.60-4.45 (m, 2H), 4.40-4.31 (m, 1H), 4.30-4.05 (m, 2H), 3.31-3.28 (m, 1H), 3.00-2.75 (m, 3H), 2.70-2.60 (m, 3H), 2.44 (s, 3H), 2.10-1.90 (m, 2H), 1.63 (d, 2H), 0.63 (dd, 3H),
235 Compound 428	3-(((1R)-1-((9S)-5-(6-chloro-5-(trifluoromethyl)-1H-indazol-4-yl)-4-fluoro-2-((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-9-methyl-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine 	LCMS m/z = 708 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆): δ 13.85-13.65 (m, 1H), 8.08 (d, 1H), 8.01 (d, 1H), 7.87 (s, 1H), 7.70 (d, 1H), 6.55-6.50 (m, 1H), 5.65-5.55 (m, 2H), 5.27-5.12 (m, 1H), 4.60-4.25 (m, 4H), 4.15-4.05 (m, 1H), 3.10-2.97 (m, 2H), 2.41 (s, 3H), 2.25-2.10 (m, 2H), 2.00-1.90 (m, 1H), 1.62 (d, 3H), 0.63 (dd, 3H)
236 Compound 223	4-(((S)-10-((S)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-	Peak 2 LCMS m/z = 672 [M+H] ⁺ 1H NMR (400 MHz, DMSO-d ₆): δ 7.99 (d, 1H), 7.72 (d, 1H), 6.80 (s, 2H), 6.71 (dd, 1H), 6.43 (q, 1H), 6.26 (s, 1H), 5.58 (s, 2H), 5.29-5.21 (m, 1H), 4.34 (dd, 1H), 4.20 (d, 1H), 4.05 (d, 1H), 3.95-3.85 (m,

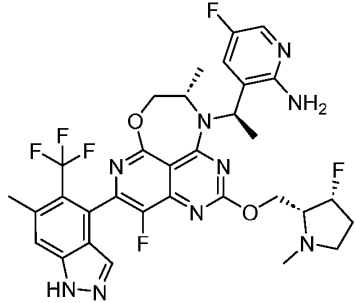
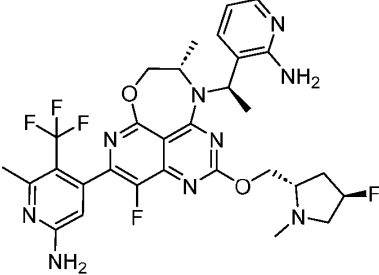
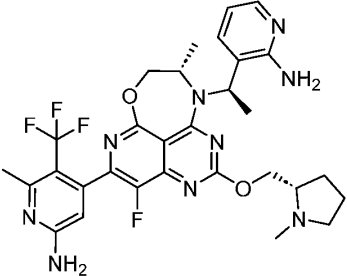
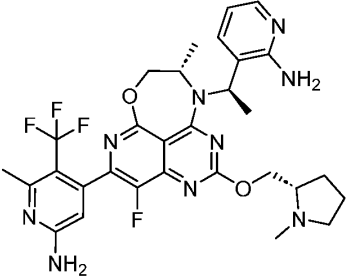
	methyl-5-(trifluoromethyl)pyridin-2-amine 	2H), 3.13-3.05 (m, 2H), 3.01 (s, 1H), 2.86-2.77 (m, 1H), 2.48 (d, 3H), 2.17-2.10 (m, 1H), 2.10-1.95 (m, 2H), 1.90-1.70 (m, 3H), 1.61 (d, 3H), 1.15 (d, 3H).
237 Compound 234	4-((S)-10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethyl-6-fluoronaphthalen-2-ol 	LCMS m/z = 686 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆): δ 9.98 (br s, 1H), 8.31-7.97 (m, 1H), 7.78-7.68 (m, 2H), 7.39-7.29 (m, 2H), 7.07-6.95 (m, 1H), 6.74-6.67 (m, 1H), 6.58-6.49 (m, 1H), 5.70-5.59 (m, 2H), 5.40-5.19 (m, 1H), 4.59-4.50 (m, 1H), 4.39-4.29 (m, 1H), 4.19-3.98 (m, 3H), 3.2-3.01 (m, 3H), 2.89-2.79 (m, 1H), 2.31-1.97 (m, 4H), 1.91-1.73 (m, 3H), 1.66-1.50 (m, 4H), 0.89-0.75 (m, 3H), 0.61-0.51 (m, 3H).
238 Compound 327	4-((S)-10-((R)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-9-methyl-2-(((R)-1-methylpyrrolidin-2-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine 	LCMS m/z = 628 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆): δ 7.99 (dd, 1H), 7.70 (dd, 1H), 6.81 (s, 2H), 6.69 (dd, 1H), 6.52 (q, 1H), 6.25 (s, 1H), 5.57 (s, 2H), 4.64-4.44 (m, 2H), 4.32 (d, 1H), 4.23 (dd, 1H), 4.07-3.98 (m, 1H), 3.01-2.93 (m, 1H), 2.67-2.58 (m, 1H), 2.47 (d, 3H), 2.37 (s, 3H), 2.19 (q, 1H), 2.01-1.91 (m, 1H), 1.77-1.62 (m, 3H), 1.60 (d, 3H), 0.54 (d, 3H)
239 Compound 288	3-((1R)-1-((9S)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-2-(((R)-1-methylpyrrolidin-2-yl)methoxy)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 652 [M+H]⁺ 1H NMR (400 MHz, DMSO-d₆): δ 13.52-13.48 (m, 1H), 8.01 (dd, 1H), 7.80-7.68 (m, 3H), 6.75-6.65 (m, 1H), 6.61-6.49 (m, 1H), 5.69 (s, 1H), 5.61 (s, 1H), 4.60-4.44 (m, 2H), 4.38-4.36 (m, 1H), 4.29-4.20 (m,

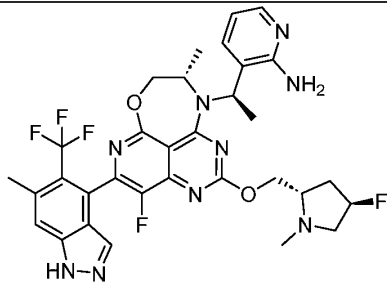
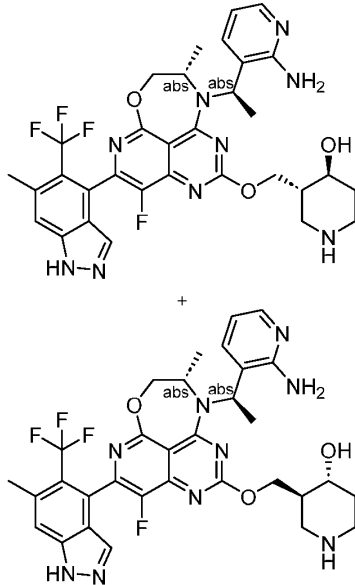
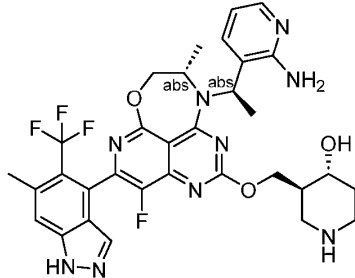
		1H), 4.10-4.00 (m, 1H), 3.01-2.93 (m, 1H), 2.70-2.60 (m, 4H), 2.37 (s, 3H), 2.25-2.15 (m, 1H), 2.02-1.89 (m, 1H), 1.76-1.58 (m, 6H), 0.60 (dd, 3H)
240 Compound 286	3-(((1<i>R</i>)-1-((9<i>S</i>)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1<i>H</i>-indazol-4-yl)-2-((<i>R</i>)-2-methylpyrrolidin-2-yl)methoxy)-8,9-dihydro-10<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[<i>de</i>]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS $m/z = 652$ $[M+H]^+$ 1H NMR (400 MHz, DMSO-d_6): δ 13.52-13.48 (m, 1H), 8.01 (dd, 1H), 7.75-7.65 (m, 3H), 6.74-6.66 (m, 1H), 6.61-6.51 (m, 1H), 5.72 (s, 1H), 5.63 (s, 1H), 4.60-4.50 (m, 1H), 4.38-4.36 (m, 1H), 4.24-4.12 (m, 2H), 4.10-4.01 (m, 1H), 2.99-2.77 (m, 2H), 2.69-2.60 (m, 4H), 1.84-1.70 (m, 3H), 1.62 (d, 3H), 1.55-1.45 (m, 1H), 1.21 (s, 3H), 0.60 (dd, 3H).
241 Compound 421	2-(((9<i>S</i>)-10-((<i>R</i>)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1<i>H</i>-indazol-4-yl)-9,10-dihydro-8<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[<i>de</i>]naphthalen-2-yl)oxy)ethan-1-ol 	LCMS $m/z = 599$ $[M+H]^+$ 1H NMR (400 MHz, DMSO-d_6): δ 13.52-13.48 (m, 1H), 8.01 (dd, 1H), 7.78-7.66 (m, 3H), 6.74-6.68 (m, 1H), 6.61-6.51 (m, 1H), 5.63-5.56 (m, 2H), 4.94 (t, 1H), 4.60-4.26 (m, 4H), 4.09-3.99 (m, 1H), 3.77 (q, 2H), 2.70-2.61 (m, 3H), 1.61 (d, 3H), 0.60 (dd, 3H).
242 Compound 294	3-(((1<i>R</i>)-1-((9<i>S</i>)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1<i>H</i>-indazol-4-yl)-2-(((<i>S</i>)-1-methylpiperidin-3-yl)methoxy)-8,9-dihydro-10<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[<i>de</i>]naphthalen-10-yl)ethyl)pyridin-2-amine	LCMS $m/z = 666$ $[M+H]^+$ 1H NMR (400 MHz, DMSO-d_6): δ 13.52-13.46 (m, 1H), 8.01 (d, 1H), 7.72 (t, 3H), 6.72-6.56 (m, 2H), 5.75-5.55 (m, 2H), 4.55-4.52 (m, 1H), 4.35-4.30 (m, 3H), 4.06-4.03 (m, 1H), 2.82-2.64 (m, 5H), 2.16 (s, 3H), 2.08-2.06 (m, 1H), 1.91-1.83 (m, 2H), 1.73-1.61 (m, 5H),

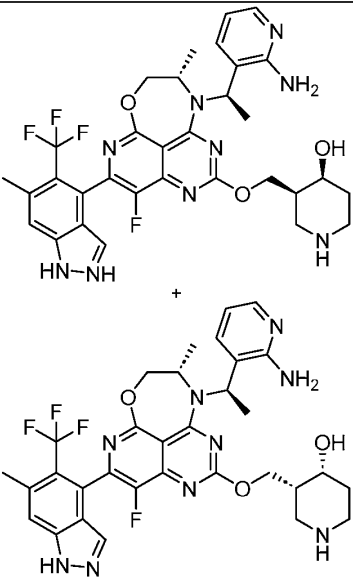
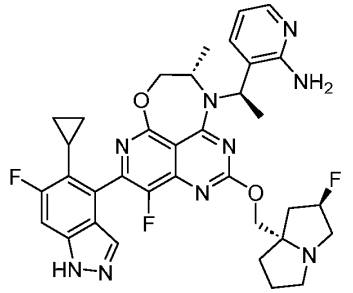
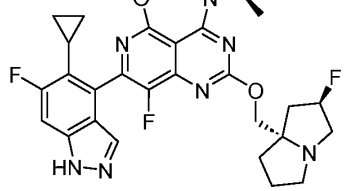
		1.51–1.48 (m, 1H), 1.11–1.15 (m, 1H), 0.60 (dd, 3H).
243 Compound 402	5-fluoro-3-((1<i>R</i>)-1-((9<i>S</i>)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1<i>H</i>-indazol-4-yl)-2-(((<i>R</i>)-1-methylpiperidin-3-yl)methoxy)-8,9-dihydro-10<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[<i>de</i>]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 684 $[M+H]^+$ ¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ 13.52–13.46 (m, 1H), 8.01 (d, 1H), 7.77–7.68 (m, 3H), 6.57–6.50 (m, 1H), 5.66–5.53 (m, 2H), 4.60–4.49 (m, 1H), 4.43–4.30 (m, 2H), 4.27–4.05 (m, 2H), 2.83 (d, 1H), 2.69–2.60 (m, 4H), 2.18 (s, 3H), 2.12–2.01 (m, 1H), 1.98–1.78 (m, 2H), 1.76–1.59 (m, 5H), 1.57–1.42 (m, 1H), 1.16–1.02 (m, 1H), 0.63 (dd, 3H)
244 Compound 397	3-((1<i>R</i>)-1-((9<i>S</i>)-5-(5-chloro-6-methyl-1<i>H</i>-indazol-4-yl)-4-fluoro-2-(((2<i>R</i>,7<i>aS</i>)-2-fluorotetrahydro-1<i>H</i>-pyrrolizin-7<i>a</i>(5<i>H</i>)-yl)methoxy)-9-methyl-8,9-dihydro-10<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[<i>de</i>]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine 	LCMS m/z = 680 $[M+H]^+$ ¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ 13.31–13.28 (m, 1H), 8.01 (d, 1H), 7.79–7.64 (m, 3H), 6.54 (br s, 1H), 5.69–5.52 (m, 2H), 5.38–5.19 (m, 1H), 4.60–4.49 (m, 1H), 4.41–4.30 (m, 1H), 4.20–4.05 (m, 3H), 3.15–3.07 (m, 2H), 3.06–3.00 (m, 1H), 2.88–2.78 (m, 1H), 2.57–2.53 (m, 3H), 2.21–1.99 (m, 3H), 1.91–1.75 (m, 3H), 1.62 (d, 3H), 0.63 (br d, 3H)
245 Compound 387	4-((<i>S</i>)-10-((<i>R</i>)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2<i>S</i>,4<i>R</i>)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-9-methyl-9,10-dihydro-8<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[<i>de</i>]naphthalen-5-yl)-6-chloro-5-(trifluoromethyl)pyridin-2-amine 	LCMS m/z = 684 $[M+H]^+$ ¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ 8.00 (d, 1H), 7.68 (dd, 1H), 7.40 (s, 2H), 6.45–6.35 (m, 2H), 5.54 (s, 2H), 5.33–5.07 (m, 1H), 4.59–4.31 (m, 4H), 4.15–4.03 (m, 1H), 3.51–3.40 (m, 2H), 3.01–2.91 (m, 1H),

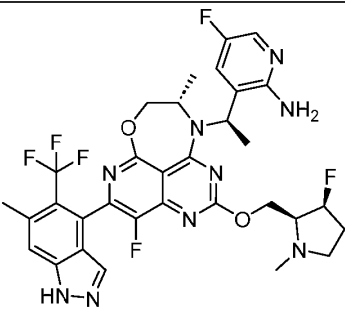
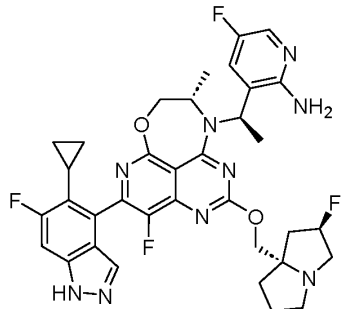
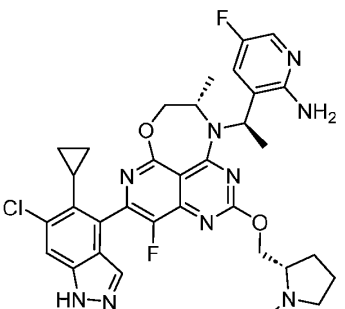
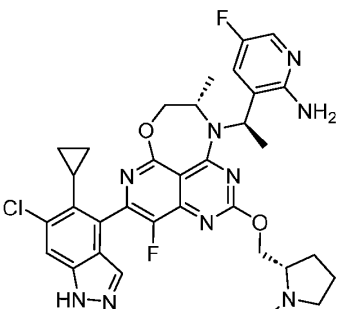
		2.41 (s, 3H), 2.24–2.09 (m, 1H), 2.05–1.85 (m, 1H), 1.60 (d, 3H), 0.57 (d, 3H)
246 Compound 373	4-((<i>S</i>)-10-((<i>R</i>)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-9-methyl-2-(((<i>S</i>)-1-methylpyrrolidin-2-yl)methoxy)-9,10-dihydro-8<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-chloro-5-(trifluoromethyl)pyridin-2-amine 	LCMS m/z = 666 $[M+H]^+$ ¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ 7.99 (d, 1H), 7.68 (dd, 1H), 7.39 (s, 2H), 6.49–6.35 (m, 2H), 5.53 (s, 2H), 4.59–4.23 (m, 4H), 4.13–4.02 (m, 1H), 3.00–3.94 (m, 1H), 2.68–2.59 (m, 1H), 2.37 (s, 3H), 2.26–2.15 (m, 1H), 2.01–1.90 (m, 1H), 1.77–1.61 (m, 3H), 1.60 (d, 3H), 0.57 (d, 3H)
247 Compound 344	3-((1<i>R</i>)-1-((9<i>S</i>)-5-(6-chloro-5-cyclopropyl-1<i>H</i>-indazol-4-yl)-4-fluoro-2-(((2<i>S</i>,4<i>R</i>)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-9-methyl-8,9-dihydro-10<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine 	LCMS m/z = 680 $[M+H]^+$ ¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ 13.28 (br s, 1H), 7.98 (d, 1H), 7.85–7.62 (m, 3H), 6.62–6.45 (m, 1H), 5.58 (d, 2H), 5.28–5.05 (m, 1H), 4.61–4.30 (m, 4H), 4.13–4.02 (m, 1H), 3.45–3.35 (m, 2H), 3.01–2.91 (m, 1H), 2.40 (s, 3H), 2.25–2.11 (m, 1H), 2.02–1.84 (m, 2H), 1.95–1.71 (m, 2H), 0.95–0.71 (m, 2H), 0.63 (dd, 3H), 0.28–0.05 (m, 2H)
248 Compound 437	4-((<i>S</i>)-10-((<i>R</i>)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2<i>R</i>,7<i>aS</i>)-2-fluorotetrahydro-1<i>H</i>-pyrrolizin-7<i>a</i>(5<i>H</i>)-yl)methoxy)-9-methyl-9,10-dihydro-8<i>H</i>-7-oxa- 	LCMS m/z = 704 $[M+H]^+$ ¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ 8.01 (d, 1H), 7.70 (dd, 1H), 7.51–7.37 (m, 2H), 6.74–6.46 (m, 4H), 5.66–5.54 (m, 2H), 5.37–5.20 (m,

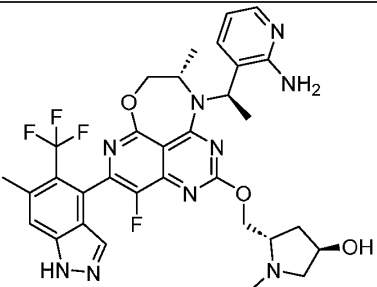
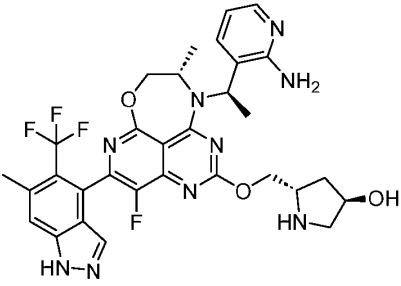
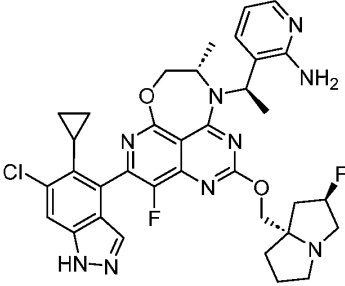
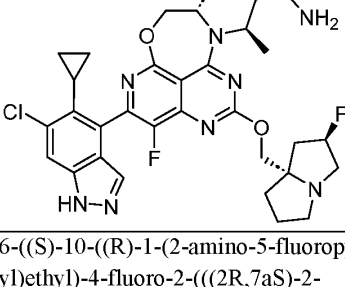
	1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-ethyl-6-fluoroquinolin-2-amine 	1H), 4.58-4.50 (m, 1H), 4.36 (t, 1H), 4.19-4.08 (m, 3H), 3.17-2.99 (m, 3H), 2.87-2.78 (m, 1H), 2.45-2.37 (m, 1H), 2.28-1.99 (m, 4H), 1.92-1.74 (m, 3H), 1.66-1.58 (m, 3H), 0.89-0.74 (dt, 3H), 0.63-0.54 (t, 3H)
249 Compound 419	3-((1 <i>R</i>)-1-((9 <i>S</i>)-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1 <i>H</i> -indazol-4-yl)-8,9-dihydro-10 <i>H</i> -7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS $m/z = 666 [M+H]^+$ 1H NMR (400 MHz, DMSO- d_6): δ 13.51-13.46 (m, 1H), 8.00 (t, 1H), 7.55-7.65 (m, 3H), 6.70 (t, 1H), 6.55 (t, 1H), 5.69-5.65 (m, 2H), 4.60-4.48 (m, 1H), 4.47-4.17 (m, 3H), 4.09-3.99 (m, 1H), 2.67-2.61 (m, 3H), 2.34-2.27 (m, 1H), 2.21-2.15 (m, 7H), 1.62 (d, 3H), 0.68-0.53 (m, 5H), 0.43 (br s, 2H)
250 Compound 248	3-(1-((9 <i>S</i>)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1 <i>H</i> -indazol-4-yl)-2-(((<i>S</i>)-1-methylpyrrolidin-2-yl)methoxy)-8,9-dihydro-10 <i>H</i> -7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS $m/z = 652 [M+H]^+$ 1H NMR (400 MHz, DMSO- d_6): δ 13.61-13.49 (m, 1H), 9.78 (br s, 1H), 8.16-8.02 (m, 2H), 7.78-7.62 (m, 2H), 7.08-6.72 (m, 2H), 6.58-6.48 (m, 1H), 4.92-4.83 (m, 1H), 4.68-4.55 (m, 2H), 4.44-4.32 (m, 1H), 4.15 (t, 1H), 3.88-3.82 (m, 1H), 3.65-3.60 (m, 1H), 3.20-3.13 (m, 1H), 2.99 (s, 3H), 2.71-2.63 (m, 3H), 2.31-2.24 (m, 1H), 2.15-2.03 (m, 1H), 2.01-1.88 (m, 2H), 1.67 (d, 3H), 0.69 (dd, 3H)
251 Compound 385	5-fluoro-3-((1 <i>R</i>)-1-((9 <i>S</i>)-4-fluoro-2-(((2 <i>R</i> ,3 <i>R</i>)-3-fluoro-1-methylpyrrolidin-2-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1 <i>H</i> -indazol-4-yl)-8,9-dihydro-10 <i>H</i> -7-oxa-1,3,6,10-	LCMS $m/z = 688 [M+H]^+$ 1H NMR (400 MHz, DMSO- d_6): δ 13.47-13.44 (m, 1H), 8.01 (d, 1H), 7.74-7.70 (m, 3H), 6.55-6.51 (m,

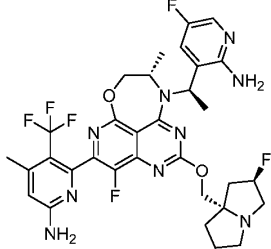
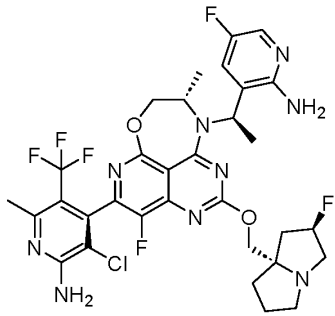
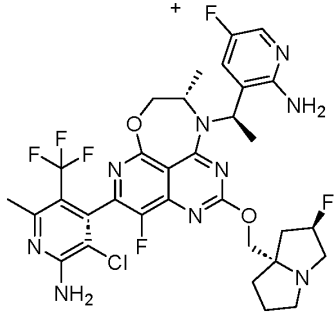
	tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	1H), 5.64-5.56 (m, 2H), 5.32-5.19 (m, 1H), 4.60-4.51 (m, 3H), 4.40-4.32 (m, 1H), 4.13-4.08 (m, 1H), 3.11 (t, 1H), 2.67-2.61 (m, 4H), 2.38-2.31 (m, 3H), 2.25-2.21 (m, 2H), 2.20-2.08 (m, 1H), 1.93-1.62 (m, 3H), 0.64 (dd, 3H)
252 Compound 326	4-((<i>S</i>)-10-((<i>R</i>)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-2-(((2<i>S</i>,4<i>R</i>)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-9-methyl-9,10-dihydro-8<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine 	LCMS m/z = 646 $[M+H]^+$ 1H NMR (400 MHz, DMSO-d_6): δ 8.00 (dd, 1H), 7.70 (d, 1H), 6.81 (s, 2H), 6.70 (dd, 1H), 6.53-6.48 (m, 1H), 6.25 (s, 1H), 5.57 (s, 2H), 5.27-5.13 (m, 1H), 4.55-4.41 (m, 3H), 4.32 (d, 1H), 4.02 (t, 1H), 3.51-3.40 (m, 1H), 2.99-2.95 (m, 1H), 2.58-2.51 (m, 1H), 2.47 (d, 3H), 2.42 (s, 3H), 2.23-2.09 (m, 1H), 2.03-1.85 (m, 1H), 1.59 (d, 3H), 0.53 (d, 3H)
253 Compound 325	4-((<i>S</i>)-10-((<i>R</i>)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-9-methyl-2-(((<i>S</i>)-1-methylpyrrolidin-2-yl)methoxy)-9,10-dihydro-8<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-6-methyl-5-(trifluoromethyl)pyridin-2-amine 	LCMS m/z = 628 $[M+H]^+$ 1H NMR (400 MHz, DMSO-d_6): δ 7.99 (dd, 1H), 7.70-7.69 (m, 1H), 6.81 (s, 2H), 6.70 (dd, 1H), 6.51 (dd, 1H), 6.25 (s, 1H), 5.55 (s, 2H), 4.52 (dd, 1H), 4.44 (dd, 1H), 4.33-4.25 (m, 2H), 4.03-4.00 (m, 1H), 3.00-2.96 (m, 1H), 2.65-2.60 (m, 1H), 2.50 (s, 3H), 2.48 (s, 3H), 2.23-2.16 (m, 1H), 1.99-1.90 (m, 1H), 1.72-1.59 (m, 6H), 0.54 (d, 3H)
254 Compound 319	3-(((1<i>R</i>)-1-((9<i>S</i>)-4-fluoro-2-(((2<i>S</i>,4<i>R</i>)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1<i>H</i>-indazol-4-yl)-8,9-dihydro-10<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 670 $[M+H]^+$ 1H NMR (400 MHz, DMSO-d_6): δ 13.53-13.46 (m, 1H), 8.01 (dd, 1H), 7.74-7.71 (m, 3H), 6.72-6.69 (m, 1H), 6.55 (t, 1H), 5.68 (s, 1H), 5.60 (s, 1H), 5.30-5.10 (m, 1H), 4.47-4.43 (m, 1H), 4.05 (t, 1H), 3.48-3.41 (m, 1H), 3.00-2.96 (m, 1H), 2.65 (d,

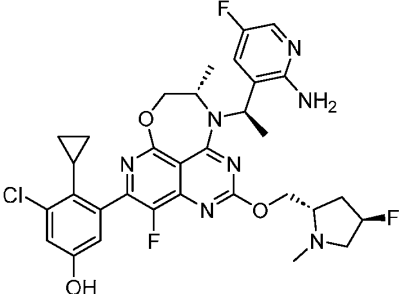
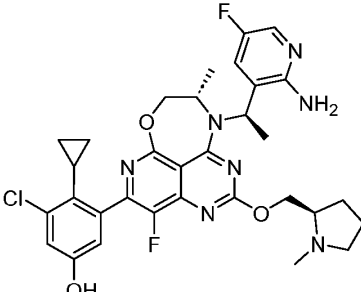
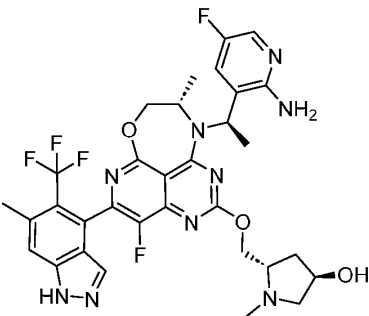
		3H), 2.42 (s, 3H), 2.31-2.10 (m, 1H), 2.05-1.86 (m, 1H), 1.62 (d, 3H), 1.49-1.39 (m, 1H), 1.32-1.11 (m, 2H), 0.89-0.73 (m, 1H), 0.64-0.57 (m, 3H)
255 Compound 293	(3<i>RS</i>,4<i>SR</i>)-3-(((9<i>S</i>)-10-((<i>R</i>)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1<i>H</i>-indazol-4-yl)-9,10-dihydro-8<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[<i>de</i>]naphthalen-2-yl)oxy)methyl)piperidin-4-ol 	LCMS $m/z = 668 [M+H]^+$ 1H NMR (400 MHz, DMSO-d_6): δ 13.54 (bs, 1H), 8.00 (dd, 1H), 7.74-7.71 (m, 3H), 6.72-6.69 (m, 1H), 6.60-6.51 (m, 1H), 5.68-5.51 (m, 2H), 4.80-4.51 (m, 3H), 4.39-4.22 (m, 2H), 4.06-4.03 (m, 1H), 3.50-3.52 (m, 2H), 3.15-3.11 (m, 1H), 2.92-2.94 (m, 1H), 2.68-2.63 (m, 3H), 2.50-2.42 (m, 1H), 2.34-2.33 (m, 1H), 1.87-1.77 (m, 2H), 1.61 (d, 3H), 1.45-1.43 (m, 1H), 0.59 (dd, 3H)
256 Compound 291	(3<i>RS</i>,4<i>RS</i>)-3-(((9<i>S</i>)-10-((<i>R</i>)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1<i>H</i>-indazol-4-yl)-9,10-dihydro-8<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[<i>de</i>]naphthalen-2-yl)oxy)methyl)piperidin-4-ol 	LCMS $m/z = 668 [M+H]^+$ 1H NMR (400 MHz, DMSO-d_6): δ 13.51 (bs, 1H), 8.00 (d, 1H), 7.74-7.71 (m, 3H), 6.71-6.56 (m, 2H), 5.63 (dd, 2H), 4.55-4.33 (m, 6H), 4.04-3.93 (m, 2H), 2.77-2.64 (m, 6H), 2.34-2.07 (m, 1H), 1.62-1.55 (m, 5H), 0.59 (dd, 3H)

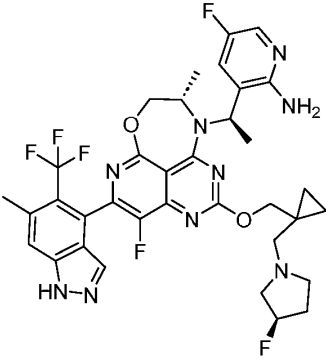
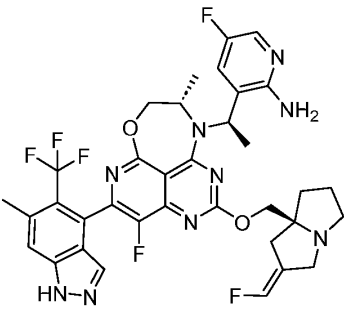
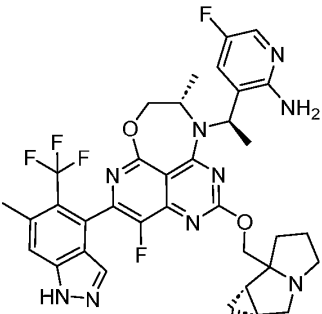
		
257 Compound 386	3-((1<i>R</i>)-1-((9<i>S</i>)-5-(5-cyclopropyl-6-fluoro-1<i>H</i>-indazol-4-yl)-4-fluoro-2-(((2<i>R</i>,7<i>aS</i>)-2-fluorotetrahydro-1<i>H</i>-pyrrolizin-7<i>a</i>(5<i>H</i>)-yl)methoxy)-9-methyl-8,9-dihydro-10<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS $m/z = 672 [M+H]^+$ ¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ 13.21-13.17 (m, 1H), 8.00 (d, 1H), 7.78-7.71 (m, 2H), 7.42 (d, 1H), 6.71 (dd, 1H), 6.55 (br s, 1H), 5.66 (s, 2H), 5.36-5.23 (m, 1H), 4.61-4.50 (m, 1H), 4.34 (d, 1H), 4.16 (s, 2H), 4.05 (t, 1H), 3.12-3.09 (m, 2H), 3.02 (s, 1H), 2.86-2.83 (m, 1H), 2.18-2.04 (m, 3H), 1.92-1.77 (m, 4H), 1.62 (d, 3H), 0.67-0.57 (m, 5H), 0.30-0.27 (m, 2H)
258 Compound 361	5-fluoro-3-((1<i>R</i>)-1-((9<i>S</i>)-4-fluoro-2-(((2<i>S</i>,3<i>S</i>)-3-fluoro-1-methylpyrrolidin-2-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1<i>H</i>-indazol-4-yl)-8,9-dihydro-10<i>H</i>-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS $m/z = 688 [M+H]^+$ ¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ 13.54-13.47 (m, 1H), 8.01 (d, 1H), 7.74-7.69 (m, 3H), 6.56-6.50 (m, 1H), 5.66-5.57 (m, 2H), 5.46-5.33 (m, 1H), 4.59-4.51 (m, 3H), 4.40-4.32 (m, 1H), 4.12 (t, 1H), 3.14-3.09 (m, 1H), 2.68-2.67 (m, 3H), 2.65-2.61 (m, 1H), 2.35 (s, 3H), 2.35-2.13 (m, 2H), 1.95-1.79 (m, 1H), 1.63 (d, 3H), 0.63 (dd, 3H)

		
259 Compound 435	3-((1 <i>R</i>)-1-(((9 <i>S</i>)-5-(5-cyclopropyl-6-fluoro-1 <i>H</i> -indazol-4-yl)-4-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)-9-methyl-8,9-dihydro-10 <i>H</i> -7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine 	LCMS $m/z = 690$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6): δ 13.21 (br s, 1H), 8.03 (s, 1H), 7.79-7.45 (m, 3H), 6.55 (br s, 1H), 5.65 (s, 2H), 5.39-5.20 (m, 1H), 4.57-4.53 (m, 1H), 4.38-4.33 (m, 1H), 4.15-4.11 (m, 3H), 3.11-3.02 (m, 3H), 2.86-2.80 (m, 1H), 2.16-2.04 (m, 3H), 1.87-1.65 (m, 5H), 1.63 (d, 3H), 0.67-0.29 (m, 6H)
260 Compound 343	3-((1 <i>R</i>)-1-(((9 <i>S</i>)-5-(6-chloro-5-cyclopropyl-1 <i>H</i> -indazol-4-yl)-4-fluoro-9-methyl-2-(((<i>S</i>)-1-methylpyrrolidin-2-yl)methoxy)-8,9-dihydro-10 <i>H</i> -7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)-5-fluoropyridin-2-amine 	LCMS $m/z = 663$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6): δ 13.26-13.22 (m, 1H), 8.01 (d, 1H), 7.81-7.69 (m, 3H), 6.56-6.53 (m, 1H), 5.62-5.61 (m, 2H), 4.45-4.26 (m, 4H), 4.12-4.11 (m, 1H), 2.97-2.96 (m, 1H), 2.65-2.51 (m, 1H), 2.37-2.31 (m, 3H), 2.20-2.16 (m, 1H), 1.98-1.91 (m, 2H), 1.72-1.63 (m, 7H), 0.91-0.60 (m, 4H), 0.32-0.12 (m, 2H)
261 Compound 287	(3 <i>R</i> ,5 <i>S</i>)-5-(((9 <i>S</i>)-10-((<i>R</i>)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1 <i>H</i> -indazol-4-yl)-9,10-dihydro-8 <i>H</i> -7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol 	LCMS $m/z = 668$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6): δ 13.51-13.46 (m, 1H), 8.01 (d, 2H), 7.72-7.70 (m, 3H), 6.72-6.69 (m, 1H), 6.57-6.50 (m, 1H), 6.09-5.78 (m, 2H), 4.79 (d, 2H), 4.54-4.03 (m,

		4H), 3.60-3.62 (m, 1H), 3.33-3.21 (m, 1H), 2.84-2.86 (m, 1H), 2.68-2.64 (m, 3H), 2.36-2.32 (m, 3H), 2.16-1.80 (m, 3H), 1.62 (d, 3H), 0.60 (dd, 3H)
262 Compound 285	(3 <i>R</i> ,5 <i>S</i>)-5-(((9 <i>S</i>)-10-((<i>R</i>)-1-(2-aminopyridin-3-yl)ethyl)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1 <i>H</i> -indazol-4-yl)-9,10-dihydro-8 <i>H</i> -7-oxa-1,3,6,10-tetraazacyclohepta[<i>de</i>]naphthalen-2-yl)oxy)methyl)pyrrolidin-3-ol 	LCMS $m/z = 654$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6): δ 13.53-13.47 (m, 1H), 8.01-8.00 (m, 1H), 7.74-7.68 (m, 3H), 6.72-6.69 (m, 1H), 6.57-6.55 (m, 1H), 5.67-5.59 (m, 2H), 4.61 (d, 1H), 4.55-4.53 (m, 1H), 4.38-4.21 (m, 4H), 4.06-4.03 (m, 1H), 3.70-3.61 (m, 1H), 2.90-2.89 (m, 1H), 2.69-2.64 (m, 4H), 1.83-1.72 (m, 1H), 1.63-1.57 (m, 5H), 0.60 (dd, 3H).
263 Compound 342	obtain 3-(((1 <i>R</i>)-1-((9 <i>S</i>)-5-(6-chloro-5-cyclopropyl-1 <i>H</i> -indazol-4-yl)-4-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)-9-methyl-8,9-dihydro-10 <i>H</i> -7-oxa-1,3,6,10-tetraazacyclohepta[<i>de</i>]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS $m/z = 688$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6): δ 13.26-13.21 (m, 1H), 8.01 (d, 1H), 7.81-7.71 (m, 3H), 6.72-6.69 (m, 1H), 6.59-6.51 (m, 1H), 5.68-5.67 (m, 2H), 5.37-5.23 (m, 1H), 4.57-4.55 (m, 1H), 4.38-4.35 (m, 1H), 4.15 (d, 2H), 4.09-4.02 (m, 1H), 3.12-3.03 (m, 3H), 2.89-2.81 (m, 1H), 2.20-2.11 (m, 1H), 2.18-2.01 (m, 2H), 1.91-1.72 (m, 4H), 1.64-1.62 (m, 3H), 0.92-0.71 (m, 2H), 0.61 (dd, 3H), 0.31-0.05 (m, 2H).
264 Compound 420	6-(((<i>S</i>)-10-((<i>R</i>)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2 <i>R</i> ,7 <i>aS</i>)-2-fluorotetrahydro-1 <i>H</i> -pyrrolizin-7 <i>a</i> (5 <i>H</i>)-yl)methoxy)-9-methyl-9,10-dihydro-8 <i>H</i> -7-oxa-1,3,6,10-tetraazacyclohepta[<i>de</i>]naphthalen-5-yl)-4-methyl-5-(trifluoromethyl)pyridin-2-amine 	LCMS $m/z = 690$ $[M+H]^+$ 1H NMR (400 MHz, DMSO- d_6) δ 8.03 (d, 1H), 7.73 (dd, 1H), 6.90 - 6.72 (m, 2H), 6.49 (d, 2H), 5.85 - 5.51 (m, 3H), 4.68 (d, 1H), 4.62 - 4.50 (m, 2H), 4.30 (d, 1H), 4.18 - 4.10 (m, 1H), 3.98 - 3.95 (m, 1H),

		3.92 - 3.72 (m, 3H) , 3.24 - 3.21 (m, 1H), 2.63 - 2.52 (m, 1H) ,2.35 (d, 4H), 2.17 - 2.12 (m, 2H), 2.06 - 1.98 (s, 1H), 1.60 (d, 3H), 0.59 (d, 3H).
265 Compound 413	(R)-4-((S)-10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-3-chloro-6-methyl-5-(trifluoromethyl)pyridin-2-amine or (S)-4-((S)-10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-3-chloro-6-methyl-5-(trifluoromethyl)pyridin-2-amine  	LCMS m/z = 724 [M+H]⁺ ¹H NMR: (400 MHz, DMSO-d₆) δ ppm 8.00 (d, 1H) 7.68 (dd, 1H) 7.23 - 7.35 (m, 1H) 6.49 (q, 1H) 5.58 (s, 2H) 5.19 - 5.40 (m, 1H) 4.47 - 4.58 (m, 1H) 4.37 (d, 1H) 4.03 - 4.16 (m, 3H) 3.02 - 3.11 (m, 3H) 2.80 - 2.89 (m, 1H) 2.48 (br d, 3H) 1.99 - 2.21 (m, 3H) 1.74 - 1.89 (m, 3H) 1.61 (br d, 3H) 0.56 (d, 3H)
266 Compound 369	3-((S)-10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-2-(((2S,4R)-4-fluoro-1-methylpyrrolidin-2-yl)methoxy)-9-methyl-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol	LCMS m/z = 656 [M+H]⁺ ¹H NMR (300 MHz, DMSO- d₆): 9.95 (s, 1H), 7.99 (d, 1H), 7.70-7.64 (dd, 1H), 6.92 (d, 1H), 6.73 (d, 1H), 6.54-6.44 (m, 1H), 5.58 (brs, 2H), 5.32-5.08 (m, 1H), 4.6-4.3 (m, 4H),

		4.15-4.02 (m, 1H), 3.51-3.35 (m, 1H), 3.01-2.92 (m, 1H), 2.58-2.52 (m, 1H), 2.46-2.42 (m, 1H), 2.41 (s, 3H), 2.31-1.71 (m, 4H), 0.68-0.51 (m, 5H), 0.01-0.09 (m, 2H)
267 Compound 355	3-((S)-10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-9-methyl-2-(((R)-1-methylpyrrolidin-2-yl)methoxy)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-5-yl)-5-chloro-4-cyclopropylphenol 	LCMS m/z = 638 [M+H] ⁺ 1H NMR (300 MHz, DMSO- d ₆): 10.05 (brs, 1 H), 7.98 (d, 1 H), 7.70-7.66 (dd, 1 H), 6.92 (d, 1 H), 6.73 (d, 1 H), 6.53-6.49 (m, 1 H), 5.58 (brs, 2 H), 4.54-4.42 (m, 2 H), 4.21-4.39 (m, 2 H), 4.16-4.06 (m, 2 H), 2.98-2.91 (m, 1 H), 2.66-2.55 (m, 1 H), 2.36 (s, 3H), 2.15-2.25 (m, 1 H), 2.02-1.92 (m, 1H), 1.51-1.81 (m, 8H), 0.71-0.51 (m, 5 H), 0.01 (m, 2 H)
268 Compound 408	(3R,5S)-5-((((9S)-10-((R)-1-(2-amino-5-fluoropyridin-3-yl)ethyl)-4-fluoro-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-9,10-dihydro-8H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol 	LCMS m/z = 686 [M+H] ⁺
269 Compound 409	5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-((1-(((R)-3-fluoropyrrolidin-1-yl)methyl)cyclopropyl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-	LCMS m/z = 728 [M+H] ⁺

	tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	
270 Compound 411	5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-(((S,E)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 726 [M+H] ⁺
271 Compound 410	5-fluoro-3-((1R)-1-((9S)-4-fluoro-2-(((1aR,6bS)-hexahydrocyclopropa[a]pyrrolizin-6a(4H)-yl)methoxy)-9-methyl-5-(6-methyl-5-(trifluoromethyl)-1H-indazol-4-yl)-8,9-dihydro-10H-7-oxa-1,3,6,10-tetraazacyclohepta[de]naphthalen-10-yl)ethyl)pyridin-2-amine 	LCMS m/z = 708 [M+H] ⁺

Example 272: KRAS G12D SOS1-mediated TR-FRET Assay

[00767] The ability of compounds to inhibit SOS1-mediated nucleotide exchange was measured using a TR-FRET assay. In a 10- μ L final assay volume, 5 μ L of GST-tagged KRAS G12D and 1 nM anti-GST-Tb were added to pre-dispensed compounds. The assay buffer consisted of 10 mM HEPES, pH 7.4, 150 mM NaCl, 0.05% BSA, 0.0025% Igepal and 5 mM MgCl₂. Then, 5 μ L of SOS1 and 10 nM EDA-GTP-DY-647P1 were added to initiate the nucleotide exchange reaction. After a 60-minute incubation at room temperature, the reaction was measured in a plate reader using excitation and emission wavelengths of 337 nm and 615/665 nm, respectively. IC₅₀ values were established using a four-parameter fit model. The results are shown in Table 3, where A is ≤ 10 nM; B is > 10 nm and ≤ 100 nM; C is > 100 nM and ≤ 1000 nM; D is > 1000 nM and ≤ 3000 nM; and E is > 3000 nM.

Table 3.

Comp. No.	KRAS-G12D-GDP-SOS-NEA	KRAS-G12V-GDP-SOS-NEA	KRAS-G12C-GDP-SOS-NEA	KRAS-WT-GDP-SOS-NEA
102	A			
103	A			
104	A			
105	B			
106	A			
107	A			
108	B			
109	A	A	A	A
110	A			
111	A			
112	A	A	A	A
113	A			
114	B			
115	B	A		
116	B			
117	B	A		
118	A	A	A	A
119	B			

120	A	A	A	A
121	A	A	A	A
122	A	A	A	A
123	A			
124	B			
125	A			
126	A	A	A	A
127	C			
128	C			
129	A	A	A	A
130	A	A	A	A
131	B			
132	C			
133	D			
134	B			
136	C			
137	C			
138	A	A	A	A
140	A	A	A	A
141	A	A	A	A
142	A			
143	A	A	A	A
144	A	A	A	B
145	A	A	A	A
146	A	A	A	A
148	A			
149	B			
150	B	A	A	A
151	A	A	A	A
152	A	A		
153	A	A	A	A
154	B			
155	A	A	A	A
156	C	B		
157	A	A	A	
158	A	A	A	

159	A	A	A	
160	D	C		
161	B	A	A	
162	A	A	A	
163	A			
164	A	A	A	
165	C			
166	A			
167	B			
168	E			
169	C			
170	A			
171	B			
172	A	A		
173	A	A	A	
174	B			
175	B	A		
176	A			
177	A			
178	A			
179	A	A		
180	C	C		
181	B	A		
182	B	A		
183	A	A		
184	B	B		
185	A	A		
186	A	A		
187	A	A		
188	A	A		
189	C	C		
190	B	A	A	B
191	C	B		
192	C	C		
193	B	A		
195	B	A		

196	C	B		
198	B	A		
199	A	A		
200	A	A		
201	C	B		
202	C	B		
203	A	A		
204	A	A		
205	B	A		
206	B	B		
207	C	B		
208	A	A		
209	D	C		
210	B	A		
211	A	A	A	A
212	A	A	A	A
213	A	A	A	A
214	A	A		
215	A	A		
216	C	B		
217	B	A		
218	A	A	A	A
219	A	A	A	A
220	D	C		
221	E	C		
222	A	A		
223	B	B		
224	B	A		
225	B	A		
226	D	B		
227	C	B		
228	C	B		
229	A	A	A	A
230	C	B		
231	C	C		
232	A	A	A	A

233	B	B		
234	A	A	A	A
235	A	A	A	A
236	E	C		
237	B	A		
238	C	C		
239	A	A	A	A
240	B	A		
241	A	A	A	A
242	B	B		
243	E	E		
244	A	A		
245	A	A		
246	A	A		
247	B	A		
248	A	A	A	A
249	A	A	A	A
250	B	B		
251	B	A		
252	C	B		
253	C	B		
254	C	B		
255	A	A	A	A
264	A	A	A	
265	A	A	A	
273	A	A		
278	A	A		
279	A	A		
280	A	A		
281	A	A		
285	A	A		
286	A	A		
287	A	A		
288	A	A		
291	A	A		
293	A	A		

294	A	A		
295	B	A		
296	A	A	A	
298	A	A		
303	A	A		
305	A	A	A	
308	A	A		
311	B	A		
314	A	A		
315	A	A		
317	A	A	A	
319	A	A	A	
320	A	A		
321	A	A	A	
322	A	A	A	
323	B	A		
324	B	A		
325	A	A		
326	A	A		
327	B	A		
335	A	A		
336	A	A		
337	A	A		
338	A	A		
339	A	A		
340	A	A		
341	A	A		
342	A	A		
343	A	A		
344	A	A		
345	A	A		
346	A	A		
347	A	A		
348	A	A		
349	A	A		
350	A	A		

351	C	A		
352	A	A		
353	B	A		
354	A	A		
355	A	A		
356	A	A		
357	A	A		
358	A	A		
359	A	A		
360	A	A		
361	A	A		
362	A	A		
363	A	A		
364	A	A		
365	A	A		
366	A	A		
367	A	A		
368	A	A		
369	A	A		
370	A	A		
371	A	A		
372	A	A		
373	B	A		
374	B	A		
375	B	A		
376	B	A		
377	A	A		
378	B	A		
379	A	A		
380	B	A		
381	A	A		
382	A	A		
383	A	A		
384	A	A		
385	A	A		
386	A	A		

387	B	A		
388	A	A		
389	A	A		
390	A	A		
391	A	A		
392	B	A		
393	A	A		
394	A	A		
395	B	A		
396	A	A		
397	A	A		
398	A	A		
399	A	A		
400	A	A		
401	A	A		
402	A	A		
403	B	A		
404	A	A		
405	A	A		
406	A	A		
407	A	A		
408	A	A		
409	A	A		
410	A	A		
411	A	A		
412	A	A		
413	A	A	A	
414	A	A		
415	A	A		
416	A	A		
417	A	A		
418	A	A	A	
419	A	A		
420	A	A	A	
421	B	A		
422	B	B		

423	A	A		
424	A	A		
425	A	A		
426	A	A		
427	A	A		
428	A	A		
429	B	A		
430	A	A		
431	B	A		
432	A	A		
433	B	A		
434	A	A		
435	A	A		
436	A	A		
437	A	A		
438	A	A		
439	A	A		
440	A	A		
441	A	A		
442	A	A		
443	A	A		
444	A	A		
445	A	A		
446	A	A		
447	A	A		
448	A	A		
449	A	A		
450	A	A		
451	C	C		
452	A	A		
453	A	A		
454	A	A		
455	A	A		
456	B	A		
457	A	A		
458	A	A		

459	A	A		
460	A	A		
461	A	A		
462	A	A		
463	A	A		

Example 273: Active KRAS G12D / CRAF RBD TR-FRET Binding Assay

[00768] The ability of compounds to inhibit activation of KRAS G12D (GMPPNP loaded) and its interaction with effector protein, CRAF, was measured using a TR-FRET assay. In a 10-
5 µl final assay volume, 2.5 µL of biotinylated KRAS G12D and 2.5 µL FLAG-tagged CRAF-RBD were added to pre-dispensed compounds. The assay buffer consisted of 25 mM HEPES, pH 7.4, 0.002% Tween20, 0.1% BSA, 100 mM NaCl and 5 mM MgCl2. Then, 1 nM Tb-anti-FLAG and 5 nM SA-XL665 were added to detect the interaction. After a 60-minute incubation at room temperature, the reaction was measured in a plate reader using excitation and emission
10 wavelengths of 340 nm and 620/665 nm, respectively. IC50 values were established using a four-parameter fit model. The results are shown in Table 4, where ≤ 10 nM; B is > 10 nm and ≤ 100 nM; C is > 100 nM and ≤ 1000 nM; D is > 1000 nM and ≤ 3000 nM; and E is > 3000 nM.

Table 4.

Comp. No.	KRAS-G12D-GMPPNP-RAF	KRAS-G12V-GMPPNP-RAF	KRAS-G12C-GMPPNP-RAF	KRAS-WT-GMPPNP-RAF
101	E			
102	B			
103	B			
104	B			
106	B			
107	B			
108	C			
109	B	B	C	B
110	B			
111	B			
112	B	B	B	B
113	B			
114	C			
115	B	C		

116	C			
117	C	C		
118	A	B	B	B
119	C			
120	A	B	A	B
121	B	B	B	B
122	B	C	C	C
123	B			
124	B			
125	B			
126	C	C	C	C
129	C	C	C	C
130	B	C	C	C
132	E			
134	D			
136	D			
137	E			
138	A	B	B	B
140	C	C	C	E
141	B	C	C	B
142	B			
143	B	C	C	C
144	C	D	C	D
145	B	B	B	B
146	B	B	B	B
148	C			
149	C			
150	C	E	D	D
151	C	E	E	E
152	C	E		
153	B	B	C	C
154	C			
155	B	C	C	E
156	C	C		
157	B	B	B	
158	A	B	B	

159	C	C	E	
160	E	E		
161	B	B	B	
162	A	B	B	
163	C			
164	C	C	C	
165	E			
166	A			
167	C			
169	E			
170	B			
171	C			
172	A	B		
173	B	C	C	
174	C			
175	C	E		
176	A			
177	C			
178	B			
179	A	B		
180	E	E		
181	C	E		
182	C	C		
183	B	B		
184	D	E		
185	C	C		
186	B	B		
187	C	C		
188	B	B		
189	E	E		
190	E	E	E	E
191	D	E		
192	E	E		
193	C	E		
195	D	E		
196	D	E		

198	E	E		
199	B	C		
200	B	B		
201	E	E		
202	D	E		
203	C	C		
204	B	C		
205	C	C		
206	C	E		
207	E	E		
208	C	C		
209	E	E		
210	C	E		
211	B	C	C	C
212	A	B	B	B
213	C	C	E	E
214	E	E		
215	C	C		
216	E	E		
217	C	E		
218	C	C	D	E
219	C	C	D	C
220	E	E		
221	E	E		
222	B	B		
223	C	C		
224	B	C		
225	C	E		
226	E	E		
227	E	E		
228	E	E		
229	C	C	C	C
230	D	E		
231	C	E		
232	C	C	E	E
233	E	E		

234	A	B	A	A
235	C	E	E	E
236	E	E		
237	C	C		
238	E	E		
239	C	C	C	E
240	D	E		
241	B	B	B	B
242	C	D		
243	E	E		
244	B	C		
245	C	D		
246	B	C		
247	C	D		
248	C	E	C	D
249	C	E	E	E
250	E	E		
251	C	E		
252	E	E		
253	E	E		
254	E	E		
255	B	C	C	C
264	C	C		
273	A	B		
285	B	C		
286	C	E		
287	C	D		
291	C	E		
293	C	E		
294	C	E		
296	A	B		
298	C	E		
303	C	E		
305	B	C		
308	C	E		
311	D	E		

314	A	C		
317	B	B		
319	B	E		
320	C	C		
322	C	D	E	D
325	D	E		
327	E	E		
404	E	E		
405	C			
406	C			
407	B			
408	C			
409	D			
410	B			
411	B			
412	B			
413	C	E		
414	E	E		
415	C	E		
416	C	E		
417	C	D		
418	C	C		
419	C	E		
420	C	C	C	C
421	E	E		
422	C	E		

Example 274: p-ERK HTRF Assay

[00769] The potency of test compounds in inhibiting phosphorylation of ERK was determined by p-ERK HTRF assay in human cancer cell lines expressing either mutant or wild-type KRAS. Cells (8000 cells per well) were plated in 384-well cell culture plates. After overnight incubation at 37 °C and 5% CO₂, cells were treated with a 3-fold, 10 points dilution of indicated compounds or DMSO (0.1% DMSO final) for 3 hours. Cells were then lysed, and the lysates transferred to assay plates and incubated with phospho-ERK HTRF detection reagents according to the manufacturer's protocol. The HTRF signal was measured using an

EnVision multimode plate reader. Curves were fitted and IC50 values calculated using a four-parameter logistic model (XLFit; equation 201). The results are shown in Table 5, where A is ≤ 10 nM; B is > 10 nM and ≤ 100 nM; C is > 100 nM and ≤ 1000 nM; D is > 1000 nM and ≤ 3000 nM; and E is > 3000 nM.

5 Table 5.

Comp. No.	GP2D	SW620	NCIH358	ASPC-1	KE39	SW480	BXPC3	A375	PC9
102			C	D		C	E		E
103			C	C		B	E		E
104			B	B		B	E		E
105							E		E
106	B		C	C		C	E		E
107			D	E		C	E		E
109			D	E		C	E		E
110			E	E		E	E		E
111			B	B		B	E		D
112	A	B	B	B	C	B	E	E	E
113	A	B	B	B	B	B		E	E
116			C	D		C		E	E
118	A	A	A	A	A			E	C
119	C	D	D					E	E
120	A	A	A	B	B			E	E
121	B	B	B	C	C			E	E
122	E	E	E					E	E
123	C	C	D					E	E
124	E	E	E					E	E
125	C	E	E					E	E
126	C	C	C					E	E
129	D	C	D					E	E
130	A	B	B					E	E
134	C	D	E					E	E
136	E	E	E					E	E
137	E	E	E					E	E
138	A	A	A					E	E
140	B	C	C					E	E
141	B	C	C					E	E

142	C	C	C					E	E
143	C	E	E					E	E
144	C	C	E					E	E
145	B	B	C					E	E
146	C	C	D					E	E
148	C	E	E					E	E
149	C	C	E					E	E
150	C	C	C		C			E	
151	A	A	A		B			E	
152	A	A	A		A			E	
153	B	B	B		C			E	
154	E	E	E		E			E	
155	A	A	A		A			E	
157	C	C	C		C			E	
158	A	B	B		B			E	
159	A	A	A		B			E	
161	C	C	D		C			E	
162	B	B	C		C			E	
163	C	E	E		E			E	
164	B	B	C		B			E	
166	B	C	C		D			E	
167	E	E	E		E			E	
169	C	C	E		E			E	
170	B	C	C		D			E	
171	D	E	E		E			E	
172	A	A	A		A			E	
173	B	B	C		B			E	
174	C	E	E		E			E	
175	B	B	A		B			E	
176	B	C	B		C			E	
177	B	B	C		B			E	
178	C	C	C		E			E	
179	B	B	B		C			E	
180	C	E	E		C			E	
181	B	C	C		C			E	
182	C	C	C		C			E	

183	C	C	C		C			E	
184	C							E	
185	B							E	
186	A	A	A		A			E	
187	B	C	C		B			E	
188	A	A	B		B			E	
189	E							E	
190	C	B						E	
191	C							E	
192	D							E	
193	C							E	
195	C							E	
196	C							E	
198	C							E	
199	A	B	B		A			E	
200	A	A	A		A			E	
201	D							E	
202	C							E	
203	B							E	
204	A	A	B		A			E	
205	D	E	E		E			E	
206	E	E	E		E			E	
207	D							E	
208	B							E	
209	E							E	
210	B							E	
211	A	A	A		A			E	
212	A	A	A		A			E	
213	A	A	A		A			E	
214	A	A	B		B			E	
215	B	C	C		C			E	
216	E							E	
217	C							E	
218	A	A	A		A			E	
219	A	A	A		A			E	
220	E							E	

221	E	E	E		E			E	
222	A	A	A		A			E	
223	B	A	A		B			E	
224	A	A	A		B			E	
225	B	B	B		B			E	
226	E							E	
227	C							E	
228	C							E	
229	A	A	A		A			E	
230	C							E	
231	D							E	
232	B	A	A		B			E	
233	E							E	
234	A	A	A		A			E	
235	B	A	A		A			E	
236	E							E	
237	B							E	
238	E							E	
239	B							E	
240	B	A	A		B			E	
241	B	A	B		B			E	
242	C	C	C		C			E	
243	E							E	
244	B							E	
245	C							E	
246	C							E	
247	D							E	
248	A	A	A		A			E	
249	B	A	A		A			E	
250	C	C							
251	B	C							
252	C	C	B		C			E	
253	C	C							
254	D	C							
255	A	A	A						
264	A	A	A		B			E	

265	A	A	A		A			E	
273	A	A	A		B			E	
278	A	A	A		A			E	
279	A	A	A		B			E	
280	A	A	A		A			E	
281	A	A	A		A			E	
285	C	C	C		D			E	
286	B	B							
287	B	B	B		C			E	
288	A	A	A		A			E	
291	E	C	C		E			E	
293	E	C	C		E			E	
294	B	A	A		B			E	
295	A	A	A		A			E	
296	A	A	A		A			E	
298	B	A	A		B			E	
303	B	C	B		C			E	
305	A	A	A		A			E	
308	B	A	A		B			E	
311	C	B							
314	A	A	A		A			E	
315	A	A	A		A			E	
317	A	A	A		A			E	
319	A	A	A		A			E	
320	A	A	A		A			E	
321	A	A	A		A			E	
322	A	A	A		A			E	
323	C	B	C		C			E	
324	C	B	B		C			E	
325	B	A	B		B			E	
326	B	A	A		B			E	
327	C	A	B		B			E	
335	A	A	A		A			E	
336	A	A	A		B			E	
337	A	A	A		A			E	
338	A	A	A		A			E	

339	A	A	A		A			E	
340	A	A	A		A			E	
341	A	A	A		B			E	
342	A	A	A		A			E	
343	A	A	A		A			E	
344	A	A	A		A			E	
345	B	A	A		B			E	
346	A	A	A		A			E	
347	A	A	A		B			E	
348	A	A	A		B			E	
349	A	A	A		B			E	
350	B	B	A		B			E	
351	E	E	E		E			E	
352	A	A	A		A			E	
353	C	B	B		C			E	
354	A	A	A		A			E	
355	B	A							
356	A	A							
357	A	A							
358	A	A							
359	A	A							
360	A	A							
361	A	A							
362	A	A	A		B			E	
363	A	A	A		A			E	
364	A	A	A		A			E	
365	B	A	A		B			E	
366	A	A	A		A			E	
367	A	A	A		A			E	
368	A	A							
369	A	A							
370	A	A	A		B			E	
371	A	A	A		A			E	
372	A	A	A		B			E	
373	B	B	B		C			E	
374	B	A							

375	B	B							
376	B	A	A		B			E	
377	A	A	A		B			E	
378	B	A							
379	A	A	A		B			E	
380	B	A	A		B			E	
381	A	A	A		A			E	
382	A	A	A		B			E	
383	A	A	A		A			E	
384	A	A	A		A			E	
385	A	A	A		A			E	
386	A	A	A		A			E	
387	B	B							
388	A	A	A		A			E	
389	B	A							
390	A	A	A		B			E	
391	A	B	A		B			E	
392	B		B		B			E	
393	A	A	A		A			E	
394	A	A	A		B			E	
395	B	B	B		B			E	
396	A	A	A		B			E	
397	A	A	A		A			E	
398	A	A	A		A			E	
399	A	A	A		A			E	
400	B	B	B		C			E	
401	A	A	A		A			E	
402	B	A	B		B			E	
403	B	B	B		B			E	
404	B	B	B		B			E	
405	A	A							
406	B	A	B		B			E	
407	A	A	A		B			E	
408	B	B	B		C			E	
409	A	A	B		B			E	
410	A	A	A		A			E	

411	A	A	A		A			E	
412	A	A	A		A			E	
413	A	A	B		B			E	
414	B	B	B		B			E	
415	B	A	B		B			E	
416	A	A	A		A			E	
417	B	B	C		C			E	
418	A	A	A		A			E	
419	B	A	A		B			E	
420	A	A	A		A			E	
421	C	B	B		C			E	
422	C	C							
423	A	A	A		A			E	
424	A	A	A		B			E	
425	A	A	A		A			E	
426	B	A	A		B			E	
427	B	A	A		B			E	
428	B	A	A		B			E	
429	B	A	B		B			E	
430	A	A	A		A			E	
431	B	B	B		B			E	
432	A	A	A		A			E	
433	C	C	B		B			E	
434	B	A	A		B			E	
435	A	A	A		A			E	
436	A	A	A		B			E	
437	A	A	A		A			E	
438	A	A	A		B			E	
439	B	B	B		B			E	
440	B	B	B		C			E	
441	A	A	A		A				
442	A	A	A		A			E	
443	A	A	A		A			E	
444	A	A	A		A			E	
445	A	A	A		A			E	
446	B	B	B		C			E	

447	B	B	B		C			E	
448	B	B	B		C			E	
449	B	B	B		C			E	
450	A	A	A		A			E	
451	B	B	B		C			E	
452	A	A	A		A			E	
453	A	A							
454	A	A	A		A			E	
455	A	A	A		A			E	
456	B	A							
457	A	A	A		B			A	
458	A	A	A		A			E	
459	A	A	A		A			E	
460	A	A	A		A			E	
461	A	A							
462	A	A	A		B			E	
463	A	A	A		A			E	

Example 275: Cell Proliferation Assay

- [00770] The anti-proliferative activity of compounds was assessed by CellTiter-Glo (CTG) assay in human cancer cell lines expressing either mutant or wild-type KRAS. Cells were
- 5 seeded into 384-well plates at densities of 500-3000 cells per well in complete growth medium. After overnight incubation at 37 °C and 5% CO₂, cells were treated with a 3-fold, 10 points dilution of indicated compounds or DMSO (0.1% DMSO final) and cell viability was assessed 3 days post-treatment according to the manufacturer's protocol. The luminescent signal was measured using an EnVision multimode plate reader. Curves were fitted and IC₅₀ values
- 10 calculated using a four-parameter logistic model (XLFit; equation 201). The results are shown in Table 6, where A is ≤ 10 nM; B is > 10 nM and ≤ 100 nM; C is > 100 nM and ≤ 1000 nM; D is > 1000 nM and ≤ 3000 nM; and E is > 3000 nM.

Table 6.

Comp. No.	GP2D	SW620	NCIH358	ASPC-1	KE39	SW480	A375	PC9
102			D	E		E		E
111		B	C	E				E

112			C	E		E	E	E
113	A	A	C	E		B	E	E
118	A	A	A		A		E	E
120	A	A	B		E		E	E
121	E	B	C				E	E
126	E	C	E				E	E
130	E	B	D				E	E
134	E	E	E				E	E
138	A	B	B				E	E
140	C	C	E		E		E	
141	C	C	D				E	E
142	C	C	D				E	E
145	B	B	D		E		E	
151	B	A	B		E		E	
152	A	A	A		E		E	
153	B	C	C		E		E	
155	A	A	A		A		E	
158	B	B	B		E		E	
159	B	A	A		E		E	
162	C	C	C		E		E	
164	B	C	D		E		E	
166	C	E	E		E		E	
170	E	E	E		E		E	
171	E	E	E		E		E	
172	A	A	A		E		E	
174	E	E	E		E		E	
175	B	B	B		E		E	
176	B	B	C		E		E	
177	B	C	D		E		E	
179	B	B	C				E	
180	E	E	E		E		E	
181	C	C	C		E		E	
184	E						E	
185	C						E	
186	B	A	A		E		E	
187	C	C	C		E		E	

188	B	B	C		E		E	
189	E						E	
190	E	B						
195	C						E	
196	E						E	
198	E						E	
199	B	B	C		C		E	
200	A	A	B		C		E	
201	E						E	
202	E						E	
203	C						E	
204	B	A	C		E		E	
205	E	E	E		E		E	
206	E	E	E		E		E	
207	E						E	
208	C						E	
209	E						E	
210	E						E	
211	A	A	A		E		E	
212	A	A	A				E	
213	A	A	A				E	
214	A	B	C		E		E	
215	B	C	E		E		E	
216	E						E	
217	C						E	
218	A	A	A		E		E	
219	B	A	B				E	
220	E						E	
221	E	E	E		E		E	
222	A	A	B				E	
223	E	B	B				E	
224	A	A	A				E	
225	E	B	C				E	
226	E						E	
227	E						E	
228	E						E	

229	B	A	B				E	
230	E						E	
231	E						E	
232	C	B	C				E	
233	E						E	
234	A	A	A				E	
235	B	B	C				E	
236	E						E	
237	E						E	
238	E						E	
239	B						E	
240	C	B	C				E	
241	C	B	C				D	
242	D	E	E				E	
243	E						E	
244	C						E	
245	E						E	
246	C						E	
247	E						E	
248	B	A	A		A		E	
249	B	A	B		B		E	
250	E	E						
251	C	C						
252	E	C	C		E		E	
253	E	E						
254	E	E						
255	A	A						
264	B	A	B		A		E	
265	B	A	B		A		E	
273	A	A	A		A		E	
278	A	A	A		A		E	
279	A	A	A		A		E	
280	A	A	A		A		E	
281	A	A	A		A		E	
285	E	E	E		C		E	
286	C	B						

287	C	B	B		C		E	
288	B	A	A		A		E	
291	E	E	E		E		E	
293	E	E	E		E		E	
294	C	A	B		B		E	
295	A	A	A		A		E	
296	A	A	A		A		E	
298	B	B	B		B		E	
303	C	B	B		C		E	
305	A	A	A		A		E	
308	B	B	C		B		E	
311	C	C						
314	A	A	A		A		E	
315	B	A	A		A		E	
317	A	A	A		A		E	
319	A	A	A		A		E	
320	B	A	B		A		E	
321	B	A	B		B		E	
322	B	A	B		B		E	
323	C	E	D		C		E	
324	C	C	C		C		E	
325	C	B	C		B		E	
326	C	B	C		B		E	
327	C	B	C		C		E	
335	B	A	B				E	
336	B	B	B				E	
337	B	A	B				E	
338	B	A	B				E	
339	B	A	B				E	
340	B	A	B				E	
341	E	C	C				E	
342	A	A	A				E	
343	B	A	B				E	
344	B	A	A				E	
345	B	A	B		A		E	
346	A	A	A		A		E	

347	B	A	B		A		E	
348	B	A	B		A		E	
349	B	A	A		A		E	
350	C	B	B		B		E	
351	E	E	E		E		E	
352	A	A	A		A		E	
353	E	C	C		C		E	
354	A	A	A		A		E	
355	B	A						
356	B	A						
357	B	A						
358	B	A						
359	B	A						
360	B	A						
361	C	A						
362	B	B	B		A		E	
363	A	A	A		A		E	
364	A	A	A		A		E	
365	C	B	B		B		E	
366	A	A	A		A		E	
367	A	A	A		A		E	
368	E	E						
369	A	A						
370	B	A	B		A		E	
371	A	A	A		A		E	
372	B	B	B		B		E	
373	C	B	C		B		E	
374	C	B						
375	C	B						
376	C	B	C		B		E	
377	B	A	B		B		E	
378	C	B						
379	B	A	B		A		E	
380	C	B	C		B		E	
381	B	A	B		A		E	
382	B	A	B		A		E	

383	A	A	A		A		E	
384	A	A	A		A		E	
385	B	A	B		B		E	
386	A	A	A		A		E	
387	C	B						
388	B	A	B		A		E	
389	B	B						
390	B	B			B		E	
391	B	A	B		B		E	
392	B	B			B		E	
393	B	A	B		B		E	
394	B	A	B		B		E	
395	C	B	C		B		E	
396	A	A	A		A		E	
397	A	A	B		A		E	
398	A	A	A		A		E	
399	B	A	B		A		E	
400	C	B	B		B		E	
401	A	A	A		A		E	
402	B	B	B		B		E	
403	C	B	B		B		E	
404	C	B	C		B		E	
405	B	B						
406	B	B	B		B		E	
407	B	A	A		A		E	
408	C	B	C		B		E	
409	C	B	B		B		E	
410	A	A	A		A		E	
411	A	A	A		A		E	
412	A	A	A		A		E	
413	B	B	B		B		E	
414	C	B	C		B		E	
415	C	B	C		B		E	
416	B	A	B		A		E	
417	C	C	E		C		E	
418	A	A	A		A		E	

419	B	A	B		B		E	
420	B	A	B		A		E	
421	E	B	C		C		E	
422	D	D						
423	A	A	A		A		E	
424	C	B	B		B		E	
425	A	A	A		A		E	
426	B	B	B		B		E	
427	C	B	B		B		E	
428	C	B	B		B		E	
429	E	B	C		B		E	
430	A	A	A		A		E	
431	C	B	C		C		E	
432	A	A	A		A		E	
433	C	E	E		B		E	
434	B	B	B		B		E	
435	A	A	A		A		E	
436	B	B	B		B		E	
437	B	A	B		A		E	
438	B	A	B		B		E	
439	C	B	C		B		E	
440	E	C	C		C		E	
441	A	A	A				E	
442	A	A	A				E	
443	A	A	A				E	
444	A	A	A				E	
445	A	A	A				E	
446	C	B	C				E	
447	C	B	B				E	
448	B	B	B				E	
449	C	B	B				E	
450	B	A	B				E	
451	B	B	B				E	
452	A	A	A				E	
453	A	A						
454	B	A	B				E	

455	B	A	B				E	
456	C	B						
457	B	A	B		B		E	
458	B	A	B		A		E	
459	A	A	A		A		E	
460	A	A	A		A		E	
461	A	A						
462	B	A	B		B		E	
463	B	A	B		A		B	

Example 276: SPR Assay

[00771] SPR measurements were performed using a Biacore 8K equipped with CAP sensor chips (Cytiva). Avi-tagged KRAS4b^{G12D}-(1-169) was biotinylated, loaded with either GDP or GMPPNP, and immobilized to the sensor chip using standard biotin-capture procedures. The resulting immobilization levels ranged from 500 to 700 resonance units with estimated surface activity of ~100%. Interactions with KRAS were analyzed in 9-point or 11-point dose response using twofold serial dilutions. The top dose of the dilution series was adjusted from 10 μM to 200 nM depending on the anticipated potency range of the compound. The running buffer for all experiments was 20 mM HEPES pH8, 50 mM NaCl, 2mM MgCl₂, 1 mM DTT, 0.05 % Tween, 2%DMSO. For binding experiments run in multicycle kinetic mode, the association phase was 60 s and the dissociation phase was 300 s. For experiments using single cycle kinetic mode, the contact time was 90 s and the dissociation phase was 1200 s. After each cycle, needles were washed with 50% DMSO. For data analyses, the data were fit using a 1:1 kinetic model after reference signal subtraction using Biacore 8K evaluation software. The results are shown in Table 7, where A is ≤ 10 nM; B is > 10 nm and ≤ 100 nM; C is > 100 nM and ≤ 1000 nM; D is > 1000 nM and ≤ 3000 nM; and E is > 3000 nM.

Table 7.

Comp. No.	KRAS-G12D-GDP	KRAS-G12V-GDP	KRAS-G12C-GDP	KRAS-WT-GDP	KRAS-G12D-GMPPNP	KRAS-G12V-GMPPNP	KRAS-WT-GMPPNP
102	A				B		
103	A				B		
104	A				B		

105	B				D		
106	A	A			A		
107	A				B		
108	A	A					
112	A	A		A	B	B	B
113	A	A		A	A	B	C
114	A				C		
117					C	D	
118	A	A		A	A	B	B
119	A				C		
120	A	A		A	A	A	A
121	A				C		
122	A				B		
123	A				C		
125	A				C		
126	A				C		
127	B				E		
129	A				B		
130	A	A		A	B	C	C
132	B				E		
136	C				E		
138	A	A		A	A	A	B
140	A	A		A	C	D	D
141	A				B		
142	A				B		
143	A	A		A	B	C	C
144	A				C		
145	A	A		A	B	B	B
146	A				B		
148	A				C		
150	C				D		
151	A	A		A			
152	A				C		
153	A				B		
154	B				C		
155	A	A		A	C		

158	A	A		A	B	B	B
159	A	A		A	C		
162	A				A		
163	A				C		
164	A				C		
166	A	A		A	A	B	A
172	A				A	B	
173	A				B	C	
176	A				A	A	
177	A				C	D	
178	A				B	D	
179	A	A			A	A	
186	A	A			B	C	
188	A	A			B	C	
200	A	A			B	C	
211	A	A	A	A	A	C	
212	A	A	A	A	A	C	
218	A	A	A	A	B	E	
232	A	A	A	A	D	E	
235	B	A	A	A	B	E	
240	A	A	A	A	B		
264	A						
265	A	A	A	A	E	E	
273	A						
278	A	A					
288	A	A	A	A	C		
280	A	A					
281	A	A					
295	A	A	A	A	C		
296	A						
298	A						
305	A	A	A	A	C	E	E
308	A						
315	A	A	A	A	C	E	
317	A						
319	A	A	A	A			

320	A						
321	B	A	A	A			
363	A	A					
364	A	A					
366	A	A					
367	A	A					
371	A	A					
383	A	A					
384	A	A					
386	A	A					
398	A	A					
399	A	A					
400	A	A					
401	A	A	A	A	B	C	C
410	A	A	A	A	C	E	E
412	A	A	A	A	B	C	C
413	A	A	A	A	E		
418	A	A	A	A	C	D	D
420	A	A	A	A	C	E	E
423	A						
425	A						
430	A						
432	A						
437	A						
459	A						

INCORPORATION BY REFERENCE

[00772] All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety for all purposes as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS AND SCOPE

[00773] In the claims articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions

that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in,
5 employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process.

[00774] Furthermore, the invention encompasses all variations, combinations, and permutations in which one or more limitations, elements, clauses, and descriptive terms from
10 one or more of the listed claims is introduced into another claim. For example, any claim that is dependent on another claim can be modified to include one or more limitations found in any other claim that is dependent on the same base claim. Where elements are presented as lists, *e.g.*, in Markush group format, each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the
15 invention, or aspects of the invention, is/are referred to as comprising particular elements and/or features, certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements and/or features. For purposes of simplicity, those embodiments have not been specifically set forth *in haec verba* herein. It is also noted that the terms
20 “comprising” and “containing” are intended to be open and permits the inclusion of additional elements or steps. Where ranges are given, endpoints are included. Furthermore, unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or sub-range within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

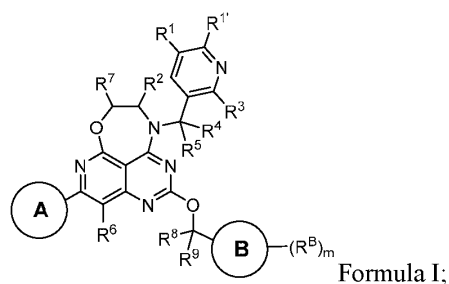
25 [00775] This application refers to various issued patents, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference. If there is a conflict between any of the incorporated references and the instant specification, the specification shall control. In addition, any particular embodiment of the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims.
30 Because such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the invention can be excluded from any claim, for any reason, whether or not related to the existence of prior art.

[00776] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments described herein. The scope of the present embodiments described herein is not intended to be limited to the above Description, but rather is as set forth in the appended claims. Those of ordinary skill in the art
5 will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

CLAIMS

What is claimed is:

1. A compound represented by Formula I:



- 5 or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

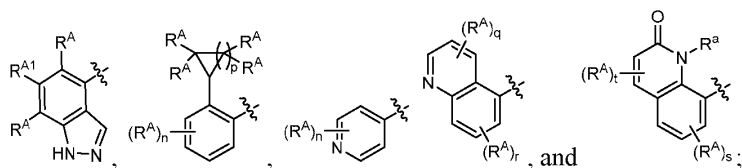
R^1 is selected from the group consisting of halogen, C₃-C₄cycloalkyl, C₁-C₆alkyl, C₂-C₆alkenyl, and C₂-C₆alkynyl; wherein cycloalkyl, alkyl, alkenyl, and alkynyl may optionally be substituted with one, two, or three halogens;

- 10 R^2 is hydrogen or C₁-C₆alkyl optionally substituted with one or more halogens or hydroxyl; and

ring A is selected from the group consisting of indazolyl, quinolinyl, quinolinonyl, benzothiophenyl, benzothiazolyl, pyrazolopyridyl, pyridyl, phenyl, and naphthyl, wherein ring A is substituted with one or more substituents each independently selected from R^A ;

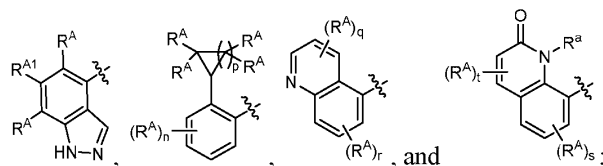
or:

- 15 R^1 is hydrogen; R^2 is C₁-C₆alkyl optionally substituted with one or more halogens or hydroxyl; and ring A is selected from the group consisting of:



or:

R^1 is hydrogen; R^2 is hydrogen; and ring A is selected from the group consisting of:



- R^A is independently selected for each occurrence from the group consisting of hydrogen, halogen, deuterium, hydroxyl, -CN, -NO₂, -NR^aR^b, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, and phenyl may optionally be substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, oxo, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;
- R^{A1} is selected from the group consisting of hydrogen, deuterium, chloro, -CN, -NO₂, -NR^aR^b, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, and phenyl may optionally be substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, oxo, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;

$R^{1'}$ is hydrogen or halogen;

- R^3 is selected from the group consisting of -NR^aR^b, halogen, C₁-C₂alkyl, and hydrogen, wherein alkyl may optionally be substituted with one, two, or three halogens;

R^4 is selected from the group consisting of hydrogen and C₁-C₂alkyl, wherein alkyl may optionally be substituted with one, two, or three halogens;

R^5 is C₁-C₂alkyl optionally be substituted with one, two, or three halogens;

- R^6 is selected from the group consisting of halogen, hydrogen, deuterium, and C₁-C₃alkyl;

R^7 is selected from the group consisting of hydrogen and C₁-C₆alkyl optionally substituted with one or more halogens or hydroxyl;

R^8 and R^9 are each independently selected from the group consisting of hydrogen, deuterium, and C₁-C₃alkyl;

Ring B is selected from the group consisting of 4-12 membered heterocyclyl containing at least one ring nitrogen;

R^B is independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, -CN, -NR^aR^b, -COOH, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, =CHF, and =CH-C₁-C₆alkyl; wherein C₁-C₆alkyl may optionally be substituted with one, two, or three substituents each independently selected from the group consisting of hydroxyl, halogen, and C₁-C₃alkoxy; or

Ring B and R^B are absent and replaced with a substituent selected from the group consisting of -CH₂OH and C₃-C₄cycloalkyl, wherein cycloalkyl is substituted with a substituent selected from the group consisting of -CH₂OH and -CH₂-NR^aR^b, and

R^a and R^b are each independently selected from the group consisting of hydrogen and C₁-C₆alkyl, wherein C₁-C₆alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, and C₁-C₆alkoxy; or

R^a and R^b , together with the nitrogen to which they are attached, may be joined together to form a 4-7 membered heterocyclyl optionally substituted by one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;

m and n are each independently 0, 1, 2, 3, or 4;

p is 1, 2, or 3;

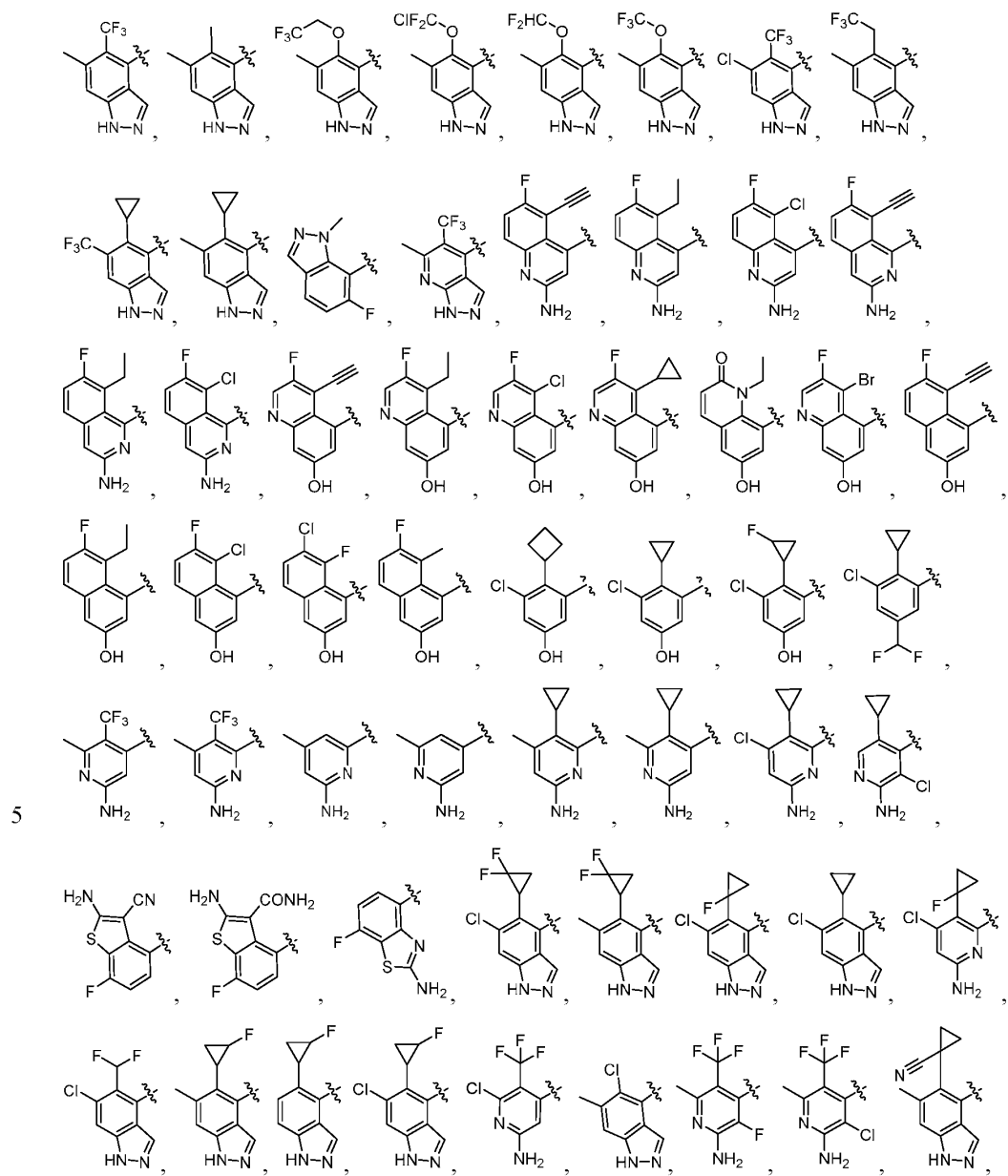
q, r, and s are each independently 0, 1, 2, or 3; and

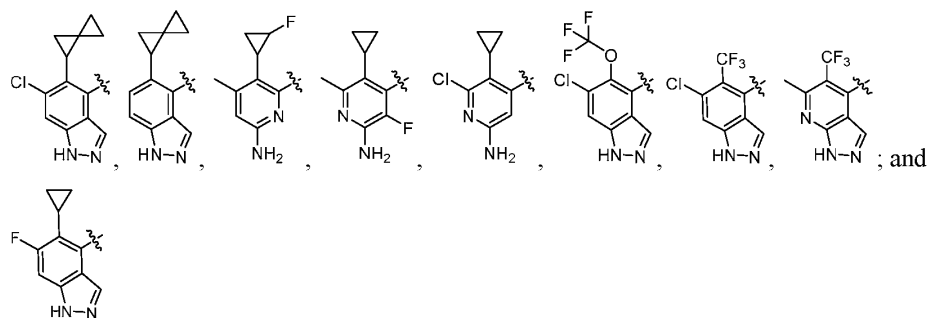
t is 0, 1, or 2.

2. The compound of claim 1, wherein R^1 is selected from the group consisting of fluoro, chloro, cyclopropyl, trifluoromethyl, -CH₂CH₂CH₃, and propenyl; and R^2 is hydrogen or -CH₃.

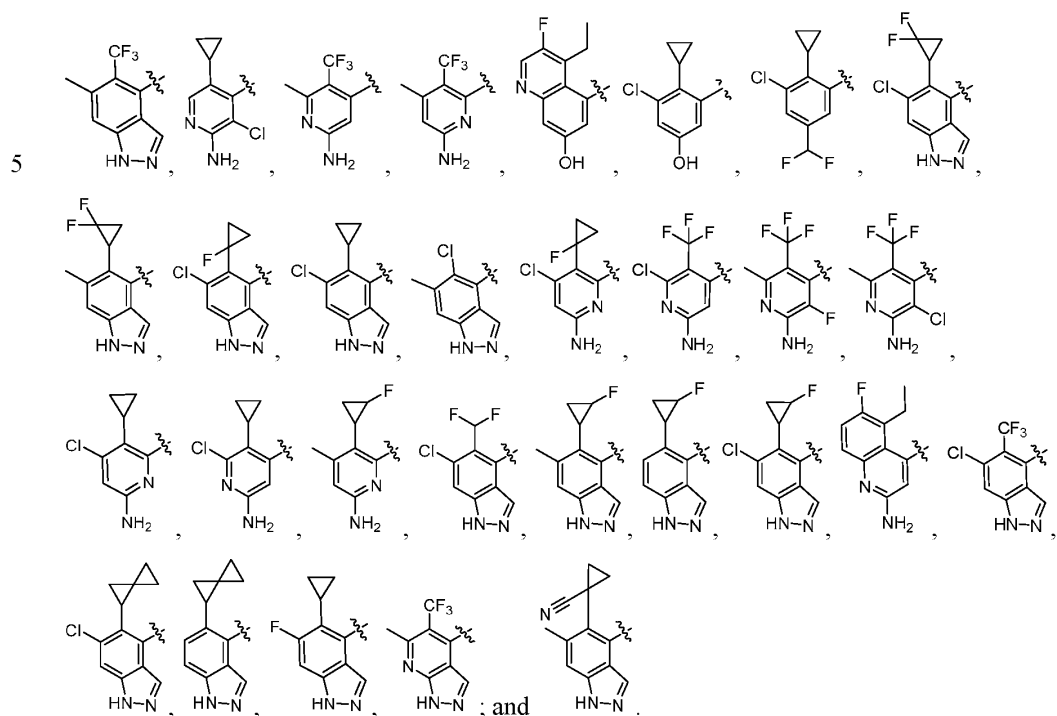
3. The compound of claim 1 or 2, wherein R^A is independently selected for each occurrence from the group consisting of halogen, hydroxyl, cyano, -NH₂, -C(O)NH₂, C₁-C₄alkyl, and C₂-C₄alkynyl, C₁-C₄alkoxy, and C₃-C₆cycloalkyl, wherein alkyl, alkynyl, alkoxy, and cycloalkyl may optionally be substituted with one, two, or three halogens or -CN.

4. The compound of any one of claims 1-3, wherein ring A is selected from the group consisting of:



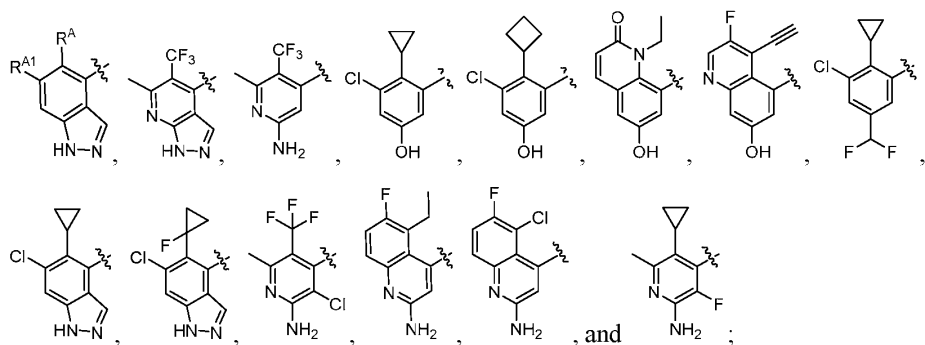


5. The compound of any one of claims 1-4, wherein ring A is selected from the group consisting of:



6. The compound of claim 1, wherein R¹ is hydrogen and R² is -CH₃.

10 7. The compound of claim 1 or 6, wherein ring A is selected from the group consisting of:

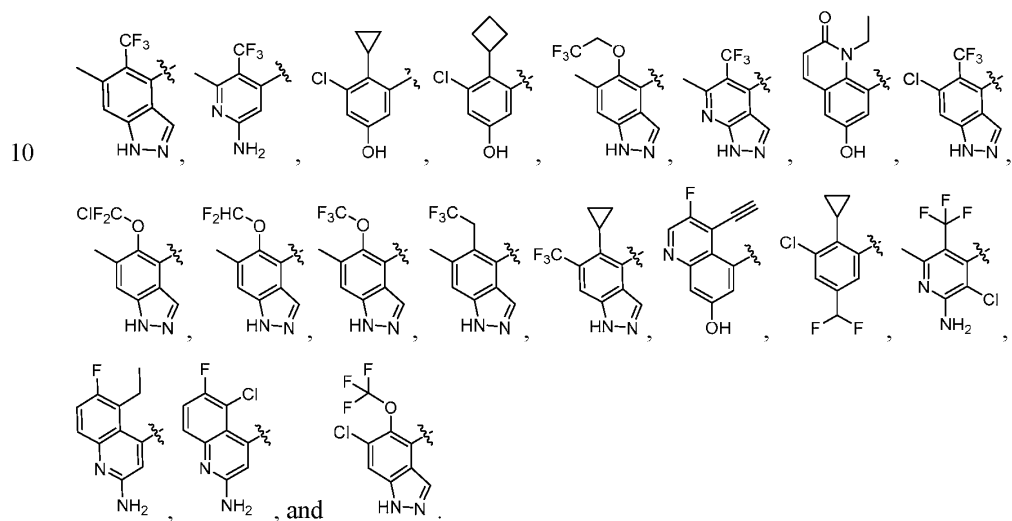


wherein:

R^A is selected from the group consisting of C₁-C₃alkyl, C₁-C₃alkoxy, and C₃-C₄cycloalkyl; wherein alkyl and alkoxy are each substituted with one, two, or three halogens; and

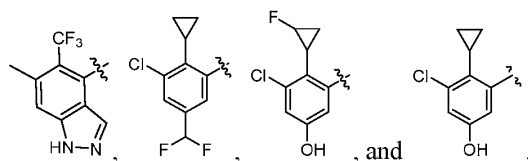
R^{A1} is selected from the group consisting of chloro, $-CH_3$, and $-CF_3$.

8. The compound of any one of claims 1 and 6-7, wherein ring A is selected from the group consisting of:

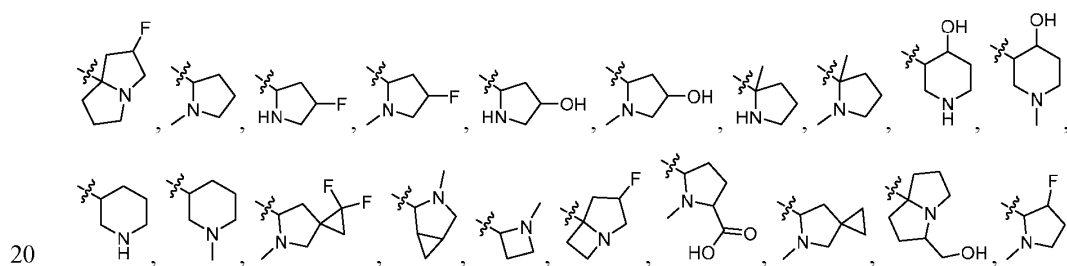


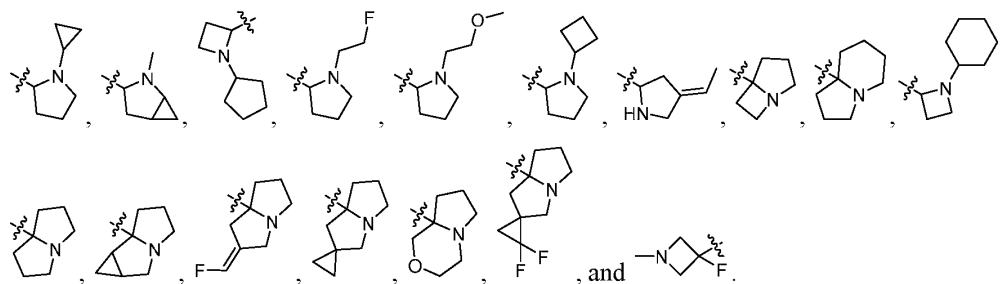
9. The compound of claim 1, wherein R¹ is hydrogen and R² is hydrogen.

10. The compound of claim 1 or 9, wherein ring A is selected from the group consisting of



11. The compound of any one of claims 1-10, wherein R^3 is selected from the group consisting of $-NH_2$, chloro, and $-CHF_2$.
12. The compound of any one of claims 1-11, wherein R^3 is $-NH_2$.
13. The compound of any one of claims 1-12, wherein R^4 is hydrogen and R^5 is $-CH_3$.
14. The compound of any one of claims 1-13, wherein R^6 is fluoro.
15. The compound of any one of claims 1-14, wherein R^7 is hydrogen or $-CH_3$.
16. The compound of any one of claims 1-15, wherein R^8 and R^9 are each independently selected from the group consisting of hydrogen, deuterium, and $-CH_3$.
17. The compound of any one of claims 1-16, wherein R^B is independently selected for each occurrence from the group consisting of halogen, hydroxyl, $-COOH$, $=CHCH_3$, $=CHF$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and C_1 - C_3 alkyl optionally substituted with hydroxyl, halogen, or $-OCH_3$.
18. The compound of any one of claims 1-17, wherein R^B is independently selected for each occurrence from the group consisting of halogen, hydroxyl, $-CH_3$, $=CHCH_3$, $=CHF$, $-COOH$, $-CH_2OH$, $-CH_2CH_2F$, $CH_2CH_2OCH_3$, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.
19. The compound of any one of claims 1-18, wherein ring B is selected from the group consisting of:



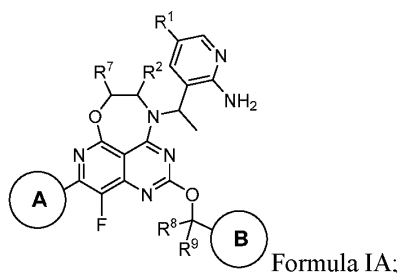


20. The compound of any one of claims 1-16, wherein ring B and R^B are absent and replaced with -CH₂OH or cyclopropyl; wherein cyclopropyl is substituted with -CH₂OH or -CH₂NR^aR^b.

5 21. The compound of any one of claims 1-16 and 20, wherein ring B and R^B are absent and

replaced with a substituent selected from the group consisting of -CH₂OH, , , , and .

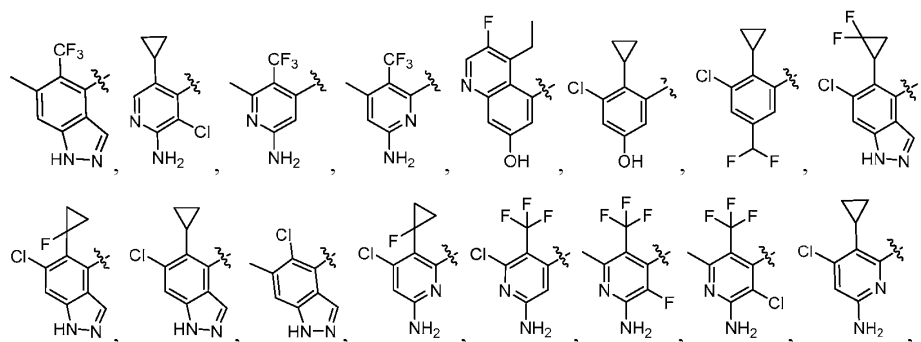
22. The compound of claim 1, wherein the compound is represented by Formula IA:

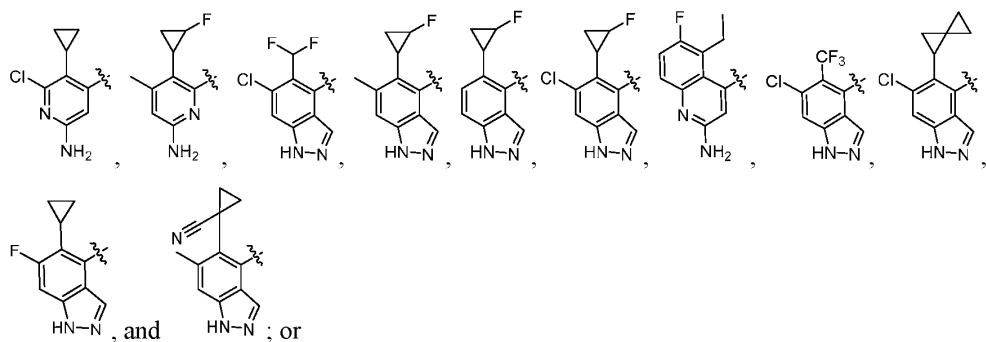


Formula IA:

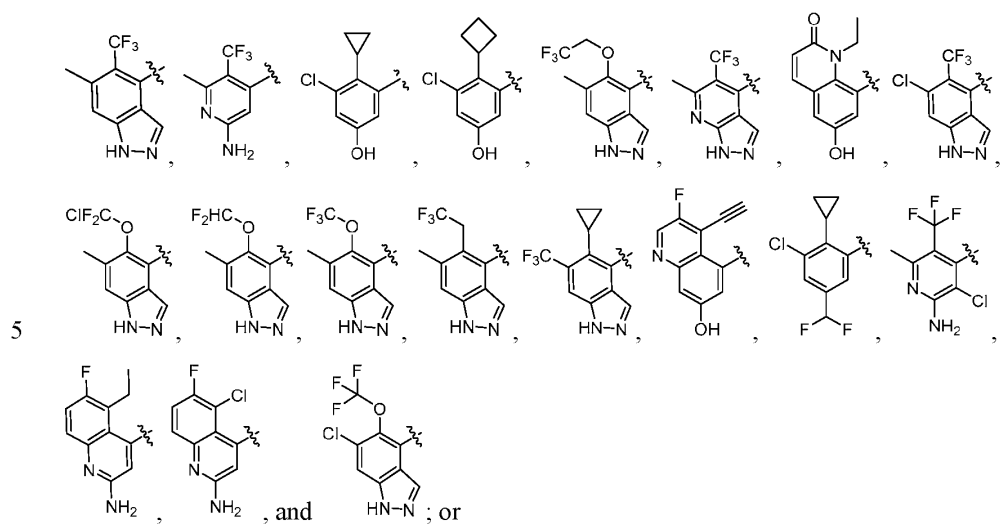
10 or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

R¹ is halogen, R² is hydrogen or -CH₃, and ring A is selected from the group consisting of

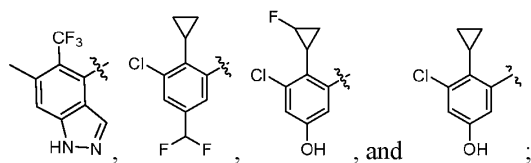




R¹ is hydrogen, R² is -CH₃, and ring A is selected from the group consisting of:



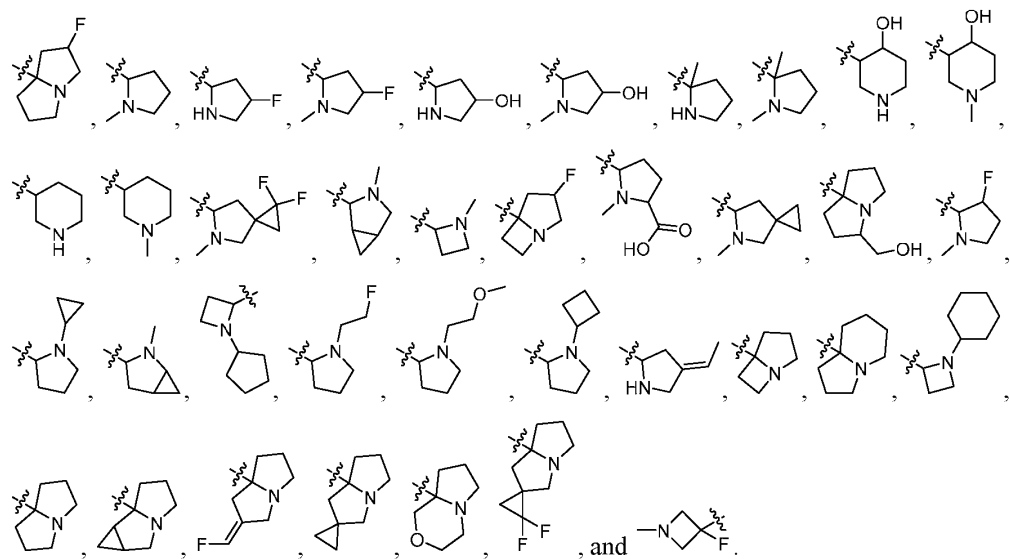
R¹ is hydrogen, R² is hydrogen, and ring A is selected from the group consisting of:



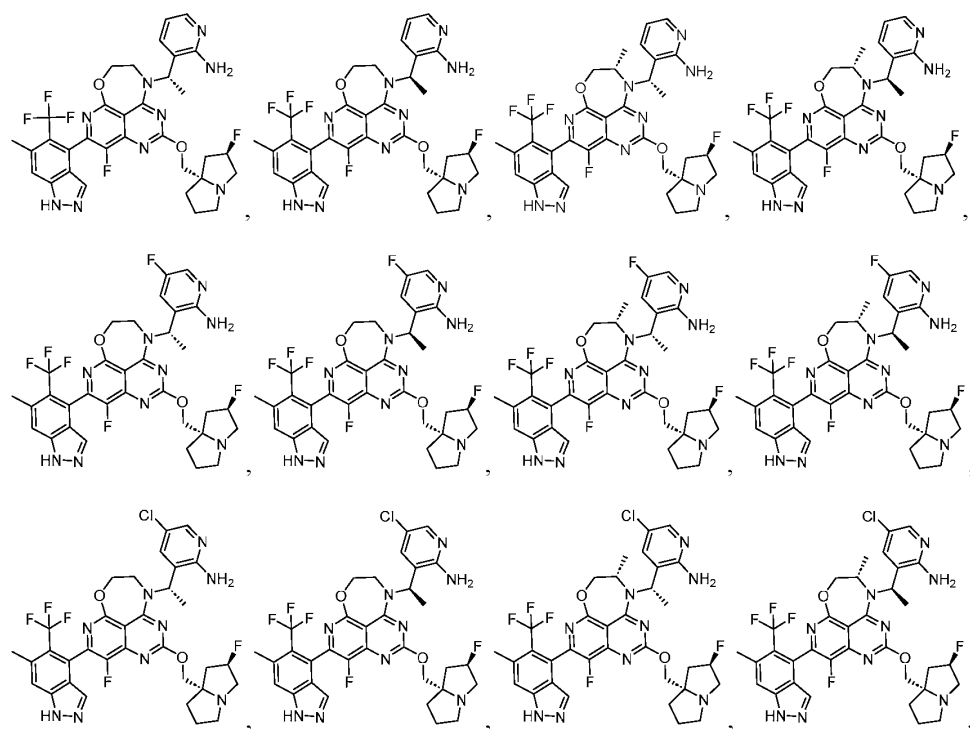
R⁷ is selected from the group consisting of hydrogen and -CH₃;

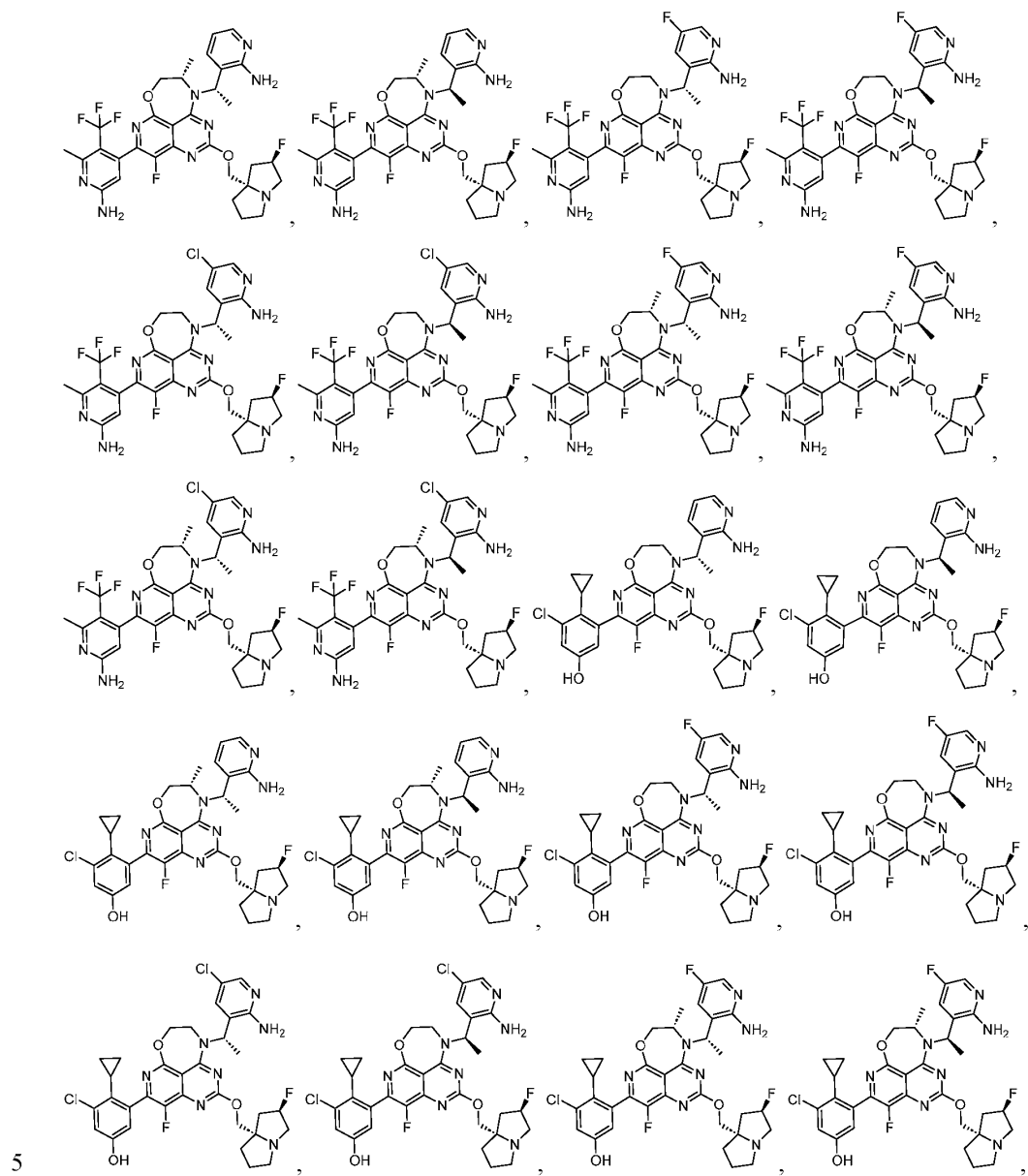
R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, deuterium, and -CH₃; and

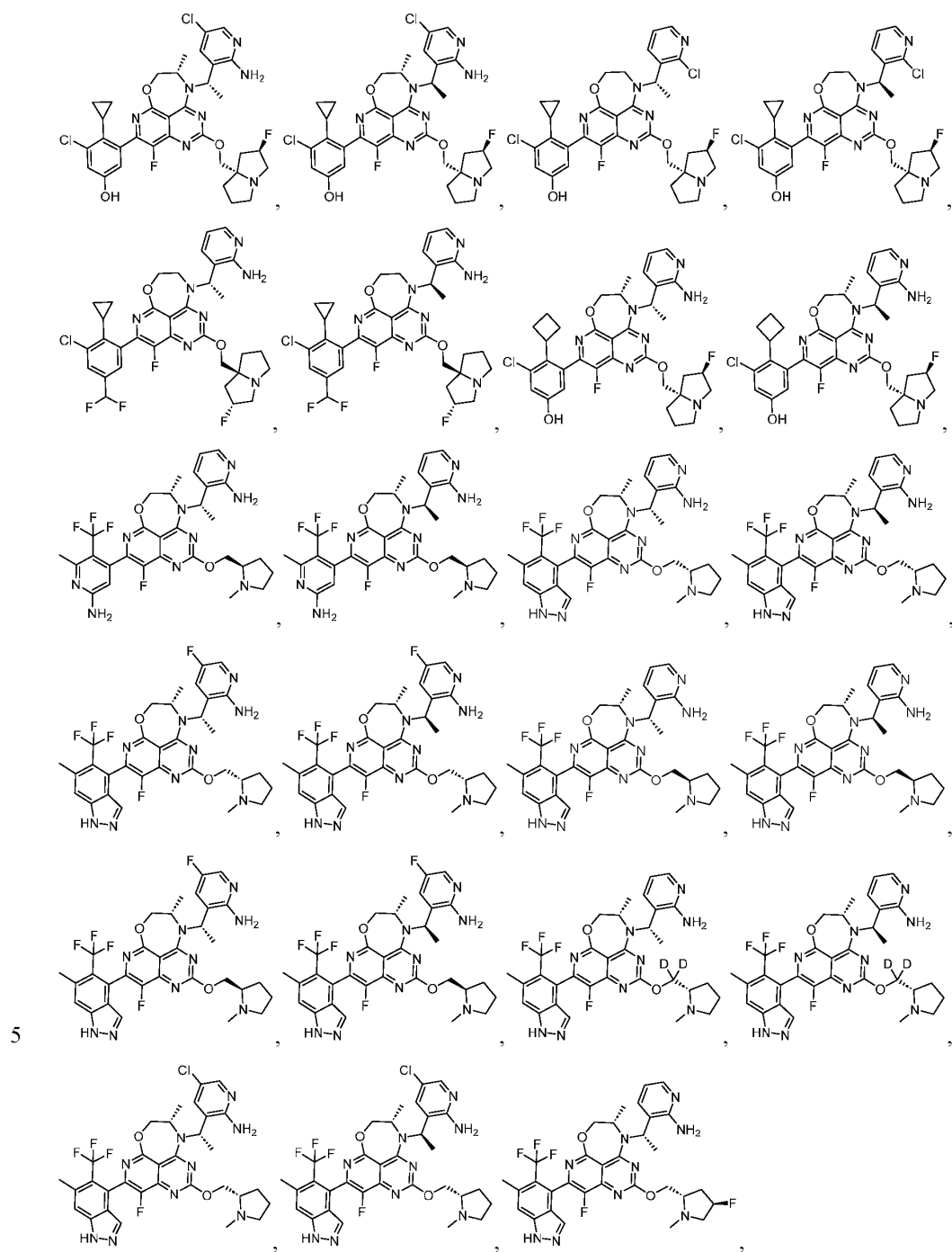
B is selected from the group consisting of

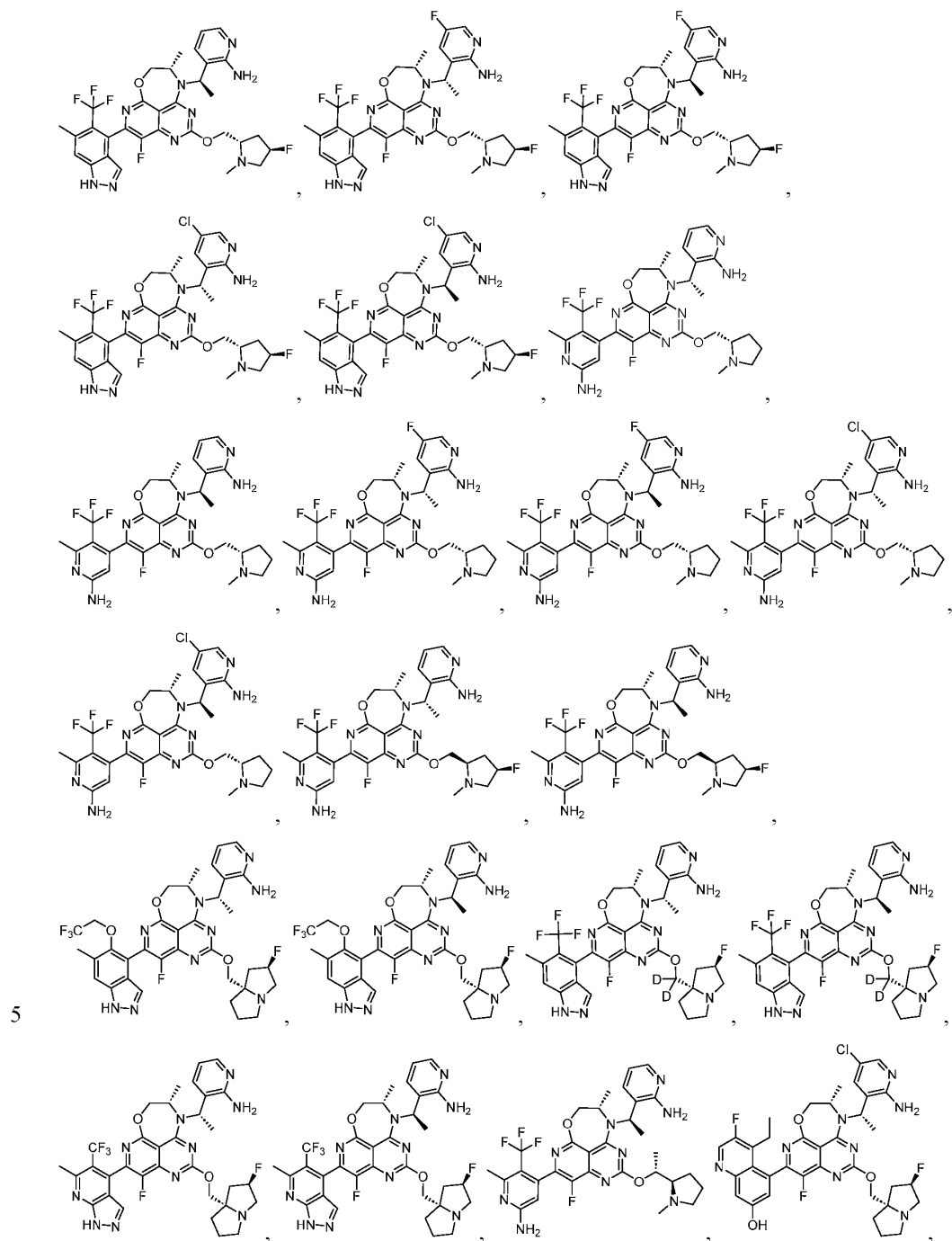


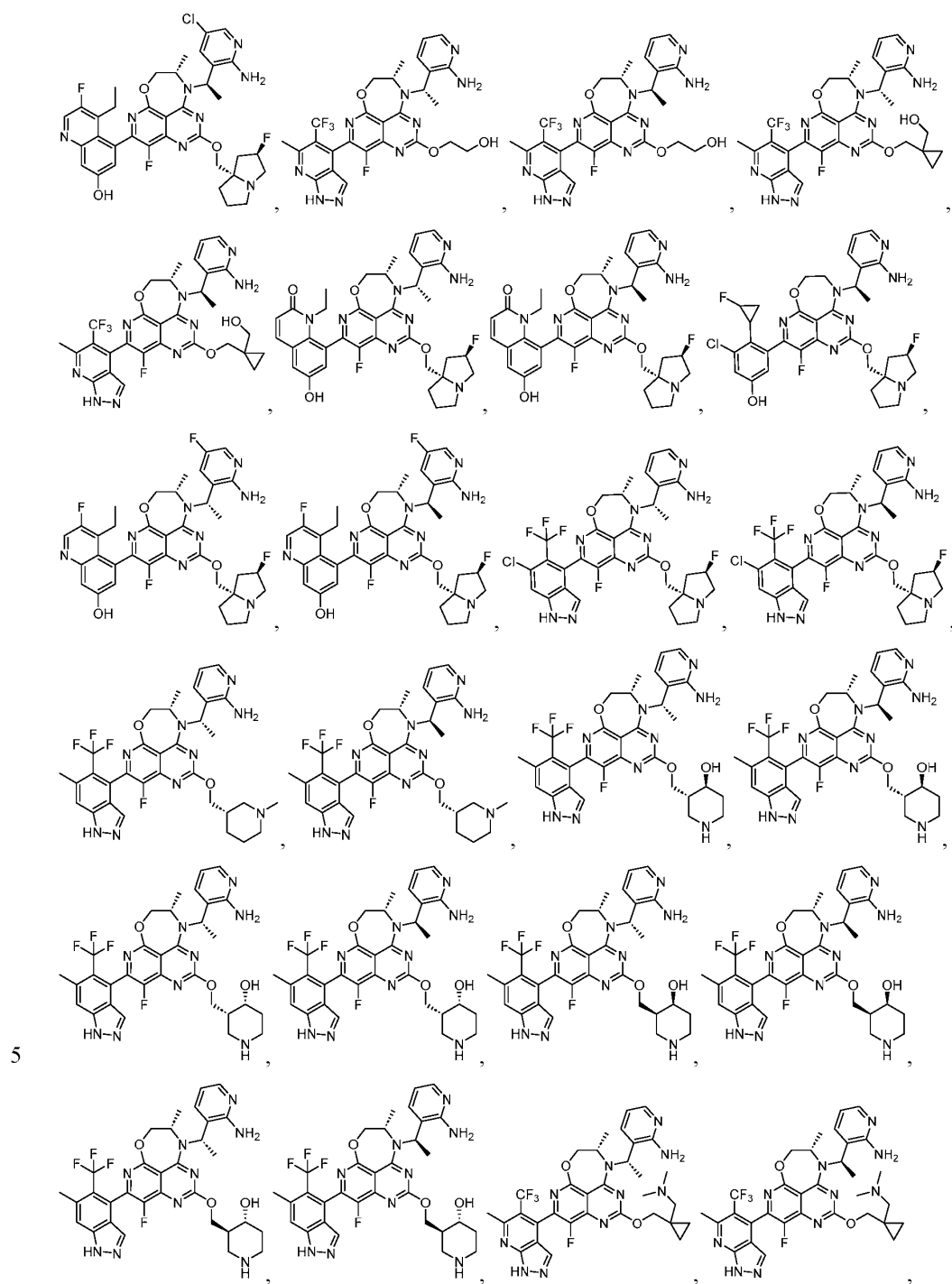
- 5 23. The compound of claim 1, wherein the compound is selected from the group consisting of

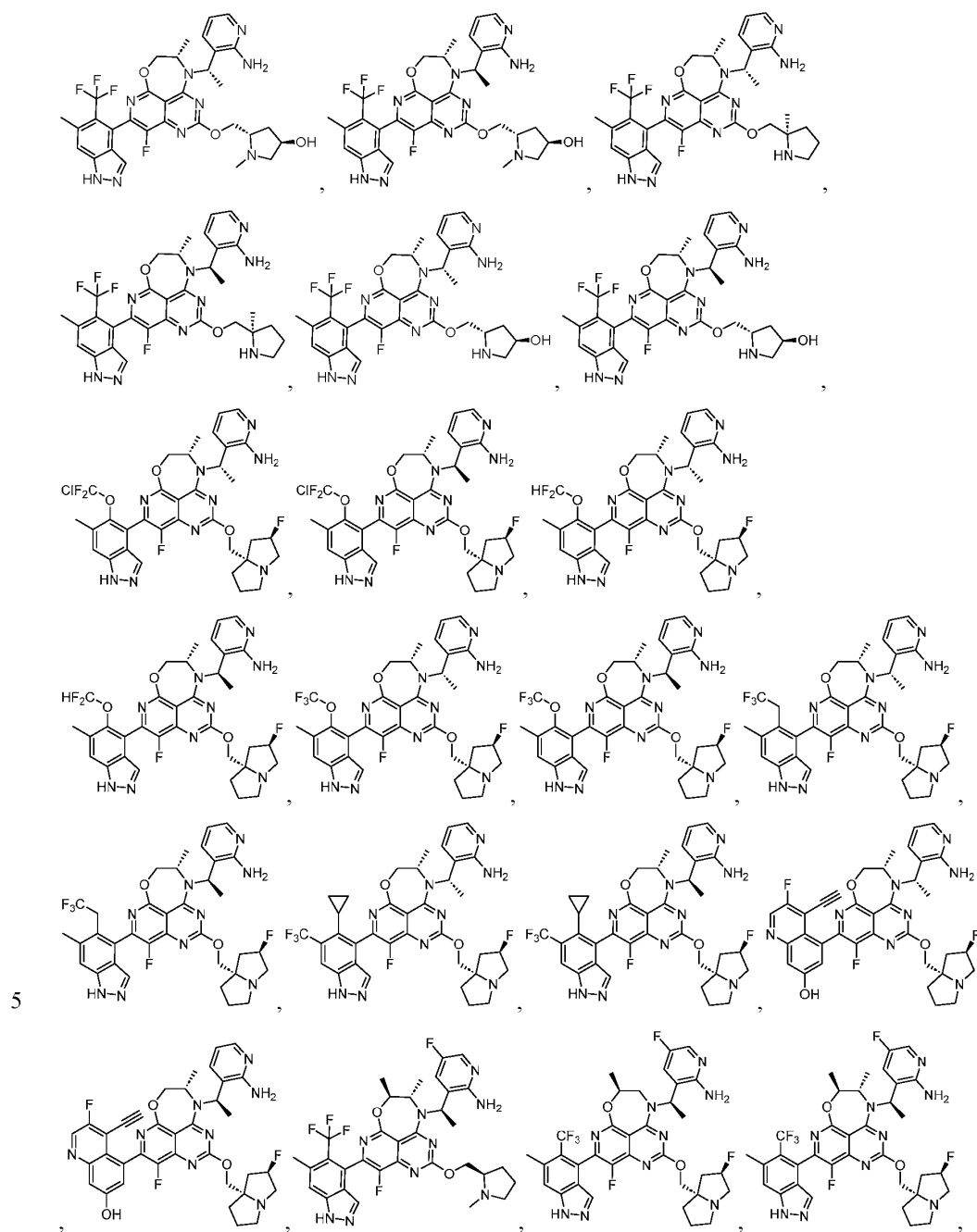


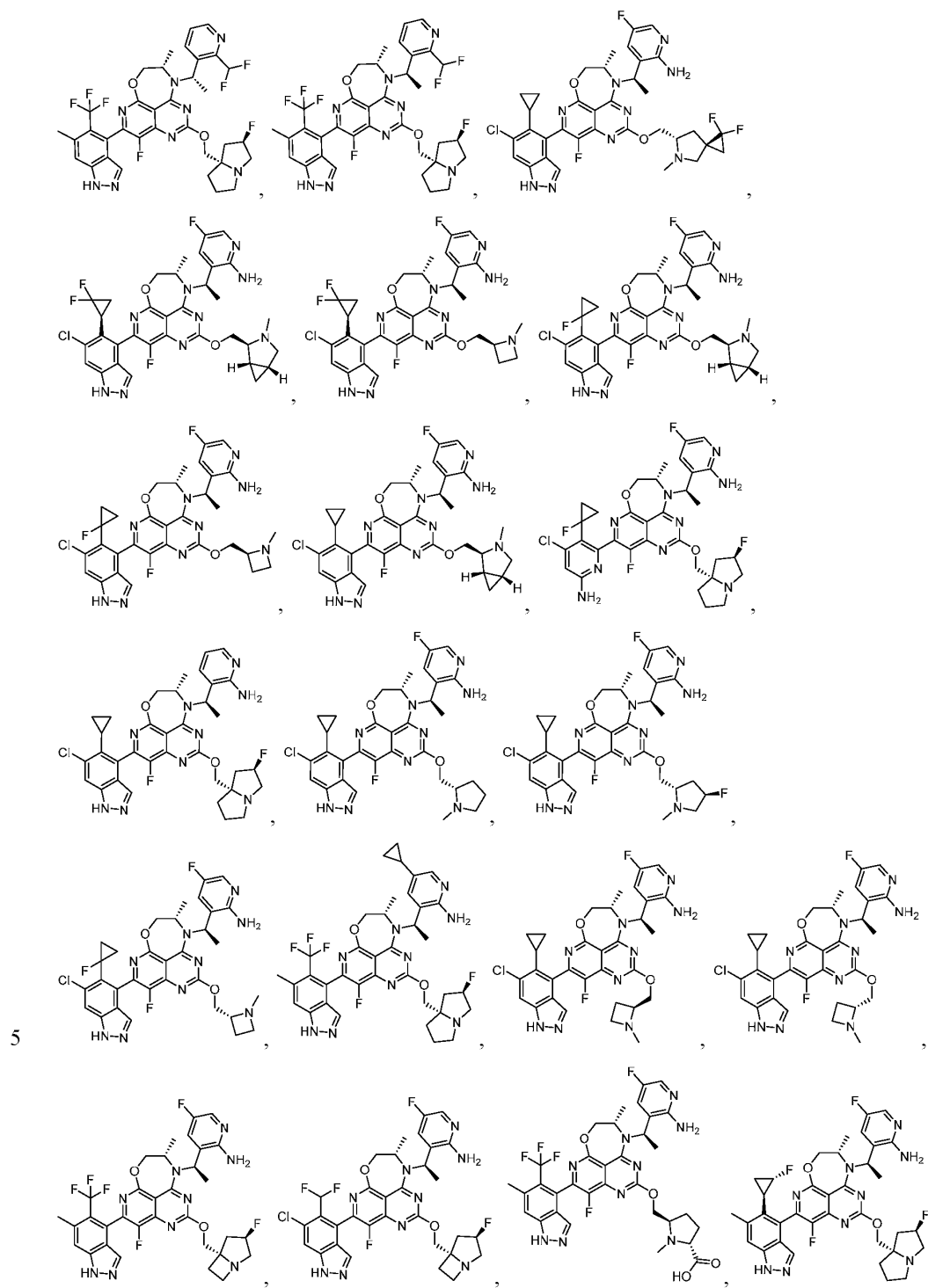


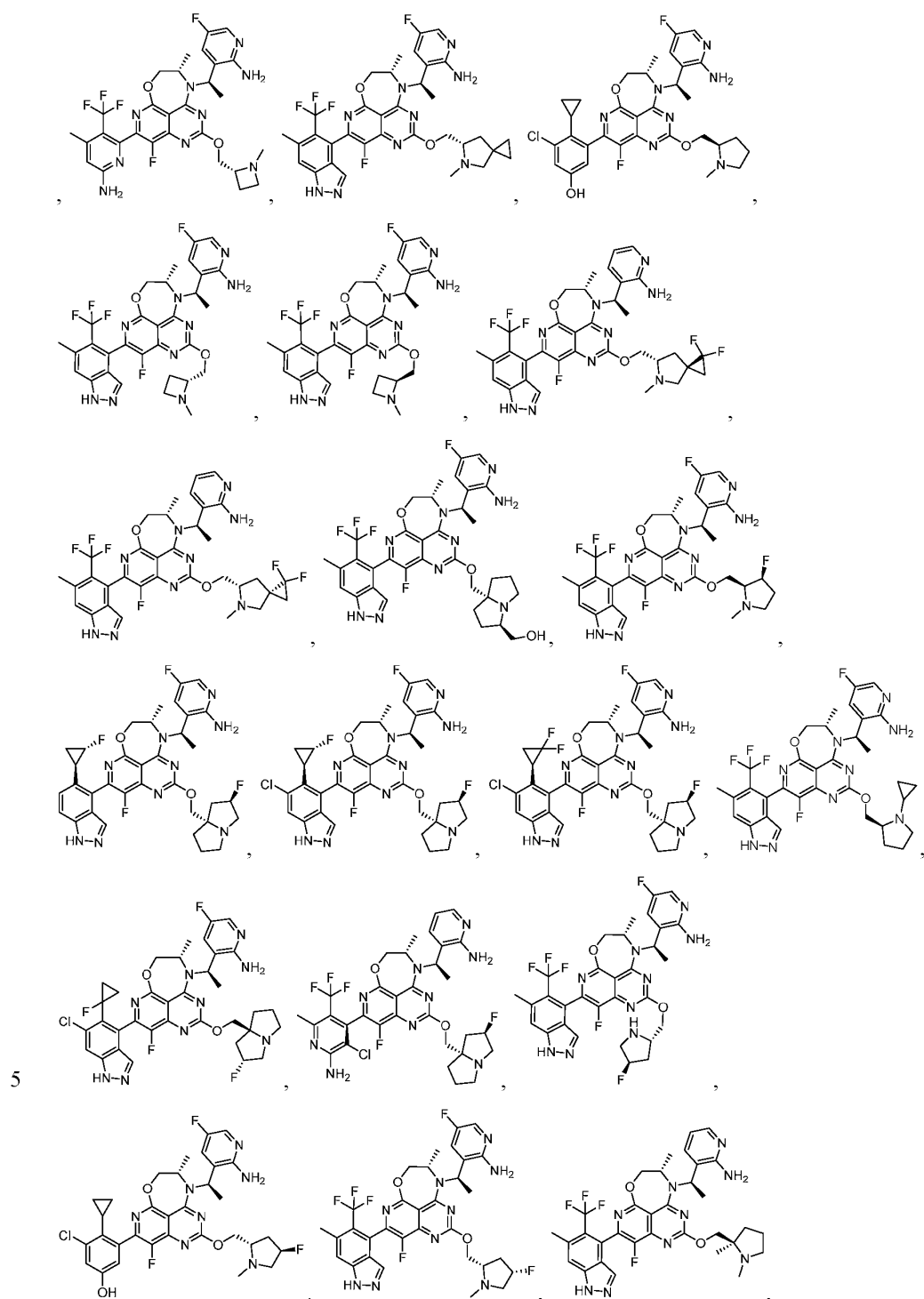


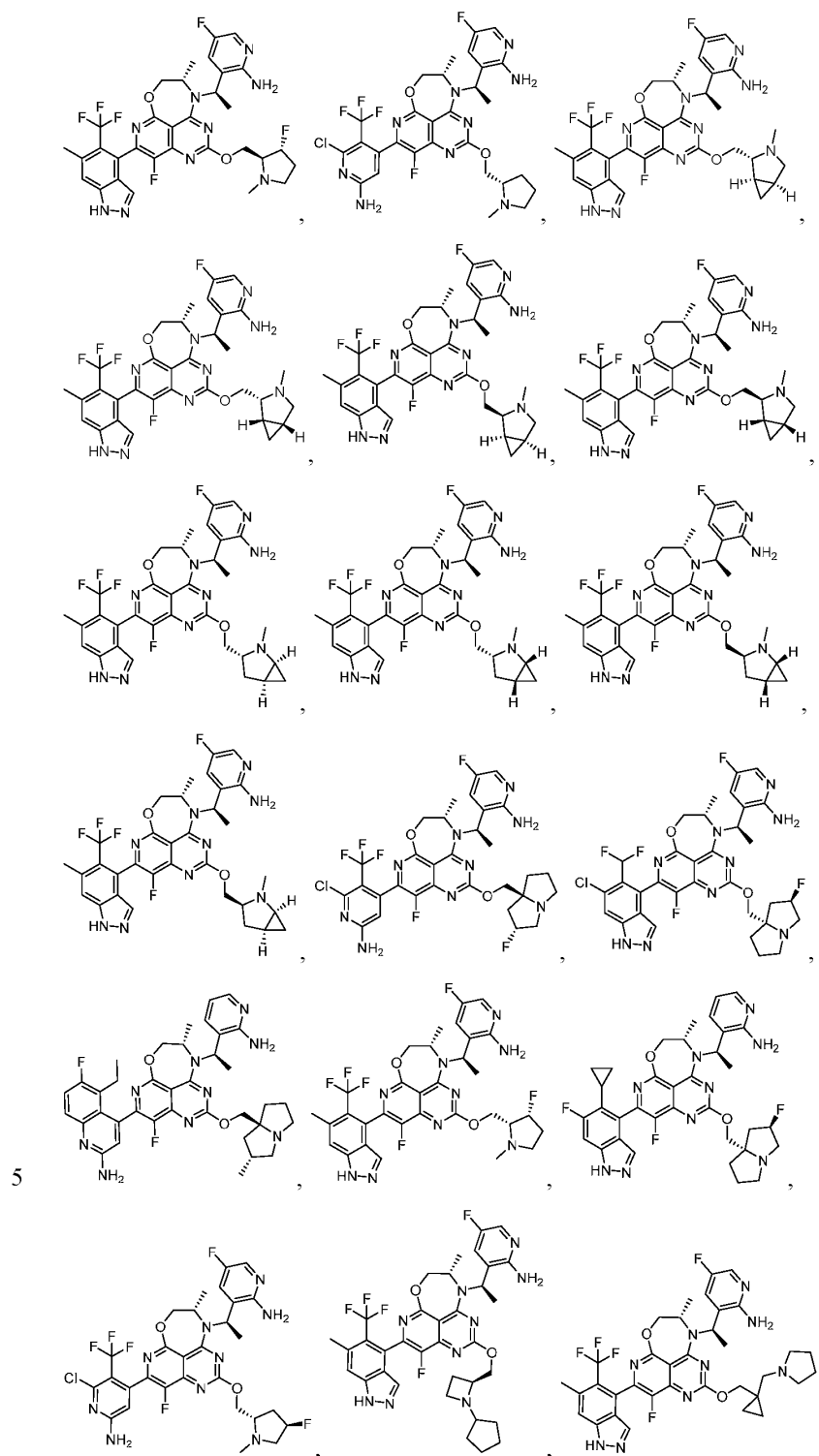


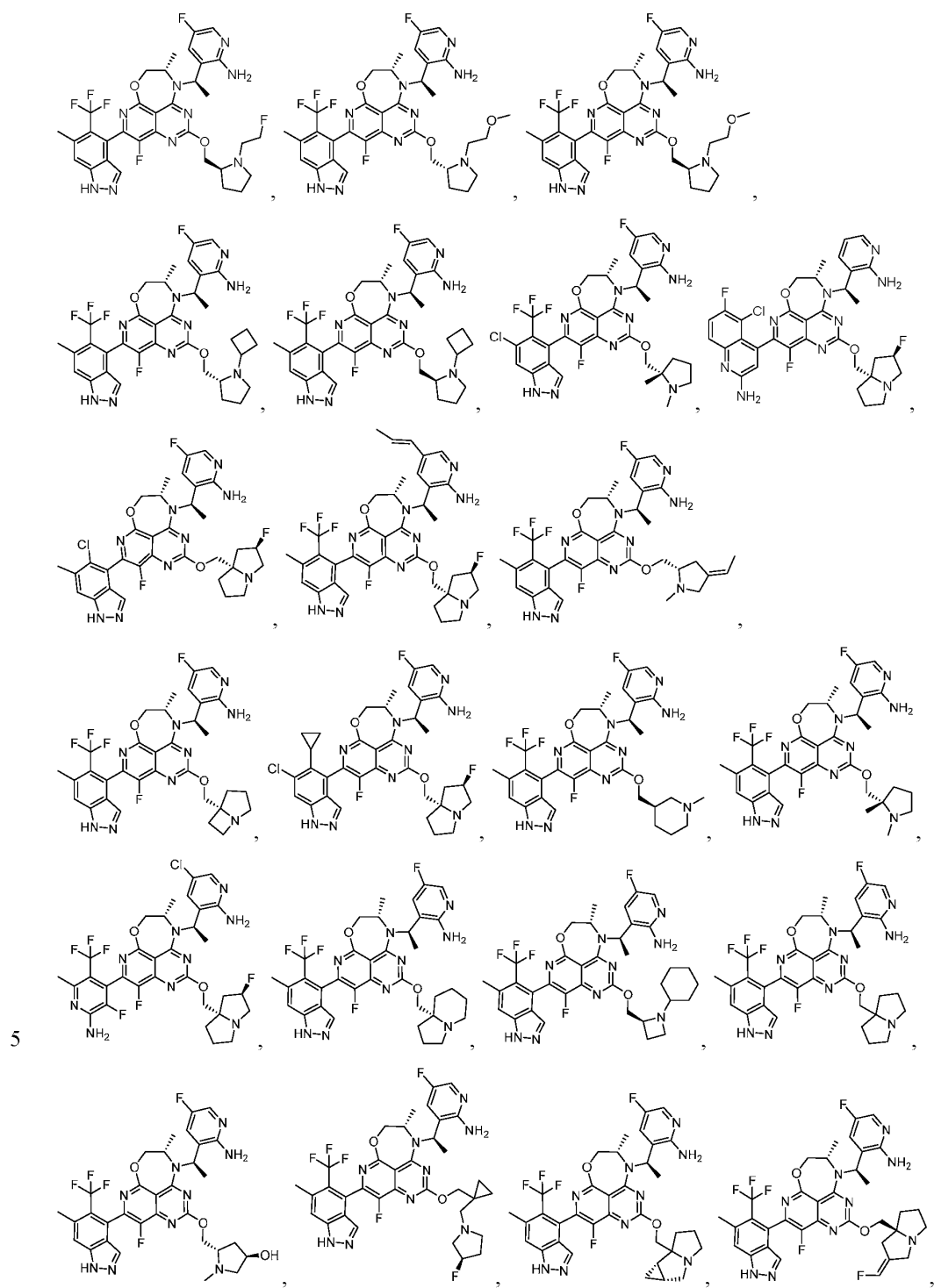


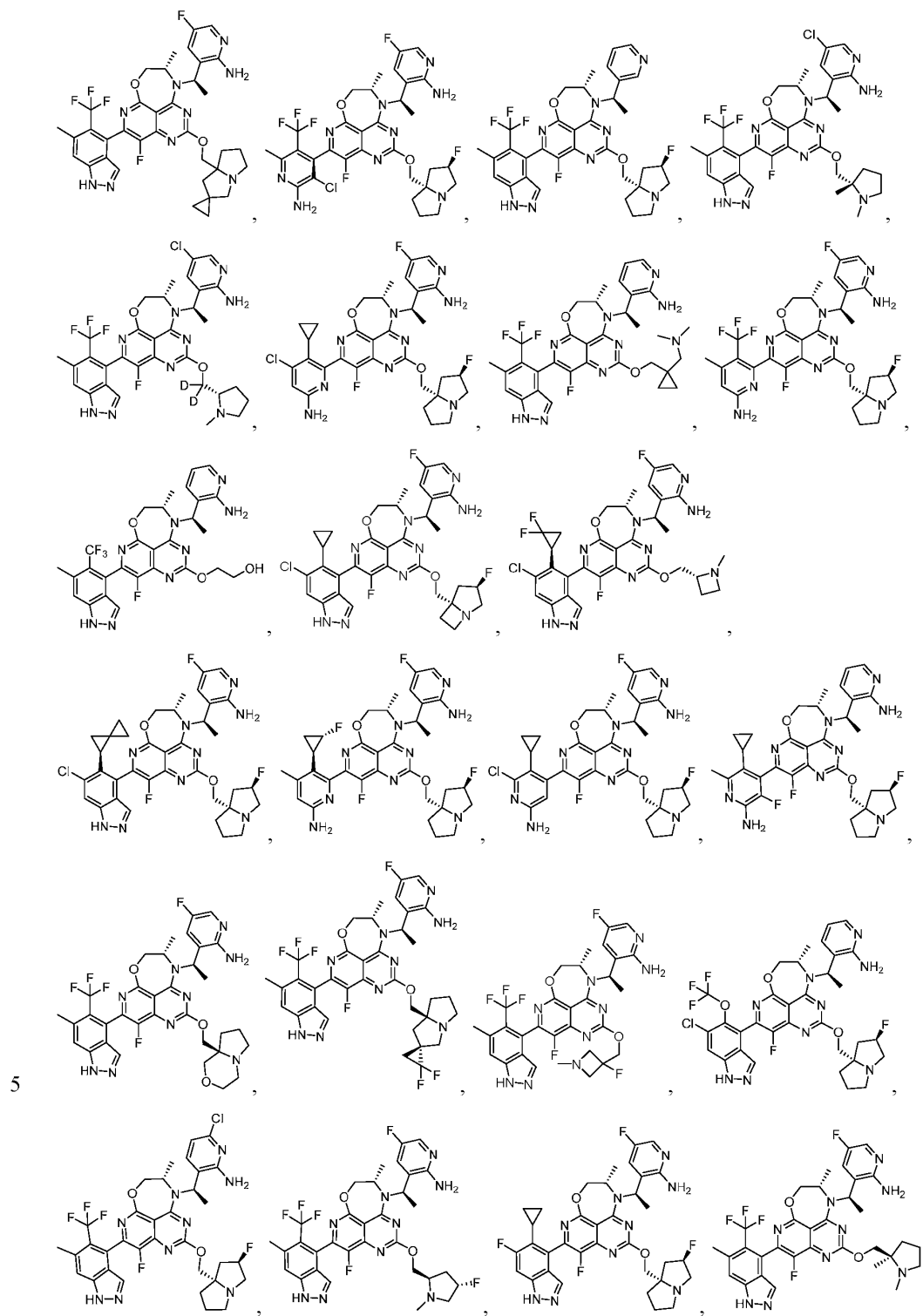


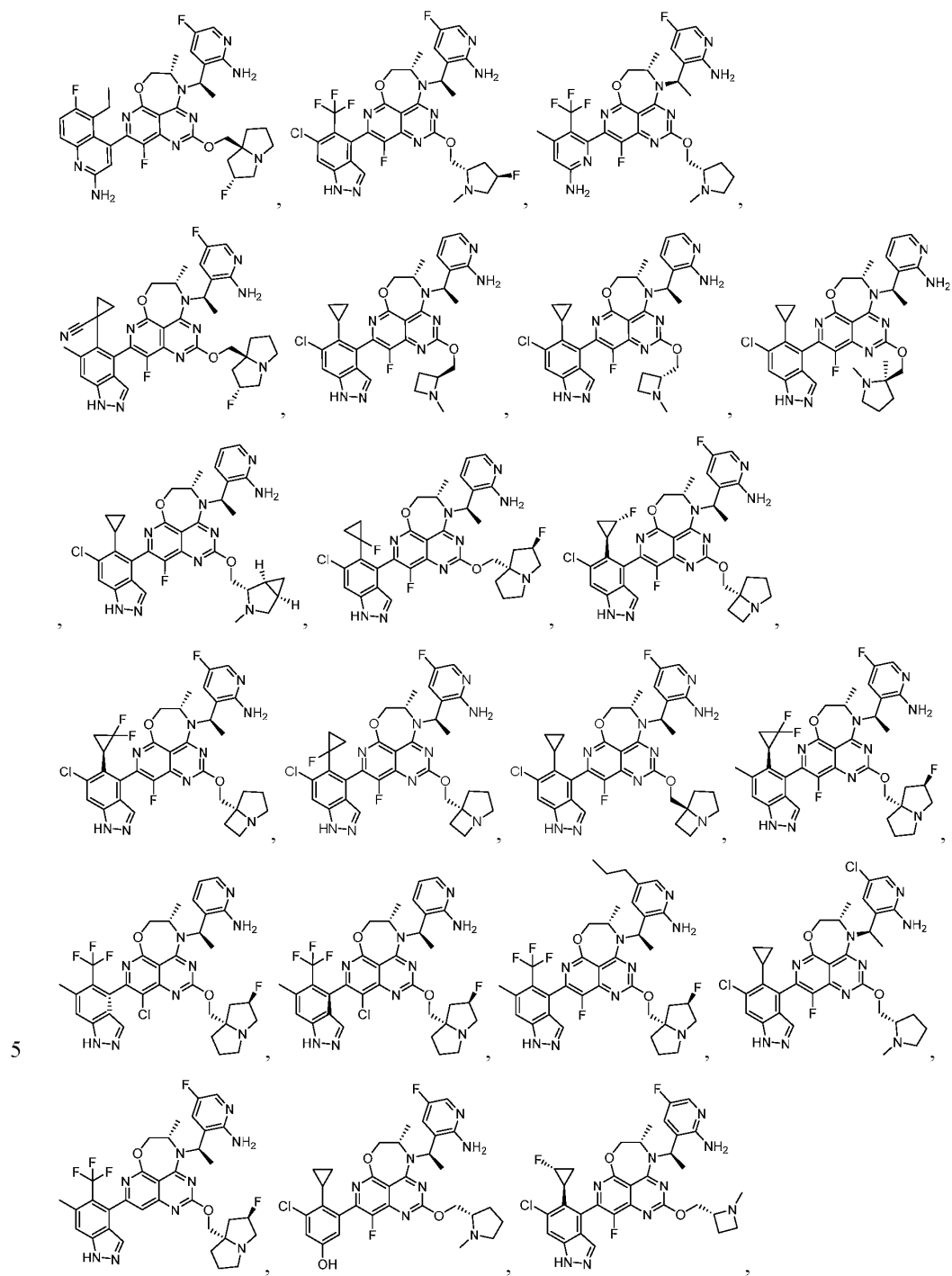


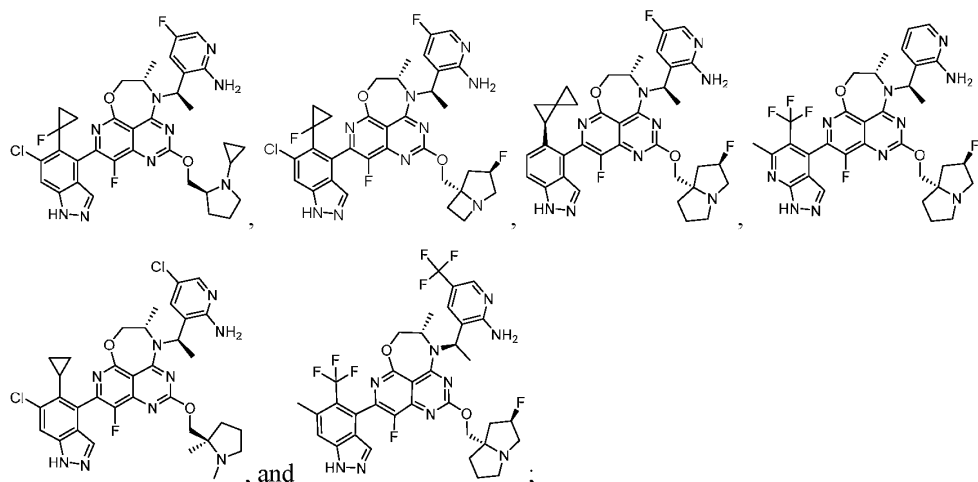






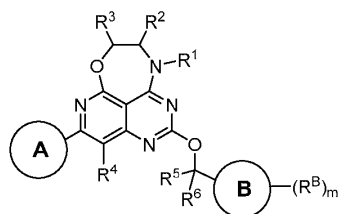






or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

24. A compound represented by Formula II:



Formula II;

or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

ring A is selected from the group consisting of indazolyl, quinolinyl, quinolinonyl, benzothiophenyl, benzothiazolyl, pyridinyl, pyrimidinyl, and phenyl; wherein ring A is substituted with one, two, or three substituents each independently selected from R^A ;

- 10 R^A is independently selected for each occurrence from the group consisting of hydrogen, halogen, deuterium, hydroxyl, -CN, -NO₂, -NR^aR^b, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and
- 15 -NR^aS(O)₂C₁-C₆alkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, and phenyl may optionally be substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, oxo, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;

R^1 is selected from the group consisting of C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃-C₆cycloalkyl, -CH(CH₃)-(C₃-C₆cycloalkyl), -CH₂-(C₃-C₆cycloalkyl), phenyl, 5-membered

heteroaryl, and $-\text{CR}^{\text{c}}\text{R}^{\text{d}}-(5\text{-membered heteroaryl})$; wherein alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, and heteroaryl may optionally be substituted with one, two, three, or four substituents each independently selected from R^{11} ;

R^2 is selected from the group consisting of hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $-\text{CH}(\text{CH}_3)-(\text{C}_3\text{-C}_6\text{cycloalkyl})$, $-\text{CH}_2-(\text{C}_3\text{-C}_6\text{cycloalkyl})$, phenyl, 5-membered heteroaryl, and $-\text{CR}^{\text{c}}\text{R}^{\text{d}}-(5\text{-membered heteroaryl})$; wherein alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, and heteroaryl may optionally be substituted with one, two, three, or four substituents each independently selected from R^{22} ;

R^{11} and R^{22} are independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{NR}^{\text{a}}\text{R}^{\text{b}}$, oxo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, phenyl, $-\text{COOH}$, $-\text{C}(=\text{O})\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{NR}^{\text{a}}(\text{C}=\text{O})\text{R}^{\text{b}}$, $-\text{O}(\text{C}=\text{O})\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-\text{NR}^{\text{a}}(\text{C}=\text{O})\text{OR}^{\text{b}}$, $-\text{NR}^{\text{a}}(\text{C}=\text{O})\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $-(\text{C}=\text{O})\text{C}_1\text{-C}_6$ alkyl, $-(\text{C}=\text{O})\text{OC}_1\text{-C}_6$ alkyl, $-\text{O}(\text{C}=\text{O})\text{C}_1\text{-C}_6$ alkyl, $-\text{O}(\text{C}=\text{O})\text{OC}_1\text{-C}_6$ alkyl, $-\text{SH}$, $-\text{SC}_1\text{-C}_6$ alkyl, $-\text{S}(\text{O})\text{C}_1\text{-C}_6$ alkyl, $-\text{S}(\text{O})_2\text{C}_1\text{-C}_6$ alkyl, $-\text{S}(\text{O})_2\text{NR}^{\text{a}}\text{R}^{\text{b}}$, and $-\text{NR}^{\text{a}}\text{S}(\text{O})_2\text{C}_1\text{-C}_6$ alkyl;

R^3 is selected from the group consisting of hydrogen and $\text{C}_1\text{-C}_6$ alkyl optionally substituted with one or more halogens or hydroxyl;

R^4 is selected from the group consisting of halogen, hydrogen, deuterium, and $\text{C}_1\text{-C}_3$ alkyl;

R^5 and R^6 are each independently selected from the group consisting of hydrogen, deuterium, and $\text{C}_1\text{-C}_3$ alkyl;

Ring B is selected from the group consisting of 5-10 membered heterocyclyl containing at least one ring nitrogen;

R^{B} is independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, $-\text{CN}$, $-\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $\text{C}_1\text{-C}_6$ alkyl, and $\text{C}_1\text{-C}_6$ alkoxy;

R^{a} and R^{b} are each independently selected from the group consisting of hydrogen and $\text{C}_1\text{-C}_6$ alkyl, wherein $\text{C}_1\text{-C}_6$ alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, and $\text{C}_1\text{-C}_6$ alkoxy; or

R^{a} and R^{b} , together with the nitrogen to which they are attached, may be joined together to form a 4-7 membered heterocyclyl optionally substituted by one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, $-\text{NR}^{\text{a}}\text{R}^{\text{b}}$, $\text{C}_1\text{-C}_6$ alkyl, and $\text{C}_1\text{-C}_6$ alkoxy; and

m is 0, 1, 2, 3, or 4;

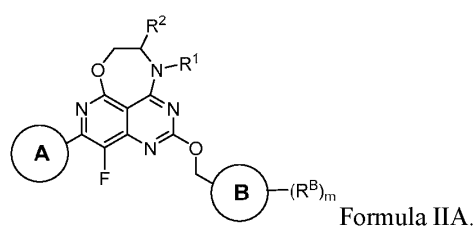
wherein if ring A is benzothiophenyl, then R¹ is CH₃ or substituted C₁-C₆alkyl.

25. The compound of claim 24, wherein R³ is hydrogen or CH₃.

26. The compound of claim 24 or 25, wherein R⁴ is fluoro.

5 27. The compound of any one of claims 24-26, wherein R⁵ and R⁶ are each hydrogen.

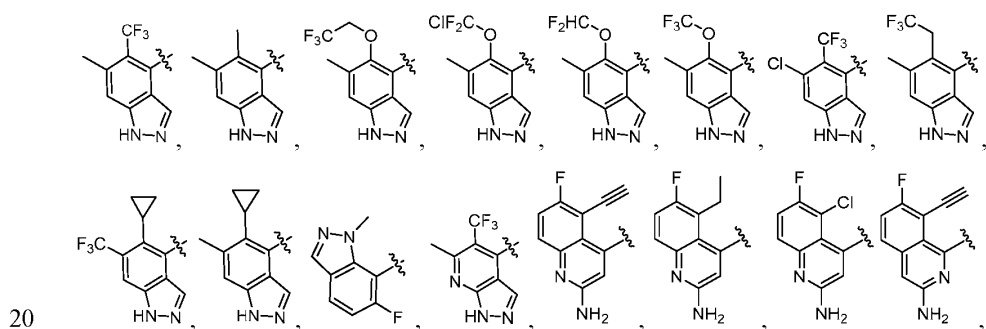
28. The compound of any one of claims 24-27, wherein the compound is represented by Formula IIA:

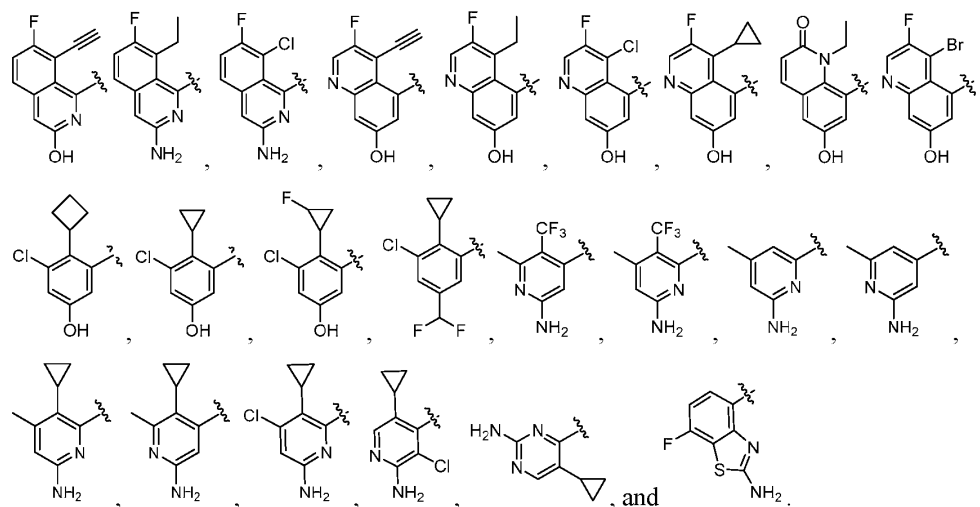


29. The compound of any one of claims 24-28, wherein ring A is selected from the group
10 consisting of indazolyl, quinolinyl, quinolinonyl, benzothiazolyl, pyridinyl, pyrimidinyl, and phenyl; wherein ring A is substituted with one, two, or three substituents each independently selected from R^A.

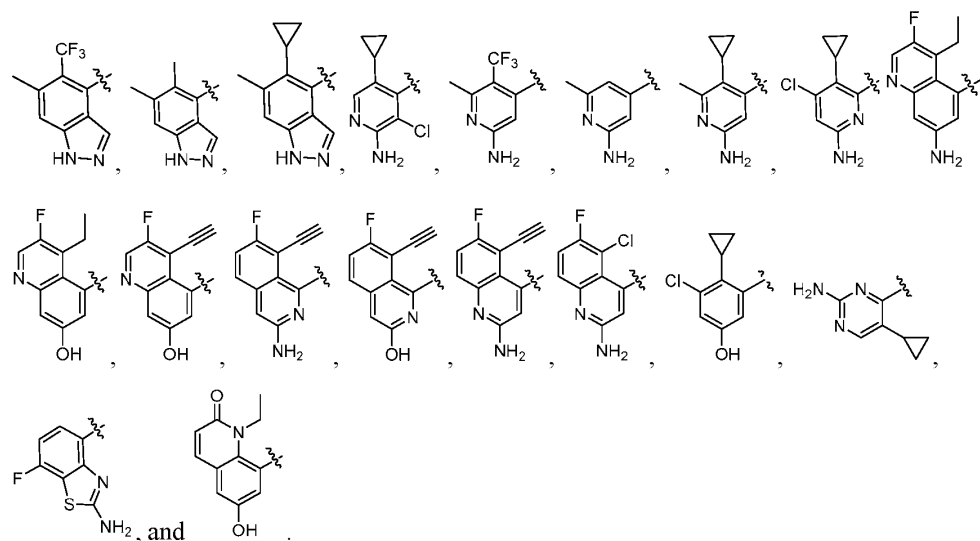
30. The compound of any one of claims 24-29, wherein R^A is independently selected for each
occurrence from the group consisting of halogen, hydroxyl, -NH₂, C₁-C₄alkyl, and C₂-C₄kynyl,
15 C₁-C₄alkoxy, and C₃-C₄cycloalkyl, wherein alkyl, alkynyl, alkoxy, and cycloalkyl may optionally be substituted with one, two, or three halogens.

31. The compound of any one of claims 24-30, wherein ring A is selected from the group consisting of:



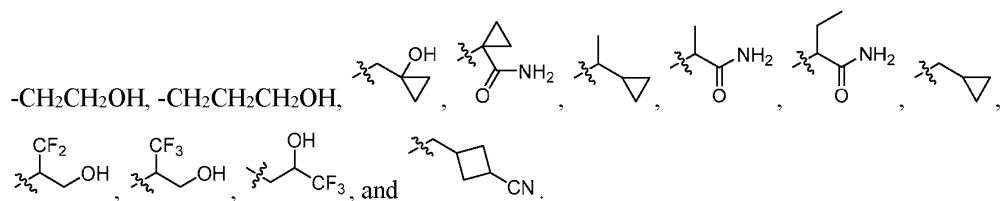


32. The compound of any one of claims 24-31, wherein ring A is selected from the group
 5 consisting of



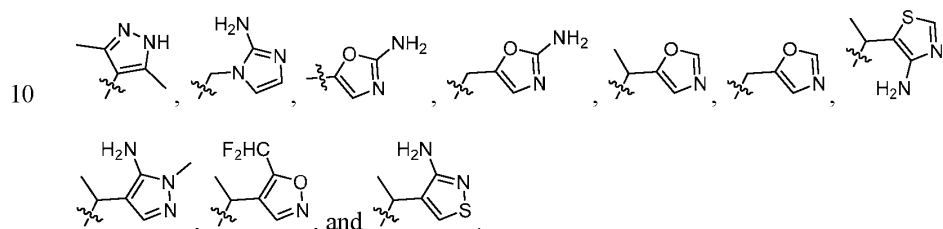
33. The compound of any one of claims 24-32, wherein R^1 is selected from the group
 10 consisting of C_1 - C_6 alkyl, C_3 - C_4 cycloalkyl, $-\text{CH}(\text{CH}_3)-(\text{C}_3$ - C_4 cycloalkyl), and $-\text{CH}_2-(\text{C}_3$ - C_4 cycloalkyl), wherein alkyl and cycloalkyl may optionally be substituted by one, two, three, or four groups each independently selected from the group consisting of halogen, hydroxyl, cyano, and $-\text{C}(=\text{O})\text{NR}^a\text{R}^b$.

34. The compound of any one of claims 24-33, wherein R^1 is selected from the group consisting
 15 of $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{F}_2\text{Cl}$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{CHF}_2$, $-\text{CH}(\text{CH}_3)\text{CHF}_2$,



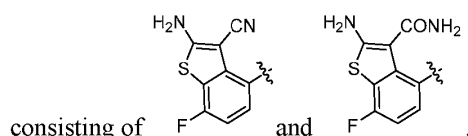
35. The compound of any one of claims 24-32, wherein R^1 is selected from the group consisting of 5-membered heteroaryl, $-\text{CH}_2$ -(5-membered heteroaryl), and $-\text{CH}(\text{CH}_3)$ -(5-membered heteroaryl), wherein heteroaryl may optionally be substituted with one or two substituents each independently selected from the group consisting of $-\text{NR}^a\text{R}^b$ and C_1 - C_3 alkyl, and wherein alkyl may optionally be substituted with one, two or three halogens.

36. The compound of any one of claims 24-32 and 35, wherein R^1 is selected from the group consisting of



37. The compound of any one of claims 24-28, wherein ring A is benzothiophenyl substituted with one, two or three substituents each independently selected from the group consisting of halogen, cyano, $-\text{NH}_2$, and $-\text{C}(\text{O})\text{NH}_2$.

38. The compound of any one of claims 24-28 and 37, wherein ring A is selected from the group



39. The compound of any one of claims 24-28 and 37-38, wherein R^1 is selected from the group consisting of $-\text{CH}_3$, $-\text{CH}_2\text{CHF}_2$, and $-\text{CH}_2\text{CH}_2\text{OH}$.

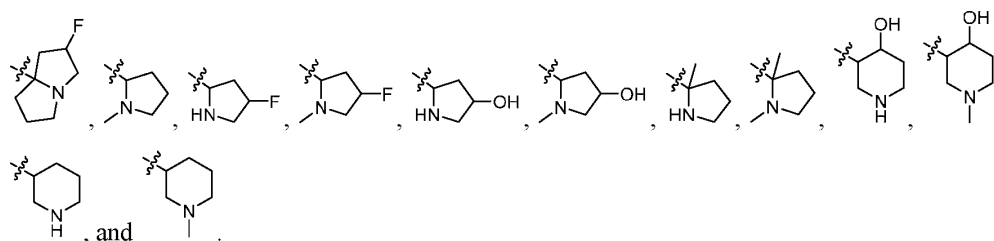
40. The compound of any one of claims 24-39, wherein R^2 is selected from the group consisting of hydrogen and C_1 - C_6 alkyl, wherein alkyl may optionally be substituted with one, two, or three substituents each independently selected from the group consisting of halogen and hydroxyl.

41. The compound of any one of claims 24-40, wherein R^2 is selected from the group consisting of hydrogen, $-\text{CH}_3$, and $-\text{CH}_2\text{CH}_2\text{OH}$.

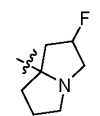
42. The compound of any one of claims 24-41, wherein R^B is selected from the group consisting of halogen, hydroxyl, and C_1 - C_3 alkyl.

43. The compound of any one of claims 24-42, wherein R^B is selected from the group consisting of halogen, hydroxyl, and $-CH_3$.

5 44. The compound of any one of claims 24-43, wherein ring B is selected from the group consisting of:

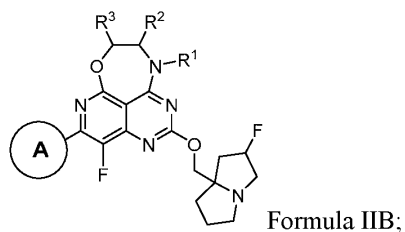


45. The compound of any one of claims 24-44, wherein ring B is



10

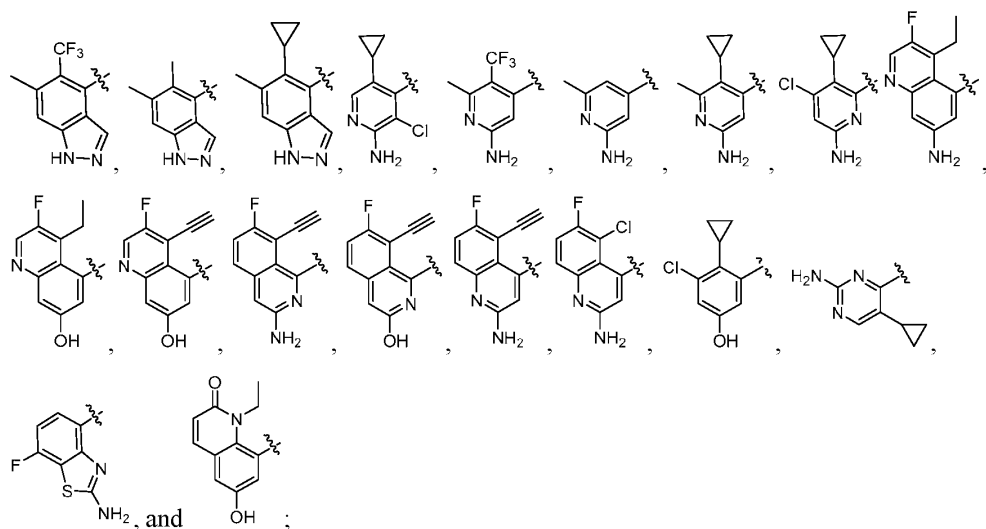
46. The compound of claim 24, wherein the compound is represented by Formula IIB:



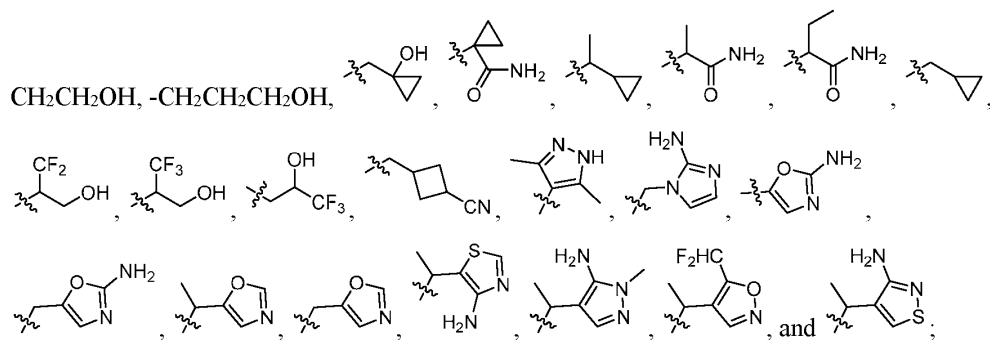
Formula IIB;

or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

Ring A is selected from the group consisting of

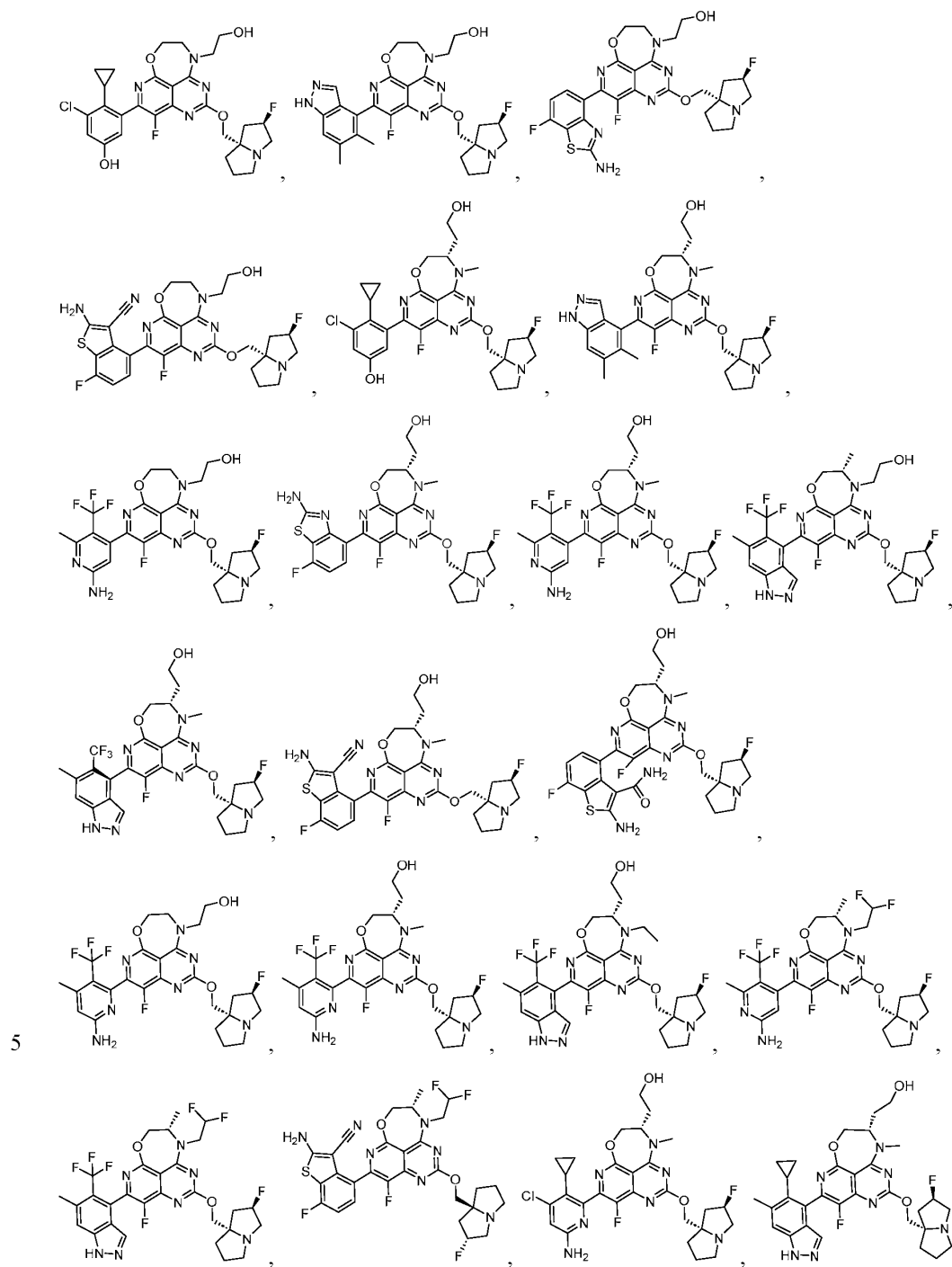


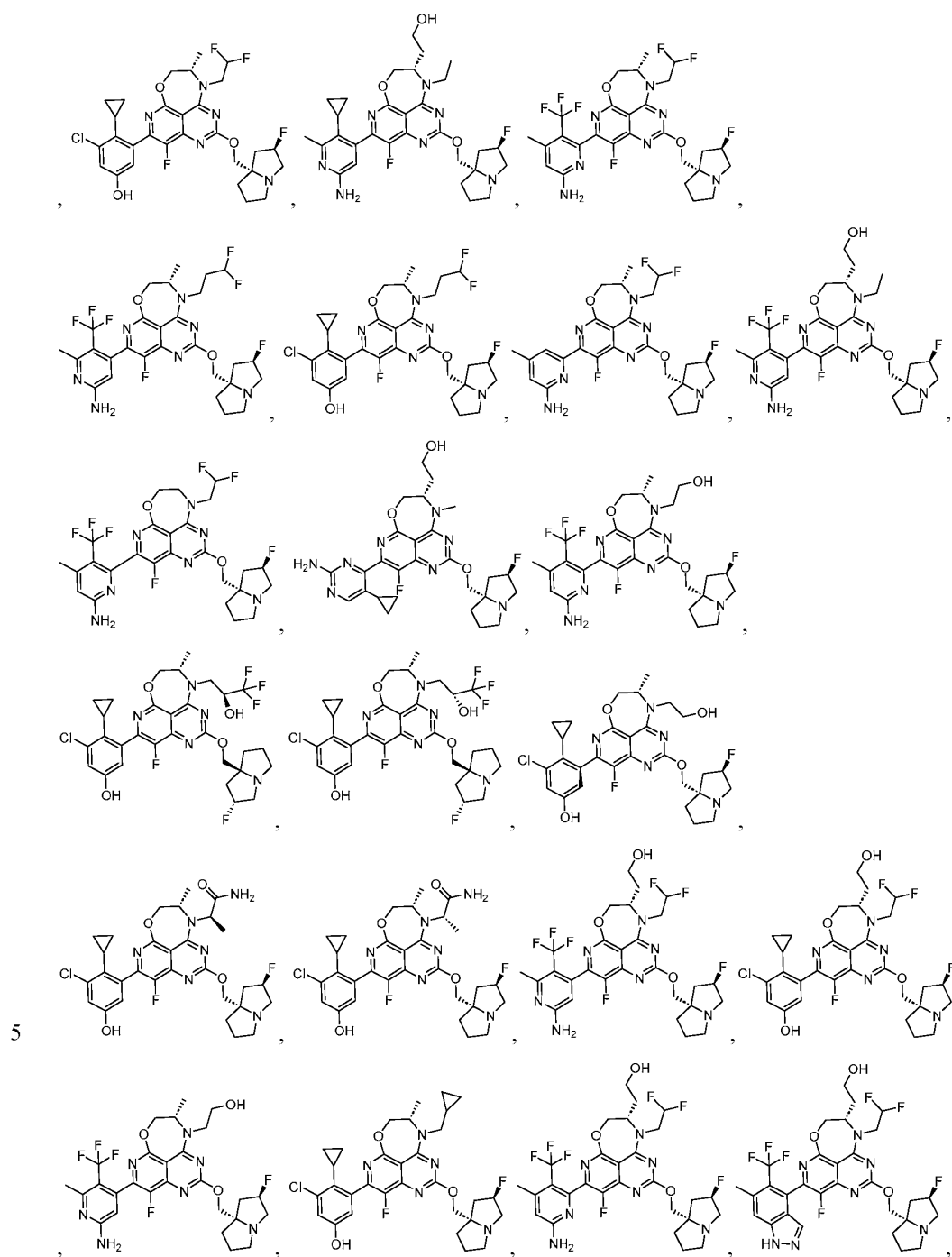
R¹ is selected from the group consisting of -CH₃, -CH₂CH₃, -CH₂CN, -CH₂CHF₂, -
 5 CH₂F₂Cl, -CH₂CF₃, -CH₂CH₂CHF₂, -CH(CH₃)CHF₂, -CH₂CH₂OH, -CH₂CH₂CH₂OH,
 -CH₃, -CH₂CH₃, -CH₂CN, -CH₂CHF₂, -CH₂F₂Cl, -CH₂CF₃, -CH₂CH₂CHF₂, -

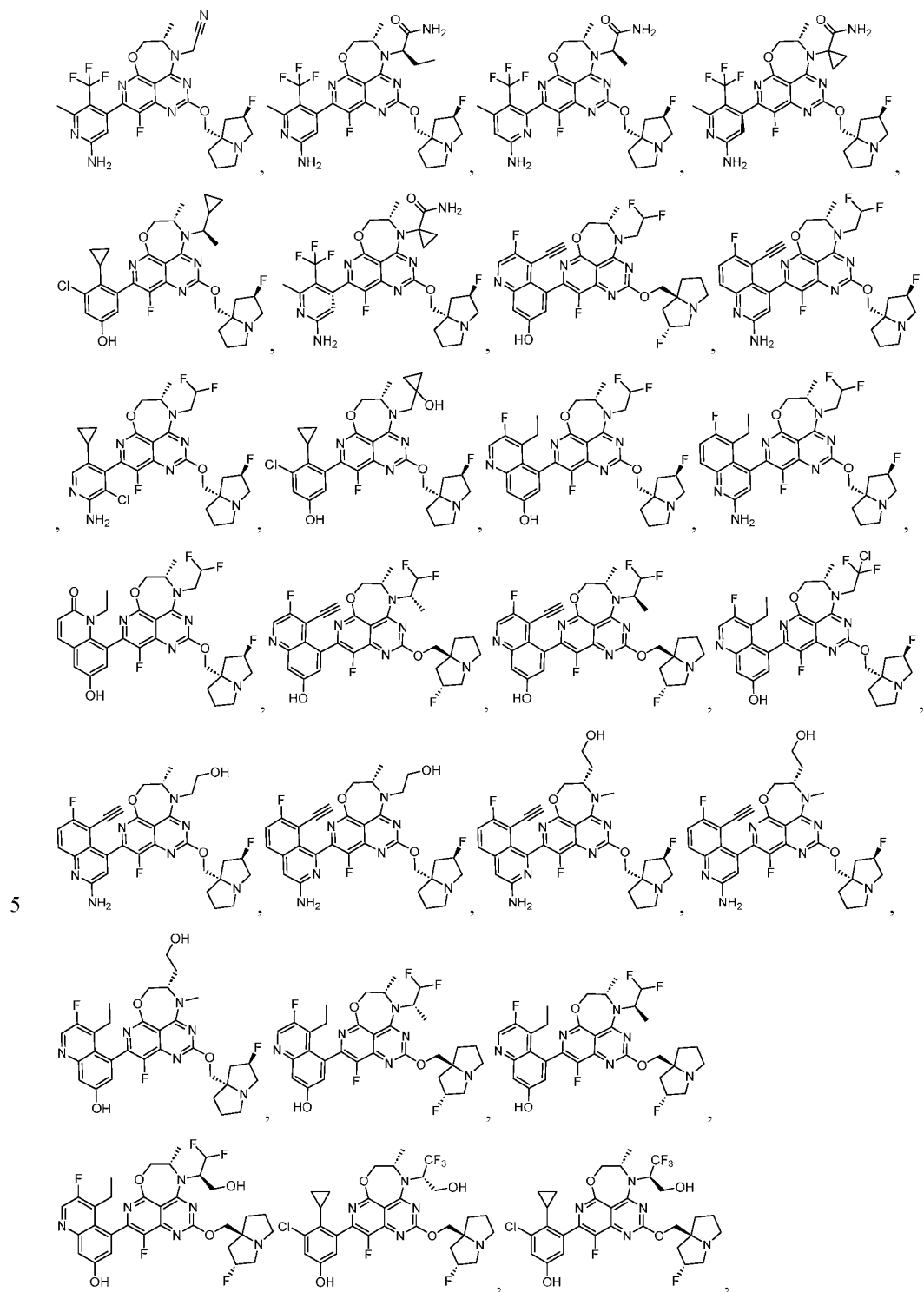


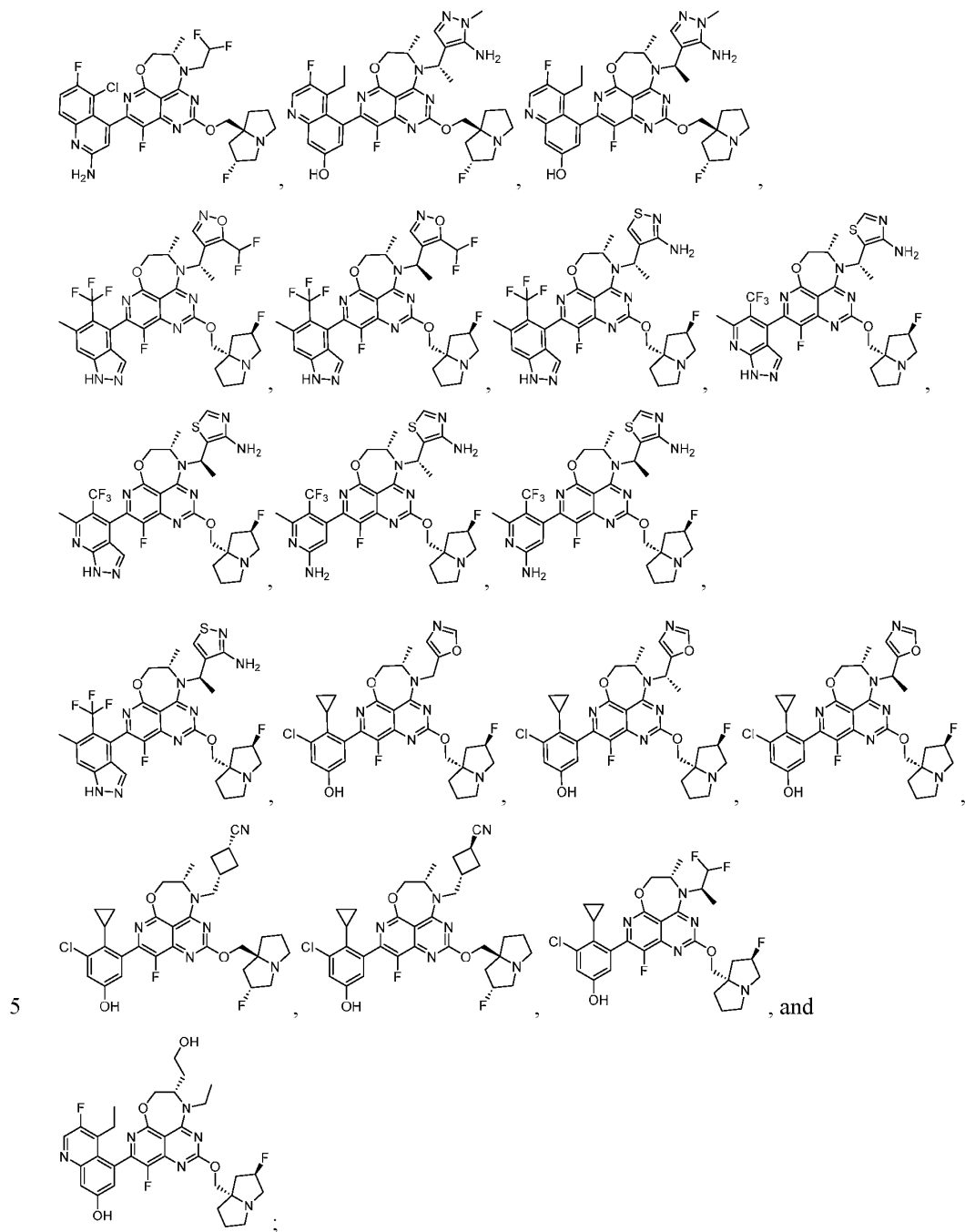
10 R² is selected from the group consisting of hydrogen, -CH₃, and -CH₂CH₂OH; and
 R³ is hydrogen or CH₃.

47. The compound of claim 24, wherein the compound is selected from the group consisting of



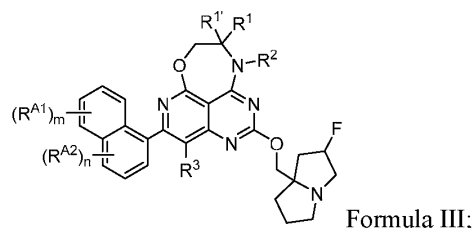






or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

48. A compound represented by Formula III:



or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:

R^{A1} and R^{A2} are independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, -CN, -NO₂, -NR^aR^b, C₁-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -(C=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl, wherein each alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, and phenyl may optionally be substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, oxo, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;

$R^{1'}$ is hydrogen and R^1 is selected from the group consisting of hydrogen, -CH₃, -CF₃, -CH₂CH₂OH, -CH₂C(CH₃)₂OH, C₂-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, phenyl, 5-membered heteroaryl, and -CR^cR^d-(5-membered heteroaryl); wherein alkyl is substituted with one, two, three, or four substituents each independently selected from R^{11} ; and wherein alkenyl, alkynyl, cycloalkyl, phenyl, and heteroaryl may optionally be substituted with one, two, three, or four substituents each independently selected from R^{22} ; and

R^2 is selected from the group consisting of hydrogen, -CH₃, -CH₂CH₂OH, -CH₂CH₂CH₂OH, -CH₂CH(CH₃)OH, -CH₂C(CH₃)₂OH, C₂-C₆alkyl, C₂-C₆alkenyl, C₂-C₆alkynyl, C₃cycloalkyl, C₅-C₆cycloalkyl, phenyl, 5-membered heteroaryl, and -CR^cR^d-(5-membered heteroaryl); wherein alkyl is substituted with one, two, three, or four substituents each independently selected from R^{11} ; and wherein alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, and heteroaryl may optionally be substituted with one, two, three, or four substituents each independently selected from R^{22} ;

or:

R^1 and $R^{1'}$, together with the carbon atom to which they are attached, may be joined together to form C₃-cycloalkyl optionally substituted with one, two or three halogens or hydroxyl; and R^2 is C₁-C₆alkyl substituted with one, two, or three substituents each

independently selected from the group consisting of halogen, hydroxyl, cyano, -COOH, and C(=O)NR^aR^b; or

R¹ and R^{1'}, together with the carbon atom to which they are attached, may be joined together to form C₄-cycloalkyl optionally substituted with one, two or three halogens or hydroxyl; and R² is C₁-C₆alkyl optionally substituted with one, two, or three substituents each independently selected from the group consisting of halogen, hydroxyl, cyano, -COOH, and C(=O)NR^aR^b;

R¹¹ is independently selected for each occurrence from the group consisting of halogen, deuterium, -CN, -NO₂, -NR^aR^b, oxo, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -COOH, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -C(=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl;

R²² is independently selected for each occurrence from the group consisting of halogen, deuterium, hydroxyl, -CN, -NO₂, -NR^aR^b, oxo, C₁-C₆alkyl, C₁-C₆alkoxy, C₃-C₆cycloalkyl, phenyl, -COOH, -C(=O)NR^aR^b, -NR^a(C=O)R^b, -O(C=O)NR^aR^b, -NR^a(C=O)OR^b, -NR^a(C=O)NR^aR^b, -C(=O)C₁-C₆alkyl, -(C=O)OC₁-C₆alkyl, -O(C=O)C₁-C₆alkyl, -O(C=O)OC₁-C₆alkyl, -SH, -SC₁-C₆alkyl, -S(O)C₁-C₆alkyl, -S(O)₂C₁-C₆alkyl, -S(O)₂NR^aR^b, and -NR^aS(O)₂C₁-C₆alkyl;

R³ is selected from the group consisting of halogen, hydrogen, deuterium, and C₁-C₃alkyl;

R^a and R^b are each independently selected from the group consisting of hydrogen and C₁-C₆alkyl, wherein C₁-C₆alkyl optionally substituted with one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, and C₁-C₆alkoxy; or

R^a and R^b, together with the nitrogen to which they are attached, may be joined together to form a 4-7 membered heterocyclyl optionally substituted by one or more substituents each independently selected from the group consisting of halogen, deuterium, hydroxyl, -NR^aR^b, C₁-C₆alkyl, and C₁-C₆alkoxy;

R^c and R^d are each independently selected from the group consisting of hydrogen and C₁-C₆alkyl;

m is 0, 1, 2, 3, or 4; and

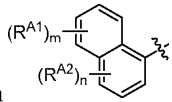
n is 0, 1, or 2;

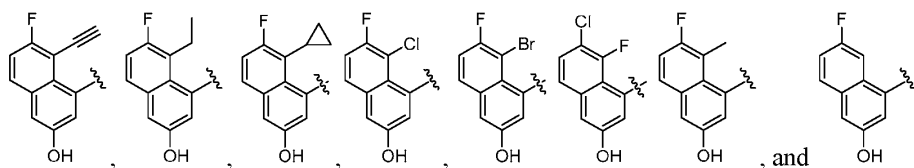
wherein:

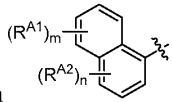
if R^1 is hydrogen, then R^2 is not hydrogen, $-CH_3$, or CH_2CH_2OH ; and

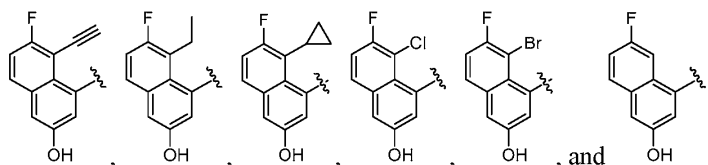
if R^1 is $-CH_3$, then R^2 is not hydrogen, $-CH_3$, $-CH_2CF_2$, $-CH_2CF_3$, or $-CH_2CH(CH_3)OH$.

49. The compound of claim 48, wherein R^{A1} and R^{A2} are independently selected for each occurrence from the group consisting of halogen, hydroxyl, cyano, $-NH_2$, C_1 - C_4 alkyl, and C_2 - C_4 alkynyl, C_1 - C_4 alkoxy, and C_3 - C_4 cycloalkyl, wherein alkyl, alkynyl, alkoxy, and cycloalkyl may optionally be substituted with one, two, or three halogens.
50. The compound of claim 48 or 49, wherein m is 1 or 2 and R^{A1} is independently selected for each occurrence from the group consisting of halogen, C_1 - C_4 alkyl, C_2 - C_4 alkynyl, and C_3 - C_4 cycloalkyl.
51. The compound of any one of claims 48-50, wherein n is 1 and R^{A2} is hydroxyl or $-NH_2$.

52. The compound of any one of claims 48-51, wherein  is selected from the group consisting of



53. The compound of any one of claims 48-52, wherein  is selected from the group consisting of

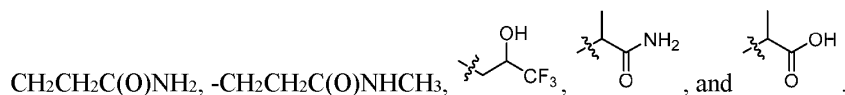


54. The compound of any one of claims 48-53, wherein $R^{1'}$ is hydrogen.
55. The compound of any one of claims 48-54, wherein R^1 is hydrogen.

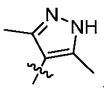
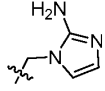
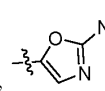
56. The compound of any one of claims 48-55, wherein R^2 is selected from the group consisting of $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, and $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$.

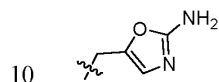
57. The compound of any one of claims 48-54, wherein R^1 is $-\text{CH}_3$.

58. The compound of any one of claims 48-54 and 57, wherein R^2 is selected from the group consisting of $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$,



59. The compound of any one of claims 48-54, wherein R^1 is selected from the group consisting

of $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$, , , , and



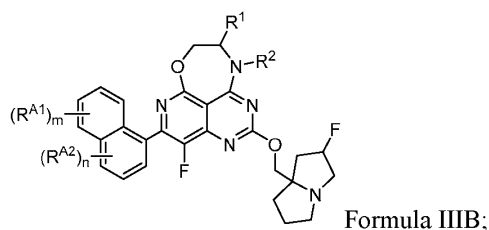
60. The compound of any one of claims 48-54 and 59, wherein R^2 is selected from the group consisting of hydrogen, $-\text{CH}_3$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, and $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$.

61. The compound of any one of claims 48-53, wherein $R^{1'}$ and R^1 , together with the carbon atom to which they are attached, are joined together to form C_3 -cycloalkyl optionally substituted with hydroxyl; and R^2 is $-\text{CH}_2\text{CH}_2\text{OH}$.

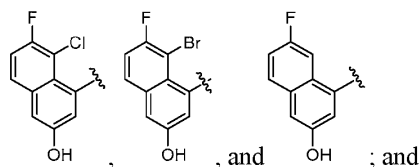
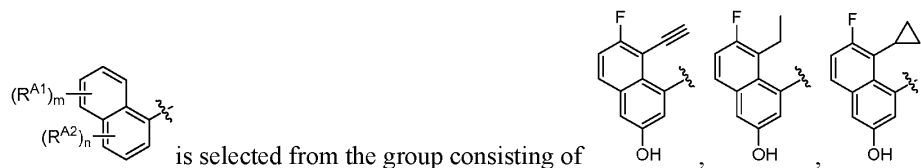
62. The compound of any one of claims 48-53, wherein $R^{1'}$ and R^1 , together with the carbon atom to which they are attached, are joined together to form C_4 -cycloalkyl optionally substituted with hydroxyl; and R^2 is $-\text{CH}_3$.

63. The compound of any one of claims 48-54, wherein R^3 is hydrogen.

64. The compound of claim 48, wherein the compound is represented by Formula IIIB:

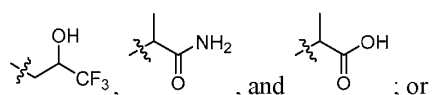


or a pharmaceutically acceptable salt and/or a stereoisomer thereof, wherein:



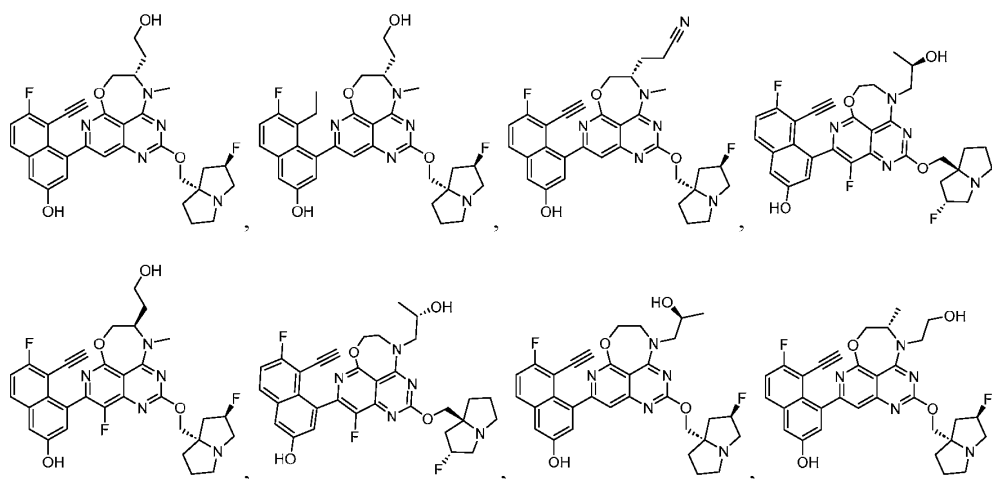
R^1 is hydrogen; and R^2 is selected from the group consisting of $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, and
 5 $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$; or

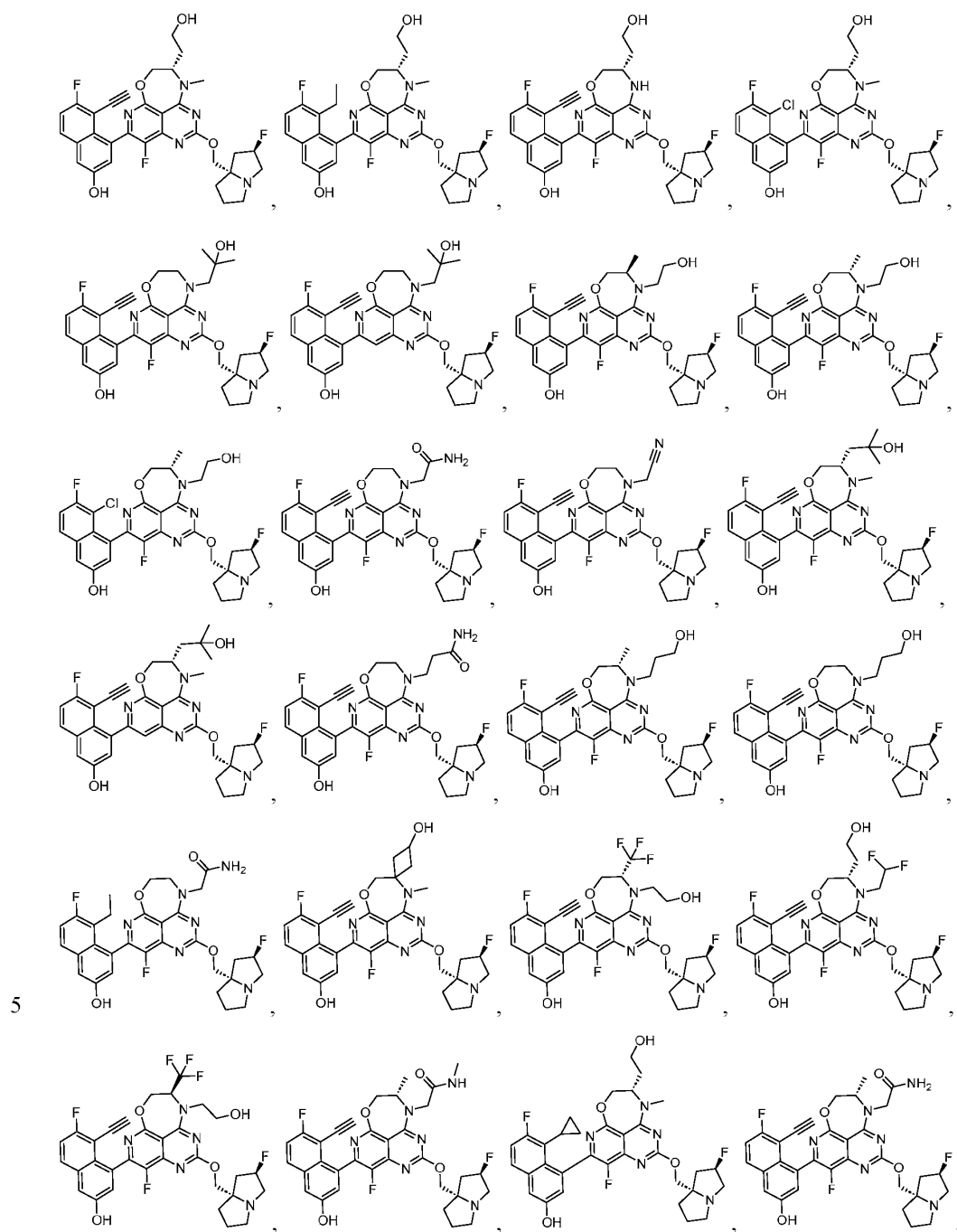
R^1 is $-\text{CH}_3$; and R^2 is selected from the group consisting of $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$,

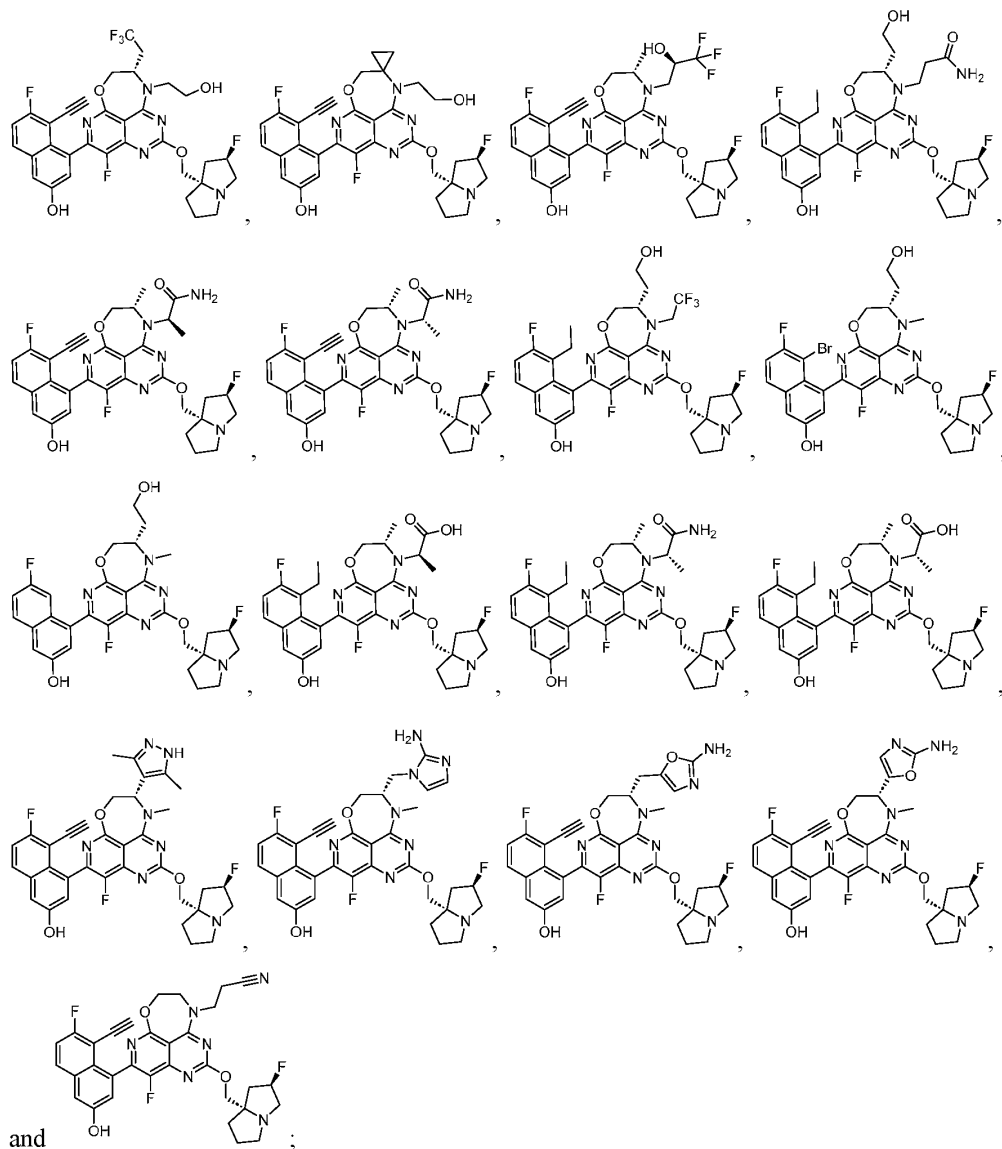


R^1 is selected from the group consisting of $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{OH}$; and R^2 is selected from the group consisting of hydrogen, $-\text{CH}_3$, $-\text{CH}_2\text{CHF}_2$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$, and $-\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NHCH}_3$.
 10

65. The compound of claim 49, wherein the compound is selected from the group consisting of

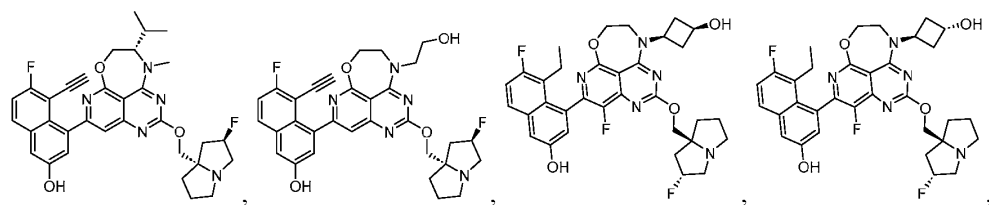


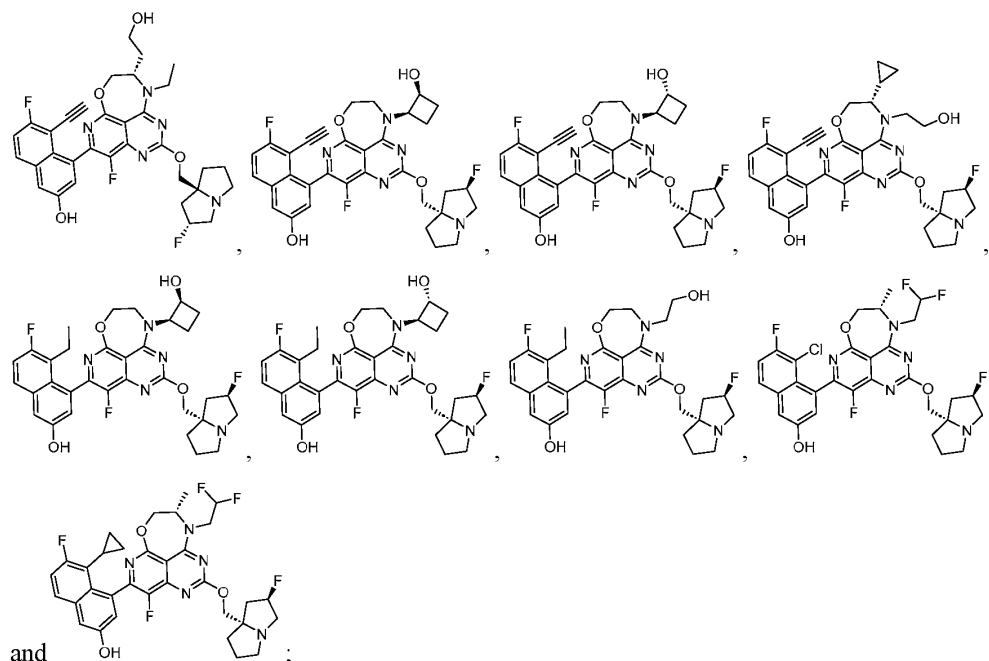




or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

66. A compound selected from the group consisting of:





or a pharmaceutically acceptable salt and/or a stereoisomer thereof.

- 5 67. A pharmaceutical composition comprising a compound of any one of claims 1-66, or a pharmaceutically acceptable salt and/or a stereoisomer thereof, and a pharmaceutically acceptable excipient.
68. A method of treating a Ras-related disease or disorder in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any
- 10 one of claims 1-66.
69. The method of claim 68, wherein the disease or disorder is characterized by aberrant Ras activity in the patient due to a Ras mutation.
70. The method of claim 68 or 69, wherein the Ras mutation is a K-Ras mutation, a H-Ras mutation, or a N-Ras mutation.
- 15 71. The method of any one of claims 68-70, wherein the disease or disorder is a cancer.
72. A method of treating a cancer in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-66.
73. The method of claim 72, wherein the cancer is a Ras-mutated cancer.
74. The method of claim 72 or 73, wherein the cancer is a K-Ras-mutated cancer.