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(54) **Titre :** INHIBITEURS PAN-KRAS D'AZAQUINAZOLINE
(54) **Title:** AZAQUINAZOLINE PAN-KRAS INHIBITORS

(57) **Abrégé/Abstract:**

The present invention relates to compounds that inhibit at least one of KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and KRas Q61H, pharmaceutical compositions comprising the compounds and methods of use therefor.



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Abstract:

The present invention relates to compounds that inhibit at least one of KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and KRas Q61H, pharmaceutical compositions comprising the compounds and methods of use therefor.

DEMANDE OU BREVET VOLUMINEUX

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AZAQUINAZOLINE PAN-KRas INHIBITORS

FIELD OF THE INVENTION

[00001] The present invention relates to compounds that inhibit multiple mutated forms of KRas, i.e., pan-KRas inhibitors. In particular, the present invention relates to pan-KRas compounds, pharmaceutical compositions comprising the compounds and methods of use therefor.

BACKGROUND OF THE INVENTION

[00002] Kirsten Rat Sarcoma 2 Viral Oncogene Homolog (“KRas”) is a small GTPase and a member of the Ras family of oncogenes. KRas serves as a molecular switch cycling between inactive (GDP-bound) and active (GTP-bound) states to transduce upstream cellular signals received from multiple tyrosine kinases to downstream effectors to regulate a wide variety of processes, including cellular proliferation (e.g., see Alamgeer et al., (2013) *Current Opin Pharmacol.* 13:394-401).

[00003] The role of activated KRas in malignancy was observed over thirty years ago (e.g., see Santos et al., (1984) *Science* 223:661-664). Aberrant expression of KRas accounts for up to 20% of all cancers and oncogenic KRas mutations that stabilize GTP binding and lead to constitutive activation of KRas. KRas mutations at codons 12, 13, 61 and other positions of the KRas primary amino acid sequence are present in 88% of all pancreatic adenocarcinoma patients, 50% of all colon/rectal adenocarcinoma patients, and 32% lung adenocarcinoma patients (e.g., see Prior et al., (2020) *Cancer Res* 80:2969–74). A recent publication also suggested wild type Kras inhibition could be a viable therapeutic strategy to treat KRas^{WT} dependent cancers (e.g., see Bery et al., (2020) *Nat. Commun.* 11: 3233).

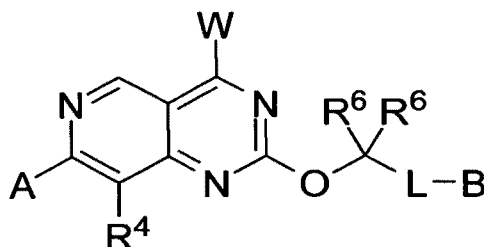
[00004] The well-known role of KRas in malignancy and the discovery of these frequent mutations in KRas in various tumor types made KRas a highly attractive target of the pharmaceutical industry for cancer therapy. Notwithstanding thirty years of large-scale discovery efforts to develop inhibitors of KRas for treating cancer, no KRas inhibitor has yet demonstrated sufficient safety and/or efficacy to obtain regulatory approval (e.g., see McCormick (2015) *Clin Cancer Res.* 21 (8):1797-1801).

[00005] Compounds that inhibit KRas activity are still highly desirable and under investigation, including those that disrupt effectors such as guanine nucleotide exchange factors (e.g., see Sun et al., (2012) *Angew Chem Int Ed Engl.* 51(25):6140-6143 doi: 10.1002/anie.201201358) as well recent advances in the covalent targeting of an allosteric pocket of KRas G12C (e.g., see Ostrem et al., (2013) *Nature* 503:548-551 and Fell et al., (2018) *ACS Med. Chem. Lett.* 9:1230-1234). Clearly there remains a continued interest and effort to develop inhibitors of KRas, particularly inhibitors of activating KRas mutants-.

[00006] Thus, there is a need to develop new pan-KRas inhibitors that demonstrate sufficient efficacy for treating KRas-mediated cancers.

SUMMARY OF THE INVENTION

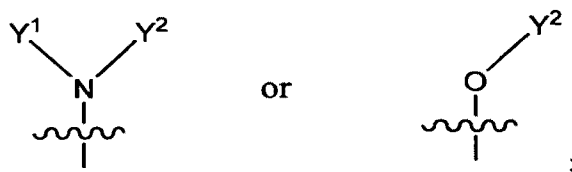
[00007] In one aspect of the invention, compounds are provided that inhibit KRas activity. In certain embodiments, the compounds are represented by Formula (I):



Formula (I)

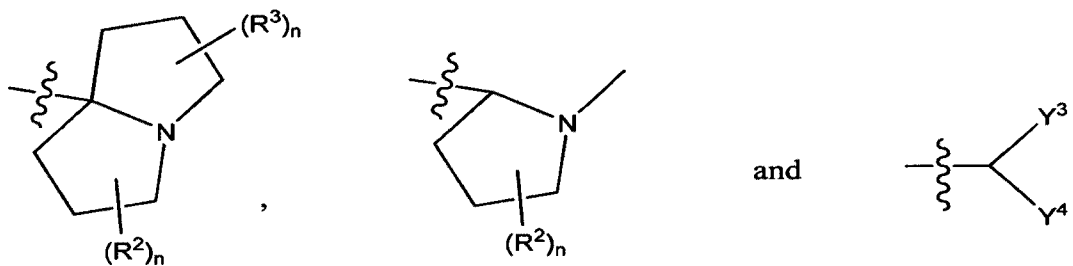
or a pharmaceutically acceptable salt thereof, wherein:

[00008] W is:



[00009] A is aryl or heteroaryl, wherein the aryl or the heteroaryl is optionally substituted with 1-4 R^1 ;

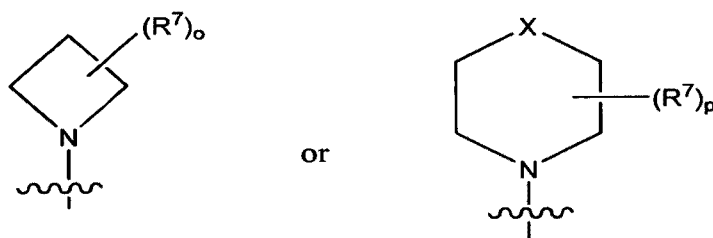
[000010] B is selected from:



[000011] Y^1 is hydrogen, L-hydroxy optionally substituted with 1-4 R^8 , L-alkoxy optionally substituted with 1-4 R^8 , halogen, L-C3-C6 cycloalkyl optionally substituted with 1-4 R^9 , L-heteroaryl optionally substituted with 1-4 R^8 , L-aryl optionally substituted with 1-4 R^8 , L-C(O)-NH₂, and L-heterocycle substituted with 1-2 oxo (=O) or oxo-containing substituent, and optionally further substituted with 1-2 R^8 ;

[000012] Y^2 is hydrogen or C1-C4 alkyl;

[000013] or Y^1 and Y^2 join to form:

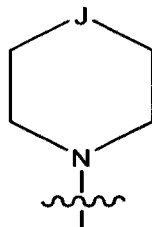


[000014] where X is selected from: a bond, -S-, -O-, -N< bound to a fused ring, -CH₂-, -CH₂-N-, -CH₂-N-CH₂-, -CH₂-CH₂-CH₂-, -CH₂-CH₂-, -O-CH₂- and -S-CH₂-;

[000015] Y^3 is hydrogen or C1-C4 alkyl;

[000016] Y^4 is hydrogen or C1-C4 alkyl;

[000017] or Y^3 and Y^4 join to form:



where J is selected from: a bond, -O-, -NH-, -CH₂-, -C(C1-C3 alkyl)₂-, -CH(C1-C3alkyl)- and -N(C1-C3 alkyl)-;

[000018] each R¹ is independently halogen, cyano, hydroxy, C1-C4 alkyl, -S-C1-C3 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C2-C4 hydroxyalkynyl, C1-C3 cyanoalkyl, triazolyl, C1-C3 haloalkyl, -O-C1-C3 haloalkyl, -S-C1-C3 haloalkyl, C1-C3 alkoxy, hydroxyC1-C3 alkyl, -CH₂C(=O)N(R⁵)₂, -C3-C4 alkynyl(NR⁵)₂, -N(R⁵)₂, deuterioC2-C4 alkynyl, (C1-C3 alkoxy)haloC1-C3 alkyl-, or C3-C6 cycloalkyl wherein said C3-C6 cycloalkyl is optionally substituted with halogen or C1-C3 alkyl;

[000019] each R² is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-OC(O)N(R⁵)₂, -CO₂R⁵, or -CO₂N(R⁵)₂;

[000020] each R³ is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-OC(O)N(R⁵)₂, -CO₂R⁵, or -CO₂N(R⁵)₂;

[000021] each R⁴ is independently hydrogen, halogen or C1 – C3 alkyl;

[000022] each R⁵ is independently hydrogen or C1-C3 alkyl, or two R⁵ join to form cycloalkyl or heterocycle;

[000023] each R⁶ is independently hydrogen, hydroxy, C1-C4 hydroxyalkyl or heteroaryl,

[000024] or two R⁶ join to form C3-C6 cycloalkyl or heterocycle;

[000025] each R⁷ is independently hydrogen, C1-C3 alkyl, hydroxy, halogen, C1-C3 haloalkyl, -L-NH₂, -NH(C1-C3 alkyl), -N(C1-C3 alkyl)₂, oxo (=O), -O-(C1-C3 alkyl), -(C1-C3 alkyl)-OH, -C(O)OH, -C(O)O(C1-C3 alkyl), -C(O)N(R¹⁰)₂, -NHC(O)H, -CN, aryl, -(CH₂)₁₋₂S(O)₂N(R¹⁰)₂, -NH-S(O)₂N(R¹⁰)₂, -O-S(O)₂N(R¹⁰)₂, S(O)₂R¹⁰, or heteroaryl or

heterocycle optionally independently substituted with 1-2 substituents independently selected from C1-C3 alkyl, -CN and C(O)NH₂,

[000026] two R⁷ on the same atom optionally join to form a spirocyclic ring selected from C3-C6 cycloalkyl and heterocycle, where said spirocyclic ring is optionally substituted with 1-4 substituents independently selected from oxo (=O), halogen, hydroxy, C1-C3 alkyl and -O-(C1-C3 alkyl),

[000027] two R⁷ on adjacent atoms optionally join to form a bond or a fused ring selected from C3-C6 cycloalkyl optionally substituted with 1-4 R⁸, heteroaryl optionally substituted with 1-4 R⁸, aryl optionally substituted with 1-4 R⁸, and heterocycle optionally substituted with 1-4 R⁸, and

[000028] two R⁷ on non-adjacent atoms optionally join to form a 1-2 carbon bridge;

[000029] each R⁸ is independently C1-C3 alkyl, hydroxy, halogen, -N(R¹⁰)₂, -N(R¹⁰)C(O)R¹⁰, oxo (=O), -O-(C1-C3 alkyl), -(C1-C3 alkyl)-OH, -C(O)OH, -C(O)O(C1-C3 alkyl), -C(O)N(R¹⁰)₂, heteroaryl or -CN;

[000030] each R⁹ is independently C1-C3 alkyl, hydroxy, halogen, oxo (=O), -O-(C1-C3 alkyl), -(C1-C3 alkyl)-OH, -C(O)OH, -C(O)O(C1-C3 alkyl), -C(O)NH₂, -C(O)NH(C1-C3 alkyl), -C(O)N(C1-C3 alkyl)₂ or -CN;

[000031] each R¹⁰ is independently hydrogen, halogen, C1-C3 alkyl, or two R¹⁰ join to form cycloalkyl or heterocycle optionally substituted with 1-2 C1-C3 alkyl;

[000032] each L is independently a bond, -C1-C4 alkyl-, -C1-C4 alkyl-NH-, -NH-, -N(C1-C3 alkyl)- or cyclopropyl-CH₂-;

[000033] each n is 0-3;

[000034] o is 1-6; and

[000035] p is 1-8.

[000036] In another aspect of the invention, pharmaceutical compositions are provided comprising a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

[000037] In yet another aspect of the invention, methods for inhibiting the activity of cells containing wild type KRas or one or more KRas mutations, for instance the KRas mutations G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H, in a cell, comprising contacting the cell with a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein. In one embodiment, the contacting is *in vitro*. In one embodiment, the contacting is *in vivo*.

[000038] Also provided herein is a method of inhibiting cell proliferation, *in vitro* or *in vivo*, the method comprising contacting a cell with an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

[000039] Also provided are methods for treating cancer in a patient comprising administering a therapeutically effective amount of a compound or pharmaceutical composition of the present invention or a pharmaceutically acceptable salt thereof to a patient in need thereof.

[000040] Also provided herein is a method of treating a KRas wild type, KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H-associated disease or disorder in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein.

[000041] Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein for use in therapy.

[000042] Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof as defined herein for use in the treatment of cancer.

[000043] Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof for use in the inhibition of KRas wild type or multiple types of KRas mutations, for instance KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H mutations.

[000044] Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof as defined herein, for use in the treatment of a KRas wild type associated disease or disorder or a KRas mutation G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H-associated disease or disorder.

[000045] Also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of cancer.

[000046] Also provided herein is a use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the inhibition of activity of the wild type form of KRas or mutated forms of KRas, including the mutations: G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H.

[000047] Also provided herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as defined herein, in the manufacture of a medicament for the treatment of a KRas wild type associated disease or disorder or a KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H-associated disease or disorder.

[000048] Also provided herein is a method for treating cancer in a patient in need thereof, the method comprising (a) determining that the cancer is associated with KRas wild type or a KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H mutation (i.e., a KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H-associated cancer); and (b) administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[000049] One potential utility of the herein-described pan-KRas inhibitors, including pan-KRas inhibitors such as (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-

methylpiperidin-3-ol (Example 5 herein), is for the treatment of cancers that develop resistance following long-term treatment with KRas G12C inhibitors. Thus, embodiments of the invention include those wherein a patient suffering from cancer is treated with a herein-described pan-KRas inhibitor such as Example 5 after treatment with a G12C inhibitor becomes ineffective or less effective due to the emergence of resistance-imparting mutations.

[000050] Treatment of KRas G12C mutant cancers with covalent KRas G12C inhibitors such as adagrasib (MRTX849) or sotorasib (AMG510) may result in the incorporation of additional mutations that confer resistance to adagrasib. These mutations could confer resistance through numerous mechanisms.

[000051] Mutations that change the mutant cysteine at codon 12 to another amino acid would render the current covalent KRas G12C inhibitors ineffective since current inhibitors make a covalent bond with the mutant cysteine amino acid side chain. Likewise, in patients that have one wild type KRas allele in addition to the KRas G12C-mutant allele, mutations in the wild type codon 12 glycine to another codon would allow bypass signaling in these tumors through the novel mutant protein. The repertoire of codon 12 mutations that can occur with a single nucleotide substitution in the wild type gene (glycine codon) includes mutations commonly observed in cancer such as G12S, G12V, G12R, G12C. The repertoire of codon 12 mutations that can occur with single nucleotide base substitutions of the cysteine codon 12 include mutations not frequently observed in cancer, G12Y, G12F and G12W, in addition to G12S and G12R.

[000052] Second-site mutations may also occur in another location in the KRas G12C mutant gene that confers resistance to KRas G12C inhibitor treatment. These mutations may confer resistance through different mechanisms. RAS proteins are small GTPases that normally cycle between an active, GTP-bound state and an inactive, GDP-bound state. RAS proteins are loaded with GTP through guanine nucleotide exchange factors (GEFs; e.g., SOS1) which are activated by upstream receptor tyrosine kinases, triggering subsequent interaction with effector proteins that activate RAS-dependent signaling. RAS proteins hydrolyze GTP to GDP through their intrinsic GTPase activity which is dramatically enhanced by GTPase-activating proteins (GAPs). Mutations at codons 12 and 13 in RAS proteins impair GAP-stimulated GTP hydrolysis leaving RAS predominantly in the GTP-bound, active state. Covalent KRas G12C inhibitors in current clinical development only bind GDP-bound KRas G12C. Mutations such as Q61 codon mutations, which

may or may not occur on the same allele as the G12C mutation, reduce the intrinsic GTPase activity of KRas and may represent a mechanism of resistance to KRas G12C inhibitor treatment by shifting KRas into the GTP-loaded state where it is not susceptible to covalent inhibition. Co-mutations such as R68, H95 and Y96 may be present along with the KRas G12C mutation and may diminish the binding affinity of KRas G12C inhibitors to the Switch II binding pocket.

[000053] The herein-described pan-KRas inhibitors may demonstrate activity against common as well as uncommon codon 12 mutations or mutations that occur in the KRas protein that diminish binding of KRas G12C inhibitors to the KRas protein.

[000054] Also provided herein is a process for preparing a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[000055] Also provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof obtained by a process of preparing the compound as defined herein.

DETAILED DESCRIPTION OF THE INVENTION

[000056] The present invention relates to inhibitors of KRas wild type and/or multiple mutated forms of KRas, for instance KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H mutations. In particular, the present invention relates to compounds that inhibit the activity of KRas wild type and/or KRas mutations such as G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H, pharmaceutical compositions comprising a therapeutically effective amount of the compounds and methods of use therefor.

DEFINITIONS

[000057] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents, patent applications, and publications referred to herein are incorporated by reference.

[000058] As used herein, “wild type KRas” refers to a non-mutant form of a mammalian KRas protein. The assignment of amino acid codon and residue positions for human KRas is based on the amino acid sequence identified by UniProtKB/Swiss-Prot P01116: Variantp.Gly12Asp. As used herein, a “wild type KRas inhibitor” refers to compounds of the present invention that are

represented by Formula (I), as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of wild type KRas G12A. A "wild type KRas-associated disease or disorder" as used herein refers to diseases or disorders associated with or mediated by or having wild type KRas. A non-limiting example of a wild type KRas-associated disease or disorder is a wild type KRas-associated cancer.

[000059] As used herein, "KRas G12A" refers to a mutant form of a mammalian KRas protein that contains an amino acid substitution of an alanine for a glycine at amino acid position 12. The assignment of amino acid codon and residue positions for human KRas is based on the amino acid sequence identified by UniProtKB/Swiss-Prot P01116: Variantp.Gly12Asp. As used herein, a "KRas G12A inhibitor" refers to compounds of the present invention that are represented by Formula (I), as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of KRas G12A. A "KRas G12A-associated disease or disorder" as used herein refers to diseases or disorders associated with or mediated by or having a KRas G12A mutation. A non-limiting example of a KRas G12A-associated disease or disorder is a KRas G12A-associated cancer.

[000060] As used herein, "KRas G12C" refers to a mutant form of a mammalian KRas protein that contains an amino acid substitution of a cysteine for a glycine at amino acid position 12. The assignment of amino acid codon and residue positions for human KRas is based on the amino acid sequence identified by UniProtKB/Swiss-Prot P01116: Variantp.Gly12Asp. As used herein, a "KRas G12C inhibitor" refers to compounds of the present invention that are represented by Formula (I), as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of KRas G12C. A "KRas G12C-associated disease or disorder" as used herein refers to diseases or disorders associated with or mediated by or having a KRas G12C mutation. A non-limiting example of a KRas G12C-associated disease or disorder is a KRas G12CD-associated cancer.

[000061] As used herein, "KRas G12D" refers to a mutant form of a mammalian KRas protein that contains an amino acid substitution of an aspartic acid for a glycine at amino acid position 12. The assignment of amino acid codon and residue positions for human KRas is based on the amino acid sequence identified by UniProtKB/Swiss-Prot P01116: Variantp.Gly12Asp. As used herein, a "KRas G12D inhibitor" refers to compounds of the present invention that are

represented by Formula (I), as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of KRas G12D. A "KRas G12D-associated disease or disorder" as used herein refers to diseases or disorders associated with or mediated by or having a KRas G12D mutation. A non-limiting example of a KRas G12D-associated disease or disorder is a KRas G12D-associated cancer.

[000062] As used herein, "KRas G12R" refers to a mutant form of a mammalian KRas protein that contains an amino acid substitution of an arginine for a glycine at amino acid position 12. The assignment of amino acid codon and residue positions for human KRas is based on the amino acid sequence identified by UniProtKB/Swiss-Prot P01116: Variantp.Gly12Asp. As used herein, a "KRas G12R inhibitor" refers to compounds of the present invention that are represented by Formula (I), as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of KRas G12R. A "KRas G12R-associated disease or disorder" as used herein refers to diseases or disorders associated with or mediated by or having a KRas G12R mutation. A non-limiting example of a KRas G12R-associated disease or disorder is a KRas G12R-associated cancer.

[000063] As used herein, "KRas G12S" refers to a mutant form of a mammalian KRas protein that contains an amino acid substitution of a serine for a glycine at amino acid position 12. The assignment of amino acid codon and residue positions for human KRas is based on the amino acid sequence identified by UniProtKB/Swiss-Prot P01116: Variantp.Gly12Asp. As used herein, a "KRas G12S inhibitor" refers to compounds of the present invention that are represented by Formula (I), as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of KRas G12S. A "KRas G12S-associated disease or disorder" as used herein refers to diseases or disorders associated with or mediated by or having a KRas G12S mutation. A non-limiting example of a KRas G12S-associated disease or disorder is a KRas G12S-associated cancer.

[000064] As used herein, "KRas G12V" refers to a mutant form of a mammalian KRas protein that contains an amino acid substitution of a valine for a glycine at amino acid position 12. The assignment of amino acid codon and residue positions for human KRas is based on the amino acid sequence identified by UniProtKB/Swiss-Prot P01116: Variantp.Gly12Asp. As used herein, a "KRas G12V inhibitor" refers to compounds of the present invention that are represented by

Formula (I), as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of KRas G12V. A "KRas G12V-associated disease or disorder" as used herein refers to diseases or disorders associated with or mediated by or having a KRas G12V mutation. A non-limiting example of a KRas G12V-associated disease or disorder is a KRas G12V-associated cancer.

[000065] As used herein, "KRas G13D" refers to a mutant form of a mammalian KRas protein that contains an amino acid substitution of an aspartic acid for a glycine at amino acid position 13. The assignment of amino acid codon and residue positions for human KRas is based on the amino acid sequence identified by UniProtKB/Swiss-Prot P01116: Variantp.Gly12Asp. As used herein, a "KRas G13D inhibitor" refers to compounds of the present invention that are represented by Formula (I), as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of KRas G13D. A "KRas G13D-associated disease or disorder" as used herein refers to diseases or disorders associated with or mediated by or having a KRas G13D mutation. A non-limiting example of a KRas G13D-associated disease or disorder is a KRas G13D-associated cancer.

[000066] As used herein, "KRas Q61H" refers to a mutant form of a mammalian KRas protein that contains an amino acid substitution of a histidine for a glutamine at amino acid position 61. The assignment of amino acid codon and residue positions for human KRas is based on the amino acid sequence identified by UniProtKB/Swiss-Prot P01116: Variantp.Gly12Asp. As used herein, a "KRas Q61H inhibitor" refers to compounds of the present invention that are represented by Formula (I), as described herein. These compounds are capable of negatively modulating or inhibiting all or a portion of the enzymatic activity of KRas Q61H. A "KRas Q61H-associated disease or disorder" as used herein refers to diseases or disorders associated with or mediated by or having a KRas Q61H mutation. A non-limiting example of a KRas Q61H-associated disease or disorder is a KRas Q61H-associated cancer.

[000067] As used herein, the term "subject," "individual," or "patient," used interchangeably, refers to any animal, including mammals such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the patient is a human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. In some embodiments, the

subject has been identified or diagnosed as having a cancer having wild type KRas or a KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H mutation (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the subject has a tumor that is positive for wild type KRas or a KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H mutation (e.g., as determined using a regulatory agency-approved assay or kit). The subject can be a subject with a tumor(s) that is positive for wild type KRas or a KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H mutation (e.g., identified as positive using a regulatory agency-approved, e.g., FDA-approved, assay or kit). The subject can be a subject whose tumors have wild type KRas or a KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H mutation (e.g., where the tumor is identified as such using a regulatory agency-approved, e.g., FDA-approved, kit or assay). In some embodiments, the subject is suspected of having wild type KRas or a KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D or KRas Q61H gene-associated cancer. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has wild type KRas or a KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H mutation (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein).

[000068] In some embodiments of any of the methods or uses described herein, an assay is used to determine whether the patient has wild type KRas or a KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H mutation using a sample (e.g., a biological sample or a biopsy sample (e.g., a paraffin-embedded biopsy sample) from a patient (e.g., a patient suspected of having wild type KRas-associated or a KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H-associated cancer, a patient having one or more symptoms of wild type KRas-associated or a KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H-associated cancer, and/or a patient that has an increased risk of developing wild type KRas-associated or a KRas G12A, G12C, G12D, G12R, G12S, G12V, G13D and/or Q61H-associated cancer) can include, for example, next generation sequencing, immunohistochemistry, fluorescence microscopy, break apart FISH analysis, Southern blotting, Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR and quantitative real-time RT-PCR). As is well-known in the art, the assays are typically performed, e.g., with at least one labelled nucleic acid probe or at least one labelled antibody or antigen-binding fragment thereof.

[000069] The term “regulatory agency” is a country’s agency for the approval of the medical use of pharmaceutical agents with the country. For example, a non-limiting example of a regulatory agency is the U.S. Food and Drug Administration (FDA).

[000070] The term "acyl" refers to $-C(O)CH_3$.

[000071] The terms "C1-C6 alkyl", "C1-C4 alkyl" and "C1-C3 alkyl" as employed herein refers to straight and branched chain aliphatic groups having from 1-6 carbon atoms, or 1-4 carbon atoms, or 1-3 carbon atoms, respectively. Examples of alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl.

[000072] The terms “C1-C3 haloalkyl” and “C1-C4 haloalkyl” refer to a C1-C3 alkyl chain or C1-C4 alkyl chain, respectively, as defined herein in which one or more hydrogen has been replaced by a halogen. Examples include trifluoromethyl, difluoromethyl and fluoromethyl.

[000073] An "C1-C4 alkylene," group is a C1-C4 alkyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Exemplary alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene.

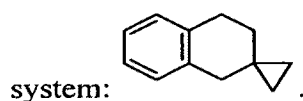
[000074] The terms “C1-C3 alkoxy” and “C1 – C4 alkoxy” refer to $-OC1 - C3$ alkyl and $-OC1-C4$ alkyl, respectively, wherein the alkyl portion is as defined herein above.

[000075] The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, for example 3 to 8 carbons, and as a further example 3 to 6 carbons, wherein the cycloalkyl group additionally is optionally substituted with one or more R^8 or R^9 groups as defined herein. Examples of cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. The term “cycloalkyl” also includes bridged cycloalkyls, such as bicyclo[1.1.1]pentanyl.

[000076] As used herein, the terms “C1-C3 hydroxyalkyl” and “C1-C4 hydroxyalkyl” refer to $-C1-C3$ alkylene-OH and $-C1-C4$ alkylene-OH, respectively.

[000077] As used herein, the term “C2-C4 hydroxyalkynyl” refers to $-C2-C4$ alkynylene-OH.

[000078] An "aryl" group is a C₆-C₁₄ aromatic moiety comprising one to three aromatic rings, which is optionally substituted with one or more R⁸ or R⁹ groups as defined herein. As one embodiment, the aryl group is a C₆-C₁₀ aryl group. Examples of aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, fluorenyl, and dihydrobenzofuranyl. "Aryl" also refers to bicyclic or tricyclic ring systems in which one or two rings, respectively, of said aryl ring system may be saturated or partially saturated, and wherein if said ring system includes two saturated rings, said saturated rings may be fused or spirocyclic. An example of an aryl ring system comprising two saturated rings wherein the rings are spirocyclic includes the following ring



[000079] An "araC1-C6 alkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. An example of an aralkyl group is (C₆-C₁₀)aryl(C₁-C₆)alkyl-, including, without limitation, benzyl, phenethyl, and naphthylmethyl. An example of a substituted araC1-C6 alkyl is wherein the alkyl group is substituted with hydroxyalkyl.

[000080] A "heterocyclyl" or "heterocyclic" group is a ring structure having from 3 to 12 atoms, for example 4 to 8 atoms, wherein one or more atoms are selected from the group consisting of N, O, and S wherein the ring N atom may be oxidized to N-O, and the ring S atom may be oxidized to SO or SO₂, the remainder of the ring atoms being carbon. The heterocyclyl may be a monocyclic, a bicyclic, a spirocyclic or a bridged ring system. The heterocyclic group is optionally substituted with one or more R⁸ or R⁹ groups on ring carbon or ring nitrogen at one or more positions, wherein R⁶ is as defined for Formula I. The heterocyclic group is also independently optionally substituted on a ring nitrogen atom with alkyl, aralkyl, alkylcarbonyl, or on sulfur with lower alkyl. Examples of heterocyclic groups include, without limitation, epoxy, azetidiny, aziridiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidiny, pyrrolidinonyl, piperidiny, piperazinyl, imidazolidiny, imidazopyridiny, thiazolidiny, dithianyl, trithianyl, dioxolanyl, oxazolidiny, oxazolidinonyl, decahydroquinolinyl, piperidonyl, 4-piperidinonyl, quinuclidiny, thiomorpholinyl, thiomorpholinyl 1,1 dioxide, morpholinyl, azepanyl, oxazepanyl, azabicyclohexanyls, azabicycloheptanyl, azabicyclooctanyls, azabicyclononanyls (e.g., octahydroindoliziny), azaspiroheptanyls, dihydro-1H,3H,5H-oxazolo[3,4-c]oxazolyl, tetrahydro-

1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizine], hexahydro-1H-pyrroliziny, hexahydro-1H-pyrrolo[2,1-c][1,4]oxaziny, octahydroindoliziny, oxaazaspirononanyls, oxaazaspirooctanyls, diazaspirononanyls, oxaazabicycloheptanyls, hexahydropyrroliziny 4(1H)-oxide, tetrahydro-2H-thiopyrany 1-oxide and tetrahydro-2H-thiopyrany 1,1-dioxide. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[000081] As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to three heteroatoms per ring, or from one to three heteroatoms in at least one ring, selected from the group consisting of N, O, and S. Examples of heteroaryl groups include acridiny, azociny, benzimidazolyl, benzofurany, benzothiofurany, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, carbazolyl, 4aH-carbazolyl, carboliny, chromany, chromenyl, cinnoliny, 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole, furany, furazany, imidazolyl, imidazolyl, 1H-indazolyl, indolenyl, indoliny, indoliziny, indolyl, 3H-indolyl, isobenzofurany, isochromany, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, methylenedioxyphenyl, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny, oxazolyl, oxazolidiny, pyrimidiny, phenanthridiny, phenanthroliny, phenaziny, phenothiaziny, phenoxathiiny, phenoxaziny, phthalaziny, piperony, pteridiny, puriny, pyrany, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyridoazole, pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidiny, pyrroliny, 2H-pyrroly, pyrroly, quinazoliny, quinoliny, 4H-quinoliziny, quinoxaliny, quinuclidiny, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, 6H-1,2,5-thiadiaziny, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triaziny, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. "Heteroaryl" also refers to bicyclic ring systems having, in addition to carbon atoms, from one to three heteroatoms per ring selected from the group consisting of N, O, and S in which one ring system may be saturated or partially saturated.

[000082] As used herein, "an effective amount" of a compound is an amount that is sufficient to negatively modulate or inhibit the activity of one or more of wild type KRas, KRas G12A, KRas

G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D or KRas Q61H. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

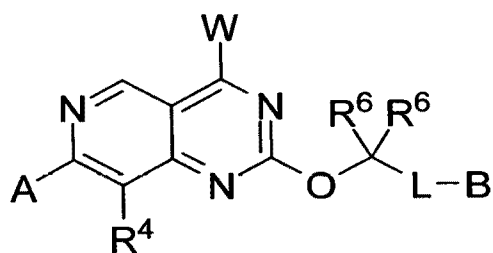
[000083] As used herein, a "therapeutically effective amount" of a compound is an amount that is sufficient to ameliorate, or in some manner reduce a symptom or stop or reverse progression of a condition, or negatively modulate or inhibit the activity of one or more of wild type KRas, KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D or KRas Q61H. Such amount may be administered as a single dosage or may be administered according to a regimen, whereby it is effective.

[000084] As used herein, treatment means any manner in which the symptoms or pathology of a condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein.

[000085] As used herein, amelioration of the symptoms of a particular disorder by administration of a particular pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

COMPOUNDS

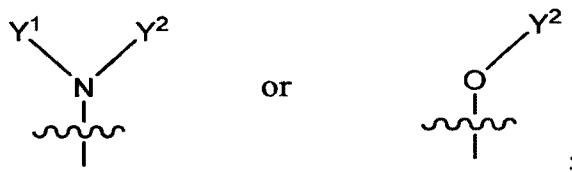
[000086] In certain embodiments of the invention there are provided compounds of Formula (I):



Formula (I)

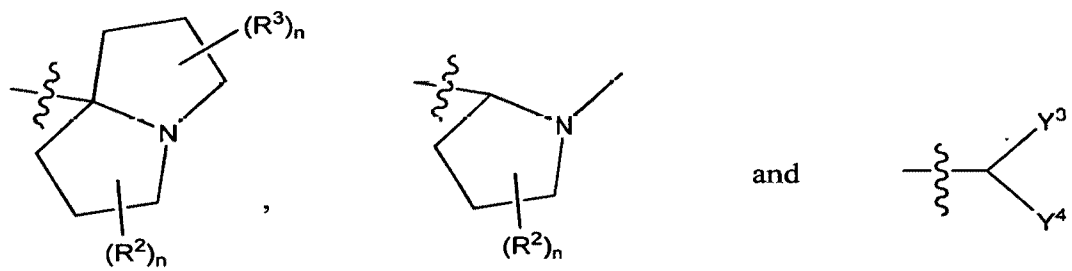
or a pharmaceutically acceptable salt thereof, wherein:

[000087] W is:



[000088] A is aryl or heteroaryl, wherein the aryl or the heteroaryl is optionally substituted with 1-4 R^1 ;

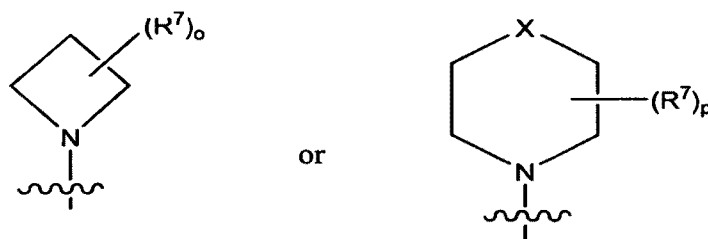
[000089] B is selected from:



[000090] Y^1 is hydrogen, L-hydroxy optionally substituted with 1-4 R^8 , L-alkoxy optionally substituted with 1-4 R^8 , halogen, L-C3-C6 cycloalkyl optionally substituted with 1-4 R^9 , L-heteroaryl optionally substituted with 1-4 R^8 , L-aryl optionally substituted with 1-4 R^8 , L-C(O)-NH₂, and L-heterocycle substituted with 1-2 oxo (=O) or oxo-containing substituent, and optionally further substituted with 1-2 R^8 ;

[000091] Y^2 is hydrogen or C1-C4 alkyl;

[000092] or Y^1 and Y^2 join to form:

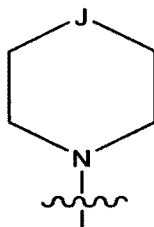


where X is selected from: a bond, -S-, -O-, -N< bound to a fused ring, -CH₂-, -CH₂-N-, -CH₂-N-CH₂-, -CH₂-CH₂-CH₂-, -CH₂-CH₂-, -O-CH₂- and -S-CH₂-;

[000093] Y³ is hydrogen or C1-C4 alkyl;

[000094] Y⁴ is hydrogen or C1-C4 alkyl;

[000095] or Y³ and Y⁴ join to form:



where J is selected from: a bond, -O-, -NH-, -CH₂-, -C(C1-C3 alkyl)₂-, -CH(C1-C3alkyl)- and -N(C1-C3 alkyl)-;

[000096] each R¹ is independently halogen, cyano, hydroxy, C1-C4 alkyl, -S-C1-C3 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C2-C4 hydroxyalkynyl, C1-C3 cyanoalkyl, triazolyl, C1-C3 haloalkyl, -O-C1-C3 haloalkyl, -S-C1-C3 haloalkyl, C1-C3 alkoxy, hydroxyC1-C3 alkyl, -CH₂C(=O)N(R⁵)₂, -C3-C4 alkynyl(NR⁵)₂, -N(R⁵)₂, deuterioC2-C4 alkynyl, (C1-C3 alkoxy)haloC1-C3 alkyl-, or C3-C6 cycloalkyl wherein said C3-C6 cycloalkyl is optionally substituted with halogen or C1-C3 alkyl;

[000097] each R² is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-OC(O)N(R⁵)₂, -CO₂R⁵, or -CO₂N(R⁵)₂;

[000098] each R³ is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-OC(O)N(R⁵)₂, -CO₂R⁵, or -CO₂N(R⁵)₂;

[000099] each R⁴ is independently hydrogen, halogen or C1 – C3 alkyl;

[0000100] each R⁵ is independently hydrogen or C1-C3 alkyl, or two R⁵ join to form cycloalkyl or heterocycle;

[0000101] each R⁶ is independently hydrogen, hydroxy, C1-C4 hydroxyalkyl or heteroaryl,

[0000102] or two R⁶ join to form C3-C6 cycloalkyl or heterocycle;

[0000103] each R⁷ is independently hydrogen, C1-C3 alkyl, hydroxy, halogen, C1-C3 haloalkyl, -L-NH₂, -NH(C1-C3 alkyl), -N(C1-C3 alkyl)₂, oxo (=O), -O-(C1-C3 alkyl), -(C1-C3 alkyl)-OH, -C(O)OH, -C(O)O(C1-C3 alkyl), -C(O)N(R¹⁰)₂, -NHC(O)H, -CN, aryl, -(CH₂)₁₋₂S(O)₂N(R¹⁰)₂, -NH-S(O)₂N(R¹⁰)₂, -O-S(O)₂N(R¹⁰)₂, S(O)₂R¹⁰, or heteroaryl or heterocycle optionally independently substituted with 1-2 substituents independently selected from C1-C3 alkyl, -CN and C(O)NH₂,

[0000104] two R⁷ on the same atom optionally join to form a spirocyclic ring selected from C3-C6 cycloalkyl and heterocycle, where said spirocyclic ring is optionally substituted with 1-4 substituents independently selected from oxo (=O), halogen, hydroxy, C1-C3 alkyl and -O-(C1-C3 alkyl),

[0000105] two R⁷ on adjacent atoms optionally join to form a bond or a fused ring selected from C3-C6 cycloalkyl optionally substituted with 1-4 R⁸, heteroaryl optionally substituted with 1-4 R⁸, aryl optionally substituted with 1-4 R⁸, and heterocycle optionally substituted with 1-4 R⁸, and

[0000106] two R⁷ on non-adjacent atoms optionally join to form a 1-2 carbon bridge;

[0000107] each R⁸ is independently C1-C3 alkyl, hydroxy, halogen, -N(R¹⁰)₂, -N(R¹⁰)C(O)R¹⁰, oxo (=O), -O-(C1-C3 alkyl), -(C1-C3 alkyl)-OH, -C(O)OH, -C(O)O(C1-C3 alkyl), -C(O)N(R¹⁰)₂, heteroaryl or -CN;

[0000108] each R⁹ is independently C1-C3 alkyl, hydroxy, halogen, oxo (=O), -O-(C1-C3 alkyl), -(C1-C3 alkyl)-OH, -C(O)OH, -C(O)O(C1-C3 alkyl), -C(O)NH₂, -C(O)NH(C1-C3 alkyl), -C(O)N(C1-C3 alkyl)₂ or -CN;

[0000109] each R¹⁰ is independently hydrogen, halogen, C1-C3 alkyl, or two R¹⁰ join to form cycloalkyl or heterocycle optionally substituted with 1-2 C1-C3 alkyl;

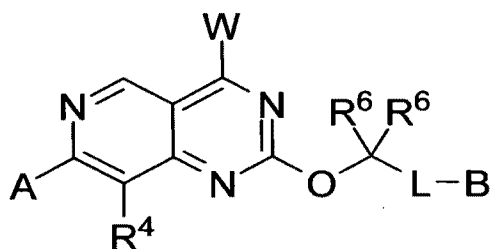
[0000110] each L is independently a bond, -C1-C4 alkyl-, -C1-C4 alkyl-NH-, -NH-, -N(C1-C3 alkyl)- or cyclopropyl-CH₂-;

[0000111] each n is 0-3;

[0000112] o is 1-6; and

[0000113] p is 1-8.

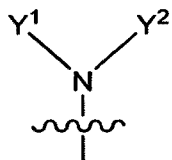
[0000114] Embodiments of the invention also include compounds of Formula (I):



Formula (I)

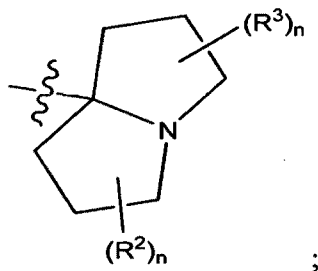
or a pharmaceutically acceptable salt thereof, wherein:

[0000115] W is:

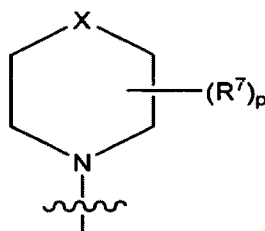


[0000116] A is naphthyl optionally substituted with 1-4 R¹;

[0000117] B is:



[0000118] Y¹ and Y² join to form:



where X is selected from: -CH₂-, -CH₂-CH₂- and -O-CH₂-;

[0000119] each R¹ is independently halogen, cyano, hydroxy, C1-C4 alkyl, -S-C1-C3 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C2-C4 hydroxyalkynyl, C1-C3 cyanoalkyl, triazolyl, C1-C3 haloalkyl, -O-C1-C3 haloalkyl, -S-C1-C3 haloalkyl, C1-C3 alkoxy, hydroxyC1-C3 alkyl, -CH₂C(=O)N(R⁵)₂, -C3-C4 alkynyl(NR⁵)₂, -N(R⁵)₂, deuterioC2-C4 alkynyl, (C1-C3 alkoxy)haloC1-C3 alkyl-, or C3-C6 cycloalkyl wherein said C3-C6 cycloalkyl is optionally substituted with halogen or C1-C3 alkyl;

[0000120] each R² is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-OC(O)N(R⁵)₂, -CO₂R⁵, or -CO₂N(R⁵)₂;

[0000121] each R³ is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-OC(O)N(R⁵)₂, -CO₂R⁵, or -CO₂N(R⁵)₂;

[0000122] each R⁴ is independently hydrogen, halogen or C1 - C3 alkyl;

[0000123] each R⁵ is independently hydrogen or C1-C3 alkyl, or two R⁵ join to form cycloalkyl or heterocycle;

[0000124] each R⁶ is independently hydrogen, hydroxy, C1-C4 hydroxyalkyl or heteroaryl,

[0000125] or two R⁶ join to form C3-C6 cycloalkyl or heterocycle;

[0000126] each R⁷ is independently hydrogen, C1-C3 alkyl, hydroxy, halogen, C1-C3 haloalkyl,

-L-NH₂,
 -NH(C1-C3 alkyl), -N(C1-C3 alkyl)₂, oxo (=O), -O-(C1-C3 alkyl), -(C1-C3 alkyl)-OH,
 -C(O)OH, -C(O)O(C1-C3 alkyl), -C(O)N(R¹⁰)₂, -NHC(O)H,
 -CN, aryl, -(CH₂)₁₋₂S(O)₂N(R¹⁰)₂, -NH-S(O)₂N(R¹⁰)₂, -O-S(O)₂N(R¹⁰)₂, S(O)₂R¹⁰, or heteroaryl or

heterocycle optionally independently substituted with 1-2 substituents independently selected from C1-C3 alkyl, -CN and C(O)NH₂,

[0000127] two R⁷ on the same atom optionally join to form a spirocyclic ring selected from C3-C6 cycloalkyl and heterocycle, where said spirocyclic ring is optionally substituted with 1-4 substituents independently selected from oxo (=O), halogen, hydroxy, C1-C3 alkyl and -O-(C1-C3 alkyl),

[0000128] two R⁷ on adjacent atoms optionally join to form a bond or a fused ring selected from C3-C6 cycloalkyl optionally substituted with 1-4 R⁸, heteroaryl optionally substituted with 1-4 R⁸, aryl optionally substituted with 1-4 R⁸, and heterocycle optionally substituted with 1-4 R⁸, and

[0000129] two R⁷ on non-adjacent atoms optionally join to form a 1-2 carbon bridge;

[0000130] each R⁸ is independently C1-C3 alkyl, hydroxy, halogen, -N(R¹⁰)₂, -N(R¹⁰)C(O)R¹⁰, oxo (=O), -O-(C1-C3 alkyl), -(C1-C3 alkyl)-OH, -C(O)OH, -C(O)O(C1-C3 alkyl), -C(O)N(R¹⁰)₂, heteroaryl or -CN;

[0000131] each R⁹ is independently C1-C3 alkyl, hydroxy, halogen, oxo (=O), -O-(C1-C3 alkyl), -(C1-C3 alkyl)-OH, -C(O)OH, -C(O)O(C1-C3 alkyl), -C(O)NH₂, -C(O)NH(C1-C3 alkyl), -C(O)N(C1-C3 alkyl)₂ or -CN;

[0000132] each R¹⁰ is independently hydrogen, halogen, C1-C3 alkyl, or two R¹⁰ join to form cycloalkyl or heterocycle optionally substituted with 1-2 C1-C3 alkyl;

[0000133] each L is independently a bond, -C1-C4 alkyl-, -C1-C4 alkyl-NH-, -NH-, -N(C1-C3 alkyl)- or cyclopropyl-CH₂-;

[0000134] each n is 0-3;

[0000135] o is 1-6; and

[0000136] p is 1-8.

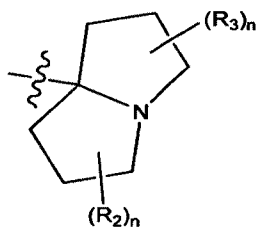
[0000137] Embodiments also include such compounds or salts wherein each R^1 is independently selected from halogen, hydroxy, C1-C3 alkoxy and C1-C4 alkyl.

[0000138] Embodiments also include such compounds or salts wherein each R^2 , if present, is selected from hydrogen and halogen, and wherein each R^3 , if present, is selected from hydrogen and halogen.

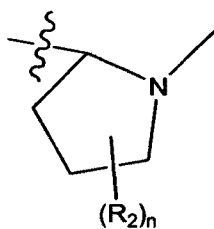
[0000139] Embodiments also include such compounds or salts wherein each R^7 is independently selected from hydrogen, C1-C4 alkyl, hydroxy, C1-C3 alkoxy, and wherein two R^7 on non-adjacent atoms optionally join to form a 1-2 carbon bridge.

[0000140] Embodiments also include such compounds or salts wherein each R^6 is independently hydrogen or hydroxy.

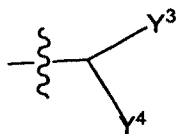
[0000141] Embodiments also include such compounds or salts wherein B is:



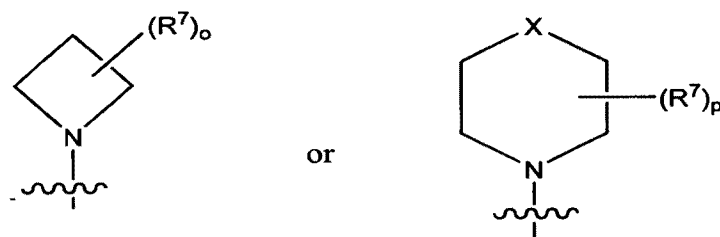
[0000142] Embodiments also include such compounds or salts wherein B is:



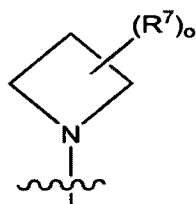
[0000143] Embodiments also include such compounds or salts wherein B is:



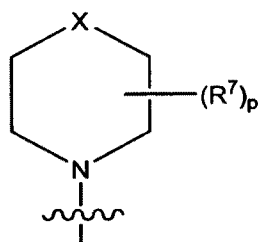
[0000144] Embodiments also include such compounds or salts wherein Y¹ and Y² join to form:



[0000145] Embodiments also include such compounds or salts wherein Y¹ and Y² join to form:



[0000146] Embodiments also include such compounds or salts wherein Y¹ and Y² join to form:



[0000147] Embodiments also include such compounds or salts wherein A is naphthyl.

[0000148] Embodiments also include such compounds or salts wherein A is indazolyl.

[0000149] Embodiments also include such compounds or salts wherein A is phenyl.

[0000150] Embodiments also include such compounds or salts wherein A is pyridyl.

[0000151] In certain embodiments of the invention at least one R¹ is C1-C4 alkyl.

- [0000152] In certain embodiments of the invention at least one R^1 is halogen, preferably fluorine or chlorine.
- [0000153] In certain embodiments of the invention at least one R^1 is hydroxy
- [0000154] In certain embodiments of the invention at least one R^2 is C1-C4 alkyl.
- [0000155] In certain embodiments of the invention at least one R^2 is halogen, preferably fluorine or chlorine.
- [0000156] In certain embodiments of the invention at least one R^2 is hydroxy.
- [0000157] In certain embodiments of the invention at least one R^3 is C1-C4 alkyl.
- [0000158] In certain embodiments of the invention at least one R^3 is halogen, preferably fluorine or chlorine.
- [0000159] In certain embodiments of the invention at least one R^3 is hydroxy.
- [0000160] In certain embodiments of the invention R^4 is halogen, preferably fluorine.
- [0000161] In certain embodiments of the invention at least one R^5 is C1-C4 alkyl.
- [0000162] In certain embodiments of the invention at least one R^5 is hydrogen.
- [0000163] In certain embodiments of the invention at least one R^6 is C1-C4 alkyl.
- [0000164] In certain embodiments of the invention, two R^6 join to form C3-C6 cycloalkyl or heterocycle.
- [0000165] In certain embodiments of the invention at least one R^6 is hydrogen.
- [0000166] In certain embodiments of the invention both R^6 are C1-C4 alkyl.
- [0000167] In certain embodiments of the invention both R^6 are hydrogen.
- [0000168] In certain embodiments Y^1 is L-C3-C6 cycloalkyl, L-heteroaryl, L-aryl, or L-heterocycle. In certain of these embodiments, L is a bond. In certain of these embodiments L is C1-C4 alkyl. In certain of these embodiments L is NH or N(C1-C3) alkyl.

[0000169] In certain embodiments Y^1 is L-heteroaryl where the heteroaryl is thietane dioxide, iso-thiazolidine dioxide, imidazopyrazine, pyridine or pyrimidine.

[0000170] In certain embodiments Y^1 is L-C3-C6 cycloalkyl where the cycloalkyl is preferably cyclobutane, cyclopentane, cyclohexane or cycloheptane.

[0000171] In certain embodiments Y^1 is L-heterocycle where the heterocycle is preferably pyrrolidinone.

[0000172] In certain embodiments of the invention Y^2 is hydrogen.

[0000173] In certain embodiments of the invention Y^2 is C1-C4 alkyl;

[0000174] In certain embodiments of the invention at least one R^8 is C1-C4 alkyl, preferably methyl.

[0000175] In certain embodiments of the invention at least one R^8 is hydroxy or C1-C3 alkyl-hydroxy.

[0000176] In certain embodiments of the invention one or two R^8 is oxo (=O).

[0000177] In certain embodiments of the invention at least one R^8 is aryl or heteroaryl.

[0000178] In certain embodiments of the invention at least one R^8 is C(O)OH.

[0000179] In certain embodiments of the invention at least one R^8 is -C(O)NH₂, -C(O)NH(C1-C3 alkyl) or -C(O)N(C1-C3 alkyl)₂.

[0000180] In certain embodiments of the invention R^8 is -NH₂, -NH(C1-C3 alkyl); -N(C1-C3 alkyl)₂.

[0000181] In certain embodiments of the invention at least one R^9 is C1-C4 alkyl, preferably methyl.

[0000182] In certain embodiments of the invention at least one R^9 is hydroxy or C1-C3 alkyl-hydroxy.

[0000183] In certain embodiments of the invention one or two R^9 is oxo (=O).

[0000184] In certain embodiments of the invention at least one R⁹ is aryl or heteroaryl.

[0000185] In certain embodiments of the invention at least one R⁹ is C(O)OH.

[0000186] In certain embodiments of the invention at least one R⁹ is -C(O)NH₂, -C(O)NH(C1-C3 alkyl) or -C(O)N(C1-C3 alkyl)₂.

[0000187] In certain embodiments of the invention Y¹ and Y² join to form a piperidine, azepane, azocane, thiazepine, diazepane, oxazepane, azetidine, pyrrolidine, piperazine bound to a fused ring via nitrogen or thiomorpholine.

[0000188] In certain embodiments of the invention, two R⁷ on the same atom join to form a spirocyclic ring selected from C3-C6 cycloalkyl and heterocycle, where said spirocyclic ring is optionally substituted with oxo (=O), halogen, hydroxy, C1-C3 alkyl and -O-(C1-C3 alkyl).

[0000189] In certain embodiments of the invention, two R⁷ on adjacent atoms optionally join to form a bond or a fused ring selected from C3-C6 cycloalkyl optionally substituted with 1-4 R⁸; heteroaryl optionally substituted with 1-4 R⁸; aryl optionally substituted with 1-4 R⁸, and heterocycle optionally substituted with 1-4 R⁸.

[0000190] In certain embodiments of the invention, two R⁷ on non-adjacent atoms optionally join to form a 1-2 carbon bridge.

[0000191] Non-limiting examples of compounds of Formula (I) are selected from the group consisting of the compounds described in the below Examples, and pharmaceutically acceptable salts thereof.

[0000192] In one embodiment, the compounds of Formula (I) include bis-hydrochloride, tris-hydrochloride, trifluoroacetic acid, bis-trifluoroacetic acid, and tris-trifluoroacetic acid salts of the above compounds. The compounds of Formula (I) or pharmaceutically acceptable salt thereof may be formulated into pharmaceutical compositions.

PHARMACEUTICAL COMPOSITIONS

[0000193] In another aspect, the invention provides pharmaceutical compositions comprising a wild type KRas, KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V,

KRas G13D and/or KRas Q61H inhibitor according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, intraperitoneal, intradermal, intracardiac, intraventricular, intracranial, intracerebrospinal, intrasynovial, intrathecal administration, intramuscular injection, intravitreal injection, intravenous injection, intra-arterial injection, oral, buccal, sublingual, transdermal, topical, intranasal, intratracheal, intrarectal, subcutaneous, and topical administration. In certain embodiments, compounds of the invention are administered intravenously in a hospital setting. In one embodiment, administration may be by the oral route. In some embodiments, the provided pharmaceutical compositions may be administered to a subject in need of treatment by injection systemically, such as by intravenous injection; or by injection or application to the relevant site, such as by direct injection via syringe, or direct application to the site when the site is exposed in surgery; or by topical administration.

[0000194] Parenteral administration can be by bolus injection or continuous infusion. Pharmaceutical compositions for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative.

[0000195] The provided pharmaceutical compositions can also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the formulations may be modified with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0000196] The pharmaceutical compositions may, if desired, be presented in a vial, pack or a medical device, including but not limited to a dispenser device which may contain one or more unit dosage forms containing the active ingredient. In one embodiment the dispenser device can comprise a syringe having a single dose of the liquid formulation ready for injection. The syringe can be accompanied by instructions for administration.

[0000197] The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with

a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, Pa., 1990.

[0000198] As used herein, the term pharmaceutically acceptable salt refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula $-NR^+Z^-$, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, $-O$ -alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamate, mandelate, benzyloate, and diphenylacetate).

[0000199] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. In one embodiment, a dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, for example 0.1 to 100 mg/kg per day, and as a further example 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01-3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

[0000200] The pharmaceutical compositions comprising compounds of the present invention may be used in the methods of use described herein.

METHODS OF USE

[0000201] In yet another aspect, the invention provides for methods for inhibiting wild type KRas, KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V and/or KRas Q61H activity in a cell, comprising contacting the cell in which inhibition of wild type KRas, KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V and/or Q61H activity is desired with an effective amount of a compound of Formula (I), pharmaceutically acceptable salts thereof, or pharmaceutical compositions containing the compound or pharmaceutically acceptable salt thereof. In one embodiment, the contacting is in vitro. In one embodiment, the contacting is in vivo.

[0000202] As used herein, the term "contacting" refers to the bringing together of indicated moieties in an in vitro system or an in vivo system. For example, "contacting" wild type KRas, KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and/or KRas Q61H with a compound provided herein includes the administration of a compound provided herein to an individual or patient, such as a human, having wild type KRas or a KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and/or KRas Q61H mutation, as well as, for example, introducing a compound provided herein into a sample containing a cellular or purified preparation containing wild type KRas or a KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D or KRas Q61H mutation..

[0000203] In one embodiment, a cell in which inhibition of wild type KRas or KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and/or KRas Q61H activity is desired is contacted with an effective amount of a compound of Formula (I) or pharmaceutically acceptable salt thereof to negatively modulate the activity of one or more of wild type KRas or KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and KRas Q61H.

[0000204] By negatively modulating the activity of one or more of wild type KRas or KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and KRas

Q61H, the methods described herein are designed to inhibit undesired cellular proliferation resulting from enhanced wild type KRas or KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and/or KRas Q61H activity within the cell. The cells may be contacted in a single dose or multiple doses in accordance with a particular treatment regimen to affect the desired negative modulation of wild type KRas or KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and/or KRas Q61H. The ability of compounds to bind one or more of wild type KRas or KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and KRas Q61H may be monitored in vitro using well known methods, including those described in Examples A and B below. In addition, the inhibitory activity of exemplary compounds in cells may be monitored, for example, by measuring the inhibition of one or more of wild type KRas or KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and/or KRas Q61H activity of the amount of phosphorylated ERK, for example using the method described in Example C below.

[0000205] In another aspect, methods of treating cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt thereof are provided.

[0000206] The compositions and methods provided herein may be used for the treatment of a wild type KRas-associated or KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and/or KRas Q61H-associated cancer in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of Formula (I), a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the compound or pharmaceutically acceptable salt thereof are provided. In one embodiment, the wild type KRas-associated or KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and/or KRas Q61H-associated cancer is lung cancer.

[0000207] The compositions and methods provided herein may be used for the treatment of a wide variety of cancers including tumors such as lung, prostate, breast, brain, skin, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that may be treated by the compositions and methods of the invention include 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. More specifically, these compounds can be used to treat: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous

cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. In certain embodiments, the cancer is non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer or pancreatic cancer. In certain embodiments, the cancer is non-small cell lung cancer.

[0000208] The concentration and route of administration to the patient will vary depending on the cancer to be treated. The compounds, pharmaceutically acceptable salts thereof and pharmaceutical compositions comprising such compounds and salts also may be co-administered with other anti-neoplastic compounds, e.g., chemotherapy, or used in combination with other treatments, such as radiation or surgical intervention, either as an adjuvant prior to surgery or post-operatively.

[0000209] Also provided herein is a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein for use in therapy.

[0000210] Also provided herein is a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein for use in the treatment of cancer.

[0000211] Also provided herein is a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for use in the inhibition of wild type KRas or KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and/or KRas Q61H.

[0000212] Also provided herein is a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof as defined herein, for use in the treatment of wild type KRas-associated or a KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and/or KRas Q61H-associated disease or disorder.

[0000213] Also provided herein is the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the treatment of cancer.

[0000214] Also provided herein is a use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, as defined herein in the manufacture of a medicament for the inhibition of activity of wild type KRas or KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and/or KRas Q61H.

[0000215] Also provided herein is the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, as defined herein, in the manufacture of a medicament for the treatment of wild type KRas-associated or a KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and/or KRas Q61H-associated disease or disorder.

[0000216] Also provided herein is a method for treating cancer in a patient in need thereof, the method comprising (a) determining that cancer is associated with wild type KRas or a KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D and/or KRas Q61H mutation (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit); and (b) administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[0000217] One skilled in the art will recognize that, both in vivo and in vitro trials using suitable, known and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder.

[0000218] One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy patients and/or those suffering from a given disorder, may be completed according to methods well known in the clinical and medical arts.

REACTION SCHEMES AND EXAMPLES

[0000219] The compounds of the present invention may be prepared from commercially available reagents using the synthetic methods and reaction schemes described herein, or using other reagents and conventional methods well known to those skilled in the art. For instance,

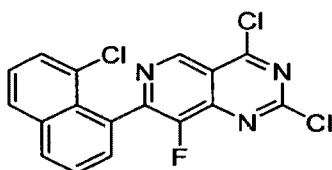
compounds of the present invention may be prepared according to the reaction schemes and examples outlines below.

[0000220] The compounds of the present invention may have one or more chiral center and may be synthesized as stereoisomeric mixtures, isomers of identical constitution that differ in the arrangement of their atoms in space. The compounds may be used as mixtures or the individual components/isomers may be separated using commercially available reagents and conventional methods for isolation of stereoisomers and enantiomers well-known to those skilled in the art, e.g., using CHIRALPAK® (Sigma-Aldrich) or CHIRALCEL® (Diacel Corp) chiral chromatographic HPLC columns according to the manufacturer's instructions. Alternatively, compounds of the present invention may be synthesized using optically pure, chiral reagents and intermediates to prepare individual isomers or enantiomers. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention. Unless otherwise indicated, whenever the specification, including the claims, refers to compounds of the invention, the term "compound" is to be understood to encompass all chiral (enantiomeric and diastereomeric) and racemic forms.

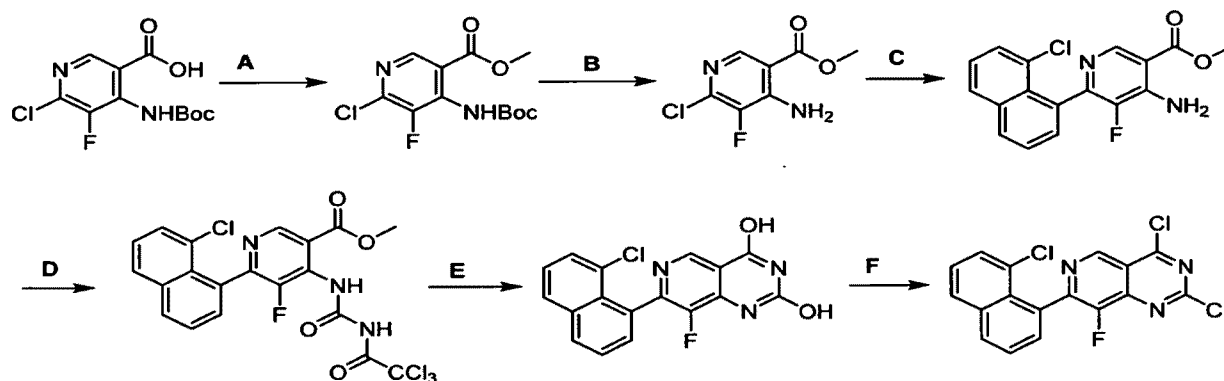
[0000221] The compounds of the present invention may be in anhydrous, solvated or hydrated forms, and all such forms are included within the scope of the invention.

[0000222] The following Intermediates are intended to illustrate further certain embodiments of the invention and are not intended to limit the scope of the invention.

Intermediate 1



2,4-dichloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidine



[0000223] Step A. methyl 4-(tert-butoxycarbonylamino)-6-chloro-5-fluoropyridine-3-carboxylate. To a solution of 4-((tert-butoxycarbonyl)amino)-6-chloro-5-fluoronicotinic acid (14.3 g, 49.2 mmol, 1 *equiv.*) in MeOH (70 mL) and toluene (210 mL) was added TMSCHN₂ (2 M in hexane, 44.3 mL, 1.8 *equiv.*) slowly. After stirring at 15 °C for 2 hours, the mixture was quenched with 2N HCl (100 mL) and layers were separated. The organic phase was washed with saturated aqueous NaHCO₃ (150 mL), followed by brine (150 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 10:1 to 1:1) to give methyl 4-(tert-butoxycarbonylamino)-6-chloro-5-fluoropyridine-3-carboxylate (15 g, 91%). Colorless oil; R_f = 0.50 (3:1 petroleum ether/ethyl acetate); ¹H NMR (400 MHz, CDCl₃): δ 8.85 (br s, 1H), 8.68 (s, 1H), 3.98 (s, 3H), 1.57-1.49 (m, 9H); LCMS [ESI, M+1]: 305.

[0000224] Step B. methyl 4-amino-6-chloro-5-fluoropyridine-3-carboxylate. To a solution of methyl 4-(tert-butoxycarbonylamino)-6-chloro-5-fluoropyridine-3-carboxylate (15 g, 49.2 mmol, 1.0 *equiv.*) in MeCN (150 mL) was added HCl·dioxane (4 M, 290 mL, 23.6 *equiv.*) at 0 °C. The mixture was stirred at 15 °C for 0.5 hour, and the solvent was removed under reduced pressure. The residue was diluted with saturated Na₂CO₃ solution (100 mL) and extracted with ethyl acetate (3 × 200 mL). The organic layers were dried over Na₂SO₄ and concentrated in vacuum to give methyl 4-amino-6-chloro-5-fluoropyridine-3-carboxylate (9.07 g, 89%) which was used directly in the next step without further purification. Orange solid; LCMS [ESI, M+1]: 205.

[0000225] Step C. methyl 4-amino-6-(8-chloro-1-naphthyl)-5-fluoropyridine-3-carboxylate. A mixture of methyl 4-amino-6-chloro-5-fluoropyridine-3-carboxylate (6 g, 29.3 mmol, 1.0 *equiv.*), (8-chloronaphthalen-1-yl)trimethylstannane (21.0 g, 64.5 mmol, 2.2 *equiv.*), CuI (1.68 g,

8.80 mmol, 0.3 *equiv.*), Pd(dppf)Cl₂ (2.15 g, 2.93 mmol, 0.1 *equiv.*), and BINAP (3.65 g, 5.87 mmol, 0.2 *equiv.*) in toluene (120 mL) was degassed and then heated to 100 °C for 11 hours under N₂. The mixture was filtered and the filtrate was concentrated in vacuum. The residue was diluted with water (50 mL) and extracted with ethyl acetate (2 × 60 mL). The organic layers were dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by chromatography (Al₂O₃, petroleum ether/ethyl acetate 30/1 to 1/1). The product was triturated with a mixed solution (DMAc/methanol 1/2, 30 mL) at 15 °C for 10 minutes to give methyl 4-amino-6-(8-chloro-1-naphthyl)-5-fluoro-pyridine-3-carboxylate (5.33 g, 54%). Yellow solid; R_f = 0.20 (3:1 petroleum ether/ethyl acetate); LCMS [ESI, M+1]: 331.

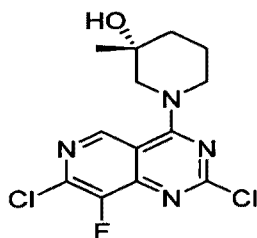
[0000226] Step D. methyl 6-(8-chloro-1-naphthyl)-5-fluoro-4-[(2,2,2-trichloroacetyl)carbamoylamino] pyridine-3-carboxylate. To a solution of methyl 4-amino-6-(8-chloro-1-naphthyl)-5-fluoro-pyridine-3-carboxylate (5.5 g, 16.6 mmol, 1.0 *equiv.*) in THF (82 mL) was added 2,2,2-trichloroacetyl isocyanate (3.45 g, 18.3 mmol, 2.17 mL, 1.1 *equiv.*) dropwise. The mixture was stirred at 15 °C for 10 minutes, and the mixture was concentrated in vacuum. The residue was triturated with MTBE (20 mL) at 15 °C for 15 minutes to give methyl 6-(8-chloro-1-naphthyl)-5-fluoro-4-[(2,2,2-trichloroacetyl)carbamoylamino] pyridine-3-carboxylate (8 g, crude). Yellow solid; LCMS [ESI, M+1]: 520.

[0000227] Step E. 7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol. A suspension of methyl 6-(8-chloro-1-naphthyl)-5-fluoro-4-[(2,2,2-trichloroacetyl)carbamoylamino] pyridine-3-carboxylate (8 g, 15.4 mmol, 1.0 *equiv.*) in NH₃•MeOH (20 mL, 20% purity) was stirred at 15 °C for 0.5 hour, the mixture was concentrated in vacuum. The residue was triturated with MTBE (30 mL) at 15 °C for 15 minutes to give 7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol (5.3 g, two steps 93%). Yellow solid; ¹H NMR (400 MHz, DMSO): δ 9.59-8.27 (m, 1H), 8.24-8.13 (m, 1H), 8.11-8.03 (m, 1H), 7.74-7.61 (m, 2H), 7.60-7.52 (m, 2H), 3.59-3.31 (m, 2H); LCMS [ESI, M+1]: 342.

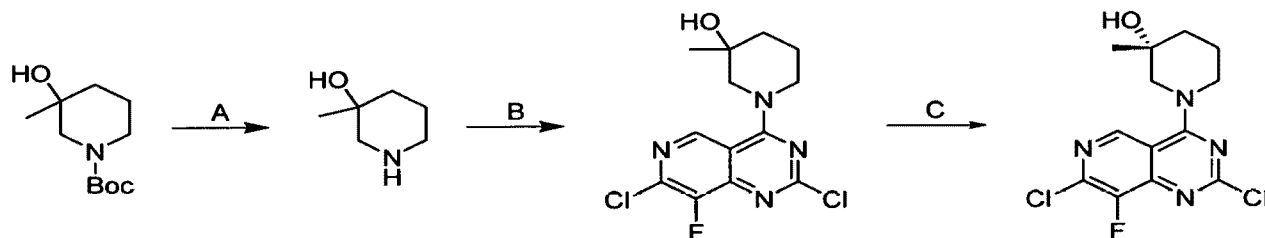
[0000228] Step F. 2,4-dichloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidine. A solution of POCl₃ (1.62 g, 10.6 mmol, 985 μL, 36.2 *equiv.*) and N-ethyl-N-isopropylpropan-2-amine (189 mg, 1.46 mmol, 255 μL, 5.0 *equiv.*) was stirred at 0 °C, followed by the addition of 7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol (0.1 g, 293 μmol, 1.0 *equiv.*). The suspension was stirred at 110 °C for 1 hour, the mixture was concentrated in vacuum to give

2,4-dichloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidine (0.11 g, crude) which was used directly in the next step without further purification. Black oil.

Intermediate 2



(R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

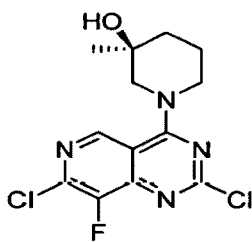


[0000229] Step A. 3-methylpiperidin-3-ol: To the solution of tert-butyl 3-hydroxy-3-methylpiperidine-1-carboxylate (2.45 g, 11.4 mmol) in acetonitrile (9 mL) was added HCl•dioxane (4 M, 18 mL) at 0°C, and the mixture was stirred at 0°C for 0.5 h. After completion, the reaction mixture was concentrated to give 3-methylpiperidin-3-ol (1.75 g, crude) as a yellow oil which was used in the next step without further purification.

[0000230] Step B. 1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To the mixture of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (3.65 g, 14.5 mmol), DIEA (7.47 g, 57.8 mmol) in dichloromethane (40 mL) was added 3-methylpiperidin-3-ol (1.75 g, crude) at -40°C, and the mixture was stirred at -40°C for 0.5 hour. After completion, the reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (100 mL). The combined organic phase was dried over anhydrous Na₂SO₄ and concentrated to give a residue. The residue was purified by column chromatography (5% to 50% EA/PE) to give 1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (2.05 g, 43% yield). Yellow Solid. LCMS (ESI, M+1): m/z 331.0.

[0000231] Step C. (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: 1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (2.05 g) was separated by SFC(column: DAICEL CHIRALCEL OJ (250 mm × 30 mm, 10 μm); mobile phase: [0.1 % NH₃WATER MeOH];B%: 20% - 20%, 3.7; 1035min) to give (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (1.00 g, 48%). Yellow Solid; LCMS (ESI, M+1): m/z 331.1.

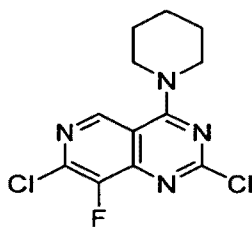
Intermediate 3



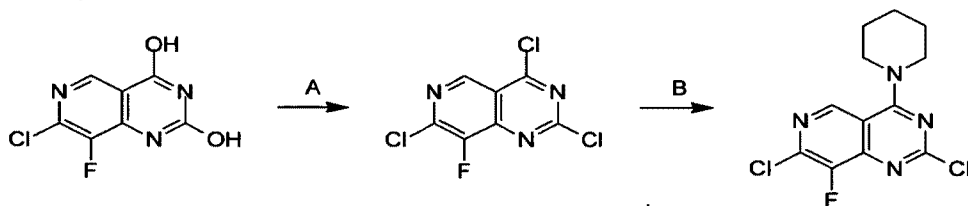
(S)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

[0000232] (S)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol was isolated as the other enantiomer in step C of the synthesis of intermediate 2. (1.05 g, 52%, yellow solid) LCMS (ESI, M+1): m/z 331.1.

Intermediate 4



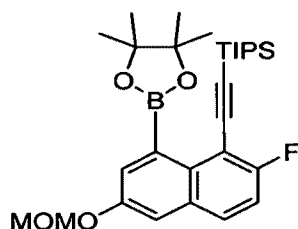
2,7-dichloro-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine



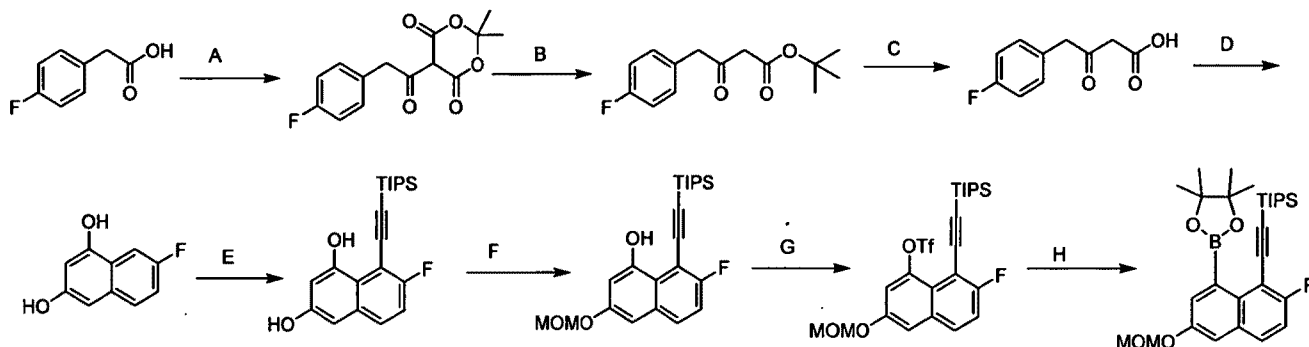
[0000233] Step A. 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine: To a mixture of 7-chloro-8-fluoropyrido[4,3-d]pyrimidine-2,4-diol (2.8 g, 13.0 mmol) in POCl₃ (20 mL) was added DIEA (5.04 g, 39.0 mmol, 6.79 mL) in one portion at 25 °C under N₂. The mixture was heated to 110 °C and stirred for 2 h. The mixture was concentrated in reduced pressure to give a residue. The residue was purified by silica gel chromatography (Silica gel, Petroleum ether/Ethyl acetate = 20/1, 3/1) to afford 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (3.1 g, 89% yield) as a yellow solid; LCMS (ESI, M+1): m/z 251.9.

[0000234] Step B. 2,7-dichloro-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine: To a mixture of 2,4,7-trichloro-8-fluoro-pyrido[4,3-d]pyrimidine (100 mg, 396 μmol) and DIPEA (76.8 mg, 594 μmol, 103 μL) in DCM (1 mL) was added piperidine (40.5 mg, 475 μmol, 46.9 μL) in portions at -40 °C under N₂. The mixture was stirred at -40 °C for 1 hour. The reaction mixture was filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Silica gel, Petroleum ether/Ethyl acetate = 1/0 to 0/1) affording 1-(2, 7-dichloro-8-fluoropyrido[4, 3-d] pyrimidin-4-yl)-3-methylpiperidin-3-ol (105 mg, 88% yield) as a yellow solid. LCMS (ESI, M+1): m/z 301.0.

Intermediate 5



((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane



[0000235] Step A. 5-(2-(4-fluorophenyl)acetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione. To a solution of 2-(4-fluorophenyl)acetic acid (500 g, 3.24 mol, 1 *equiv.*), Meldrum's acid (514 g, 3.57 mol, 1.1 *equiv.*), DMAP (33.7 g, 275 mmol, 0.085 *equiv.*) in CH₃CN (1500 mL) was added DIPEA (901 g, 6.97 mol, 1.21 L, 2.15 *equiv.*) while maintaining the temperature below 45 °C, and then pivaloyl chloride (430 g, 3.57 mol, 439 mL, 1.1 *equiv.*) was slowly added over 3 hours while maintaining the temperature below 45 °C. The resulted solution was stirred at 45°C for 3 hours. The mixture solution was cooled to 0°C, then 1N HCl (5 L) was slowly added, and the resulted solution was stirred at 0°C for 2 hours. Lot of solid was generated, and the mixture was filtered to give the crude yellow solid. The crude was washed with CH₃CN/WATER (3 L/12 L) to give 5-(2-(4-fluorophenyl)acetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (800 g, 88% yield). White Solid; ¹H NMR (400 MHz, DMSO-d₆) δ = 15.35 (s, 1H), 7.40-7.38 (m, 2H), 7.05-7.01 (m, 2H), 4.40 (s, 2H), 1.72 (s, 6H).

[0000236] Step B. tert-butyl 4-(4-fluorophenyl)-3-oxobutanoate. A solution of 5-(2-(4-fluorophenyl)acetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (1 kg) in t-BuOH (3 L) was stirred at 90°C for 2 hours, then the mixture solution was concentrated to give the crude solid, and the crude solid was washed with petroleum ether (350 mL) to give tert-butyl 4-(4-fluorophenyl)-3-oxobutanoate (850 g, 94% yield). Light-yellow Solid; ¹H NMR (400 MHz, DMSO-d₆) δ = 7.27-7.18 (m, 2H), 7.18-7.08 (m, 2H), 3.86 (s, 2H), 3.55 (s, 2H), 1.40 (s, 9H).

[0000237] Step C. 4-(4-fluorophenyl)-3-oxobutanoic acid. A solution of tert-butyl 4-(4-fluorophenyl)-3-oxobutanoate (800 g, 3.17 mol, 1 *equiv.*) and TFA (2.46 kg, 21.6 mol, 1.6 L, 6.81

equiv.) in DCM (1.6 L) was stirred at 20 °C for 1 hour. The mixture was concentrated to dryness. The residue was washed with petroleum ether (500 mL) to give 4-(4-fluorophenyl)-3-oxobutanoic acid (516 g, 83 % yield). White Solid; ¹H NMR (400 MHz, CDCl₃-d) δ = 10.01 (s, 1H), 7.20-7.17 (m, 2H), 7.07-7.03 (m, 2H), 3.84 (s, 2H), 3.54-3.52 (m, 2H).

[0000238] Step D. 7-fluoronaphthalene-1,3-diol. A solution of 4-(4-fluorophenyl)-3-oxobutanoic acid (450 g, 2.29 mol, 1 *equiv.*) in CF₃SO₃H (8.5 kg, 56 mol, 5 L, 25 *equiv.*) was stirred at 25 °C for 24 hours, the reaction was cooled to 0°C, and slowly added to ice-water (15 L). Precipitates were formed, and the mixture was filtered to give the crude product. Then the crude was slurred with petroleum ether (1 L), and filtered to give the 7-fluoronaphthalene-1,3-diol (325 g, 79% yield). Light-yellow Solid.

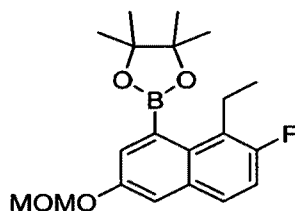
[0000239] Step E. 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol. To the mixture of 7-fluoronaphthalene-1,3-diol (120 g, 673 mmol, 1 *equiv.*), 2-bromoethynyl(triisopropyl)silane (184 g, 707 mmol, 1.05 *equiv.*), AcOK (132 g, 1.34 mol, 2 *equiv.*) in dioxane (800 mL) was added dichlororuthenium;1-isopropyl-4-methyl-benzene dimer (41.3 g, 67.4 mmol, 0.1 *equiv.*) under N₂. The mixture was stirred at 110°C for 2 hours. The mixture was filtered and concentrated to give a residue. Then the residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=1/0 to 5/1) to give 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol (213 g, 88% yield) was obtained. Black Oil; LCMS [ESI, M+1]: 359.2

[0000240] Step F. 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol. To the mixture of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol (170 g, 474 mmol, 1 *equiv.*), DIEA (184 g, 1.42 mol, 3 *equiv.*) and DCM (1700 mL) was added MOMCl (49.8 g, 618 mmol, 1.3 *equiv.*) at 0°C. The mixture was warmed to 15 °C and stirred for 0.5 hour. The reaction mixture was diluted with ice-water (1000 mL) and extracted with ethyl acetate (500 mL × 2). The combined organic phase was washed with brine (1000 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate = 1/0 to 50/1) to give 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (96 g, 50% yield). Yellow Solid; ¹H NMR (400 MHz, CDCl₃-d) δ = 9.13 (s, 1H), 7.68-7.64 (m, 1H), 7.21-7.16 (m, 1H), 6.97-6.96 (m, 1H), 6.81-6.80 (m, 1H), 5.26 (s, 2H), 3.51 (s, 3H), 1.24-1.17 (m, 21H). LCMS [ESI, M+1]: 403.2.

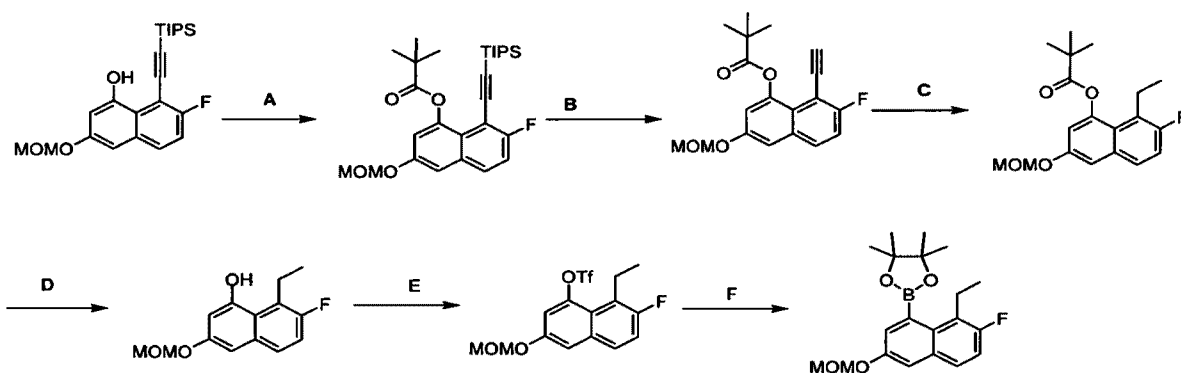
[0000241] Step G: 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate. To the solution of 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (80 g, 198 mmol, 1 *equiv.*), DIEA (77.0 g, 596 mmol, 104 mL, 3 *equiv.*) in DCM (1200 mL) was added Tf₂O (84.1 g, 298 mmol, 49.2 mL, 1.5 *equiv.*) at -40 °C, and the mixture was stirred at -40 °C for 0.5 hour. The reaction mixture was diluted with ice-water (500 mL), and then extracted with DCM (300 mL). The combined organic phase was dried over Na₂SO₄ and concentrated to dryness. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate = 1/0 to 60/1) to afford 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (100 g, 94% yield). Yellow oil;

[0000242] Step H. ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane. To the mixture of 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (105 g, 196 mmol, 1 *equiv.*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (100 g, 393 mmol, 2 *equiv.*), AcOK (57.8 g, 589 mmol, 3 *equiv.*) in toluene (1100 mL) was added Pd(dppf)Cl₂ (14.4 g, 20 mmol, 0.1 *equiv.*). The mixture was degassed and stirred at 130 °C for 3 hours. The reaction mixture was filtered and concentrated to give a residue. To the residue was added EtOAc (1000 mL) and water (800 mL). The organic phase was washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate = 100/1 to 3/1) and triturated with MeCN (40 mL) to give ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (41 g, 43% yield). Yellow Solid; ¹H NMR (400 MHz, CDCl₃-d) δ = 7.69-7.65 (m, 1H), 7.51 (d, *J* = 2.4 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 8.8 Hz, 1H), 5.28 (s, 2H), 3.50 (s, 3H), 1.44 (s, 12H), 1.18-1.16 (m, 21H); LCMS [ESI, M+1]: 513.4.

Intermediate 6



2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0000243] Step A. 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl pivalate. To the solution of 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (2.00 g, 4.97 mmol, 1.0 *equiv.*), DMAP (122 mg, 999 μ mol, 0.2 *equiv.*), TEA (1.51 g, 14.9 mmol, 3.0 *equiv.*) in DCM (20 mL) was added 2,2-dimethylpropanoyl chloride (1.80 g, 14.9 mmol, 3.0 *equiv.*) dropwise at 0 °C, and then the mixture was stirred at 20 °C for 1 hour. After completion, the reaction mixture was diluted with DCM (15 mL) and water (15 mL), and then the aqueous layer was extracted with DCM (10mL), The combined organic phase was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=1/0 to 15/1) to give the title compound (3.00 g, crude). Yellow oil. LCMS [ESI, M+1]:487.2.

[0000244] Step B. 8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl pivalate. To the solution of 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl pivalate (3.00 g, 6.16 mmol, 1.0 *equiv.*) in DMF (50 mL) was added CsF (9.36 g, 61.6 mmol, 10 *equiv.*), and the mixture was stirred at 20°C for 0.25 hour. After completion, to the reaction mixture was

added water (250 mL), and then the mixture was extracted with ethyl acetate (2 × 120mL). The combined organic phase was washed with brine 100 mL, dried over Na₂SO₄ and concentrated to give the title compound (2.20 g, crude). Yellow oil. LCMS [ESI, M+1]:331.1.

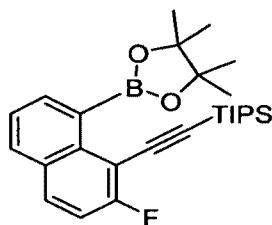
[0000245] Step C. 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl pivalate. To the solution of 8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl pivalate (2.00 g, 6.05 mmol, 1.0 *equiv.*) in MeOH (20 mL) was added Pd/C (200 mg, 10% purity) under N₂. The suspension was degassed in vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 20 °C for 20 minutes. After completion, the mixture was filtered and concentrated to give the title compound (1.06 g, crude). LCMS [ESI, M+1]:335.1.

[0000246] Step D. 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol. To the solution of 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl pivalate (1.00 g, 2.99 mmol, 1.0 *equiv.*) in MeOH (15 mL) was added KOH (504 mg, 8.98 mmol, 3.0 *equiv.*), and the mixture was stirred at 20 °C for 0.5 hour. After completion, the reaction solution was adjusted to pH = 4 with 0.5 M HCl at 0 °C and extracted with ethyl acetate (80 mL × 2), the combined organic phase was washed with brine 50 mL, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=50/1 to 10/1) to give the title compound (570 mg, four steps 51% yield). Yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.55-7.43 (m, 1H), 7.18 (t, *J* = 9.2 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 5.32 (s, 1H), 5.25 (s, 2H), 3.52 (s, 3H), 3.40-3.25 (m, 2H), 1.30 (t, *J* = 7.6 Hz, 3H) .

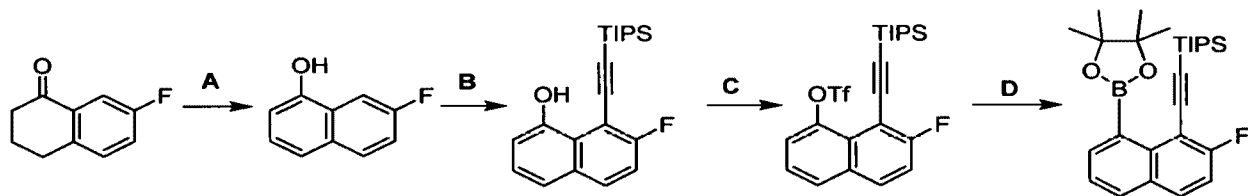
[0000247] Step E. 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethane sulfonate. To the solution of 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (520 mg, 2.08 mmol, 1.0 *equiv.*), DIEA (806 mg, 6.24 mmol, 3.0 *equiv.*) in DCM (10 mL), trifluoromethylsulfonyl trifluoromethanesulfonate (879 mg, 3.12 mmol, 1.5 *equiv.*) was added dropwise at -40°C, and then the mixture was stirred at -40°C for 0.5 hr. After completion, the reaction mixture was quenched with ice-water (15 mL), and then extracted with DCM (2 × 15 mL). The combined organic phase was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=100/1 to 30/1) to give the title compound (620 mg, 78% yield). Yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.67-7.59 (m, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.37 (d, *J* = 2.4 Hz, 1H), 7.33-7.27 (m, 1H), 5.29 (s, 2H), 3.53 (s, 3H), 3.33-3.14 (m, 2H), 1.25 (t, *J* = 7.6 Hz, 3H) .

[0000248] Step F. 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To the mixture of 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethane sulfonate (500 mg, 1.31 mmol, 1.0 *equiv.*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (665 mg, 2.62 mmol, 2.0 *equiv.*), AcOK (385 mg, 3.92 mmol, 3.0 *equiv.*) in dioxane (6 mL) was added Pd(dppf)Cl₂ (96.0 mg, 131 μmol, 0.1 *equiv.*) under N₂. The mixture was degassed and stirred at 100 °C for 1 hour. After completion, the mixture was diluted with ethyl acetate (20 mL) and water (10 mL), and extracted with ethyl acetate (10 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=100/1 to 25/1) to give the title compound (143 mg, 30% yield). Yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.62-7.53 (m, 1H), 7.44-7.34 (m, 2H), 7.21 (t, *J* = 9.2 Hz, 1H), 5.28 (s, 2H), 3.51 (s, 3H), 3.20-3.06 (m, 2H), 1.45 (s, 12H), 1.30-1.25 (m, 3H).

Intermediate 7



((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane



[0000249] Step A. 7-fluoronaphthalen-1-ol. To a solution of 7-fluoro-3,4-dihydronaphthalen-1(2H)-one (75.0 g, 457 mmol, 1.00 *equiv.*) in acetic acid (1.50 L) and hydrogen bromide in AcOH (33%, 7.50 mL) was added bromine (80.3 g, 503 mmol, 25.9 mL, 1.1 *equiv.*) in acetic acid (50 mL) at 0 °C, and the mixture was stirred at 25 °C for 3 hours. The mixture was diluted with DCM

(1.5 L), washed with water (3 × 500 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to afford a brown oil, which was dissolved in DMF (750 mL). Lithium bromide (67.4 g, 777 mmol, 19.5 mL, 1.70 *equiv.*), lithium carbonate (57.4 g, 777 mmol, 1.70 *equiv.*) were added. The reaction mixture was stirred at 160° C for 3.5 hours. The reaction was diluted with ethyl acetate (1.00 L), washed with brine (2 × 500 mL), dried with anhydrous sodium sulfate, filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=1/0 to 5/1) affording the title compound (61.0 g, 82% yield). Brown solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.84-7.77 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.31-7.24 (m, 2H), 6.84 (d, *J* = 7.6 Hz, 1H), 5.39 (s, 1H).

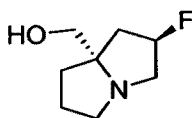
[0000250] Step B. 7-fluoro-8-(2-triisopropylsilylethynyl)naphthalen-1-ol. To a solution of (bromoethynyl)triisopropylsilane (72.0 g, 275 mmol, 1.20 *equiv.*) and 7-fluoronaphthalen-1-ol (37.2 g, 230 mmol, 1.0 *equiv.*) in DCE (500 mL) were added dichlororuthenium;1-isopropyl-4-methyl-benzene (21.1 g, 34.4 mmol, 0.15 *equiv.*), K₂CO₃(31.7 g, 230 mmol, 1.0 *equiv.*) and NaOAc (3.77 g, 45.9 mmol, 0.20 *equiv.*). The mixture was stirred at 40 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, petroleum ether/ethyl acetate=1/0 to 50/1) affording the title compound (73.0 g, 93% yield). Yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 9.10 (s, 1H), 7.79 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.41-7.33 (m, 2H), 7.23 (t, *J* = 8.8 Hz, 1H), 7.08-7.00 (m, 1H), 1.24-1.14 (m, 21H); LCMS [ESI, M+1, 2M+1]: 343.1, 685.3.

[0000251] Step C. [7-fluoro-8-(2-triisopropylsilylethynyl)-1-naphthyl] trifluoromethanesulfonate. To a solution of 7-fluoro-8-(2-triisopropylsilylethynyl)naphthalen-1-ol (73.0 g, 213 mmol, 1.00 *equiv.*) in DCM (600 mL) were added DIEA (55.1 g, 426 mmol, 74.2 mL, 2.00 *equiv.*) and Tf₂O (90.2 g, 320 mmol, 52.7 mL, 1.50 *equiv.*) at -40 °C. The mixture was stirred at -40 °C for 0.5 hour. The combined reaction mixture was filtered and concentrated under reduced pressure to give a residue. The mixture was purified by column chromatography (Silica gel, petroleum ether/ethyl acetate= 1/0 to 50/1) affording the title compound (78.0 g, 77% yield). Yellow solid; ¹H NMR (400 MHz, CDCl₃) δ 7.88-7.79 (m, 2H), 7.59-7.52 (m, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 8.8 Hz, 1H), 1.32-1.16 (m, 21H).

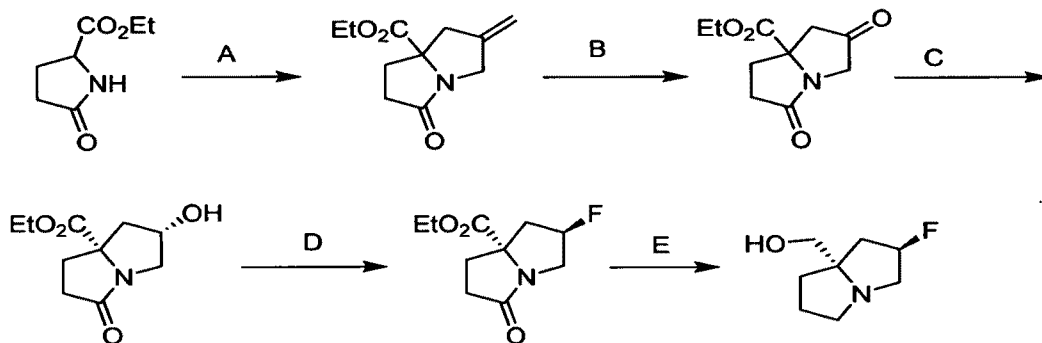
[0000252] Step D. ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane. To a solution of [7-fluoro-8-(2-triisopropylsilylethynyl)-1-naphthyl]

trifluoromethanesulfonate (20.0 g, 42.1 mmol, 1.00 *equiv.*) and bis(pinacolato)diboron (16.0 g, 63.2 mmol, 1.50 *equiv.*) in dioxane (6.00 mL) were added KOAc (8.27 g, 84.3 mmol, 2.0 *equiv.*) and Pd(dppf)Cl₂ (3.08 g, 4.21 mmol, 0.10 *equiv.*). The mixture was stirred at 110 °C for 12 hours. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, petroleum ether/ethyl acetate=1/0 to 10/1) affording the title compound (9.0 g, 47% yield). Yellow solid; ¹H NMR (400 MHz, CDCl₃) δ 7.85-7.75 (m, 3H), 7.43 (dd, *J* = 7.2, 8.0 Hz, 1H), 7.30-7.24 (m, 1H), 1.45 (s, 12H), 1.21-1.14 (m, 21H); LCMS [ESI, M+1]: 453.2.

Intermediate 8



((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol



[0000253] Step A. Ethyl 2-methylene-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate. To a mixture of ethyl 5-oxopyrrolidine-2-carboxylate (1.50 kg, 9.54 mol, 1.00 *equiv.*) and 3-chloro-2-(chloromethyl)prop-1-ene (1.91 kg, 15.3 mol, 1.77 L, 1.60 *equiv.*) in THF (7.50 L) was added LiHMDS (1 M, 19.1 L, 2.00 *equiv.*) drop-wise at -40 °C under N₂. The mixture was stirred at 25 °C for 20 hrs. The reaction mixture was poured into HCl (1 M, 2.50 L) and pH was adjusted to 7 with HCl (2 M) at 0 °C. The mixture was extracted with EtOAc (4.50 L × 3). The combined organic layers were washed with brine (4.50 L), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=10/1 to 1/1, R_f = 0.40) to afford the title compound (898 g, 3.88

mol, 40.6% yield, 82% purity) as a yellow oil. LCMS: R_t = 0.716 min, m/z = 210.1 (M+H). ^1H NMR: 400 MHz CDCl_3 δ : 5.02-5.07 (m, 2H), 4.28 (m, 1H), 4.16-4.22 (m, 2H), 3.71 (dd, J = 15.6, 1.6 Hz, 1H), 3.04 (m, 1H), 2.73-2.80 (m, 1H), 2.57-2.64 (m, 1H), 2.41-2.49 (m, 2H), 2.03-2.17 (m, 2H), 1.24-1.30 (m, 3H).

[0000254] Step B. ethyl 2,5-dioxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate. To a mixture of ethyl 2-methylene-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (165 g, 646 mmol, 1.00 *equiv.*) in DCM (1650 mL) and MeOH (165 mL) was added O_3 (15 psi) at -70°C under N_2 . The solution became pale blue, and then the mixture was purged by N_2 for 30 min. Me_2S (80.4 g, 1.29 mol, 95.0 mL, 2.00 *equiv.*) was added to the mixture at -70°C . The mixture was stirred at 25°C for 16 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=10/1 to 1/1, R_f = 0.50) to afford the title compound (821 g, 3.62 mol, 93.3% yield, 93.1% purity) as a yellow oil. LCMS: R_t = 0.543 min, m/z = 212.1 (M+H). ^1H NMR: 400 MHz CDCl_3 δ : 4.23 (m, 2H), 4.12 (m, 1H), 3.56 (m, 1H), 2.96-3.01 (m, 2H), 2.77-2.86 (m, 1H), 2.43-2.50 (m, 2H), 2.14-2.22 (m, 1H), 1.28 (m, 1H).

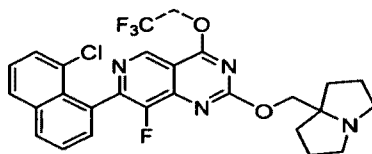
[0000255] Step C. ethyl 2-hydroxy-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate. To a solution of ethyl 2,5-dioxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (257 g, 1.22 mol, 1.00 *equiv.*) in EtOH (1300 mL) was slowly added NaBH_4 (13.8 g, 365 mmol, 0.30 *equiv.*) at 0°C under N_2 . The mixture was stirred at 0°C for 10 min. The reaction was quenched with saturated NH_4Cl (65.0 mL) at 5°C and stirred at 5°C for 0.5 hr, then the mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=10/1 to 1/1) to afford the title compound (56.8% yield) as a yellow oil. ^1H NMR: 400 MHz CDCl_3 δ : 4.65 (s, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.95 (dd, J = 12.8, 6.0 Hz, 1H), 3.10 (d, J = 12.8 Hz, 1H), 2.75-2.84 (m, 2H), 2.49-2.49 (m, 2H), 2.39-2.45 (m, 1H), 2.02-2.10 (m, 1H), 1.84 (dd, J = 13.6, 6.0 Hz, 1H), 1.30 (t, J = 7.2 Hz, 1H).

[0000256] Step D. ethyl (2S,7aR)-2-fluoro-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate. To a solution of ethyl 2-hydroxy-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (150 g, 642 mmol, 1.00 *equiv.*) in DCM (750 mL) was added a solution of DAST (131 g, 813 mmol, 107 mL, 1.50 *equiv.*) drop-wise at -70°C under N_2 . The reaction mixture was warmed to 25°C stirred at 25°C for 16 hours. The reaction mixture was quenched with MeOH

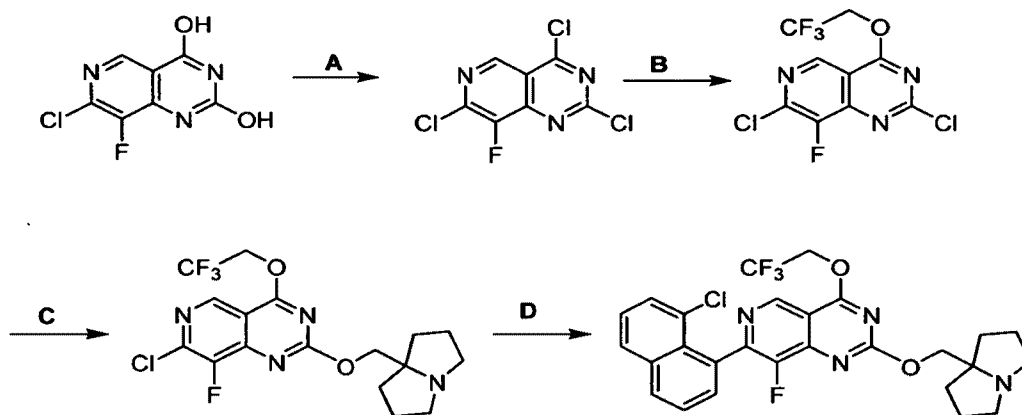
(40.0 mL) at 10°C, then diluted with water (750 mL) and extracted with DCM (750 mL × 3). The combined organic layers were washed with brine (750 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate = 1/0 to 0/1, R_f = 0.30) to afford ethyl 2-fluoro-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (50.6% yield, 74.7% purity) as a yellow oil. This compound (61 g, 283.43 mmol, 1.00 *equiv.*) was further purified by HPLC (column: Welch ultimate XB-NH₂ 250*50*10um; mobile phase: [Heptane-EtOH(0.1%NH₃WATER)]; B%: 10%-10%, 10min) to give a yellow oil (49.0 g, 226.08 mmol, 99.3% purity). ¹H NMR: 400 MHz CDCl₃ δ: 5.30 (m, 1H), 4.10-4.23 (m, 3H), 3.11-3.14 (m, 1H), 2.67-2.76 (m, 3H), 2.41-2.45 (m, 1H), 2.03-2.12 (m, 2H), 1.23-1.29 (m, 3H). SFC separation (column: DAICEL CHIRALPAK IC(250mm*50mm,10um); mobile phase: [0.1%NH₃•H₂O-IPA]; B%: 40%-40%, 4.7min; 200min/min, desired product: Peak 2, R_t = 1.959 min) of the racemic material (280 g, 1.22 mol, 1 *equiv.*) gave the title compound (114 g, 96.0% purity).

[0000257] Step E. ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol. To a suspension of LiAlH₄ (33.1 g, 871 mmol, 1.50 *equiv.*) in THF (625 mL) was added a solution of ethyl (2S,7aR)-2-fluoro-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (125 g, 581 mmol, 1.00 *equiv.*) in THF (375 mL) drop-wise at 0°C under N₂. The reaction mixture was warmed to 70 °C and stirred at 70 °C for 3 hours. The mixture was cooled to 0 °C. Then to the mixture was added water (33.0 mL), NaOH (15%, 99.0 mL) and water (99 mL) dropwise in sequence 0 °C. After addition, the mixture was stirred at 0 °C stirred for 5 min. The mixture was filtered, and the filtered cake was washed with EtOAc (1000 mL × 2). The filtrate was dried with MgSO₄, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, DCM: MeOH = 100/1 to 10/1) to afford the title compound (180 g, 1.10 mol, 94.7% yield, 97.3% purity) as a yellow oil. ¹H NMR: 400 MHz CDCl₃ δ: 5.12-5.27 (m, 1H), 3.25 (s, 2H), 3.14-3.18 (m, 2H), 3.12-3.13 (m, 1H), 3.02-3.09 (m, 1H), 2.01-2.11 (m, 2H), 1.75-1.86 (m, 4H).

Intermediate 9



7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine



[0000258] Step A. 2,4,7-trichloro-8-fluoro-pyrido[4,3-d]pyrimidine. To a mixture of -chloro-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol (20 g, 92.8 mmol, 1.00 *equiv.*) in toluene (100 mL) was added POCl₃ (42.7 g, 278 mmol, 25.9 mL, 3.00 *equiv.*) and N-ethyl-N-isopropylpropan-2-amine (36.0 g, 278 mmol, 48.5 mL, 3.00 *equiv.*) at 0 °C. The mixture was stirred at 110 °C for 3 hours. After completion, the mixture was concentrate under reduced pressure at 40 °C to dryness affording 2,4,7-trichloro-8-fluoro-pyrido[4,3-d]pyrimidine (23.4 g, crude) as a black oil.

[0000259] Step B. 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. To a solution of 2,2,2-trifluoroethanol (11.1 g, 111 mmol, 8.01 mL, 1.20 *equiv.*) in toluene (200 mL) was added t-BuONa (26.7 g, 278 mmol, 3.00 *equiv.*) at 0 °C. The mixture was first stirred at 10 °C for 0.5 hour. Then the above mixture was added to 2,4,7-trichloro-8-fluoro-pyrido[4,3-d]pyrimidine (23.4 g, 92.7 mmol, 1.00 *equiv.*) in toluene (200 mL) at -10 °C. After addition, the mixture was stirred at -10 °C ~ 25 °C for 16 hours. After monitored, a mixture of t-BuONa (1.78 g, 18.5 mmol, 0.2 *equiv.*) and 2,2,2-trifluoroethanol (1.85 g, 18.5 mmol, 1.33 mL, 0.20 *equiv.*) in toluene (20.0 mL) was added thereto at 0 °C. The mixture was continued to stir at 25 °C for 30

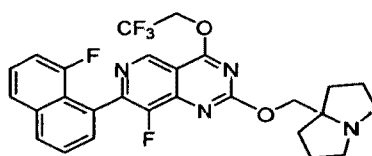
hours. After completion, the mixture was poured onto Silica gel column, purified by column chromatography (Silica gel, petroleum ether/ethyl acetate=30/1 to 10/1), and then further purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) affording 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (16.3 g, 55.6% yield); Yellow solid; LCMS [ESI, M+1]: 316.

[0000260] Step C. 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. To a mixture of (tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (17.9 g, 126 mmol, 2.00 *equiv.*), 4Å MS (15.0 g) and N-ethyl-N-isopropylpropan-2-amine (16.4 g, 126 mmol, 22.0 mL, 2.00 *equiv.*) in 2-methyltetrahydrofuran (200 mL) was added 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (20.0 g, 63.3 mmol, 1.00 *equiv.*) in 2-methyltetrahydrofuran (200 mL) at 0 ~ 5 °C. The mixture was stirred at 0 - 25 °C for 2 hours. After completion, the mixture was filtered and washed with ethyl acetate (100 mL). The filtrate was quenched by saturated NH₄Cl aqueous solution (300 mL), and the organic layer was separated and dried over anhydrous Na₂SO₄. The mixture was filtered, and the filtrate was concentrated under reduced pressure at 40 °C to dryness. The crude product was triturated with CH₃CN (20 mL) at 25 °C for 15 minutes and filtered, the filter cake was dried in vacuum at 40 °C affording the title compound (18.2 g, 64.6% yield). Light yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.99 (s, 1H), 5.03 (q, *J* = 8.4 Hz, 2H), 4.32 (s, 2H), 3.23-3.05 (m, 2H), 2.67 (td, *J* = 6.8, 10.4 Hz, 2H), 2.11-1.96 (m, 2H), 1.96-1.85 (m, 4H), 1.74-1.69 (m, 2H); LCMS [ESI, M+1]: 421.

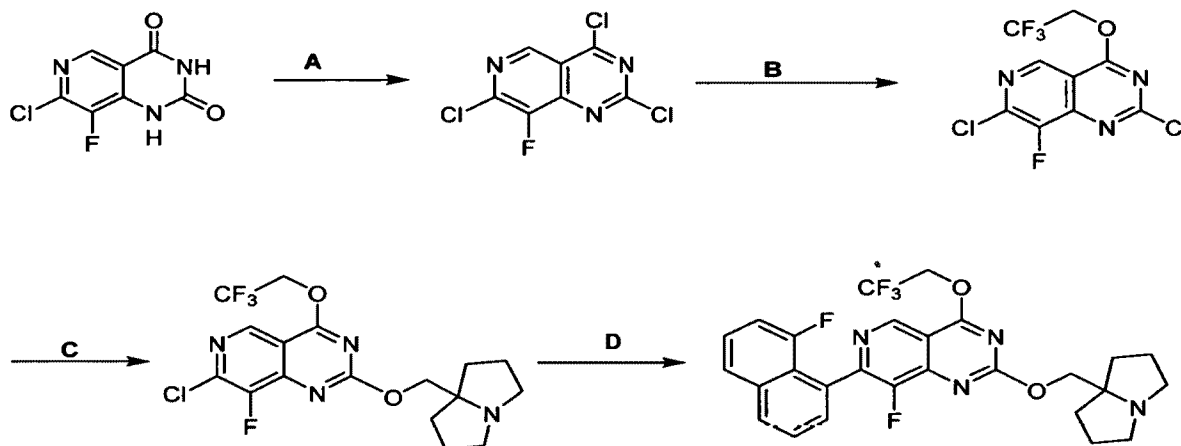
[0000261] Step D. 7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. To a mixture of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (5.00 g, 11.9 mmol, 1.00 *equiv.*), (8-chloronaphthalen-1-yl)trimethylstannane (7.73 g, 23.8 mmol, 2.00 *equiv.*) in toluene (150 mL) was added 4Å MS (5.00 g) at 25 °C. The mixture was stirred at 25 °C for 1 hour. Then CuI (792 mg, 4.16 mmol, 0.35 *equiv.*), Pd(dppf)Cl₂ (1.30 g, 1.78 mmol, 0.15 *equiv.*) and BINAP (1.85 g, 2.97 mmol, 0.25 *equiv.*) were added thereto at 25 °C. The mixture was degassed in vacuum and purged with N₂ several times over 30 minutes. Then the mixture was heated to 90 °C and stirred for 2 hours. The mixture was cooled to 25 °C, and then (8-chloronaphthalen-1-yl)trimethylstannane (1.93 g, 5.94 mmol, 0.50 *equiv.*) was added thereto at

25 °C. The mixture was heated to 90 °C and stirred for 1 hour. After completion, the mixture was filtered, and the filtrate was concentrated under reduced pressure at 40 °C to dryness. The crude product was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) affording the title compound (2.3 g, 33.9% yield); Yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.25 (s, 1H), 8.02 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.89 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.65-7.60 (m, 1H), 7.59-7.53 (m, 2H), 7.46-7.41 (m, 1H), 5.08 (q, *J* = 8.0 Hz, 2H), 4.46 (s, 2H), 3.32 (br d, *J* = 3.8 Hz, 2H), 2.83-2.70 (m, 2H), 2.20-2.09 (m, 2H), 2.03-1.90 (m, 4H), 1.82-1.72 (m, 2H); LCMS [ESI, M+1]: 547.

Intermediate 10



8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine



[0000262] Step A. 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine. To a solution of 7-chloro-8-fluoropyrido[4,3-d]pyrimidine-2,4(1H,3H)-dione (100 g, 463 mmol, 1.00 *equiv.*) in toluene (500 mL) were added POCl₃ (213 g, 1.39 mol, 129 mL, 3.00 *equiv.*) and DIEA (179 g, 1.39 mol, 242 mL, 3.00 *equiv.*) at 0 °C. The mixture was stirred at 110 °C for 5 h. The reaction was distilled in

vacuum (80 °C, water pump) to give 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (100 g, 396.10 mmol, 85.39% yield) as brown oil.

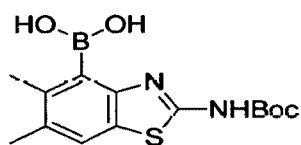
[0000263] Step B. 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (100 g, 396 mmol, 1.00 *equiv.*) and 2, 2, 2-trifluoroethanol (59.4 g, 594 mmol, 42.7 mL, 1.50 *equiv.*) in toluene (2 L) was added t-BuONa (152 g, 1.58 mol, 4.00 *equiv.*) at 25 °C. The mixture was stirred at 25 °C for 2 hr. The reaction mixture was filtered through a pad of Celite, washed with brine (3 L × 2) and concentrated under reduced pressure to give a residue, which was purified by reversed-phase HPLC (water (0.1% formic acid) - ACN) to give 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (45.0 g, 140 mmol, 35.5% yield, 99.0% purity) as a brown solid. LCMS: M+1, 316.

[0000264] Step C. 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. A mixture of (tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (35.7 g, 253 mmol, 2.00 *equiv.*), DIEA (32.7 g, 253 mmol, 44.0 mL, 2.00 *equiv.*) and 4Å molecular sieves (40.0 g) in 2-methyltetrahydrofuran (400 mL) was stirred at 25 °C for 1 hr. Then a solution of 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (40.0 g, 126 mmol, 1.00 *equiv.*) in 2-methyltetrahydrofuran (400 mL) was added and the resulting mixture was stirred at 25 °C for 2 hrs. The reaction mixture was filtered. The filtrate was washed with sat. aq. NH₄Cl solution (1 L × 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was triturated with acetonitrile (300 mL) at 25 °C for 30 min to give 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (26.0 g, 61.1 mmol, 48.3% yield, 99.0% purity) as a light yellow solid. LCMS: M+1, 421.

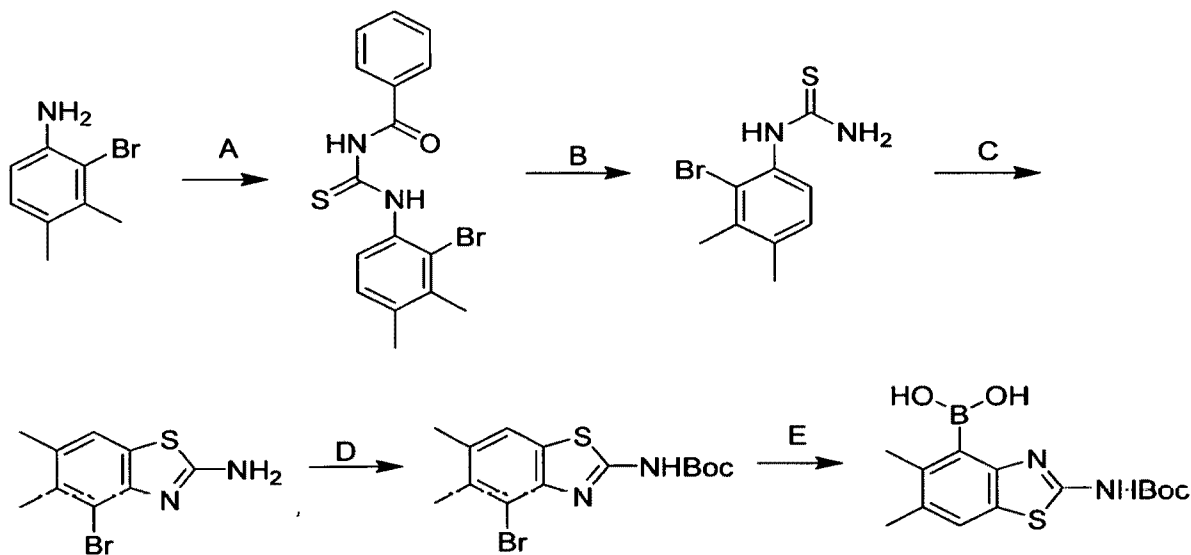
[0000265] Step D. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. A mixture of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (17.0 g, 40.4 mmol, 1.00 *equiv.*), 2-(8-fluoronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (16.4 g, 60.6 mmol, 1.50 *equiv.*), BrettPhos Pd G3 (4.25 g, 4.69 mmol, 1.16 *equiv.*), K₃PO₄ (1.5 M, 80.8 mL, 3.00 *equiv.*) in toluene (170 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 65 °C for 4 hrs under N₂ atmosphere. The reaction mixture was filtered. The filtrate was extracted with toluene (170 mL × 3). The combined

organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed-phase HPLC (water (0.1% formic acid) - ACN) to give 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (10.85 g, 16.6 mmol, 41.2% yield, 95.8% purity) as a yellow solid. NMR: δ 9.28 (s, 1H), 8.23 (d, $J = 8.1$ Hz, 1H), 7.97 (d, $J = 8.1$ Hz, 1H), 7.81-7.76 (m, 1H), 7.68 (dd, $J = 0.9, 7.2$ Hz, 1H), 7.61 (dt, $J = 5.1, 7.9$ Hz, 1H), 7.34 (dd, $J = 7.1, 13.3$ Hz, 1H), 5.47-5.37 (m, 2H), 4.77-4.67 (m, 2H), 3.56-3.49 (m, 2H), 3.22 (td, $J = 6.0, 11.7$ Hz, 2H), 2.27-2.00 (m, 8H); LCMS: $M+1$, 531.

Intermediate 11



(2-((tert-butoxycarbonyl)amino)-5,6-dimethylbenzo[d]thiazol-4-yl)boronic acid



[0000266] Step A. N-((2-bromo-3,4-dimethylphenyl)carbamothioyl)benzamide: To a solution of 2-bromo-3,4-dimethylaniline (2.17 g, 10.9 mmol) in acetone (30 mL) was added benzoyl isothiocyanate (1.9 g, 11.6 mmol) in acetone (10 mL) at 25 °C. The mixture was stirred at 25 °C for 5 minutes. The reaction mixture was concentrated under reduced pressure to give a residue.

The residue was dispersed in petroleum ether/ethyl acetate=20/1 (40 mL) and stirred for 0.5 hour. The mixture was filtered and the solid was dried under reduced pressure to give N-((2-bromo-3,4-dimethylphenyl)carbamothioyl)benzamide (3.56 g, 90% yield) as a light yellow solid; ¹H NMR (400 MHz, CDCl₃) δ = 12.45 (br s, 1H), 9.21 (br s, 1H), 7.95-7.92 (m, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.67-7.59 (m, 1H), 7.58-7.56 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 2.44 (s, 3H), 2.37 (s, 3H).

[0000267] Step B. 1-(2-bromo-3,4-dimethylphenyl)thiourea: A mixture of N-((2-bromo-3,4-dimethylphenyl)carbamothioyl)benzamide (3.30 g, 9.08 mmol) and NaOH (50 mL, 10% aqueous) was stirred at 80 °C for 3 hours. A white precipitate appeared. After completion, the reaction mixture was cooled to 10 °C. The mixture was filtered and filter cake was washed with water until the pH of the filtrate was 8~9. The filter cake was washed with petroleum ether (10 mL) and dried under reduced pressure to give 1-(2-bromo-3,4-dimethylphenyl)thiourea (2.2 g, 90% yield) as a white solid; LCMS (ESI, M+1): *m/z* 259.0, 261.0.

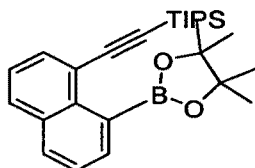
[0000268] Step C. 4-bromo-5,6-dimethylbenzo[d]thiazol-2-amine: To a solution of 1-(2-bromo-3,4-dimethylphenyl)thiourea (2.20 g, 8.49 mmol) in CHCl₃ (30 mL) was added drop-wise Br₂ (1.36 g, 8.49 mmol) in CHCl₃ (2 mL) at 0 °C. The mixture was stirred at 70 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with ethyl acetate (200 mL), saturated Na₂S₂O₃ aqueous (50 mL) and saturated NaHCO₃ aqueous solution (50 mL). The mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give 4-bromo-5,6-dimethylbenzo[d]thiazol-2-amine (2 g, 88% yield) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.66 (s, 2H), 7.43 (s, 1H), 2.34 (s, 3H), 2.29 (s, 3H). LCMS (ESI, M+1): *m/z* 257.0, 259.0.

[0000269] Step D. tert-butyl (4-bromo-5,6-dimethylbenzo[d]thiazol-2-yl)carbamate: A mixture of 4-bromo-5,6-dimethylbenzo[d]thiazol-2-amine (2 g, 7.78 mmol), (Boc)₂O (2.1 g, 9.62 mmol), DIPEA (3.04 g, 23.5 mmol) and DMAP (96 mg, 786 μmol) in THF (40 mL) was stirred at 25 °C for 16 hour. Then DIPEA (1.04 g, 8.04 mmol) and (Boc)₂O (570 mg, 2.61 mmol) was added. The mixture was stirred at 25 °C for 4 hours. After completion, the reaction mixture was diluted with water (50 mL) and ethyl acetate (200 mL). The mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The

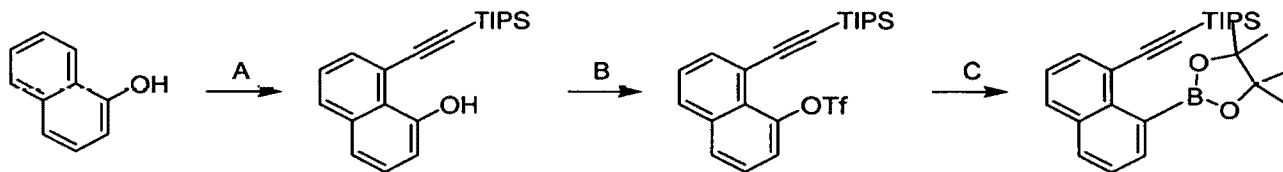
residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=1/19] to give tert-butyl (4-bromo-5,6-dimethylbenzo[d]thiazol-2-yl)carbamate (2.6 g, 91% yield) as a light yellow solid; LCMS (ESI, M-55): m/z 300.9, 302.9.

[0000270] Step E. (2-((tert-butoxycarbonyl)amino)-5,6-dimethylbenzo[d]thiazol-4-yl)boronic acid: A mixture of tert-butyl (4-bromo-5,6-dimethylbenzo[d]thiazol-2-yl)carbamate (1 g, 2.80 mmol), 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5,5-dimethyl-1,3,2-dioxaborinane (1.58 g, 7.00 mmol) and AcOK (1.00 g, 10.2 mmol) in dioxane (15 mL) was degassed and purged with N₂ for 3 times. Then [2-(2-aminophenyl)phenyl]-chloro-palladium;tricyclohexylphosphane (100 mg, 169 μ mol, 0.06 *equiv.*) was added. The mixture was stirred at 80 °C for 40 hours under N₂ atmosphere. After completion, the reaction mixture was diluted with water (1 mL) and brine (1 mL), and extracted with ethyl acetate (2 mL $\times$ 4). The combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=1/9] to give (2-((tert-butoxycarbonyl)amino)-5,6-dimethylbenzo[d]thiazol-4-yl)boronic acid (0.73 g, 65% yield) as a light yellow solid; LCMS (ESI, M+1): m/z 323.1.

Intermediate 12



triisopropyl((8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane



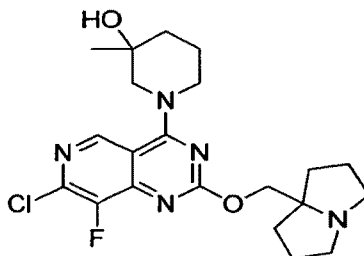
[0000271] Step A. 8-((triisopropylsilyl)ethynyl)naphthalen-1-ol: To a solution of naphthalen-1-ol (500 mg, 3.47 mmol, 1.25 mL), potassium carbonate (479 mg, 3.47 mmol), dichlororuthenium;1-isopropyl-4-methyl-benzene (531 mg, 867 μ mol) and sodium acetate (56.9 mg, 694 μ mol) in DCE (20.0 mL) was added 2-bromoethynyl(triisopropyl)silane (1.09 g, 4.16

mmol). The reaction was stirred at 40 °C for 12 hours. The reaction mixture was cooled to 25 °C and filtered. The filtrate was concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (Petroleum ether/ethyl acetate=1/0 to 10/1) to give 8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (760 mg, 67% yield) as a brown solid; ¹H NMR (400 MHz, CDCl₃) δ = 9.22 (s, 1H), 7.81 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.64 (dd, *J* = 1.2, 6.8 Hz, 1H), 7.42-7.34 (m, 3H), 7.01 (dd, *J* = 4.0, 5.6 Hz, 1H), 1.25-1.13 (m, 21H).

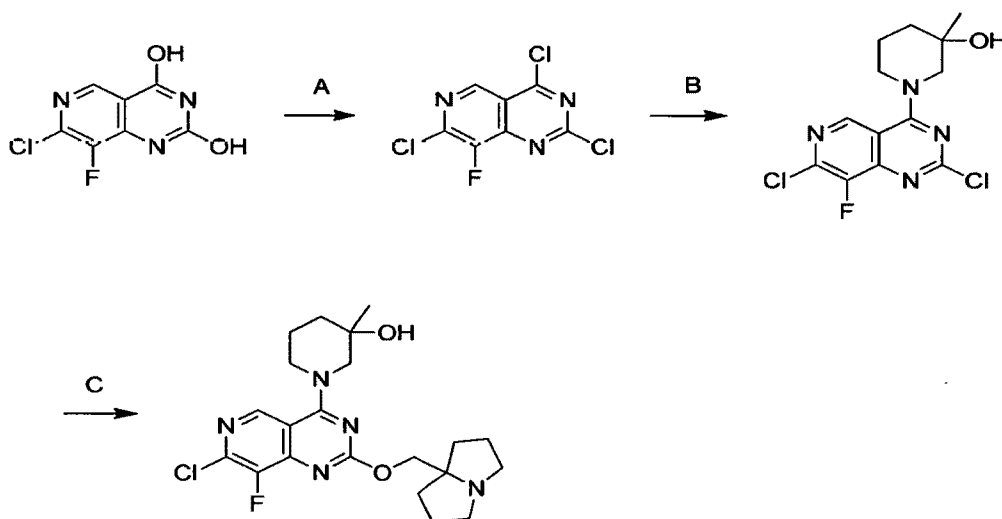
[0000272] Step B. 8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate: To a solution of 8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (760 mg, 2.34 mmol) and DIEA (605 mg, 4.68 mmol, 816 μL) in DCM (8.00 mL) was added Tf₂O (991 mg, 3.51 mmol, 580 μL) at -40 °C. The reaction was stirred at 25 °C for 0.5 hour. The reaction was quenched with water (10.0 mL). The aqueous phase was extracted with DCM (2 × 20.0 mL). The combined organic phase was washed with brine (2 × 20 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=1/0 to 10/1) to give 8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (1.00 g, 93% yield) as a brown oil; ¹H NMR (400 MHz, CDCl₃) δ = 7.92-7.84 (m, 3H), 7.56-7.47 (m, 3H), 1.26-1.12 (m, 21H).

[0000273] Step C. triisopropyl((8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane: To a solution of 8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (950 mg, 2.08 mmol) in dioxane (15.0 mL) were added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (687 mg, 2.70 mmol), Pd(dppf)Cl₂ (152 mg, 208 μmol) and KOAc (408 mg, 4.16 mmol). The reaction was stirred at 110 °C for 5 hours under nitrogen. The reaction was filtered and concentrated in vacuum to give a residue. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=1/0 to 20/1) to give triisopropyl((8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane (340 mg, 38% yield) as a red oil; ¹H NMR (400 MHz, CDCl₃) δ = 7.78-7.66 (m, 3H), 7.39-7.26 (m, 3H), 1.36 (s, 12H), 1.12-1.05 (m, 21H).

Intermediate 13



1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



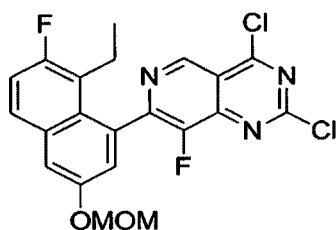
[0000274] Step A. 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine: To a mixture of 7-chloro-8-fluoropyrido[4,3-d]pyrimidine-2,4-diol (2.8 g, 13.0 mmol) in POCl₃ (20 mL) was added DIEA (5.04 g, 39.0 mmol, 6.79 mL) in one portion at 25 °C under N₂. The mixture was heated to 110 °C and stirred for 2 hours. After completion, the mixture was concentrated under reduced pressure at 45 °C. The residue was purified by silica gel chromatography (Silica gel, Petroleum ether/Ethyl acetate = 20/1, 3/1) to afford 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (3.1 g, 89% yield) as a yellow solid; LCMS (ESI, M+1): m/z 251.9.

[0000275] Step B. 1-(2,4,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (3 g, 11.9 mmol) and DIEA (6.14 g, 47.5 mmol, 8.28 mL) in DCM (10 mL) was added 3-methylpiperidin-3-ol hydrochloride

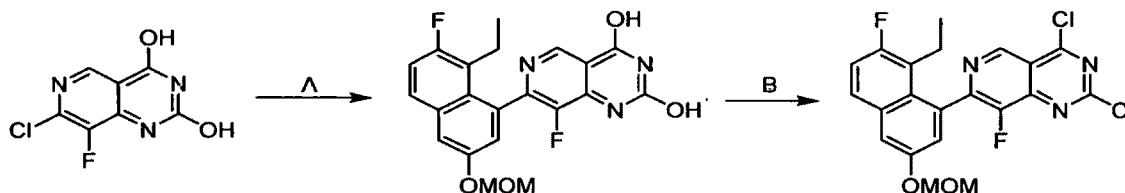
(1.52 g, 13.2 mmol) in portions at -40 °C under N₂. The mixture was stirred at -40 °C for 1 hour. After completion, the mixture was filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Silica gel, Petroleum ether/Ethyl acetate = 1/0, 0/1) affording 1-(2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (2.81 g, 71% yield) as a yellow solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.18 (s, 1H), 4.73 (s, 1H), 4.46 (d, *J* = 12.4 Hz, 1H), 4.12 (d, *J* = 13.2 Hz, 1H), 3.57 (d, *J* = 13.2 Hz, 1H), 3.31-3.21 (m, 1H), 2.03-1.89 (m, 1H), 1.73-1.60 (m, 3H), 1.16 (s, 3H); LCMS (ESI, M+1): *m/z* 331.0.

[0000276] Step C. 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of (hexahydro-1H-pyrrolizin-7a-yl)methanol (1.43 g, 10.1 mmol) and 1-(2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (2.8 g, 8.45 mmol) in dioxane (18 mL) were added DIEA (3.28 g, 25.4 mmol, 4.42 mL) and 4Å molecular sieves (1.5 g, 8.45 mmol) in one portion at 25 °C under N₂. The mixture was heated to 90 °C and stirred for 20 hours. After completion, the mixture was filtered and concentrated in vacuum. The crude product was purified by reversed phase flash chromatography (water (0.1% formic acid) - ACN) affording 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-methylpiperidin-3-ol (1.6 g, 41% yield) as a yellow solid; ¹H NMR (400 MHz, CDCl₃): δ 8.89 (s, 1H), 4.46-4.37 (m, 1H), 4.36-4.29 (m, 1H), 4.26-4.18 (m, 2H), 3.42-3.33 (m, 1H), 3.31-3.24 (m, 1H), 3.14-3.06 (m, 2H), 2.74-2.60 (m, 3H), 2.05-1.97 (m, 3H), 1.92-1.82 (m, 5H), 1.70-1.61 (m, 4H), 1.33 (s, 3H); LCMS (ESI, M+1): *m/z* 436.2.

Intermediate 14



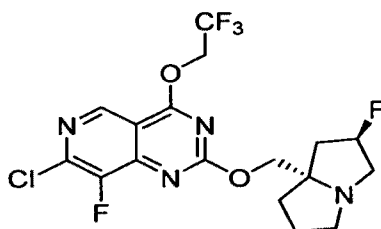
2,4-dichloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-*d*]pyrimidine



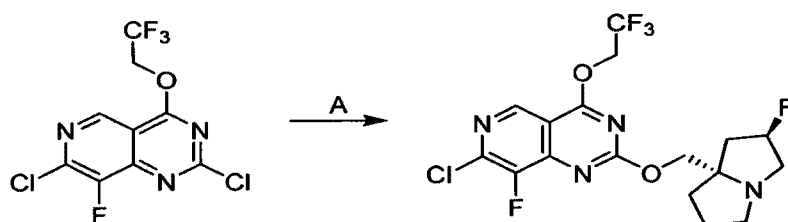
[0000277] Step A. 7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol: To a mixture of 7-chloro-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol, 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (14.0 g, 39.0 mmol) and K₃PO₄ (1.5 M, 46.4 mL) in EtOH (140 mL) was added cataCXium-A-Pd-G3 cataCXium-A-Pd-G3 (1.39 g, 1.90 mmol) under N₂. The mixture was degassed and heated to 78 °C for 9.5 hours under N₂. The reaction mixture was concentrated in vacuum. Then the mixture was diluted with ethyl acetate (500 mL) and filtered. The filtrate was diluted with water (100 mL). The organic phase was separated. The aqueous phase was extracted with ethyl acetate (80 mL). The combined organic layers were washed with brine (120 mL) and dried over with anhydrous Na₂SO₄. The mixture was filtered and concentrated in vacuum to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give 7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol (2.34 g, 24% yield) as a yellow solid. LCMS [ESI, M+H]: m/z 414.1.

[0000278] Step B. 2,4-dichloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine: A mixture of POCl₃ (278 mg, 1.81 mmol, 169 µL) in toluene (3 mL) were added DIEA (141 mg, 1.09 mmol, 190 µL) and 7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol (150 mg, 363 µmol). The reaction mixture was stirred at 110 °C for 25 minutes. After completion, the mixture was concentrated in vacuum and the pH value was adjusted to 8 with ice cold saturated NaHCO₃ solution. Then the mixture was extracted with ethyl acetate (8 mLX2). The combined organic layer was washed with brine (10 mL) and dried over Na₂SO₄. The mixture was filtered and concentrated in vacuum to give 2,4-dichloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine (164 mg, crude) as a brown oil, which was used in the next step without further purification.

Intermediate 15

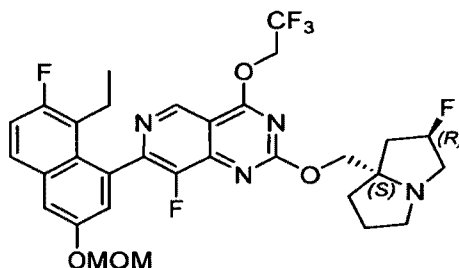


7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine

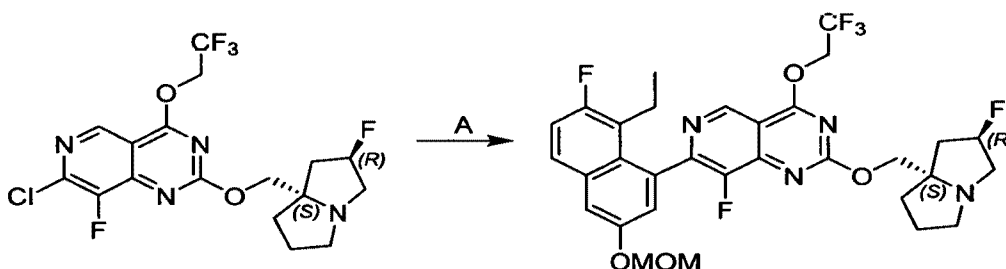


[0000279] Step A. 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a mixture of 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (33.3 g, 1.0 *equiv.*), DIEA (54.5 g, 4.0 *equiv.*) and 4Å molecular sieves (4.0 g) in THF (340 mL) was added ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (20.1 g, 1.2 *equiv.*). The reaction was stirred at 40 °C for 14 hours. The reaction mixture was diluted with water (20mL) and was extracted with EtOAc (3 × 20 mL), the combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to afford the title compound (28.8 g, 62% yield) as a yellow solid; ¹H NMR (400 MHz, chloroform-d) δ 8.98 (s, 1H), 5.40 - 5.19 (m, 1H), 5.02 (q, *J* = 8.0 Hz, 1H, 2H), 4.40 - 4.27 (m, 2H), 3.34 - 3.12 (m, 3H), 3.05 - 2.94 (m, 1H), 2.32 - 2.06 (m, 3H), 2.03 - 1.84 (m, 3H); LCMS [ESI, M+1]: 439.1.

Intermediate 16

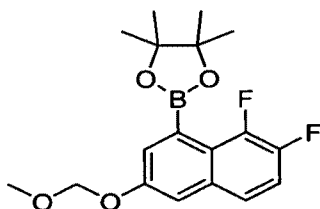


7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine

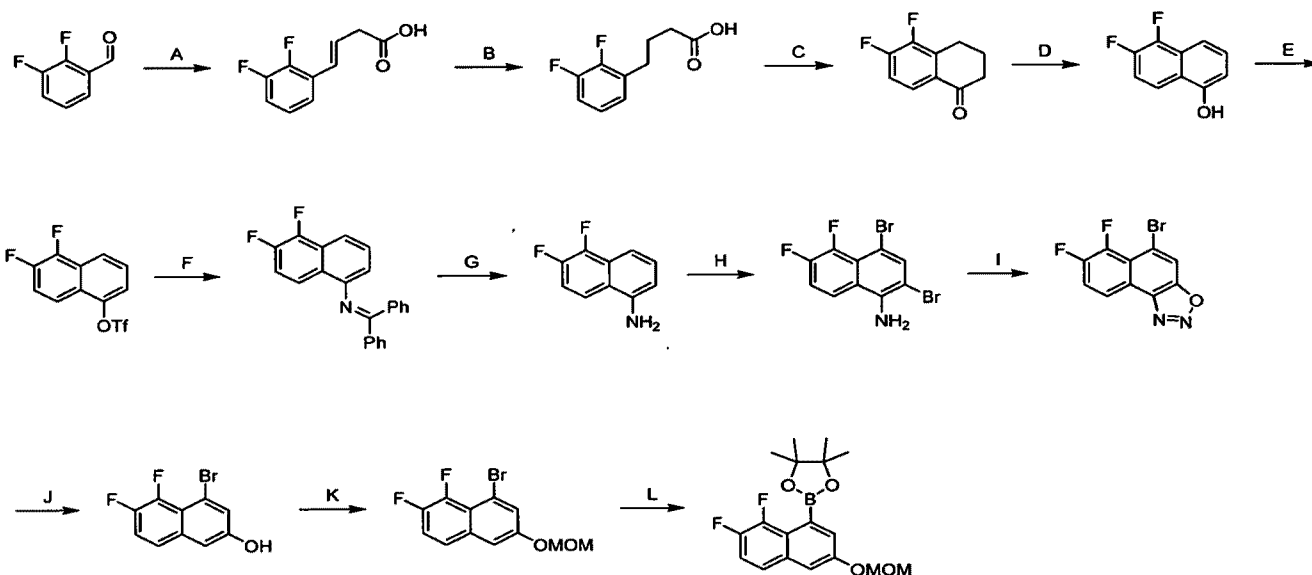


[0000280] Step A. 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a mixture of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (1.0 g, 1.0 equiv.), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.64 g, 2.0 equiv.) and Cs₂CO₃ (1.5 M, 3.0 equiv.) in methoxycyclopentane (15.0 mL) was added CataCXium A Pd G3 (332 mg, 0.20 equiv.). The reaction was stirred at 100 °C for 2 hours. The mixture was filtered. To the filtrate water (20 mL) was added and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated, and purified by reversed phase flash chromatography [C18, mobile phase: [water (0.1% formic acid)/acetonitrile]] to afford the title compound (820 mg, 56% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 637.3.

Intermediate 17



2-[7,8-difluoro-3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



[0000281] Step A. (E)-4-(2,3-difluorophenyl)but-3-enoic acid: To a solution of 2,3-difluorobenzaldehyde (100 g, 1.0 *equiv.*) and 2-carboxyethyl(triphenyl)phosphonium bromide (321 g, 1.1 *equiv.*) in THF (1 L) was added t-BuOK (1 M in THF, 1.41 L, 2.0 *equiv.*) at -70°C . The mixture was stirred at -70°C for 1 hour. Then the mixture was warmed up to 20°C and stirred for 1 hour. The reaction mixture was diluted with water (1 L) and concentrated under reduced pressure to remove the THF. Then the mixture was filtered and the filtrate was adjusted to pH ~ 2 with HCl (1M). The mixture was extracted with ethyl acetate (3×1000 mL). The combined organic layers were washed with brine (1000 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give the residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate 10:1 to 2:1) to afford the title compound (75 g, 50% yield) as a pink solid; ^1H NMR (400MHz, chloroform- d) δ = 11.50 (br s, 1H), 7.25 - 7.17 (m, 1H), 7.12 - 6.96 (m, 2H), 6.67 (d, J = 16.0 Hz, 1H), 6.42 (td, J = 7.2, 16.0 Hz, 1H), 3.36 (dd, J = 1.2, 7.2 Hz, 2H).

[0000282] Step B. 4-(2,3-difluorophenyl)butanoic acid: To a solution of (E)-4-(2,3-difluorophenyl)but-3-enoic acid (14 g, 1.0 *equiv.*) in EtOAc (500 mL) was added dry Pd/C (3 g, 10% purity) under N₂. The suspension was degassed and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 20°C for 1 hour. The reaction mixture was filtered and the filtrate was concentrated to afford the title compound (13.5 g, 95% yield) as a yellow solid and used to next step without purification.

[0000283] Step C. 5,6-difluoro-3,4-dihydronaphthalen-1(2H)-one: To a solution of 4-(2,3-difluorophenyl)butanoic acid (13.5 g, 1.0 *equiv.*) in DCM (300 mL) was added DMF (246 mg, 0.05 *equiv.*) and oxalyl chloride (17.1 g, 2.0 *equiv.*). The mixture was stirred at 20 °C for 0.5 hour. The mixture was concentrated under vacuum and then the residue was dissolved in DCM (300 mL). Then, to the mixture was added AlCl₃ (12.3 g, 1.5 *equiv.*). The reaction mixture was stirred at 40 °C for 1 hour before being quenched with water (200 mL) and extracted with DCM (3 × 300 mL). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 100:1 to 5:1) to afford the title compound (11 g, 98% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 183.2.

[0000284] Step D. 5,6-difluoronaphthalen-1-ol: To a solution of 5,6-difluoro-3,4-dihydronaphthalen-1(2H)-one (11 g, 1.0 *equiv.*) and HBr (1.48 g, 0.1 *equiv.*) in AcOH (240 mL) was added a solution of Br₂ (9.65 g, 1.0 *equiv.*) in AcOH (40 mL) at 0 °C. The mixture was stirred at 25 °C for 1 hour. Then the mixture was diluted with DCM (100 mL) and washed with water (3×100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to afford a brown oil which was dissolved in DMF (260 mL). LiBr (8.91 g, 102 mmol, 2.58 mL, 1.7 *equiv.*), Li₂CO₃ (7.59 g, 102 mmol, 1.7 *equiv.*) was added. The reaction mixture was stirred at 160° C for 1 hour. The reaction mixture was diluted with ethyl acetate (400 mL) and washed with water (3 × 300 mL). The organic layer was washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 50:1 to 10:1) to afford the title compound (10 g, 90% yield) as a yellow solid; ¹H NMR (400MHz, chloroform-d) δ = 8.06 - 7.88 (m, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.32 (dt, *J* = 7.6, 9.6 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 5.44 (s, 1H).

[0000285] Step E. 5,6-difluoronaphthalen-1-yl trifluoromethanesulfonate: To a solution of 5,6-difluoronaphthalen-1-ol (21 g, 1.0 *equiv.*) in DCM (200 mL) was added DIEA (37.6 g, 2.5 *equiv.*) and Tf₂O (42.7 g, 1.3 *equiv.*) at 0°C. The mixture was stirred at 20 °C for 1 hour. The reaction mixture was diluted with water (200 mL) and extracted with DCM (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 20: 1 to 5:1) to afford the title compound (30 g, 82% yield) as a colorless oil; ¹H NMR (400MHz, chloroform-d) δ = 8.14 (d, *J* = 8.4 Hz, 1H), 7.91 - 7.82 (m, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.57 - 7.46 (m, 2H).

[0000286] Step F. N-(diphenylmethylene)-5,6-difluoronaphthalen-1-amine: A mixture of 5,6-difluoronaphthalen-1-yl trifluoromethanesulfonate (30 g, 1.0 *equiv.*), diphenylmethanimine (52.2 g, 3.0 *equiv.*), Pd₂(dba)₃ (8.80 g, 0.1 *equiv.*), Xantphos (11.1 g, 0.2 *equiv.*) and Cs₂CO₃ (93.9 g, 3 *equiv.*) in toluene (500 mL) was degassed and stirred at 90 °C for 12 hours under N₂ atmosphere. The reaction mixture was diluted with water (300 mL) and extracted with ethyl acetate (3 × 400 mL). The combined organic layers were washed with brine (300 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 100:1 to 5:1) to afford title compound (40 g, 92% yield) as a yellow solid; LCMS (ESI, M+1): *m/z* = 344.0.

[0000287] Step G. 5,6-difluoronaphthalen-1-amine: A solution of N-(5,6-difluoronaphthalen-1-yl)-1,1-diphenylmethanimine (40 g, 116 mmol, 1.0 *equiv.*) in HCl•MeOH (4 M, 300 mL, 10.3 *equiv.*) was stirred at 10 °C for 0.5 hour. The mixture was concentrated under vacuum. The pH of the residue was adjusted to ~ 8 with saturated aqueous NaHCO₃ solution and extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 20:1 to 3:1) to afford the title compound (14 g, 66% yield) as a yellow solid; ¹H NMR (400MHz, chloroform-d) δ = 7.61 - 7.51 (m, 2H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.33 - 7.27 (m, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 4.31 - 4.13 (S, 2H); LCMS (ESI, M+1): *m/z* = 180.2.

[0000288] Step H. 2,4-dibromo-5,6-difluoronaphthalen-1-amine: To a solution of 5,6-difluoronaphthalen-1-amine (10 g, 1.0 *equiv.*) in AcOH (200 mL) was added a solution of Br₂

(19.4 g, 2.18 *equiv.*) in AcOH (100 mL) at 0 °C. The mixture was stirred at 70 °C for 1 hour. The reaction mixture was filtered and the filter cake was washed with AcOH (200 mL). Then the residue was diluted with 15% aqueous of NaOH (100 mL). The mixture was stirred for 20 minutes and filtered. The solid was washed with water (200 mL) and dried under vacuum to afford the title compound (16 g, 85% yield) as a yellow solid. LCMS (ESI, M+1): m/z = 337.9.

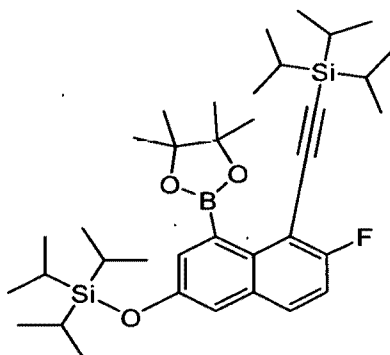
[0000289] Step I. 5-bromo-6,7-difluoronaphtho[1,2-d][1,2,3]oxadiazole: 2,4-dibromo-5,6-difluoronaphthalen-1-amine (16 g, 47.5 mmol, 1.0 *equiv.*) was dissolved in AcOH (280 g, 98.2 *equiv.*) and propionic acid (26.5 g, 7.53 *equiv.*) and cooled to 0 °C. Then NaNO₂ (4.91 g, 1.5 *equiv.*) was added and the mixture was stirred at 20 °C for 1 hour. The reaction mixture was filtered and the filter cake was washed with water (300 mL) to afford the title compound (11.3 g, 83% yield) as a yellow solid and used to next step without purification; ¹H NMR (400MHz, chloroform-d) δ = 7.51 - 7.40 (m, 1H), 7.24 (s, 1H), 7.08 - 6.99 (m, 1H).

[0000290] Step J. 4-bromo-5,6-difluoronaphthalen-2-ol: To a suspension of 5-bromo-6,7-difluoronaphtho[1,2-d][1,2,3]oxadiazole (11.3 g, 1.0 *equiv.*) in EtOH (150 mL) and THF (50 mL) at 0 °C was added NaBH₄ (3.49 g, 2.33 *equiv.*). Bubbles evolved immediately. The mixture was stirred at 0 °C for 0.5 hour. The mixture was quenched with water (50 mL) and concentrated under vacuum to remove EtOH. The mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 20:1 to 3:1) to afford the title compound (6.3 g, 59% yield) as a black solid; LCMS (ESI, M-1): m/z = 257.1.

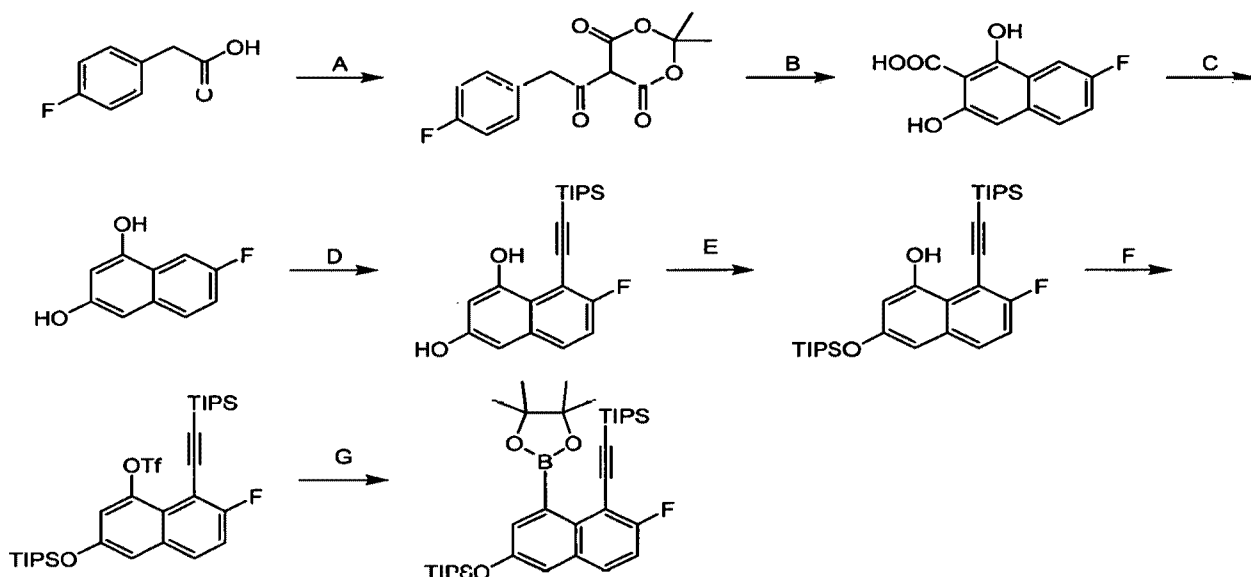
[0000291] Step K. 8-bromo-1,2-difluoro-6-(methoxymethoxy)naphthalene: To a solution of 4-bromo-5,6-difluoronaphthalen-2-ol (6.3 g, 1.0 *equiv.*) in DCM (120 mL) was added DIEA (7.86 g, 2.5 *equiv.*) and MOMCl (3.44 g, 1.76 *equiv.*). The mixture was stirred at 0 °C for 0.5 hour. The reaction mixture was diluted with water (50 mL) and extracted with DCM (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 20:1 to 5:1) to afford the title compound (5.5 g, 75% yield) as a yellow solid; ¹H NMR (400MHz, chloroform-d) δ = 7.61 (d, J = 2.4 Hz, 1H), 7.52 - 7.46 (m, 1H), 7.39 - 7.30 (m, 2H), 5.27 (s, 2H), 3.52 (s, 3H).

[0000292] Step L. 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: A mixture of 8-bromo-1,2-difluoro-6-(methoxymethoxy)naphthalene (3 g, 1.0 *equiv.*), Pin₂B₂ (6.28 g, 2.5 *equiv.*), KOAc (2.91 g, 3.0 *equiv.*), Pd(dppf)Cl₂ (724 mg, 0.1 *equiv.*) in dioxane (60 mL) was degassed and stirred at 110 °C for 1 hour under N₂ atmosphere. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 50:1 to 5:1) to afford the title compound (2 g, 58% yield) as a white solid; ¹H NMR (400MHz, chloroform-d) δ = 7.49 - 7.44 (m, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 7.41 - 7.39 (m, 1H), 7.33 - 7.27 (m, 1H), 5.29 (s, 2H), 3.51 (s, 3H), 1.45 (s, 12H).

Intermediate 18



((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane



[0000293] Step A. 5-(2-(4-fluorophenyl)acetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione: To a mixture of 2-(4-fluorophenyl)acetic acid (250 g, 1 *equiv.*) and 2,2-dimethyl-1,3-dioxane-4,6-dione (257 g, 1.1 *equiv.*) in ACN (1.25 L) was added DMAP (16.9 g, 0.09 *equiv.*) at 15 °C. DIPEA (451 g, 2.1 *equiv.*) was added dropwise below 30 °C for 1 hour. Pivaloyl chloride (215 g, 1.1 *equiv.*) was added dropwise below 40 °C for 1 hour. The mixture was stirred at 45 °C for 3 hours. The mixture was cooled to 0 °C. 4 N aqueous HCl (5.0 L) was added dropwise to adjust pH to 5 while maintaining the temperature between below 15 °C. The mixture was stirred at 0 °C for 1 hour. The mixture was diluted with H₂O (15 L) and the pH of the mixture was adjusted to 2 with 4N HCl. The mixture was filtered. The filter cake was washed with H₂O until the pH of filter cake was 5 ~ 6. The solid was dried under reduced pressure to afford the tittle compound (500 g, crude) as a white solid; ¹H NMR (400 MHz, chloroform-d) δ = 7.36 (dd, *J* = 5.6, 8.4 Hz, 2H), 7.01 (t, *J* = 8.4 Hz, 2H), 4.38 (s, 2H), 1.72 (s, 6H).

[0000294] Step B. 7-fluoro-1,3-dihydroxy-2-naphthoic acid: 5-(2-(4-fluorophenyl)acetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (490 g, 1 *equiv.*, crude) was added into CF₃SO₃H (2.04 kg, 7.8 *equiv.*) portion wise maintaining the temperature below 30 °C. The mixture was stirred at 20 °C for 2 hour. The mixture was poured into ice water (30 L) slowly. The mixture was filtered. The filter cake was washed with water until the pH of the filtrate was 3~4 to afford the tittle compound (500 g, crude, wet) as a brown solid.

[0000295] Step C. 7-fluoronaphthalene-1,3-diol: A mixture of 7-fluoro-1,3-dihydroxy-2-naphthoic acid (375 g, crude, wet) in H₂O (1.8 L) and ACN (1.8 L) was stirred at 78 °C for 13 hours. The mixture was concentrated to remove ACN. The mixture was diluted with H₂O (1 L) and saturated NaHCO₃ aqueous (0.3 L), and then extracted with ethyl acetate (4 × 0.5 L). The combined organic layers were washed with saturated aqueous NaHCO₃ (0.5 L), water (0.5 L) and brine (0.5 L), dried over anhydrous Na₂SO₄ and concentrated. The residue was treated with n-heptanes (0.8 L) for 1 hour. The mixture filtered and the solid was dried under reduced pressure to afford the tittle compound (145 g, 60% yield over three steps) as light a red solid; ¹H NMR (400 MHz, DMSO-d₆) δ = 10.18 (s, 1H), 9.48 (s, 1H), 7.65-7.56 (m, 2H), 7.23 (dt, *J* = 2.8, 8.8 Hz, 1H), 6.64 (d, *J* = 1.6 Hz, 1H), 6.56 (d, *J* = 1.6 Hz, 1H).

[0000296] Step D. 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol: A mixture of 7-fluoronaphthalene-1,3-diol (173 g, 1 *equiv.*), (bromoethynyl)triisopropylsilane (266 g, 1.05 *equiv.*), AcOK (191 g, 2 *equiv.*) and dichloro(p-cymene)ruthenium(II) dimer (17.8 g, 0.03 *equiv.*) in dioxane (1.5 L) was degassed and stirred at 100 °C for 3.5 hours. The reaction mixture was filtered through a pad of Celite. The filter cake was washed with ethyl acetate (4 × 500 mL). The filtrate was concentrated under reduced pressure to give a residue. The residue was dissolved in ethyl acetate (3 L). The solution was washed with saturated NaHCO₃ aqueous (0.5 L) and brine (0.2 L), dried over anhydrous Na₂SO₄, and concentrated to give a residue. The residue was purified by column chromatography [SiO₂, petroleum ether/ethyl acetate 15:1 to 10:1] to afford a crude product. The crude product was dispersed in n-heptanes (0.5 L) and stirred for 1 hour. The mixture was filtered and the filter cake was washed with n-heptanes (0.5 L). The solid was dried under reduced pressure to afford the tittle compound (204 g, 56% yield) as a light yellow solid; ¹H NMR (400 MHz, DMSO-d₆) δ = 10.04 (s, 1H), 9.58 (s, 1H), 7.63 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 6.58 (d, *J* = 2.0 Hz, 1H), 1.13 (s, 21H).

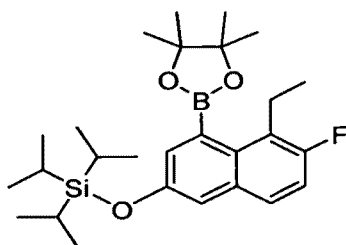
[0000297] Step E. 7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-ol: To a solution of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol (197 g, 1 *equiv.*) and DIPEA (142 g, 2.0 *equiv.*) in DCM (1 L) was added TIPSCI (122 g, 1.2 *equiv.*) dropwise between 0 and 10 °C for 1 hour. The mixture was stirred 25 °C for 1 hour. The mixture was poured H₂O (2 L). The DCM phase was separated and washed with brine (3 × 1 L). The DCM phase was dried over anhydrous Na₂SO₄

and filtered to afford the tittle compound (282 g, in DCM) as a red liquid, which was used in next step directly.

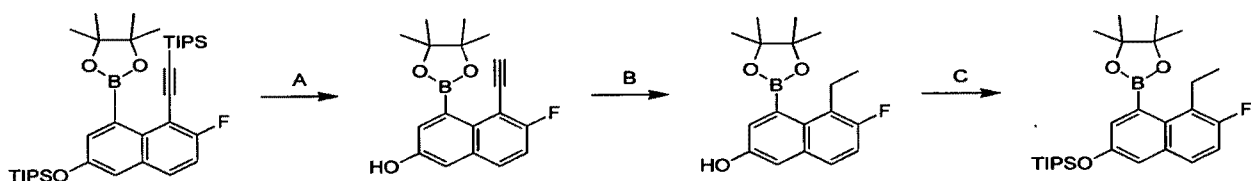
[0000298] Step F. 7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yltrifluoromethanesulfonate: To a solution of 7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-ol (282 g, 1 *equiv.*) and DIPEA (248 g, 3.5 *equiv.*) in DCM (1.7 L) was added Tf₂O (263 g, 1.7 *equiv.*) dropwise at -40 °C for 3 hours. The mixture was stirred at -40 °C for 0.5 hour. The mixture was poured into water (1 L). The DCM layer was separated and washed with water (3 × 3 L), 0.001N HCl (3 × 2 L), H₂O (1.5 L), brine (2 × 1 L), dried over anhydrous Na₂SO₄ and concentrated to give a residue. The residue was purified by column chromatography [SiO₂, petroleum ether] to afford the tittle compound (321 g, crude) as a light red oil; ¹H NMR (400 MHz, chloroform-d) δ = 7.67 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.34-7.25 (m, 3H), 1.34-1.14 (m, 42H); ¹⁹F NMR (376 MHz, chloroform-d) δ = -79, -105.

[0000299] Step G. ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane: A mixture of 7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yltrifluoromethanesulfonate (229 g, 1 *equiv.*), TEA (144 g, 4.0 *equiv.*), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (182 g, 4.0 *equiv.*) and Pd(dppf)Cl₂ (16 g, 0.06 *equiv.*) in MeCN (1.5 L) was degassed stirred at 78 °C for 4 hours under N₂ atmosphere. The mixture was slowly quenched with of MeOH (0.5 L) maintaining the temperature below 25 °C producing a precipitate. The mixture was filtered and the filter cake was washed with MeOH (1 L). The solid was dispersed in MeOH (0.5 L) and stirred for 0.5 hour. The mixture was filtered. The solid was dried under reduced pressure to afford the tittle compound (170 g, 69% yield over three steps, crude) as a white solid; ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.60 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.22-7.17 (m, 2H), 1.43 (s, 12H), 1.32-1.12 (m, 42H); LCMS (ESI, M+1): *m/z* = 625.6.

Intermediate 19



((5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)triisopropylsilane



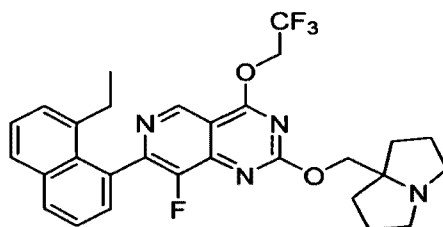
[0000300] Step A. 5-ethynyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol: To a solution of ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane (1.50 kg, 1.0 *equiv.*) in DMSO (15.0 L) was added CsF (2.19 kg, 6.0 *equiv.*) in one portion at 25 °C under N₂. The reaction mixture was stirred at 25 °C for 12 hrs. The mixture was diluted with EtOAc (5.00 L) and water (20.0 L) and the layers were separated. The aqueous phase was extracted with EtOAc (5.00 L × 3). The combined organic phase was washed with brine (5.00 L × 5), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude product was triturated with n-heptanes (4.5 L) at 50 °C for 6 hrs. The mixture was cooled to room temperature and filtered to afford the title compound (600 g, 1.86 mol, 80.1% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.48-7.46 (m, 1H), 7.30-7.29 (d, J=2.4, 1H), 7.12-7.08 (m, 1H), 7.00-6.98 (m, 1H), 5.56 (s, 1H), 3.61 (s, 1H), 1.37 (s, 12H).

[0000301] Step B. 5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol: To a solution of 5-ethynyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (40.0 g, 1.00 *equiv.*) in THF (400 mL) was added Pd/C (4.00 g, 10.0% purity). The mixture was purged with H₂ three times and stirred at 25 °C under H₂ (15 Psi) for 5 hrs. The mixture was filtered through a diatomite powder pad and washed with THF

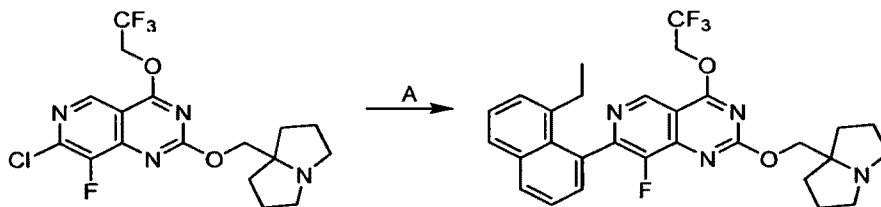
(200 mL $\times$ 2), the filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether/EtOAc 50:1 to 3:1) to afford the title compound (74.0 g, 88.5% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ 7.57-7.55 (m, 1H), 7.41-7.37 (m, 1H), 7.23-7.18 (m, 2H), 5.28 (s, 1H), 3.15-3.12 (m, 2H), 1.45 (s, 12H), 1.29-1.26 (m, 3H).

[0000302] Step C. ((5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)triisopropylsilane: To a solution of 5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (73.0 g, 1.0 equiv.) in DMF (750 mL) was added imidazole (47.2 g, 3.0 equiv.) and TIPSCl (89.0 g, 2.0 equiv.). The mixture was stirred at 25 °C for 12 hours. The mixture was diluted with H_2O (500 mL) and extracted with MTBE (3 $\times$ 300 mL). The combined organic phase was washed with brine (3 $\times$ 300 mL), dried over anhydrous Na_2SO_4 , concentrated and purified by silica gel chromatography [petroleum ether/ethyl acetate 100:1 to 20:1] to afford the title compound (102 g, 94% yield) as a yellow solid; ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.43-7.40 (m, 1H), 7.22-7.21 (m, 1H), 7.13-7.09 (m, 2H), 3.07-3.01 (m, 2H), 1.36 (s, 12H), 1.23-1.18 (m, 6H), 1.06-0.97 (m, 18H).

Intermediate 20



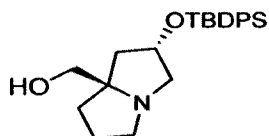
7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine



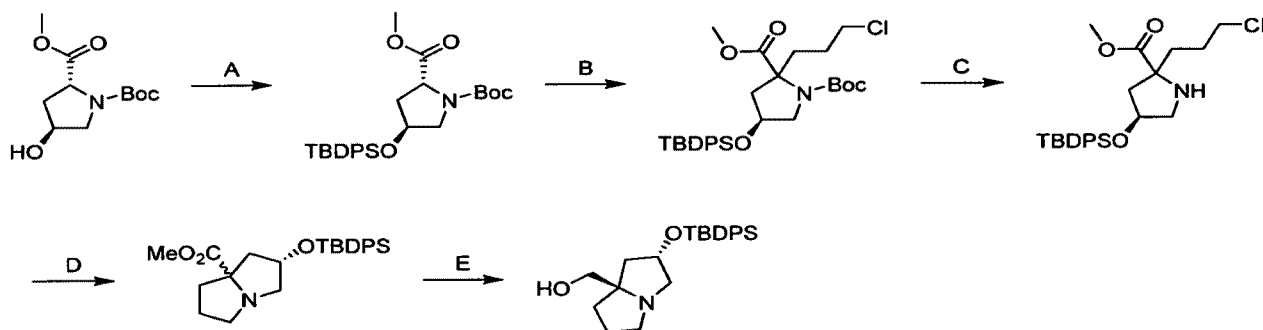
[0000303] Step A. 7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: A mixture of 7-chloro-8-fluoro-2-

((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (200 mg, 1.00 *equiv.*), 2-(8-ethyl-1-naphthyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (201 mg, 1.50 *equiv.*), CataCXium A Pd G3 (34.6 mg, 0.10 *equiv.*), K₃PO₄ (1.5 M, 3.0 *equiv.*) in THF (2 mL) was degassed and stirred at 60 °C for 12 hours under N₂ atmosphere. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (15 mL × 3). The combined organic layers were washed with brine (5 mL × 2), dried over Na₂SO₄, concentrated and purified by reversed-phase HPLC [column: Phenomenex Luna C18 150 × 25mm × 10um; mobile phase: [water (0.225% formic acid)-ACN]; B%: 25%-55%, 10min] to afford the title compound (20.0 mg, 7.8% yield) as an off-white solid; LCMS (ESI, M+1): m/z = 541.3.

Intermediate 21



((2S,7aR)-2-((tert-butyldiphenylsilyl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol



[0000304] Step A: ((2R,4S)-1-tert-butyl 2-methyl 4-((tert-butyldiphenylsilyl)oxy)pyrrolidine-1,2-dicarboxylate: To a solution of (2R,4S)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (20.0 g, 1.0 *equiv.*) and imidazole (11.1 g, 2.0 *equiv.*) in DCM (200 mL) was added TBDPSCl (33.6 g, 31.4 mL, 1.50 *equiv.*). The mixture was stirred at 25 °C for 1 hour. After reaction completion, the reaction mixture was added water (150 mL), separated, the aqueous layer was extracted with EtOAc (2 × 100 mL), the combined organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (SiO₂,

petroleum ether / ethyl acetate 100:1-30:1) to afford the title compound (39 g, 93 % yield) as a white solid; LCMS (ESI, M-100): m/z = 384.3.

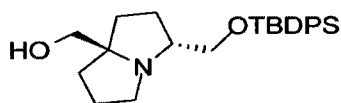
[0000305] Step B. (4S)-1-tert-butyl 2-methyl 4-((tert-butyldiphenylsilyl)oxy)-2-(3-chloropropyl)pyrrolidine-1,2-dicarboxylate: To a solution of (2R,4S)-1-tert-butyl 2-methyl 4-((tert-butyldiphenylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (37.0 g, 1.0 *equiv.*) in THF (400 mL) was added LDA (2 M, 49.7 mL, 1.30 *equiv.*) at -70 °C slowly. The mixture was stirred at -70 °C for 1 hour. To the mixture was added 1-bromo-3-chloro-propane (60.2 g, 37.6 mL, 5.0 *equiv.*) at -70 °C. The mixture was stirred at -70 - 20 °C for 12 hours. Upon completion, the reaction mixture was diluted with water (300 mL), separated, the aqueous layer was extracted with EtOAc (2 × 100 mL), the combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was purified by reversed phase flash chromatography (C18, 0.1 % formic acid condition) and column chromatography (SiO₂, petroleum ether / ethyl acetate 100:1 - 20:1) to afford the title compound (8.70 g, 20% yield) as a colorless oil; LCMS (ESI, M-55, M-100): 504.3, 461.2.

[0000306] Step C. (4S)-methyl 4-((tert-butyldiphenylsilyl)oxy)-2-(3-chloropropyl)pyrrolidine-2-carboxylate: To a solution of (4S)-1-tert-butyl 2-methyl 4-((tert-butyldiphenylsilyl)oxy)-2-(3-chloropropyl)pyrrolidine-1,2-dicarboxylate (8.60 g, 1.0 *equiv.*) in MeCN (40 mL) was added HCl·dioxane (4 M, 40 mL, 10.4 *equiv.*). The mixture was stirred at 20 °C for 0.5 hour. Upon completion, the reaction mixture was concentrated to afford the title compound (7.8 g, crude, HCl salt) as a yellow solid.

[0000307] Step D. (2S)-methyl 2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizine-7a-carboxylate (90122-E): To a solution of (4S)-methyl 4-((tert-butyldiphenylsilyl)oxy)-2-(3-chloropropyl)pyrrolidine-2-carboxylate (7.80 g, 1.0 *equiv.*, HCl) in ACN (80 mL) was added NaHCO₃ (7.12 g, 3.30 mL) and KI (281 mg). The mixture was stirred at 50 °C for 12 hours. Upon completion, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (2 × 50 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 250*80mm*10 um; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 75%-100%, 20min) to afford the title compound (1.3 g, two steps 18% yield) as a colorless oil.

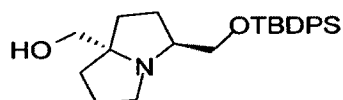
[0000308] Step E. ((2S,7aR)-2-((tert-butyldiphenylsilyl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol: To a solution of (2S)-methyl 2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizine-7a-carboxylate (1.30 g, 1.0 *equiv.*) in THF (15 mL) was added LiAlH₄ (349 mg, 3.0 *equiv.*) at -40 °C. The mixture was stirred at -40 °C for 1 hour. Upon completion, the reaction mixture was quenched with saturated aqueous Na₂SO₄ solution (1 mL), filtered and concentrated to afford the title compound (1.1 g, 91% yield) as a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.70-7.60 (m, 4H), 7.48-7.35 (m, 6H), 4.49-4.30 (m, 1H), 3.12 (d, *J* = 2.4 Hz, 2H), 3.06-2.98 (m, 2H), 2.95 (dd, *J* = 4.8, 11.2 Hz, 1H), 2.73 (dd, *J* = 4.4, 11.2 Hz, 1H), 2.07-1.89 (m, 3H), 1.81-1.65 (m, 3H), 1.06 (s, 9H); LCMS (ESI, M+1): *m/z* = 396.7.

Intermediate 22



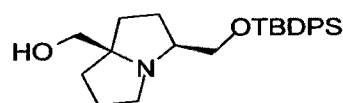
((3R,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol

Intermediate 23



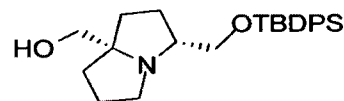
((3S,7aS)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol

Intermediate 24

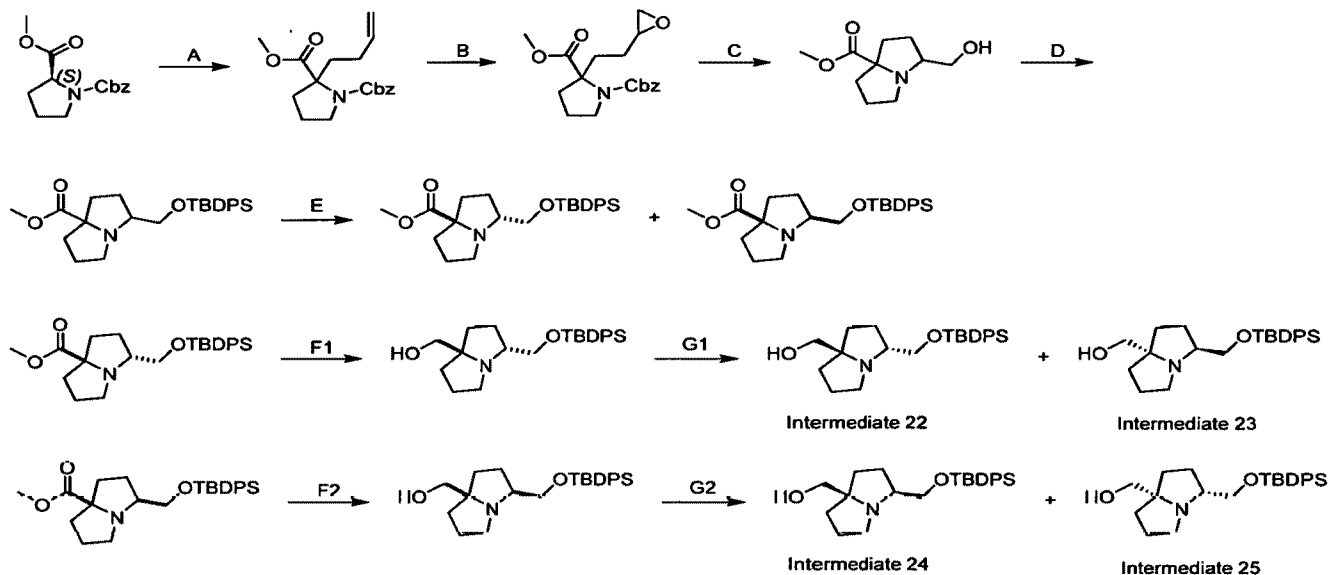


((3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol

Intermediate 25



((3R,7aS)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol



[0000309] Step A. benzyl 2-methyl 2-(but-3-en-1-yl)pyrrolidine-1,2-dicarboxylate: To a solution of 1-benzyl 2-methyl (S)-pyrrolidine-1,2-dicarboxylate (220 g, 1 *equiv.*) in THF (2.2 L) was added LiHMDS (1 M, 1.00 L, 1.2 *equiv.*) at -65°C. The mixture was stirred at -65°C for 1 hour. Then 4-bromobut-1-ene (225.61 g, 2 *equiv.*) was added to the mixture at -65°C. The mixture was stirred at 25 °C for 12 hours. The mixture was quenched with saturated aqueous NH₄Cl (500 mL) and extracted with ethyl acetate (3 × 500 mL). The combined organic layer was dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to dryness. The residue was purified by column chromatography [SiO₂, petroleum ether/ethyl acetate 10:1 to 5:1] to afford the title compound (220 g, 74.6% yield) as a yellow oil; ¹H NMR (400 MHz, chloroform-d) δ = 7.25 (s, 5H), 5.88-5.63 (m, 1H), 5.17-5.05 (m, 2H), 5.04-4.88 (m, 2H), 3.83-3.62 (m, 3H), 3.54-3.42 (m, 2H), 2.48 -2.17 (m, 1H), 2.15-2.03 (m, 3H), 2.02-1.77 (m, 4H); LCMS[ESI, M+1]: m/z = 318.2.

[0000310] Step B. benzyl 2-methyl 2-(2-(oxiran-2-yl)ethyl)pyrrolidine-1,2-dicarboxylate: To a solution of benzyl 2-methyl 2-(but-3-en-1-yl)pyrrolidine-1,2-dicarboxylate (242 g, 1 *equiv.*) in DCM (2.40 L) was added m-CPBA (309 g, 85% purity, 2 *equiv.*) in portions at 0 °C. The mixture was stirred at 25°C for 5 hours. The mixture was quenched by addition of saturated aqueous Na₂SO₃ solution (500 mL), extracted with dichloromethane (3 × 500 mL). The combined organic

layers were washed with saturated brine (2 × 200 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography [SiO₂, petroleum ether/ethyl acetate 10:1 to 5:1] to afford the title compound (200 g, 62.9% yield) as a yellow oil. ¹H NMR (400 MHz, chloroform-d) δ = 7.43-7.10 (m, 5H), 5.20-4.93 (m, 2H), 3.78-3.56 (m, 3H), 3.48-3.34 (m, 2H), 2.89-2.53 (m, 2H), 2.46-2.10 (m, 2H), 2.06-1.97 (m, 3H), 1.91-1.71 (m, 2H), 1.59-1.31 (m, 2H); LCMS[ESI, M+1]: m/z = 334.1.

[0000311] Step C. methyl 3-(hydroxymethyl)hexahydro-1H-pyrrolizine-7a-carboxylate: To a suspension of Pd/C (16.0 g, 10% purity) in MeOH (1.0 L) was added benzyl 2-methyl 2-(2-(oxiran-2-yl)ethyl)pyrrolidine-1,2-dicarboxylate (130 g, 1 equiv.) under N₂ atmosphere. The suspension was degassed under vacuum and purged with H₂ (50 psi) several times. The mixture was stirred at 25 °C under H₂ (50 psi) for 1 hour. The mixture was filtered and the filtrate was concentrated to afford the title compound (75 g, 96.5% yield) as a yellow oil; ¹H NMR (400 MHz, chloroform-d) δ (ppm) = 3.88 - 3.73 (m, 1H), 3.73 - 3.66 (m, 1H), 3.61 - 3.54 (m, 1H), 3.42 - 3.35 (m, 1H), 3.09 - 3.03 (m, 1H), 2.99 - 2.88 (m, 1H), 2.74 - 2.65 (m, 1H), 2.55 - 2.48 (m, 1H), 2.31 (td, *J* = 4.7, 12.4 Hz, 1H), 2.14 (br d, *J* = 1.6 Hz, 1H), 1.89 - 1.74 (m, 5H), 1.73 - 1.45 (m, 2H).

[0000312] Steps D and E. methyl 3-(((tert-butyl)diphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizine-7a-carboxylate: To a solution of methyl 3-(hydroxymethyl)-1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate (165 g, 1 equiv.) and imidazole (169 g, 3 equiv.), DMAP (10.1 g, 0.1 equiv.) in DCM (1.4 L) was added TBDPSCl (296 g, 1.3 equiv.) drop-wise at 0°C. The mixture was stirred at 25°C for 2 hours. The reaction mixture was washed with H₂O (2 × 500 mL), the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduce pressure to give a residue. The residue was purified by column chromatography (SiO₂, 0.1%NH₃H₂O, Petroleum ether/Ethyl acetate 20:1 to 1:1) to afford peak 1 (330 g, crude), lower polarity, as a yellow oil and peak 2 (166 g, 44.9% yield), higher polarity as a yellow oil; Peak 1: LCMS[ESI, M+1]: m/z = 438.3; Peak 2 LCMS[ESI, M+1]: m/z = 438.3.

[0000313] Step F1: rac-((3R,7aR)-3-(((tert-butyl)diphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol: To a mixture of rac-(3R,7aR)-methyl 3-(((tert-butyl)diphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizine-7a-carboxylate (160 g, 70% purity, 1 equiv.) in THF (2 L) was added LiAlH₄ (12.63 g, 1.3 equiv.) portion wise at -40°C. The mixture

was stirred at -40°C for 3 hours. The reaction mixture was quenched with H₂O (13 mL), 15% aqueous NaOH (13 mL), H₂O (39 mL), dried over anhydrous Na₂SO₄ at 0°C, filtered and concentrated. The residue was purified by reversed phase flash chromatography (C18, water (0.1% formic acid)-ACN) to afford the title compound (85 g, 64.87% yield) as a yellow oil. LCMS [ESI, M+1]: m/z = 410.2.

[0000314] Step G1. ((3R,7aR)-3-(((tert-butyl)diphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol and ((3S,7aS)-3-(((tert-butyl)diphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol: The stereoisomers of rac-((3R,7aR)-3-(((tert-butyl)diphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol (175 g) were separated by SFC (column: Phenomenex-Cellulose-2 (250mm × 50mm, 10um); mobile phase: [0.1%NH₃-H₂O IPA]; B%: 40%-40%, 4.9min) to afford title compounds ((3R,7aR)-3-(((tert-butyl)diphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol (54 g, 40% yield) as a yellow oil ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.71 (br t, *J* = 7.4 Hz, 4H), 7.47 - 7.34 (m, 6H), 3.77 - 3.57 (m, 2H), 3.35 - 3.21 (m, 2H), 3.01 - 2.78 (m, 3H), 1.98 - 1.84 (m, 2H), 1.83 - 1.64 (m, 4H), 1.64 - 1.51 (m, 3H), 1.13 - 1.01 (m, 10H), -0.89 - -0.90 (m, 1H); LCMS (ESI, M+1): m/z = 410.3; SFC: 100% ee.

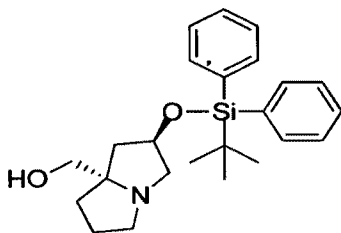
[0000315] and ((3S,7aS)-3-(((tert-butyl)diphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol (62 g, 48% yield) as a yellow oil. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.77 - 7.64 (m, 4H), 7.48 - 7.35 (m, 6H), 3.96 - 3.62 (m, 1H), 3.57 - 3.30 (m, 2H), 3.18 - 2.85 (m, 3H), 2.01 - 1.90 (m, 2H), 1.89 - 1.70 (m, 4H), 1.69 - 1.56 (m, 2H), 1.11 - 1.03 (m, 10H); LCMS (ESI, M+1): m/z = 410.3; SFC: 99.3% ee.

[0000316] Step F2: rac-((3S,7aR)-3-(((tert-butyl)diphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol: To a solution of methyl 3-[[tert-butyl(diphenyl)silyl]oxymethyl]-1,2,3,5,6,7-hexahydropyrrolizine-8-carboxylate (83.0 g, 1 *equiv.*) in THF (830 mL) was added LAH (8.05 g, 1.3 *equiv.*) portion wise at -40°C. The mixture was stirred at -40°C for 2 hours. The reaction mixture was quenched with H₂O (8.00 mL), NaOH (15%, 8.00 mL) and H₂O (24.0 mL), dried over anhydrous Na₂SO₄, filtered and concentrated to afford the title compound (72.0 g, crude) as yellow oil. LCMS [ESI, M+1]: m/z = 410.2.

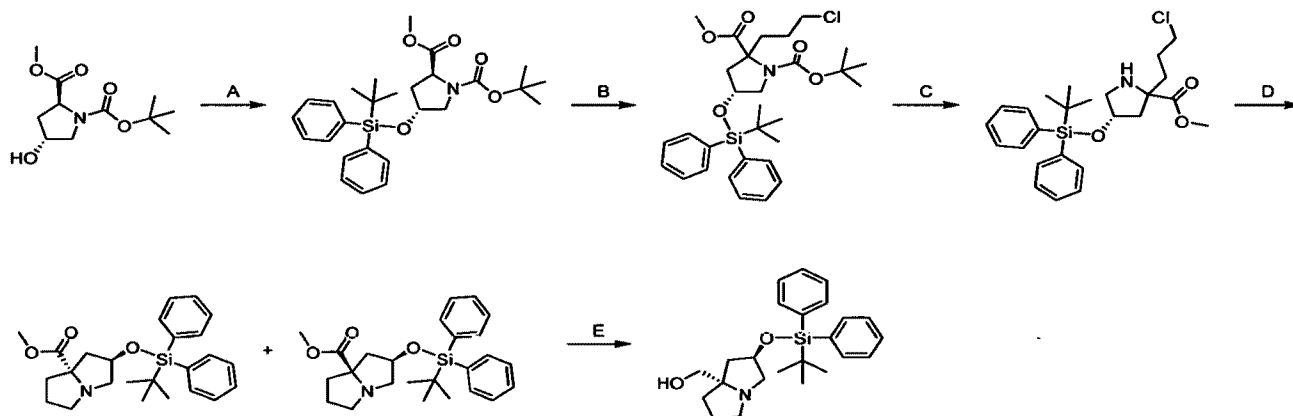
[0000317] Step G2: ((3S,7aR)-3-(((tert-butylidiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol and ((3R,7aS)-3-(((tert-butylidiphenylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol: The stereoisomers of rac-((3S,7aR)-3-(((tert-butylidiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol (110g) were separated by SFC (column: REGIS (s,s) WHELK-O1 (250 mm × 50 mm, 10 μm); mobile phase: [0.1%NH₃-H₂O ETOH];B%: 40%-40%, 3.7min) to afford title compounds ((3S,7aR)-3-(((tert-butylidiphenylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a (5H)-yl)methanol (45 g, 40% yield) as yellow oil ¹H NMR (400 MHz, chloroform-d) δ = 7.77- 7.63 (m, 4H), 7.52-7.31 (m, 6H), 3.96-3.86 (m, 1H), 3.82-3.68 (m, 1H), 3.33-3.22 (m, 2H), 3.22-3.13 (m, 1H), 2.86-2.79 (m, 1H), 2.76-2.64 (m, 1H), 2.00-1.92 (m, 1H), 1.82-1.48 (m, 7H), 1.31-1.21 (m, 1H), 1.07 (s, 9H) LCMS[ESI, M+1]: m/z = 410.3.

[0000318] and ((3R,7aS)-3-(((tert-butylidiphenylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (90466-H2B) (45 g, 40% yield) as a yellow oil. ¹H NMR (400 MHz, chloroform-d) δ = 7.75-7.64 (m, 4H), 7.35 (br s, 6H), 3.96-3.88 (m, 1H), 3.78-3.72 (m, 1H), 3.35-3.23 (m, 2H), 3.22-3.13 (m, 1H), 2.87-2.79 (m, 1H), 2.74-2.65 (m, 1H), 2.00-1.92 (m, 1H), 1.83-1.63 (m, 4H), 1.63-1.43 (m, 3H), 1.28-1.23 (m, 1H), 1.10-1.04 (m, 9H); LCMS[ESI, M+1]: m/z = 410.3.

Intermediate 26



((2R,7aS)-2-(((tert-butylidiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol



[0000319] Step A. (2S,4R)-1-tert-butyl 2-methyl 4-(((tert-butyldiphenylsilyl)oxy)pyrrolidine-1,2-dicarboxylate: To a solution of (2S,4R)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (20.0 g, 1.0 equiv.) in DCM (250 mL) was added imidazole (11.1 g, 2.0 equiv.) and TBDPSCl (26.9 g, 1.20 equiv.) at 0 °C. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was diluted with H₂O (100 mL) and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by column chromatography [SiO₂, Petroleum ether/Ethyl acetate 1:0 to 10:1] to afford the title compound (38.8 g, 98% yield) as an off-white solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.68-7.57 (m, 4H), 7.49-7.36 (m, 6H), 4.58-4.36 (m, 2H), 3.74-3.63 (m, 3H), 3.59-3.35 (m, 2H), 2.31-2.15 (m, 1H), 1.95-1.80 (m, 1H), 1.50-1.39 (m, 9H), 1.06 (s, 9H).

[0000320] Step B. (4R)-1-tert-butyl 2-methyl 4-(((tert-butyldiphenylsilyl)oxy)-2-(3-chloropropyl) pyrrolidine-1,2-dicarboxylate: To a solution of (2S,4R)-1-tert-butyl 2-methyl 4-(((tert-butyldiphenylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (36.0 g, 1.0 equiv.) in THF (200 mL) was added LDA (2.0 M in THF, 48.4 mL, 1.30 equiv.). The mixture was stirred at -70 °C for 1 hour. To the reaction mixture was added 1-bromo-3-chloropropane (58.6 g, 5.0 equiv.) at -70 °C. The mixture was stirred at 20 °C for 12 hours. The reaction mixture was diluted with H₂O (200 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by reversed phase flash chromatography

[C18, water (0.1% formic acid)-ACN] to afford the title compound (36.0 g, 86% yield) as a yellow oil; ^1H NMR (400 MHz, CDCl_3) δ = 7.68-7.59 (m, 4H), 7.49-7.34 (m, 6H), 4.46-4.19 (m, 1H), 3.88-3.66 (m, 2H), 3.62-3.55 (m, 3H), 3.53-3.22 (m, 2H), 2.38-1.71 (m, 6H), 1.46-1.36 (m, 9H), 1.10-1.01 (m, 9H).

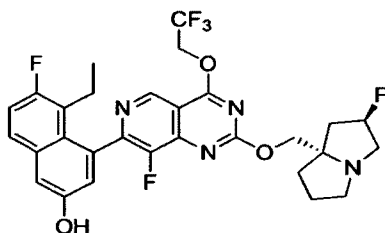
[0000321] Step C. (4R)-methyl 4-((tert-butyldiphenylsilyl)oxy)-2-(3-chloropropyl)pyrrolidine-2-carboxylate: To a solution of (4R)-1-tert-butyl 2-methyl 4-((tert-butyldiphenylsilyl)oxy)-2-(3-chloropropyl)pyrrolidine-1,2-dicarboxylate (36.0 g, 1.0 equiv.) in ACN (200 mL) was added $\text{HCl} \cdot \text{dioxane}$ (4.0 M, 200 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour. The mixture was concentrated under reduced pressure to afford the title compound (34.0 g, crude, HCl) as a yellow solid.

[0000322] Step D. (2R,7aS)-methyl 2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizine-7a-carboxylate (peak A) and (2R,7aR)-methyl 2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizine-7a-carboxylate (peak B): To a solution of (4R)-methyl 4-((tert-butyldiphenylsilyl)oxy)-2-(3-chloropropyl)pyrrolidine-2-carboxylate (34.0 g, 1.0 equiv, HCl) in ACN (300 mL) was added NaHCO_3 (28.8 g, 5.0 equiv.) and KI (1.14 g, 0.1 equiv.). The mixture was stirred at 50 °C for 12 hours. The reaction mixture was diluted with H_2O (150 mL) and extracted with ethyl acetate (3 $\times$ 100 mL). The combined organic phase was dried over anhydrous sodium sulfate, concentrated and purified by prep-HPLC [column: Waters Xbridge C18 150 $\times$ 50mm $\times$ 10 μm ; mobile phase: water (10 mM NH_4HCO_3)-ACN; B%: 73%-93%, 11.5 min] and another prep-HPLC [column: Phenomenex luna C18 250mm $\times$ 100mm $\times$ 10 μm ; mobile phase: water(10 mM NH_4HCO_3)-ACN; B%: 55%-85% over 30 min] to afford the peak A (10.0 g, two steps 34% yield) and the peak B (6.0 g, two steps 21% yield) as yellow oil. LCMS (ESI, M+1): m/z = 424.1.

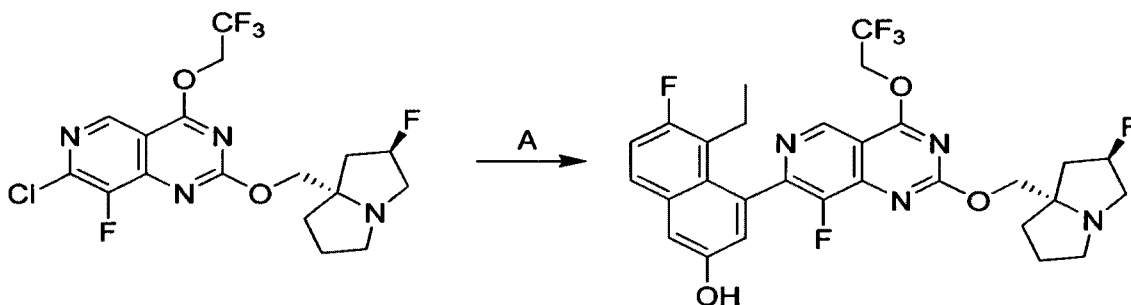
[0000323] Step E. ((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methanol: To a solution of (2R,7aS)-methyl 2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizine-7a-carboxylate (4.50 g, 1.0 equiv.) in THF (100 mL) was added LiAlH_4 (1.21 g, 3.0 equiv.) at -40 °C. The mixture was stirred at -40 °C for 1 hour. The reaction mixture was quenched by addition of H_2O (4.0 mL) at 0 °C. The mixture was dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound (4.20 g, 94% yield) as a yellow oil; ^1H NMR (400 MHz, CDCl_3) δ = 7.68-7.62 (m, 4H), 7.46-7.36 (m, 6H), 4.43-4.35 (m, 1H), 3.11 (s, 2H), 3.03-

2.94 (m, 3H), 2.76-2.69 (m, 1H), 2.02-1.89 (m, 3H), 1.80-1.69 (m, 3H), 1.06 (s, 9H); LCMS (ESI, M+1): m/z = 396.1.

Intermediate 27



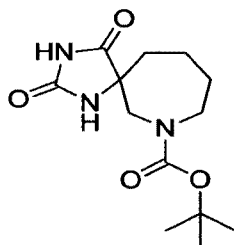
5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol



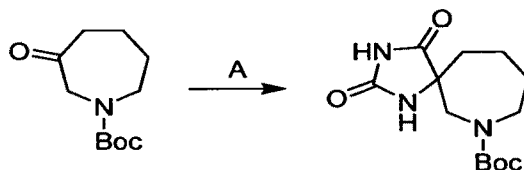
[0000324] Step A. 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol: To a solution of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (28.4 g, 1.0 equiv.), 5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (25.6 g, 1.25 equiv.) and Cs₂CO₃ (1.5 M in H₂O, 129 mL, 3.0 equiv.) in methoxycyclopentane (300 mL) was added Ad₂nBuP-Pd-G3 (7.07 g, 0.15 equiv.). The reaction was stirred at 100 °C for 3 hours under N₂. The mixture was diluted with water (300 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to afford

the title compound (16.8 g, 40% yield) as a yellow solid; ^1H NMR (400 MHz, chloroform- d) δ = 9.19 (d, J = 10.4 Hz, 1H), 7.54 (dd, J = 5.6, 8.8 Hz, 1H), 7.26-7.21 (m, 1H), 7.16-7.11 (m, 1H), 6.96-6.84 (m, 1H), 5.46-5.22 (m, 1H), 5.05-4.71 (m, 2H), 4.56-4.32 (m, 2H), 3.48-3.21 (m, 3H), 3.13-3.01 (m, 1H), 2.47-2.32 (m, 4H), 2.32-2.08 (m, 4H), 0.78 (t, J = 7.2 Hz, 3H); LCMS (ESI, $M+1$): m/z = 593.2.

Intermediate 28

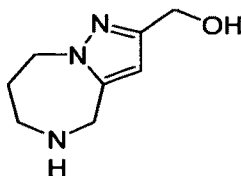


tert-butyl 2,4-dioxo-1,3,7-triazaspiro[4.6]undecane-7-carboxylate

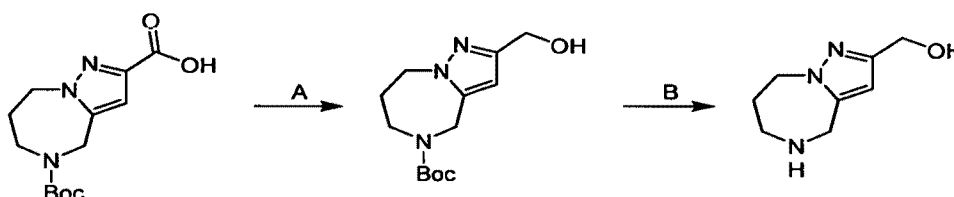


[0000325] Step A. tert-butyl 2,4-dioxo-1,3,7-triazaspiro[4.6]undecane-7-carboxylate: To a solution of tert-butyl 3-oxoazepane-1-carboxylate (2.00 g, 1.0 equiv.) and $(\text{NH}_4)_2\text{CO}_3$ (2.70 g, 3.0 equiv.) in EtOH (10 mL) and H_2O (10 mL) was added KCN (1.12 g, 1.83 equiv.). The reaction was stirred at 85 °C for 16 hours. The mixture was cooled to 25 °C, then diluted with water (20 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated to afford the title compound (2.20 g, 83% yield) as a white solid; ^1H NMR (400 MHz, DMSO- d_6) δ = 11.39-9.68 (m, 1H), 7.97-7.52 (m, 1H), 3.45 (s, 2H), 3.29-3.12 (m, 2H), 1.82-1.65 (m, 3H), 1.64-1.47 (m, 3H), 1.45-1.31 (m, 9H); LCMS (ESI, $M-55$): m/z = 228.0.

Intermediate 29



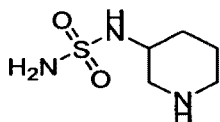
5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-ylmethanol



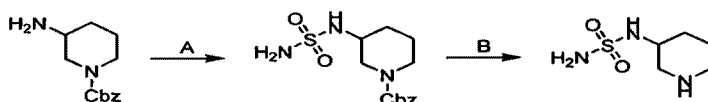
[0000326] Step A. tert-butyl 2-(hydroxymethyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: To a solution of 5-(tert-butoxycarbonyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (500 mg, 1.0 *equiv.*) in THF (10 mL) was added LiAlH₄ (135 mg, 2.0 *equiv.*) at 0 °C. The mixture was stirred at 0 °C for 1.5 hours and at 20 °C for 3 hours. The mixture was quenched with ice water (20 mL) and extracted with ethyl acetate (50 mL). The organic phase concentrated to give the title compound (260 mg, 33% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 268.2.

[0000327] Step B. 5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-ylmethanol: To the solution of tert-butyl 2-(hydroxymethyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (260 mg, 1.0 *equiv.*) in ACN (4 mL) was added HCl·dioxane (4 M, 2.43 mL, 10 *equiv.*) at 0 °C. The reaction was stirred at 0 °C for 0.5 hour. The reaction mixture was concentrated to give a residue. The residue was dissolved in methanol (2 mL) and the pH was adjusted to 8 with saturated aqueous NaHCO₃. The mixture was filtered and concentrated to give a residue. The residue was dissolved with dichloromethane (5 mL), filtered and concentrated to afford the title compound (250 mg, crude) as a yellow oil; LCMS (ESI, M+1): m/z = 167.9.

Intermediate 30



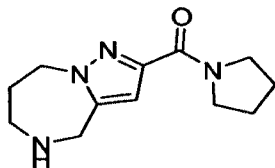
3-(sulfamoylamino)piperidine



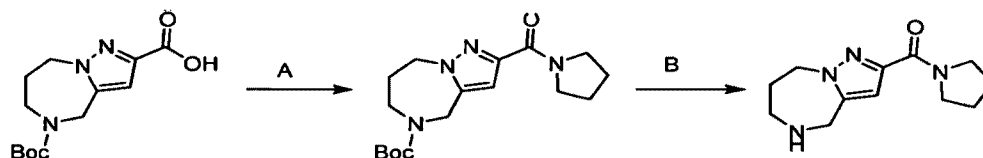
[0000328] Step A. benzyl 3-(sulfamoylamino)piperidine-1-carboxylate: To a solution of benzyl 3-aminopiperidine-1-carboxylate (500 mg, 1.0 *equiv.*) in dioxane (10 mL) was added sulfamide (410 mg, 254 μ L, 2.0 *equiv.*). After stirring at 80 °C for 12 hours, another portion of sulfamide (615 mg, 382 μ L, 3.0 *equiv.*) was added. The mixture was stirred at 80 °C for 5 hours. The reaction mixture was concentrated and purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (423 mg, 56% yield) as a colorless oil; LCMS (ESI, M+1): m/z = 314.0.

[0000329] Step B. 3-(sulfamoylamino)piperidine: To a solution of benzyl 3-(sulfamoylamino)piperidine-1-carboxylate (420 mg, 1.0 *equiv.*) in methanol (10 mL) was added Pd/C (0.1 g, 10% purity) under N₂ atmosphere. The suspension was degassed and purged with H₂ 3 times. The mixture was stirred under H₂ (15 Psi) at 20 °C for 12 hours. The reaction mixture was filtered under N₂ and the filtrate was concentrated to afford the title compound (240 mg, 99% yield) as a colorless oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.65-7.01 (m, 5H), 6.70 (br d, J = 7.2 Hz, 1H), 6.56 (s, 2H), 5.17-4.99 (m, 2H), 4.19-4.07 (m, 1H), 3.81 (br d, J = 12.4 Hz, 1H), 3.11 (br s, 1H), 2.86-2.63 (m, 2H), 1.99-1.88 (m, 1H), 1.75-1.60 (m, 1H), 1.47-1.29 (m, 2H).

Intermediate 31



pyrrolidin-1-yl(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanone

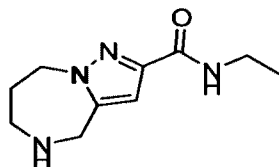


[0000330] Step A. tert-butyl-2-(pyrrolidine-1-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: To a solution of 5-*tert*-butoxycarbonyl-4,6,7,8-tetrahydropyrazolo[1,5-*a*][1,4]diazepine-2-carboxylic acid (160 mg, 1.0 *equiv.*), pyrrolidine (121 mg, 3.0 *equiv.*) and triethylamine (74.8 mg, 103 μ L, 1.3 *equiv.*) in DMF (1.5 mL) was added HATU (281 mg, 1.3 *equiv.*) at 0°C. The mixture was stirred at 25 °C for 0.5 hour. Upon reaction completion, the mixture was filtered and the filtrate was partitioned between ethyl acetate (10 mL) and water (10 mL). The organic phase was separated, washed with brine (2 $\times$ 5 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, **petroleum ether/ethyl acetate 1:1 to 0:1**) to afford the title compound (110 mg, 58% yield) as a white solid; LCMS [ESI, M+1]: m/z = 335.2.

[0000331] Step B. pyrrolidin-1-yl(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanone: To a solution of *tert*-butyl 2-(pyrrolidine-1-carbonyl)-4,6,7,8-tetrahydropyrazolo[1,5-*a*][1,4]diazepine-5-carboxylate (110 mg, 1.0 *equiv.*) in DCM (1.5 mL) was added trifluoroacetic acid (565 mg, 367 μ L, 15.1 *equiv.*) at 0°C. The mixture was stirred at 25 °C for 0.5 hour. The reaction mixture was concentrated under reduced pressure to afford the title compound (65.0 mg, 84% yield) as a yellow liquid; LCMS [ESI, M+1]: m/z = 235.2.

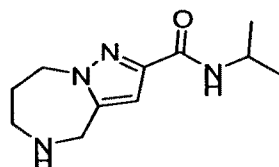
[0000332] Intermediates 32, 33, 34 and 51 were synthesized according to the procedure described for Intermediate 31.

Intermediate 32



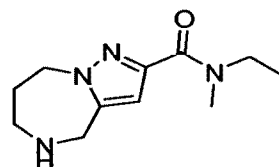
N-ethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

Intermediate 33



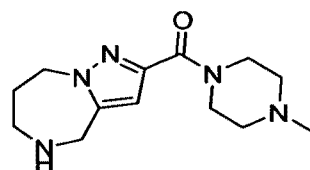
N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

Intermediate 34



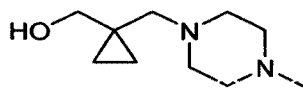
N-ethyl-N-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

Intermediate 51

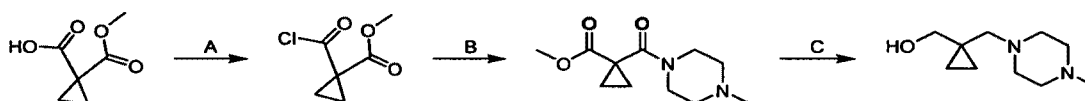


(4-methylpiperazin-1-yl)(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanone

Intermediate 35



(1-((4-methylpiperazin-1-yl)methyl)cyclopropyl)methanol

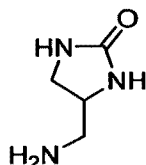


[0000333] Step A. methyl 1-(chlorocarbonyl)cyclopropanecarboxylate: To a mixture of 1-(methoxycarbonyl)cyclopropanecarboxylic acid (2.0 g, 1.0 *equiv.*), DMF (101 mg, 0.1 *equiv.*) in DCM (15 mL) was added (COCl)₂ (2.64 g, 1.82 mL, 1.5 *equiv.*). The mixture was stirred at 0-20 °C for 1 hour. The mixture was concentrated and purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate 5:1 to 1:1) to afford the title compound (2.2 g, 97% yield) as a yellow oil.

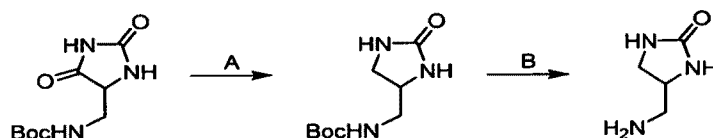
[0000334] Step B. methyl 1-(4-methylpiperazine-1-carbonyl)cyclopropanecarboxylate: To a mixture of methyl 1-chlorocarbonylcyclopropanecarboxylate (2.2 g, 1.0 *equiv.*), TEA (4.11 g, 3.0 *equiv.*) in DCM (15 mL) was added 1-methylpiperazine (1.63 g, 1.2 *equiv.*). The mixture was stirred at 0-20 °C for 1 hour. The mixture was concentrated and the residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate 3:1 to 1:1) to afford the title compound (2.18 g, 71% yield) as a white solid; ¹HNMR (400 MHz, chloroform-d) δ = 3.77-3.31 (m, 7H), 2.39-2.10 (m, 7H), 1.45-1.32 (m, 2H), 1.29-1.17 (m, 2H).

[0000335] Step C. (1-((4-methylpiperazin-1-yl)methyl)cyclopropyl)methanol: To a solution of methyl 1-(4-methylpiperazine-1-carbonyl)cyclopropanecarboxylate (1.5 g, 1.0 *equiv.*) in THF (40 mL) was added LiAlH₄ (503 mg, 2.0 *equiv.*) portion wise under N₂. The suspension was degassed and purged with N₂ for 3 times. The mixture was stirred at 0-15 °C for 2 hours. The mixture was quenched with water (500 μL), 15% NaOH aqueous (500 μL), water (1.5 mL), and filtered. The filter cake was washed with EtOAc (3 × 15 mL), and the filtrate was dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate 3:1 to 0:1) to afford the title compound (716 mg, 59% yield) as a colorless oil.

Intermediate 36



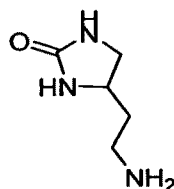
4-(aminomethyl)imidazolidin-2-one



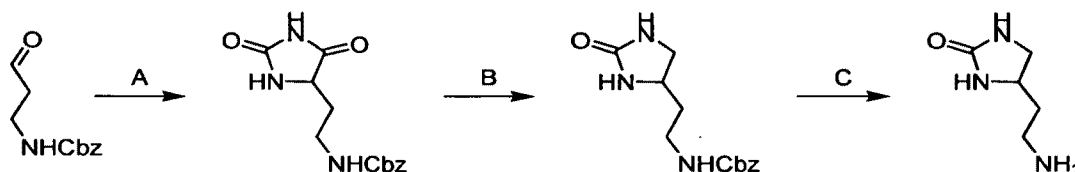
[0000336] Step A. tert-butyl ((2-oxoimidazolidin-4-yl)methyl)carbamate: A mixture of tert-butyl N-[(2,5-dioxoimidazolidin-4-yl)methyl]carbamate (100 mg, 1.0 *equiv.*) and $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (10.0 M, 2.0 *equiv.*) in THF (3 mL) at 0 °C was degassed and stirred at 60°C for 1 hour under N_2 atmosphere. The reaction mixture was quenched by addition of MeOH (10 mL) at 0°C. Then it was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the title compound (60.0 mg, 64% yield) as a white solid; ^1H NMR (400 MHz, DMSO-d_6) δ = 7.77 (br s, 1H), 6.97-6.78 (m, 1H), 6.37-5.98 (m, 1H), 4.02 (br dd, J = 4.4, 6.4 Hz, 1H), 3.14-2.96 (m, 2H), 2.84-2.58 (m, 1H), 1.37 (s, 9H).

[0000337] Step B. 4-(aminomethyl)imidazolidin-2-one: To a solution of tert-butyl N-[(2-oxoimidazolidin-4-yl)methyl]carbamate (60.0 mg, 1.0 *equiv.*) in MeOH (2 mL) was added HCl (1 M, 5.0 *equiv.*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to afford the title compound (50.0 mg, crude) as a white solid. The crude product was used for the next step directly.

Intermediate 37



4-(2-aminoethyl)imidazolidin-2-one



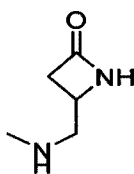
[0000338] Step A. benzyl (2-(2,5-dioxoimidazolidin-4-yl)ethyl)carbamate: Ammonium carbonate (25.5 g, 11.0 *equiv.*) was added to benzyl *N*-(3-oxopropyl)carbamate (5.00 g, 1.00 *equiv.*) in methanol (40.0 mL) and water (36.0 mL) under a flow nitrogen gas. To the reaction mixture was added potassium cyanide (1.97 g, 1.25 *equiv.*) and the resulting was stirred at 20 °C for 12 hours. The suspension was filtered and the filter cake was dried under reduced to afford the title compound (3.10 g, 37.8% yield) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.88 (s, 1H), 7.38 - 7.30 (m, 5H), 5.02 (s, 2H), 3.99 (dd, *J* = 4.8, 8.0 Hz, 1H), 3.11 (d, *J* = 6.0 Hz, 2H), 1.92 - 1.79 (m, 1H), 1.69 - 1.55 (m, 1H).

[0000339] Step B. benzyl (2-(2-oxoimidazolidin-4-yl)ethyl)carbamate: To a solution of benzyl *N*-[2-(2,5-dioxoimidazolidin-4-yl)ethyl]carbamate (1.00 g, 1.0 *equiv.*) in tetrahydrofuran (15.0 mL) was added borane dimethyl sulfide complex (10 M, 1.80 mL, 5.0 *equiv.*) at 0 °C. The mixture was stirred at 50 °C for 1.5 hours. The mixture was quenched with methanol (10.0 mL). The mixture was concentrated in vacuum to produce a residue. The residue was purified by prep-HPLC (column: Welch Ultimate XB-CN 250 × 50 × 10um; mobile phase: [Hexane-EtOH]; B%: 10%-35%, 12min). The desired fraction was collected and lyophilized to give a residue. The residue was further re-purified by column chromatography on silica gel (ethyl acetate) to afford the title compound (150 mg, 13.9% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.41 - 7.30 (m, 5H), 6.31 (s, 1H), 6.09 (s, 1H), 5.01 (s, 2H), 3.58 (q, *J* = 6.8 Hz, 1H), 3.02 (s, 2H), 2.89 (s, 1H), 1.58 - 1.55 (m, 2H).

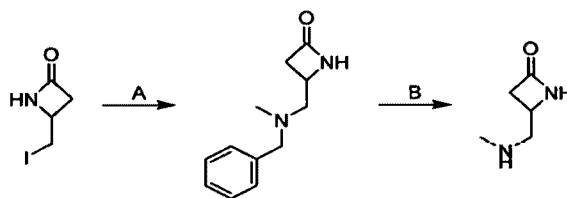
[0000340] Step C. 4-(2-aminoethyl)imidazolidin-2-one: To a solution of benzyl *N*-[2-(2-oxoimidazolidin-4-yl)ethyl]carbamate (80.0 mg, 1.00 *equiv.*) in tetrahydrofuran (5.00 mL) was

added palladium/carbon (20 mg, 10% purity) under nitrogen atmosphere. The suspension was degassed and purged with hydrogen for 3 times. The mixture was stirred under hydrogen (15 psi) at 20 °C for 2 hours. The mixture was filtered and the filter cake was washed with methanol (10.0 mL). The filtrate was concentrated to afford the title compound (40 mg, crude) as a white solid.

Intermediate 38



4-((methylamino)methyl)azetidin-2-one

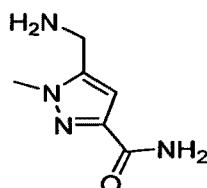


[0000341] Step A. 4-((benzyl(methyl)amino)methyl)azetidin-2-one: To a solution of 4-(iodomethyl)azetidin-2-one (100 mg, 1.0 *equiv.*) and *N*-methyl-1-phenyl-methanamine (86.2 mg, 1.5 *equiv.*) in acetonitrile (1.5 mL) was added potassium carbonate (196 mg, 3.0 *equiv.*). The mixture was stirred at 60 °C for 2 hours. After completion, the reaction mixture was cooled to 25 °C and filtered. Then the filtrate was partitioned between ethyl acetate (10 mL) and water (10 mL). The organic phase was separated, and then it was washed with saturated salt solution (2 × 5 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, **petroleum ether/ethyl acetate=1/1** to 0/1) to afford the title compound (42.0 mg, 43% yield) as a yellow liquid; LCMS [ESI, M+1]: $m/z = 205.0$.

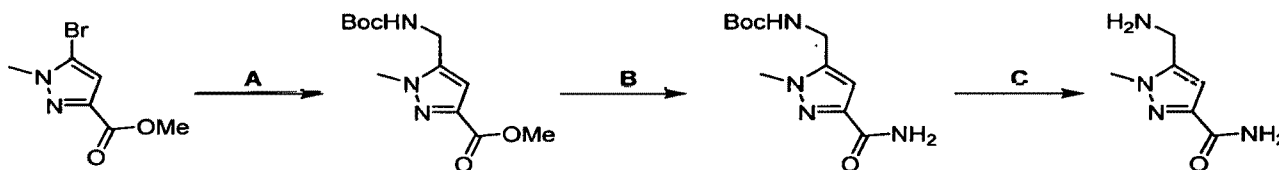
[0000342] Step B. 4-((methylamino)methyl)azetidin-2-one: A mixture of 4-[[benzyl(methyl)amino]methyl]azetidin-2-one (60.0 mg, 1.0 *equiv.*) and Pd/C (20.0 mg, 10% purity) in methyl alcohol (0.5 mL) was degassed and purged with hydrogen for 3 times, and then the mixture was stirred at 25 °C for 2 hours under hydrogen atmosphere (15 psi). The reaction

mixture was concentrated under reduced pressure to afford the title compound (13.0 mg, 39% yield) as yellow liquid; The crude product was used for the next step directly.

Intermediate 39



5-(aminomethyl)-1-methyl-1H-pyrazole-3-carboxamide



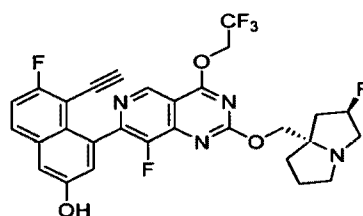
[0000343] Step A. methyl 5-(((tert-butoxycarbonyl)amino)methyl)-1-methyl-1H-pyrazole-3-carboxylate: A mixture of methyl 5-bromo-1-methyl-1H-pyrazole-3-carboxylate (900 mg, 1 equiv.), Potassium [((tert-Butoxycarbonyl)amino)methyl]trifluoroborate (1.46 g, 1.5 equiv.), Pd(OAc)₂ (73.8 mg, 0.08 equiv.) and XPhos (313 mg, 0.16 equiv.) and Cs₂CO₃ (4.02 g, 3 equiv.) in THF (50 mL) and water (5 mL) was degassed and stirred at 100 °C for 2 hours under N₂ atmosphere. The reaction mixture was diluted with water 20 mL and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL × 1), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue, which was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate 5:1 to 3:1) to give the title compound (420 mg, 1.56 mmol, 37.96% yield) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 6.64 (s, 1H), 4.76 (s, 1H), 4.29 (d, *J* = 8.0 Hz, 2H), 3.84 (d, *J* = 8.0 Hz, 6H), 1.39 (s, 9H).

[0000344] Step B. tert-butyl ((3-carbamoyl)-1-methyl-1H-pyrazol-5-yl)methyl)carbamate: A mixture of methyl 5-(((tert-butoxycarbonyl)amino)methyl)-1-methyl-1H-pyrazole-3-carboxylate (400 mg, 1 equiv.) in NH₃•H₂O (3.64 g, 4 mL, 25% NH₃, 17.48 equiv.) was stirred at 20 °C for 2 hours under N₂ atmosphere. The reaction mixture was diluted with water (20 mL) and extracted

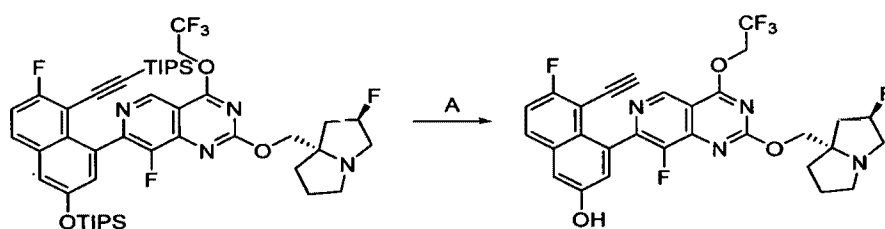
with ethyl acetate (20 mL $\times$ 3). The combined organic layers were washed with brine (10 mL $\times$ 1), dried over anhydrous sodium sulfate, filtered and concentrated to give the title compound (220 mg, 58% yield) as a white solid.

[0000345] Step C. 5-(aminomethyl)-1-methyl-1H-pyrazole-3-carboxamide: To a mixture of tert-butyl ((3-carbamoyl-1-methyl-1H-pyrazol-5-yl)methyl)carbamate (100 mg, 1 equiv.) in CH₂Cl₂ (0.5 mL) was added TFA (770 mg, 0.5 mL, 17.2 equiv.) at 0 °C, the mixture was stirred at 25 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to give the title compound (170 mg, crude, TFA) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.37 (s, 3H), 7.46 (s, 1H), 7.18 (m, 1H), 6.74 (s, 1H), 4.18 (d, *J* = 5.2 Hz, 2H), 3.88 (s, 3H).

Intermediate 40



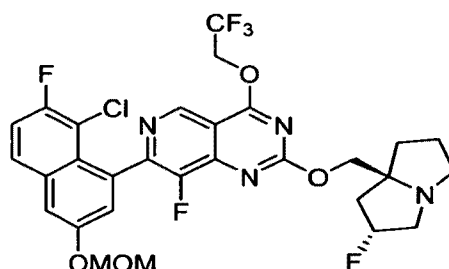
5-ethynyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol



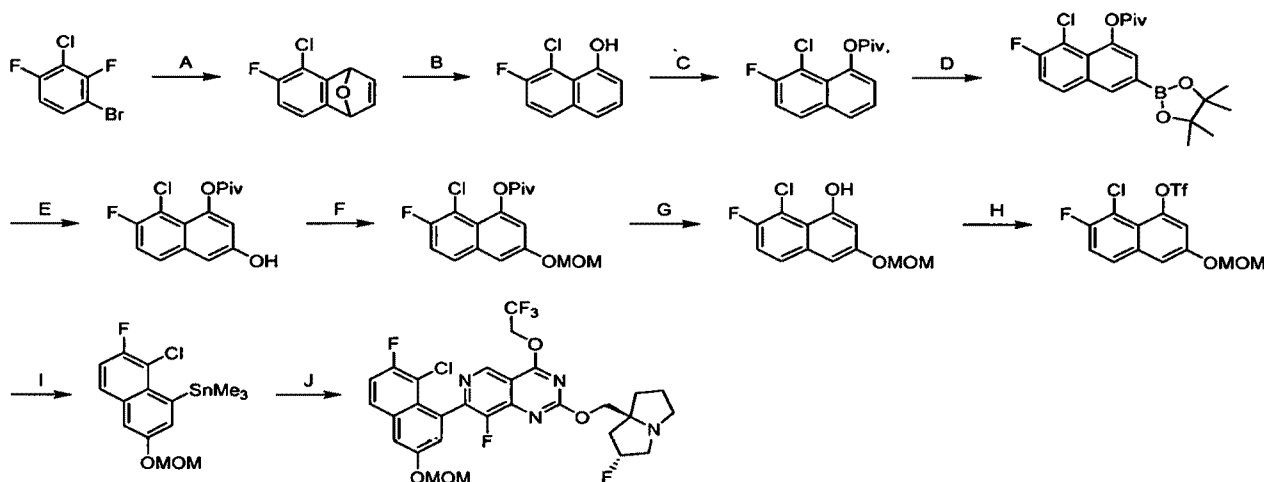
[0000346] Step A. 5-ethynyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol: To a solution of 8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (1.50 g, 1 equiv.) in DMF (20 mL)

was added CsF (2.53 g, 10 equiv.). The mixture was stirred at 20 °C for 2 hrs. The reaction mixture was concentrated under reduced pressure and purified by reversed phase HPLC (water (0.1% formic acid) - ACN) to afford the title compound (0.6 g, 57% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 589.3

Intermediate 41



7-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine



[0000347] Step A. 5-chloro-6-fluoro-1,4-dihydro-1,4-epoxynaphthalene: To a solution 1-bromo-3-chloro-2,4-difluorobenzene (250 g, 1 equiv.) and furan (150 g, 2 equiv.) in toluene (2.5 L) was added *n*-BuLi (2.5 M, 1.2 equiv.) dropwise over 0.5 hour at -15 °C. The reaction mixture

was stirred at 20 °C for 12 hours. After reaction completion, the mixture was quenched with water (2 L) and filtered. The filtrate was separated. The aqueous layer was extracted with ethyl acetate (2 × 2 L). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by reversed phase flash [C18, water (0.1% formic acid) - ACN, 0-80% MeCN] to afford the title compound (81 g, 37% yield) as a yellow oil; ¹H NMR (400 MHz, chloroform-d) δ 7.11-7.06 (m, 2H), 7.06-7.01 (m, 1H), 6.73 (dd, *J* = 7.6, 9.6 Hz, 1H), 5.88 (s, 1H), 5.74 (s, 1H).

[0000348] Step B. 8-chloro-7-fluoronaphthalen-1-yl pivalate: A reaction mixture of 5-chloro-6-fluoro-1,4-dihydro-1,4-epoxynaphthalene (162 g, 1 equiv.) in concentrated HCl (1.02 kg, 12.2 equiv.) and EtOH (1.2 L) was heated to 80 °C for 6 hours. The reaction mixture was concentrated in vacuum. The pH of the residue was adjusted to 7 with saturated aqueous NaHCO₃ and extracted with ethyl acetate (2 × 2 L). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was triturated with petroleum ether (100 mL), filtered and the solid was dried under vacuum to afford the title compound (124 g, 76% yield) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ 7.92 (s, 1H), 7.75 (dd, *J* = 5.2, 8.8 Hz, 1H), 7.44-7.36 (m, 2H), 7.33-7.26 (m, 1H), 7.12-7.06 (m, 1H).

[0000349] Step C. 8-chloro-7-fluoronaphthalen-1-yl pivalate: A mixture of 8-chloro-7-fluoronaphthalen-1-ol (124 g, 1 equiv.) and DIEA (489 g, 6 equiv.), 4 Å molecular sieves (120 g) in dichloromethane (1.5 L) was stirred for 10 minutes at 20 °C. Then PivCl (231 g, 1.3 equiv.) was added to the mixture dropwise at -40 °C. The reaction mixture was stirred at -40 °C for 20 minutes. The reaction mixture was quenched with water (1 L) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 1 L). The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by silica gel chromatography (petroleum ether / ethyl acetate 1:0 to 20:1) to afford the title compound (196 g, 92% yield) as a yellow solid; ¹H NMR (400 MHz, chloroform-d) δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.83-7.76 (m, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.53-7.44 (m, 1H), 7.43-7.35 (m, 1H).

[0000350] Step D. 8-chloro-7-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl pivalate: A mixture of 8-chloro-7-fluoronaphthalen-1-yl pivalate (8.00 g, 1.0 equiv.), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (7.24 g, 1.0 equiv.), (1,5-Cyclooctadiene)(methoxy)iridium(I) dimer (944 mg, 0.05 equiv.) and 4-tert-butyl-2-(4-tert-butyl-

2-pyridyl)pyridine (918 mg, 0.12 equiv.) in n-hexane (220 mL) was degassed and stirred at 65 °C for 1 hour under N₂ atmosphere. The mixture was filtered, concentrated and purified by column chromatography [SiO₂, Petroleum ether/Ethyl acetate 10:1 to 3:1] to afford the title compound (18.8 g, crude) as a yellow solid.

[0000351] Step E. 8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl pivalate: To a solution of 8-chloro-7-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl pivalate (50.0 g, 1.0 equiv.) and H₂O₂ (116 g, 98.3 mL, 30% purity, 8.3 equiv.) in THF (300 mL) was added AcOH (502 g, 478 mL, 68 equiv.) at 0 °C. The solution was stirred at 20 °C for 2 hours. The reaction mixture was quenched by saturated sodium sulfite (500 mL), extracted with ethyl acetate (3 × 100 mL), washed with brine (200 mL), dried over Na₂SO₄, concentrated and purified by reversed phase flash chromatography (C 18, water (0.1% NH₃•H₂O)- ACN) to afford the title compound (5.4 g, 15% yield) as a gray solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 10.25 (s, 1H), 7.86 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.51 (t, *J* = 9.2 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 6.87 (d, *J* = 2.1 Hz, 1H), 1.36 (s, 9H).

[0000352] Step F. 8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl pivalate: To a solution of 8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl pivalate (5.4 g, 1.0 equiv.) in DCM (55 mL) were added DIPEA (7.06 g, 9.51 mL, 3 equiv.) and chloro(methoxy)methane (2.72 g, 2.57 mL, 1.8 equiv.) dropwise at 0 °C. The mixture was stirred at 0 °C for 1.5 hours. The solution was diluted with water (50 mL), extracted with ethyl acetate (2 × 50 mL), dried over Na₂SO₄, concentrated and purified by column chromatography [SiO₂, Petroleum ether/Ethyl acetate 20:1 to 5:1] to afford the title compound (6 g, 97% yield) as a yellow solid.

[0000353] Step G. 8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol: To a solution of 8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl pivalate (8.00 g, 1.0 equiv.) in MeOH (120 mL) was added KOH (5.38 g, 4.0 equiv.) at 0 °C. The mixture was stirred at 20 °C for 1 hour. The solution was diluted with water (40 mL), extracted with ethyl acetate (3 × 40 mL), washed with brine (100 mL), dried over Na₂SO₄, concentrated and purified by column chromatography [SiO₂, Petroleum ether/Ethyl acetate 10:1 to 5:1] to afford the title compound (5.6 g, 93% yield) as a yellow solid.

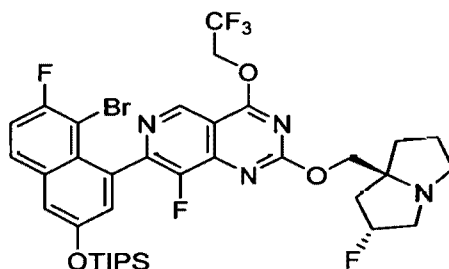
[0000354] Step H. 8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate: To a solution of 8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (5.00 g, 1.0 equiv.) in DCM (60 mL) were added DIEA (2.52 g, 3.39 mL, 1.0 equiv.) and trifluoromethanesulfonic anhydride (8.24 g, 4.82 mL, 1.5 equiv.) dropwise at -40 °C. The mixture was stirred at -40 °C for 1.5 hours. The solution was diluted with water (40 mL), extracted with ethyl acetate (3 × 40 mL), washed with brine (100 mL), dried over Na₂SO₄, concentrated and purified by column chromatography [SiO₂, Petroleum ether/Ethyl acetate 50:1 to 10:1] to afford the title compound (6.9 g, 91% yield) as a yellow solid; ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.69 (dd, *J* = 5.2, 9.2 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.42-7.34 (m, 2H), 5.30 (s, 2H), 3.53 (s, 3H).

[0000355] Step I. (8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)trimethylstannane: To the mixture of [8-chloro-7-fluoro-3-(methoxymethoxy)-1-naphthyl] trifluoromethanesulfonate (2 g, 1 equiv.), trimethyl(trimethylstannyl)stannane (5.40 g, 3.2 equiv.), LiCl (654.37 mg, 3.0 equiv.) in toluene (80 mL) was added Pd(PPh₃)₄ (595 mg, 0.1 equiv.) under N₂. The mixture was stirred at 110 °C for 16 hours. The mixture was quenched with water (200 mL), extracted with ethyl acetate (100 mL × 3), the combined organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate 1:0 to 10:1) to afford the title compound (2 g, 96.35% yield) as a colorless oil; ¹H NMR (400 MHz, CDCl₃) δ = 7.58-7.56 (m, 1H), 7.49-7.48 (m, 1H), 7.28-7.27 (d, *J* = 2.4 Hz, 1H), 7.22-7.20 (m, 1H), 5.19 (s, 2H), 5.43 (s, 3H); 0.40-0.27 (m, 9H).

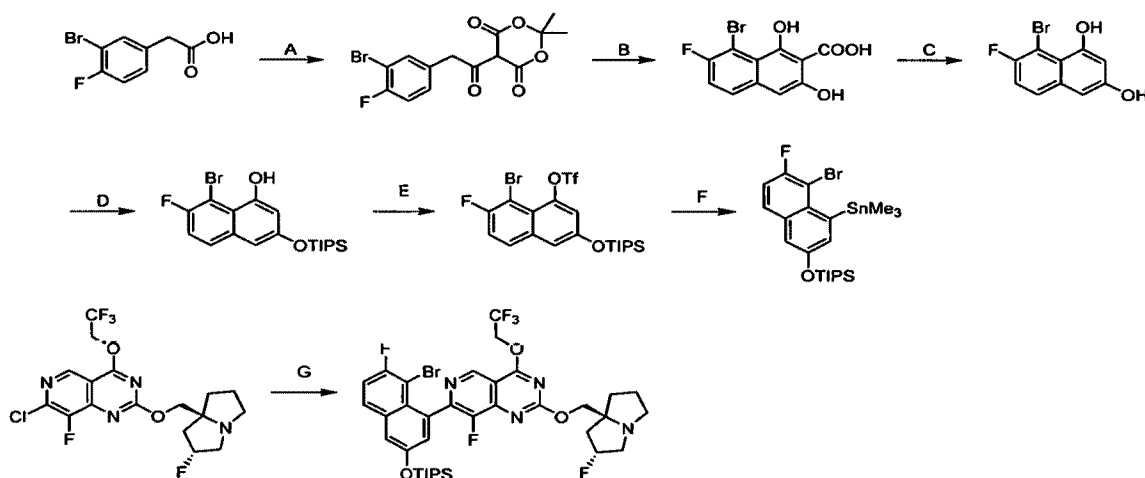
[0000356] Step J. 7-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a solution of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (625 mg, 1 equiv.) and [8-chloro-7-fluoro-3-(methoxymethoxy)-1-naphthyl]trimethylstannane (1.72 g, 3 equiv.) in toluene (25 mL) was added Pd(dppf)Cl₂ (104, 0.1 equiv.), BINAP (177 mg, 285 μmol, 0.2 equiv.) and CuI (81.4 mg, 0.3 equiv.), the mixture was de-gassed and heated to 90°C for 4 hours under N₂. The resulting suspension was cooled to 20 °C, filtered, the filtrate was concentrated under reduced pressure. The crude product was purified by reversed-

phase HPLC (water (0.1% formic acid) to afford the title compound (776 mg, 1.21 mmol, 84.73% yield) as a yellow solid; ^1H NMR (400 MHz, CDCl_3) δ = 9.25 (s, 1H), 7.79-7.75 (dd, J = 5.6 Hz, 9.2 Hz, 1H), 7.57-7.56 (d, J = 1.6 Hz, 1H), 7.38-7.27 (m, 2H), 5.34-5.29 (m, 3H), 5.09-5.05 (m, 2H), 4.38-4.12 (m, 2H); 3.53 (s, 3H); 3.29-3.28 (m, 2H); 3.19-3.18 (m, 1H); 3.05-3.01 (m, 1H); 2.23-2.22 (m, 3H); 2.00-1.95 (m, 3H); LCMS (ESI, M-55): m/z = 642.8.

Intermediate 42



7-(8-bromo-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine



[0000357] Step A. 5-(2-(3-bromo-4-fluorophenyl)acetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione: To a mixture of 2-(3-bromo-4-fluorophenyl)acetic acid (330 g, 210 mL, 1.0 *equiv.*) and 2,2-dimethyl-1,3-dioxane-4,6-dione (225 g, 1.1 *equiv.*) in MeCN (1.65 L) was added DMAP (14.7

g, 0.085 *equiv.*) in one portion at 15 °C under N₂ atm. Then DIPEA (394 g, 530 mL, 2.15 *equiv.*) was carefully added to the reaction in four portions over a period of 1 hour while maintaining the temperature at 15 ~ 30 °C under to give a pale yellow suspension. Then pivaloyl chloride (188 g, 192 mL, 1.10 *equiv.*) was added slowly to the reaction mixture in five portions over a period of 1 hour maintaining 25 °C ~ 40 °C. After the addition was complete, a yellow suspension was obtained. The reaction mixture was heated at 45 °C for 3 hours under N₂ atm. The mixture was cooled to 0 °C and slowly diluted with 4 N HCl (2.0 L) to adjust pH to 6 ~ 7 while maintaining the temperature between 0 ~ 15 °C. The mixture was stirred at 0 °C for 1 hour and then filtered. The filter cake was concentrated in vacuum to afford the title compound (450 g, 88% yield) as a white solid; LCMS (ESI, M-57, M-55): m/z = 300.8.

[0000358] Step B. 8-bromo-7-fluoro-1,3-dihydroxy-2-naphthoic acid: 5-[2-(3-bromo-4-fluoro-phenyl)acetyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (600 g, 1.0 *equiv.*) was slowly added to CF₃SO₃H (1.30 L) in four portions maintaining the temperature at 25 °C ~ 50 °C for 1 hour with ice-water cooled bath. Then the mixture was stirred at 20 °C for 2 hours and water (10 L) was added slowly to the reaction mixture. The mixture was filtered. The filter cake was collected and concentrated to afford the title compound (1200 g, crude) as a yellow solid.

[0000359] Step C. 8-bromo-7-fluoronaphthalene-1,3-diol: A solution of 8-bromo-7-fluoro-1,3-dihydroxy-naphthalene-2-carboxylic acid (1.3 kg, 1.0 *equiv.*) in water (700 mL) and ACN (700 mL) was stirred at 85 °C for 12 hours. The mixture was concentrated and the residue was diluted with water (1 L), extracted with ethyl acetate (2 L × 2). The organic layer was dried over Na₂SO₄, concentrated in vacuum and the residue was purified by column chromatography (Silica gel, petroleum ether/ethyl acetate 3:1) and prep-HPLC (column: Phenomenex Luna C18 200 × 40mm × 10um; mobile phase: [water (0.1% formic acid)-ACN]; B%: 27%-57%, 10min). The desired fraction was collected and extracted with ethyl acetate (20 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuum to afford the title compound (55.0 g, 13% yield two steps) as a yellow solid.

[0000360] Step D. 8-bromo-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-ol: To a solution of 8-bromo-7-fluoro-naphthalene-1,3-diol (10.0 g, 1.0 *equiv.*) and DIEA (15.1 g, 20.3 mL, 3 *equiv.*) in DCM (200 mL) was added TIPSCl (6.75 g, 7.49 mL, 0.90 *equiv.*) portion wise at 0 °C. The mixture was stirred at 0 °C for 0.5 hr. The mixture was concentrated to give a residue and the

residue was purified by column chromatography (Silica gel, ethyl acetate/petroleum ether 0:1 to 1:50) to afford the title compound (14.7 g, 91% yield) as a yellow oil.

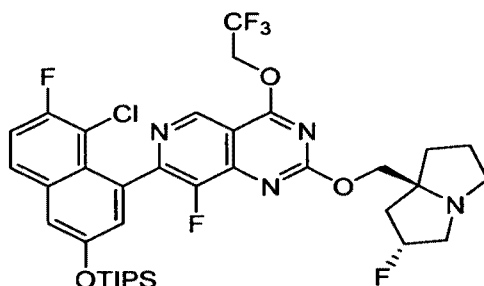
[0000361] Step E. 8-bromo-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl trifluoromethanesulfonate: To a solution of 8-bromo-7-fluoro-3-triisopropylsilyloxy-naphthalen-1-ol (14.7 g, 1.0 *equiv.*) and DIEA (13.8 g, 18.6 mL, 3.0 *equiv.*) in DCM (200 mL) was added Tf₂O (12.0 g, 7.04 mL, 1.2 *equiv.*) at -40 °C. The mixture was stirred at -40 °C for 0.5 hr. The mixture was quenched with water (200 mL) and the layers were separated. The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography (Silica gel, petroleum ether/ethyl acetate 100:1 to 30:1) to afford the title compound (15 g, 77% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 547.0.

[0000362] Step F. ((5-bromo-6-fluoro-4-(trimethylstannyl)naphthalen-2-yl)oxy)triisopropylsilane: To a mixture of (8-bromo-7-fluoro-3-triisopropylsilyloxy-1-naphthyl) trifluoromethanesulfonate (5 g, 9.17 mmol, 1 *equiv.*), trimethyl(trimethylstannyl)stannane (9.41 g, 5.96 mL, 3.13 *equiv.*) and Pd(PPh₃)₂Cl₂ (643 mg, 0.1 *equiv.*) in toluene (50 mL) was added LiCl (1.17 g, 563 μL, 3.0 *equiv.*) under N₂. The mixture was stirred at 100 °C for 12 hours under N₂. The mixture was quenched with water (100 mL) and extracted with ethyl acetate (100 mL × 3), the combined organic phase was washed with brine 100 mL, dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (Silica gel, petroleum ether) to afford the title compound (3 g, 58% yield) as a yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.65 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.28 - 7.23 (m, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 1.36 - 1.29 (m, 3H), 1.15 (d, *J* = 7.2 Hz, 18H), 0.56 - 0.39 (m, 9H).

[0000363] Step G. 7-(8-bromo-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a solution of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (650 mg, 1.0 *equiv.*) and ((5-bromo-6-fluoro-4-(trimethylstannyl)naphthalen-2-yl)oxy)triisopropylsilane (1.24 g, 1.5 *equiv.*) in toluene (10 mL) was added BINAP (184mg, 0.2 *equiv.*) and CuI (84.6 mg, 0.3 *equiv.*) at 25 °C. The suspension was thoroughly degassed and Pd(dppf)Cl₂ (108 mg, 0.1 *equiv.*) was added. The suspension was degassed and stirred at 100 °C and for 6 hours. The mixture was filtered and the residue was washed by ethyl acetate (50 mL ×

3). The filtrate was concentrated in vacuum and the residue was purified by prep-HPLC (column: Welch Xtimate C18 250*50mm*10um; mobile phase: [water (0.1% formic acid) - ACN]; B%: 27%-57%, 20min) to afford the title compound (1.4 g, 36% yield) as a yellow solid; LCMS (ESI, M+1, M+3): m/z = 799.2, 801.2.

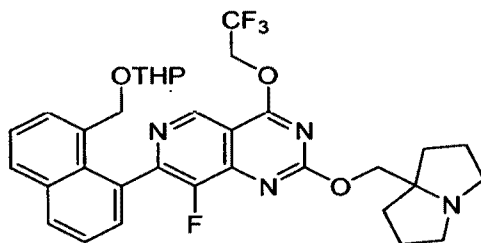
Intermediate 43



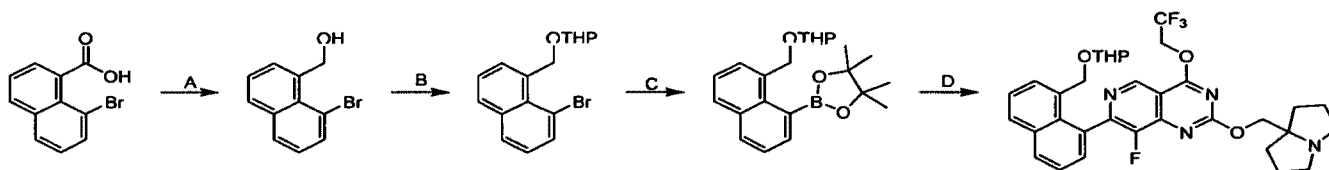
7-(8-chloro-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine

[0000364] The title compounds was synthesized from 2-(3-chloro-4-fluoro-phenyl)acetic acid according to the procedure described for Intermediate 42. LCMS [ESI, M+1]: m/z = 755.1.

Intermediate 44



8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)naphthalen-1-yl)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine



[0000365] Step A. (8-bromonaphthalen-1-yl)methanol: To a solution of 8-bromonaphthalene-1-carboxylic acid (5 g, 1.0 *equiv.*) in 2-MeTHF (70 mL) was slowly added $\text{BH}_3 \cdot \text{Me}_2\text{S}$ (10 M, 3.0 *equiv.*) at 0 °C under N_2 . The reaction was stirred at 70 °C for 12 hours. The mixture was quenched with methanol (20 mL) at 0 °C and washed with 1 M HCl (30 mL). The mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous sodium sulfate, concentrated to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate 1:0 to 0:1 to methanol) to afford the title compound (5.4 g, 70% yield) as a white solid; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.98 (dd, J = 0.8, 8.0 Hz, 1H) 7.84-7.95 (m, 3H) 7.56 (t, J = 7.6 Hz, 1H) 7.35 (t, J = 7.6 Hz, 1H) 5.39-5.48 (m, 2H) 5.32-5.39 (m, 1H).

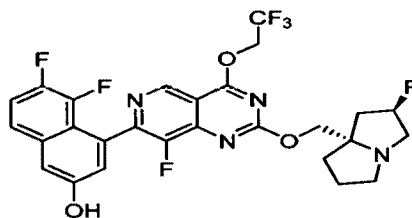
[0000366] Step B. 2-((8-bromonaphthalen-1-yl)methoxy)tetrahydro-2H-pyran: To a solution of 3,4-dihydropyran (1.22 g, 1.0 *equiv.*), 8-bromonaphthalen-1-yl)methanol (3.44 g, 1.0 *equiv.*) and 4-methylbenzenesulfonic acid (514 mg, 0.1 *equiv.*) in DCM (40 mL) was stirred at 25 °C for 5 hours. The reaction mixture was concentrated on vacuum. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate 1:0 to 50:1) to afford the title compound (4.8 g, 43% yield) as a light yellow oil. ^1H NMR (400 MHz, $\text{chloroform}-d$) δ = 7.76-7.94 (m, 4H) 7.48 (t, J = 7.70 Hz, 1H) 7.27 (s, 1H) 5.58 (s, 2H) 4.88 (t, J = 3.36 Hz, 1H) 3.93-4.02 (m, 1H) 3.56-3.64 (m, 1H) 1.73-1.98 (m, 3H) 1.64-1.69 (m, 1H) 1.61-1.56 (m, 2H)

[0000367] Step C. 4,4,5,5-tetramethyl-2-(8-(((2-((8-bromonaphthalen-1-yl)methoxy)tetrahydro-2H-pyran-2-yl)oxy)methyl)naphthalen-1-yl)-1,3,2-dioxaborolane: A mixture of 2-((8-bromonaphthalen-1-yl)methoxy)tetrahydro-2H-pyran (300 mg, 1.0 *equiv.*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (356 mg, 1.5 *equiv.*), KOAc (27.5 mg, 0.3 *equiv.*) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (68.3 mg, 0.1 *equiv.*) in dioxane (1.5 mL) was degassed and stirred at 80 °C for 2 hrs under N_2 atmosphere. The combined reaction mixture was diluted with ethyl acetate (10 mL) and water (20 mL), the aqueous layer was extracted with ethyl acetate (10 mL), the combined

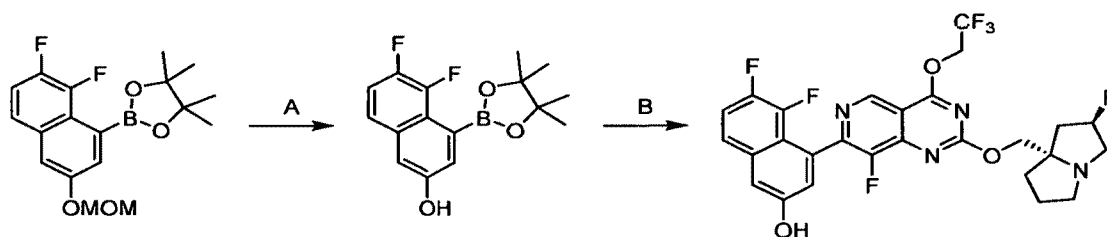
organic phase was washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate 100:1 to 15:1) to afford the title compound (290 mg, 85% yield) as a white solid; ^1H NMR (400 MHz, CDCl_3) δ (ppm) = 7.93-7.88 (m, 1H), 7.82-7.74 (m, 2H), 7.56 (d, J = 7.2 Hz, 1H), 7.48-7.39 (m, 2H), 5.74 (d, J = 13.2 Hz, 1H), 5.04-4.94 (m, 1H), 4.41-4.35 (m, 1H), 3.91-3.80 (m, 1H), 3.49-3.41 (m, 1H), 1.68-1.40 (m, 18H).

[0000368] Step D. 8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)naphthalen-1-yl)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: A mixture of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (350 mg, 1.0 equiv.), 4,4,5,5-tetramethyl-2-(8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)naphthalen-1-yl)-1,3,2-dioxaborolane (368 mg, 1.2 equiv.), CataCXium A Pd G3 (60.6 mg, 0.1 equiv.) and Cs_2CO_3 (1.5 M in water, 3.0 equiv.) in methoxycyclopentane (8 mL) was degassed and stirred at 100 °C for 2 hours under N_2 atmosphere.. The reaction mixture was diluted with ethyl acetate (50 mL) and water (60 mL), extracted with ethyl acetate (30 mL), the combined organic phase was washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [C18, water (0.1% formic acid) - ACN] to afford the title compound (234 g, 16% yield) as a yellow solid; ^1H NMR (400 MHz, chloroform- d) δ ppm = 9.22 (s, 1 H) 8.02 (d, J = 7.95 Hz, 1 H) 7.93 (d, J = 7.95 Hz, 1 H) 7.45-7.62 (m, 4 H) 5.00-5.18 (m, 2 H) 4.24-4.61 (m, 4 H) 4.09-4.20 (m, 2 H) 3.13-3.41 (m, 3 H) 2.62-2.85 (m, 2 H) 2.07-2.21 (m, 2 H) 1.85-2.02 (m, 5 H) 1.67-1.82 (m, 4 H) 1.19-1.33 (m, 3 H); LCMS (ESI, $\text{M}+1$): m/z = 627.2.

Intermediate 45



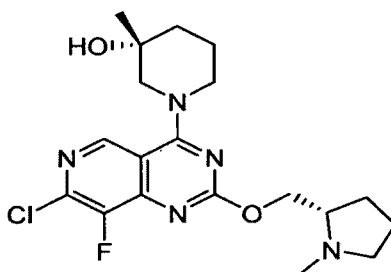
5,6-difluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol



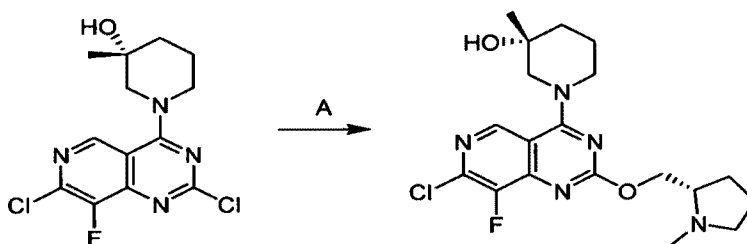
[0000369] Step A. 5,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol: To a solution of 2-[7,8-difluoro-3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (500 mg, 1.0 *equiv.*) in ACN (15 mL) was added HCl•dioxane (4 M, 7.50 mL, 21.0 *equiv.*) at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. The mixture was diluted with saturated aqueous NaHCO₃ (15 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated and purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (340 mg, 74% yield) as a red solid; LCMS (ESI, M+1): m/z = 307.4.

[0000370] Step B. 5,6-difluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol: To a mixture of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (306 mg, 1.0 *equiv.*) and 5,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (320 mg, 1.50 *equiv.*) in water (1.4 mL) and methoxycyclopentane (4.0 mL) were added cataCXium A Pd G3 (50.7 mg, 0.1 *equiv.*) and Cs₂CO₃ (1.5 M, 1.39 mL, 3.0 *equiv.*) under N₂. The mixture was stirred at 60 °C for 1 hour. The reaction mixture was diluted with water (5.0 mL), the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phase was washed with brine (15 mL), dried with anhydrous Na₂SO₄, concentrated and purified by reversed phase flash chromatography (C18, water (0.1% formic acid) - ACN) to afford the title compound (270 mg, 60% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 583.2

Intermediate 46

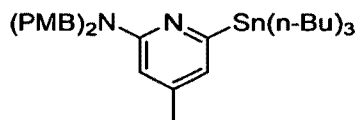


(R)-1-(7-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

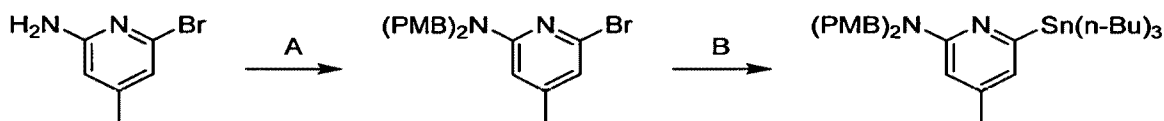


[0000371] Step A. (R)-1-(7-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (2.20 g, 1.0 equiv.) and 4Å molecular sieves (500 mg) in dioxane (15 mL) was added DIEA (2.58 g, 3.0 equiv.) and [(2S)-1-methylpyrrolidin-2-yl]methanol (1.53 g, 2.0 equiv.). The mixture was stirred at 95 °C for 20 hours. The reaction mixture was filtered and concentrated under reduced pressure to remove dioxane. The residue was diluted with H₂O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by reversed phase flash chromatography [C18, water (0.1% formic acid) - ACN] to afford the title compound (1.80 g, 66% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 410.2.

Intermediate 47



N,N-bis(4-methoxybenzyl)-4-methyl-6-(tributylstannyl)pyridin-2-amine

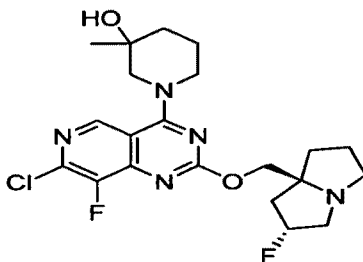


[0000372] Step A. 6-bromo-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine: To a solution of 6-bromo-4-methyl-pyridin-2-amine (180 g, 1.0 equiv.) in DMAC (1.8 L) was added NaH (115 g, 60% purity, 3.0 equiv.) at 0 °C under nitrogen atmosphere. The mixture was stirred at 25 °C for 1 hour under nitrogen atmosphere. Then 1-(chloromethyl)-4-methoxy-benzene (331 g, 2.2 equiv.) was added to the reaction mixture at 25 °C. The mixture was stirred at 25 °C for 2 hours. After reaction completion, the mixture was quenched with ammonium chloride solution (3 L) at 0 °C and diluted with ethyl acetate (4 L). The layers were separated. The organic layer was washed with brine (3 × 2 L), dried with Na₂SO₄ then concentrated in vacuum. The residue was triturated with petroleum ether (1 L) at 25 °C for 30 mins to afford the title compound (320 g, 77% yield) as a white solid; ¹H NMR (400 MHz, CDCl₃-d) δ = 7.16 (d, *J* = 8.8 Hz, 4H), 6.85 (d, *J* = 8.8 Hz, 4H), 6.60 (s, 1H), 6.17 (s, 1H), 4.64 (s, 4H), 3.80 (s, 6H), 2.13 (s, 3H); LCMS (ESI, M+1, M+3): *m/z* = 427.1, 429.1.

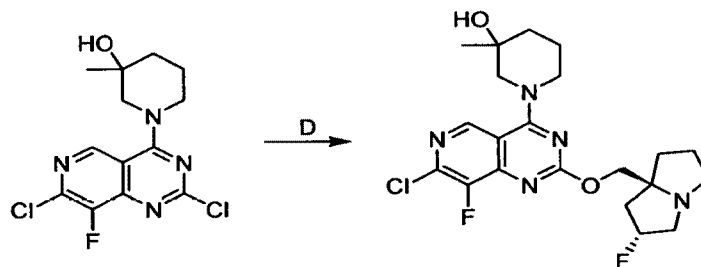
[0000373] Step B. N,N-bis(4-methoxybenzyl)-4-methyl-6-(tributylstannyl)pyridin-2-amine: A mixture of 6-bromo-N,N-bis[(4-methoxyphenyl)methyl]-4-methyl-pyridin-2-amine (200 g, 1.0 equiv.), tributyl(tributylstannyl)stannane (651 g, 2.4 equiv.), Pd₂(dba)₃ (42.9 g, 0.1 equiv.), PCy₃ (26.2 g, 0.2 equiv.) and LiCl (99.2 g, 5.0 equiv.) in dioxane (1.8 L) was degassed and stirred at 110 °C for 5 hours under N₂ atmosphere. After reaction completion, the mixture was concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 1:0 to 10:1) followed by reversed phase flash chromatography (neutral condition) to afford the title compound (190 g, 62% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃-d) δ = 7.19 (d, *J* = 8.8 Hz, 4H), 6.87 - 6.82 (m, 4H), 6.62 - 6.55 (m, 1H), 6.15 (s, 1H), 4.70 (s, 4H), 3.80 (s, 6H),

2.15 (s, 3H), 1.63 - 1.51 (m, 6H), 1.32 (qd, $J = 7.2, 14.7$ Hz, 7H), 1.09 - 1.01 (m, 5H), 0.90 - 0.84 (m, 9H). LCMS (ESI, M+1): $m/z = 639.3$.

Intermediate 48

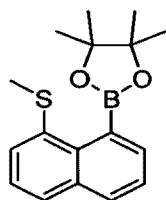


1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

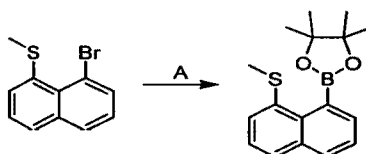


[0000374] Step D. 1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of 1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (2.22 g, 1.0 equiv.), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (1.60 g, 1.5 equiv.), 4Å molecular sieves (1.00 g) and DIEA (2.60 g, 3.0 equiv.) in dioxane (30.0 mL) was stirred at 90 °C for 15 hours. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The crude product was purified by reversed phase flash chromatography (water (0.1% formic acid) - ACN) to afford the title compound (1.90 g, 62% yield) as a yellow solid; LCMS (ESI, M+1): $m/z = 454.1$.

Intermediate 49

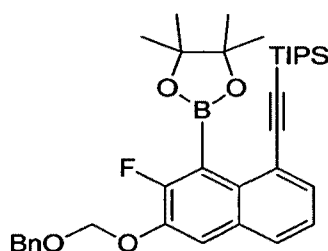


4,4,5,5-tetramethyl-2-(8-(methylthio)naphthalen-1-yl)-1,3,2-dioxaborolane

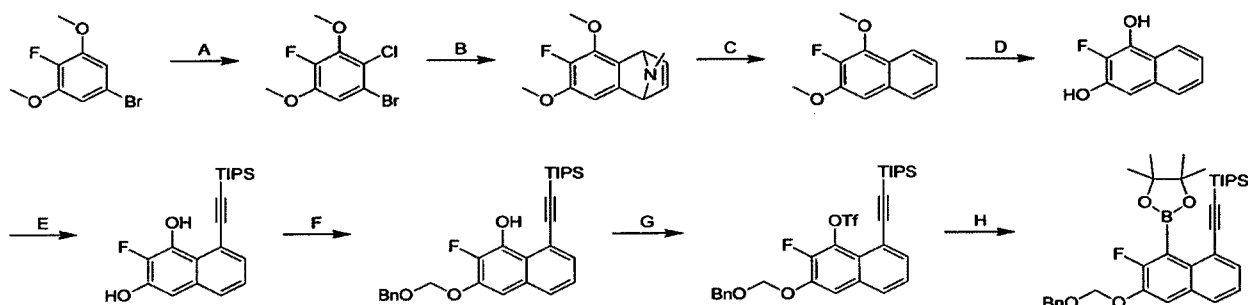


[0000375] Step A. 4,4,5,5-tetramethyl-2-(8-(methylthio)naphthalen-1-yl)-1,3,2-dioxaborolane: To a solution of 1-bromo-8-methylsulfanyl-naphthalene (1.00 g, 1.0 *equiv.*) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.53 g, 5.0 *equiv.*) in ACN (20 mL) were added TEA (1.20 g, 3.0 *equiv.*) and Pd(dppf)Cl₂ (433 mg, 0.15 *equiv.*). The mixture was stirred at 80 °C for 5 hours under N₂ atmosphere. The mixture was filtered, the filtrate was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated and purified by column chromatography [Silica gel, Petroleum ether/Ethyl acetate 1:0 to 30:1] to afford the title compound (1.00 g, 84% yield, 99% purity) as a yellow oil; ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.85 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.64 (dd, *J* = 1.2, 6.8 Hz, 1H), 7.52–7.48 (m, 1H), 7.45–7.41 (t, *J* = 8.0 Hz, 1H), 2.42 (s, 3H), 1.46 (s, 12H)

Intermediate 50



((6-((benzyloxy)methoxy)-7-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane



[0000376] Step A. 1-bromo-2-chloro-4-fluoro-3,5-dimethoxybenzene: To a solution of 5-bromo-2-fluoro-1,3-dimethoxybenzene (50.0 g, 1.0 equiv.) and TMSCl (2.31 g, 0.1 equiv.) in MeCN (500 mL) was added NCS (34.1 g, 1.2 equiv.) at 10 °C. The reaction mixture was stirred at 10 °C for 2 hours. The mixture was quenched with saturated brine (500 mL) at 0 °C and extracted with ethyl acetate (3×100 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) to afford the title compound (85 g, 74% yield) as a yellow solid; ¹H NMR (400 MHz, CDCl₃) δ 7.05-6.95 (m, 1H), 3.98 (d, *J* = 1.2 Hz, 3H), 3.89 (s, 3H).

[0000377] Step B. 6-fluoro-5,7-dimethoxy-9-methyl-1,4-dihydro-1,4-epiminonaphthalene: To a mixture of 1-bromo-2-chloro-4-fluoro-3,5-dimethoxybenzene (20.0 g, 1.0 equiv.) and 1-methylpyrrole (12.0 g, 2.0 equiv.) in THF (240 mL) was added *n*-BuLi (2.5 M, 32.65 mL, 1.1 equiv.) at -65 °C. The reaction was stirred at -65 °C for 1 hour and then at 25 °C for 16 hours. The mixture was quenched with saturated aqueous NH₄Cl solution (200 mL) and extracted with EtOAc (2×80 mL). The combined organic layers were concentrated under reduced pressure. The crude product was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) to afford the title compound (7.8 g, 44% yield) as a yellow oil. LCMS (ESI, *M*⁺+1): *m/z* = 236.

[0000378] Step C. 2-fluoro-1,3-dimethoxynaphthalene: To a solution of 6-fluoro-5,7-dimethoxy-9-methyl-1,4-dihydro-1,4-epiminonaphthalene (5.00 g, 1.0 equiv.) in DCM (60.0 mL) was added *m*-CPBA (5.18 g, 85% purity, 1.2 equiv.) at 0-5 °C. The mixture was stirred at 15 °C for 1 hr. The mixture was quenched with saturated aqueous Na₂SO₃ solution (100 mL). The organic

layer was separated and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 1:0 to 20:1) to afford the tittle compound (2.4 g, 54% yield) as a light yellow oil.

[0000379] Step D. 2-fluoronaphthalene-1,3-diol: To a solution of 2-fluoro-1,3-dimethoxynaphthalene (15.4 g, 1.0 equiv.) in DCM (250 mL) was added BBr₃ (39.3 g, 2.1 equiv.) at -30 °C. The mixture was stirred at -30 °C for 30 minutes. The mixture was quenched with MeOH (2.0 mL) and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 50:1 to 10:1) to afford the tittle compound (7.6 g, 57% yield) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.47-7.35 (m, 2H), 6.96 (d, *J* = 8.4 Hz, 1H), 5.50 (br s, 1H), 5.21 (br s, 1H); LCMS (ESI, M+1): *m/z* = 179.

[0000380] Step E. 2-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol: To a solution of 2-fluoronaphthalene-1,3-diol (7.6 g, 1.0 equiv.) and 2-bromoethynyl(*triisopropyl*)silane (13.4 g, 1.2 equiv.) in 1,4-dioxane (150 mL) were added dichloro(*p*-cymene)ruthenium(II) dimer (2.61 g, 0.1 equiv.) and AcOK (8.37 g, 2.0 equiv.). The reaction was stirred at 110 °C for 3 hours under N₂ atmosphere. The mixture was poured into H₂O (200 mL) and extracted with EtOAc (3×60 mL). The combined organic layers were concentrated under reduced pressure. The crude product was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) to afford the tittle compound (3.5 g, 22% yield) as a gray solid; ¹H NMR (400 MHz, CDCl₃) δ 7.65 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.27 (s, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 1.24-1.17 (m, 21H); LCMS (ESI, M+1): *m/z* = 359.

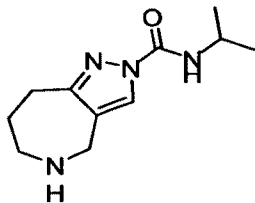
[0000381] Step F. 3-((benzyloxy)methoxy)-2-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol: To a solution of 2-fluoro-8-((*triisopropylsilyl*)ethynyl)naphthalene-1,3-diol (2.8 g, 1.0 equiv.) and DIEA (1.51 g, 1.5 equiv.) in DCM (24.0 mL) was added ((chloromethoxy)methyl)benzene (1.22 g, 1.0 equiv.) at -40 °C. The reaction was stirred at 0-10 °C for 5 hours. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 100:1 to 20:1) to afford the tittle compound (3.2 g, 77% yield) as a yellow solid; ¹H NMR (400 MHz, CDCl₃) δ 9.19 (s, 1H), 7.68 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.38-7.30 (m, 6H),

7.17 (d, $J = 7.6$ Hz, 1H), 5.47 (s, 2H), 4.80 (s, 2H), 1.24-1.12 (m, 21H); LCMS (ESI, M+1): $m/z = 479$.

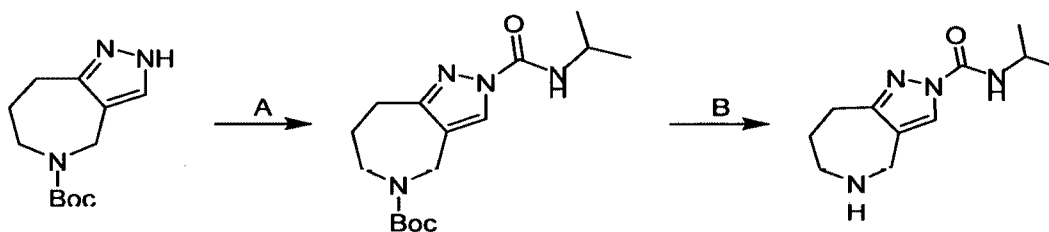
[0000382] Step G. 3-((benzyloxy)methoxy)-2-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate: To a solution of 3-((benzyloxy)methoxy)-2-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (550 mg, 1.0 equiv.) and DIEA (297 mg, 2.0 equiv.) in DCM (3.0 mL) was added TiF_2O (486 mg, 1.5 equiv.) at -40°C . The reaction was stirred at -40°C for 0.5 hour. The mixture was quenched with water (10 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 , and then filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate 100:1 to 20:1) to afford the title compound (650 mg, 92% yield) as a yellow solid; ^1H NMR (400 MHz, CDCl_3) δ 7.71 (d, $J = 7.2$ Hz, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.54 (d, $J = 7.6$ Hz, 1H), 7.37-7.33 (m, 1H), 7.30-7.23 (m, 5H), 5.44-5.38 (m, 2H), 4.76-4.68 (m, 2H), 1.19-1.13 (m, 3H), 1.12-1.03 (m, 18H).

[0000383] Step H. ((6-((benzyloxy)methoxy)-7-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane: To a solution of 3-((benzyloxy)methoxy)-2-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate (50.0 mg, 1.0 equiv.) and TEA (24.8 mg, 3.0 equiv.) in 1,4-dioxane (1.0 mL) were added $\text{Pd}(\text{dppf})\text{Cl}_2$ (5.99 mg, 0.1 equiv.) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (31.4 mg, 3.0 equiv.). The reaction mixture was stirred under N_2 at 100°C for 2 hours. The mixture poured into water (10 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate 100:1 to 50:1) to afford the title compound (32 mg, 66% yield) as a yellow oil; ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.66 (d, $J = 7.1$ Hz, 1H), 7.63 - 7.55 (m, 2H), 7.51 - 7.47 (m, 1H), 7.29 - 7.27 (m, 5H), 5.40 - 5.37 (m, 2H), 4.73 - 4.69 (m, 2H), 1.42 (s, 12H), 1.11 - 1.06 (m, 21H).

Intermediate 52



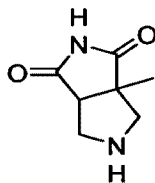
N-isopropyl-5,6,7,8-tetrahydropyrazolo[4,3-c]azepine-2(4H)-carboxamide



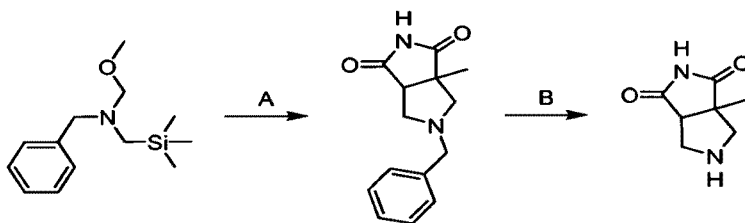
[0000384] Step A. tert-butyl 2-(isopropylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[4,3-c]azepine-5-carboxylate: To a solution of tert-butyl 4,6,7,8-tetrahydro-2H-pyrazolo[4,3-c]azepine-5-carboxylate (4.0 g, 1.0 *equiv.*) in THF (20 mL) was added portion wise CDI (2.73 g, 1 *equiv.*) and isopropylamine (1.1 g, 1.1 *equiv.*) at 25 °C. The reaction was stirred at 25 °C for 1 hour. The mixture was concentrated and purified by column chromatography (SiO₂, **petroleum ether/ethyl acetate 3:1 to 0:1**) to afford the title compound (4.5 g, 82% yield) as a white solid; LCMS (ESI, M+1): m/z = 323.2.

[0000385] Step B. N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[4,3-c]azepine-2-carboxamide: A solution of tert-butyl 2-(isopropylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[4,3-c]azepine-5-carboxylate (6.0 g, 1 *equiv.*) in HCl•MeOH (30 mL) was stirred at 25 °C for 0.5 hour. The mixture was concentrated to afford the title compound (3.2 g, 77% yield) as a white solid; LCMS (ESI, M+1): m/z = 223.2.

Intermediate 53



3a-methyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione

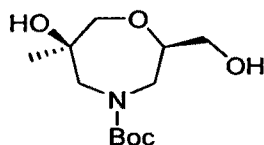


[0000386] Step A. 5-benzyl-3a-methyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione: To a mixture of 3-methylpyrrole-2,5-dione (608 mg, 1.0 equiv.) and N-(methoxymethyl)-1-phenyl-N-(trimethylsilylmethyl)methanamine (1.3 g, 1.0 equiv.) in CH₂Cl₂ (10 mL) was added a solution of TFA (62.4 mg, 40.5 μ L, 0.1 equiv.) in CH₂Cl₂ (1.0 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was diluted with sat. aq. NaHCO₃ (40 mL) and extracted with CH₂Cl₂ (3 $\times$ 50 mL). The combined organic layers were dried, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (Ethyl acetate/Petroleum ether 2 : 1) to afford the title compound (0.8 g, 60% yield) as a colorless oil; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.19 (s, 1H), 7.33-7.27 (m, 2H), 7.26-7.20 (m, 3H), 3.54-3.49 (m, 2H), 3.12-3.00 (m, 2H), 2.82 (d, *J* = 7.2 Hz, 1H), 2.40 (dd, *J* = 8.0, 9.6 Hz, 1H), 1.96-1.91 (m, 1H), 1.24 (s, 3H); LCMS (ESI, M+1): *m/z* = 245.2.

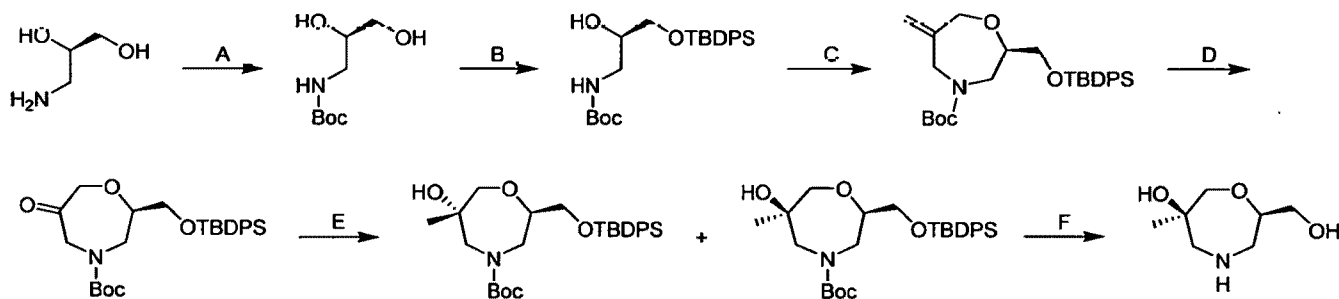
[0000387] Step B. tert-butyl N-[(5-carbamoyl-2-methyl-pyrazol-3-yl)methyl]carbamate: To a mixture of 5-benzyl-3a-methyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (0.8 g, 1.0 equiv.) in THF (30 mL) was added Pd/C (300 mg, 10% purity), the mixture was degassed and purged with H₂ and stirred at 40 °C for 12 hours under H₂ atmosphere (15 psi). The reaction

mixture was filtered and the filtrate was concentrated under the reduced pressure to afford the title compound (400 mg, 79% yield) as a colorless oil; LCMS (ESI, M+1]: m/z = 155.2.

Intermediate 54



(2R,6R)-2-(hydroxymethyl)-6-methyl-1,4-oxazepan-6-ol



[0000388] Step A. (R)-tert-butyl (2,3-dihydroxypropyl)carbamate: To a solution of (R)-3-aminopropane-1,2-diol (50.0 g, 1 equiv.) and Et₃N (84.3 g, 1.52 equiv.) in CH₃OH (1.5 L) was added Boc₂O (182 g, 1.52 equiv.) portion wise at 0 °C. The reaction was stirred at 25 °C for 12 hours. The mixture was poured into H₂O (2.0 L) and extracted with ethyl acetate (1.0 L). The organic phase was washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated to dryness. The residue was triturated with petroleum ether (150 mL) at 25 °C for 1 hour and filtered. The filter cake was washed with petroleum ether (3×50 mL) and dried to afford the title compound (48.0 g, 45% yield) as a colorless oil; ¹H NMR (400 MHz, DMSO-d₆) δ = 6.57 (t, J = 4.8 Hz, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.47 (t, J = 6.0 Hz, 1H), 3.46 – 3.40 (m, 1H), 3.31 - 3.25 (m, 2H), 3.06 - 2.99 (m, 1H), 2.87 - 2.80 (m, 2H), 1.37 (s, 9H).

[0000389] Step B. (R)-tert-butyl (3-((tert-butyldiphenylsilyl)oxy)-2-hydroxypropyl)carbamate: To a solution of (R)-tert-butyl (2,3-dihydroxypropyl)carbamate (43.0 g, 1 equiv.) in CH₂Cl₂ (900 mL) were added imidazole (18.37 g, 1.2 equiv.) and TBDPSCl (67.9

g, 1.1 equiv.). The reaction mixture was stirred at 25 °C for 12 hours. The mixture was partitioned between CH₂Cl₂ (500 mL) and H₂O (1.0 L). The organic phase was separated and washed with brine 1.0 L (2×500 mL). The organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether 0 - 20%) to afford the title compound (42.3 g, 37.9% yield) as a colorless oil; ¹H NMR (400 MHz, DMSO-d₆) δ = 7.67 - 7.63 (m, 4H), 7.46 - 7.40 (m, 6H), 6.60 (t, J = 5.2 Hz, 1H), 4.81 (s, 1H), 3.63 (s, 1H), 3.57 - 3.50 (m, 2H), 3.20 - 3.13 (m, 1H), 2.97 - 2.91 (m, 1H), 1.36 (s, 9H), 0.99 (s, 9H); LCMS (ESI, M+1): m/z = 430.2.

[0000390] Step C. (R)-tert-butyl 2-(((tert-butyl)diphenylsilyl)oxy)methyl)-6-methylene-1,4-oxazepane-4-carboxylate: To a solution of tert-butyl N-[(2R)-3-[tert-butyl(diphenyl)silyl]oxy-2-hydroxy-propyl]carbamate (20 g, 1 equiv.) in THF (400 mL) was added NaH (4.10 g, 60% purity, 2.2 equiv.) at 0 °C under N₂ atmosphere followed by 3-chloro-2-(chloromethyl)prop-1-ene (5.82 g, 1 equiv.). The reaction was stirred at 0 °C for 2 hours under N₂ atmosphere. The mixture was quenched by addition of H₂O (600 mL) at 0 °C and extracted with ethyl acetate (2×300 mL), the combined organic layers were washed with brine (20 mL) and dried over Na₂SO₄. The mixture was filtered and concentrated. The residue was purified by reversed-phase HPLC (Column: I.D.100mm*H350mm Welch Ultimate XB_C18 20-40μm; mobile phase: water (0.1% formic acid) – ACN; B% 30 - 100% 50 min) to afford the title compound (1.8 g, 7.64% yield) as a colorless oil; ¹H NMR (400 MHz, CDCl₃) δ = 7.68 - 7.66 (m, 4H), 7.42 - 7.36 (m, 6H), 5.03 - 4.90 (m, 2H), 4.66 - 4.22 (m, 3H), 4.04 - 3.98 (m, 1H), 3.78 - 3.49 (m, 4H), 2.85 - 2.77 (m, 1H), 1.47 (s, 9H), 1.07 (s, 9H); LCMS (ESI, M+1): m/z = 482.2.

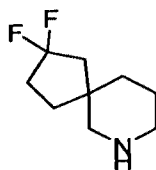
[0000391] Step D. (R)-tert-butyl 2-(((tert-butyl)diphenylsilyl)oxy)methyl)-6-oxo-1,4-oxazepane-4-carboxylate: To a solution of tert-butyl (2R)-2-[[tert-butyl(diphenyl)silyl]oxymethyl]-6-methylene-1,4-oxazepane-4-carboxylate (1.8 g, 1 equiv.) in THF (9 mL) and H₂O (9 mL) were added NaIO₄ (1.84 g, 2.3 equiv.) and K₂OsO₄•2H₂O (68.8 mg, 0.05 equiv.). The reaction mixture was stirred at 25 °C for 1 hour. The mixture was quenched by addition of aqueous Na₂SO₃ (20 mL) at 0 °C and H₂O (10 mL) and then extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with brine (30 mL) and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate 1:0 to 100:1) to afford the title compound (1.1 g, 57% yield) as a colorless oil; ¹H NMR (400 MHz, CDCl₃) δ

= 7.67 (d, J = 6.8 Hz, 4H), 7.45 - 7.38 (m, 6H), 4.50 - 4.21 (m, 3H), 4.03 - 3.97 (m, 1H), 3.83 - 3.60 (m, 4H), 3.01 - 2.96 (m, 1H), 1.47 (d, J = 10.0 Hz, 9H), 1.07 (m, 9H); LCMS (ESI, M+23): m/z= 506.2.

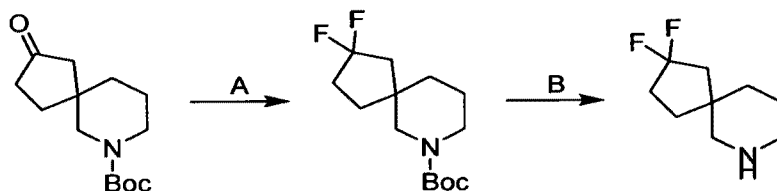
[0000392] Step E. (2R,6S)-tert-butyl 2-(((tert-butyl)diphenylsilyl)oxy)methyl)-6-hydroxy-6-methyl-1,4-oxazepane-4-carboxylate and (2R,6R)-tert-butyl 2-(((tert-butyl)diphenylsilyl)oxy)methyl)-6-hydroxy-6-methyl-1,4-oxazepane-4-carboxylate: To a solution of tert-butyl (2R)-2-[[tert-butyl(diphenyl)silyl]oxymethyl]-6-oxo-1,4-oxazepane-4-carboxylate (900 mg, 1 equiv.) in THF (13 mL) was added MeMgBr (3 M, 4.04 equiv.) under N₂ atm. at 0 °C. The reaction mixture was stirred at 25 °C for 2 hours under N₂ atmosphere. The mixture was quenched by addition of sat.aq.NH₄Cl (30 mL) at 0 °C and H₂O (15 mL), and then was extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with brine (20 mL) and concentrated. The residue was purified by flash silica gel chromatography (Ethyl acetate/Petroleum ether 0-15%) to afford two isomers: R,S (350 mg, 33% yield) as a colorless oil; ¹H NMR (400 MHz, CDCl₃) δ = 7.59 - 7.57 (m, 4H), 7.38 - 7.29 (m, 6H), 4.15 - 4.11 (m, 1H), 3.95 - 3.65 (m, 3H), 3.61 - 3.45 (m, 2H), 3.21 (d, J = 12.4 Hz, 1H), 2.82 (d, J = 15.2 Hz, 1H), 2.70 - 2.64 (m, 1H), 1.42 (s, 9H), 1.11 (s, 3H), 0.99 (s, 9H); LCMS (ESI, M-99): m/z= 400.2. and R,R (190 mg, 18% yield) as a colorless oil; LCMS (ESI, M-99): m/z= 400.2.

[0000393] Step F. (2R,6R)-2-(hydroxymethyl)-6-methyl-1,4-oxazepan-6-ol: To a solution of (2R,6R)-tert-butyl 2-(((tert-butyl)diphenylsilyl)oxy)methyl)-6-hydroxy-6-methyl-1,4-oxazepane-4-carboxylate (520 mg, 1 equiv.) in CH₂Cl₂ (2 mL) was added HCl•dioxane (4 M, 10 mL). The mixture was stirred at 25 °C for 12 hours. The mixture was concentrated, the residue was diluted with H₂O (4 mL) and the pH of the mixture was adjusted to 7 with saturated NaHCO₃ aqueous. The mixture was extracted with ethyl acetate (2 × 5 mL). The combined organic phase was dried over anhydrous Na₂SO₄ and concentrated to afford the title compound (70 mg, crude) as a light-yellow oil.

Intermediate 55



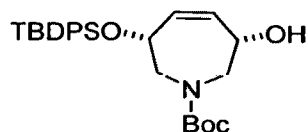
3,3-difluoro-7-azaspiro[4.5]decane



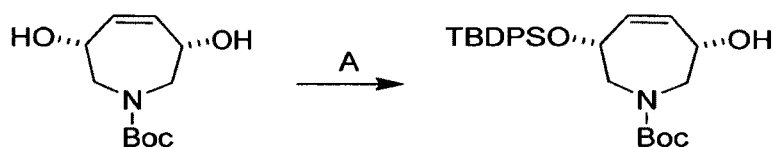
[0000394] Step A. tert-butyl 3,3-difluoro-7-azaspiro[4.5]decane-7-carboxylate: To a solution of tert-butyl 3-oxo-7-azaspiro[4.5]decane-7-carboxylate (500 mg, 1.0 equiv.) in CH₂Cl₂ (8 mL) was added DAST (541 mg, 443 μ L, 1.7 equiv.). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 $\times$ 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated and purified by column chromatography (SiO₂, petroleum ether/ethyl acetate 50:1 to 30:1) to afford the title compound (150 mg, 28% yield) as a yellow oil. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 3.52-3.10 (m, 4H), 2.25-2.10 (m, 2H), 2.05-1.95 (m, 1H), 1.94-1.83 (m, 1H), 1.78-1.68 (m, 1H), 1.61-1.49 (m, 5H), 1.46 (s, 9H); ¹⁹F NMR (377 MHz, CHLOROFORM-d) δ = -87.62--90.03 (m, 1F).

[0000395] Step B. 3,3-difluoro-7-azaspiro[4.5]decane: To a solution of tert-butyl 3,3-difluoro-7-azaspiro[4.5]decane-7-carboxylate (100 mg, 1.0 equiv.) in dioxane (4 mL) was added HCl•dioxane (4 M, 4 mL, 44.1 equiv.). The mixture was stirred at 0 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with MeOH (4 mL), the pH was adjusted 9 with NaHCO₃, the mixture was stirred for 0.3 hours. The reaction mixture was concentrated to afford the title compound (70.0 mg, 91.1% yield, HCl salt, crude) as a colorless oil.

Intermediate 56

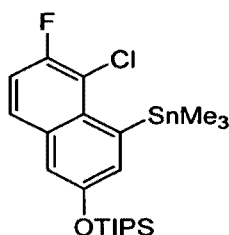


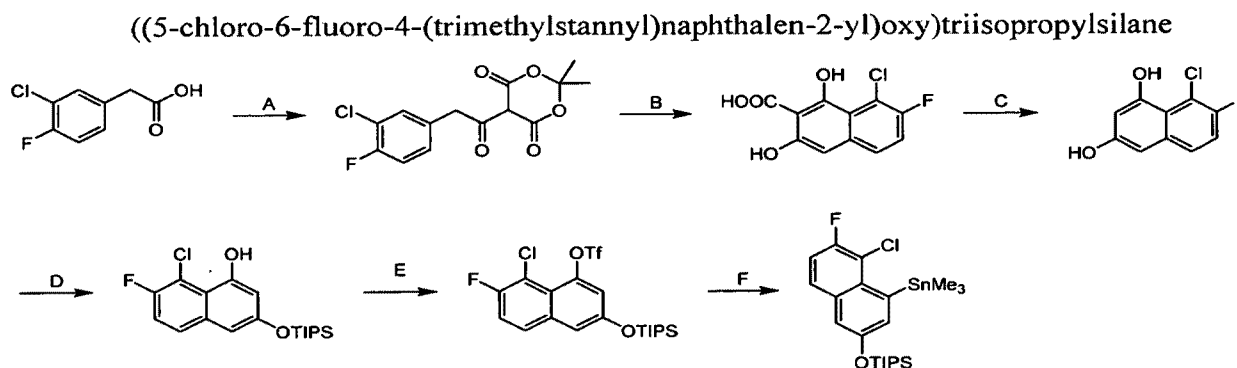
tert-butyl (3R,6S)-3-((tert-butyldiphenylsilyl)oxy)-6-hydroxy-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate



[0000396] Step A. tert-butyl (3R,6S)-3-((tert-butyldiphenylsilyl)oxy)-6-hydroxy-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate: To a solution of tert-butyl 3,6-dihydroxy-2,3,6,7-tetrahydroazepine-1-carboxylate (3.00 g, 1 equiv.) in DMF (20 mL) was added imidazole (2.67 g, 3 equiv.) and TBDPSCl (4.32 g, 1.2 equiv.). The mixture was stirred at 40 °C for 12 hours. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 3). Combined organic phase was washed with brine (20.0 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/ Ethyl acetate 10:1 to 5:1) to afford the title compound (1.8 g, 29.4% yield) as a white solid; ¹H NMR (400 MHz, CDCl₃) δ = 7.67 - 7.55 (m, 4H), 7.40 - 7.27 (m, 6H), 5.64 - 5.45 (m, 2H), 4.33 - 4.25 (m, 1H), 4.22 - 4.07 (m, 1H), 3.82 - 3.46 (m, 2H), 3.40 - 2.91 (m, 2H), 2.54 - 2.14 (m, 1H), 1.38 (br s, 3H), 1.24 (s, 6H), 1.00 (s, 9H).

Intermediate 57





[0000397] Step A. 5-(2-(3-chloro-4-fluorophenyl)acetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione: To a mixture of 2-(3-chloro-4-fluorophenyl)acetic acid (330 g, 1 equiv.) and 2,2-dimethyl-1,3-dioxane-4,6-dione (277 g, 1.1 equiv.) in MeCN (1500 mL) was added DMAP (18.2 g, 0.09 equiv.) at 20 °C. Then DIEA (486 g, 2.15 equiv.) was added into the mixture slowly over the course of 1 hour under 15-30 °C. Following that 2,2-dimethylpropanoyl chloride (232.10 g, 1.1 equiv.) was added into the mixture over the course of 1 hour 1 hour while maintaining the temperature at 25-40 °C. After the additions were complete the mixture was stirred at 45 °C for 3 hours. The mixture was cooled to 0 °C, then the pH was adjusted to 3 with HCl (4N, 5 L) and mixture was stirred at 0 °C for 1 hour. The filter cake was triturated with MeCN (3 L) to afford the title compound (933 g, 84% yield) as a yellow solid that was used in next step without further purification. ¹HNMR (400 MHz, CDCl₃) δ= 15.36 (br s, 1H), 7.46 (dd, *J* = 2.0, 6.8 Hz, 1H), 7.30 - 7.25 (m, 1H), 7.10 (t, *J* = 8.8 Hz, 1H), 4.39 - 4.34 (m, 1H), 1.74 (s, 6H).

[0000398] Step B. 8-chloro-7-fluoro-1,3-dihydroxy-2-naphthoic acid: A mixture of 5-(2-(3-chloro-4-fluorophenyl)acetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (650 g, 1.0 equiv.) in CF₃SO₃H (1300 mL) was stirred at 5-20°C. Then the mixture was stirred at 10 °C for 2 hours. After reaction completion, the mixture was poured into ice water (2 L) and filtered. The filter cake was washed with water (5 L) and dried to afford the title compound (2000 g, crude) as yellow solid and used in next step without further purification.

[0000399] Step C. 8-chloro-7-fluoronaphthalene-1,3-diol: A mixture of 8-chloro-7-fluoro-1,3-dihydroxy-2-naphthoic acid (1.2 kg, 1.0 equiv.) in MeCN (700 mL) and H₂O (700 mL) was stirred at 85 °C for 12 hours under N₂. The mixture was concentrated under vacuum to remove

acetonitrile. The residue was extracted with ethyl acetate (2 L × 2), dried over Na₂SO₄ and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether / ethyl acetate 3:1) and prep-HPLC (column: Phenomenex Luna C18 200*40mm*10um; mobile phase: water (0.1% formic acid) - ACN; B%: 27%-57%, 10min). The desired fraction was collected and extracted with ethyl acetate (2 L), dried over Na₂SO₄ and concentrated under vacuum to afford the title compound (17 g, 16% yield two steps) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ 10.17 (s, 1H), 9.71 (s, 1H), 7.58 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.32 (t, *J* = 8.8 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.63 (d, *J* = 2.0 Hz, 1H).

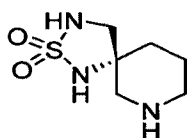
[0000400] Step D. 8-chloro-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-ol: To a solution of 8-chloro-7-fluoronaphthalene-1,3-diol (10 g, 1 equiv.) and DIEA (12.2 g, 2.0 equiv.) in DCM (150 mL) was added TIPSCl (8.16 g, 0.9 equiv.) at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. The mixture was concentrated in vacuum and the residue was purified by column chromatography (SiO₂, petroleum ether / ethyl acetate 10:1) to afford the title compound (15 g, 86% yield) as a yellow oil.

[0000401] Step E. 8-chloro-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl trifluoromethanesulfonate: To a mixture of 8-chloro-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-ol (15 g, 1.0 equiv.) and DIEA (15.8 g, 3.0 equiv.) in DCM (150 mL) was added Tf₂O (17.2 g, 1.5 equiv.) at 40 °C. The mixture was stirred at -40 °C for 0.5 hour. The mixture was concentrated in vacuum and the residue was purified by column chromatography (SiO₂, petroleum ether / ethyl acetate 10:1) to afford the title compound (19 g, 90% yield) as a yellow oil.

[0000402] Example F. ((5-chloro-6-fluoro-4-(trimethylstannyl)naphthalen-2-yl)oxy)triisopropylsilane: To a mixture of 8-chloro-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl trifluoromethanesulfonate (5 g, 1.0 equiv.), trimethyl(trimethylstannyl)stannane (12.7 g, 3.88 equiv.) and LiCl (1.27 g, 3.0 equiv.) in toluene (50 mL) was added Pd(PPh₃)₄ (1.15 g, 0.1 equiv.) under N₂. The mixture was stirred at 100 °C for 12 hours under N₂. The mixture was quenched with water (20 mL) and extracted with ethyl acetate (100 mL × 3), the combined organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue and the residue was purified by column chromatography (SiO₂, petroleum ether) and reversed phase flash [water (0.1%, FORMIC ACID)/acetonitrile] to afford the title compound

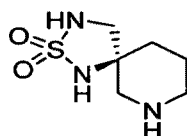
(3 g, 55% yield) as yellow oil. ^1H NMR (400 MHz, CDCl_3) δ = 7.60 (dd, J = 5.6, 9.2 Hz, 1H), 7.52 (d, J = 2.4 Hz, 1H), 7.31 - 7.26 (m, 1H), 7.20 (d, J = 2.4 Hz, 1H), 1.35 - 1.30 (m, 3H), 1.15 (d, J = 7.2 Hz, 18H), 0.51 - 0.35 (m, 9H)

Intermediate 58

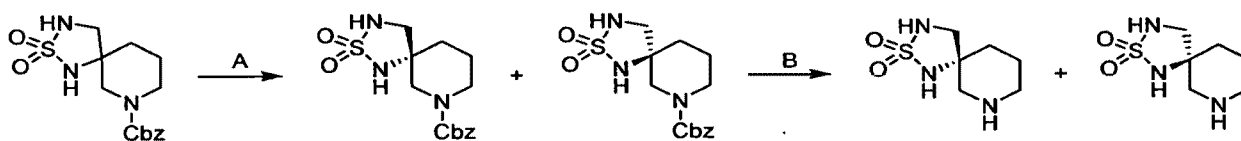


(*R*)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide

Intermediate 59



(*S*)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide

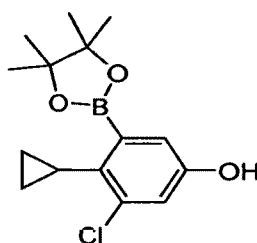


[0000403] Step A. benzyl (*R*)-2-thia-1,3,7-triazaspiro[4.5]decane-7-carboxylate 2,2-dioxide and benzyl (*S*)-2-thia-1,3,7-triazaspiro[4.5]decane-7-carboxylate 2,2-dioxide: Racemic benzyl 2-thia-1,3,7-triazaspiro[4.5]decane-7-carboxylate 2,2-dioxide (46.5 g) was separated by chiral SFC (column: DAICEL CHIRALPAK IC(250mm*50mm,10um); mobile phase: [0.1% $\text{NH}_3\text{H}_2\text{O}$ -IPA]; B%: 55%-55%, 7min) to afford the two title compound isomers: R-isomer (22 g, 41% yield, 99.9%ee) as a yellow solid and S-isomer (22 g, 42% yield, 99.9%ee) as a yellow solid. LCMS (ESI, $\text{M}+1$): m/z = 326.1.

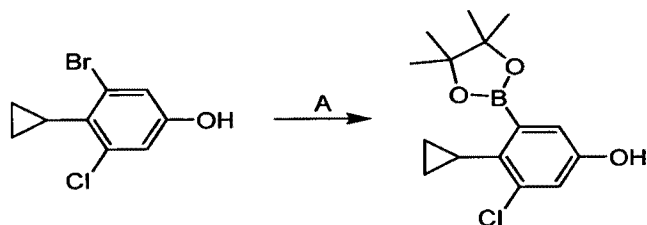
[0000404] Step B. (R)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide: To a solution of (R)-2-thia-1,3,7-triazaspiro[4.5]decane-7-carboxylate 2,2-dioxide (20.0 g, 1.00 equiv.) in methanol (160 mL) was added Pd/C (10%, 3.00 g) under nitrogen atmosphere. The suspension was degassed and stirred under hydrogen (15 Psi) at 25 °C for 2 hours. The reaction mixture was filtered and concentrated under reduced pressure to afford the title compound (11 g, 93% yield) as a yellow solid. ¹H NMR (400 MHz, MeOD-d₄) δ = 3.37 - 3.32 (m, 1H), 3.13 (d, J = 11.7 Hz, 1H), 2.93 - 2.84 (m, 1H), 2.82 - 2.72 (m, 2H), 2.72 - 2.62 (m, 1H), 1.82 (br dd, J = 4.8, 6.7 Hz, 1H), 1.79 - 1.70 (m, 1H), 1.65 (td, J = 4.2, 8.3 Hz, 1H), 1.60 - 1.49 (m, 1H)

[0000405] (S)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide: To a solution of benzyl benzyl (S)-2-thia-1,3,7-triazaspiro[4.5]decane-7-carboxylate 2,2-dioxide. (22.0 g, 1.00 equiv.) in methanol (160 mL) was added Pd/C (10%, 3.00 g) under nitrogen atmosphere. The suspension was degassed and stirred under hydrogen (15 Psi) at 25 °C for 2 hours. The reaction mixture was filtered and concentrated under reduced pressure to afford the title compound (11.8 g, 91% yield) as a yellow solid. ¹H NMR (400 MHz, MeOD-d₄) δ = 3.37 - 3.32 (m, 1H), 3.15 (s, 1H), 3.19 - 3.07 (m, 1H), 2.92 - 2.83 (m, 1H), 2.82 - 2.72 (m, 2H), 2.72 - 2.62 (m, 1H), 1.82 (br dd, J = 4.8, 6.7 Hz, 1H), 1.79 - 1.71 (m, 1H), 1.70 - 1.60 (m, 1H), 1.59 - 1.48 (m, 1H)

Intermediates 60

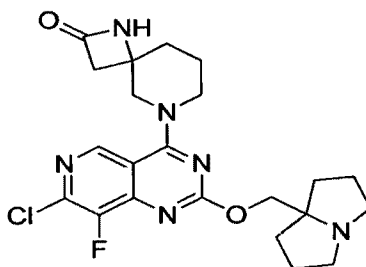


3-chloro-4-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

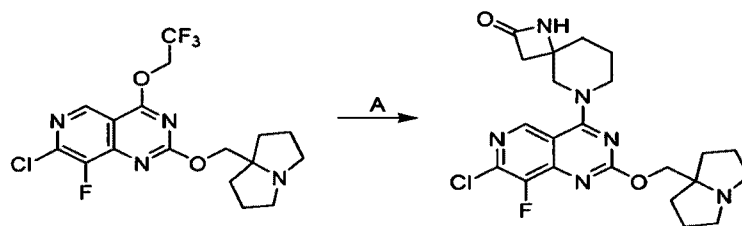


[0000406] Step A. 3-chloro-4-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol: To a solution of 3-bromo-5-chloro-4-cyclopropylphenol (2.00 g, 1.0 equiv.) in dioxane (50 mL) was added KOAc (2.38 g, 3.0 equiv.), Pin₂B₂ (4.00 g, 2.0 equiv.) and Pd(dppf)Cl₂ (591 mg, 0.1 equiv.). The mixture was stirred at 100 °C for 4 hours under nitrogen atmosphere. The reaction mixture was poured into saturated aqueous NH₄Cl solution (5 mL) and extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash silica gel chromatography [ethyl acetate in petroleum ether 0 - 35%] to afford the title compound (1.10 g, 46% yield) as a white solid; ¹H NMR (400 MHz, CHLOROFORM-d) δ = 6.92 (d, *J* = 2.6 Hz, 1H), 6.87 (d, *J* = 2.6 Hz, 1H), 5.33 (br s, 1H), 1.99 - 1.90 (m, 1H), 1.39 (s, 12H), 1.00 - 0.94 (m, 2H), 0.53 - 0.47 (m, 2H).

Intermediate 61

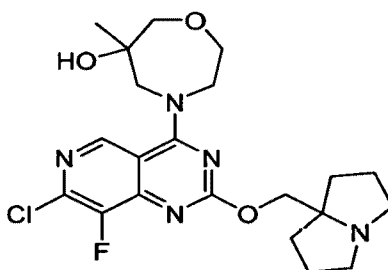


6-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one

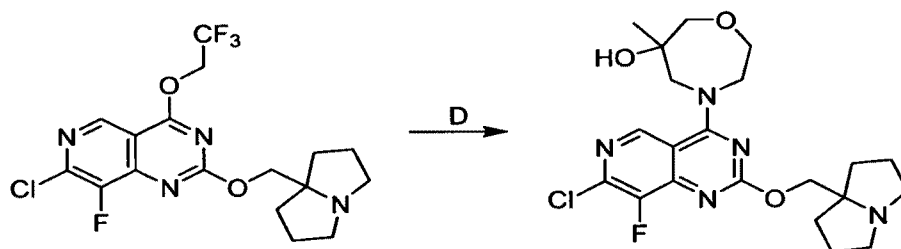


[0000407] Step A. 6-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one: To a mixture of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (200 mg, 475 μ mol, 1.0 equiv.), 1,6-diazaspiro[3.5]nonan-2-one (60.0 mg, 428 μ mol, 0.9 equiv.), 4Å molecular sieves (10.0 mg) in DMF (2 mL) was added DIEA (184 mg, 1.43 mmol, 248 μ L, 3.0 equiv.). The mixture was stirred at 40 °C for 4 hours. After reaction completion, the mixture was filtered to give a filtrate. The crude product was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) to give the title compound (60.0 mg, 130 μ mol, 27% yield) as a yellow solid; LCMS (ESI, M+1): m/z= 461.3.

Intermediate 62

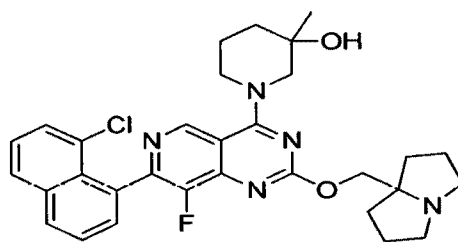


4-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol

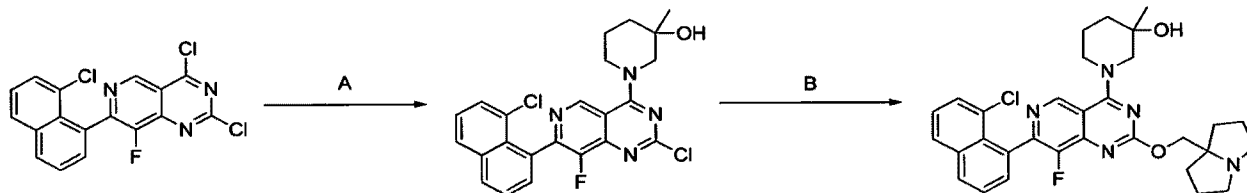


[0000408] Step A. 4-(7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol: A mixture of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (0.45 g, 1 equiv.), 6-methyl-1,4-oxazepan-6-ol (210 mg, 1.5 equiv.), DIPEA (276 mg, 2 equiv.) and 4Å molecular sieves (50 mg) in DMF (4 mL) was stirred at 40 °C for 14 hours under N₂ atmosphere. The reaction mixture was filtered and the filtrate was concentrated to give a residue. The residue was purified by reversed phase flash chromatography (water (0.1% formic acid) - ACN) to afford the title compound (205 mg, 40.3% yield) as a light-yellow solid; LCMS (ESI, M+1): m/z = 452.0.

EXAMPLE 1



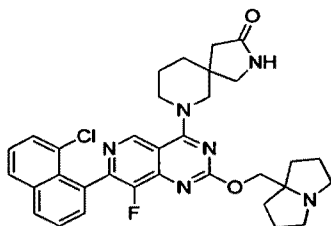
1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



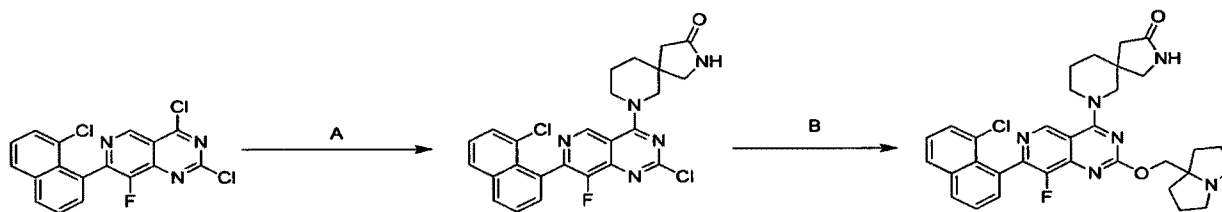
[0000409] Step A. 1-[2-chloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol: To a mixture of 2,4-dichloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidine (1.48 g, 3.90 mmol) in dichloromethane (15 mL) was added DIEA (5.05 g, 39.0 mmol, 6.80 mL) and 3-methylpiperidin-3-ol (270 mg, 2.34 mmol) at - 40 °C under N₂. The mixture was stirred at - 40 °C for 0.5 h. After completion, the mixture was quenched by water (10 mL). The aqueous phase was extracted with dichloromethane (2 × 8 mL), the combined organic layer was washed with brine (10 mL) and dried over with Na₂SO₄. The mixture was filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give 1-[2-chloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (128 mg, 35% yield) as yellow solid; ¹H NMR (400 MHz, DMSO-d₆): δ 9.37 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.77-7.71 (m, 1H), 7.66 (t, *J* = 7.6 Hz, 2H), 7.61-7.55 (m, 1H), 4.84 (d, *J* = 16.4 Hz, 1H), 4.54-4.41 (m, 1H), 4.18 (br dd, *J* = 6.0, 12.8 Hz, 1H), 3.68-3.54 (m, 1H), 2.08-2.00 (m, 1H), 1.75-1.66 (m, 3H), 1.20-1.17 (m, 3H); LCMS (ESI, M+1): *m/z* 457.1.

[0000410] Step B. 1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of 1-[2-chloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (112 mg, 245 μmol) and (tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (69.2 mg, 490 μmol) in dioxane (2.0 mL) was added DIEA (95.0 mg, 735 μmol, 128 μL). The mixture was stirred at 90 °C for 15 h. After completion, the mixture was diluted with ethyl acetate (8 mL) and water (8 mL). The aqueous phase was extracted with ethyl acetate (2 × 5 mL) and dichloromethane : methanol = 10:1 (1 × 5 mL). The organic layers were concentrated in vacuum. The residue was purified by prep-HPLC (Water s Xbridge 150*25mm* 5um; mobile phase: [water (10mM NH₄HCO₃) - ACN]; B%: 22% - 52%, 10 min) to afford the title compound (23.7 mg, 16% yield) as off-white solid. ¹H NMR (400 MHz, CDCl₃-d): δ 9.13 (d, *J* = 2.4 Hz, 1H), 8.04-7.97 (m, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.64-7.52 (m, 3H), 7.45-7.38 (m, 1H), 4.50-4.25 (m, 4H), 3.57-3.45 (m, 1H), 3.35 (br dd, *J* = 6.8, 13.2 Hz, 1H), 3.26-2.98 (m, 3H), 2.75-2.61 (m, 2H), 2.18-2.03 (m, 3H), 1.96-1.84 (m, 5H), 1.78-1.71 (m, 4H), 1.36 (d, *J* = 2.4 Hz, 3H); LCMS (ESI, M+1): *m/z* 562.1

EXAMPLE 2



7-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one

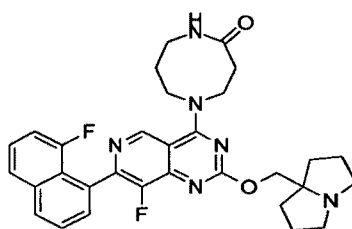


[0000411] Step A. 7-[2-chloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 2,4-dichloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidine (0.15 g, 396 μ mol) in dichloromethane (5.0 mL) was added DIEA (512 mg, 3.96 mmol) at -40 °C. After the mixture was stirred at -40 °C for 10 minutes, 2,9-diazaspiro[4.5]decan-3-one (73.3 mg, 475 μ mol) was added into the mixture. The mixture was stirred at -40 °C for 10 minutes. After completion, the mixture was diluted with water (10 mL) and extracted with dichloromethane (2 $\times$ 10 mL). The combined organic layer was washed with brine (10 mL), and then dried over Na₂SO₄. The mixture was filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give 7-[2-chloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.5]decan-3-one (120 mg, 45% yield) as a yellow Solid; LCMS [ESI, M+1]: m/z = 496.0.

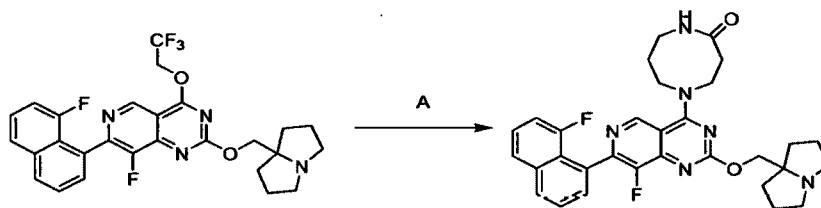
[0000412] Step B. 7-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: A mixture of 7-[2-chloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.5]decan-3-one (100 mg, 201 μ mol), (tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (56.9 mg, 403 μ mol) and DIEA (130 mg, 1.01 mmol, 175 μ L) in dioxane (1.0 mL) was stirred at

80 °C for 9 hours. After completion, the mixture was diluted with water (5.0 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine (10 mL), and then dried over Na₂SO₄. The mixture was filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: water s Xbridge 150*25mm * 5um; mobile phase: [water (10mM NH₄HCO₃) - ACN]; B%: 24% - 54%, 10 min) to give the title compound (23.0 mg, 18% yield) as yellow solid; LCMS [ESI, M+1]: m/z = 601. ¹H NMR (400 MHz, chloroform-d) δ 8.98 (d, J = 2.0 Hz, 1H), 8.00 (dd, J = 1.6, 7.8 Hz, 1H), 7.88 (td, J = 1.2, 8.4 Hz, 1H), 7.63-7.52 (m, 3H), 7.42 (t, J = 7.6 Hz, 1H), 6.00 (br d, J = 8.8 Hz, 1H), 4.30-4.18 (m, 2H), 4.09 (q, J = 12.4 Hz, 2H), 3.84-3.71 (m, 1H), 3.64 (dd, J = 13.2, 18.0 Hz, 1H), 3.48-3.38 (m, 1H), 3.21 (dd, J = 4.4, 10.0 Hz, 1H), 3.16-3.06 (m, 2H), 2.64 (td, J = 6.8, 10.0 Hz, 2H), 2.38-2.23 (m, 2H), 2.15-2.04 (m, 2H), 1.94-1.86 (m, 7H), 1.74-1.60 (m, 3H).

EXAMPLE 3



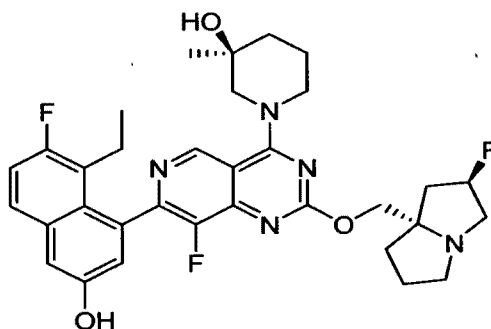
5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,5-diazocan-2-one



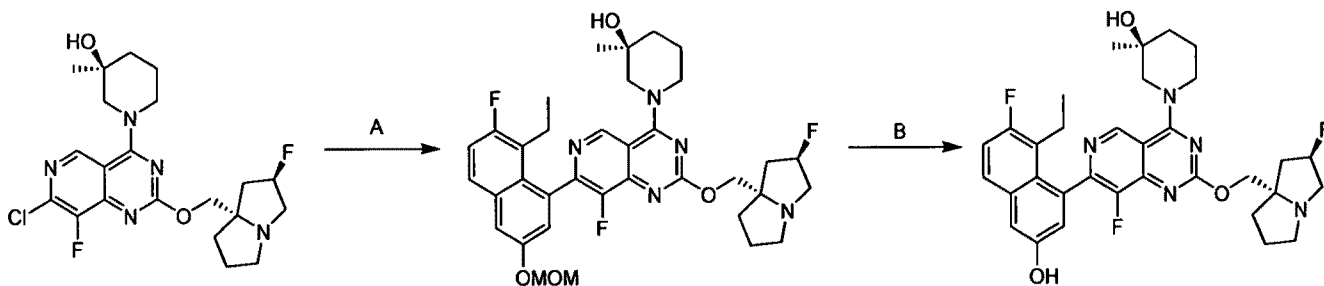
[0000413] Step A. 5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,5-diazocan-2-one: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((2,2,2-trifluoroethoxy)methoxy)pyrido[4,3-d]pyrimidine (100 mg, 188 μmol), 4Å MS (50 mg) and 1,5-diazocan-2-one (48.3 mg, 377 μmol) in DMF (2.00 mL) was added DIEA (73.1 mg, 565 μmol). The mixture

was stirred at 90 °C for 2 hours. After completion, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL) and dried over Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: water s Xbridge 150*25mm* 5um; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 17%-47%, 9 min) affording 5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,5-diazocan-2-one (18.6 mg, 17% yield) as white solid; ¹H NMR (400 MHz, CDCl₃-d) δ 9.08 (s, 1H), 8.00 (dt, J = 1.6, 8.0 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.68-7.56 (m, 2H), 7.49-7.42 (m, 1H), 7.17-7.06 (m, 1H), 6.03-5.86 (m, 1H), 4.45-3.92 (m, 6H), 3.40-3.29 (m, 2H), 3.15-3.07 (m, 2H), 3.04-2.91 (m, 2H), 2.68-2.60 (m, 2H), 2.15-1.96 (m, 5H), 1.91-1.87 (m, 3H), 1.72-1.62 (m, 2H); LCMS (ESI, M+1): m/z = 559.3.

EXAMPLE 4



(S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

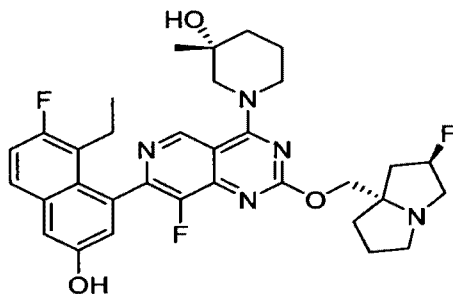


[0000414] Step A. (S)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-

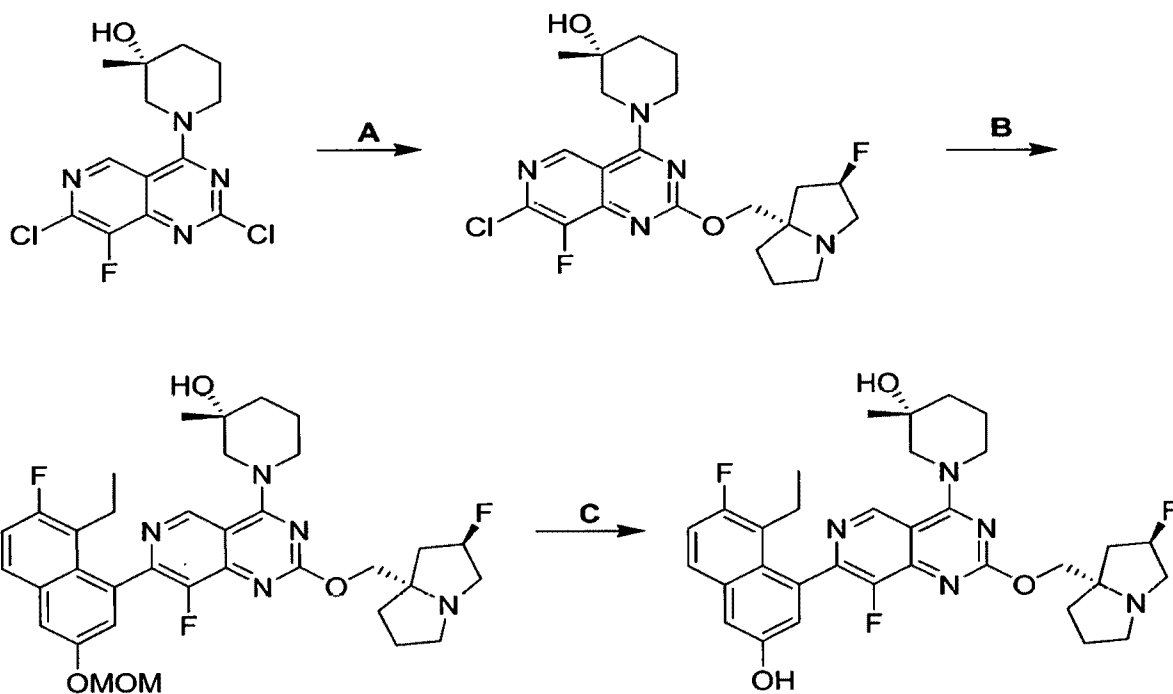
methylpiperidin-3-ol: To a mixture of 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (103 mg, 286 μmol , 1.3 equiv.) and (S)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (100 mg, 220 μmol , 1.0eq, synthesized according to example 5 step A replacing (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol with (S)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol) in THF (1.5 mL) was added cataCXium®-A-Pd-G3 (24.07 mg, 33.05 μmol , 0.15 equiv.) in one portion at 25 °C under N₂. Then K₃PO₄ (1.5 M, 440 μL , 3.0 equiv.) was added under N₂. The mixture was heated to 60 °C and stirred for 4 hours. After completion, the mixture was filtered and concentrated in vacuum. The crude product was purified by reversed phase flash chromatography (water (0.1% formic acid) - ACN) to give title compound as yellow oil; ¹H NMR (400 MHz, CDCl₃-d) δ = 9.14 (d, J = 8.0 Hz, 1H), 7.76 (dd, J = 6.0, 8.8 Hz, 1H), 7.55-7.50 (m, 1H), 7.27-7.24 (m, 1H), 7.23-7.20 (m, 1H), 5.37-5.20 (m, 3H), 4.52-4.35 (m, 2H), 4.33-4.20 (m, 2H), 3.52 (s, 3H), 3.50-3.40 (m, 1H), 3.36-3.14 (m, 4H), 3.04-2.77 (m, 2H), 2.59-2.47 (m, 1H), 2.29-2.11 (m, 4H), 1.98-1.85 (m, 4H), 1.80-1.69 (m, 2H), 1.36 (s, 3H), 0.84 (q, J = 7.6 Hz, 3H); LCMS (ESI, M+1-Boc): m/z = 652.3.

[0000415] Step B. (S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (70 mg, 107 μmol , 1 equiv.) in MeCN (1.4 mL) was added HCl•dioxane (4 M, 1.4 mL, 52 equiv.) at 5 °C. The reaction mixture was stirred at 5 °C for 0.5 hour. Upon completion, the reaction mixture was diluted with MeCN (3 mL) and basified with saturated NaHCO₃ solution to pH > 7. The reaction mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: water s Xbridge 150×25mm×5 μm ; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 40%-70%, 5 min) to give title compound as (32.5 mg, 50% yield) white solid; ¹H NMR δ = 9.21-8.99 (m, 1H), 7.51 (dd, J = 6.0, 9.2 Hz, 1H), 7.17 (t, J = 9.2 Hz, 1H), 7.10 (dd, J = 2.4, 15.6 Hz, 1H), 6.89-6.61 (m, 1H), 5.42-5.18 (m, 1H), 4.45-4.09 (m, 4H), 3.48-3.16 (m, 4H), 3.14-2.94 (m, 2H), 2.58-2.31 (m, 2H), 2.30-2.06 (m, 4H), 2.03-1.95 (m, 2H), 1.74-1.70 (m, 1H), 1.67-1.40 (m, 3H), 1.23 (d, J = 4.8 Hz, 3H), 0.81-0.75 (m, 3H); LCMS (ESI, M+1): m/z = 608.2.

EXAMPLE 5



(R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



[0000416] Step A. (R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To the mixture of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (20.0 g, 60.4 mmol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (10.6 g, 66.4 mmol), 4Å molecular sieves (5.00 g) in dioxane (80 mL) was added DIEA (23.4 g, 181 mmol), and the mixture was stirred at 90 °C for 10 hours. Upon completion, the reaction mixture was filtered. The mixture was

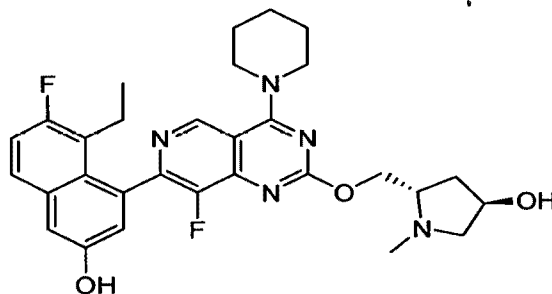
diluted with ethyl acetate (300 mL) and water (200 mL), and aqueous layer was then extracted with ethyl acetate (300 mL). The combined organic phase was washed with brine (200 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (19.5 g, 71% yield) as yellow solid; LCMS (ESI, M+1): m/z = 454.2.

[0000417] Step B. (R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To the solution of (R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (40.0 g, 88.1 mmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (42.9 g, 119 mmol), K₃PO₄ (1.5 M in water, 117 mL) in THF (200 mL) was added cataCXium-A-Pd-G3 (6.42 g, 8.81 mmol) under N₂. The mixture was stirred at 65 °C for 8 hours. Upon completion, the reaction mixture was diluted with ethyl acetate (300 mL) and water (200 mL). The aqueous layer was extracted with ethyl acetate (300 mL). The combined organic phase was washed with brine (200 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (37.4 g, 65% yield) as yellow solid; LCMS (ESI, M+1): m/z = 652.3.

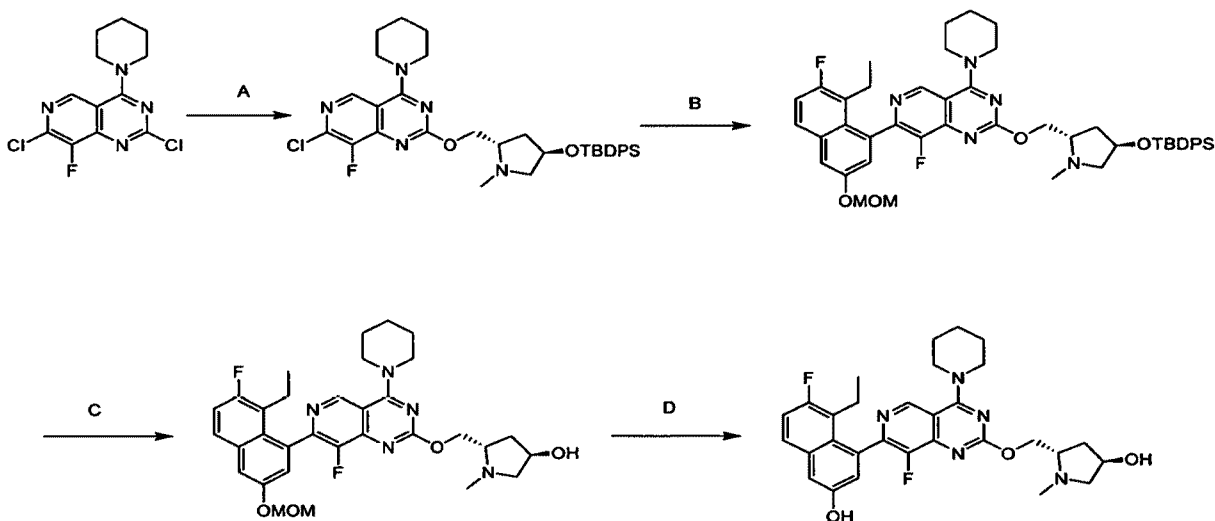
[0000418] Step C. (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To the solution of (R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (38.0 g, 58.3 mmol) in ACN (190 mL) was added HCl•dioxane (4 M, 190 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. Upon completion, the mixture was concentrated to give a residue. To the residue were added ethyl acetate (300 mL) and then sat. NaHCO₃ (to adjust the pH to 8). The aqueous layer was

extracted with ethyl acetate (300 mL). The combined organic phase was washed with brine (300 mL) and dried over with Na₂SO₄. The mixture was filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, and the pH value was adjusted to 8 with NaHCO₃ (30 g). The mixture was concentrated in vacuum to remove acetonitrile, and then was extracted with dichloromethane (2 × 800 mL). The combined organic layer was washed with brine (600 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated in vacuum. The residue was dissolved in acetonitrile (100 mL) and water (200 mL), and lyophilized to afford (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (25.3 g, 71% yield). Yellow Solid; ¹H NMR (400 MHz, CDCl₃) δ = 9.20 - 8.94 (m, 1H), 7.52 - 7.44 (m, 1H), 7.18 - 7.11 (m, 1H), 7.07 - 7.01 (m, 1H), 6.39 (s, 1H), 5.49 - 5.15 (m, 1H), 4.46 - 3.94 (m, 5H), 3.49 - 2.90 (m, 7H), 2.00 (br s, 6H), 1.98 - 1.63 (m, 4H), 1.59 - 1.36 (m, 2H), 1.17 (d, J = 5.6 Hz, 3H), 0.82 - 0.73 (m, 3H); ¹H NMR (400 MHz, METHANOL-d₄) δ = 9.20 (d, J = 0.8 Hz, 1H), 7.71 - 7.63 (m, 1H), 7.30 (d, J = 2.8 Hz, 1H), 7.24 (t, J = 9.2 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 5.39 - 5.22 (m, 1H), 4.57 - 4.22 (m, 4H), 3.68 - 3.54 (m, 1H), 3.50 - 3.39 (m, 1H), 3.29 - 3.13 (m, 3H), 3.05 - 2.96 (m, 1H), 2.53 - 2.11 (m, 6H), 2.04 - 1.94 (m, 2H), 1.94 - 1.73 (m, 4H), 1.28 (d, J = 9.6 Hz, 3H), 0.84 - 0.77 (m, 3H); LCMS (ESI, M+1): m/z = 608.3.

EXAMPLE 6



(3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol



[0000419] Step A. 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-chloro-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine: A solution of 2,7-dichloro-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine (140 mg, 465 μ mol) and ((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methanol (189 mg, 511 μ mol) in toluene (3.00 mL) was added tBuONa (134 mg, 1.39 mmol). The mixture was stirred at 0°C for 1 hr. The mixture was concentration in vacuum and was purified by prep-TLC (Silica gel, PE:EA=2:1) to give 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-chloro-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine (200 mg, 68% yield) as a yellow oil.

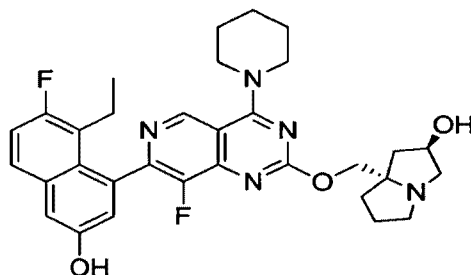
[0000420] Step B. 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine: A mixture of 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-chloro-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine (170 mg, 268 μ mol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (193 mg, 536 μ mol), cataCXium-A-Pd-G3cataCXium-A-Pd-G3 (19.5 mg, 26.8 μ mol) and K₃PO₄ (1.5 M in water, 536 μ L) in dioxane (5.00 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 1.5 hour under N₂ atmosphere. The mixture was diluted with water (40.0 mL) and extracted with ethyl acetate (2 $\times$ 20.0 mL). The organic layers were dried over Na₂SO₄, concentrated in vacuum, and was purified by column (Silica gel, PE:EA=1:0 to 0:1) to give 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-

methylpyrrolidin-2-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine (200 mg, 54% yield, 60% purity) as a yellow oil. LCMS [ESI, M+1]: m/z = 832.4.

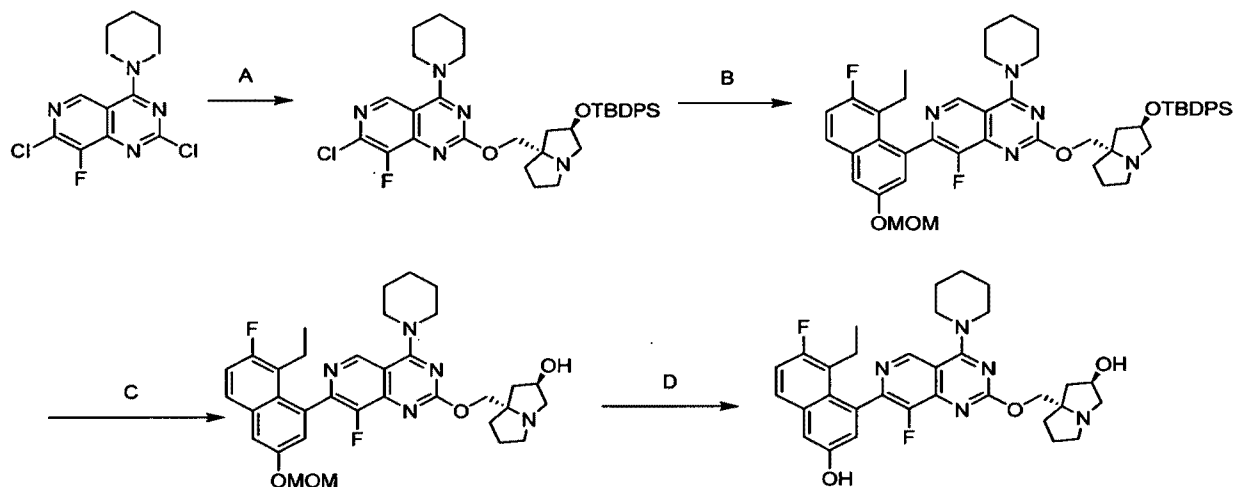
[0000421] Step C. (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol: To a solution of 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine (200 mg, 144 μ mol, 60% purity) in DMF (6.0 mL) was added CsF (65.7 mg, 433 μ mol, 15.9 μ L). After stirred at 40 °C for 4 hours, the mixture was diluted with water (40 mL) and layers were separated. The aqueous phase was extracted with ethyl acetate (2 $\times$ 20 mL). Combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum to give (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol (80 mg, crude) as a yellow oil. LCMS [ESI, M+1]: m/z = 594.3.

[0000422] Step D. (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol: A solution of (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol (80.0 mg, 135 μ mol) in HCl•EtOAc (4 M, 1 mL) was stirring at 20 °C for 1 hour. The mixture was concentrated in vacuum. The pH of the mixture was adjusted to 8 with sat. NaHCO₃ (5 mL). The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 $\times$ 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: water s Xbridge BEH C18 100 $\times$ 25mm $\times$ 5 μ m; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 30%-60%, 10min) to give title compound (28.0 mg, 37% yield, 98% purity) as a white solid. ¹H NMR (400 MHz, DMSO) δ 9.93 (s, 1H), 9.05 (s, 1H), 7.78-7.75 (m, 1H), 7.39-7.30 (m, 2H), 7.03 (d, J = 2.6 Hz, 1H), 4.78 (d, J = 4.4 Hz, 1H), 4.43-4.34 (m, 1H), 4.28-4.12 (m, 2H), 3.94 (s, 4H), 3.20-3.17 (m, 1H), 2.81 (s, 1H), 2.34 (s, 4H), 2.19-2.06 (m, 2H), 1.90-1.72 (m, 8H), 0.73 (t, J = 7.3 Hz, 3H); LCMS [ESI, M+1]: m/z = 550.3.

EXAMPLE 7



(2R,7aS)-7a-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-2-ol



[0000423] Step A. 2-(((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine: A solution of 2,7-dichloro-8-fluoro-4-(1-piperidyl)pyrido[4,3-d]pyrimidine (200 mg, 664 μmol) and ((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (315 mg, 797 μmol) in toluene (3.00 mL) was added drop-wise t-BuONa (191 mg, 1.99 mmol). The mixture was stirred at 0 °C for 1 hour under N₂. The reaction mixture was quenched by the addition of water (50.0 mL) at 0 °C, and extracted with DCM (30.0 mL $\times$ 3). The combined organic layers were washed with brine (40.0 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-TLC (Silica gel, EtOAc/MeOH =50/1) to give 2-(((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoro-4-(piperidin-

1-yl)pyrido[4,3-d]pyrimidine (300 mg, 68% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.69 (s, 1H), 7.70 - 7.62 (m, 4H), 7.45 - 7.31 (m, 6H), 4.55 - 4.44 (m, 1H), 4.17 - 4.08 (m, 1H), 4.04 - 3.96 (m, 1H), 3.87 - 3.80 (m, 4H), 3.50 (s, 2H), 3.19 - 2.99 (m, 3H), 2.83 - 2.73 (m, 1H), 2.20 - 1.82 (m, 7H), 1.75 - 1.70 (m, 2H), 1.52 - 1.31 (m, 1H), 1.06 (s, 9H). LCMS [ESI, M+1]: m/z = 660.4.

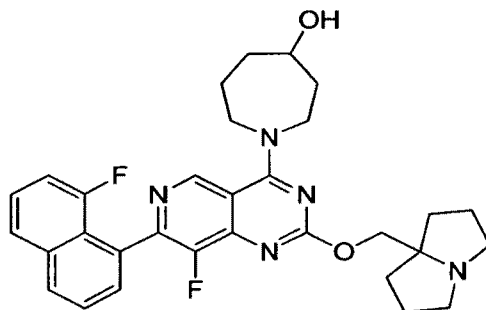
[0000424] Step B. 2-(((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 2-(((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine (240 mg, 363 μmol), and 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (393 mg, 1.09 mmol) in dioxane (5.00 mL) were added K₃PO₄ (1.50 M, 727 μL) and cataCXium-A-Pd-G3 (26.5 mg, 36.4 μmol) under N₂. The mixture was stirred at 100 °C for 1 hour under N₂. The reaction mixture was quenched with water (60 mL) at 0 °C and extracted with EtOAc (30.0 mL × 3). The combined organic layers were washed with brine (40.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (Silica gel, EtOAc/MeOH = 50/1) to give the title compound (300 mg, 77% yield) as a yellow solid; LCMS [ESI, M+1]: m/z = 858.4.

[0000425] Step C. (2R,7aS)-7a-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-2-ol: To a solution of 2-(((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine (250 mg, 262 μmol, 90% purity) in DMF (1.00 mL) was added CsF (398 mg, 2.62 mmol, 96.7 μL). The mixture was stirred at 40 °C for 4 hrs. The reaction mixture was quenched with water (40.0 mL) at 0 °C and extracted with EtOAc (30.0 mL × 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (150 mg, crude) as a yellow solid. LCMS [ESI, M+1]: m/z = 620.4.

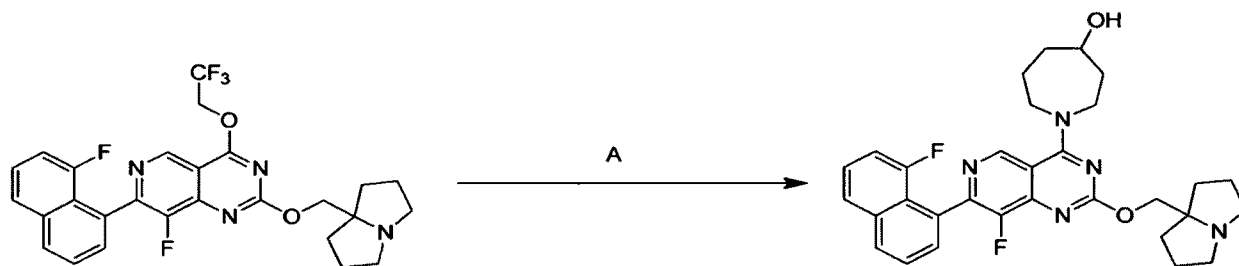
[0000426] Step D. (2R,7aS)-7a-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-2-ol: To a

solution of (2R,7aS)-7a-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-2-ol (100 mg, 129 μ mol, 80% purity) in EtOAc (1.00 mL) was added drop-wise HCl/EtOAc (4 M, 1.00 mL). The mixture was stirred at 20 °C for 12 hrs. The reaction mixture was quenched with sat. NaHCO₃ (20.0 mL) at 0 °C and then extracted with EtOAc (15.0 mL $\times$ 3). The combined organic layers were washed with brine (20.0 mL) and dried over Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: water s Xbridge BEH C18 100 $\times$ 25mm $\times$ 5 μ m; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 25%-65%, 10min) to give the title compound (19.85 mg, 26% yield, 99.0% purity) as a light-yellow solid.; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.93 (s, 1H), 9.04 (s, 1H), 7.81 - 7.73 (m, 1H), 7.38 - 7.30 (m, 2H), 7.04 - 7.00 (m, 1H), 4.80 - 4.72 (m, 1H), 4.36 - 4.24 (m, 1H), 4.07 - 3.86 (m, 6H), 3.10 - 3.01 (m, 1H), 2.97 - 2.88 (m, 1H), 2.82 - 2.71 (m, 1H), 2.45 (br s, 1H), 2.41 - 2.29 (m, 1H), 2.15 - 2.08 (m, 2H), 1.93 - 1.68 (m, 10H), 1.64 - 1.54 (m, 1H), 0.76 - 0.68 (m, 3H). LCMS [ESI, M+1]: m/z = 576.1

EXAMPLE 8

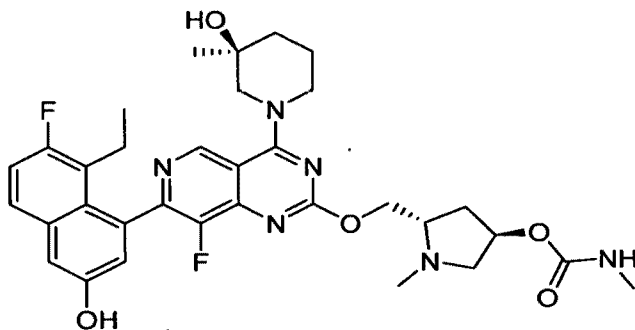


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-ol

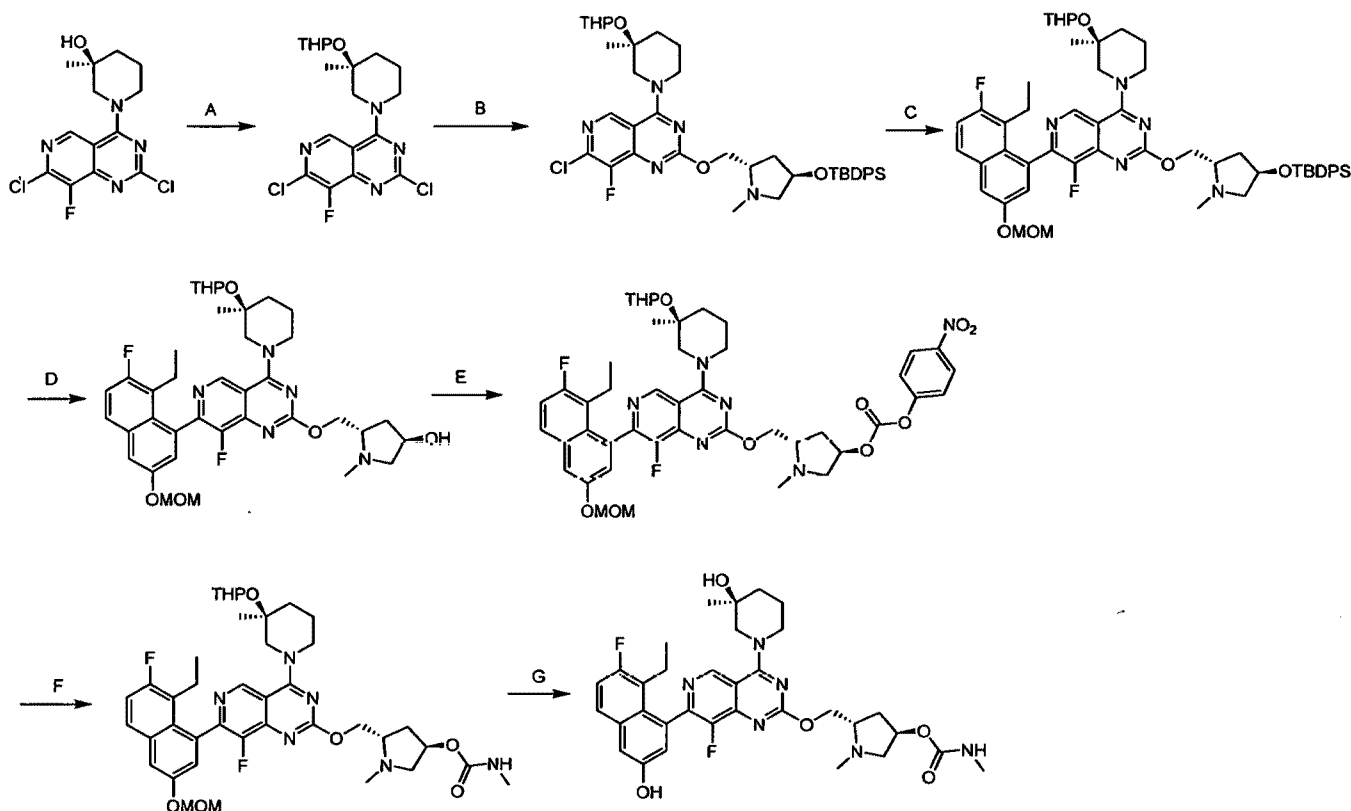


[0000427] Step A. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-ol: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (100 mg, 189 μ mol) and azepan-4-ol hydrochloride (42.9 mg, 283 μ mol, HCl) in DMF (3.00 mL) was added DIEA (73.1 mg, 566 μ mol, 98.5 μ L, 3 equiv.). The mixture was stirred at 60 °C for 16 hours. Upon completion, the mixture was filtered. The filtrate was purified by prep-HPLC (column: water s Xbridge BEH C18 100×25mm×5 μ m; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 20%-60%, 10min) and re-purified by prep-HPLC (column: Welch Xtimate C18 150×25mm×5 μ m; mobile phase: [water (0.04% HCl)-ACN]; B%: 10%-35%, 8min) affording 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-ol (23.8 mg, 37% yield, HCl salt) as a white solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.04 (br s, 1H), 9.25 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.80-7.73 (m, 1H), 7.68 (d, *J* = 6.4 Hz, 1H), 7.64-7.56 (m, 1H), 7.34 (dd, *J* = 7.2, 13.2 Hz, 1H), 4.63 (s, 2H), 4.15-4.03 (m, 3H), 4.02-3.93 (m, 1H), 3.87-3.77 (m, 1H), 3.60-3.45 (m, 2H), 3.25-3.12 (m, 2H), 2.24-1.92 (m, 11H), 1.90-1.79 (m, 1H), 1.78-1.68 (m, 1H), 1.68-1.57 (m, 1H); ¹H NMR (400 MHz, MeOD-*d*₄) δ = 9.35 (s, 1H), 8.28-8.19 (m, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.81-7.73 (m, 2H), 7.66-7.56 (m, 1H), 7.34-7.25 (m, 1H), 4.83 (s, 2H), 4.41-4.15 (m, 4H), 4.12-3.97 (m, 1H), 3.81-3.69 (m, 2H), 3.36-3.32 (m, 1H), 3.30-3.27 (m, 1H), 2.45-2.32 (m, 3H), 2.32-2.21 (m, 5H), 2.20-2.09 (m, 3H), 2.07-1.97 (m, 1H), 1.95-1.78 (m, 2H); LCMS [ESI, M+1]: *m/z* = 546.2.

EXAMPLE 9



[(3R,5S)-5-[[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-4-[(3S)-3-hydroxy-3-methyl-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] N-methylcarbamate



[0000428] Step A. 2,7-dichloro-8-fluoro-4-((3S)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidine: To the mixture of (S)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (2.00 g, 6.04 mmol), TsOH·WATER (115 mg, 605 μmol) in dichloromethane (30 mL) was added 3,4-dihydro-2H-pyran (1.02 g, 12.1 mmol) at 0°C. The mixture was stirred at 20°C for 1.5 h. After completion, the mixture was diluted with dichloromethane (30 mL). The mixture was washed with sat. NaHCO₃ (40 mL) and the aqueous solution was extracted with dichloromethane (30 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated to give a residue. The residue was purified by column chromatography (10% to 50% EA/PE) to give the title compound (1.95 g, 65% yield) as yellow oil; LCMS (ESI, M+1): m/z = 415.4

[0000429] Step B. 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-chloro-8-fluoro-4-((3S)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidine: To the mixture of 2,7-dichloro-8-fluoro-4-((3S)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidine (1.48 g, 3.57 mmol) and ((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methanol (1.45 g, 3.92 mmol) in dioxane (12 mL) was added DIEA (1.38 g, 10.7 mmol). The mixture was stirred at 90°C for 10 h. The mixture was concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give the title compound (1.00 g, 36% yield) as yellow solid; ¹H NMR (400 MHz, CDCl₃-d): δ 9.07-8.95 (m, 1H), 7.68-7.60 (m, 4H), 7.44 - 7.34 (m, 6H), 4.88 - 4.66 (m, 1H), 4.52 - 4.44 (m, 2H), 4.42 - 4.29 (m, 2H), 4.26 - 4.19 (m, 1H), 3.90 - 3.58 (m, 1H), 3.51 - 2.95 (m, 5H), 2.47 (d, *J* = 1.2 Hz, 3H), 2.43 - 2.36 (m, 1H), 2.19 - 2.06 (m, 2H), 2.05 - 1.84 (m, 2H), 1.73 - 1.65 (m, 1H), 1.55 - 1.33 (m, 5H), 1.31 - 1.23 (m, 5H), 1.06 (s, 9H). LCMS (ESI, M+1): *m/z* = 748.3.

[0000430] Step C. 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3S)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidine: To the mixture of 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-chloro-8-fluoro-4-((3S)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidine (400 mg, 534 μmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (384 mg, 1.07 mmol), K₃PO₄ (1.50 M, 1.07 mL) in toluene (8 mL) was added [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butylphosphane;methanesulfonate (38.9 mg, 53.4 μmol). The mixture was degassed and stirred at 90°C for 1.5 h. The reaction mixture was diluted with ethyl acetate (30 mL) and water (15 mL), and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile, MeOH] to give title compound (400 mg, 78% yield) as yellow solid; LCMS (ESI, M+1): *m/z* = 946.3.

[0000431] Step D. (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3S)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-

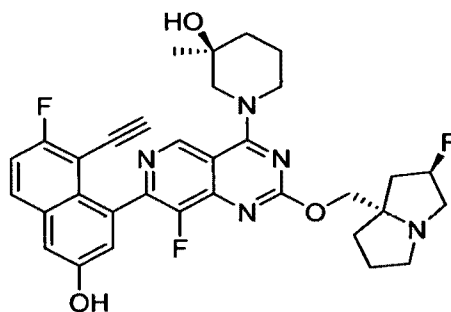
d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol: To the mixture of 2-(((2S,4R)-4-((tert-butylidiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3S)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidine (950 mg, 1.00 mmol) in DMF (10 mL) was added CsF (2.28 g, 15.0 mmol). The mixture was stirred at 40°C for 4 h. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give the title compound (600 mg, 83% yield) as yellow solid; LCMS (ESI, M+1): m/z = 708.4.

[0000432] Step E. (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3S)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-yl (4-nitrophenyl) carbonate: To the mixture of (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3S)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol (100 mg, 141 µmol), and (4-nitrophenyl) carbonochloridate (103 mg, 509 µmol) in THF (4 mL) was added *t*-BuOK (1 M in THF, 424 µl) at 0°C. The mixture was stirred at 15°C for 0.5 h. The mixture was diluted with ethyl acetate (10 mL) and water (5 mL), and the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give the title compound (110 mg, 84% yield) as yellow oil; LCMS (ESI, M+1): m/z 873.3.

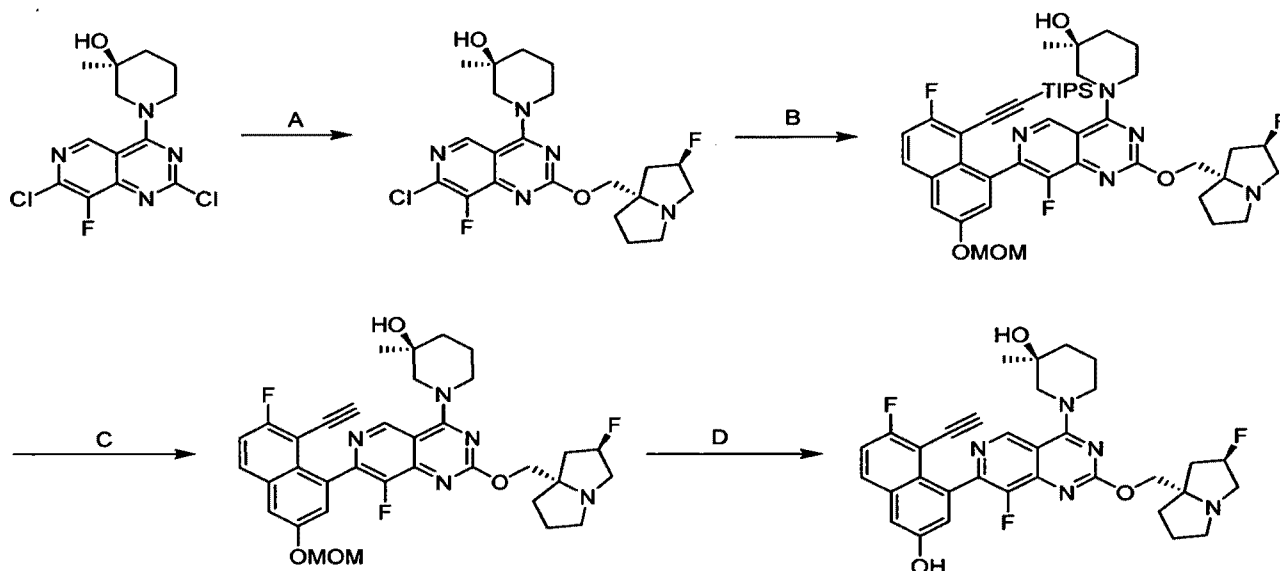
[0000433] Step F. [(3R,5S)-5-[[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-4-[(3S)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methylpyrrolidin-3-yl] N-methylcarbamate: A mixture of (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3S)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-yl (4-nitrophenyl) carbonate (52.0 mg, 59.6 µmol) and methanamine (2 M in THF, 745 µl) in DMF (1 mL) was stirred at 25 °C for 0.5 h. After completion, the residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give the title compound (29.0 mg, 51% yield) as yellow solid. LCMS (ESI, M+1): m/z = 765.2.

[0000434] Step G. [(3R,5S)-5-[[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-4-[(3S)-3-hydroxy-3-methyl-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] N-methylcarbamate: To a mixture of [(3R,5S)-5-[[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-4-[(3S)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] N-methylcarbamate (41.0 mg, 53.6 μ mol) in MeCN (0.7 mL) was added HCl•MeOH (4 M, 1.4 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. After completion, the mixture was concentrated in vacuum. Then the pH value was adjusted to 8 with saturated NaHCO₃ solution. The mixture was triturated with methanol (2 $\times$ 10 mL) and filtered. The filtrate was concentrated in vacuum. The residue was purified by prep-HPLC (Phenomenex Gemini-NX C18 75*30mm*3 μ m; mobile phase: [water (0.05% ammonia hydroxide v/v) - ACN]; B%: 23% - 53%, 11.5 min) to afford the title compound (18.6 mg, 54% yield) as white solid. ¹H NMR (400 MHz, METHANOL-d₄): δ 9.21 (d, *J* = 2.4 Hz, 1H), 7.67 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.29 (d, *J* = 2.8 Hz, 1H), 7.24 (t, *J* = 9.2 Hz, 1H), 7.06 (t, *J* = 2.0 Hz, 1H), 5.10 - 5.04 (m, 1H), 4.57 - 4.47 (m, 3H), 4.29 (br t, *J* = 12.2 Hz, 1H), 3.68-3.57 (m, 1H), 3.53 - 3.42 (m, 2H), 3.09 - 3.00 (m, 1H), 2.69 (s, 3H), 2.52 (s, 3H), 2.50 - 2.41 (m, 2H), 2.22 - 2.08 (m, 4H), 1.92 - 1.75 (m, 3H), 1.28 (d, *J* = 10.0 Hz, 3H), 0.81 (q, *J* = 7.6 Hz, 3H). ¹⁹F NMR (400 MHz, METHANOL-d₄) δ = -121.268, -139.169. HPLC: >99% ee, Chiralcel OD-3 50 $\times$ 4.6mm I.D., 3 μ m A: 60% MeOH + 40% ACN (w/ 0.05% DEA), B: CO₂, 3mL/min, 220 nm, tr: 0.597 min; LCMS (ESI, M+1): m/z = 637.0.

EXAMPLE 10



(S)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



[0000435] Step A. (S)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (S)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (300 mg, 906 μ mol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (150 mg, 942 μ mol), DIPEA (311 mg, 2.41 mmol) and 4Å molecular sieves (150 mg) in dioxane (1.8 mL) was stirred at 90 °C for 24 hours under N₂ atmosphere. The reaction mixture was filtered, and the filter cake was washed with dichloromethane (20 mL). The filtrate was concentrated under reduced pressure and the residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=4/1] to give the title compound as light yellow foam (247 mg, 57% yield). LCMS (ESI, M+1): m/z = 454.2.

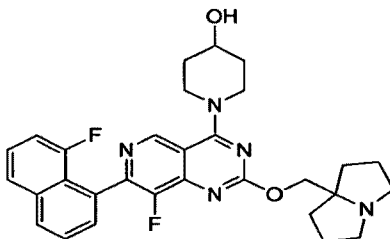
[0000436] Step B. (S)-1-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (S)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (290 mg, 639 μ mol), K₃PO₄ (1.5 M in water, 1.3 mL) in THF (5.2 mL) was degassed and purged with N₂ for 3 times. cataCXium-A-Pd-G3 (47 mg, 64.5 μ mol) and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (460 mg, 898 μ mol) were added. The reaction mixture was stirred at

65 °C for 6 hours. The reaction mixture was diluted with water (1 mL) and brine (1 mL), and then extracted with ethyl acetate (2 mL × 4). The combined organic layers were concentrated under reduced pressure and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=9/11] to give title compound as light yellow foam (410 mg, 77% yield). LCMS (ESI, M+1): m/z = 804.1.

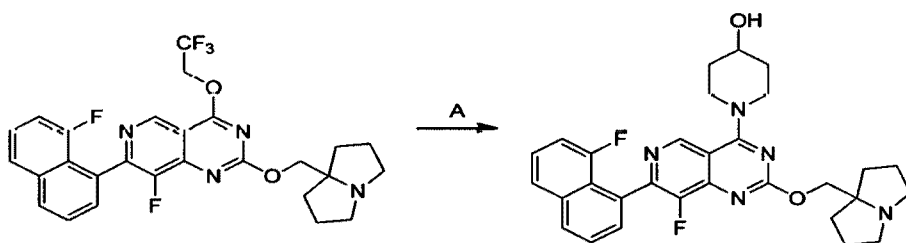
[0000437] Step C. (S)-1-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (S)-1-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (400 mg, 497 μmol) in DMF (3 mL) was added CsF (760 mg, 5.00 mmol). The mixture was stirred at 15 °C for 1 hour. The reaction mixture was filtered. The filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=3/2] to give the title compound as light yellow solid (310 mg, 95% yield). LCMS (ESI, M+1): m/z = 648.2.

[0000438] Step D. (S)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (S)-1-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (100 mg, 154 μmol) in MeCN (1.5 mL) was dropwise added HCl/dioxane (4 M, 1.5 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in ethyl acetate (5 mL) and treated with saturated NaHCO₃ aqueous (5 mL). The mixture was extracted with ethyl acetate (5 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 × 30mm × 3μm; mobile phase: [water (0.225% formic acid)-ACN]; B%: 15%-45%, 9 min) to give the title compound as yellow solid (59.5 mg, 61% yield, 0.5% FORMIC ACID). ¹H NMR (400 MHz, methanol-d₄) δ = 9.16 (d, J = 51.2, 1H), 7.88-7.84 (m, 1H), 7.36-7.29 (m, 2H), 7.23 (dd, J = 2.4, 17.2 Hz, 1H), 5.43 (d, J = 51.8, 1H), 4.65-4.38 (m, 4H), 3.66-3.35 (m, 6H), 3.27-3.20 (m, 1H), 2.45-1.75 (m, 10H), 1.27 (d, J = 20.0, 3H). ¹⁹F NMR (377 MHz, methanol-d₄) δ = -111.68, -140.68, -173.93. LCMS (ESI, M+1): m/z = 604.1.

EXAMPLE 11

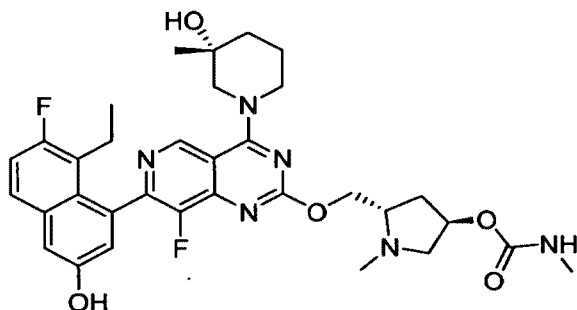


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-4-ol

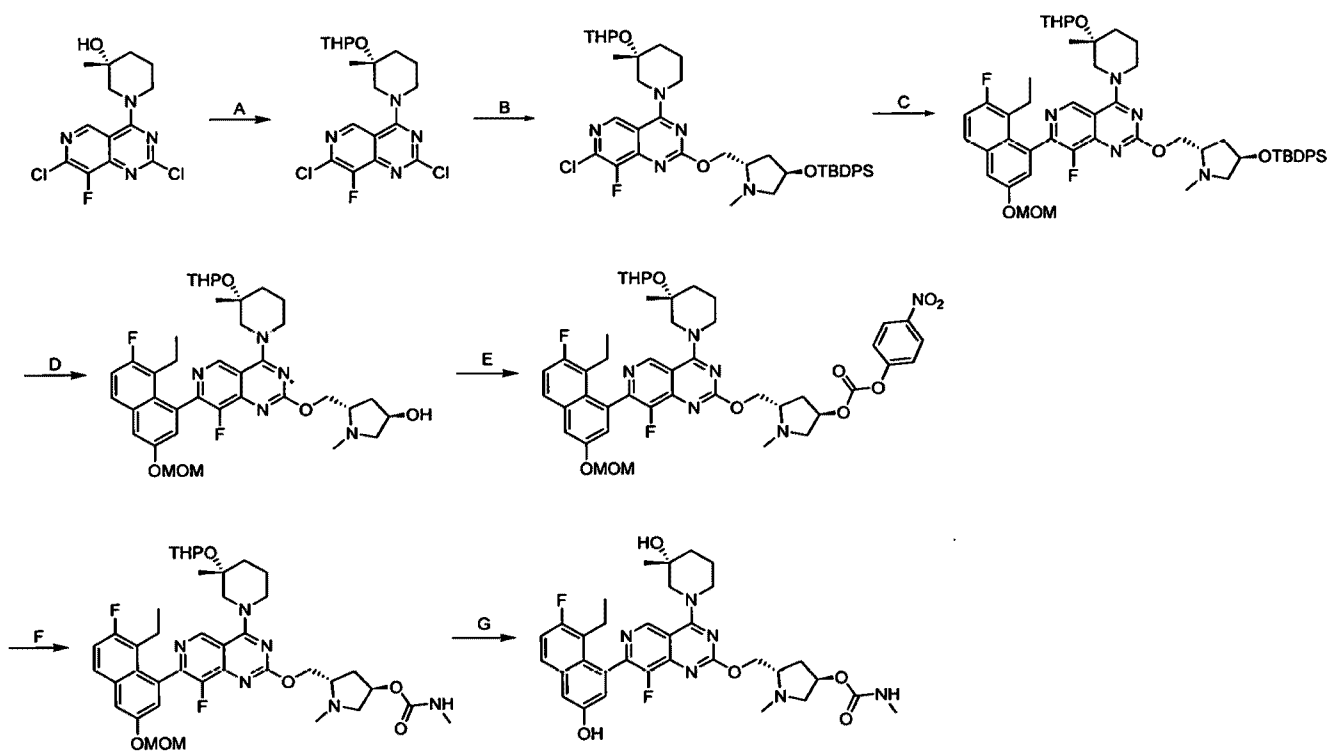


[0000439] Step A: 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-4-ol: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μmol) in DMF (2.00 mL) were added piperidin-4-ol (19.1 mg, 189 μmol) and DIEA (36.5 mg, 283 μmol , 49.3 μL). The reaction was degassed and purged with N_2 for 3 times and stirred at 40 $^\circ\text{C}$ for 2 hours. Upon completion, the reaction was filtered and purified by prep-HPLC (column: water s Xbridge BEH C18 100 $\times$ 25mm $\times$ 5 μm ; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 20%-60%, 10 min) affording the title compound (24.1 mg, 48% yield, 99.9% purity) as a white solid. ^1H NMR (400 MHz, MeOD) δ = 9.04 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.74-7.66 (m, 1H), 7.63-7.57 (m, 1H), 7.57-7.48 (m, 1H), 7.19 (dd, J = 7.6, 12.8 Hz, 1H), 4.49-4.35 (m, 2H), 4.28 (s, 2H), 4.11-3.97 (m, 1H), 3.87-3.71 (m, 2H), 3.15-3.01 (m, 2H), 2.78-2.63 (m, 2H), 2.15-2.02 (m, 4H), 1.97-1.82 (m, 4H), 1.80-1.69 (m, 4H); LCMS (ESI, $\text{M}+1$): m/z 532.1.

EXAMPLE 12



(3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-yl methylcarbamate



[0000440] Step A. 2,7-dichloro-8-fluoro-4-((3R)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]: A mixture of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (2.00 g, 6.04 mmol), TsOH·H₂O (115 mg, 604 μmol)

and DHP (1.02 g, 12.1 mmol, 1.10 mL) in dichloromethane (20 mL) was stirred at 15 °C for 1 h. After completion, the mixture was concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give the title compound (2.3 g, 77% yield). Yellow oil. LCMS (ESI, M+1): m/z 415.0

[0000441] Step B. tert-butyl-[(3R,5S)-5-[[7-chloro-8-fluoro-4-[(3R)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl]oxy-diphenyl-silane: A mixture of 2,7-dichloro-8-fluoro-4-[(3R)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidine (2 g, 4.82 mmol), [(2S,4R)-4-[tert-butyl(diphenyl)silyl]oxy-1-methyl-pyrrolidin-2-yl]methanol (3.56 g, 9.63 mmol) and DIEA (1.87 g, 14.5 mmol, 2.52 mL) in dioxane (20 mL) was stirred at 90 °C for 12 h. After completion, the mixture was diluted with water (30 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give the title compound (1.7 g, 38% yield). Yellow oil. LCMS (ESI, M+1): m/z 748.2.

[0000442] Step C. 2-(((2S,4R)-4-((tert-butyl)diphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3R)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidine: To a mixture of tert-butyl-[(3R,5S)-5-[[7-chloro-8-fluoro-4-[(3R)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl]oxy-diphenyl-silane (1.20 g, 1.60 mmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (869 mg, 2.41 mmol), K₃PO₄ (1.5 M, 3.21 mL) in toluene (10 mL) was added [cataCXium-A-Pd-G3 (117 mg, 160 μmol) under N₂. The mixture was stirred at 90°C for 1.5 h. After completion, the reaction mixture was diluted with ethyl acetate (10 mL) and water (5 mL). The aqueous layer was extracted with ethyl acetate (10 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give 2-(((2S,4R)-4-((tert-butyl)diphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-

fluoro-4-((3R)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidine (768 mg, 50% yield). Black oil; LCMS (ESI, M+1): m/z 946.5.

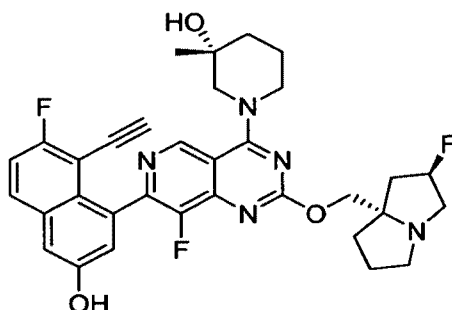
[0000443] Step D. (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3R)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol: To a mixture of 2-(((2S,4R)-4-((tert-butylidiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3R)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidine (650 mg, 687 μ mol) and DMF (7 mL) was added CsF (1.56 g, 10.3 mmol), and the mixture was stirred at 40°C for 16 h. The mixture was filtered and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3R)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol (230 mg, 47% yield). Yellow Solid; LCMS [ESI, M+1]: m/z 708.5.

[0000444] Step E. [(3R,5S)-5-[[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-4-[(3R)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] (4-nitrophenyl) carbonate: To a mixture of (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3R)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol (40.0 mg, 56.5 μ mol) and (4-nitrophenyl) carbonochloridate (41.0 mg, 203 μ mol) in THF (1 mL) was added t-BuOK (1 M in THF, 170 μ L) at 0 °C. The mixture was stirred at 25 °C for 1 h. After completion, the mixture was diluted with ethyl acetate (4 mL) and water (3 mL), and then separated. The aqueous phase was extracted with ethyl acetate (3 mL). The combined organic layer was washed with brine (4 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give [(3R,5S)-5-[[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-4-[(3R)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] (4-nitrophenyl) carbonate (49.0 mg, 73% yield). Yellow solid. LCMS (ESI, M+1): m/z 873.4.

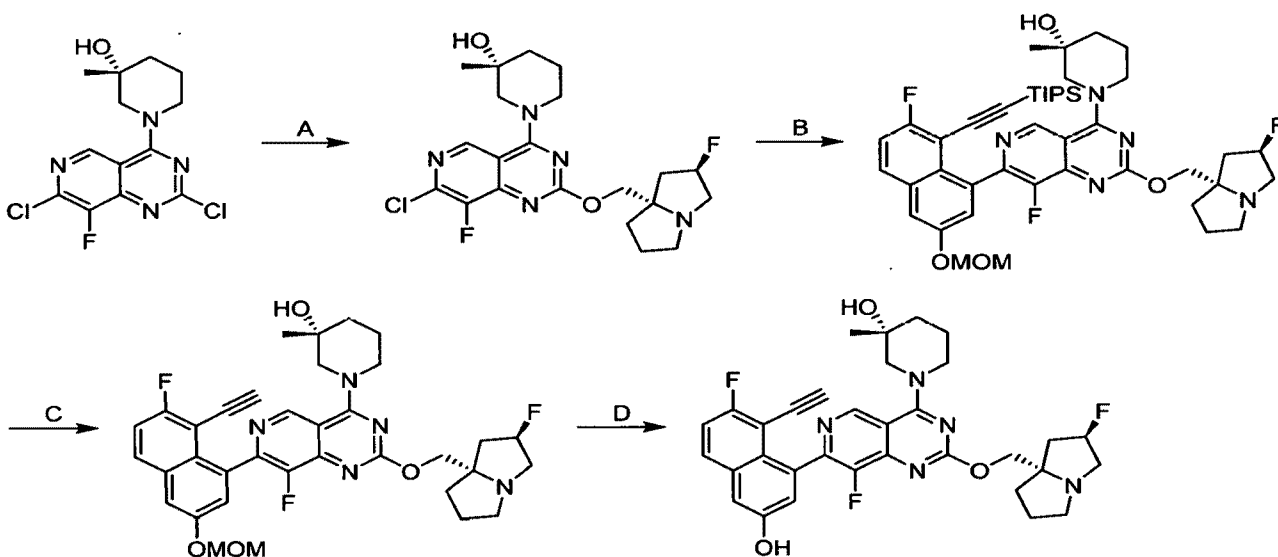
[0000445] Step F. [(3R,5S)-5-[[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-4-[(3R)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] N-methylcarbamate: A mixture of [(3R,5S)-5-[[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-4-[(3R)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] (4-nitrophenyl) carbonate (49.0 mg, 56.1 μ mol) and methanamine (2 M in THF, 702 μ L) in DMF (1 mL) was stirred at 25 °C for 0.5 h. After completion, the residue was purified directly by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give [(3R,5S)-5-[[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-4-[(3R)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] N-methylcarbamate (33.0 mg, 59% yield). Yellow oil. LCMS (ESI, M+1): m/z 765.4.

[0000446] Step G. [(3R,5S)-5-[[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-4-[(3R)-3-hydroxy-3-methyl-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] N-methylcarbamate: To a mixture of [(3R,5S)-5-[[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-4-[(3R)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] N-methylcarbamate (34.0 mg, 44.4 μ mol) and MeCN (0.5 mL) was added HCl•MeOH (4 M, 1 mL) at 0 °C and the mixture was stirred at a 0°C for 0.5 h. After completion, the mixture was concentrated in vacuum. Then the pH value was adjusted to 9 with saturated NaHCO₃ solution and the mixture was triturated with methanol (2 $\times$ 8 mL). The filtrate was concentrated in vacuum. The residue was purified by prep-HPLC (column: Shim-pack C18 150*25*10 μ m; mobile phase: [water (0.225% formic acid) - ACN]; B%: 20% - 40%, 10 min) to afford [(3R,5S)-5-[[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-4-[(3R)-3-hydroxy-3-methyl-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] N-methylcarbamate (8.34 mg, 28% yield, 0.6 formic acid salt). ¹H NMR (400 MHz, METHANOL-d₄): δ 9.22 (br d, J = 3.2 Hz, 1H), 7.68 (br dd, J = 5.6, 8.4 Hz, 1H), 7.30 (br d, J = 2.0 Hz, 1H), 7.25 (br t, J = 9.2 Hz, 1H), 7.06 (br s, 1H), 5.13 (br s, 1H), 4.62-4.53 (m, 3H), 4.31 (br t, J = 12.0 Hz, 1H), 3.67-3.56 (m, 2H), 3.49-3.43 (m, 1H), 2.67 (br d, J = 15.2 Hz, 8H), 2.53-2.42 (m, 1H), 2.25-2.13 (m, 4H), 1.89-1.75 (m, 3H), 1.29 (br d, J = 9.6 Hz, 3H), 0.81 (q, J = 7.2 Hz, 3H). ¹⁹F NMR (400 MHz, METHANOL-d₄) δ = -121.123, -139.247. LCMS (ESI, M+1): m/z 637.3.

EXAMPLE 13



(R)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



[0000447] Step A. (R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol ((300 mg, 906 μ mol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (150 mg, 942 μ mol), DIPEA (334 mg, 2.58 mmol) and 4Å molecular sieves (150 mg) in dioxane (1.8 mL) was stirred at 90 °C for 15 hours under N₂ atmosphere. The reaction mixture was filtered. The filter cake was washed with dichloromethane (20 mL). The filtrate was concentrated under reduced pressure, and purified by

reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=11/9] to give the product as light yellow gum (260 mg, 61% yield). LCMS (ESI, M+1): m/z 454.1.

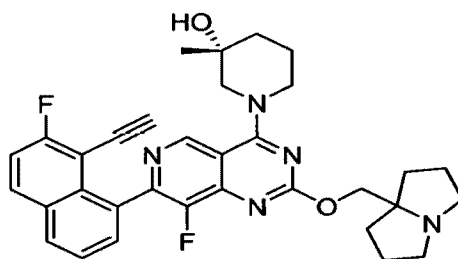
[0000448] Step B. (R)-1-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (150 mg, 330 μ mol), and K₃PO₄ (1.5 M in water, 0.7 mL) in THF (3.5 mL) was degassed and purged with N₂ for 3 times. cataCXium-A-Pd-G3 (25 mg, 34.3 μ mol) was added, followed by ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (228 mg, 445 μ mol). The mixture was stirred at 65 °C for 3 hours. The reaction mixture was diluted with water (5 mL), and extracted with ethyl acetate (5 mL, $\times$ 4). The combined organic layers were concentrated under reduced pressure, and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=7/13] to give the product as yellow foam (219 mg, 79% yield). LCMS (ESI, M+1): m/z 804.4.

[0000449] Step C. (R)-1-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (375 mg, 466 μ mol) in DMF (3.5 mL) was added CsF (709 mg, 4.67 mmol). The mixture was stirred at 20 °C for 0.5 hour. The reaction mixture was filtered. The filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=11/9] to give the product as yellow solid (270 mg, 87% yield). LCMS (ESI, M+1): m/z 648.4.

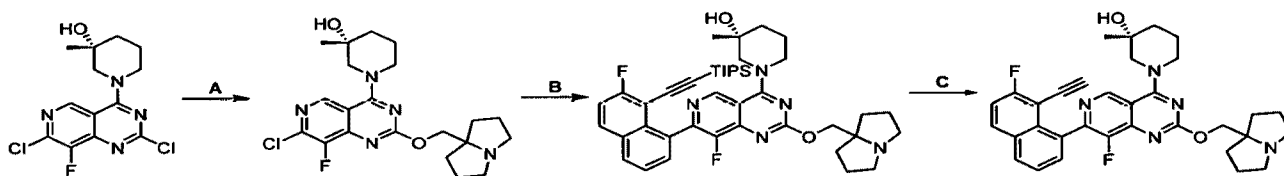
[0000450] Step D. (R)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of (R)-1-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (100 mg, 154 μ mol) in MeCN (3 mL) was added HCl/dioxane (4 M, 2 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for

0.5 hour. The reaction mixture was concentrated under reduced pressure to give a residue at room temperature (without heating). The residue was dissolved in ethyl acetate (5 mL) and saturated NaHCO_3 aqueous (5 mL). The mixture was extracted with ethyl acetate (5 mL $\times$ 3). The combined organic layers were dried over anhydrous Na_2SO_4 , concentrated under reduced pressure, and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile = 3/2] to give the product as yellow solid (63.2 mg, 63% yield, 0.4 FORMIC ACID). ^1H NMR (400 MHz, methanol- d_4) δ = 9.15 (d, J = 51.6, 1H), 7.88-7.84 (m, 1H), 7.36-7.32 (m, 2H), 7.23 (dd, J = 2.8, 18.4 Hz, 1H), 5.40 (d, J = 53.2, 1H), 4.68-4.37 (m, 4H), 3.66-3.35 (m, 6H), 3.21-3.15 (m, 1H), 2.34-1.75 (m, 10H), 1.27 (d, J = 20.0, 3H). ^{19}F NMR (377 MHz, methanol- d_4) δ = -111.66, -140.59, -173.84. LCMS (ESI, M+1): m/z 604.3.

EXAMPLE 14



(R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



[0000451] Step A. (R)-1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (400 mg, 1.21 mmol), (hexahydro-1H-pyrrolizin-7a-yl)methanol (239 mg, 1.69 mmol), 4Å molecular sieves (40.0 mg) in dioxane (8 mL) was added DIEA (468 mg, 3.62 mmol), the mixture was stirred at 90 °C for 3 hours. Upon completion, the reaction solution was filtered and concentrated to give a residue. The

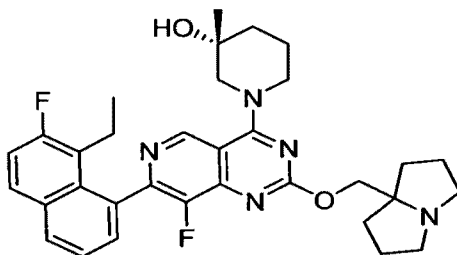
residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (R)-1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (244 mg, 44% yield). Yellow Solid; LCMS (ESI, M+1): m/z 436.3.

[0000452] Step B. (R)-1-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To the solution of (R)-1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (200 mg, 459 μ mol), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (291 mg, 642 μ mol), K_3PO_4 (1.5 M, 918 μ L) in THF (3 mL) was added cataCXium-A-Pd-G3 (33.4 mg, 45.9 μ mol) under N_2 . The mixture was stirred at 60 °C for 1 hours. Upon completion, the mixture solution was diluted with ethyl acetate (15 mL) and water (5 mL), and the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (R)-1-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (291 mg, 87% yield). Off-white Solid; LCMS (ESI, M+1): m/z 726.5.

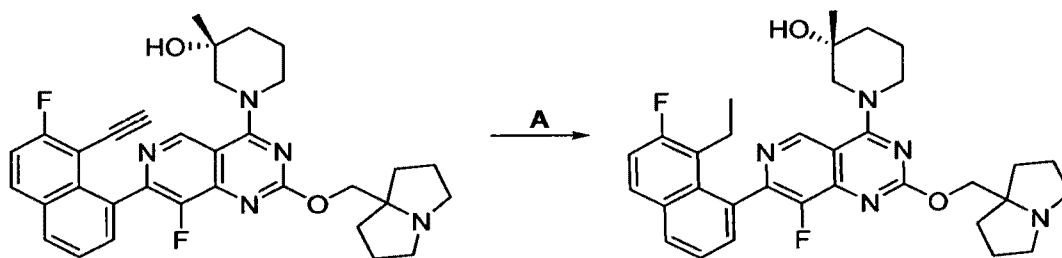
[0000453] Step C. (R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To the solution of (R)-1-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (100 mg, 138 μ mol) in DMF (1.5 mL) was added CsF (209 mg, 1.38 mmol, 10 equiv.). The mixture was stirred at 20 °C for 1 hour. Upon completion, the mixture was filtered and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were lyophilized to afford (R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (51.72 mg, 60% yield, 0.77% FORMIC ACID). Yellow Solid; ^1H NMR (400 MHz, METHANOL- d_4) δ = 9.31 - 9.07 (m, 1H), 8.18 - 8.05 (m, 2H), 7.73 - 7.61 (m, 2H), 7.50 - 7.39 (m, 1H), 4.74 - 4.24 (m, 4H), 3.72 - 3.38

(m, 5H), 3.18 - 3.01 (m, 2H), 2.34 - 2.21 (m, 2H), 2.19 - 1.92 (m, 7H), 1.86 - 1.66 (m, 3H), 1.36 - 1.17 (m, 3H); LCMS (ESI, M+1): m/z 570.4.

EXAMPLE 15



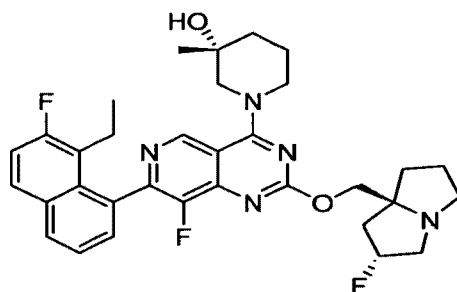
(R)-1-(6-(8-ethyl-7-fluoronaphthalen-1-yl)-5-fluoro-3-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-1-yl)-3-methylpiperidin-3-ol



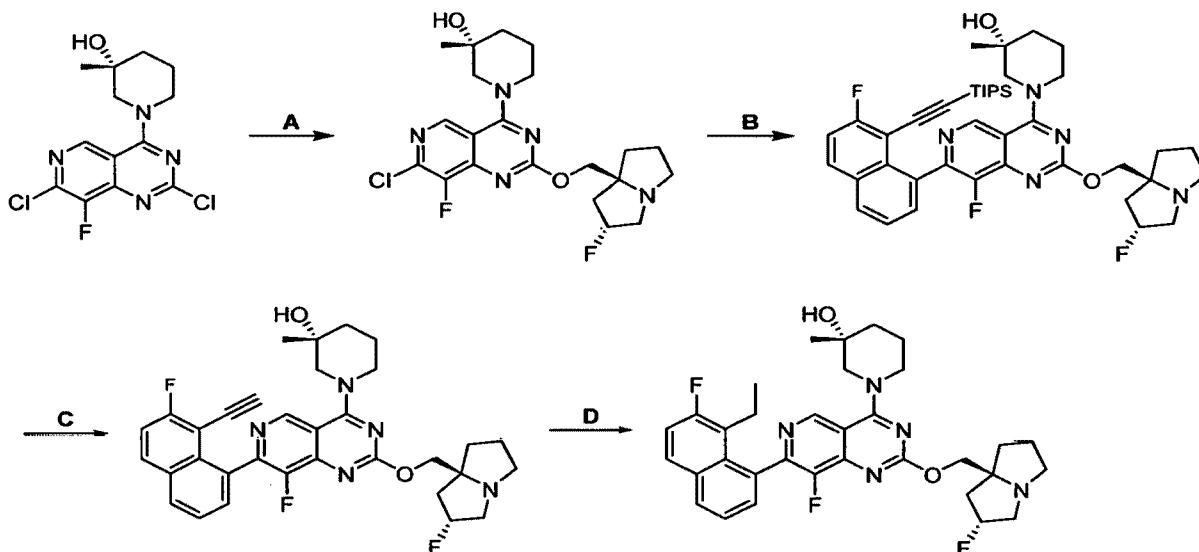
[0000454] Step A. (R)-1-(6-(8-ethyl-7-fluoronaphthalen-1-yl)-5-fluoro-3-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-1-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (50.0 mg, 87.8 μ mol) in MeOH (2 mL) was added Pd/C (20 mg, 10% purity) under N₂. The suspension was degassed in vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 20 °C for 1 hour. Upon completion, the mixture was filtered and concentrated to give a residue. The residue was purified by prep - HPLC (column: water s Xbridge 150 $\times$ 25mm $\times$ 5 μ m; mobile phase: [water (10 mM NH₄HCO₃) - ACN]; B%: 50% - 80%, 10min) to give (R)-1-(6-(8-ethyl-7-fluoronaphthalen-1-yl)-5-fluoro-3-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-1-yl)-3-methylpiperidin-3-ol (16.83 mg, 33% yield). White Solid; ¹H NMR (400 MHz, CHLOROFORM-

d) δ = 9.14 (d, J = 7.2 Hz, 1H), 7.97 - 7.92 (m, 1H), 7.83 - 7.75 (m, 1H), 7.52 - 7.42 (m, 2H), 7.33 - 7.27 (m, 1H), 4.50 - 4.37 (m, 2H), 4.32 - 4.20 (m, 2H), 3.52 - 3.41 (m, 1H), 3.38 - 3.27 (m, 1H), 3.17 - 3.08 (m, 2H), 3.04 - 2.88 (m, 1H), 2.70 - 2.52 (m, 3H), 2.32 - 2.21 (m, 1H), 2.13 - 2.02 (m, 3H), 1.93 - 1.83 (m, 5H), 1.79 - 1.68 (m, 4H), 1.35 (s, 3H), 0.90 - 0.83 (m, 3H); LCMS (ESI, $M+1$): m/z 574.4.

EXAMPLE 16



(R)-1-(7-(8-ethyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



[0000455] Step A. (R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (200 mg, 604 μ mol),

((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (145 mg, 911 μ mol), and 4Å molecular sieves (20 mg) in dioxane (3 mL) was added DIEA (234 mg, 1.81 mmol). The mixture was stirred at 90 °C for 14 hours. Upon completion, the reaction solution was diluted with ethyl acetate (10 mL) and water (5 mL), and the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (168 mg, 56% yield). Yellow Solid; LCMS (ESI, M+1): m/z 454.3.

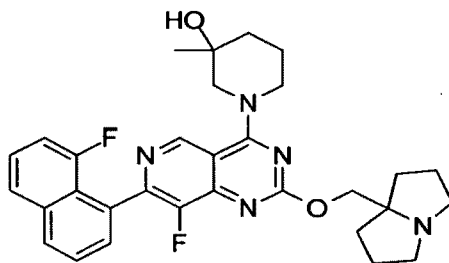
[0000456] Step B. (R)-1-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (180 mg, 397 μ mol), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (234 mg, 517 μ mol), and K₃PO₄ (1.5 M, 793 μ L) in THF (3 mL) was added cataCXium-A-Pd-G3 (28.9 mg, 39.7 μ mol) under N₂. The mixture was stirred at 60 °C for 2 hours. Upon completion, the reaction mixture was diluted with ethyl acetate (15 mL) and water (10 mL). The mixture was extracted with ethyl acetate (15 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (R)-1-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (260 mg, 86% yield). Yellow Solid; LCMS (ESI, M+1): m/z 744.5.

[0000457] Step C. (R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To the solution of (R)-1-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (260 mg, 349 μ mol) in DMF (2 mL) was added CsF (531 mg, 3.49 mmol). The mixture was stirred at 20 °C for 0.5 hour. Upon completion, the mixture was filtered and

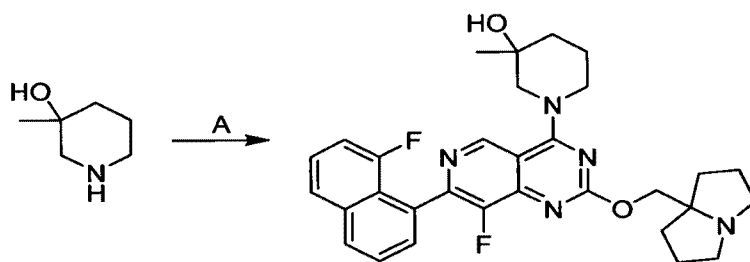
purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (190 mg, 89% yield). Yellow Solid; LCMS (ESI, M+1): m/z 588.4.

[0000458] Step D. (R)-1-(7-(8-ethyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (50.0 mg, 85.1 μ mol) in MeOH (2.0 mL) was added Pd/C (20 mg, 10% purity) under N₂. The suspension was degassed in vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15 psi) at 20 °C for 1 hour. Upon completion, the mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: water s Xbridge 150 $\times$ 25 mm $\times$ 5 μ m; mobile phase: [water (10 mM NH₄HCO₃) - ACN]; B%: 53% - 83%, 10 min) to give (R)-1-(7-(8-ethyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (18.2 mg, 36% yield). White Solid; ¹H NMR (400 MHz, CHLOROFORM-d) δ = 9.15 (d, *J* = 6.8 Hz, 1H), 8.01 - 7.89 (m, 1H), 7.85 - 7.75 (m, 1H), 7.55 - 7.40 (m, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 5.40 - 5.16 (m, 1H), 4.50 - 4.37 (m, 2H), 4.35 - 4.29 (m, 1H), 4.26 - 4.18 (m, 1H), 3.54 - 3.41 (m, 1H), 3.38 - 3.09 (m, 4H), 3.06 - 2.85 (m, 2H), 2.64 - 2.47 (m, 1H), 2.31 - 2.05 (m, 5H), 2.01 - 1.86 (m, 4H), 1.80 - 1.67 (m, 2H), 1.35 (s, 3H), 0.94 - 0.79 (m, 3H); LCMS (ESI, M+1): m/z 592.4.

EXAMPLE 17

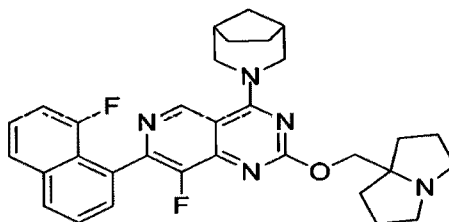


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

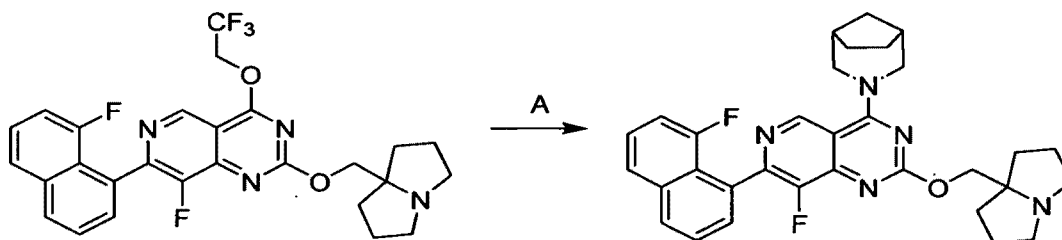


[0000459] Step A. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of 3-methylpiperidin-3-ol and DIEA (51.1 mg, 396 μ mol) and 4Å molecular sieves (50 mg) in DMF (2 mL) was added 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (69.9 mg, 132 μ mol) in one portion at 20 °C under N₂. The mixture was heated to 40 °C and stirred for 12 hours. Upon completion, the mixture was filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: water s X-bridge 150*25mm*5 μ m; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 31%-61%,10min) to afford 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (24.34 mg, 33.5% yield); White solid. ¹H NMR (400 MHz, methanol-d₄) δ 9.20 (d, *J* = 6.0 Hz, 1H) 8.10 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.53 (td, *J* = 5.2 Hz, 8.0 Hz, 1H), 7.19 (dd, *J* = 5.2 Hz, 8.0 Hz, 1H), 4.54 (d, *J* = 8.4 Hz, 1H), 4.33-4.25 (m, 3H), 3.63 (dd, *J* = 2.8 Hz, 13.2 Hz, 1H), 3.50-3.40 (m, 1H), 3.14-3.06 (m, 2H), 2.76-2.68 (m, 2H), 2.23-2.03 (m, 3H), 1.97-1.73 (m, 9H), 1.29 (d, *J* = 5.2Hz, 3H); LCMS (ESI, M+1): *m/z* 546.2.

EXAMPLE 18

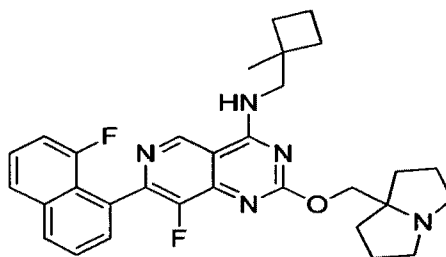


4-((1R,5S)-3-azabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine

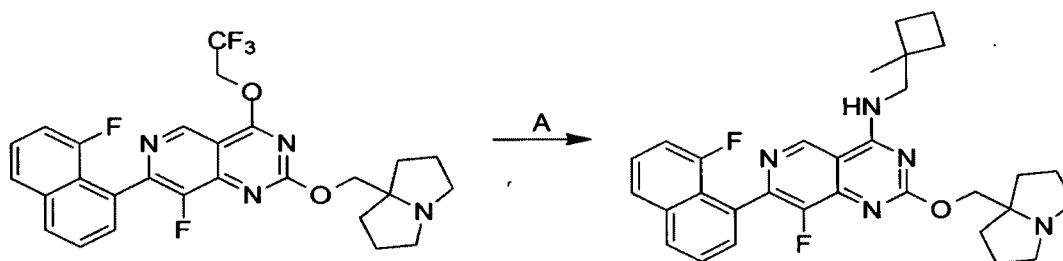


[0000460] Step A. 4-((1R,5S)-3-azabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μ mol) in DMF (1.0 mL) were added DIEA (36.5 mg, 283 μ mol, 49.3 μ L) and (1R,5S)-3-azabicyclo[3.2.1]octane (31.4 mg, 283 μ mol). The mixture was stirred at 40 °C for 1 hour. Upon completion, the residue was purified by prep-IPLC (column: 3_Phenomenex Luna C18 75 $\times$ 30mm $\times$ 3 μ m; mobile phase: [water (0.2% formic acid salt)-MeOH]; B%: 25%-60%, 9min.) affording 4-((1R,5S)-3-azabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine (22.7 mg, 42% yield) as a white solid. ¹H NMR (400MHz, CDCl₃) δ 9.06 (s, 1H), 7.99 (br d, J = 7.6 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.66-7.54 (m, 2H), 7.48-7.40 (m, 1H), 7.15-7.08 (m, 1H), 4.70 (br d, J = 12.0 Hz, 1H), 4.61 (br d, J = 12.0 Hz, 1H), 4.46 (s, 2H), 3.59-3.43 (m, 4H), 2.82-2.72 (m, 2H), 2.43 (br s, 2H), 2.31-2.22 (m, 2H), 2.13-1.92 (m, 4H), 1.90-1.77 (m, 3H), 1.76-1.55 (m, 5H); LCMS [ESI, M+1]: m/z 542.1.

EXAMPLE 19

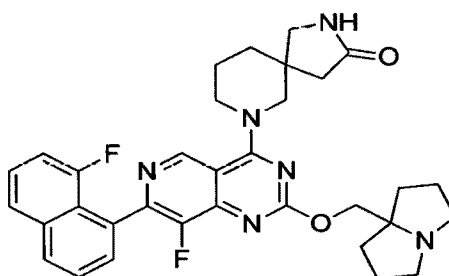


8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-((1-methylcyclobutyl)methyl)pyrido[4,3-d]pyrimidin-4-amine

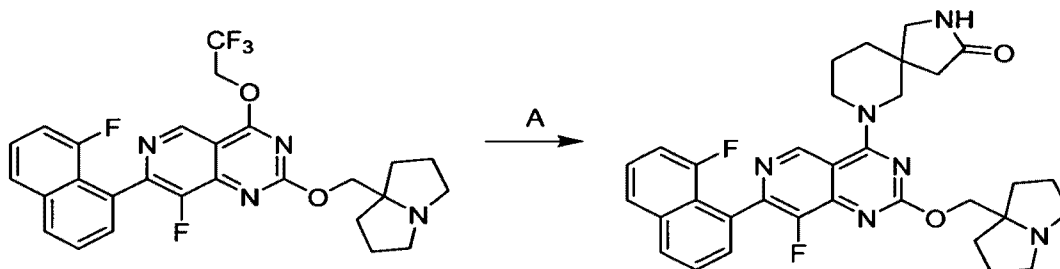


[0000461] Step A. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-((1-methylcyclobutyl)methyl)pyrido[4,3-d]pyrimidin-4-amine: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μ mol) in DMF (1.0 mL) were added DIEA (60.9 mg, 471 μ mol, 82.1 μ L) and (1-methylcyclobutyl)methanamine (38.4 mg, 283 μ mol, HCl). The mixture was stirred at 40 °C for 1 hour. Upon completion, the residue was purified by prep-HPLC (column: Phenomenex Luna C18 200 $\times$ 40mm $\times$ 10 μ m; mobile phase: [water (0.2%FORMIC ACID)-ACN]; B%: 20%-50%, 8min.) affording 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-((1-methylcyclobutyl)methyl)pyrido[4,3-d]pyrimidin-4-amine (10.4 mg, 19% yield) as a white solid. ¹H NMR (400MHz, CDCl₃) δ 8.94 (s, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.65-7.59 (m, 1H), 7.59-7.55 (m, 1H), 7.48-7.40 (m, 1H), 7.14-7.06 (m, 1H), 6.39 (br s, 1H), 4.42 (s, 2H), 3.81-3.66 (m, 2H), 3.49-3.38 (m, 2H), 2.80-2.70 (m, 2H), 2.28-2.14 (m, 2H), 2.07-1.89 (m, 8H), 1.87-1.71 (m, 4H), 1.32-1.20 (m, 3H); LCMS [ESI, M+1]: m/z 530.1.

EXAMPLE 20

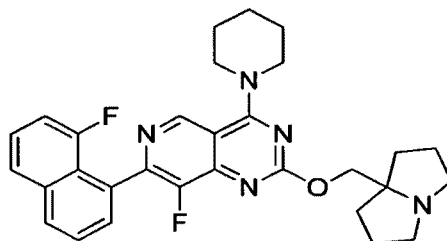


7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one

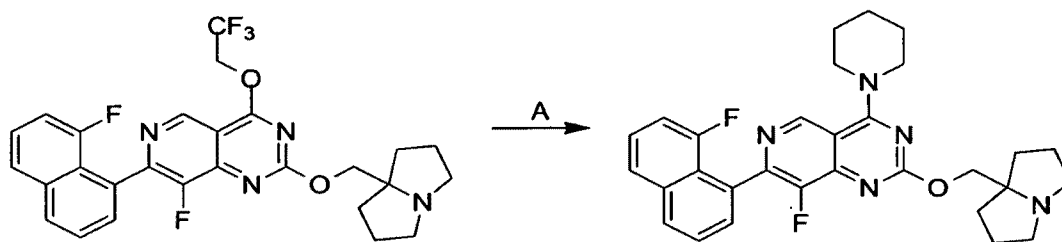


[0000462] Step A. 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μ mol), DIFA (60.9 mg, 471 μ mol, 82.1 μ L) and 4Å molecular sieves (5.0 mg) in DMF (2.0 mL) was added 2,7-diazaspiro[4.5]decan-3-one (44.9 mg, 236 μ mol, HCl). The mixture was stirred at 40 °C for 12 h. After completion, the mixture was filtered and concentrated. The residue was purified by prep-HPLC [Water s Xbridge 150 $\times$ 25 mm $\times$ 5 μ m; A: water (10mM NH_4HCO_3), B: ACN; B%: 17%-50% over 9min] and the desired fractions were lyophilized to afford 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (10.6 mg, 19% yield). Off-white solid; ^1H NMR (400 MHz, CDCl_3) δ = 8.99 (s, 1H), 8.00 (br d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.66-7.54 (m, 2H), 7.49-7.40 (m, 1H), 7.17-7.06 (m, 1H), 6.03-5.87 (m, 1H), 4.31-4.16 (m, 2H), 4.15-4.02 (m, 2H), 3.80-3.68 (m, 1H), 3.61 (br dd, J = 8.0, 12.8 Hz, 1H), 3.43 (dd, J = 10.0, 12.8 Hz, 1H), 3.22 (d, J = 10.0 Hz, 1H), 3.16-3.06 (m, 2H), 2.70-2.56 (m, 2H), 2.38-2.22 (m, 2H), 2.14-2.03 (m, 2H), 1.94-1.84 (m, 8H), 1.70-1.61 (m, 2H); LCMS (ESI, $\text{M}+1$): m/z 585.3.

EXAMPLE 21

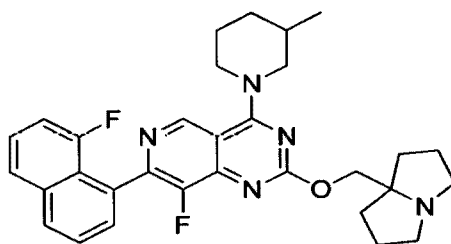


8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine

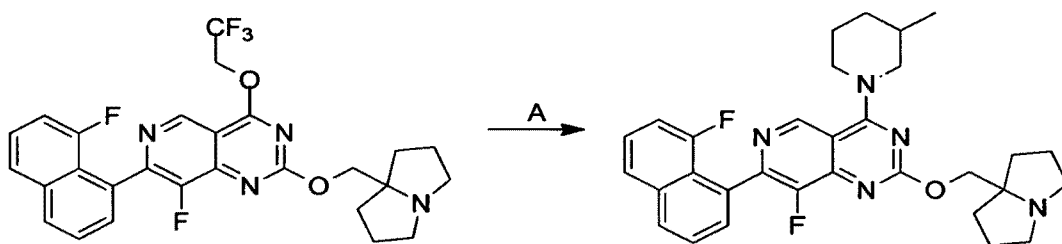


[0000463] Step A. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μ mol) in DMF (1.0 mL) were added DIEA (36.5 mg, 283 μ mol, 49.3 μ L) and piperidine (12.0 mg, 141 μ mol, 14.0 μ L). The mixture was stirred at 40 °C for 1 hour. Upon completion, the residue was purified by prep-HPLC (column: water s Xbridge BEH C18 100 $\times$ 25mm $\times$ 5 μ m; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 35%-70%, 10mins.) affording 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine (12.5 mg, 26% yield) as a white solid. ¹H NMR (400MHz, CDCl₃) δ 9.01 (s, 1H), 8.02-7.96 (m, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.66-7.56 (m, 2H), 7.48-7.41 m, 1H), 7.16-7.07 (m, 1H), 4.25-4.17 (m, 2H), 3.96 (br s, 4H), 3.16-3.07 (m, 2H), 2.68-2.60 (m, 2H), 2.16-2.06 (m, 2H), 1.91-1.84 (m, 4H), 1.82 (br s, 6H), 1.69-1.62 (m, 2H); LCMS [ESI, M+1]: *m/z* 516.1.

EXAMPLE 22

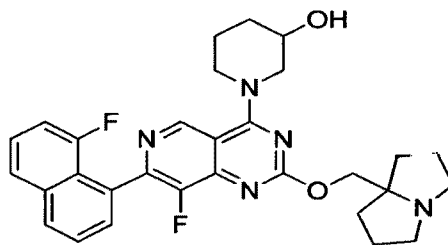


8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine

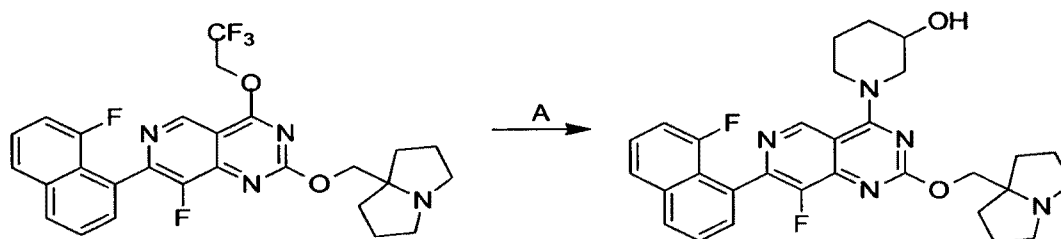


[0000464] Step A. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μmol) in DMF (1.0 mL) were added DIEA (36.5 mg, 283 μmol , 49.3 μL) and 3-methylpiperidine (28.0 mg, 283 μmol , 33.2 μL). The mixture was stirred at 40 °C for 1 hour. Upon completion, the residue was purified by prep-HPLC (column: water s Xbridge BEH C18 100 $\times$ 25mm $\times$ 5 μm ; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 40%-80%, 10mins.) affording 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine (7.87 mg, 16% yield) as a white solid. ^1H NMR (400MHz, CDCl_3) δ 9.00 (s, 1H), 7.99 (br d, J = 7.6 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.67-7.57 (m, 2H), 7.48-7.41 (m, 1H), 7.15-7.08 (m, 1H), 4.61 (br d, J = 13.2 Hz, 1H), 4.49 (br d, J = 12 Hz, 1H), 4.29-4.16 (m, 2H), 3.26-3.17 (m, 1H), 3.15-3.07 (m, 2H), 3.01-2.88 (m, 1H), 2.68-2.60 (m, 2H), 2.15-2.06 (m, 2H), 2.04-1.74 (m, 8H), 1.69-1.59 (m, 2H), 1.39-1.25 (m, 1H), 1.02 (d, J = 6.6 Hz, 3H); LCMS [ESI, $\text{M}+1$]: m/z 530.1.

EXAMPLE 23

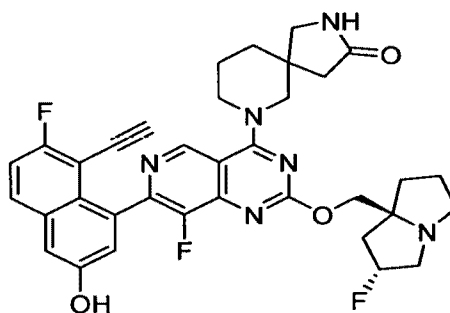


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol

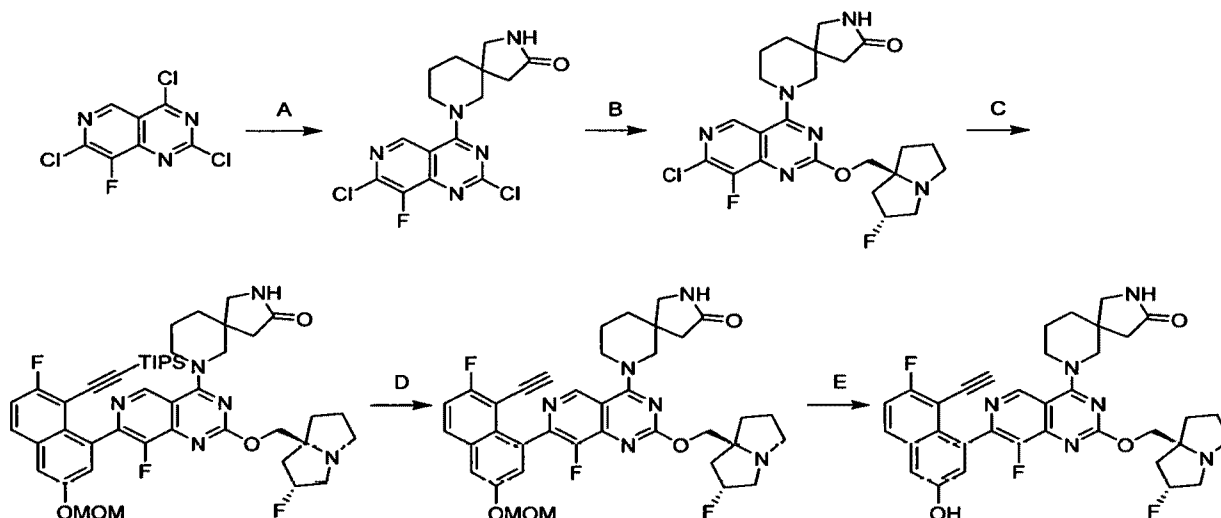


[0000465] Step A. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μ mol) in DMF (1.0 mL) were added DIEA (36.5 mg, 283 μ mol, 49.3 μ L) and piperidin-3-ol (28.6 mg, 283 μ mol, 33.2 μ L). The mixture was stirred at 40 °C for 1 hour. Upon completion, the residue was purified by prep-HPLC (column: water s Xbridge BEH C18 100 $\times$ 25mm $\times$ 5 μ m; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 20%-60%, 10mins.) affording 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol (17.7 mg, 35% yield) as a white solid. ¹H NMR (400MHz, CDCl₃) δ 9.10 (d, *J* = 2.2 Hz, 1H), 7.99 (br d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.65-7.56 (m, 2H), 7.48-7.41 (m, 1H), 7.15-7.08 (m, 1H), 4.29-4.19 (m, 2H), 4.10 (br s, 1H), 4.06-3.88 (m, 4H), 3.24 (br s, 1H), 3.15-3.05 (m, 2H), 2.72-2.58 (m, 2H), 2.14-1.93 (m, 5H), 1.93-1.76 (m, 5H), 1.67-1.60 (m, 2H); LCMS [ESI, M+1]: *m/z* 532.1.

EXAMPLE 24



7-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one



[0000466] Step A. 7-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (2.0 g, 6.85 mmol, 86% purity) in dichloromethane (20 mL) were added DIEA (3.54 g, 27.4 mmol, 4.77 mL) and 2,7-diazaspiro[4.5]decan-3-one (1.44 g, 7.53 mmol, HCl) at -40 °C. The mixture was stirred at -40 °C for 1 h. After completion, the mixture was added water (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and filtered. The mixture was concentrated in vacuum. The residue was purified by reversed phase flash chromatography (C18, water (0.1 % formic acid)/ACN) affording 7-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (1.60 g, 63% yield). Yellow solid; LCMS (ESI, M+1): m/z 370.0.

[0000467] Step B. 7-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 7-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (300 mg, 810 μmol), DIEA (314 mg, 2.43 mmol, 423 μL) and 4Å molecular sieves (10 mg) in dioxane (2.0 mL) was added ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (142 mg, 891

μmol). The mixture was stirred at 95 °C for 16 h. After completion, water (5.0 mL) was added and the mixture was extracted with EtOAc (2 × 5.0 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by reversed phase flash chromatography (C18, water (0.1 % formic acid)/ACN) affording the title compound (120 mg, 19% yield). Yellow solid; LCMS (ESI, M+1): m/z 493.2.

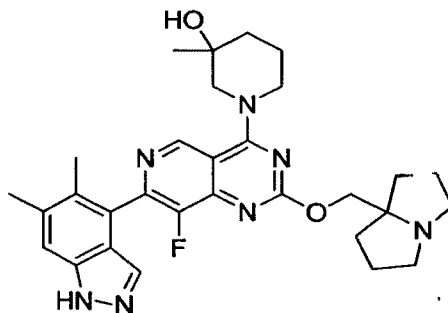
[0000468] Step C. 7-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 7-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (100 mg, 203 μmol), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (208 mg, 406 μmol) and K₃PO₄ (1.5 M, 406 μL) in THF (3.0 mL) was cataCXium-A-Pd-G3 (14.8 mg, 20.3 μmol). The mixture was stirred at 60 °C for 2 h. After completion, water (5.0 mL) was added and the mixture was extracted with EtOAc (2 × 5.0 mL). The combined organic layer was dried over anhydrous Na₂SO₄ and filtered. The mixture was concentrated in vacuum. The residue was purified by reversed phase flash chromatography (C18, water (0.1 % formic acid)/ACN) affording 7-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (80 mg, 45% yield). Yellow solid; LCMS (ESI, M+1): m/z 843.5.

[0000469] Step D. 7-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of 7-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (75.0 mg, 89.0 μmol) in DMF (1.5 mL) was added CsF (40.5 mg, 267 μmol, 9.84 μL). The mixture was stirred at 20 °C for 1 h. After completion, water (5.0 mL) was added and the mixture was extracted with EtOAc (2 × 5.0 mL). The combined organic layer was dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography (C18, water (0.1 % formic acid)/ACN) affording 7-(7-(8-ethynyl-7-fluoro-3-

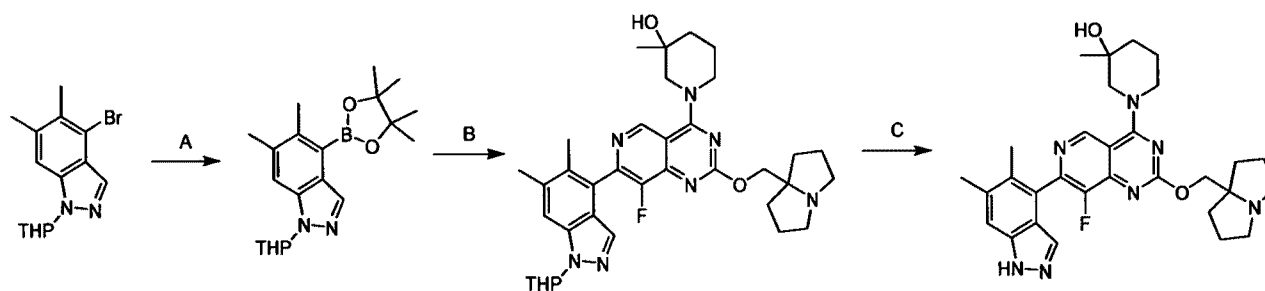
(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (60 mg, 98% yield). Yellow solid; LCMS (ESI, M+1): m/z 687.3.

[0000470] Step E. 7-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of 7-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (55.0 mg, 80.1 μ mol) in MeCN (0.5 mL) was added HCl•dioxane (4 M, 1.0 mL). The mixture was stirred at 20 °C for 0.5 h. After completion, the mixture was concentrated at 20 °C. The residue was purified by prep-HPLC [Water s Xbridge 150 $\times$ 25 mm $\times$ 5 μ m; A: water (10mM NH₄HCO₃), B: ACN; B%: 33%-63% over 10 min] and the desired fractions were lyophilized to afford 7-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (6.16 mg, 12% yield). Yellow solid; ¹H NMR (400 MHz, DMSO-d₆) δ = 10.20 (s, 1H), 9.02 (d, *J* = 5.6 Hz, 1H), 7.98 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.74-7.59 (m, 1H), 7.47 (t, *J* = 9.2 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.20 (t, *J* = 2.4 Hz, 1H), 5.56-5.23 (m, 1H), 4.48-4.11 (m, 2H), 4.11-3.86 (m, 3H), 3.86-3.67 (m, 2H), 3.26-2.89 (m, 4H), 2.52 (br s, 2H), 2.34-2.09 (m, 4H), 2.07-1.71 (m, 8H); LCMS (ESI, M+1): m/z 643.3.

EXAMPLE 25



1-(7-(5,6-dimethyl-1H-indazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



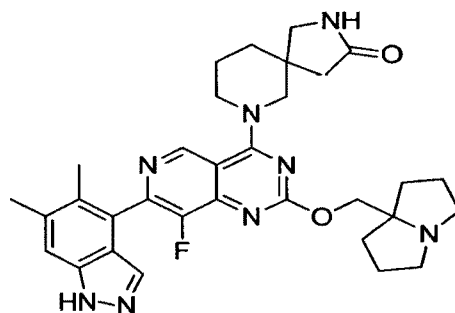
[0000471] Step A. 5,6-dimethyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole: To a solution of 4-bromo-5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (2.00 g, 6.47 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.29 g, 12.9 mmol) and KOAc (1.90 g, 19.4 mmol) in dioxane (40 mL) was added Pd(dppf)Cl₂ (473 mg, 647 μmol). The mixture was stirred at 110 °C for 1 hour. After completion, water (30 mL) was added and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layer was dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, petroleum ether: ethyl acetate=100:1-15:1) affording 5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (1.60 g, 67% yield). Yellow oil; LCMS (ESI, M+1): m/z = 357.0.

[0000472] Step B. 1-(7-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (290 mg, 665 μmol) and 5,6-dimethyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (355 mg, 998 μmol) in THF (6 mL) was added K₃PO₄ (1.5 M, 1.33 mL) in one portion at 25 °C under N₂. Then cataCXium-A-Pd-G3 (96.90 mg, 133 μmol) was added. The mixture was heated to 60 °C and stirred for 2 h. The mixture was filtered and concentrated in vacuum. The crude product was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) to afford the title compound (300 mg, 69% yield). LCMS (ESI, M+1): m/z 630.5.

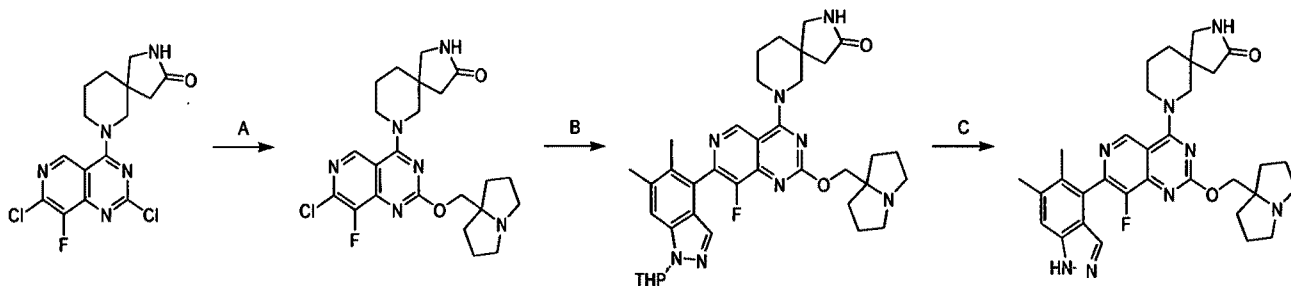
[0000473] Step C. 1-(7-(5,6-dimethyl-1H-indazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of 1-(7-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-8-fluoro-2-((tetrahydro-1H-

pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (290 mg, 460 μ mol) and ACN (0.2 mL) was added HCl•dioxane (4 M, 1.98 μ L) in one portion at 25°C under N₂. The mixture was stirred at 25 °C for 10 minutes. The mixture was filtered and concentrated in vacuum. The residue was purified by prep-HPLC to afford the title compound (76.4 mg, 30% yield). ¹H NMR 400 MHz, (DMSO-d₆) δ 13.0 (br s, 1H), 9.30 (d, *J* = 9.8Hz, 1H), 8.23 (s, 1H), 7.33-7.23 (m, 2H), 4.20-4.15 (m, 1H), 4.17-4.02 (m, 3H), 3.31-3.27 (m, 2H), 3.05-2.95 (m, 2H), 2.35-2.27 (m, 2H), 2.44 (s, 3H), 2.13 (d, *J* = 4.4Hz, 3H), 2.04-1.27 (m, 12H), 1.18 (s, 3H). LCMS (ESI, M+1): *m/z* 546.1.

EXAMPLE 26



7-(7-(5,6-dimethyl-1H-indazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one



[0000474] Step A. 7-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 7-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (300 mg, 810 μ mol), 4Å molecular sieves (10 mg) and DIEA (314 mg, 2.43 mmol, 423 μ L) in dioxane (2 mL) was added (hexahydro-1H-pyrrolizin-7a-yl)methanol (126 mg, 891 μ mol). The mixture was stirred at 95 °C

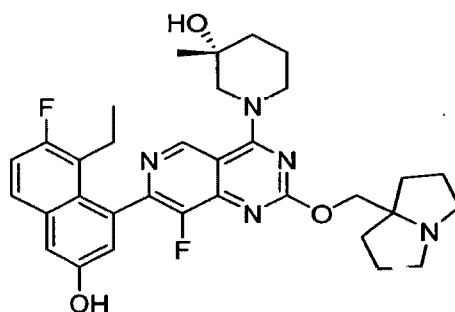
for 16 h. After completion, water (5.0 mL) was added and the mixture was extracted with EtOAc (2 × 5.0 mL). The combined organic layer was dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography (C18, water (0.1 % formic acid)/ACN) to afford 7-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (130 mg, 33% yield). Yellow solid; LCMS (ESI, M+1): m/z = 475.3.

[0000475] Step B. 7-(7-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 7-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (130 mg, 274 μmol), 5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (243.78 mg, 684.27 μmol) and K₃PO₄ (1.5 M, 547 μL) in THF (3 mL) was added cataCXium-A-Pd-G3 (39.9 mg, 54.7 μmol). The mixture was stirred at 60 °C for 2 hour. After completion, to the reaction mixture was added water (5.0 mL), and the mixture extracted with EtOAc (2 × 5.0 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography (C18, water (0.1 % formic acid)/ACN) affording 7-(7-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (120 mg, 65% yield). Yellow solid; LCMS (ESI, M+1): m/z = 669.3.

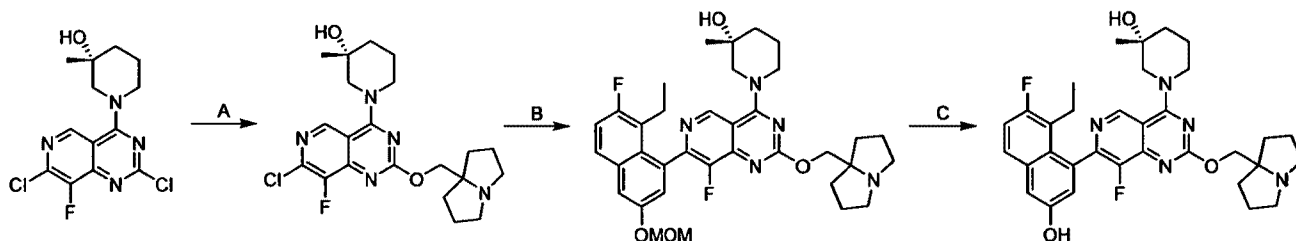
[0000476] Step C. 7-(7-(5,6-dimethyl-1H-indazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of 7-(7-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (30 mg, 44.9 μmol) in MeCN (0.5 mL) was added HCl•dioxane (4 M, 1.0 mL). The mixture was stirred at 20 °C for 0.5 hour. After completion, the mixture was concentrated at 20 °C. The residue was purified by prep-HPLC [Water s Xbridge 150 × 25mm × 5um; A: water (10mM NH₄HCO₃), B: ACN, B%: 16%-46% over 10 min) to afford the title compound (7.08 mg, 26% yield). White solid; ¹H NMR (400 MHz, CDCl₃) δ = 10.87-10.17 (m, 1H), 8.98 (d, J = 4.0 Hz, 1H), 7.56 (d, J = 13.2 Hz, 1H), 7.31 (br d, J = 4.8 Hz, 1H), 6.55-5.99 (m,

1H), 4.28-4.12 (m, 2H), 4.02 (br d, $J = 12.8$ Hz, 2H), 3.66-3.52 (m, 1H), 3.42 (br d, $J = 12.0$ Hz, 1H), 3.31 (br t, $J = 10.0$ Hz, 1H), 3.14-3.00 (m, 3H), 2.64-2.52 (m, 2H), 2.46-2.36 (m, 3H), 2.19 (s, 2H), 2.13 (br d, $J = 5.2$ Hz, 3H), 2.07-1.97 (m, 2H), 1.88-1.74 (m, 8H), 1.60-1.54 (m, 2H); LCMS (ESI, M+1): $m/z = 585.2$.

EXAMPLE 27



(R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

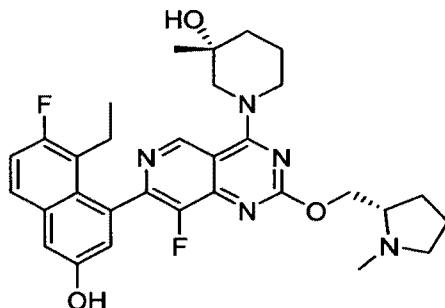


[0000477] Step A. (R)-1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (125 mg, 377 μmol), (hexahydro-1H-pyrrolizin-7a-yl)methanol (56 mg, 396 μmol), DIPEA (133 mg, 1.03 mmol) and 4Å molecular sieves (56 mg) in dioxane (0.7 mL) was stirred at 90 °C for 21 hours under N_2 atmosphere. The reaction mixture was filtered and the filter cake was washed with dichloromethane (20 mL). The filtrate was concentrated under reduced pressure and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=7/3] to give the product as white solid (40 mg, 21% yield). LCMS (ESI, M+1): $m/z = 436.2$.

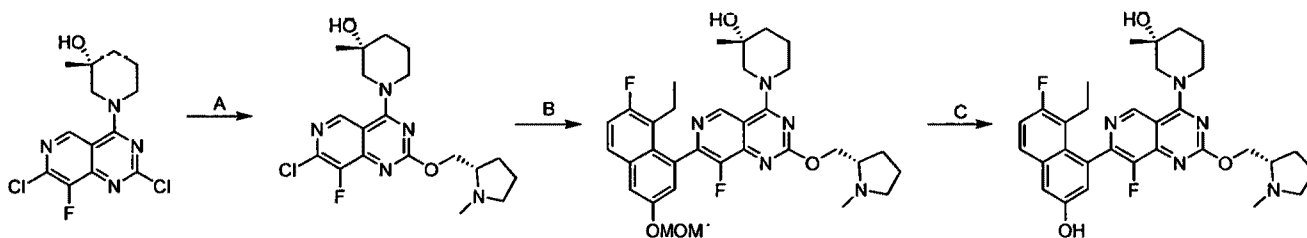
[0000478] Step B. (R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (R)-1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (40 mg, 91.8 μ mol), K₃PO₄ (1.5 M in water, 0.2 mL) in THF (1 mL) was degassed and purged with N₂ for 3 times. cataCXium-A-Pd-G3 (14 mg, 19.2 μ mol) was added and followed by 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (50 mg, 139 μ mol). The mixture was stirred at 65 °C for 4 hours. The reaction mixture was diluted with water (2 mL) and extracted with ethyl acetate (2 mL $\times$ 4). The combined organic layers were concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=13/7] to give the product as brown gum (41 mg, 65% yield). LCMS (ESI, M+1): m/z 634.1.

[0000479] Step C. (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (41 mg, 64.7 μ mol) in MeCN (2 mL) was added HCl/dioxane (4 M, 1.5 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. The reaction mixture was concentrated under reduced pressure to give a residue at room temperature. The residue was dissolved in ethyl acetate (5 mL) and saturated NaHCO₃ aqueous (5 mL). The mixture was extracted with ethyl acetate (5 mL $\times$ 4). The combined organic layers were dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 $\times$ 25mm $\times$ 10 μ m; mobile phase: [water (0.225% formic acid)-ACN]; B%: 15%-45%, 10 minutes) to give the product as yellow solid (9.02 mg, 22% yield, 0.7% FORMIC ACID). ¹H NMR (400 MHz, methanol-d₄) δ = 9.26 (s, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 1H), 7.26 (t, *J* = 9.2 Hz, 1H), 7.06 (t, *J* = 2.4 Hz, 1H), 4.62-3.55 (m, 3H), 4.34 (t, *J* = 11.6 Hz, 1H), 3.67-3.61 (m, 1H), 3.55-3.40 (m, 3H), 3.14-3.11 (m, 2H), 2.25-2.15 (m, 1H), 2.13-2.03 (m, 10H), 2.02-1.73 (m, 3H), 1.30 (d, *J* = 9.2 Hz, 3H), 0.81 (q, *J* = 7.6 Hz, 3H). ¹⁹F NMR (377 MHz, methanol-d₄) δ = -121.11, -139.56. LCMS (ESI, M+1): m/z 590.4.

EXAMPLE 28



(3R)-1-[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-[[[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol



[0000480] Step A. (3R)-1-[7-chloro-8-fluoro-2-[[[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol: A mixture of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (150 mg, 453 μ mol), [(2S)-1-methylpyrrolidin-2-yl]methanol (157 mg, 1.36 mmol, 161 μ l), DIEA (176 mg, 1.36 mmol, 237 μ l) and 4Å molecular sieves (15.0 mg, 453 μ mol) in dioxane (2 mL) was stirred at 90 °C for 15 hours. After completion, the mixture was diluted with ethyl acetate (5 mL) and water (5 mL), and then separated. The aqueous phase was extracted with ethyl acetate (5 mL). The combined organic layer was washed with brine (8 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (3R)-1-[7-chloro-8-fluoro-2-[[[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (135 mg, 70% yield). Yellow oil. LCMS (ESI, M+1): m/z 410.2.

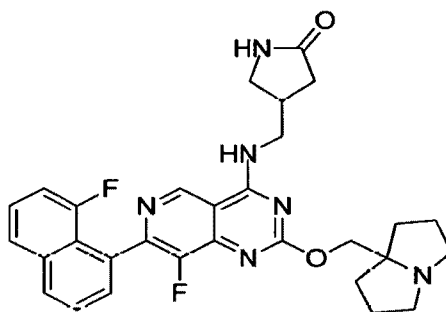
[0000481] Step B. (3R)-1-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol:

To a mixture of (3R)-1-[7-chloro-8-fluoro-2-[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (135 mg, 329 μ mol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (237 mg, 659 μ mol) and K_3PO_4 (1.5 M, 659 μ l) in THF (2.1 mL) was added [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butyl-phosphane;methanesulfonate (24.0 mg, 32.9 μ mol) under N_2 . The mixture was degassed and then heated to 60 °C for 3 hours under N_2 . After completion, the mixture was diluted with ethyl acetate (2 mL) and water (2 mL), and then separated. The aqueous phase was extracted with ethyl acetate (3 mL). The combined organic layer was washed with brine (4 mL) and dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (3R)-1-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (100 mg, 50% yield). Yellow oil; LCMS (ESI, M+1): m/z 608.3.

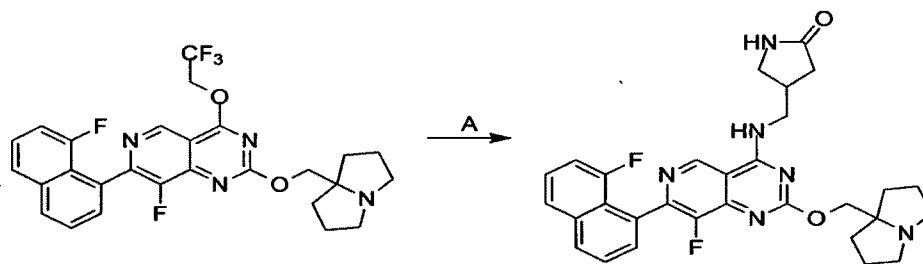
[0000482] Step C. (3R)-1-[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol: To a mixture of (3R)-1-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (40.0 mg, 65.8 μ mol) in MeCN (0.5 mL) was added HCl•dioxane (4 M, 1 mL) at 0 °C and the mixture was stirred at 0 °C for 0.5 hour. After completion, the mixture was concentrated in vacuum. Then the pH value was adjusted to 9 with saturated $NaHCO_3$ solution and the mixture was washed with methanol (2 $\times$ 8 mL). The mixture was filtered and concentrated in vacuum. The residue was purified by prep-HPLC (Shim-pack C18 150 $\times$ 25 $\times$ 10 μ m; mobile phase: [water (0.225% formic acid) - ACN]; B%: 20% - 40%, 10 min) to afford (3R)-1-[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (14.4 mg, 36% yield, 0.6 FORMIC ACID). White solid. ^1H NMR (400 MHz, METHANOL- d_4): δ 9.24 (d, J = 3.2 Hz, 1H), 7.68 (dd, J = 6.0, 8.8 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.25 (t, J = 9.2 Hz, 1H), 7.06 (br s, 1H), 4.78 - 4.71 (m, 1H), 4.66 - 4.56 (m, 2H), 4.33 (br t, J = 11.6 Hz, 1H), 3.66 - 3.59 (m, 1H), 3.54 - 3.41 (m, 3H), 3.00 - 2.93 (m, 1H), 2.89 (s, 3H), 2.51 - 2.41 (m, 1H), 2.35 - 2.27 (m, 1H), 2.23 - 2.13 (m, 2H), 2.09 - 1.96 (m, 3H), 1.89 - 1.76 (m, 3H), 1.29 (br d, J = 8.8 Hz, 3H), 0.81 (q, J = 7.6 Hz, 3H). ^{19}F NMR (400 MHz, METHANOL- d_4) δ =

-121.070, -139.482. HPLC: >99% ee, Chiralcel OJ-3 50×4.6mm I.D., 3μm; Mobile phase: Phase A for CO₂, and Phase B for MeOH (0.05% DEA); Gradient elution: MeOH (0.05% DEA) in CO₂ from 5% to 40%; Flow rate: 3mL/min; Detector: PDA; Column Temp: 35C; Back Pressure: 100Bar ". LCMS (ESI, M+1): m/z 564.3.

EXAMPLE 29



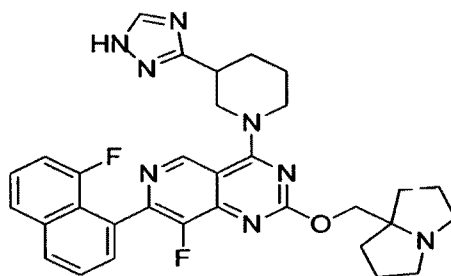
4-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one



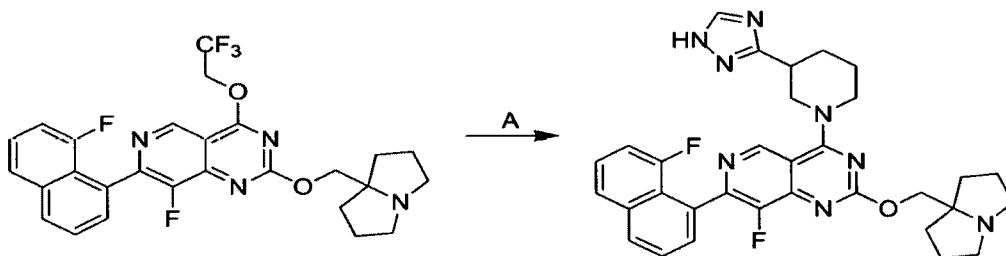
[0000483] Step A. 4-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μmol) in DMF (1.0 mL) were added DIEA (36.5 mg, 283 μmol, 49.3 μL) and 4-(aminomethyl)pyrrolidin-2-one (42.6 mg, 283 μmol, HCl). The mixture was stirred at 40 °C for 1 hour. Upon completion, the residue was purified by prep-HPLC (column: Phenomenex Luna C18 200×40mm×10μm; mobile phase: [water (0.2%FORMIC ACID)-ACN]; B%: 20%-50%, 8mins) to afford 4-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one (18.5 mg, 33% yield, formic acid salt) as a white solid. ¹H NMR

(400MHz, CDCl₃) δ 9.45-9.15 (m, 2H), 8.01-7.89 (m, 1H), 7.74-7.70 (m, 1H), 7.65-7.50 (m, 2H), 7.48-7.35 (m, 1H), 7.17-7.05 (m, 1H), 6.34 (br d, J = 72.0Hz, 1H), 4.55-4.34 (m, 2H), 3.79-3.64 (m, 2H), 3.60-3.52 (m, 1H), 3.48-3.33 (m, 2H), 3.20-3.03 (m, 1H), 2.96-2.71 (m, 3H), 2.47-2.35 (m, 1H), 2.35-2.17 (m, 2H), 2.16-2.03 (m, 3H), 2.02-1.89 (m, 2H), 1.89-1.75 (m, 2H); ¹H NMR (400MHz, MeOD-d₄) δ 9.20 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.75-7.66 (m, 1H), 7.61-7.57 (m, 1H), 7.54 (dt, J = 5.0, 8.0 Hz, 1H), 7.22-7.15 (m, 1H), 4.61-4.57 (m, 2H), 3.97-3.84 (m, 1H), 3.81-3.75 (m, 1H), 3.66-3.53 (m, 3H), 3.30-3.27 (m, 1H), 3.22-3.10 (m, 2H), 3.08-2.92 (m, 1H), 2.60-2.51 (m, 1H), 2.35-2.24 (m, 3H), 2.24-2.09 (m, 4H), 2.09-1.96 (m, 2H); LCMS (ESI, M+1): m/z 545.1.

EXAMPLE 30



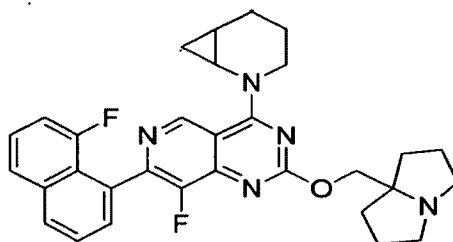
4-(3-(1H-1,2,4-triazol-3-yl)piperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine



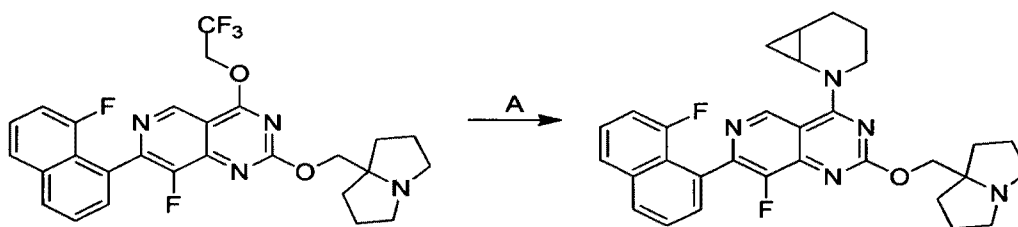
[0000484] Step A. 4-(3-(1H-1,2,4-triazol-3-yl)piperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine: A mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μ mol) in DMF (1.00 mL) was added DIEA (73.1 mg, 566 μ mol) and 3-(1H-1,2,4-triazol-3-yl)piperidine (35.6 mg, 189 μ mol,

HCl). The mixture was stirred at 40 °C for 8 hours. The mixture was filtered and was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75×30mm×3μm; mobile phase: [water (0.2%FORMIC ACID)-ACN]; B%: 15%-45%, 8min) to afford 4-(3-(1H-1,2,4-triazol-3-yl)piperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine (23.4 mg, 42% yield) as a white solid. ¹H NMR (400MHz, MeOD) δ 9.13 (s, 1H), 8.55 (s, 0.6H), 8.30 (s, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 7.1 Hz, 1H), 7.56-7.51 (m, 1H), 7.22-7.17 (m, 1H), 4.65-4.49 (m, 3H), 3.91-3.67 (m, 2H), 3.49-3.45 (m, 2H), 3.36 (d, *J* = 5.5 Hz, 2H), 3.14-3.05 (m, 2H), 2.34 (d, *J* = 9.2 Hz, 1H), 2.26-2.21 (m, 2H), 2.16-2.04 (m, 6H), 2.02-1.91 (m, 3H); LCMS (ESI, M+1): *m/z* 583.2.

EXAMPLE 31



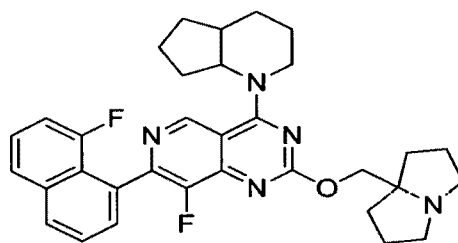
4-(2-azabicyclo[4.1.0]heptan-2-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine



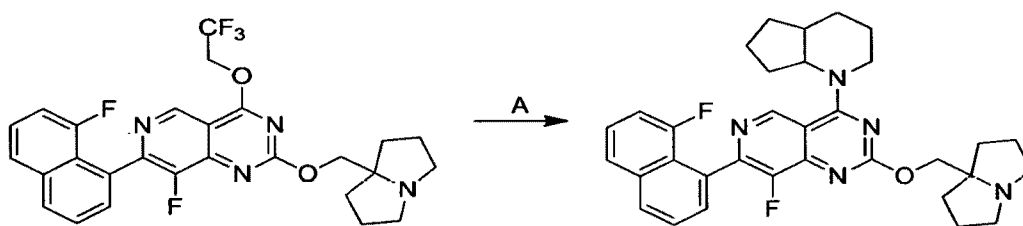
[0000485] Step A. 4-(2-azabicyclo[4.1.0]heptan-2-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine: A mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μmol) in DMF (1.00 mL) were added DIEA (36.5 mg, 283 μmol) and 2-azabicyclo[4.1.0]heptane (25.2 mg, 189 μmol, HCl). The mixture was stirred at 50 °C for 16 hours. The mixture was filtered and was purified by prep-HPLC

(column: water s Xbridge BEH C18 100×25mm×5μm; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 25%-65%, 12 min) to afford 4-(2-azabicyclo[4.1.0]heptan-2-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine (12.1 mg, 24% yield) as a white solid. ¹H NMR (400MHz, MeOD) δ 9.89 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.73-7.68 (m, 1H), 7.63-7.58 (m, 1H), 7.57-7.49 (m, 1H), 7.24-7.16 (m, 1H), 4.35-4.22 (m, 2H), 3.43-3.40 (m, 2H), 3.15-3.06 (m, 2H), 3.02-2.96 (t, *J* = 12.5 Hz, 1H), 2.76-2.69 (m, 2H), 2.12-2.05 (m, 4H), 1.97-1.83 (m, 5H), 1.80-1.69 (m, 3H), 1.59-1.54 (d, *J* = 2.8 Hz, 1H), 1.29-1.24 (td, *J* = 5.8, 9.6 Hz, 1H), 0.88-0.80 (m, 1H); LCMS (ESI, M+1): *m/z* 528.2.

EXAMPLE 32



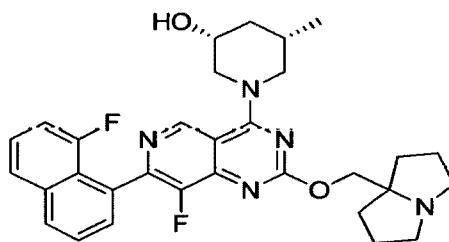
8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(octahydro-1H-cyclopenta[b]pyridin-1-yl)pyrido[4,3-d]pyrimidine



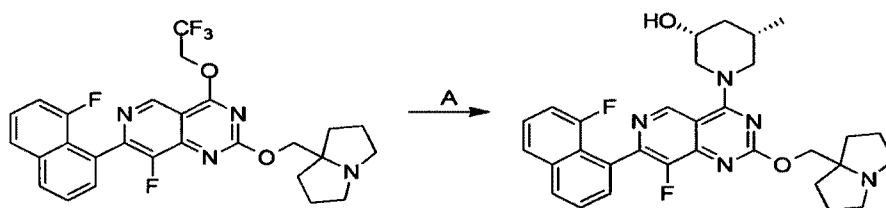
[0000486] Step A. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(octahydro-1H-cyclopenta[b]pyridin-1-yl)pyrido[4,3-d]pyrimidine: A mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μmol) in DMF (1 mL) were added DIEA (36.5 mg, 283 μmol) and octahydro-1H-cyclopenta[b]pyridine (30.5 mg, 243 μmol). The mixture was stirred at 50 °C for 16 hours. The mixture was filtered and was purified by prep-HPLC (column: water s Xbridge BEH C18 100×25mm×5μm; mobile phase: [water (10mM NH₄HCO₃)-

ACN]; B%: 40%-80%, 12min) to afford 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(octahydro-1H-cyclopenta[b]pyridin-1-yl)pyrido[4,3-d]pyrimidine (2.07 mg, 4% yield) as a white solid. ¹H NMR (400MHz, MeOD) δ 9.02 (s, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.72-7.68 (m, 1H), 7.63-7.56 (m, 1H), 7.55-7.51 (m, 1H), 7.22-7.17 (m, 1H), 5.04-4.99 (m, 1H), 4.65-4.62 (m, 1H), 4.35-4.26 (m, 2H), 3.58-3.43 (m, 1H), 3.17-3.07 (m, 2H), 2.81-2.69 (m, 2H), 2.22-2.05 (m, 5H), 2.00-1.84 (m, 7H), 1.83-1.74 (m, 5H), 1.67-1.52 (m, 2H); LCMS (ESI, M+1): *m/z* 556.2.

EXAMPLE 33



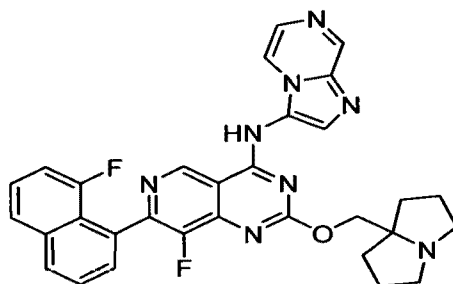
(3R,5S)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol



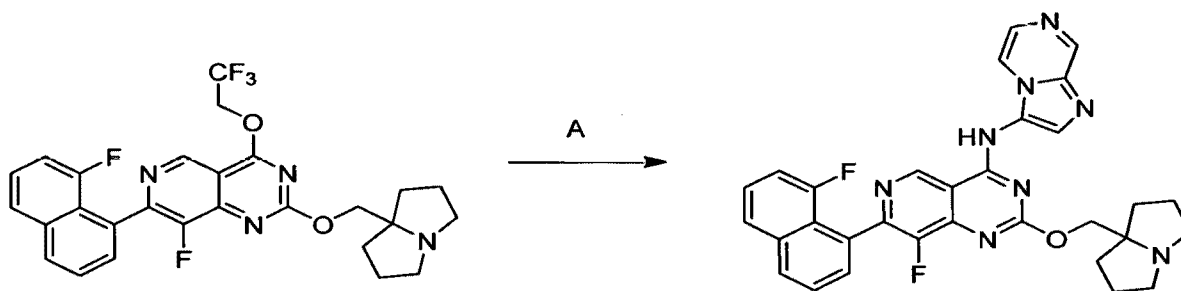
[0000487] Step A. (3R,5S)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol: To a solution of (3R,5S)-5-methylpiperidin-3-ol (15 mg, 98.9 μmol, HCl) and 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (52.5 mg, 98.9 μmol) in DMF (0.1 mL) was added DIEA (63.9 mg, 495 μmol). The mixture was stirred at 40 °C for 1 hour. The reaction mixture was quenched by water (10 mL) at

20 °C, and extracted with EtOAc (4 mL × 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: water s Xbridge BEH C18 150 × 25mm × 5μm; mobile phase: [water (0.05%NH₃•H₂O+10mM NH₄HCO₃)-ACN]; B%: 30%-60%, 8min) to give the title compound (8.92 mg, 16% yield) as a light yellow solid. ¹H NMR (400MHz, DMSO-d₆): δ 9.07 (d, *J* = 2.2 Hz, 1H), 8.18 (br d, *J* = 8.2 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.78 - 7.70 (m, 1H), 7.67 - 7.54 (m, 2H), 7.31 (dd, *J* = 7.6, 13.2 Hz, 1H), 5.20 (d, *J* = 4.2 Hz, 1H), 4.60 (br d, *J* = 10.3 Hz, 1H), 4.42 (br d, *J* = 10.9 Hz, 1H), 4.11 - 4.00 (m, 2H), 3.75 (td, *J* = 4.8, 9.8 Hz, 1H), 2.96 - 2.88 (m, 3H), 2.88 - 2.80 (m, 1H), 2.58 - 2.51 (m, 3H), 2.07 (brd, *J* = 12.1 Hz, 1H), 1.93 - 1.84 (m, 3H), 1.84 - 1.69 (m, 4H), 1.62 - 1.51 (m, 2H), 1.16 (q, *J* = 11.7 Hz, 1H), 0.98 (d, *J* = 6.6 Hz, 3H); LCMS (ESI, M+1): *m/z* 546.2.

EXAMPLE 34



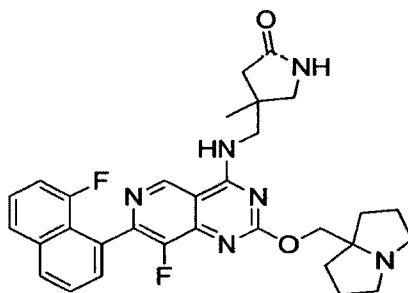
8-fluoro-7-(8-fluoronaphthalen-1-yl)-N-(imidazo[1,2-a]pyrazin-3-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine



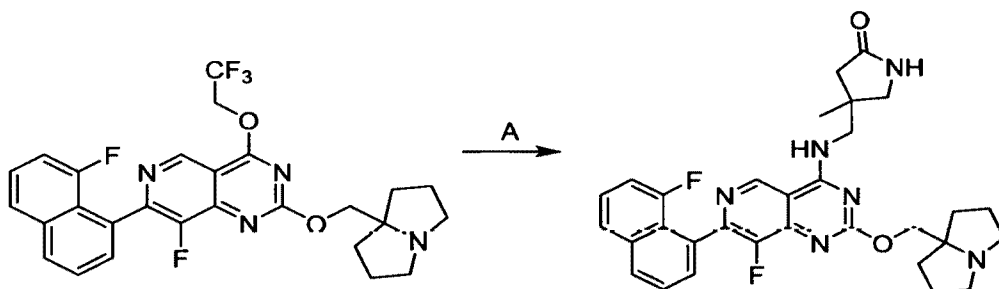
[0000488] Step A: 8-fluoro-7-(8-fluoronaphthalen-1-yl)-N-(imidazo[1,2-a]pyrazin-3-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: To a solution of

imidazo[1,2-a]pyrazin-3-amine (3.0 equiv.) in DMF (1 mL) were added 4Å molecular sieves (20 mg), t-BuONa (2.00 equiv.) and 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (0.09 mmol, 1.00 equiv.) at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 hour. After completion, the reaction mixture was diluted with water (10.0 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: water s Xbridge 150*25mm*5um; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 27%-57%, 10 min) to afford the title compound. LCMS (ESI, M+1): m/z 565.3.

EXAMPLE 35



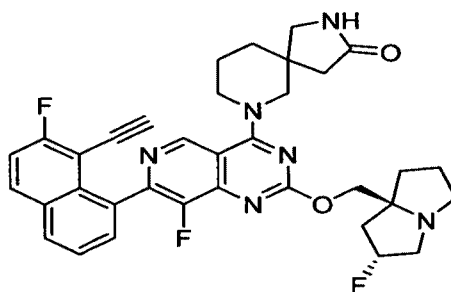
4-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)-4-methylpyrrolidin-2-one



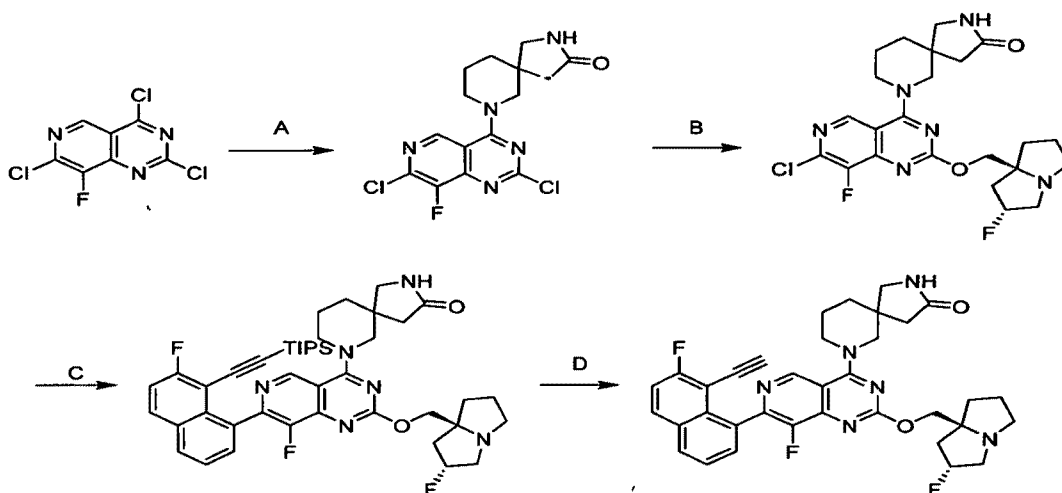
[0000489] Step A. 4-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)-4-methylpyrrolidin-2-one: To a mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (20.0 mg, 37.7 μmol) and 4-(aminomethyl)-4-

methylypyrrolidin-2-one (96.6 mg, 754 μ mol) in DMF (2.00 mL) was added DIEA (24.4 mg, 189 μ mol) at 25°C under N₂. The mixture was stirred at 40 °C for 2 hours. The reaction mixture was quenched with water (10.0 mL) and extracted with ethyl acetate (3 $\times$ 10.0 mL). The combined organic layers were washed with brine (20.0 mL), dried over sodium sulfate. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 $\times$ 30 mm $\times$ 3 μ m; mobile phase: [water (0.2%FORMIC ACID)-ACN]; B%: 20%-60%, 8min) to give 4-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)-4-methylpyrrolidin-2-one (7.29 mg, 34% yield) as white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 9.39 (d, *J* = 2.42 Hz, 1 H), 8.90 (s, 1 H), 8.18 (d, *J* = 7.72 Hz, 1 H), 7.93 (d, *J* = 7.94 Hz, 1 H), 7.77-7.69 (m, 1 H), 7.65-7.48 (m, 3 H), 7.30 (dd, *J* = 12.58, 8.16 Hz, 1 H), 4.12 (s, 2 H), 3.69 (d, *J* = 5.07 Hz, 2 H), 3.00- 2.96 (m, 2 H), 2.61 (d, *J* = 6.84 Hz, 2 H), 2.39 (d, *J* = 18.08 Hz, 2 H), 2.00-1.52 (m, 8 H), 1.64-1.60 (m, 2H), 1.19 (s, 3 H); LCMS (ESI, M+1): *m/z* 559.1

EXAMPLE 36



7-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one



[0000490] Step A. 7-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (2.0 g, 6.85 mmol) in dichloromethane (20 mL) were added DIEA (3.54 g, 27.4 mmol) and 2,7-diazaspiro[4.5]decan-3-one (1.44 g, 7.53 mmol, HCl) at -40 °C. The mixture was stirred at -40 °C for 1 hour. The mixture was diluted with water (20 mL), and extracted with EtOAc (2 × 20 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography (C18, water (0.1 % formic acid)/ACN) to afford 7-(2,7-dichloro-8-fluoropyrido [4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (1.6 g, 63% yield) as yellow solid. LCMS (ESI, M+1): m/z 370.0

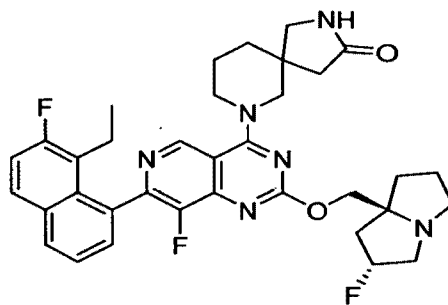
[0000491] Step B. 7-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl) methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 7-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (300 mg, 810 μmol), DIEA (314 mg, 2.43 mmol) and 4Å molecular sieves (10 mg) in dioxane (2 mL) was added ((2R,7aS)-2-fluorohexahydro-1H- pyrrolizin-7a-yl)methanol (142 mg, 891 μmol). The mixture was stirred at 95 °C for 16 hours. The mixture was diluted with water (5 mL), and extracted with EtOAc (2 × 5 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by reversed phase flash chromatography (C18, water (0.1 % formic acid)/ACN) to afford 7-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H- pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (120 mg, 19% yield) as yellow solid. LCMS (ESI, M+1): m/z 493.2

[0000492] Step C. 7-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorohexahydro-1*H*-pyrrolizin-7*a*-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 7-(7-chloro-8-fluoro-2-(((2*R*,7*aS*)-2-fluorohexahydro-1*H*-pyrrolizin-7*a*-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (300 mg, 608 μ mol), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (413 mg, 913 μ mol) and K_3PO_4 (1.5 M, 1.22 mL) in THF (6 mL) was added cataCXium-A-Pd-G3 (66.5 mg, 91.3 μ mol). The mixture was stirred at 60 °C for 2 hours. The mixture was diluted with water (10 mL), extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were washed with brine (100 mL), and dried over Na_2SO_4 . The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography (C18, 0.1% formic acid in water, 0-40% ACN) to afford 7-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorohexahydro-1*H*-pyrrolizin-7*a*-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (350 mg, 70% yield) as yellow solid. LCMS (ESI, $M+1$): m/z 783.4

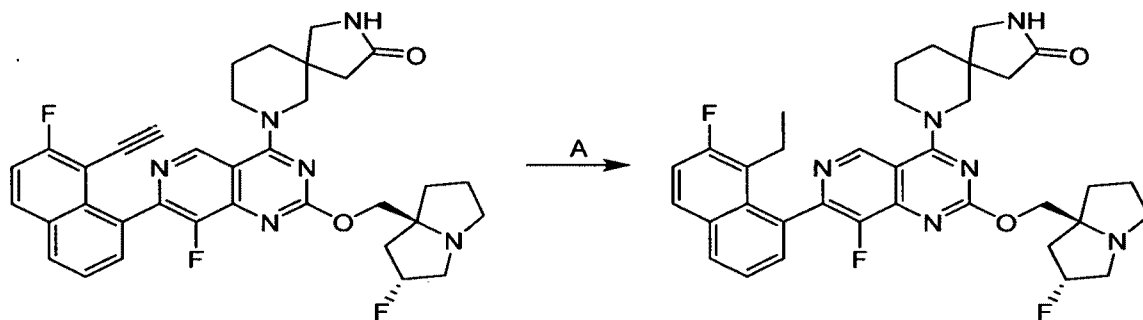
[0000493] Step D. 7-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorohexahydro-1*H*-pyrrolizin-7*a*-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of 7-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7*aS*)-2-fluorohexahydro-1*H*-pyrrolizin-7*a*-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (350 mg, 447 μ mol) in DMF (4 mL) was added CsF (339 mg, 2.23 mmol). The mixture was stirred at 25 °C for 1 hour. The mixture was diluted with water (10 mL), extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were washed with brine (100 mL), and dried over Na_2SO_4 . The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography (C18, water (0.1 % formic acid)/ACN) to give a crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 150 $\times$ 25 mm $\times$ 10 μ m; mobile phase: [water (0.225% formic acid)-ACN]; B%: 15%-45%, 10 min) to afford 7-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorohexahydro-1*H*-pyrrolizin-7*a*-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (205 mg, 0.5FA, 70% yield) as yellow solid. ^1H NMR (400 MHz, methanol- d_4): δ 9.06 (dd, J = 1.2, 2.8 Hz, 1H), 8.50 (s, 1H), 8.18-8.08 (m, 2H), 7.71-7.61 (m, 2H), 7.45 (dt, J = 0.8, 9.2 Hz, 1H), 5.56-5.31 (m, 1H), 4.53-

4.14 (m, 4H), 4.13-3.79 (m, 2H), 3.73-3.43 (m, 4H), 3.29-3.16 (m, 2H), 2.56-2.23 (m, 5H), 2.20-2.01 (m, 3H), 1.99-1.80 (m, 4H); LCMS (ESI, M+1): m/z 627.3

EXAMPLE 37



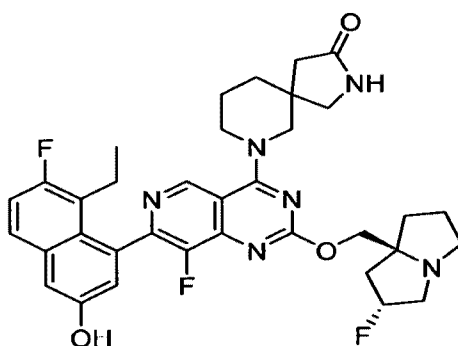
7-(7-(8-ethyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one



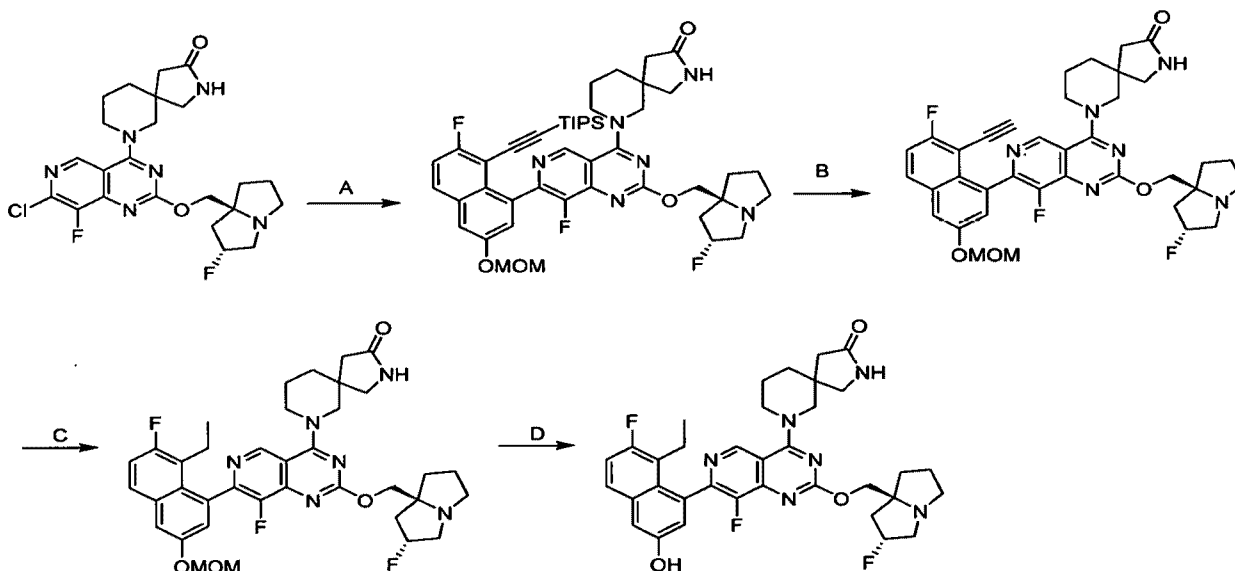
[0000494] Step A. 7-(7-(8-ethyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of 7-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (50.0 mg, 77.0 μ mol, 0.5FORMIC ACID) in MeOH (1 mL) was added Pd/C (5.0 mg, 10% purity). The suspension was degassed and purged with H₂ 3 times. The mixture was stirred at 25°C for 1 hour under H₂ (15psi). The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: water s Xbridge 150 $\times$ 25 mm $\times$ 5 μ m; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 33%-63%, 10 min) to afford the title compound (17.0 mg, 34% yield) as off-white solid. ¹H

NMR (400 MHz, CHLOROFORM-*d*) δ 8.98 (d, J = 4.0 Hz, 1H), 7.95 (dd, J = 1.2, 8.0 Hz, 1H), 7.80 (dd, J = 6.0, 9.2 Hz, 1H), 7.53-7.40 (m, 2H), 7.30 (t, J = 9.2 Hz, 1H), 5.84 (br d, J = 14.8 Hz, 1H), 5.41-5.19 (m, 1H), 4.34-4.17 (m, 2H), 4.11-3.96 (m, 2H), 3.90-3.63 (m, 2H), 3.40 (dd, J = 4.8, 9.6 Hz, 1H), 3.32-3.15 (m, 4H), 3.04-2.92 (m, 1H), 2.65-2.49 (m, 1H), 2.39-2.27 (m, 3H), 2.26-2.14 (m, 3H), 2.00-1.93 (m, 2H), 1.93-1.84 (m, 5H), 0.86 (t, J = 7.2 Hz, 3H); LCMS (ESI, $M+1$): m/z 631.3

EXAMPLE 38



7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorohexahydro-1*H*-pyrrolizin-7*a*-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one



[0000495] Step A. 7-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of 7-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (100 mg, 202.86 μ mol) and ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (156 mg, 304 μ mol) in THF (2 mL) were added K_3PO_4 (1.5 M, 406 μ L) and cataCXium-A-Pd-G3 (22.2 mg, 30.4 μ mol). The mixture was stirred at 60 °C for 2 hours. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 $\times$ 20 mL). The combined organic layers were washed with brine (100 mL), and dried over Na_2SO_4 . The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography (C18, 0.1% formic acid in water, 0-40% ACN) to afford the title compound (120 mg, 67% yield) as yellow solid. LCMS (ESI, M+1): m/z 843.4

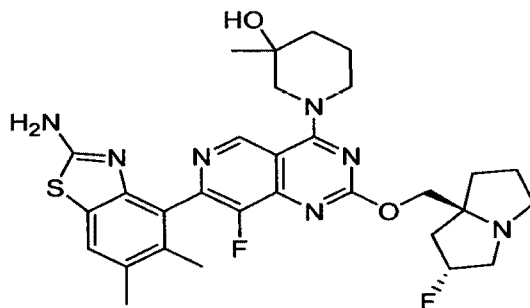
[0000496] Step B. 7-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 7-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (110 mg, 130 μ mol) and DMF (2 mL) was added CsF (198 mg, 1.30 mmol) in one portion at 25 °C under N_2 . The mixture was stirred at 25 °C for 0.5 hour. The residue was filtered. The filtrate was purified by reversed phase flash chromatography (water (0.1% formic acid) - ACN) to afford 7-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (75.0 mg, 80% yield) as yellow solid. LCMS (ESI, M+1): m/z 687.4

[0000497] Step C. 7-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 7-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (75.0 mg, 109 μ mol) and MeOH (2 mL) was added Pd/C (100 mg, 10% purity) in one portion at 25 °C under N_2 . The

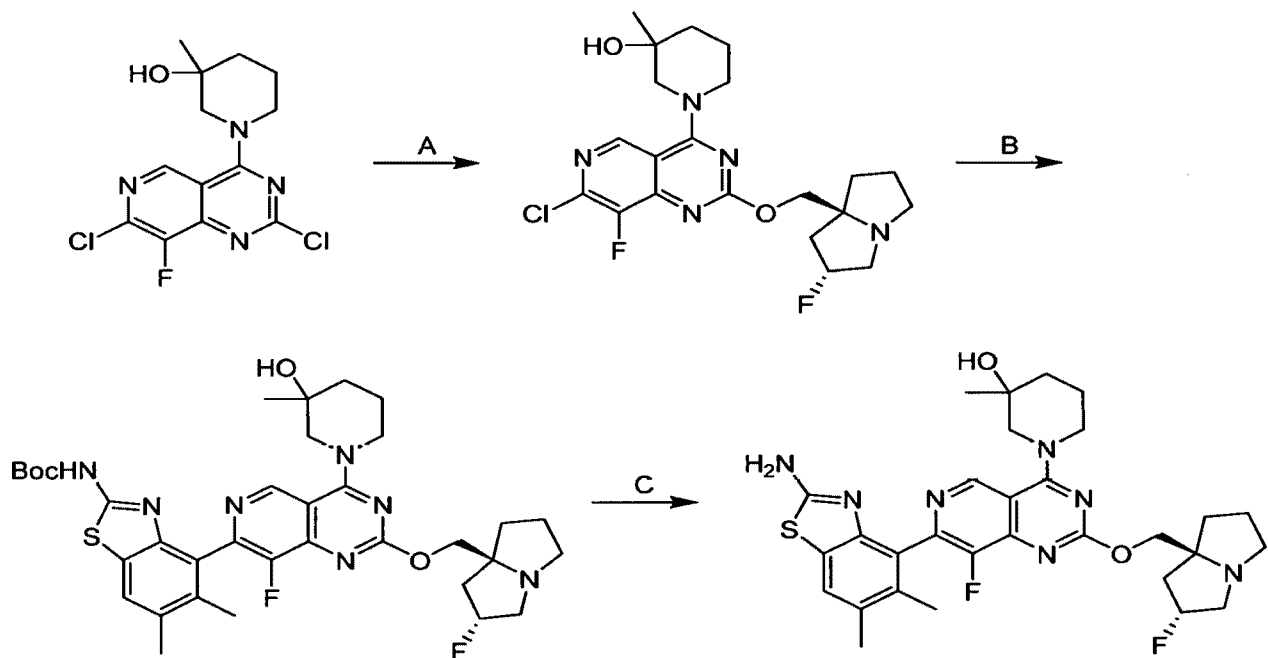
suspension was degassed and purged with H₂ 3 times. The mixture was stirred at 25 °C for 1 hour under H₂ (15 psi). The reaction mixture was filtered and concentrated under reduced pressure to afford 7-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (65.0 mg, 86% yield) as yellow solid. LCMS (ESI, M+1): m/z 691.3

[0000498] Step D. 7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 7-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (65.0 mg, 94.1 μmol) and ACN (1 mL) was added HCl•dioxane (4 M, 862 μL) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 10 minutes. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 × 30mm × 3μm; mobile phase: [water (0.225% formic acid)-ACN]; B%: 15%-45%, 7 min) to afford 7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (15.3 mg, 24% yield, 0.1% FORMIC ACID) as white solid. ¹H NMR (400 MHz, methanol-d₄): δ 9.10 (s, 1H), 7.70 (dd, *J* = 5.6 Hz, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.27 (t, *J* = 9.2 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 5.37 (d, *J* = 5.4 Hz, 1H), 4.60 (s, 1H), 4.45-3.90 (m, 6H), 3.51-3.35 (m, 3H), 3.30-3.26 (m, 1H), 3.16-3.06 (m, 1H), 2.55-2.26 (m, 5H), 2.25-2.15 (m, 2H), 2.10-1.85 (m, 7H), 0.87-0.75 (m, 3H); LCMS (ESI, M+1): m/z 647.4

EXAMPLE 39



1-(7-(2-amino-5,6-dimethylbenzo[d]thiazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



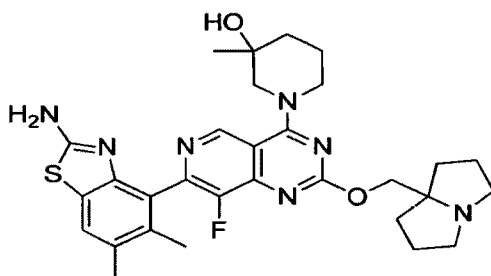
[0000499] Step A. 1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of 1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (0.200 g, 604 μ mol), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (144 mg, 906 μ mol), DIEA (234 mg, 1.81 mmol, 315 μ L) and 4Å molecular sieves (20 mg) in dioxane (1.5 mL) was stirred at 90 °C for 15 h. After completion, the mixture was filtered. Then the mixture was diluted with ethyl acetate (3 mL) and water (3 mL), and then separated. The aqueous phase was extracted with ethyl acetate (5 mL). Then the aqueous phase was extracted with dichloromethane (4 mL). The combined organic layer was dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give the title compound (184 mg, 62% yield). Yellow solid. LCMS (ESI, M+1): m/z 454.2.

[0000500] Step B. tert-butyl (4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-5,6-dimethylbenzo[d]thiazol-2-yl)carbamate: To a mixture of 1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (50.0 mg, 110 μ mol), [2-(tert-butoxycarbonylamino)-5,6-dimethyl-1,3-benzothiazol-4-yl]boronic acid (49.7 mg, 154 μ mol) and K_3PO_4 (1.5 M in water, 220 μ L) in THF (1 mL) was added [2-(2-aminophenyl)phenyl]-methylsulfonyloxy-palladium;dicyclohexyl-[3,6-dimethoxy-2-(2,4,6-triisopropylphenyl)phenyl]phosphane (9.99 mg, 11.0 μ mol) under N_2 . The mixture was de-gassed and then heated to 60 $^{\circ}C$ for 20 h under N_2 . After completion, the mixture was diluted with ethyl acetate (2 mL) and water (2 mL), and then separated. The aqueous phase was extracted with ethyl acetate (2 mL). The combined organic layer was washed with brine (3 mL) and dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give the title compound (40.0 mg, 52% yield). Yellow solid. LCMS (ESI, $M+1$): m/z 696.2.

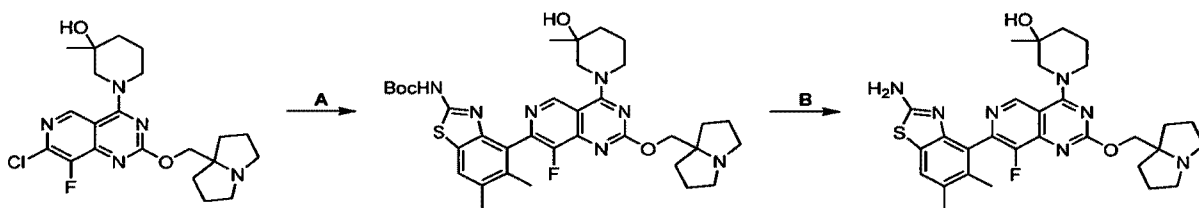
[0000501] Step C. 1-(7-(2-amino-5,6-dimethylbenzo[d]thiazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of tert-butyl (4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-5,6-dimethylbenzo[d]thiazol-2-yl)carbamate (37.0 mg, 53.2 μ mol) and dichloromethane (0.7 mL) was added TFA (2.16 g, 18.9 mmol, 1.4 mL) at 0 $^{\circ}C$ and the mixture was stirred at 0 - 28 $^{\circ}C$ for 1.5 h. After completion, the mixture was concentrated in vacuum and pH value was adjusted to 8 with cold saturated $NaHCO_3$ solution. Then the mixture was diluted with ethyl acetate (5 mL) and separated. The aqueous phase was extracted with ethyl acetate (2 $\times$ 4 mL). The combined organic layer was washed with brine (6 mL) and dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated in vacuum. The residue was purified by prep-HPLC (Phenomenexluna C18 150*25mm* 10um; mobile phase: [water (0.225% formic acid) - ACN]; B%: 15% - 45%, 10 min) to afford the title compound (16.4 mg, 50% yield, 0.3FORMIC ACID). White solid. ^1H NMR (400 MHz, METHANOL- d_4): δ 9.30 - 9.18 (m, 1H), 7.54 (s, 1H), 5.51 - 5.30 (m, 1H), 4.55 (br d, J = 13.2 Hz, 1H), 4.50 - 4.38 (m, 2H), 4.34 - 4.23 (m, 1H), 3.68 - 3.61 (m, 1H), 3.60 - 3.36

(m, 4H), 3.24 - 3.14 (m, 1H), 2.52 - 2.30 (m, 5H), 2.28 - 2.07 (m, 7H), 2.05 - 1.95 (m, 1H), 1.90 - 1.72 (m, 3H), 1.29 (s, 3H). LCMS (ESI, M+1): m/z 596.2.

EXAMPLE 40



1-(7-(2-amino-5,6-dimethylbenzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

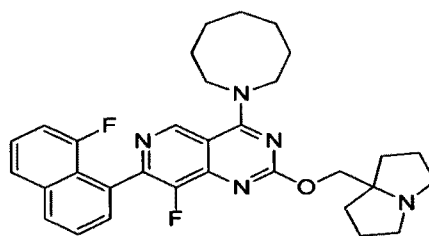


[0000502] Step A. tert-butyl (4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-5,6-dimethylbenzo[d]thiazol-2-yl)carbamate: To the mixture of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (150 mg, 344 μ mol), (2-((tert-butoxycarbonyl)amino)-5,6-dimethylbenzo[d]thiazol-4-yl)boronic acid (130 mg, 403 μ mol), and K_3PO_4 (1.5 M, 688 μ L) in THF (2 mL) was added BrettPhos Pd G3 (31.2 mg, 34.4 μ mol) under N_2 . The mixture was stirred at 60°C for 4 hours. Upon completion, the mixture was partitioned between ethyl acetate (10 mL) and water (3 mL), and the aqueous layer was extracted with ethyl acetate (5 mL). The combined organic phase was washed with brine (5 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give tert-butyl (4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-

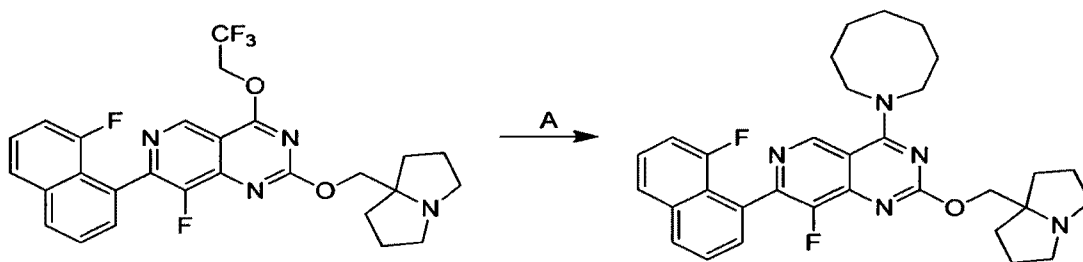
methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-5,6-dimethylbenzo[d]thiazol-2-yl)carbamate (132 mg, 52% yield). White Solid; LCMS (ESI, M+1): m/z 678.3.

[0000503] Step B. 1-(7-(2-amino-5,6-dimethylbenzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To the solution of tert-butyl (4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-5,6-dimethylbenzo[d]thiazol-2-yl)carbamate (60.0 mg, 88.5 μ mol) in dichloromethane (0.5 mL) was added TFA (770 mg, 6.75 mmol), and the mixture was stirred at 20°C for 0.5 hour. Upon completion, to the mixture was added sat. Na₂CO₃ to adjust the pH to 7 and the mixture was extracted with dichloromethane (5 ml). The mixture was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 $\times$ 25 mm $\times$ 10 μ m; mobile phase: [water (0.225% formic acid formic acid) - ACN]; B%: 15% - 45%, 10 min) to afford the title compound (32.46 mg, 61% yield, 0.4 formic acid salt). Off-white Solid; ¹H NMR (400 MHz, METHANOL-d₄) δ = 9.33 - 9.18 (m, 1H), 7.55 (s, 1H), 4.58 (s, 3H), 4.32 (br d, *J* = 13.2 Hz, 1H), 3.69 - 3.52 (m, 3H), 3.50 - 3.39 (m, 1H), 3.23 - 3.10 (m, 2H), 2.39 (s, 3H), 2.33 - 2.23 (m, 2H), 2.21 - 1.96 (m, 10H), 1.92 - 1.71 (m, 3H), 1.29 (s, 3H); LCMS (ESI, M+1): m/z 578.3.

EXAMPLE 41

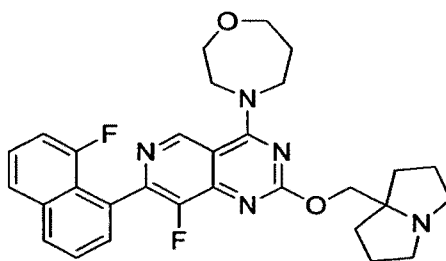


4-(azocan-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine

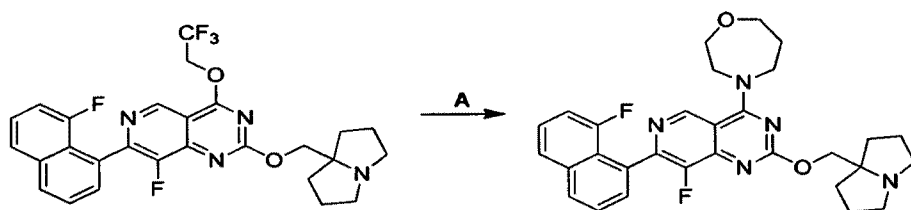


[0000504] Step A 4-(azocan-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine: To a mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.2 μ mol) and azocane (21.3 mg, 188 μ mol) in DMF (1 mL) were added DIEA (48.7 mg, 377 μ mol) and 4Å molecular sieves (30 mg) in one portion at 25 °C under N₂. The mixture was stirred at 40 °C for 12 h. After completion, the mixture was filtered. The filtrate was purification by prep-HPLC (column: Phenomenex Gemini-NX C18 75 × 30mm × 3 μ m; mobile phase: [water (0.225% formic acid)-ACN]; B%: 20%-50%, 7min) to afford 4-(azocan-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine (9.4 mg, 16.8 μ mol, 18% yield, 99% purity, 0.24FORMIC ACID). White solid; ¹H NMR (400 MHz, DMSO-d₆): δ 9.13 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.65 - 7.55 (m, 2H), 7.30 (d d, *J* = 7.6 Hz, 12.8 Hz, 1H), 4.11 (s, 2H), 4.06-3.99 (m, 4H), 2.93-3.02 (m, 2H), 2.64-2.56 (m, 2H), 2.00-1.70 (m, 10H), 1.68-1.49 (m, 8H); LCMS (ESI, M+1): *m/z* 544.3.

EXAMPLE 42

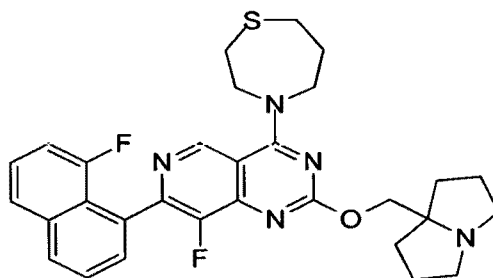


4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane

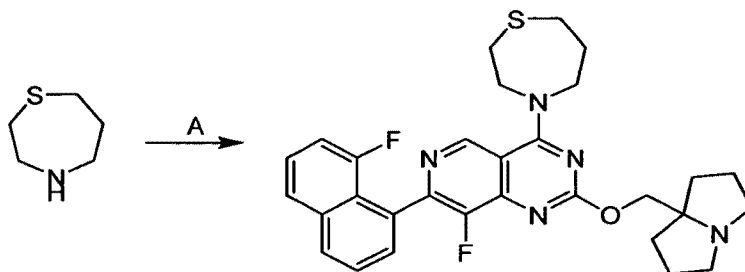


[0000505] Step A. 4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane: To a mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (20.0 mg, 34.7 μ mol, formic acid salt), 1,4-oxazepane (5.73 mg, 41.6 μ mol, HCl), and 4Å molecular sieves (5 mg) in DMF (0.5 mL) was added DIEA (17.9 mg, 139 μ mol), and the mixture was stirred at 40°C for 14 hours. Upon completion, the mixture was filtered and the filtrate was purified by prep-HPLC (column: Phenomenex luna C18 150 $\times$ 25 mm $\times$ 10 μ m; mobile phase: [water (0.225% formic acid formic acid) - ACN]; B%: 16% - 46%, 10 min) to afford 4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane (2.05 mg, 10% yield, 0.51 formic acid salt). Off-white Gum; ^1H NMR (400 MHz, CHLOROFORM- d) δ = 9.12 (s, 1H), 8.03-7.97 (m, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.67-7.58 (m, 2H), 7.48-7.42 (m, 1H), 7.16-7.08 (m, 1H), 4.51 (s, 2H), 4.26-4.18 (m, 4H), 4.08-4.01 (m, 2H), 3.91-3.85 (m, 2H), 3.61-3.50 (m, 2H), 2.85-2.76 (m, 2H), 2.31-2.23 (m, 4H), 2.04-1.96 (m, 4H), 1.90-1.83 (m, 2H); LCMS (ESI, M+1): m/z 532.4.

EXAMPLE 43

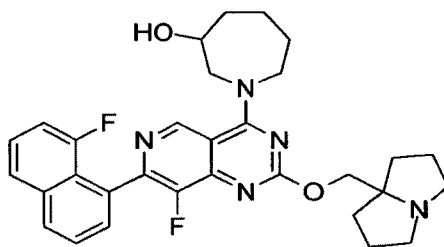


4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-thiazepane

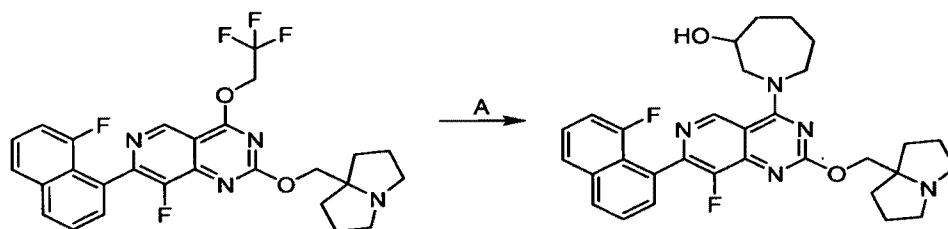


[0000506] Step A. 4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-thiazepane: To a mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50 mg, 94.2 μ mol) and 1,4-thiazepane (33.1 mg, 283 μ mol) in DMF (1 mL) were added DIEA (48.7 mg, 377 μ mol, 65.0 μ L) and 4Å molecular sieves (30 mg) in one portion at 25°C under N₂. The mixture was stirred at 40 °C for 12 h. After completion, the residue was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 × 30mm × 3 μ m; mobile phase: [water (0.225% formic acid)-ACN]; B%: 20%-50%, 7min) to afford 4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-thiazepane (5.63 mg, 9.88 μ mol, 10% yield, 99% purity, 0.37FORMIC ACID); Yellow solid; ¹H NMR (400 MHz, DMSO-d₆) δ 9.16 (s, 1H) 8.18 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.77-7.71 (m, 1H), 7.65-7.55 (m, 2H), 7.31 (d d, *J* = 13.2 Hz, 7.2 Hz, 1H), 4.30-4.23 (m, 2H), 4.19-4.13 (m, 2H), 4.12-4.06 (m, 2H), 3.14-3.10 (m, 2H), 3.00-2.90 (m, 2H), 2.76-2.70 (m, 2H), 2.60-2.54 (m, 2H), 2.22-2.15 (m, 2H), 1.95-1.70 (m, 6H), 1.65-1.55 (m, 2H); LCMS (ESI, M+1): *m/z* 548.3.

EXAMPLE 44

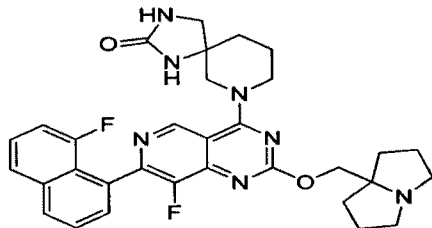


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-ol

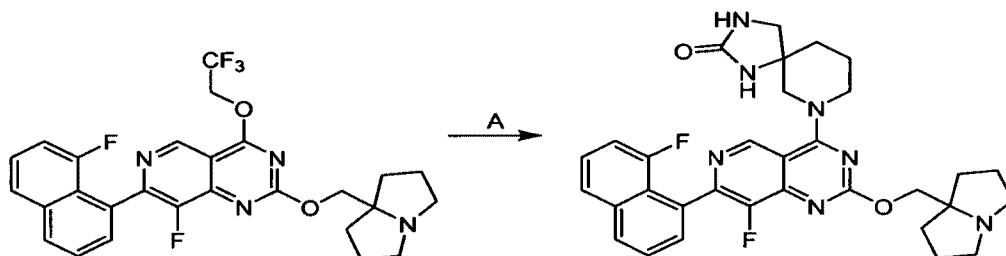


[0000507] Step A. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-ol: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (20.0 mg, 37.7 μ mol) and DIEA (14.6 mg, 113 μ mol, 19.7 μ L) in DMF (1.0 mL) was added azepan-3-ol (8.68 mg, 75.4 μ mol). The mixture was stirred at 40 °C for 24 h. After completion, the mixture was concentrated at 20 °C. The residue was purified by prep-HPLC [column: Unisil 3-100 C18 Ultra 150 $\times$ 50mm $\times$ 3 μ m; A: water (0.225% formic acid formic acid), B: ACN, B%: 18%-38% over 10min) to afford 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-ol (6.83 mg, 11.9 μ mol, 32% yield, 95.5% purity). Yellow solid; ^1H NMR (400 MHz, METHANOL- d_4) δ = 9.30 (d, J = 4.4 Hz, 1H), 8.53 (br s, 1H), 8.13 (br d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.64-7.58 (m, 1H), 7.57-7.50 (m, 1H), 7.24-7.14 (m, 1H), 4.44 (br d, J = 13.2 Hz, 1H), 4.22-4.10 (m, 3H), 3.87-3.77 (m, 1H), 3.62-3.52 (m, 2H), 3.21-3.10 (m, 2H), 2.35-2.23 (m, 2H), 2.22-2.07 (m, 6H), 2.06-1.99 (m, 5H), 1.98-1.86 (m, 1H), 1.74-1.60 (m, 1H), 1.54-1.39 (m, 1H); LCMS (ESI, M+1): m/z 546.3.

EXAMPLE 45

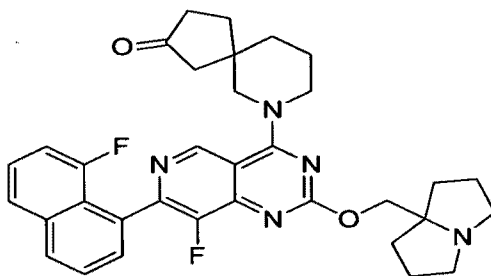


7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one.

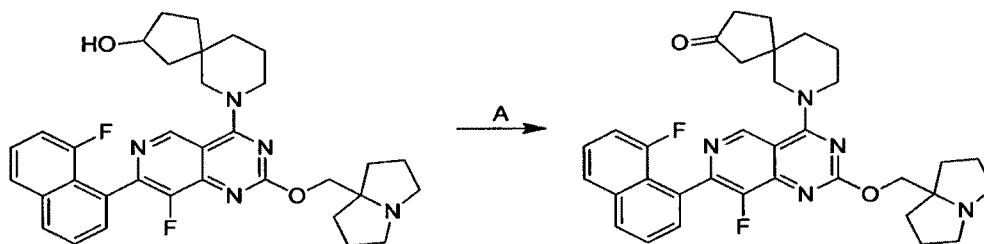


[0000508] Step A. 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (20.0 mg, 37.7 μ mol) and 1,3,7-triazaspiro[4.5]decan-2-one (8.78 mg, 56.6 μ mol) in DMF (0.2 mL) was added DIEA (48.7 mg, 377 μ mol). The mixture was stirred at 40 °C for 1 hour. The reaction mixture was quenched with water (10 mL) at 20 °C and then extracted with EtOAc (5 mL $\times$ 3). The combined organic layers were washed with brine (3 mL $\times$ 2), and dried over Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 $\times$ 30 mm $\times$ 3 μ m; mobile phase: [water (0.2%FORMIC ACID)-ACN]; B%: 20%-40%, 10 min) affording 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one (2.65 mg, 12% yield). White solid; ¹H NMR (400MHz, MeOD) δ = 9.16 (d, J = 1.5 Hz, 1H), 8.54 (s, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.74 - 7.69 (m, 1H), 7.65 - 7.59 (m, 1H), 7.54 (d, J = 5.1, 7.9 Hz, 1H), 7.20 (d, J = 7.7, 13.2 Hz, 1H), 4.65 - 4.60 (m, 1H), 4.57 - 4.50 (m, 1H), 4.44 - 4.30 (m, 1H), 4.30 - 4.18 (m, 1H), 4.01 (d, J = 6.8, 13.9 Hz, 1H), 3.96 - 3.84 (m, 1H), 3.66 - 3.55 (m, 2H), 3.44 (d, J = 5.7, 9.3 Hz, 1H), 3.32 (s, 1H), 3.24 - 3.14 (m, 2H), 2.33 - 2.24 (m, 2H), 2.15 (d, J = 6.7, 13.9 Hz, 4H), 2.09 - 1.95 (m, 5H), 1.88 (s, 1H). LCMS (ESI, M+1): m/z 586.1.

EXAMPLE 46



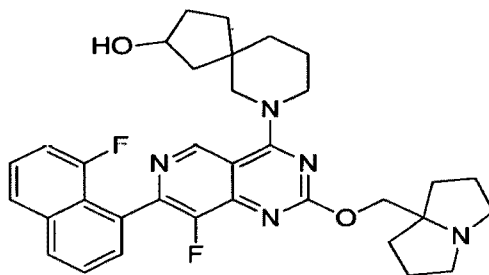
7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-one.



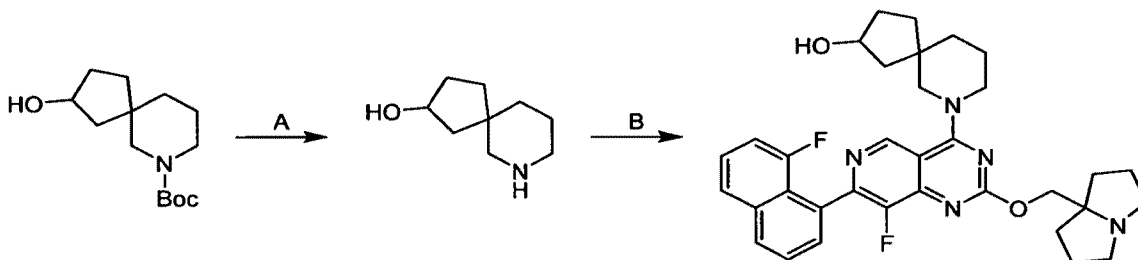
[0000509] Step A. 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-one: To a solution of 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-ol (30.0 mg, 51.2 μ mol) in dichloromethane (2.0 mL) was added Dess-Martin Reagent (43.5 mg, 102 μ mol). The mixture was stirred at 20 °C for 10 hours. After completion, the reaction mixture was quenched with saturated 10 mL Na₂SO₃ at 20 °C, and then extracted with EtOAc (5 mL $\times$ 3). The combined organic layer was washed with saturated NaHCO₃ (3 mL $\times$ 2) and brine (5 mL). The mixture was dried over anhydrous Na₂SO₄ and filtered. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Phenomenex Luna C18 75 $\times$ 30 mm $\times$ 3 μ m; mobile phase: [water (0.2%FORMIC ACID)-ACN]; B%: 15%-45%, 8 min) affording 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-one (6.51 mg, 22% yield). White solid; ¹H NMR (400MHz, DMSO-*d*₆) δ = 9.10 (s, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.78 - 7.71 (m, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 5.2, 8.0 Hz, 1H), 7.31 (d, *J* = 7.6, 13.2 Hz, 1H), 4.09 - 4.02 (m,

2H), 3.96 (s, 2H), 3.89 - 3.81 (m, 2H), 2.99 - 2.90 (m, 2H), 2.56 (d, $J = 7.0, 9.6$ Hz, 2H), 2.34 - 2.20 (m, 3H), 2.17 - 2.10 (m, 1H), 1.94 - 1.83 (m, 4H), 1.83 - 1.69 (m, 8H), 1.59 - 1.54 (m, 2H). LCMS (ESI, M+1): m/z 584.1.

EXAMPLE 47



7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-ol

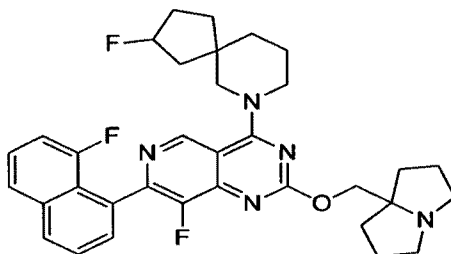


[0000510] Step A. 7-azaspiro[4.5]decan-2-ol hydrochloride: To a solution of tert-butyl 2-hydroxy-7-azaspiro[4.5]decane-7-carboxylate (70 mg, 274.13 μmol) in MeOH (1 mL) was added HCl•MeOH (4 M, 1 mL). The mixture was stirred at 20 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to afford 7-azaspiro[4.5]decan-2-ol hydrochloride (55 mg, HCl salt). Colorless oil; LCMS (ESI, M+1): m/z 156.2.

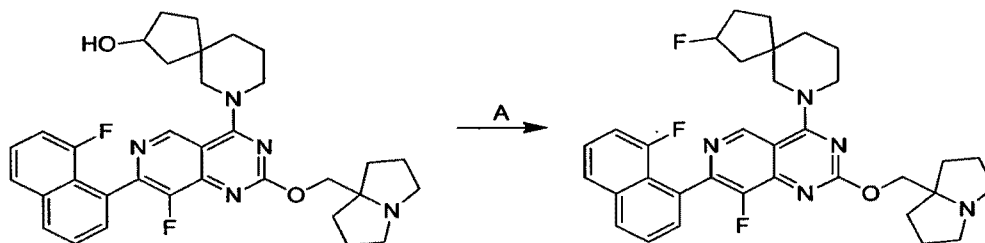
[0000511] Step B. 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-ol: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (10 mg, 18.9 μmol) and 7-azaspiro[4.5]decan-2-ol

hydrochloride (8.8 mg, 56.6 μ mol) in DMF (0.2 mL) was added DIEA (24.4 mg, 188 μ mol, 32.8 μ L). The mixture was stirred at 40 °C for 1 hr. The reaction mixture was quenched with 10 mL water at 20 °C, and then extracted with EtOAc (5 mL $\times$ 3). The combined organic layers were washed with brine (3 mL $\times$ 2), and dried over Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: water s Xbridge BEH C18 100 $\times$ 30 mm $\times$ 10 μ m; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 30% - 55%, 10 min) to afford 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-ol (2.43 mg, 21.0% yield). White solid; HPLC: 95.3%. ¹H NMR (400MHz, DMSO-*d*₆) δ = 9.11 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.75 - 7.68 (m, 1H), 7.60 (td, *J* = 3.3, 6.7 Hz, 1H), 7.58 - 7.53 (m, 1H), 7.28 (d, *J* = 7.6, 13.1 Hz, 1H), 4.52 (s, 1H), 4.11 (s, 1H), 4.04 (s, 2H), 4.02 - 3.96 (m, 1H), 3.93 - 3.84 (m, 1H), 3.83 - 3.72 (m, 2H), 2.94 - 2.86 (m, 2H), 2.54 - 2.50 (m, 2H), 1.96 (s, 1H), 1.90 - 1.82 (m, 2H), 1.81 - 1.69 (m, 8H), 1.60 - 1.50 (m, 6H), 1.47 - 1.41 (m, 1H), 1.39 - 1.30 (m, 1H). LCMS (ESI, M+1): *m/z* 586.3.

EXAMPLE 48

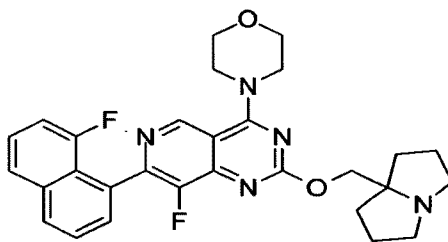


8-fluoro-4-(2-fluoro-7-azaspiro[4.5]decan-7-yl)-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine

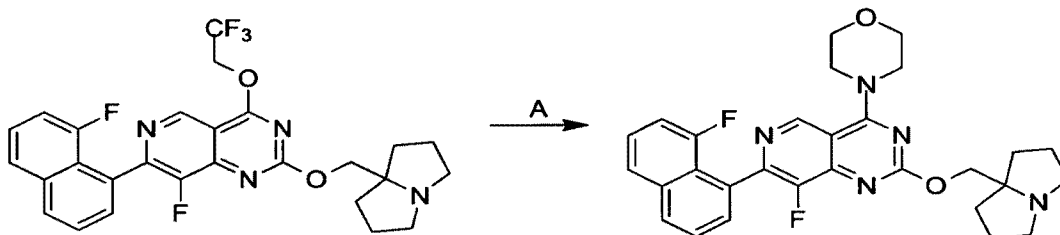


[0000512] Step A. 8-fluoro-4-(2-fluoro-7-azaspiro[4.5]decan-7-yl)-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine: To a solution of 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-ol (30.0 mg, 51.2 μ mol) in DCM (2 mL) was added bis(2-methoxyethyl)aminosulfur trifluoride (113 mg, 512 μ mol, 112 μ L) at 0 °C. The mixture was stirred at 20 °C for 10 hrs. The reaction mixture was quenched with 10 mL water at 20 °C, and then extracted with EtOAc (5 mL $\times$ 3). The combined organic layers were washed with saturated NaHCO₃ (3 mL $\times$ 2) and brine (3 mL), dried over Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 $\times$ 30mm $\times$ 3 μ m; mobile phase: [water (0.2%FORMIC ACID)-ACN]; B%: 30%-60%, 8min) affording 8-fluoro-4-(2-fluoro-7-azaspiro[4.5]decan-7-yl)-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine (5.11 mg, 16.9% yield). White solid; ¹H NMR (400MHz, DMSO-*d*₆) δ = 9.07 (s, 1H), 8.34 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.79 - 7.70 (m, 1H), 7.67 - 7.52 (m, 2H), 7.31 (d, *J* = 7.5, 13.3 Hz, 1H), 5.28 - 5.07 (m, 1H), 4.10 - 3.96 (m, 3H), 3.89 - 3.76 (m, 2H), 3.63 (d, *J* = 13.0 Hz, 1H), 2.98 - 2.87 (m, 2H), 2.58 - 2.52 (m, 2H), 1.98 - 1.64 (m, 15H), 1.62 - 1.50 (m, 3H). ¹H NMR (400MHz, MeOD-*d*₄) δ = 9.04 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.74 - 7.66 (m, 1H), 7.61 (d, *J* = 1.0, 7.2 Hz, 1H), 7.53 (d, *J* = 5.0, 8.0 Hz, 1H), 7.19 (d, *J* = 7.7, 13.0 Hz, 1H), 5.27 - 5.05 (m, 1H), 4.28 (s, 2H), 4.22 - 4.07 (m, 1H), 4.02 - 3.87 (m, 2H), 3.78 (d, *J* = 2.8, 12.9 Hz, 1H), 3.18 - 3.08 (m, 2H), 2.76 (d, *J* = 6.6, 10.5 Hz, 2H), 2.13 - 1.82 (m, 14H), 1.81 - 1.70 (m, 4H); LCMS (ESI, M+1): *m/z* 588.2.

EXAMPLE 49

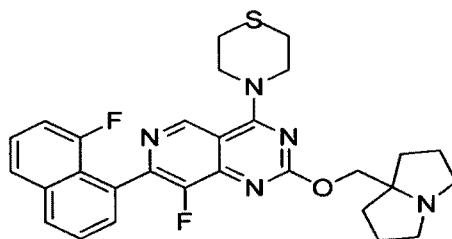


4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)morpholine

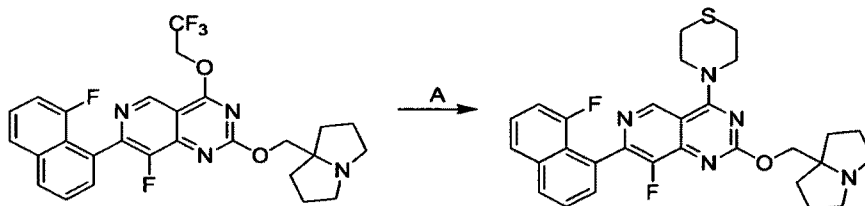


[0000513] Step A. 4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)morpholine: A mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30.0 mg, 52.0 μ mol, formic acid salt), morpholine (9.07 mg, 104 μ mol, 9.16 μ L), DIEA (26.9 mg, 208 μ mol, 36.3 μ L) and 4Å molecular sieves (5 mg) in DMF (0.5 mL) was stirred at 40 °C for 1.5 h. After completion, the mixture was filtered and purified by prep-HPLC (Shim-pack C18 150*25*10 μ m; mobile phase: [water (0.225% formic acid) - ACN]; B%: 15% - 45%, 10 min) to afford the title compound (7.45 mg, 27% yield, 0.4 FORMIC ACID). Off-white Solid. ¹H NMR (400 MHz, CDCl₃-d): δ 9.04 (s, 1H), 7.99 (td, J = 1.6, 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.66 - 7.57 (m, 2H), 7.45 (dt, J = 4.8, 8.0 Hz, 1H), 7.15 - 7.08 (m, 1H), 4.56 (s, 2H), 4.12 - 4.01 (m, 4H), 3.94 - 3.89 (m, 4H), 3.65 - 3.59 (m, 2H), 2.84 (td, J = 6.8, 10.8 Hz, 2H), 2.34 - 2.23 (m, 2H), 2.14 - 2.07 (m, 2H), 2.05 - 1.98 (m, 2H), 1.92 - 1.83 (m, 2H). ¹⁹F NMR (400 MHz, CDCl₃-d) δ = -112.256. -138.683. LCMS (ESI, M+1): m/z 518.2.

EXAMPLE 50

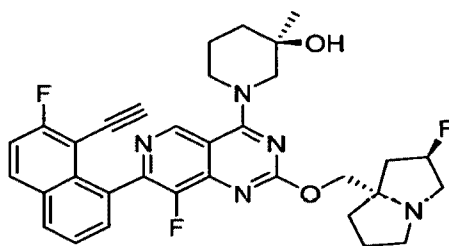


4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)thiomorpholine



[0000514] Step A. 4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)thiomorpholine: A mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30 mg, 56.6 μmol), thiomorpholine (18 mg, 174 μmol), DIPEA (30 μL), and 4Å molecular sieves (10 mg) in DMF (0.5 mL) was stirred at 40 °C for 6 hours under N₂ atmosphere. The reaction mixture was filtered and purified by prep-HPLC (column: Shim-pack C18 150 $\times$ 25 $\times$ 10 μm ; mobile phase: [water (0.225% formic acid)-ACN]; B%: 19%-49%, 10 minutes) to give the product as white solid (14.5 mg, 45% yield, 0.3% FORMIC ACID). ¹H NMR (400 MHz, DMSO-d₆) δ = 9.05 (s, 1H), 8.18 (br d, J = 8.0 Hz, 1H), 7.93 (br d, J = 8.0 Hz, 1H), 7.74 (br t, J = 7.6 Hz, 1H), 7.64-7.58 (m, 2H), 7.31 (br dd, J = 7.6, 12.8 Hz, 1H), 4.19 (br s, 4H), 4.10 (s, 2H), 2.98-2.91 (m, 6H), 2.60-2.57 (m, 2H), 1.92-1.78 (m, 6H), 1.61-1.58 (m, 2H). LCMS (ESI, M+1): m/z 534.2.

EXAMPLE 51

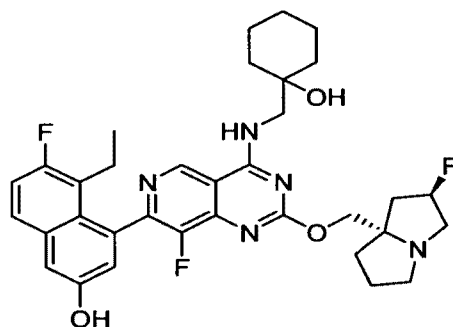


(R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

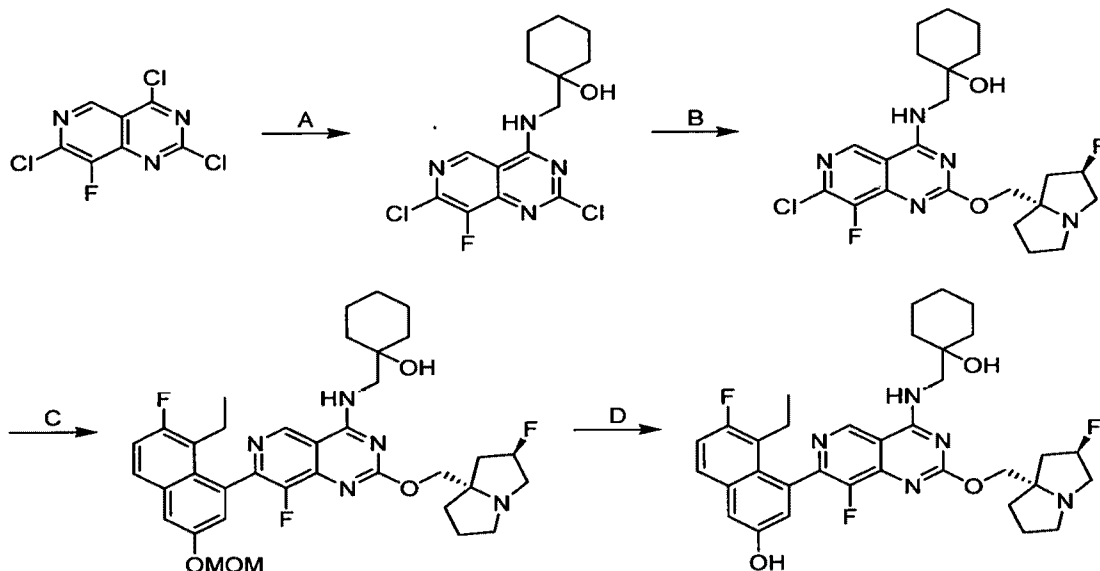
[0000515] Synthesized according to Example 16, step A to C. Yellow Solid; ¹H NMR (400 MHz, methanol-d₄) δ 9.24-9.03 (m, 1H), 8.19-8.06 (m, 2H), 7.74-7.58 (m, 2H), 7.51-7.36 (m, 1H),

5.47-5.21 (m, 1H), 4.67-4.57 (m, 2H), 4.41-4.23 (m, 3H), 3.68-3.62 (m, 1H), 3.52-3.34 (m, 2H), 3.29-3.18 (m, 2H), 3.10-2.98 (m, 1H), 2.44-2.11 (m, 4H), 2.08-1.97 (m, 2H), 1.95-1.65 (m, 4H), 1.27 (d, $J = 19.6$ Hz, 3H); LCMS (ESI, $M+1$): m/z 588.3.

EXAMPLE 52



5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(((1-hydroxycyclohexyl)methyl)amino)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol



[0000516] Step A 1-(((2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)amino)methyl)cyclohexanol: To a mixture of 1-(aminomethyl)cyclohexanol (256 mg, 1.98 mmol) and 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (500 mg, 1.98 mmol) in DMA (6 mL) was added DIEA (768 mg, 5.94 mmol) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 1 h.

After completion, the mixture was filtered and the filtrate was purification by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) affording 1-(((2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)amino)methyl)cyclohexanol (530 mg, 77% yield). Yellow solid; ¹H NMR (400 MHz, DMSO-d₆): δ 9.37 (br s, 1H), 9.31 (s, 1H), 4.53 (br s, 1H), 3.58 (s, 2H), 1.63-1.35 (m, 9H), 1.30-1.15 (m, 1H); LCMS (ESI, M+1): m/z 345.1.

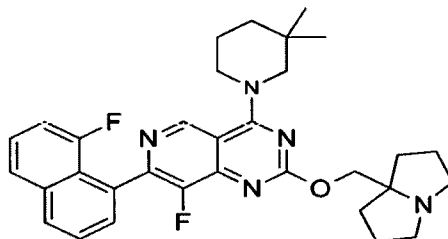
[0000517] Step B 1-(((7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)cyclohexanol: To a mixture of ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (346 mg, 2.17 mmol) and 1-(((2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)amino)methyl)cyclohexanol (500 mg, 1.45 mmol) in dioxane (5 mL) was added DIEA (561 mg, 4.35 mmol) in one portion at 25 °C under N₂. The mixture was heated to 95 °C and stirred for 12 h. After completion, the mixture was filtered and concentrated in vacuum. The residue was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) affording 1-(((7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)cyclohexanol (630 mg, 91% yield). Off-white solid; LCMS (ESI, M+1): m/z 468.2.

[0000518] Step C 1-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)cyclohexanol: To a mixture of 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (200 mg, 427 μmol) and 1-(((7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)cyclohexanol (200 mg, 555 μmol) in THF (4 mL) was added K₃PO₄ (1.5 M, 855 μL) in one portion at 25 °C under N₂. Then cataCXium-A-Pd-G3 (46.7 mg, 64.1 μmol) was added. The mixture was heated to 60 °C and stirred for 2 h. After completion, the mixture was filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography (C18, water (0.1% formic acid) - ACN) affording 1-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)cyclohexanol (110 mg, 36% yield). Yellow solid; LCMS (ESI, M+1): m/z 666.2.

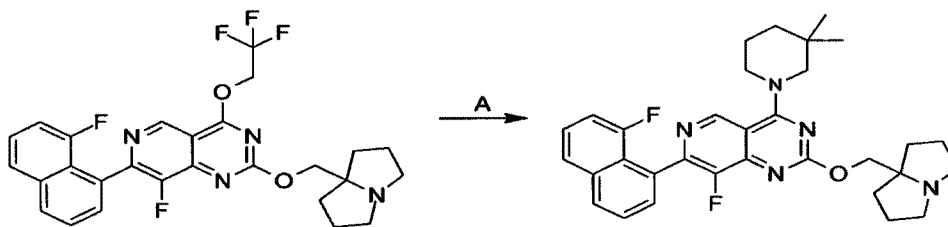
[0000519] Step D 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(((1-hydroxycyclohexyl)methyl)amino)pyrido[4,3-d]pyrimidin-7-

yl)naphthalen-2-ol: A mixture of 1-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)cyclohexanol (90 mg, 135 μ mol) and HCl•dioxane (4 M, 4.50 mL) in ACN (0.5 mL) was stirred at 20 °C for 10 min. After completion, the residue was concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 $\times$ 30mm $\times$ 3 μ m; mobile phase: [water (0.225% formic acid)-ACN]; B%: 18%-48%, 5min) affording 5-ethyl-6-fluoro-4- (8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(((1-hydroxycyclohexyl)methyl)amino)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol (52.3 mg, 60% yield, 0.35FORMIC ACID). White solid; ¹H NMR (400 MHz, DMSO-d₆): δ 9.93 (br s, 1H), 9.40 (s, 1H), 8.75 (s, 1H), 7.76 (dd, *J* = 6.0 Hz, 9.2 Hz, 1H), 7.38-7.30 (m, 2H), 8.99 (s, 1H), 5.28 (d, *J* = 54.4 Hz, 1H), 4.56 (br s, 1H), 4.15 (d, *J* = 10.4 Hz, 1H), 4.08 (d, *J* = 10.4 Hz, 1H), 3.71-3.64 (m, 1H), 3.58-3.53 (m, 1H), 3.12-3.05 (m, 2H), 3.04-2.99 (m, 1H), 2.88-2.78 (m, 1H), 2.40-2.35 (m, 1H), 2.20-1.95 (m, 4H), 1.89-1.72 (m, 3H), 1.65-1.35 (m, 10H), 1.28-1.18 (m, 1H), 0.72 (t, *J* = 7.6 Hz, 3H); LCMS (ESI, M+1): *m/z* = 622.3.

EXAMPLE 53



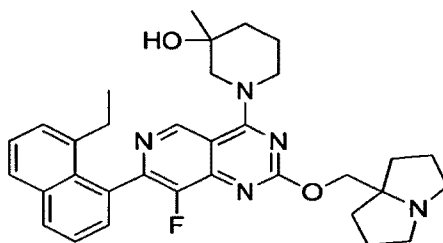
4-(3,3-dimethylpiperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine



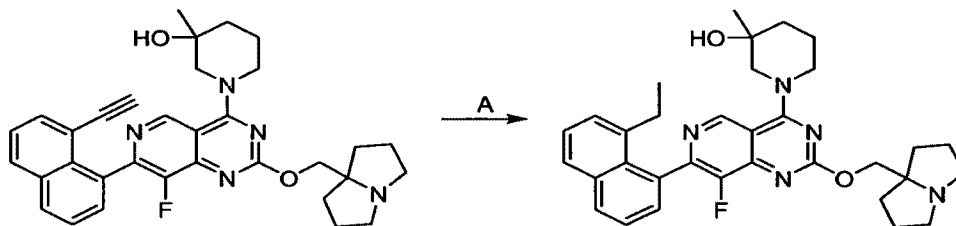
[0000520] Step A. 4-(3,3-dimethylpiperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)- 2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine: To a solution of 8-fluoro-7-

(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (100 mg, 188 μ mol) and DIEA (73.1 mg, 565 μ mol, 98.5 μ L) in DMF (1.5 mL) was added 3,3-dimethylpiperidine (42.7 mg, 377 μ mol). The mixture was stirred at 40 °C for 12 h. After completion, the mixture was concentrated at 20 °C. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (0.225% formic acid)-ACN]; B%: 27%-57%, 10min) affording 4-(3,3-dimethylpiperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine (32.8 mg, 29% yield). White solid; ¹H NMR (400 MHz, METHANOL-d₄) δ = 9.09 (s, 1H), 8.12 (br d, *J* = 8.0 Hz, 1H), 7.85 (br d, *J* = 8.4 Hz, 1H), 7.74-7.66 (m, 1H), 7.65-7.59 (m, 1H), 7.57-7.49 (m, 1H), 7.19 (dd, *J* = 7.6, 12.8 Hz, 1H), 4.47 (s, 2H), 4.08-3.94 (m, 2H), 3.83 (s, 2H), 3.44-3.36 (m, 2H), 3.06-2.95 (m, 2H), 2.26-2.15 (m, 2H), 2.13-1.98 (m, 4H), 1.98-1.86 (m, 4H), 1.69-1.59 (m, 2H), 1.03 (br d, *J* = 4.0 Hz, 6H); LCMS (ESI, M+1): *m/z* = 544.3.

EXAMPLE 54



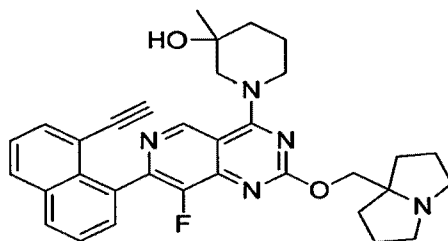
1-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



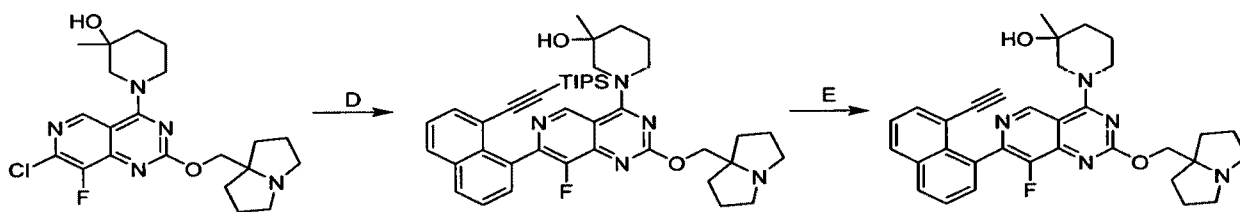
[0000521] Step A. 1-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of 1-(7-(8-ethynynaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-

d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (65 mg, 118 μ mol) in MeOH (4 mL) was added Pd/C (10 mg, 10% purity) under N₂ atmosphere. The mixture was degassed and purged with H₂ for 3 times and stirred at 25 °C for 18 hours under H₂ atmosphere (15 psi). The reaction mixture was filtered. The filtrate was concentrated under reduced pressure, purified by prep-HPLC (column: Phenomenex luna C18 150 $\times$ 25mm $\times$ 10 μ m; mobile phase: [water (0.225% formic acid)-ACN]; B%: 22%-52%, 10 minutes) to give the product as yellow solid (13.1 mg, 18% yield, 0.9 FORMIC ACID). ¹H NMR (400 MHz, DMSO-D₂O) δ = 9.20 (d, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.39 (dd, *J* = 6.8, 12.8 Hz, 2H), 4.46-4.39 (m, 3H), 4.09 (br dd, *J* = 13.6, 19.2 Hz, 1H), 3.57 (dd, *J* = 13.2, 42.4 Hz, 1H), 3.40-3.35 (m, 3H), 3.06-3.02 (m, 2H), 2.32-2.22 (m, 2H), 2.05-1.90 (m, 12H), 1.15 (d, *J* = 11.6 Hz, 3H), 0.83-0.78 (m, 3H). LCMS (ESI, M+1): *m/z* = 556.3.

EXAMPLE 55



1-(7-(8-ethynylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



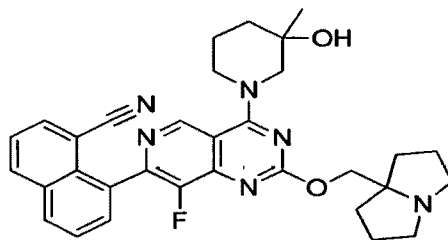
[0000522] Step A. 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol:

A mixture of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (115 mg, 264 μ mol) and K₃PO₄ (1.5 M in water, 550 μ L) in THF (3 mL) was degassed and purged with N₂ for 3 times. Triisopropyl-[2-[8-(4,4,5,5-

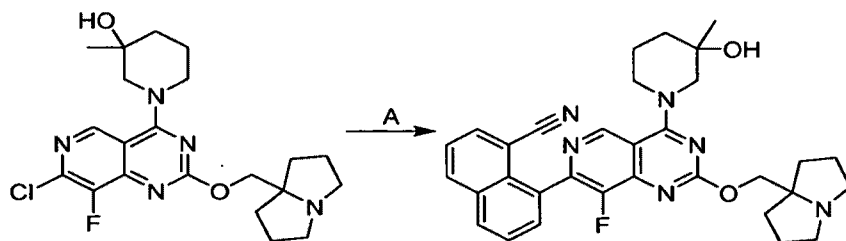
tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl]silane (130 mg, 299 μmol) was added, followed by cataCXium-A-Pd-G3 (20 mg, 27.5 μmol). The mixture was stirred at 60 °C for 3 hours under N_2 atmosphere. The combined reaction mixture was diluted with water (15ml), extracted with ethyl acetate (5 mL $\times$ 4). The combined organic phase was dried with anhydrous Na_2SO_4 . The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=1/1] to give the product as a yellow gum (131 mg, 65%). LCMS (ESI, M+1): m/z = 708.4.

[0000523] Step B. 1-(7-(8-ethynynaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (59 mg, 83.3 μmol), and CsF (127 mg, 833 μmol) in DMF (1 mL) was stirred at 25 °C for 1 hour. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: water s Xbridge 150 $\times$ 25mm $\times$ 5um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 29%-59%, 10min) to give the product as a yellow solid (19.6 mg, 42%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 9.14 (d, J = 60.4 Hz, 1H), 8.14 (t, J = 8.0 Hz, 2H), 7.73-7.56 (m, 4H), 4.78-4.72 (m, 1H), 4.46-4.26 (m, 1H), 4.11-4.03 (m, 3H), 3.68 (d, J = 4.4 Hz, 1H), 3.59 (t, J = 13.6 Hz, 1H), 2.95-2.91 (m, 2H), 2.56-2.54 (m, 3H), 1.90-1.70 (m, 10H), 1.58-1.55 (m, 2H), 1.16 (d, J = 15.2 Hz, 3H). LCMS (ESI, M+1): m/z = 552.3.

EXAMPLE 56

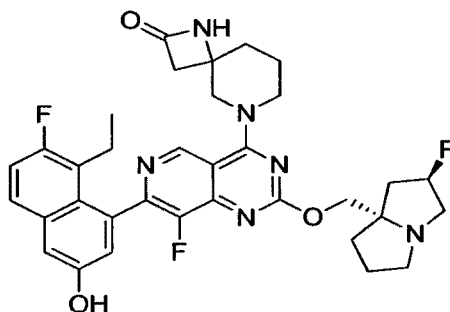


8-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-1-naphthonitrile

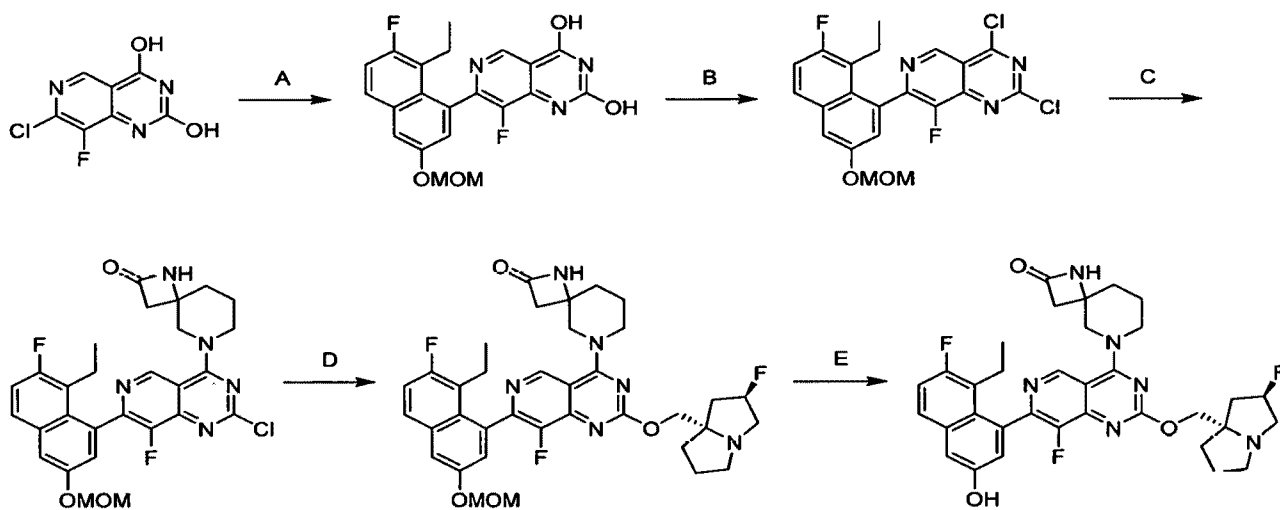


[0000524] Step A. 8-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-1-naphthonitrile: To a solution of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (50.0 mg, 115 μ mol) and 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthonitrile (48.0 mg, 172 μ mol) in toluene (2.0 mL) was added K_3PO_4 (1.5 M, 229 μ l) and cataCXium-A-Pd-G3 (12.53 mg, 17.20 μ mol). The mixture was stirred at 90 °C for 2 hours. After completion, the reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 $\times$ 20 mL). The combined organic layers were dried over Na_2SO_4 . The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10 μ m; mobile phase: [water (0.225% formic acid)-ACN]; B%: 18%-48%, 10min) to give 8-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-1-naphthonitrile (22.0 mg, 33% yield, 0.6FORMIC ACID); Yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 9.26 (s, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.29 (dd, J = 2.0, 7.2 Hz, 1H), 8.24 (s, 1H), 8.14 (dd, J = 1.2, 7.2 Hz, 1H), 7.87-7.78 (m, 2H), 7.77-7.70 (m, 1H), 4.33-4.25 (m, 1H), 4.13 (s, 2H), 4.03 (br d, J = 13.2 Hz, 2H), 3.47-3.35 (m, 2H), 3.05-2.97 (m, 2H), 2.66-2.57 (m, 2H), 2.08-1.99 m, 1H), 1.98-1.90 (m, 2H), 1.88-1.76 (m, 4H), 1.75-1.58 (m, 5H), 1.17 (br s, 3H). LCMS (ESI, M+1): m/z = 553.3.

EXAMPLE 57



6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one



[0000525] Step A. 7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol: To a mixture of 7-chloro-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol, 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (14.0 g, 39.0 mmol) and K_3PO_4 (1.5 M, 46.4 mL) in EtOH (140 mL) was added cataCXium-A-Pd-G3 (1.39 g, 1.90 mmol) under N_2 . The mixture was de-gassed and then heated to 78 °C for 9.5 h under N_2 . After completion, the mixture was concentrated in vacuum. Then the mixture was diluted with ethyl acetate (500 mL) then filtered. 100 mL water was added, and the organic layer was separated. Then the aqueous phase was extracted with ethyl acetate (80 mL). The combined organic layer was washed with brine (120 mL), dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated in vacuum to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give 7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol (2.34 g, 24% yield). Yellow solid. LCMS [ESI, M+1]: m/z = 414.1.

[0000526] Step B. 2,4-dichloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine. A mixture of $POCl_3$ (278 mg, 1.81 mmol, 169 μ L) in toluene (3 mL) were added DIEA (141 mg, 1.09 mmol, 190 μ L) and 7-[8-ethyl-7-fluoro-3-

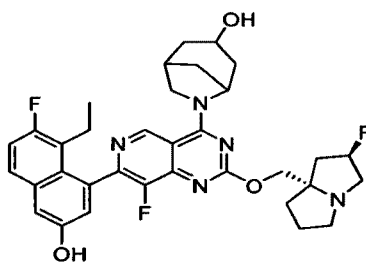
(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol (150 mg, 363 μmol) and the mixture was stirred at 110 °C for 25 mins. After completion, the mixture was concentrated in vacuum and the pH value was adjusted to 8 with cold saturated NaHCO_3 solution. Then the mixture was extracted with ethyl acetate (8 mL) twice. The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4 . The mixture was filtered and concentrated in vacuum to give 2,4-dichloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine (164 mg, crude) which was used to next step without further purification. Brown oil.

[0000527] Step C. 8-[2-chloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-1,8-diazaspiro[3.5]nonan-2-one. To a mixture of 2,4-dichloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine (147 mg, 326 μmol) and DIEA (127 mg, 979 μmol , 171 μL) in dichloromethane (2 mL) was added 1,8-diazaspiro[3.5]nonan-2-one (45.8 mg, 326 μmol) at -40 °C and the mixture was stirred at -40 °C for 20 mins. After completion, the mixture was quenched by water (10 mL) and filtered. Then the filtrate was extracted with dichloromethane twice. The combined organic layer was washed with brine (6 mL) and dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated in vacuum to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give 8-[2-chloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-1,8-diazaspiro[3.5]nonan-2-one (54.0 mg, 27% yield over two steps). Yellow solid. LCMS [ESI, M+1]: m/z = 554.2.

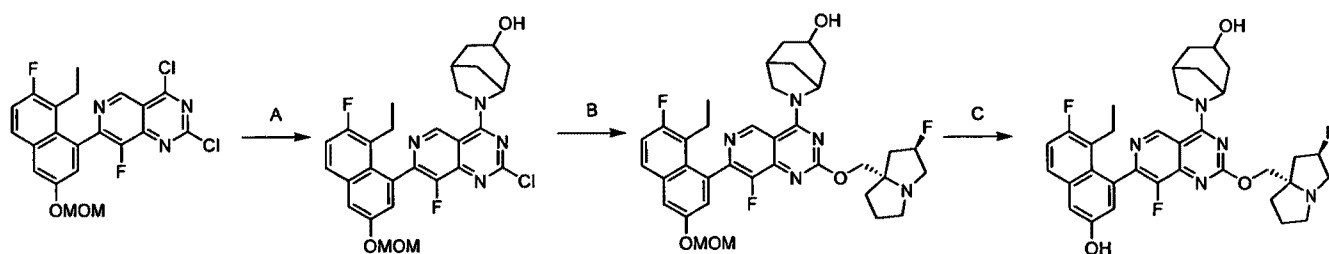
[0000528] Step D. 6-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one. A mixture of 8-[2-chloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-1,8-diazaspiro[3.5]nonan-2-one (50.0 mg, 90.3 μmol), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (43.1 mg, 271 μmol), DIEA (35.0 mg, 271 μmol , 47.2 μL) and 4Å molecular sieves (10 mg) in dioxane (1.5 mL) was stirred at 90 °C for 22 h. After completion, the mixture was filtered and concentrated in vacuum to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give the title compound (36.0 mg, 55% yield). Yellow solid. LCMS [ESI, M+1]: m/z = 677.4.

[0000529] Step E. 6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one. To a mixture of 6-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one (37.0 mg, 54.7 μ mol) and dichloromethane (0.5 mL) was added TFA (770 mg, 6.75 mmol, 0.5 mL) at 0 °C and the mixture was stirred at 0 °C for 1 h. After completion, the mixture was concentrated in vacuum. The pH value was adjusted to 9 with saturated NaHCO₃ solution and the mixture was extracted with ethyl acetate twice. The combined organic layer was dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated in vacuum to give a residue. The residue was purified by prep-HPLC (Water s Xbridge 150*25mm*5 μ m; mobile phase: [water (10mM NH₄HCO₃) - ACN]; B%: 35% - 65%, 10 min) to afford the title compound (14.3 mg, 41% yield). Yellow solid. ¹H NMR (400 MHz, METHANOL-d₄): δ 9.08 (s, 1H), 7.68 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 5.39 - 5.22 (m, 1H), 4.42 - 4.24 (m, 4H), 4.02 - 3.92 (m, 1H), 3.85 - 3.68 (m, 1H), 3.28 - 3.11 (m, 3H), 3.05 - 2.97 (m, 1H), 2.92 - 2.83 (m, 1H), 2.78 - 2.70 (m, 1H), 2.51 - 2.09 (m, 6H), 2.04 - 1.90 (m, 6H), 0.79 (td, *J* = 2.4, 7.2 Hz, 3H). ¹⁹F NMR (400 MHz, METHANOL-d₄) δ = -121.066, -138.847, -173.641; LCMS [ESI, M+1]: *m/z* = 633.3.

EXAMPLE 58



6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol

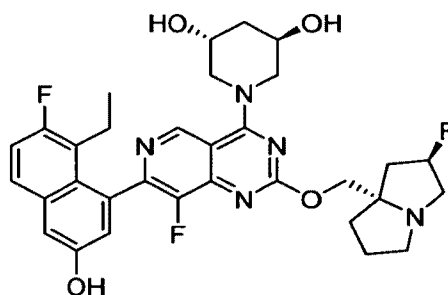


[0000530] Step A. 6-(2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol: To a solution of 2,4-dichloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidine (163 mg, 362 μ mol) and DIPEA (297 mg, 2.30 mmol) in DCM (2 mL) was added 6-azabicyclo[3.2.1]octan-3-ol (33 mg, 259 μ mol) in DCM (1 mL) at -40°C slowly. The mixture was stirred at this temperature for 10 minutes. The reaction mixture was diluted with water (5 mL), and extracted with ethyl acetate (10 mL $\times$ 4). The combined organic phase was dried with anhydrous Na_2SO_4 . The mixture was filtered and concentrated under reduced pressure to afford a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=2/3] to give the product as a red oil (88 mg, 39%). LCMS [ESI, M+1]: m/z = 541.2.

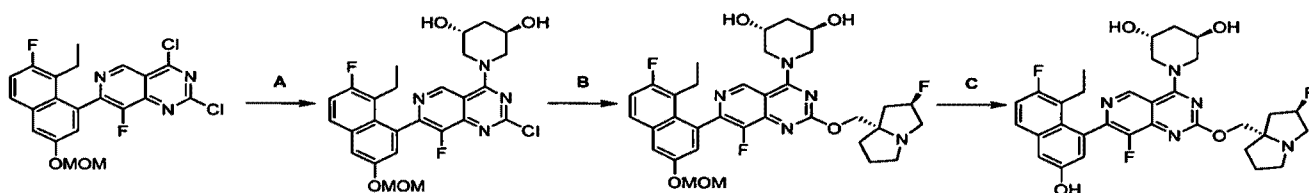
[0000531] Step B. 6-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol: A mixture of 6-(2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol (66 mg, 122 μ mol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (78 mg, 490 μ mol), DIPEA (52 mg, 402 μ mol), and 4Å molecular sieves (40 mg, 40.7 μ mol) in dioxane (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 95°C for 48 hours under N_2 atmosphere. The reaction mixture was filtered. The residue was washed with DCM (1 mL $\times$ 5). The combined DCM phase was concentrated under reduced pressure to afford a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=12/13] to give the product as a yellow oil (48 mg, 59%). LCMS [ESI, M+1]: m/z = 664.3.

[0000532] Step C. 6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol: To a solution of 6-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol (58 mg, 87.4 μ mol) in DCM (2 mL) was added dropwise TFA (2.5 mL) at 0 °C. The mixture was stirred between 0 and 15 °C for 1.5 hours. The reaction mixture was diluted with DCM (4 mL), and quenched with saturated NaHCO₃ aqueous (8 mL) at 0 °C. The residue was washed with DCM (4 mL $\times$ 4) and the combined DCM phase was concentrated under reduced pressure to afford a residue. The filtrate was purified by prep-HPLC (column: water s Xbridge 150 $\times$ 25 mm $\times$ 5 μ m; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 42%-72%, 10min) to give the product as a yellow solid. (10 mg, 18%). ¹H NMR (400 MHz, METHANOL-d₄) δ = 9.27 - 9.24 (m, 1H), 7.68 - 7.66 (m, 1H), 7.29 - 7.24 (m, 2H), 7.04 (br dd, J = 2.0, 12.4 Hz, 1H), 5.31 (d, J = 54.4 Hz, 1H), 4.98 (br s, 1H), 4.34 - 4.22 (m, 4H), 4.13 (br s, 1H), 3.22 (br d, J = 14.0 Hz, 2H), 3.02 - 3.00 (m, 1H), 2.77 - 2.64 (m, 2H), 2.47 - 1.81 (m, 14H), 0.78 (t, J = 7.2 Hz, 3H). F NMR (376 MHz, METHANOL-d₄) δ = -121, -138, -173. LCMS [ESI, M+1]: m/z = 620.3.

EXAMPLE 59



(3R,5R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol



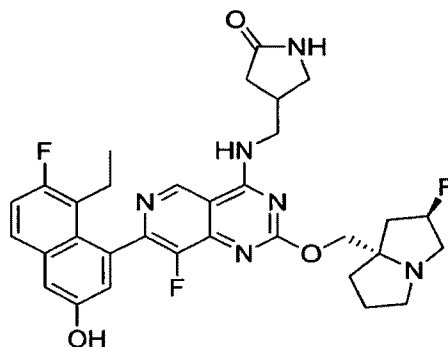
[0000533] Step A. (3R,5R)-1-(2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol: To a mixture of 2,4-dichloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidine (200 mg, 444 μ mol), and DIEA (287 mg, 2.22 mmol) in dichloromethane (3 mL) was added (3R,5R)-piperidine-3,5-diol (47.8 mg, 311 μ mol, HCl) at -40°C. The mixture was stirred at -40°C for 0.5 hour. Upon completion, the reaction mixture was partitioned between dichloromethane (6 mL) and water (5 mL), and the aqueous layer was extracted with dichloromethane (5 mL) one more time. The combined organic phase was washed with brine (5 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (3R,5R)-1-(2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol (85.0 mg, 34% yield). Yellow Oil; LCMS [ESI, M+1]: m/z = 531.2.

[0000534] Step B. (3R,5R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol. To the mixture of (3R,5R)-1-(2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol (75.0 mg, 141 μ mol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (45.0 mg, 282 μ mol), and 4Å molecular sieves (30.0 mg) in dioxane (1.5 mL) was added DIEA (54.8 mg, 424 μ mol), and the mixture was stirred at 90°C for 15 hours. Upon completion, the reaction mixture was partitioned between ethyl acetate (15 mL) and water (10 mL), and the aqueous layer was extracted with ethyl acetate (15 mL). The combined organic phase was washed with brine (20 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (3R,5R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol (45.0 mg, 45% yield). Yellow Solid; LCMS [ESI, M+1]: m/z = 654.1.

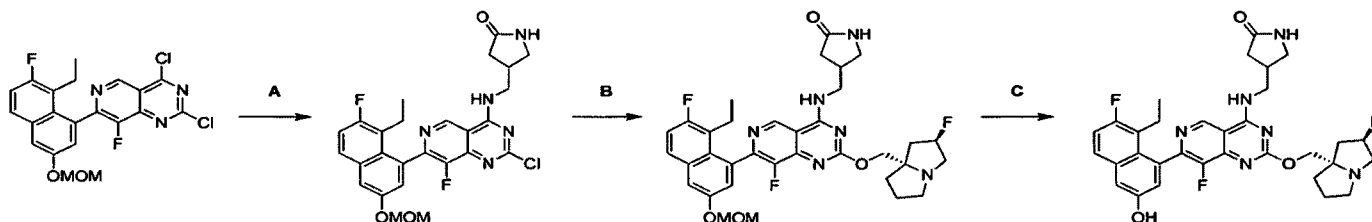
[0000535] Step C. (3R,5R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol. To the solution of (3R,5R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-

yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol (42.0 mg, 64.3 μ mol) in dichloromethane (0.8 mL) was added TFA (1.47 g, 12.9 mmol), and the mixture was stirred at 0°C for 1 hour. Upon completion, the mixture was concentrated, and the pH was adjusted to 8 with sat. NaHCO₃. The mixture was extracted with ethyl acetate (8 mL $\times$ 2), and the combined organic phase was dried over anhydrous sodium sulfate. The mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: water s Xbridge 150 $\times$ 25 mm $\times$ 5 μ m; mobile phase: [water (10 mM NH₄HCO₃) - ACN]; B%: 29% - 59%, 10 min) to afford (3R,5R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol (15.71 mg, 40% yield). White Solid; ¹H NMR (400 MHz, METHANOL-d₄) δ = 9.26 (d, *J* = 7.2 Hz, 1H), 7.72 - 7.65 (m, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.07 - 7.02 (m, 1H), 5.46 - 5.31 (m, 1H), 4.51 - 4.34 (m, 2H), 4.30 - 4.21 (m, 4H), 3.86 - 3.76 (m, 2H), 3.55 - 3.47 (m, 1H), 3.56 - 3.35 (m, 2H), 3.20 - 3.10 (m, 1H), 2.52 - 2.05 (m, 7H), 2.04 - 1.93 (m, 3H), 0.84 - 0.75 (m, 3H); LCMS [ESI, M+1]: *m/z* 610.2.

EXAMPLE 60



4-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one



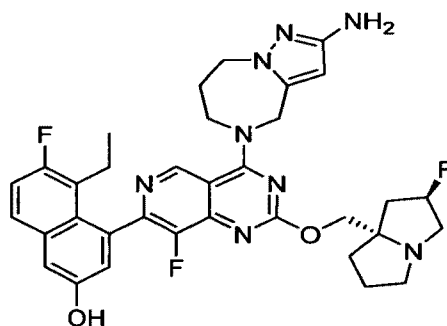
[0000536] Step A. 4-(((2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one: To the mixture of 2,4-dichloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidine (170 mg, 378 μ mol), and DIEA (244 mg, 1.89 mmol) in dichloromethane (3 mL) was added 4-(aminomethyl)pyrrolidin-2-one (34.5 mg, 302 μ mol) at -40 °C, and the mixture was stirred at -40°C for 0.5 hour. Upon completion, the reaction mixture was quenched with water and extracted with dichloromethane twice. The combined organic phase was washed with brine (5 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give the title compound (120 mg, 59% yield). Off-White Solid; LCMS [ESI, M+1]: m/z 528.2.

[0000537] Step B. 4-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one: To the mixture of 4-(((2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one (110 mg, 208 μ mol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (66.3 mg, 417 μ mol), and 4Å molecular sieves (5.0 mg) in dioxane (1.5 mL) was added DIEA (80.8 mg, 625 μ mol), and the mixture was stirred at 90 °C for 15 hours. Upon completion, the reaction mixture was quenched with water and extracted with ethyl acetate twice. The combined organic phase was washed with brine (20 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give the title compound (83.0 mg, 59% yield). Yellow Solid; LCMS [ESI, M+1]: m/z 651.2.

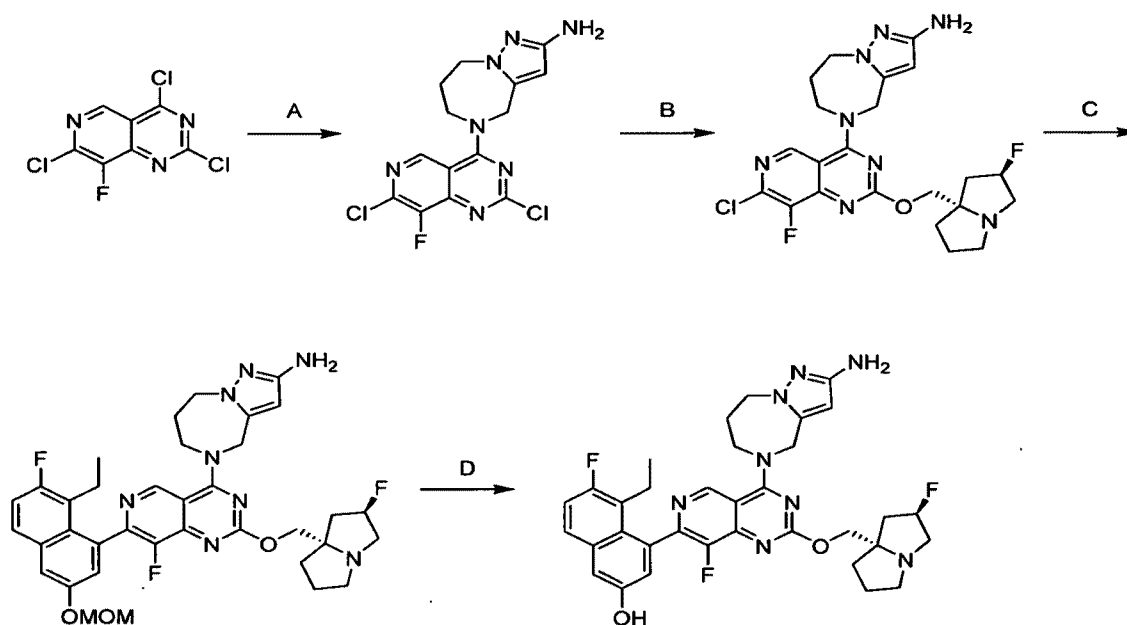
[0000538] Step C. 4-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one: To the solution of 4-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one (78.0 mg, 120 μ mol) in dichloromethane (0.8 mL) was added TFA (1.54 g, 13.5 mmol), and the mixture was stirred at 0 °C for 1 hour. Upon completion, the mixture was concentrated, and the pH was adjusted with sat.

NaHCO₃ to 8. The mixture was extracted with ethyl acetate (8 mL × 2). The combined organic phase dried over anhydrous sodium sulfate. The mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: water s Xbridge 150 × 25 mm × 5 μm; mobile phase: [water (10 mM NH₄HCO₃) - ACN]; B%: 29% - 59%, 10 min) to afford 4-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one (25.04 mg, 34% yield). White Solid; ¹H NMR (400 MHz, METHANOL-d₄) δ = 9.18 (s, 1H), 7.73 - 7.66 (m, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.27 (t, *J* = 9.6 Hz, 1H), 7.06 (d, *J* = 2.8 Hz, 1H), 5.46 - 5.28 (m, 1H), 4.46 - 4.31 (m, 2H), 3.89 - 3.76 (m, 2H), 3.67 - 3.58 (m, 1H), 3.51 - 3.34 (m, 3H), 3.30 (br s, 1H), 3.17 - 3.00 (m, 2H), 2.62 - 2.15 (m, 7H), 2.11 - 1.94 (m, 3H), 0.81 (t, *J* = 7.2 Hz, 3H); LCMS [ESI, M+1]: *m/z* 607.2.

EXAMPLE 61



4-(4-(2-amino-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol



[0000539] Step A. 5-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine: To the mixture of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (280 mg, 1.1 mmol) and DIEA (717 mg, 5.5 mmol, 966 μ L) in dichloromethane (1 mL) was added 5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (118 mg, 776 μ mol) at -40 $^{\circ}$ C and the mixture was stirred at -40 $^{\circ}$ C for 0.5 hour. After completion, the mixture was quenched by water (3 mL) and filtered. Then the mixture was extracted with dichloromethane twice. The combined organic layer was dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated in vacuum to give 5-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (474 mg, crude). Brown oil; LCMS [ESI, $\text{M}+1$]: m/z 368.0.

[0000540] Step B. 5-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine: A mixture of 5-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (454 mg, 1.2 mmol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (589 mg, 3.7 mmol), DIEA (478 mg, 3.7 mmol, 644 μ L) and 4 $\text{\AA}$ molecular sieves (400 mg) in dioxane (1 mL) was stirred at 90 $^{\circ}$ C for 16 hours. After completion,

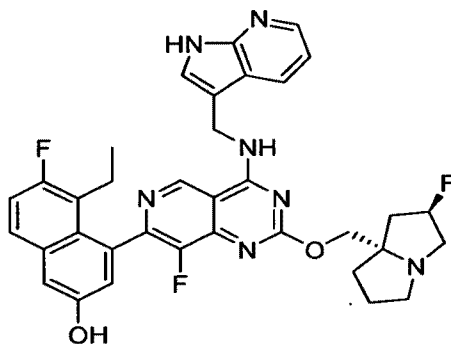
the mixture was filtered and concentrated in vacuum to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give 5-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (80 mg, 9% yield over two steps). Yellow solid; LCMS [ESI, M+1]: m/z 491.2.

[0000541] Step C. 5-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine: To the mixture of 5-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (70 mg, 143 μ mol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (67 mg, 185 μ mol), K_3PO_4 (1.5 M, 285 μ L) in THF (1 mL) was added cataCXium-A-Pd-G3 (10 mg, 14 μ mol) under N_2 , and the mixture was stirred at 60°C for 4 hours. After completion, the mixture was quenched by water (2 mL). Then the mixture was extracted with ethyl acetate twice. The combined organic layer was dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated in vacuum to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give 5-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (53 mg, 43% yield). Yellow solid; LCMS [ESI, M+1]: m/z 689.4.

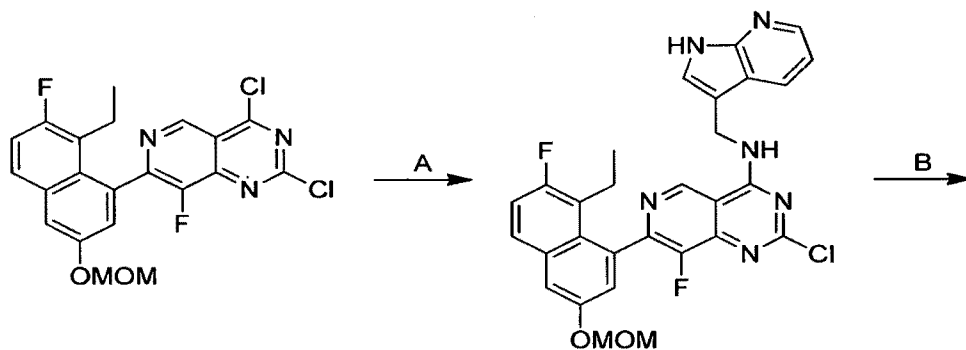
[0000542] Step D. 4-(4-(2-amino-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol. 5-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (14 mg, 20 μ mol) was added to $HCl \cdot MeOH$ (4.0 mmol, 1 mL) at 0 °C and the mixture was stirred at 0°C for 20 min. After completion, the mixture was concentrated in vacuum. The pH value was adjusted to 9.0 with saturated $NaHCO_3$ solution and the mixture was extracted with ethyl acetate (15 mL $\times$ 2). The aqueous phase was extracted with ethyl acetate (2 mL). The combined organic layer was dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated in vacuum to give a residue.

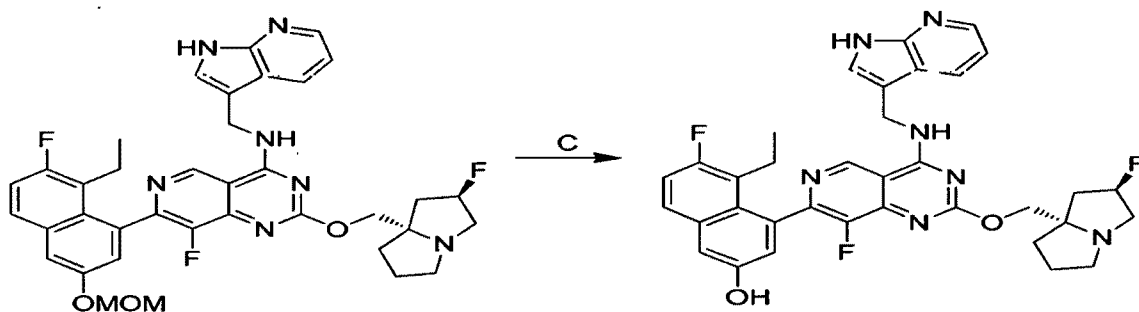
The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 20%-50%, 10 min) to afford 4-(4-(2-amino-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol (4.58 mg, 34% yield). White solid; ¹H NMR (400 MHz, METHANOL-d₄): δ = 9.19 (s, 1H), 7.67 (dd, J = 5.6, 9.2 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.25 (t, J = 9.2 Hz, 1H), 7.06 (d, J = 2.8 Hz, 1H), 5.78 (s, 1H), 5.39 - 5.22 (m, 1H), 5.18 - 5.07 (m, 2H), 4.40 - 4.21 (m, 6H), 3.24 - 3.11 (m, 2H), 3.01 (m, 1H), 2.43 - 2.30 (m, 4H), 2.27 - 2.07 (m, 4H), 2.05 - 1.86 (m, 3H), 0.83 - 0.75 (m, 3H); LCMS [ESI, M+1]: m/z 645.3.

EXAMPLE 62



4-(4-(((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol





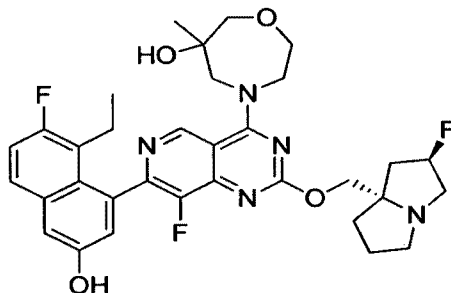
[0000543] Step A. N-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-amine: To a solution of 2,4-dichloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidine (163 mg, 362 μmol) and DIPEA (148 mg, 1.15 mmol) in DCM (2 mL) were added (1H-pyrrolo[2,3-b]pyridin-3-yl)methanamine (44 mg, 200 μmol , 2HCl) and DIPEA (74.2 mg, 574 μmol) in DMF (1.5 mL) dropwise at $-40\text{ }^{\circ}\text{C}$. The mixture was stirred at $-40\text{ }^{\circ}\text{C}$ for 0.1 h. The reaction mixture was diluted with water (50 mL) and brine (10 mL), and was extracted with ethyl acetate (20 mL $\times$ 4). The combined organic layers were dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated under reduced pressure. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=2/3] to afford the product as light yellow solid (100 mg, 57% yield). LCMS (ESI, M+1): m/z 561.1.

[0000544] Step B. N-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: A mixture of N-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-amine (150 mg, 267 μmol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (128 mg, 804 μmol), DIPEA (104 mg, 804 μmol) and 4Å molecular sieves (60 mg) in dioxane (2.5 mL) was degassed and purged with N_2 for 3 times. The mixture was stirred at $95\text{ }^{\circ}\text{C}$ for 48 hours under N_2 atmosphere. The reaction mixture was filtered through a pad of Celite. The filter cake was washed with DCM (10 mL). The combined organic phase was concentrated under reduced pressure, and purified by reversed phase flash chromatography [water

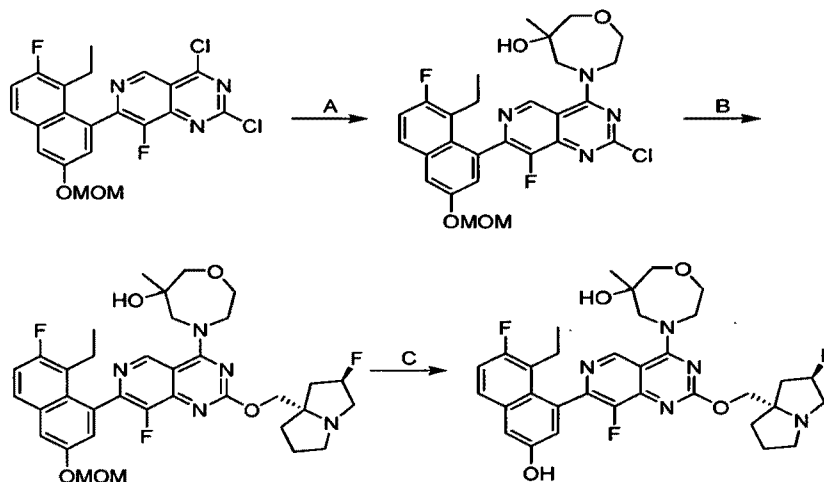
(0.1% formic acid)/acetonitrile=1/1] to afford the product as white solid (100 mg, 54% yield). LCMS (ESI, M+1): m/z 684.3.

[0000545] Step C. 4-(4-(((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol: To a solution of N-(((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine (100 mg, 146 μ mol) in DCM (2 mL) was added TFA (2.5 mL) dropwise at 0 °C. The mixture was stirred between 0 and 15 °C for 1.5 hours. The reaction mixture was concentrated under reduced pressure to give a residue at room temperature. The residue was dissolved in DCM (20 mL) and water (5 mL). The pH of the mixture was adjusted to 9 with NaHCO₃ solid below 5 °C. The mixture was extracted with DCM (10 mL $\times$ 4). The combined organic layers were dried over anhydrous Na₂SO₄ and filtered. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: water s Xbridge 150 $\times$ 25mm $\times$ 5um; A: [water (10mM NH₄HCO₃)]; B: CAN, B%: 40%-70% over 10 minutes) to afford the product as white solid (53.4 mg, 55% yield). HPLC: >99% ee, Chiralcel OJ-3 50 $\times$ 4.6 mm I.D., 3 μ m column A: CO₂, B: MeOH (w/ 0.05% DEA), 5% to 40%, 3mL/min, 220 nm, t_R: 2.009 min; ¹H NMR (400 MHz, DMSO-d₆): δ 11.59 (s, 1H), 9.91 (br s, 1H), 9.39 - 9.29 (m, 2H), 8.23 - 8.14 (m, 2H), 7.55 - 7.54 (m, 1H), 7.77 - 7.73 (m, 1H), 7.39 - 7.24 (m, 2H), 7.11 - 6.98 (m, 2H), 5.29 (d, *J* = 53.6 Hz, 1H), 4.94 - 4.90 (m, 2H), 4.20 - 4.09 (m, 2H), 3.10 - 3.08 (m, 2H), 3.08 - 3.07 (m, 1H), 3.07 - 3.01 (m, 1H), 2.10 - 1.78 (m, 8H), 0.73 - 0.64 (m, 3H); ¹⁹F NMR (376 MHz, DMSO-d₆): δ -119, -139, -172; LCMS (ESI, M+1): m/z 640.3.

EXAMPLE 63



4-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol



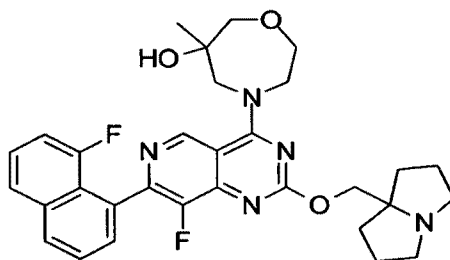
[0000546] Step A. 4-[2-chloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-6-methyl-1,4-oxazepan-6-ol: To a mixture of 2,4-dichloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine (189 mg, 420 μ mol) and DIEA (217 mg, 1.68 mmol, 292 μ L) in dichloromethane (2 mL) was added 6-methyl-1,4-oxazepan-6-ol (49.5 mg, 378 μ mol) at - 40 °C and the mixture was stirred at - 40 °C for 20 mins. After completion, the mixture was quenched by water (8 mL) and filtered. Then the mixture was extracted with dichloromethane (8 mLX2). The combined organic layer was dried over Na₂SO₄. The mixture was filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give 4-[2-chloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-6-methyl-1,4-oxazepan-6-ol (103 mg, 44% yield). Yellow solid. LCMS (ESI, M+1): m/z 545.2.

[0000547] Step B. 4-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol: A mixture of 4-[2-chloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-6-methyl-1,4-oxazepan-6-ol (103 mg, 189 μ mol), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (90.3 mg, 567 μ mol), DIEA (73.3 mg, 567 μ mol, 98.8 μ L) and 4Å molecular sieves (10 mg) in dioxane (1 mL) was

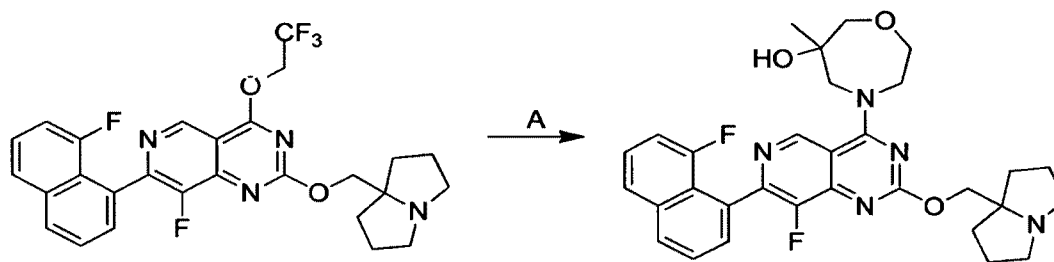
stirred at 90 °C for 21 h. After completion, the mixture was filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to the title compound (92.0 mg, 73% yield). Yellow solid. LCMS (ESI, M+1): m/z 668.3.

[0000548] Step C. 4-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol: To a mixture of 4-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol (84.0 mg, 125.8 μ mol) in dichloromethane (0.5 mL) was added TFA (770 mg, 6.75 mmol, 0.5 mL) at 0 °C and the mixture was stirred at 25°C for 0.5 h. After completion, the mixture was concentrated in vacuum. The pH value was adjusted to 9 with saturated NaHCO₃ solution and the mixture was extracted with ethyl acetate twice. The combined organic layer was dried over Na₂SO₄ and filtered. The residue was concentrated in vacuum. The residue was purified by prep-HPLC (Shim-pack C18 150*25*10 μ m; mobile phase: [water (0.225% formic acid) - ACN]; B%: 19% - 39%, 10 min) to afford the title compound (26.9 mg, 33% yield, 0.2 formic acid salt). White solid. ¹H NMR (400 MHz, METHANOL-d₄): δ 9.61 - 9.56 (m, 1H), 7.68 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.33 - 7.30 (m, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.06 (dd, *J* = 2.4, 13.6 Hz, 1H), 5.54 - 5.37 (m, 1H), 4.63 - 4.44 (m, 5H), 4.25 - 4.14 (m, 1H), 4.07 - 3.85 (m, 3H), 3.74 - 3.66 (m, 2H), 3.65 - 3.56 (m, 2H), 3.29 - 3.23 (m, 1H), 2.60 - 2.37 (m, 3H), 2.33 - 2.03 (m, 5H), 1.28 (d, *J* = 2.4 Hz, 3H), 0.84 - 0.76 (m, 3H). LCMS (ESI, M+1): m/z 624.3.

EXAMPLE 64

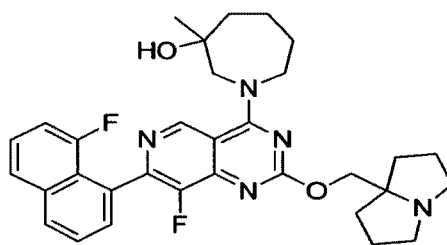


4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol

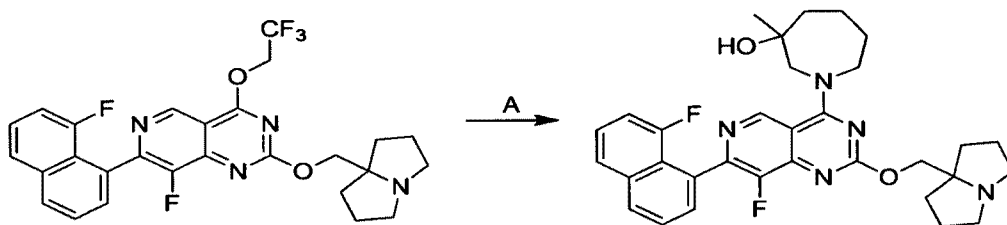


[0000549] Step A. 4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol: To the mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30 mg, 56 μ mol), 6-methyl-1,4-oxazepan-6-ol (15 mg, 113 μ mol) and 4Å molecular sieves (5.0 mg) in DMF (0.5 mL) was added DIEA (22 mg, 169 mmol). The mixture was stirred at 40 °C for 12 hours. After completion, the reaction mixture was filtered and purified by prep-HPLC (column: Phenomenex luna C18 150 $\times$ 25 mm $\times$ 10 μ m; mobile phase: [water (0.225% formic acid)-ACN]; B%: 15% - 45%, 10 min) and (column: Phenomenex Gemini-NX C18 75 $\times$ 30 mm $\times$ 3 μ m; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 25% - 55%, 8 min) to afford 4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol (3.93 mg, 12% yield). Yellow solid; ¹H NMR (400 MHz, CHLOROFORM-d): δ 9.29 (d, J = 2.4 Hz, 1H), 8.04 - 8.00 (m, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.67 - 7.44 (m, 3H), 7.14 (br dd, J = 7.6, 12.8 Hz, 1H), 5.64 - 5.21 (m, 1H), 4.73 - 4.61 (m, 1H), 4.56 - 4.43 (m, 1H), 4.39 - 4.22 (m, 2H), 4.05 - 3.80 (m, 3H), 3.76 - 3.52 (m, 3H), 3.26 - 3.08 (m, 2H), 2.79 - 2.57 (m, 2H), 2.14 - 2.01 (m, 2H), 1.93 - 1.84 (m, 4H), 1.81 - 1.74 (m, 2H), 1.42 - 1.34 (m, 3H); LCMS (ESI, M+1): m/z 562.2.

EXAMPLE 65

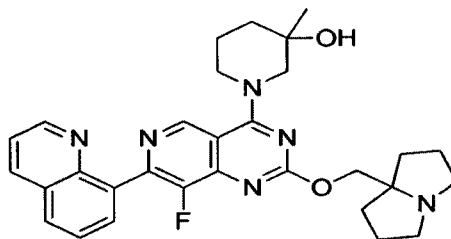


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylazepan-3-ol

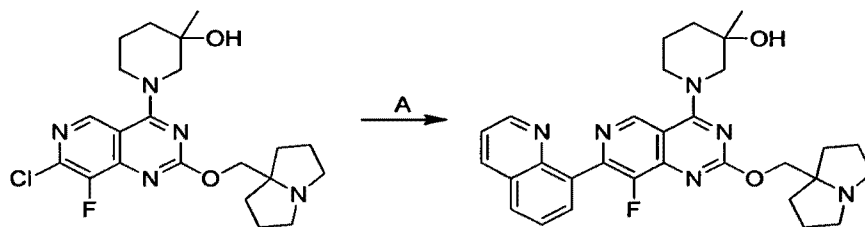


[0000550] Step A. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylazepan-3-ol: 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μ mol, 1.0 equiv.), DIEA (60.9 mg, 471 μ mol, 82.1 μ L, 5.0 equiv.) and 4Å molecular sieves (5.00 mg) in DMF (1.0 mL) was added 3-methylazepan-3-ol (24.4 mg, 189 μ mol, 2.0 equiv.). The mixture was stirred at 40 °C for 12 h. Upon completion, the reaction solution was filtered and purified by prep-HPLC [Phenomenex luna C18 150 $\times$ 25 mm $\times$ 10 μ m; A: water (0.225% formic acid formic acid), B: ACN, B%: 19%-49% over 10 min] to afford 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylazepan-3-ol (12.6 mg, 15% yield). Off-white solid; ^1H NMR (400 MHz, METHANOL- d_4) δ 9.45 (br d, J = 8.4 Hz, 1H), 8.54 (s, 1H), 8.11 (br d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.73-7.65 (m, 1H), 7.65-7.57 (m, 1H), 7.56-7.48 (m, 1H), 7.23-7.14 (m, 1H), 4.57-4.51 (m, 1H), 4.50-4.38 (m, 2H), 4.37-4.24 (m, 1H), 3.98-3.81 (m, 2H), 3.50-3.38 (m, 2H), 3.11-2.97 (m, 2H), 2.29-2.13 (m, 3H), 2.13-1.98 (m, 5H), 1.98-1.88 (m, 3H), 1.87-1.67 (m, 3H), 1.42-1.31 (m, 3H); LCMS (ESI, $M+1$): m/z 560.2.

EXAMPLE 66

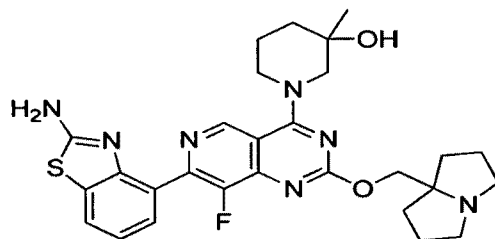


1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(quinolin-8-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

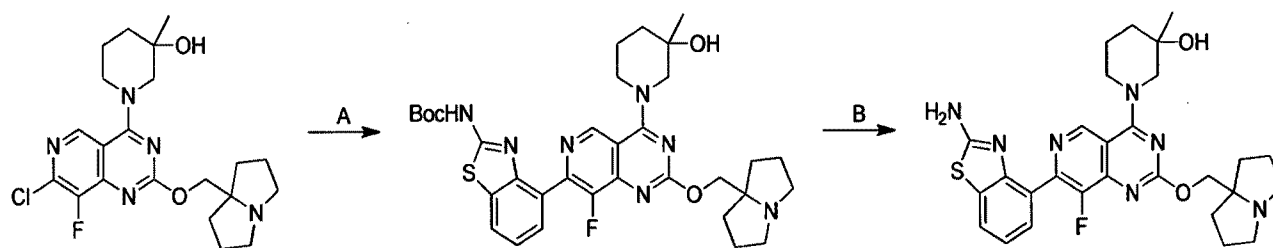


[0000551] Step A. 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(quinolin-8-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (100 mg, 229 μ mol), quinolin-8-ylboronic acid (79.4 mg, 459 μ mol, 79.4 μ L), Na_2CO_3 (72.9 mg, 688 μ mol) and tetrabutylammonium bromide (74.0 mg, 229 μ mol) in 1,2-dimethoxyethane (3.0 mL), EtOH (3.0 mL) and water (1.0 mL) was added $\text{Pd}(\text{PPh}_3)_4$ (53.0 mg, 45.9 μ mol, 0.2 equiv.). The mixture was stirred at 80 $^\circ\text{C}$ for 12 h. Upon completion, the mixture reaction was diluted water (5.0 mL) and was extracted with EtOAc (3 $\times$ 5.0 mL). The combined organic layer was dried over anhydrous Na_2SO_4 . The mixture was filtered and concentrated in vacuum. The reaction was purified by prep-HPLC [Phenomenex Gemini-NX C18 75 $\times$ 30 mm $\times$ 3 μ m; A: water (0.225% formic acid formic acid), B: ACN, B%: 8%-38% over 7 min] to afford 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(quinolin-8-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (7.25 mg, 5.8% yield). White solid; ^1H NMR (400 MHz, METHANOL-d_4) δ 9.29 (s, 1H), 8.85-8.79 (m, 1H), 8.54 (s, 1H), 8.50-8.45 (m, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.98-7.71 (m, 1H), 7.83-7.76 (m, 1H), 7.63-7.57 (m, 1H), 4.59 (br d, J = 12.8 Hz, 3H), 4.34 (br d, J = 13.2 Hz, 1H), 3.72-3.62 (m, 1H), 3.52-3.39 (m, 3H), 3.10-2.98 (m, 2H), 2.27-2.19 (m, 2H), 2.16-1.91 (m, 7H), 1.89-1.75 (m, 3H), 1.29 (s, 3H); LCMS (ESI, $\text{M}+1$): m/z 529.3.

EXAMPLE 67



1-(7-(2-aminobenzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

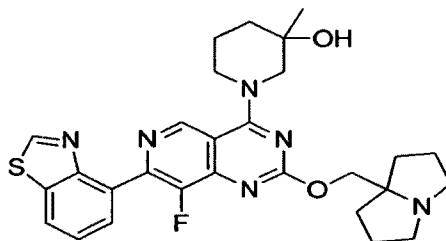


[0000552] Step A. tert-butyl (4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)benzo[d]thiazol-2-yl)carbamate: To a mixture of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (150 mg, 344 μ mol), (2-((tert-butoxycarbonyl)amino)benzo[d]thiazol-4-yl)boronic acid (202 mg, 688 μ mol) and K_3PO_4 (1.5 M, 688 μ L) in THF (2.0 mL) was added BrettPhos Pd G3 (31.2 mg, 34.4 μ mol). The mixture was stirred at 60 °C for 16 h. After completion, water (10 mL) was added and the mixture was extracted with EtOAc (2 $\times$ 10 mL). The combined organic layer was dried over Na_2SO_4 . The mixture was filtered and concentrated. The residue was purified by reversed phase flash chromatography (C18, water (0.1 % formic acid)/ACN) affording tert-butyl (4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)benzo[d]thiazol-2-yl)carbamate (190 mg, 79% yield). Yellow solid; LCMS (ESI, M+1): m/z 650.3.

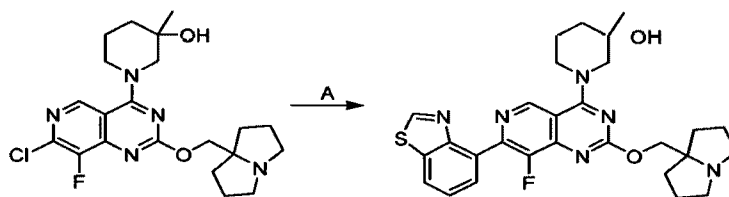
[0000553] Step B. 1-(7-(2-aminobenzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of tert-butyl (4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-

methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)benzo[d]thiazol-2-yl)carbamate (90.0 mg, 139 μ mol) in dichloromethane (1.0 mL) was added TFA (1.54 g, 13.5 mmol, 1.0 mL). The mixture was stirred at 20 °C for 0.5 h. After completion, the pH of the mixture was adjusted to $\sim$ 7 with saturated NaHCO_3 aqueous solution. The mixture was extracted with EtOAc (2×10 mL). The combined organic layer was dried over Na_2SO_4 . The mixture was filtered and concentrated. The residue was purified by prep-HPLC [Phenomenex luna C18 150×25 mm $\times$ 10 μ m; A: water (0.225% formic acid), B: ACN, B%: 9%-39% over 10min], followed by prep-HPLC [Water s Xbridge 150×5 mm $\times$ 5 μ m; A: water (10mM NH_4HCO_3), B: ACN, B%: 20%-50% over 10min] to afford 1-(7-(2-aminobenzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (9.54 mg, 12% yield). Yellow solid; ^1H NMR (400 MHz, $\text{METHANOL-}d_4$) δ 9.26 (s, 1H), 7.77 (dd, $J = 1.2, 8.0$ Hz, 1H), 7.45 (d, $J = 6.8$ Hz, 1H), 7.24 (t, $J = 8.0$ Hz, 1H), 4.66-4.56 (m, 3H), 4.33 (br d, $J = 13.2$ Hz, 1H), 3.76-3.60 (m, 3H), 3.49-3.39 (m, 1H), 3.30-3.24 (m, 2H), 2.39-2.28 (m, 2H), 2.27-2.07 (m, 7H), 1.92-1.73 (m, 3H), 1.29 (s, 3H); LCMS (ESI, $M+1$): m/z 550.1.

EXAMPLE 68



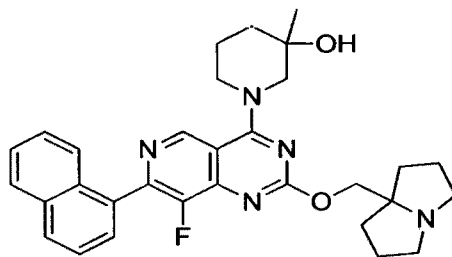
1-(7-(benzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



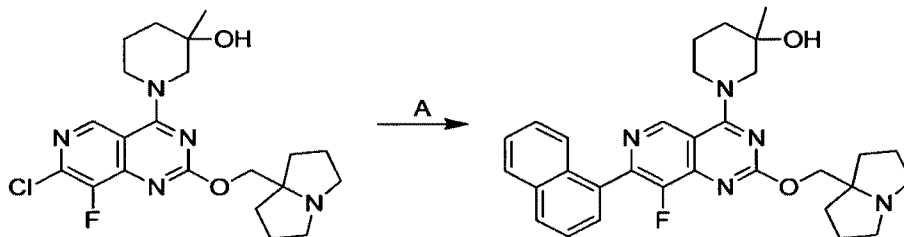
[0000554] Step A. 1-(7-(benzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of 1-(7-chloro-8-

fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (100 mg, 229 μ mol), benzo[d]thiazol-4-ylboronic acid (53.4 mg, 298 μ mol), K_3PO_4 (1.5 M, 0.5 mL) and [2-(2-aminophenyl)phenyl]palladium(1+);bis (1-adamantyl)-butylphosphane;methanesulfonate (25.1 mg, 34.4 μ mol) in THF (2.00 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 $^{\circ}C$ for 10 hours under N_2 atmosphere. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4 . The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 $\times$ 25mm $\times$ 10 μ m; mobile phase: [water (0.225% formic acid formic acid)-ACN]; B%: 11%-41%,10 min) to give 1-(7-(benzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (52.32 mg, 42 % yield). Yellow solid; ^1H NMR (400 MHz, METHANOL- d_4) δ 9.36-9.25 (m, 2H), 8.53 (s, 1H), 8.27 (dd, J = 0.8 Hz, 8.0 Hz, 1H), 7.79 (dd, J = 0.8 Hz, 7.2 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 4.67-4.59 (m, 3H), 4.40-4.30 (m, 1H), 3.72-3.62 (m, 3H), 3.48-3.39 (m, 1H), 3.30-3.20 (m, 2H), 2.36-2.28 (m, 2H), 2.27-2.05 (m, 7H), 1.90-1.74 (m, 3H), 1.29 (s, 3H); LCMS (ESI, M+1): m/z 535.3.

EXAMPLE 69

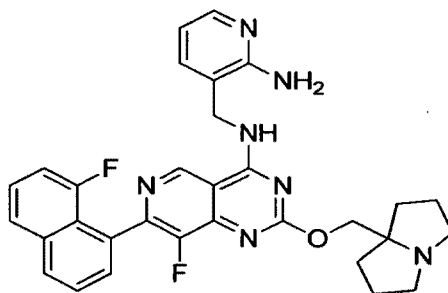


1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

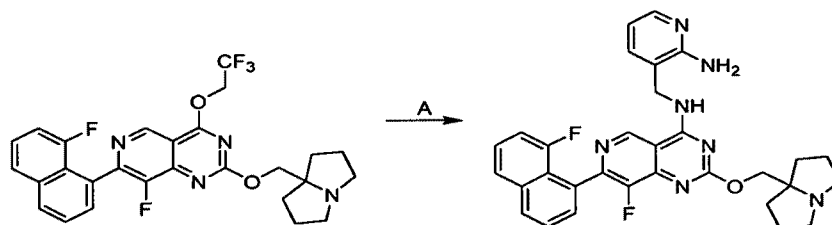


[0000555] Step A. 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (50.0 mg, 115 μ mo), naphthalen-1-ylboronic acid (39.5 mg, 229 μ mol) and K_3PO_4 (1.50 M in water, 229 μ L) in THF (1.0 mL) was added cataCXium-A-Pd-G3 (8.35 mg, 11.5 μ mol). The mixture was stirred at 60 °C for 12 h. Upon completion, the reaction mixture was diluted water (2.0 mL) and was extracted with EtOAc (3 $\times$ 2 mL). The combined organic layer was dried over Na_2SO_4 . The mixture was filtered and concentrated in vacuum. The residue was purified by prep-HPLC [Phenomenex luna C18 150 $\times$ 25 mm $\times$ 10 μ m; A: water (0.225% formic acid formic acid), B: ACN, B%: 17%-47% over 10 min] to afford 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (14.9 mg, 24% yield). Yellow solid; ^1H NMR (400 MHz, METHANOL- d_4) δ 9.34 (s, 1H), 8.52 (s, 1H), 8.09-8.04 (m, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.70 (br d, J = 8.8 Hz, 1H), 7.67-7.62 (m, 2H), 7.59-7.53 (m, 1H), 7.52-7.46 (m, 1H), 4.61-4.55 (m, 4H), 4.40-4.34 (m, 1H), 3.72-3.62 (m, 3H), 3.50-3.39 (m, 1H), 3.28-3.22 (m, 1H), 2.38-2.28 (m, 2H), 2.27-2.04 (m, 7H), 1.92-1.74 (m, 3H), 1.30 (s, 3H); LCMS (ESI, M+1): m/z 528.3.

EXAMPLE 70

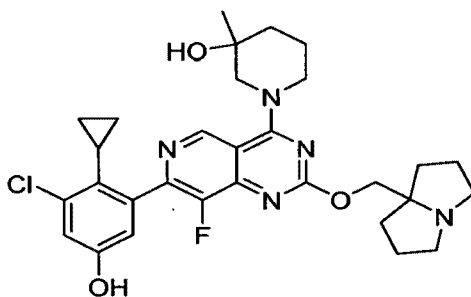


N-((2-aminopyridin-3-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

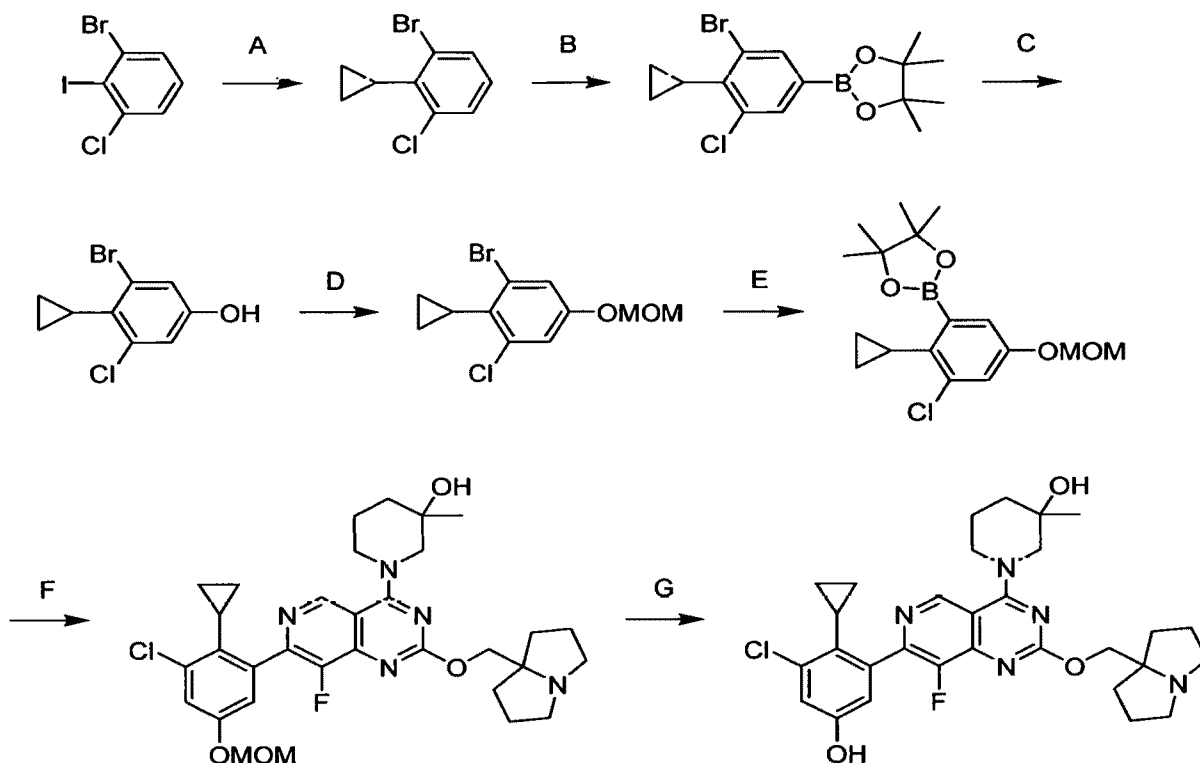


[0000556] Step A. N-((2-aminopyridin-3-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30 mg, 56.55 μ mol) and 3-(aminomethyl)pyridin-2-amine (34.8 mg, 283 μ mol) in DMF (3 mL) were added DIPEA (21.9 mg, 170 μ mol) and 4Å molecular sieves (50 mg). The mixture was stirred at 40 °C for 12 hours. The mixture was filtered and purified by prep-HPLC (column: Unisil 3-100 C18 Ultra 150×50mm×3 μ m; mobile phase: [water (0.225% formic acid)-ACN]; B%: 15%-35%, 10min) to give N-((2-aminopyridin-3-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine (11.1 mg, 35% yield, 2FORMIC ACID) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.57-9.26 (m, 2H), 8.30 (br s, 2H), 8.19 (br d, *J* = 8.4 Hz, 1H), 7.98-7.85 (m, 2H), 7.80-7.69 (m, 1H), 7.65-7.52 (m, 2H), 7.47-7.36 (m, 1H), 7.35-7.22 (m, 1H), 6.56 (dd, *J* = 5.0, 7.2 Hz, 1H), 6.06-5.88 (m, 2H), 4.65-4.55 (m, 2H), 4.16-4.02 (m, 3H), 3.02-2.87 (m, 3H), 1.97-1.66 (m, 7H), 1.64-1.49 (m, 2H); LCMS (ESI, M+1): *m/z* 554.2.

EXAMPLE 71



1-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



[0000557] Step A. 1-bromo-3-chloro-2-cyclopropyl-benzene: A mixture of cyclopropylboronic acid (1.62 g, 18.91 mmol), 1-bromo-3-chloro-2-iodo-benzene (2 g, 6.30 mmol), K₃PO₄ (4.82 g, 22.7 mmol), and Pd(dppf)Cl₂ (461 mg, 630 μmol) in 1,4-dioxane (12 mL) and water (3 mL) was degassed and purged with N₂ for 3 times. The mixture was stirred at 100 °C for 7 hours under N₂ atmosphere. Upon completion, the reaction mixture was extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with brine 15 mL and dried over Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=1/0) to give 1-bromo-3-chloro-2-cyclopropyl-benzene as a colorless liquid (1.6 g, 88% yield); ¹H NMR (400 MHz, CDCl₃) δ = 7.38 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.91 (t, *J* = 8.0 Hz, 1H), 2.31 (tt, *J* = 5.4, 8.5 Hz, 1H), 1.69 (tt, *J* = 5.8, 8.4 Hz, 1H), 1.29-1.16 (m, 1H), 1.15-1.06 (m, 3H), 0.84-0.74 (m, 2H), 0.74-0.66 (m, 3H).

[0000558] Step B. 2-(3-bromo-5-chloro-4-cyclopropyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: A mixture of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (995 mg, 7.77 mmol, 1.13

mL), 1-bromo-3-chloro-2-cyclopropyl-benzene (600 mg, 2.59 mmol), [Ir(OMe)(COD)]₂ (172 mg, 259 μ mol) and 4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine (83.5 mg, 311 μ mol) in hexane (10 mL) was degassed and purged with N₂ for 3 times. The reaction mixture was stirred at 60 °C for 3 hours under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate = 50/1) to give 2-(3-bromo-5-chloro-4-cyclopropyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (782 mg, 84% yield) as a colorless oil; ¹H NMR (400 MHz, CDCl₃) δ = 7.79 (s, 1H), 7.63 (s, 1H), 1.71 (tt, *J* = 5.8, 8.5 Hz, 1H), 1.26 (s, 12H), 1.15-1.09 (m, 2H), 0.72-0.68 (m, 2H).

[0000559] Step C. 3-bromo-5-chloro-4-cyclopropyl-phenol: To a solution of 2-(3-bromo-5-chloro-4-cyclopropyl-phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.12 g, 3.13 mmol) in water (4 mL) and THF (8 mL) were added AcOH (12.1 g, 200 mmol, 11.5 mL) and water₂ (2.05 g, 18.1 mmol, 1.74 mL, 30% purity). The mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched with Na₂S₂O₃ (10 % aq, 40 mL) at 0 °C. The mixture was extracted with ethyl acetate 60 mL (30 mL $\times$ 2). The combined organic layers were washed with brine 100 mL and dried over Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=10/1) to give 3-bromo-5-chloro-4-cyclopropyl-phenol as a colorless oil (700 mg, 90% yield); ¹H NMR (400 MHz, CDCl₃) δ = 6.93 (d, *J* = 2.6 Hz, 1H), 6.77 (d, *J* = 2.6 Hz, 1H), 5.73-5.49 (m, 1H), 1.64-1.55 (m, 1H), 1.08-1.00 (m, 2H), 0.67-0.60 (m, 2H).

[0000560] Step D. 1-bromo-3-chloro-2-cyclopropyl-5-(methoxymethoxy)benzene: To a solution of chloro(methoxy)methane (1.62 g, 20.12 mmol, 1.53 mL), 3-bromo-5-chloro-4-cyclopropyl-phenol (1.2 g, 4.85 mmol) and DIEA (1.88 g, 14.5 mmol, 2.53 mL) in DCM (15 mL) was added chloro(methoxy)methane (1.62 g, 20.1 mmol, 1.53 mL) at 0 °C. The reaction mixture was stirred at 25 °C for 2 hours. The reaction mixture was quenched with water (10 mL) at 0 °C. The mixture was extracted with EtOAc (10 mL $\times$ 3). The combined organic layers were washed with brine (30 mL) and dried over Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=30/1) to give 1-bromo-3-chloro-2-cyclopropyl-5-(methoxymethoxy)benzene as a colorless oil (923 mg, 65% yield); ¹H NMR (400 MHz, CDCl₃) δ

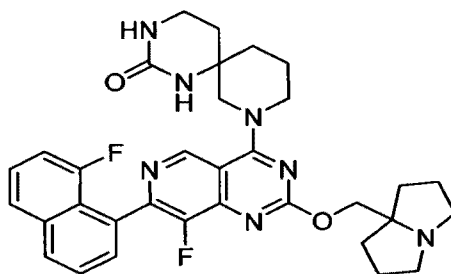
= 7.20 (d, J = 2.6 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 5.12 (s, 2H), 3.47 (s, 3H), 1.70 (tt, J = 5.7, 8.4 Hz, 1H), 1.17-1.11 (m, 2H), 0.76-0.69 (m, 2H).

[0000561] Step E. 2-[3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: To a mixture of 1-bromo-3-chloro-2-cyclopropyl-5-(methoxymethoxy)benzene (300 mg, 1.03 mmol), KOAc (303 mg, 3.09 mmol) and 4,4,5,5-tetramethyl-2-(4,5,5-trimethyl-4-methyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (521 mg, 2.06 mmol) in dioxane (4.5 mL) was added Pd(dppf)Cl₂ (75.37 mg, 103 μ mol). The mixture was stirred at 100 °C for 1 hour. Upon completion, to the reaction mixture was added water (5 mL) and the mixture was extracted with ethyl acetate 15 mL (3 $\times$ 5 mL). The organic layer was dried over by anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by prep-TLC (Silica gel, Petroleum ether/Ethyl acetate=15:1) to give 2-[3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as a colorless oil (135 mg, 39% yield); ¹H NMR (400 MHz, CDCl₃) δ = 7.11-7.08 (m, 2H), 5.14 (s, 2H), 3.46 (s, 3H), 1.98 (tt, J = 5.6, 8.5 Hz, 1H), 1.38 (s, 12H), 1.01-0.95 (m, 2H), 0.55-0.50 (m, 2H).

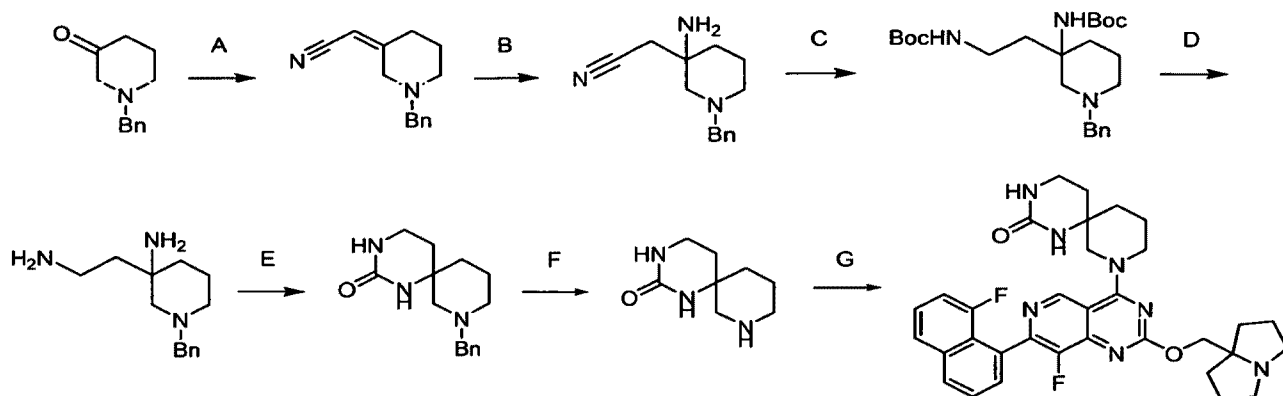
[0000562] Step F. 1-(7-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of 2-[3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (77.7 mg, 229 μ mol), 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (50 mg, 115 μ mol) and K₃PO₄ (1.5 M in water, 229.40 μ L) in THF (0.5 mL) was added cataCXium-A-Pd-G3 (8.35 mg, 11.5 μ mol). The mixture was degassed and purged with N₂ for 3 times. The mixture was stirred at 60 °C for 2.5 hours. The reaction mixture was diluted with water (5 mL) and the mixture was extracted with ethyl acetate (3 $\times$ 5 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep-TLC (Silica gel, DCM: MeOH = 10:1) to give the title compound as a brown oil (43 mg, 61% yield); ¹H NMR (400 MHz, CDCl₃) δ = 9.15 - 9.13 (m, 1H), 7.20 (d, J = 2.5 Hz, 1H), 7.08 - 7.06 (m, 1H), 5.19 - 5.16 (m, 2H), 4.46 - 4.39 (m, 2H), 4.39 - 4.34 (m, 3H), 3.55 - 3.50 (m, 1H), 3.49 (s, 2H), 3.47 (s, 3H), 3.40 (d, J = 13.5 Hz, 1H), 3.30 (br d, J = 6.6 Hz, 2H), 2.72 (td, J = 6.8, 10.4 Hz, 2H), 2.21-2.11 (m, 3H), 1.97-1.91 (m, 6H), 1.79-1.71 (m, 4H), 1.70-1.64 (m, 1H), 0.67 (br s, 2H), 0.19-0.06 (m, 2H).

[0000563] Step G. 1-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of 1-(7-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (40 mg, 65.3 μ mol) in MeCN (0.8 mL) was added HCl/EtOAc (4 M, 1.8 mL). The mixture was stirred at 20 °C for 0.5 hour. After completion, the mixture was concentrated to give a residue. The residue was purified by prep-HPLC (FA condition, column: Phenomenex luna C18 150 $\times$ 25mm $\times$ 10 μ m; mobile phase: [water (0.225% formic acid formic acid)-ACN];B%: 16%-46%,11min) to give the title compound (19.68 mg, 48% yield, FA salt); ^1H NMR (400 MHz, METHANOL- d_4) δ = 9.26 (s, 1H), 8.53 (br s, 1H), 6.98 (d, J = 2.5 Hz, 1H), 6.80 (d, J = 2.6 Hz, 1H), 4.61 (s, 2H), 4.58 (br s, 1H), 4.33 (br d, J = 13.5 Hz, 1H), 3.68-3.59 (m, 3H), 3.43 (br t, J = 11.0 Hz, 1H), 3.27-3.20 (m, 2H), 2.35-2.26 (m, 2H), 2.25-2.02 (m, 8H), 1.91-1.75 (m, 4H), 1.32-1.28 (m, 3H), 0.71-0.56 (m, 2H), 0.15-0.00 (m, 2H). LCMS (ESI, M+1): m/z 568.4.

EXAMPLE 72



8-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,8-triazaspiro[5.5]undecan-2-one



[0000564] Step A. 2-(1-benzylpiperidin-3-ylidene)acetonitrile: A mixture of 2-diethoxyphosphorylacetonitrile (9.27 g, 52.3 mmol, 8.42 mL), K_2CO_3 (8.89 g, 64.3 mmol) in THF (25 mL) was stirred for 10 min at 25 °C and 20 min at 70 °C under N_2 atmosphere. The reaction mixture was cooled to 25 °C. A mixture of 1-benzylpiperidin-3-one (10 g, 52.84 mmol) and K_2CO_3 (7.30 g, 52.84 mmol) in THF (25 mL) was added into the mixture and the reaction was stirred at 70 °C for further 18 hours. The mixture was diluted with water (350 mL) and extracted with ethyl acetate (200 mL $\times$ 2). The combined organic layers were dried over Na_2SO_4 and concentrated to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=10/1 to 4/1) to give 2-(1-benzyl-3-piperidylidene)acetonitrile (7.8 g, crude) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.27 (br s, 5H), 5.17-5.01 (m, 1H), 4.09 (dq, J = 1.5, 7.1 Hz, 1H), 3.65-3.47 (m, 2H), 2.96 (s, 2H), 2.64-2.39 (m, 4H), 2.07-1.95 (m, 1H), 1.84-1.58 (m, 2H). LCMS (ESI, $M+1$): m/z 213.2.

[0000565] Step B. 2-(3-amino-1-benzyl-3-piperidyl)acetonitrile: To a mixture of 2-(1-benzyl-3-piperidylidene)acetonitrile (4 g, 18.8 mmol) in MeOH (6 mL) was added ammonium hydroxide (39.6 g, 339 mmol, 43.5 mL, 30% purity). The mixture was heated to 80 °C and stirred for 18 hours in a sealed tube. The reaction mixture was concentrated under reduced pressure to give 2-(3-amino-1-benzyl-3-piperidyl)acetonitrile (3.5 g, crude) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.31-7.09 (m, 5H), 3.50-3.33 (m, 2H), 2.58-2.11 (m, 8H), 1.76-1.29 (m, 4H). LCMS (ESI, $M+1$): m/z 230.1.

[0000566] Step C. tert-butyl N-[1-benzyl-3-[2-(tert-butoxycarbonylamino)ethyl]-3-piperidyl]carbamate: To a mixture of 2-(3-amino-1-benzyl-3-piperidyl)acetonitrile (4.0 g, 17.4 mmol), tert-butoxycarbonyl tert-butyl carbonate (15.2 g, 69.8 mmol, 16.0 mL) and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (2.07 g, 8.72 mmol) in MeOH (40 mL) was added NaBH_4 (3.35 g, 88.5 mmol) at 0 °C in portions. The reaction mixture was stirred at 27 °C for 3 hours under N_2 atmosphere. The mixture was quenched with saturated NH_4Cl solution at 25 °C and diluted with brine (80 mL). The mixture was extracted with ethyl acetate (80 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 , then filtered and concentrated to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=0 to 20/1) to give tert-butyl N-[1-benzyl-3-[2-(tert-butoxycarbonylamino)ethyl]-3-piperidyl]carbamate (2.2 g, 25% yield) as a colorless liquid. ^1H NMR (400 MHz, CDCl_3) δ = 7.34-7.12 (m, 5H), 5.12-4.99 (m, 1H), 4.78-4.66 (m, 1H), 4.63-4.42 (m, 3H), 3.45-3.31 (m, 2H), 3.18-3.01 (m, 1H), 3.01-2.87 (m, 1H), 2.71-2.60 (m, 2H), 2.26-2.02 (m, 2H), 1.94-1.73 (m, 2H), 1.68-1.47 (m, 2H), 1.40 - 1.36 (m, 23H), 1.36-1.33 (m, 8H). LCMS (ESI, M+1): m/z 434.5.

[0000567] Step D. 3-(2-aminoethyl)-1-benzyl-piperidin-3-amine: A mixture of tert-butyl N-[1-benzyl-3-[2-(tert-butoxycarbonylamino)ethyl]-3-piperidyl]carbamate (500 mg, 1.15 mmol) and HCl/EtOAc (4 M, 7.21 mL) was stirred at 25 °C for 18 hours. The reaction mixture was concentrated under reduced pressure to give 3-(2-aminoethyl)-1-benzyl-piperidin-3-amine (250 mg, crude, HCl) as a white solid. ^1H NMR (400 MHz, METHANOL- d_4) δ = 7.79-7.63 (m, 2H), 7.56-7.29 (m, 3H), 4.57-4.35 (m, 2H), 3.69-3.42 (m, 3H), 3.25-2.99 (m, 4H), 3.24-2.95 (m, 3H), 2.22-2.03 (m, 4H), 2.00-1.94 (m, 3H). LCMS (ESI, M+1): m/z 234.0.

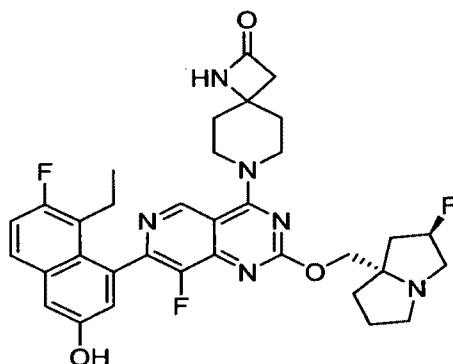
[0000568] Step E. 8-benzyl-1,3,8-triazaspiro[5.5]undecan-2-one: To a mixture of 3-(2-aminoethyl)-1-benzyl-piperidin-3-amine (250 mg, 926 μmol , HCl) in toluene (25 mL) was added TEA (281 mg, 2.78 mmol, 387 μL) and di(imidazol-1-yl)methanone (300 mg, 1.85 mmol). The reaction mixture was stirred at 80 °C for 16 hours. The reaction mixture was concentrated under reduced pressure to remove toluene. The residue was diluted with brine 5 mL and extracted with EtOAc (5 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 and filtered. The mixture was concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150 $\times$ 25mm $\times$ 10 μm ; mobile phase: [water (0.1% formic acid)-ACN]; B%: 2%-32%, 10min) to give 8-benzyl-1,3,8-triazaspiro[5.5]undecan-2-one (70 mg, 269.91 μmol , 29 %

yield) as a white solid. ^1H NMR (400 MHz, METHANOL- d_4) δ = 7.62-7.46 (m, 5H), 7.44-7.27 (m, 1H), 4.48-4.28 (m, 2H), 3.59-3.38 (m, 2H), 3.28-3.12 (m, 2H), 3.09-2.72 (m, 3H), 2.27-2.19 (m, 1H), 2.31-2.16 (m, 1H), 2.14-1.57 (m, 9H). LCMS (ESI, M+1): m/z 260.2.

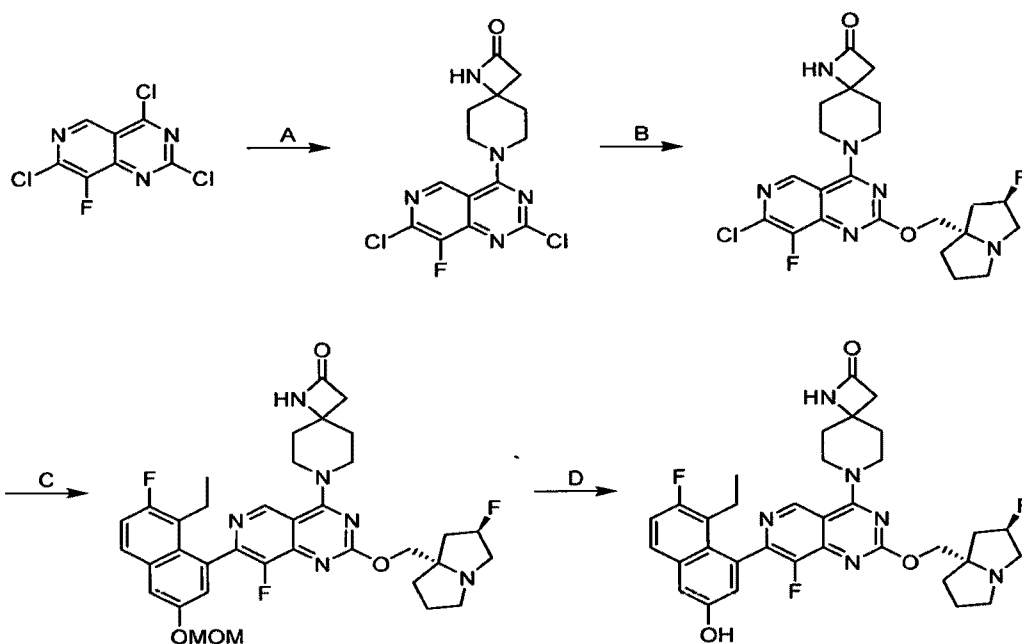
[0000569] Step F. 1,3,8-triazaspiro[5.5]undecan-2-one: To a mixture of 8-benzyl-1,3,8-triazaspiro[5.5]undecan-2-one (70 mg, 270 μmol) in MeOH (1 mL) was added Pd/C (34.5 mg, 32.4 μmol , 10% purity). The reaction mixture was stirred at 25 °C for 16 hours under H_2 (15 psi). The reaction mixture was filtered and concentrated under reduced pressure to give 1,3,8-triazaspiro[5.5]undecan-2-one (45 mg, crude) as a colorless oil. ^1H NMR (400 MHz, METHANOL- d_4) δ = 3.29-3.22 (m, 3H), 3.21-3.03 (m, 4H), 2.92-2.84 (m, 1H), 2.92-2.78 (m, 1H), 2.06-1.83 (m, 5H), 1.82-1.67 (m, 2H). LCMS (ESI, M+1): m/z 170.1.

[0000570] Step G. 8-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,8-triazaspiro[5.5]undecan-2-one: To a mixture of 1,3,8-triazaspiro[5.5]undecan-2-one (45 mg, 266 μmol) and 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (155 mg, 292 μmol) in DMF (3 mL) was added DIEA (103 mg, 798 μmol , 139 μL) and 4Å molecular sieves (100 mg) in one portion at 25 °C. The mixture was heated to 40 °C and stirred for 16 hours under N_2 atmosphere. The mixture was filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150×25mm×10 μm ; mobile phase: [water (0.225% formic acid)-ACN]; B%: 12%-42%, 11 min) to give the title compound (9.06 mg, 5.63% yield) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 9.13 (d, J = 1.9 Hz, 1H), 8.28 (s, 1H), 8.21 - 8.14 (m, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.74 (dd, J = 7.2, 8.2 Hz, 1H), 7.64-7.52 (m, 2H), 7.30 (dd, J = 7.4, 13.6 Hz, 1H), 4.32-4.19 (m, 2H), 4.05-3.80 (m, 3H), 3.79-3.66 (m, 1H), 3.24-3.05 (m, 4H), 2.86-2.75 (m, 2H), 2.04-1.69 (m, 14H), 1.65-1.52 (m, 1H). LCMS (ESI, M+1): m/z 600.2.

EXAMPLE 73



7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one



[0000571] Step A. 7-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one: To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (400 mg, 1.58 mmol), DIEA (614 mg, 4.75 mmol) and 4Å molecular sieves (10 mg) in DCM (8.0 mL) was added 1,7-diazaspiro[3.5]nonan-2-one (244 mg, 1.74 mmol) at -40 °C. The mixture was stirred at -40 °C for 1 hour. The mixture was quenched with water (10 mL) and separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give 7-

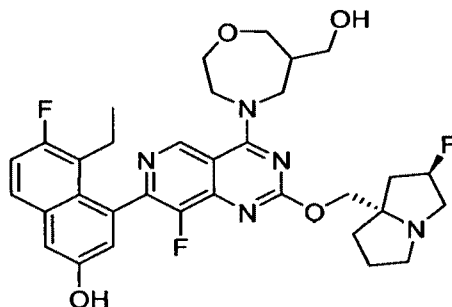
(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one (350 mg, crude) as yellow solid. (M+1). LCMS (ESI, M+1): m/z 356.1.

[0000572] Step B. 7-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one: To a solution of 7-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one (300 mg, 842 μ mol), 4Å molecular sieves (50 mg) and DIEA (326 mg, 2.53 mmol) in dioxane (6.0 mL) was added ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (161 mg, 1.01 mmol). The mixture was stirred at 90 °C for 12 hours. The mixture was quenched with water (10 mL) and extracted with EtOAc (2 $\times$ 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by reversed phase flash chromatography (C18, water (0.1% formic acid) - ACN) affording 7-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one (150 mg, 311 μ mol, 37% yield over two steps, 99.3% purity) as yellow solid. LCMS (ESI, M+1): m/z 479.2.

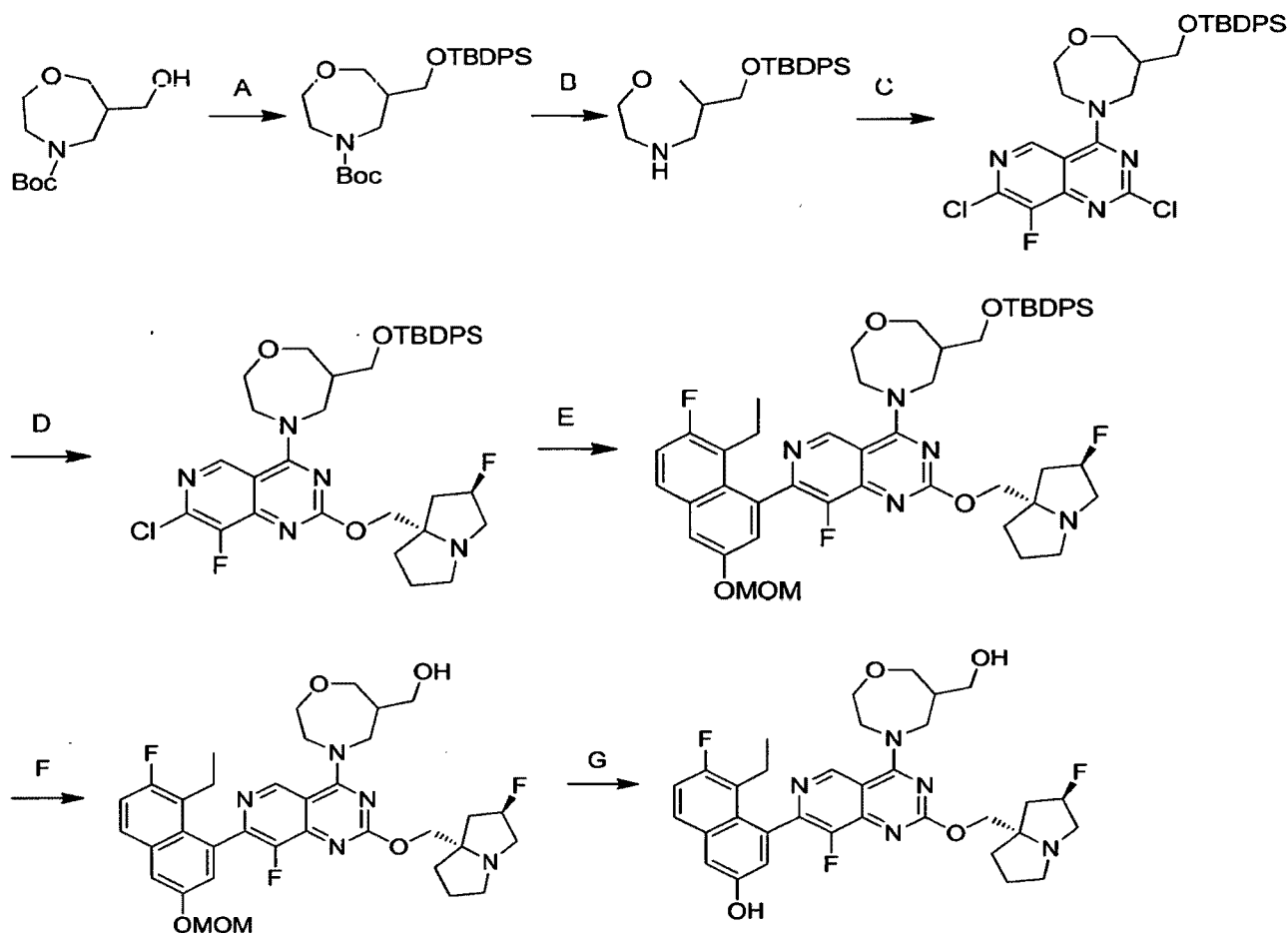
[0000573] Step C. 7-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one: To a mixture of 7-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one (90.0 mg, 188 μ mol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (135 mg, 376 μ mol) and Cs₂CO₃ (1.5 M, 376 μ L) in methoxycyclopentane (2.0 mL) was added cataCXium-A-Pd-G3 (27.4 mg, 37.6 μ mol). The mixture was stirred at 100 °C for 3 hours. The mixture was quenched with water (5 mL) and extracted with EtOAc (2 $\times$ 5 mL). The combined organic layer was dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography (C18, water (0.1 % formic acid)/ACN) affording 7-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one (100 mg, 78% yield) as yellow solid. LCMS (ESI, M+1): m/z 677.3.

[0000574] Step D. 7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one: To a solution of 7-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one (90 mg, 133 μ mol) in DCM (1.5 mL) was added TFA (2.31 g, 20.3 mmol, 1.50 mL). The mixture was stirred at 20 °C for 0.5 hour. The mixture was concentrated. The residue was purified by prep-HPLC [Water s Xbridge 150 $\times$ 25 mm $\times$ 5 μ m; A: water (10mM NH_4HCO_3), B: ACN, B%: 30%-60% over 10min) to afford 7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one (16.7 mg, 19% yield) as white solid. ^1H NMR (400 MHz, $\text{METHANOL-}d_4$): δ 9.06 (s, 1H), 7.68 (dd, J = 6.0, 8.8 Hz, 1H), 7.31 (d, J = 2.8 Hz, 1H), 7.26 (t, J = 9.6 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 5.39-5.23 (m, 1H), 4.79-4.65 (m, 1H), 4.37-4.23 (m, 2H), 4.22-4.13 (m, 1H), 4.09-3.98 (m, 1H), 4.22-3.97 (m, 1H), 3.29-3.16 (m, 1H), 3.29-3.15 (m, 2H), 3.05-2.98 (m, 1H), 2.87 (s, 2H), 2.57-2.42 (m, 1H), 2.41-2.28 (m, 1H), 2.26-2.20 (m, 1H), 2.19-2.04 (m, 5H), 2.03-1.83 (m, 4H), 0.80 (br t, J = 7.6 Hz, 3H); LCMS (ESI, $M+1$): m/z 633.3.

EXAMPLE 74



5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(6-(hydroxymethyl)-1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol



[0000575] Step A. tert-butyl 6-(((tert-butyldiphenylsilyl)oxy)methyl)-1,4-oxazepane-4-carboxylate: To a solution of tert-butyl 6-(hydroxymethyl)-1,4-oxazepane-4-carboxylate (750 mg, 3.24 mmol) in THF (20 mL) were added imidazole (662 mg, 9.73 mmol) and TBDPSCl (1.34 g, 4.86 mmol, 1.25 mL) at 0 °C. The mixture was stirred at 25 °C for 2 hours. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give tert-butyl 6-(((tert-butyldiphenylsilyl)oxy)methyl)-1,4-oxazepane-4-carboxylate (1.10 g, 71% yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.74-7.60 (m, 4H), 7.50-7.32 (m, 6H), 3.85-3.56 (m, 8H), 3.41-3.21 (m, 1H), 3.19-3.01 (m, 1H), 2.41-2.20 (m, 1H), 1.52-1.39 (m, 9H), 1.06 (s, 9H). LCMS (ESI, M-55): m/z 414.2.

[0000576] Step B. 6-(((tert-butyldiphenylsilyl)oxy)methyl)-1,4-oxazepane: To a solution of tert-butyl 6-(((tert-butyldiphenylsilyl)oxy)methyl)-1,4-oxazepane-4-carboxylate (900 mg, 1.92 mmol) in DCM (5 mL) was added TFA (13.9 g, 121 mmol, 9.00 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with water 10 mL and pH was adjusted to 8 with NaHCO₃. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na₂SO₄ and filtered. The mixture was concentrated to give 6-(((tert-butyldiphenylsilyl)oxy)methyl)-1,4-oxazepane (700 mg, crude) as yellow solid. LCMS (ESI, M+1): m/z 370.3.

[0000577] Step C. 6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane: To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (500 mg, 1.98 mmol) in DCM (10 mL) were added DIEA (768 mg, 5.94 mmol, 1.03 mL) and 6-(((tert-butyldiphenylsilyl)oxy)methyl)-1,4-oxazepane (439 mg, 1.19 mmol) at -40 °C. The mixture was stirred at -40 °C for 0.5 hour. The reaction mixture was diluted with water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give 6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane (700 mg, 60% yield); Yellow solid. LCMS (ESI, M+1): m/z 585.2.

[0000578] Step D. 6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane: To a solution of 6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane (680 mg, 1.16 mmol) in dioxane (8 mL) were added DIEA (450 mg, 3.48 mmol), 4Å molecular sieves (300 mg) and ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (370 mg, 2.32 mmol). The mixture was stirred at 95°C for 12 hours. After completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with DMF (10 mL) at 20 °C for 1 hour to give 6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane (550 mg, 63% yield) as yellow solid. LCMS (ESI, M+1): m/z 708.4.

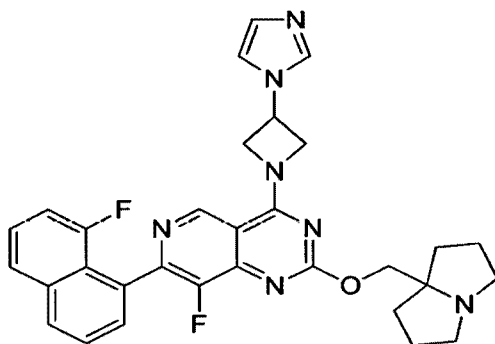
[0000579] Step E. 6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane: To a solution of 6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane (500 mg, 706 μ mol) and 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (381 mg, 1.06 mmol) in methoxycyclopentane (8 mL) were added K_3PO_4 (1.5 M, 1.41 mL) and cataCXium-A-Pd-G3 (77.1 mg, 106 μ mol). The mixture was stirred at 90 °C for 2 hours. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 $\times$ 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give 6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane (500 mg, 67% yield) as yellow solid. LCMS (ESI, M+1): m/z 906.5.

[0000580] Step F. (4-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepan-6-yl)methanol: To a solution of 6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane (300 mg, 285 μ mol, 86% purity) in DMF (5 mL) was added CsF (432 mg, 2.85 mmol). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was filtered and purified by reversed phase flash chromatography (C18, 0.1% formic acid in water, 0-60% ACN) to give (4-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepan-6-yl)methanol (180 mg, 91% yield); Yellow solid. LCMS (ESI, M+1): m/z 668.3.

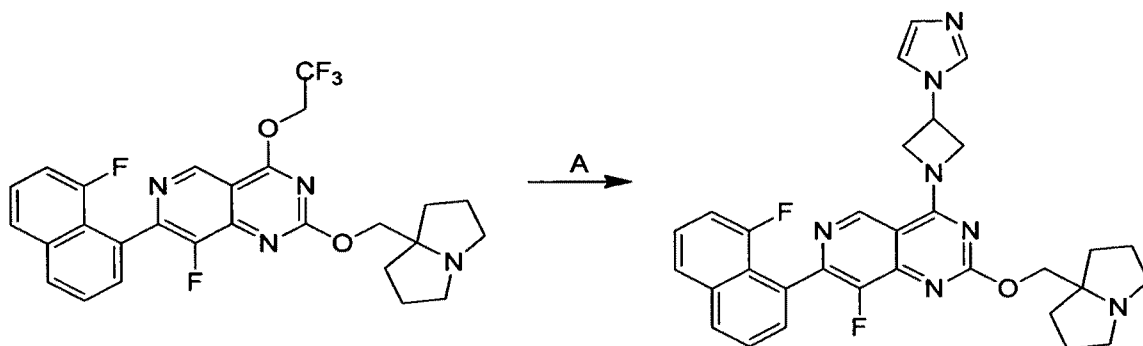
[0000581] Step G. 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(6-(hydroxymethyl)-1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol: To a solution of (4-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-

d]pyrimidin-4-yl)-1,4-oxazepan-6-yl)methanol (100 mg, 150 μ mol) in ACN (1 mL) was added HCl•dioxane (4.0 M, 2 mL). The mixture was stirred at 25 °C for 0.5 hour. After The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: water s Xbridge 150×25mm×5 μ m; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 32%-62%, 10min) to give 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(6-(hydroxymethyl)-1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol (58.0 mg, 62% yield); White solid. ¹H NMR (400 MHz, METHANOL-d₄) δ 9.19 (d, *J* = 4.4 Hz, 1H), 7.67 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.06 (dd, *J* = 2.4, 10.0 Hz, 1H), 5.41-5.19 (m, 1H), 4.59 (br s, 1H), 4.46-4.22 (m, 3H), 4.16-3.91 (m, 4H), 3.89-3.74 (m, 1H), 3.70-3.55 (m, 3H), 3.36-3.12 (m, 3H), 3.05-2.96 (m, 1H), 2.56-2.42 (m, 2H), 2.40-2.07 (m, 4H), 2.04-1.85 (m, 3H), 0.86-0.73 (m, 3H). LCMS (ESI, M+1): *m/z* 624.4.

EXAMPLE 75



4-(3-(1H-imidazol-1-yl)azetidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine



DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME 1 DE 3
CONTENANT LES PAGES 1 À 251

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME 1 OF 3
CONTAINING PAGES 1 TO 251

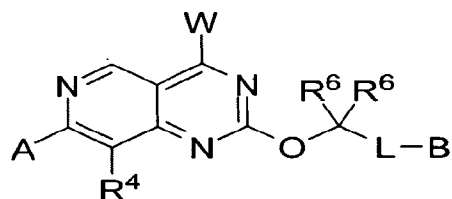
NOTE: For additional volumes, please contact the Canadian Patent Office

NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

WHAT IS CLAIMED IS:

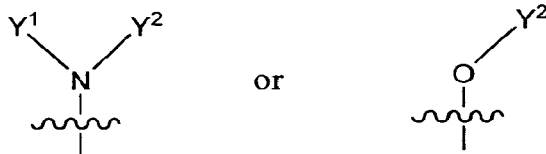
1. A compound of Formula (I):



Formula (I)

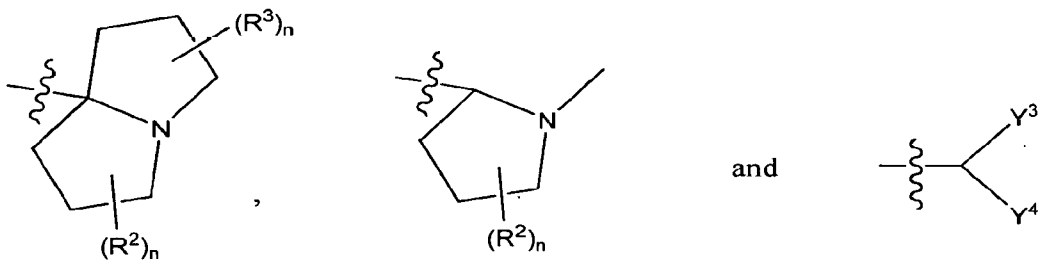
or a pharmaceutically acceptable salt thereof, wherein:

W is:



A is aryl or heteroaryl, wherein the aryl or the heteroaryl is optionally substituted with 1-4 R^1 ;

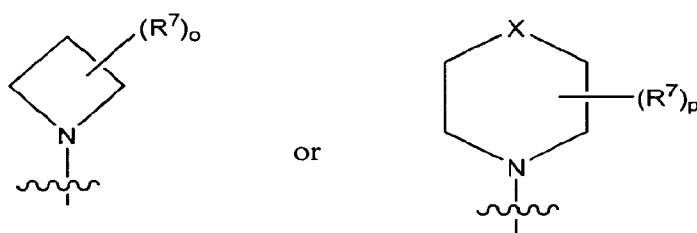
B is selected from:



Y^1 is hydrogen, L-hydroxy optionally substituted with 1-4 R^8 , L-alkoxy optionally substituted with 1-4 R^8 , halogen, L-C3-C6 cycloalkyl optionally substituted with 1-4 R^9 , L-heteroaryl optionally substituted with 1-4 R^8 , L-aryl optionally substituted with 1-4 R^8 , L-C(O)-NH₂, and L-heterocycle substituted with 1-2 oxo (=O) or oxo-containing substituent, and optionally further substituted with 1-2 R^8 ;

Y^2 is hydrogen or C1-C4 alkyl;

or Y^1 and Y^2 join to form:

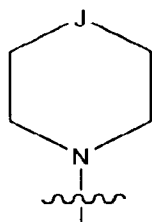


where X is selected from: a bond, -S-, -O-, -N< bound to a fused ring, -CH₂-, -CH₂-N-, -CH₂-N-CH₂-, -CH₂-CH₂-CH₂-, -CH₂-CH₂-, -O-CH₂- and -S-CH₂-;

Y^3 is hydrogen or C1-C4 alkyl;

Y^4 is hydrogen or C1-C4 alkyl;

or Y^3 and Y^4 join to form:



where J is selected from: a bond, -O-, -NH-, -CH₂-, -C(C1-C3 alkyl)₂-, -CH(C1-C3alkyl)- and -N(C1-C3 alkyl)-;

each R^1 is independently halogen, cyano, hydroxy, C1-C4 alkyl, -S-C1-C3 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C2-C4 hydroxyalkynyl, C1-C3 cyanoalkyl, triazolyl, C1-C3 haloalkyl, -O-C1-C3

haloalkyl, -S-C1-C3 haloalkyl, C1-C3 alkoxy, hydroxyC1-C3 alkyl, $-\text{CH}_2\text{C}(=\text{O})\text{N}(\text{R}^5)_2$, -C3-C4 alkynyl(NR^5)₂, $-\text{N}(\text{R}^5)_2$, deuterioC2-C4 alkynyl, (C1-C3 alkoxy)haloC1-C3 alkyl-, or C3-C6 cycloalkyl wherein said C3-C6 cycloalkyl is optionally substituted with halogen or C1-C3 alkyl;

each R^2 is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, $\text{HC}(=\text{O})-$, $-\text{L}-\text{OC}(\text{O})\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, or $-\text{CO}_2\text{N}(\text{R}^5)_2$;

each R^3 is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, $\text{HC}(=\text{O})-$, $-\text{L}-\text{OC}(\text{O})\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, or $-\text{CO}_2\text{N}(\text{R}^5)_2$;

each R^4 is independently hydrogen, halogen or C1 – C3 alkyl;

each R^5 is independently hydrogen or C1-C3 alkyl, or two R^5 join to form cycloalkyl or heterocycle;

each R^6 is independently hydrogen, hydroxy, C1-C4 hydroxyalkyl or heteroaryl,

or two R^6 join to form C3-C6 cycloalkyl or heterocycle;

each R^7 is independently hydrogen, C1-C3 alkyl, hydroxy, halogen, C1-C3 haloalkyl, $-\text{L}-\text{NH}_2$, $-\text{NH}(\text{C1-C3 alkyl})$, $-\text{N}(\text{C1-C3 alkyl})_2$, oxo ($=\text{O}$), $-\text{O}-(\text{C1-C3 alkyl})$, $-(\text{C1-C3 alkyl})-\text{OH}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{O}(\text{C1-C3 alkyl})$, $-\text{C}(\text{O})\text{N}(\text{R}^{10})_2$, $-\text{NHC}(\text{O})\text{H}$, $-\text{CN}$, aryl, $-(\text{CH}_2)_{1-2}\text{S}(\text{O})_2\text{N}(\text{R}^{10})_2$, $-\text{NH}-\text{S}(\text{O})_2\text{N}(\text{R}^{10})_2$, $-\text{O}-\text{S}(\text{O})_2\text{N}(\text{R}^{10})_2$, $\text{S}(\text{O})_2\text{R}^{10}$, or heteroaryl or heterocycle optionally independently substituted with 1-2 substituents independently selected from C1-C3 alkyl, $-\text{CN}$ and $\text{C}(\text{O})\text{NH}_2$,

two R^7 on the same atom optionally join to form a spirocyclic ring selected from C3-C6 cycloalkyl and heterocycle, where said spirocyclic ring is optionally substituted with 1-4 substituents independently selected from oxo ($=\text{O}$), halogen, hydroxy, C1-C3 alkyl and $-\text{O}-(\text{C1-C3 alkyl})$,

two R^7 on adjacent atoms optionally join to form a bond or a fused ring selected from C3-C6 cycloalkyl optionally substituted with 1-4 R^8 , heteroaryl optionally substituted with 1-4 R^8 , aryl optionally substituted with 1-4 R^8 , and heterocycle optionally substituted with 1-4 R^8 , and

two R^7 on non-adjacent atoms optionally join to form a 1-2 carbon bridge;

each R^8 is independently C1-C3 alkyl, hydroxy, halogen, $-N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, oxo ($=O$), $-O-(C1-C3 \text{ alkyl})$, $-(C1-C3 \text{ alkyl})-OH$, $-C(O)OH$, $-C(O)O(C1-C3 \text{ alkyl})$, $-C(O)N(R^{10})_2$, heteroaryl or $-CN$;

each R^9 is independently C1-C3 alkyl, hydroxy, halogen, oxo ($=O$), $-O-(C1-C3 \text{ alkyl})$, $-(C1-C3 \text{ alkyl})-OH$, $-C(O)OH$, $-C(O)O(C1-C3 \text{ alkyl})$, $-C(O)NH_2$, $-C(O)NH(C1-C3 \text{ alkyl})$, $-C(O)N(C1-C3 \text{ alkyl})_2$ or $-CN$;

each R^{10} is independently hydrogen, halogen, C1-C3 alkyl, or two R^{10} join to form cycloalkyl or heterocycle optionally substituted with 1-2 C1-C3 alkyl;

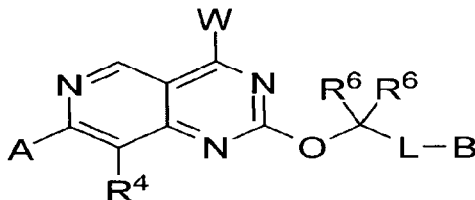
each L is independently a bond, $-C1-C4 \text{ alkyl}-$, $-C1-C4 \text{ alkyl}-NH-$, $-NH-$, $-N(C1-C3 \text{ alkyl})-$ or cyclopropyl- CH_2- ;

each n is 0-3;

o is 1-6; and

p is 1-8.

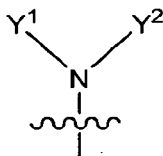
2. A compound of Formula (I):



Formula (IA)

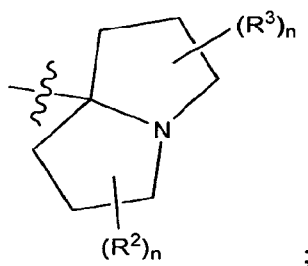
or a pharmaceutically acceptable salt thereof, wherein:

W is:

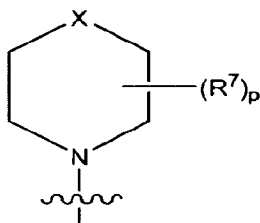


A is naphthyl optionally substituted with 1-4 R^1 ;

B is from :



Y^1 and Y^2 join to form:



where X is selected from: $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$ and $-\text{OCH}_2-$;

each R^1 is independently halogen, cyano, hydroxy, C1-C4 alkyl, -S-C1-C3 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C2-C4 hydroxyalkynyl, C1-C3 cyanoalkyl, triazolyl, C1-C3 haloalkyl, -O-C1-C3 haloalkyl, -S-C1-C3 haloalkyl, C1-C3 alkoxy, hydroxyC1-C3 alkyl, $-\text{CH}_2\text{C}(=\text{O})\text{N}(\text{R}^5)_2$, -C3-C4 alkynyl(NR^5)₂, $-\text{N}(\text{R}^5)_2$, deuterioC2-C4 alkynyl, (C1-C3 alkoxy)haloC1-C3 alkyl-, or C3-C6 cycloalkyl wherein said C3-C6 cycloalkyl is optionally substituted with halogen or C1-C3 alkyl;

each R^2 is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, $\text{HC}(=\text{O})-$, $-\text{L-OC}(\text{O})\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, or $-\text{CO}_2\text{N}(\text{R}^5)_2$;

each R^3 is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, $\text{HC}(=\text{O})-$, $-\text{L-OC}(\text{O})\text{N}(\text{R}^5)_2$, $-\text{CO}_2\text{R}^5$, or $-\text{CO}_2\text{N}(\text{R}^5)_2$;

each R^4 is independently hydrogen, halogen or C1 – C3 alkyl;

each R^5 is independently hydrogen or C1-C3 alkyl, or two R^5 join to form cycloalkyl or heterocycle;

each R^6 is independently hydrogen, hydroxy, C1-C4 hydroxyalkyl or heteroaryl,

or two R^6 join to form C3-C6 cycloalkyl or heterocycle;

each R^7 is independently hydrogen, C1-C3 alkyl, hydroxy, halogen, C1-C3 haloalkyl, $-L-NH_2$, $-NH(C1-C3 \text{ alkyl})$, $-N(C1-C3 \text{ alkyl})_2$, oxo ($=O$), $-O-(C1-C3 \text{ alkyl})$, $-(C1-C3 \text{ alkyl})-OH$, $-C(O)OH$, $-C(O)O(C1-C3 \text{ alkyl})$, $-C(O)N(R^{10})_2$, $-NHC(O)H$, $-CN$, aryl, $-(CH_2)_{1-2}S(O)_2N(R^{10})_2$, $-NH-S(O)_2N(R^{10})_2$, $-O-S(O)_2N(R^{10})_2$, $S(O)_2R^{10}$, or heteroaryl or heterocycle optionally independently substituted with 1-2 substituents independently selected from C1-C3 alkyl, $-CN$ and $C(O)NH_2$,

two R^7 on the same atom optionally join to form a spirocyclic ring selected from C3-C6 cycloalkyl and heterocycle, where said spirocyclic ring is optionally substituted with 1-4 substituents independently selected from oxo ($=O$), halogen, hydroxy, C1-C3 alkyl and $-O-(C1-C3 \text{ alkyl})$,

two R^7 on adjacent atoms optionally join to form a bond or a fused ring selected from C3-C6 cycloalkyl optionally substituted with 1-4 R^8 , heteroaryl optionally substituted with 1-4 R^8 , aryl optionally substituted with 1-4 R^8 , and heterocycle optionally substituted with 1-4 R^8 , and

two R^7 on non-adjacent atoms optionally join to form a 1-2 carbon bridge;

each R^8 is independently C1-C3 alkyl, hydroxy, halogen, $-N(R^{10})_2$, $-N(R^{10})C(O)R^{10}$, oxo ($=O$), $-O-(C1-C3 \text{ alkyl})$, $-(C1-C3 \text{ alkyl})-OH$, $-C(O)OH$, $-C(O)O(C1-C3 \text{ alkyl})$, $-C(O)N(R^{10})_2$, heteroaryl or $-CN$;

each R^9 is independently C1-C3 alkyl, hydroxy, halogen, oxo ($=O$), $-O-(C1-C3 \text{ alkyl})$, $-(C1-C3 \text{ alkyl})-OH$, $-C(O)OH$, $-C(O)O(C1-C3 \text{ alkyl})$, $-C(O)NH_2$, $-C(O)NH(C1-C3 \text{ alkyl})$, $-C(O)N(C1-C3 \text{ alkyl})_2$ or $-CN$;

each R^{10} is independently hydrogen, halogen, C1-C3 alkyl, or two R^{10} join to form cycloalkyl or heterocycle optionally substituted with 1-2 C1-C3 alkyl;

each L is independently a bond, -C1-C4 alkyl-, -C1-C4 alkyl-NH-, -NH-, -N(C1-C3 alkyl)- or cyclopropyl-CH₂-;

each n is 0-3;

o is 1-6; and

p is 1-8.

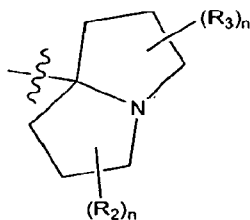
3. The compound or salt of claim 2, wherein each R1 is independently selected from halogen, hydroxy, C1-C3 alkoxy and C1-C4 alkyl.

4. The compound or salt of claim 2, wherein each R2, if present, is selected from hydrogen and halogen, and wherein each R3, if present, is selected from hydrogen and halogen.

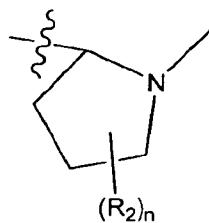
5. The compound or salt of claim 2, wherein each R7 is independently selected from hydrogen, C1-C4 alkyl, hydroxy, C1-C3 alkoxy, and wherein two R7 on non-adjacent atoms optionally join to form a 1-2 carbon bridge.

6. The compound or salt of claim 2, wherein each R6 is independently hydrogen or hydroxy.

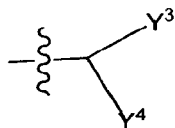
7. The compound or salt of claim 1, wherein B is:



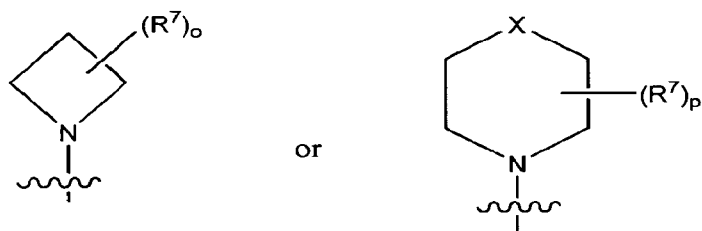
8. The compound or salt of claim 1, wherein B is:



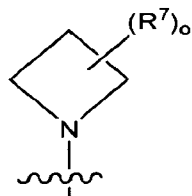
9. The compound or salt of claim 1, wherein B is:



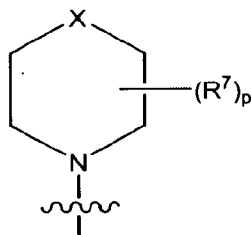
10. The compound or salt of any of claims 1-3, wherein Y¹ and Y² join to form:



11. The compound or salt of claim 4, wherein Y¹ and Y² join to form:



12. The compound or salt of claim 4, wherein Y¹ and Y² join to form:



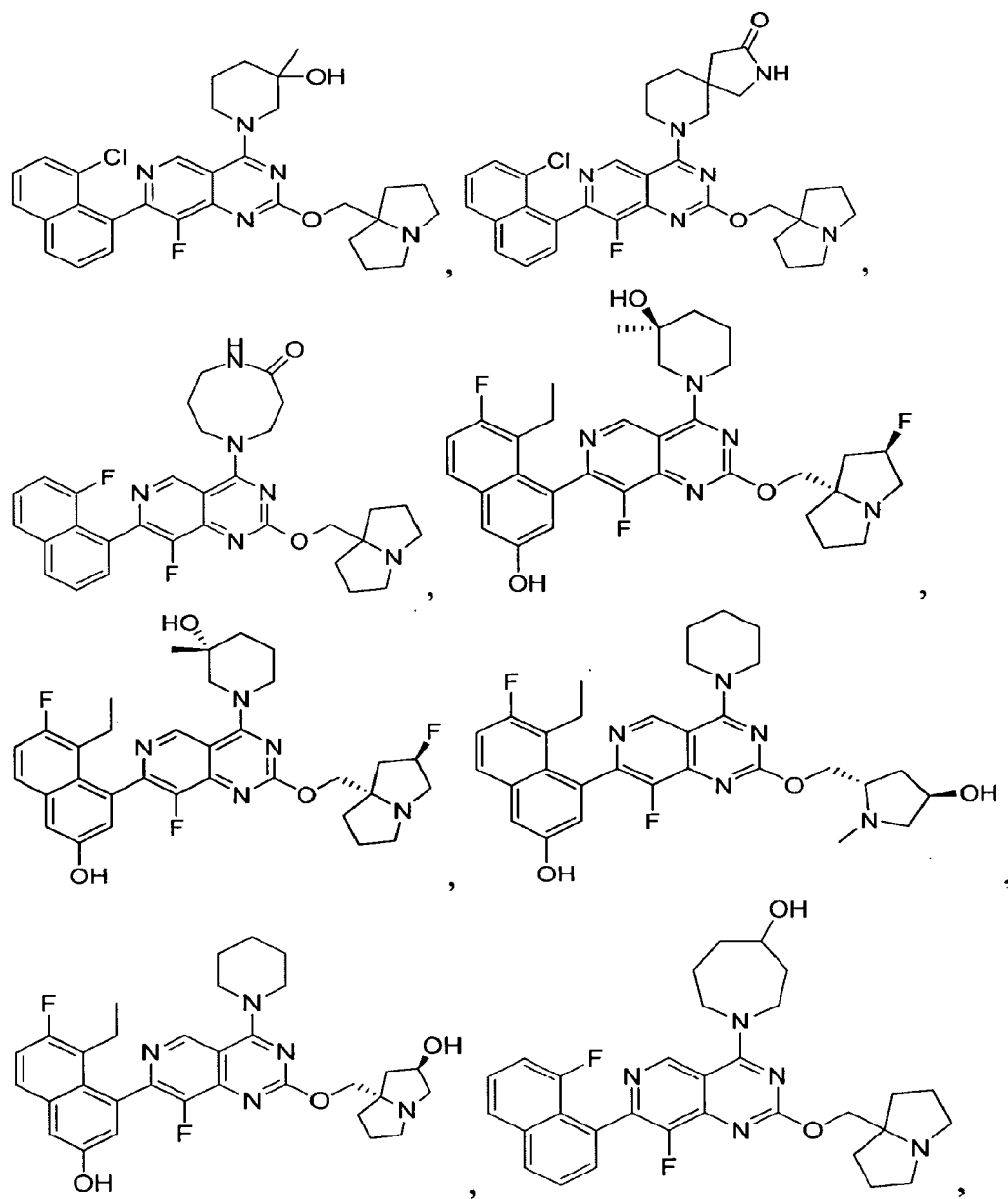
13. The compound or salt of any of claims 1-6, wherein A is naphthyl.

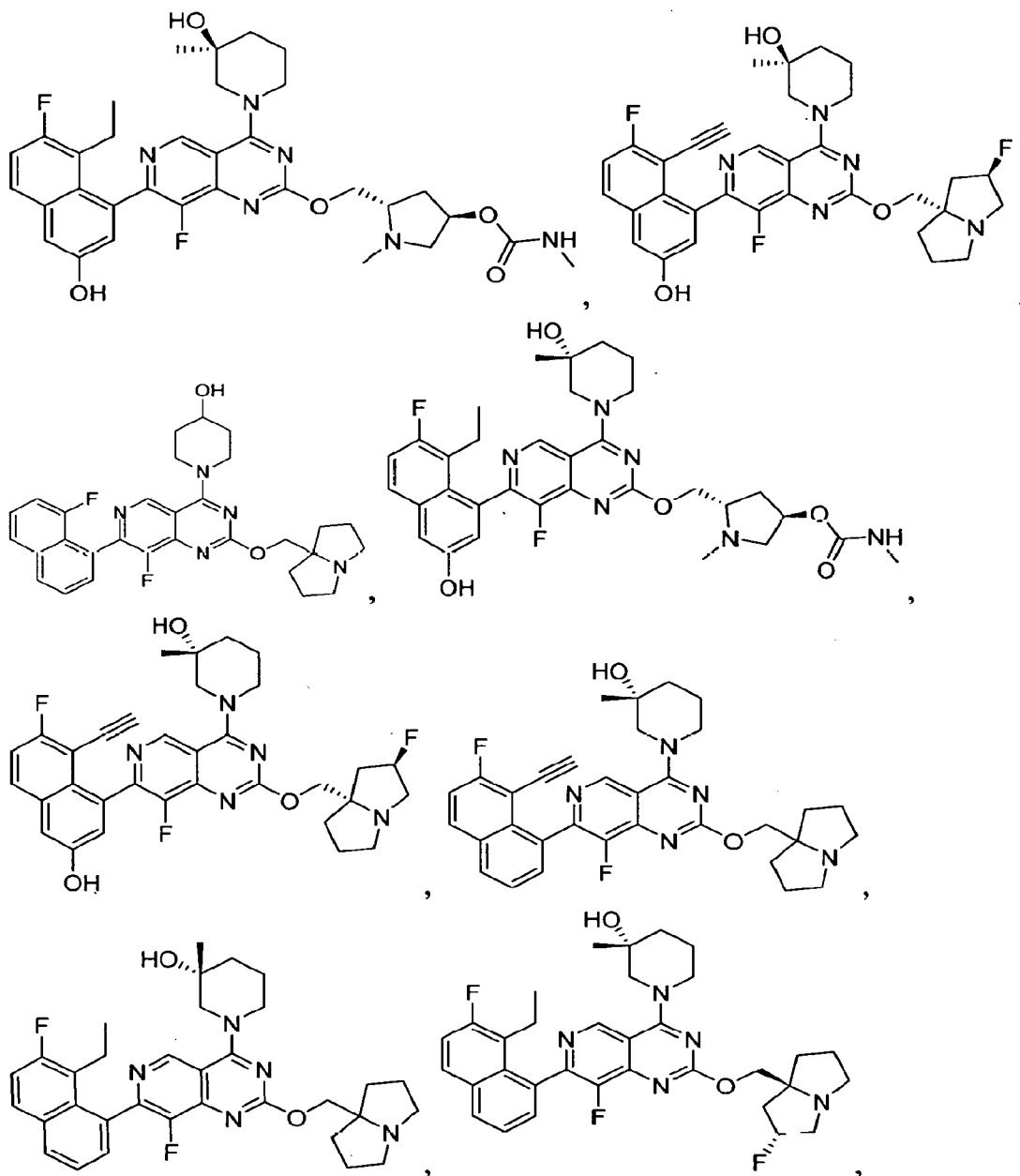
14. The compound or salt of any of claims 1-6, wherein A is indazolyl.

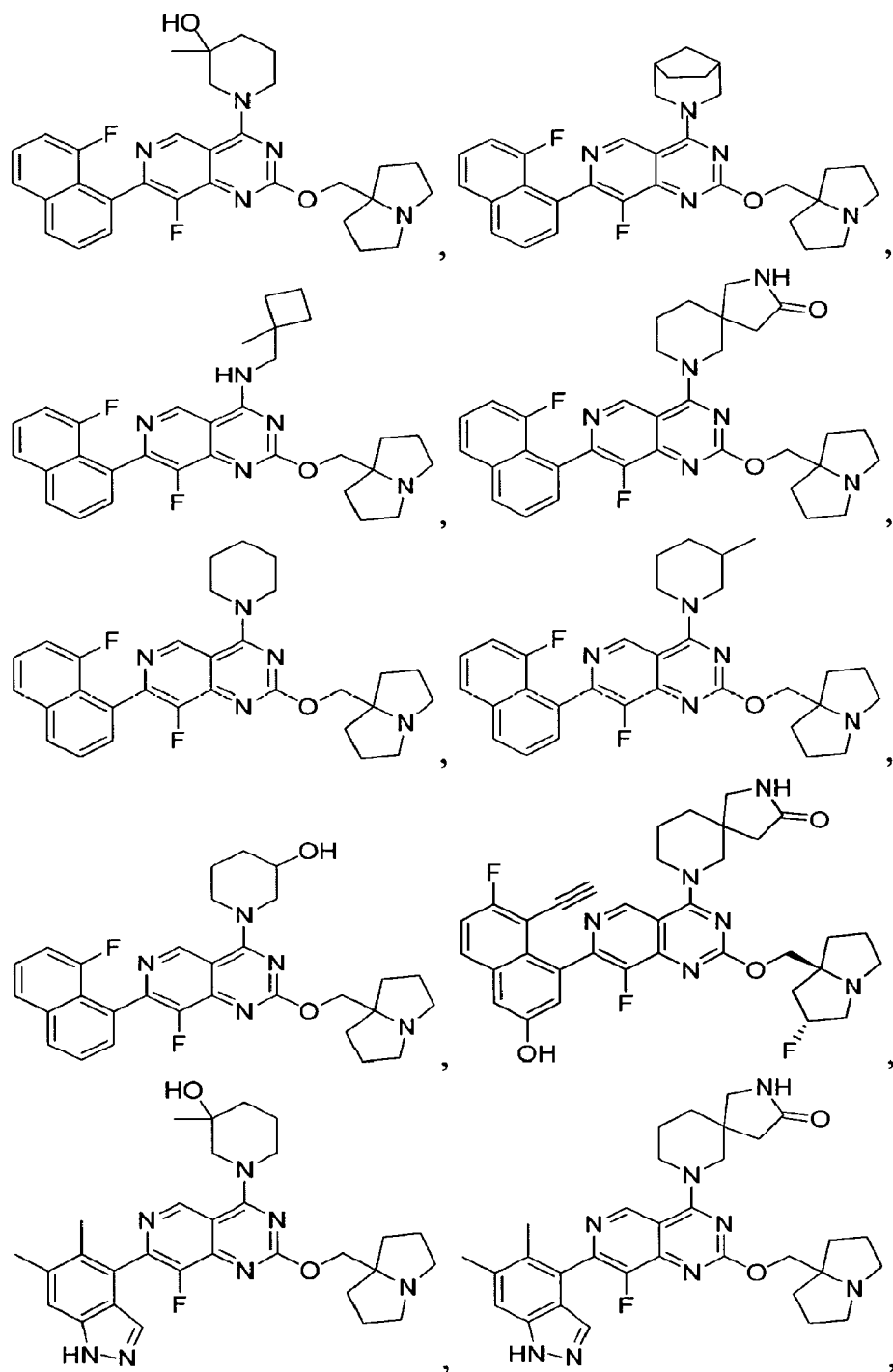
15. The compound or salt of any of claims X, wherein A is phenyl.
16. The compound or salt of any of claims X, wherein A is pyridyl.
17. The compound or salt of any of claims 1-6, wherein at least one R¹ is C1-C4 alkyl.
18. The compound or salt of any of claims 1-6, wherein at least one R¹ is halogen
19. The compound or salt of claim 10, wherein said halogen is a fluorine.
20. The compound or salt of any of claims 1-6, wherein at least one R¹ is hydroxy.
21. The compound or salt of any of claims 1-6, wherein one R² is C1-C4 alkyl.
22. The compound or salt of any of claims 1-6, wherein at least one R² is halogen.
23. The compound or salt of claim 14, wherein said halogen is a fluorine.
24. The compound or salt of any of claims 1-6, wherein at least one R² is hydroxy.
25. The compound or salt of any of claims 1-6, wherein at least one R³ is C1-C4 alkyl.
26. The compound or salt of any of claims 1-6, wherein at least one R³ is halogen.
27. The compound or salt of claim 18, wherein said halogen is fluorine.
28. The compound or salt of any of claims 1-6, wherein at least one R³ is hydroxy.
29. The compound or salt of any of claims 1-6, wherein R⁴ is halogen.
30. The compound or salt of claim 21, wherein said halogen is fluorine.
31. The compound or salt of any of claims 1-6, wherein at least one R⁵ is C1-C4 alkyl.
32. The compound or salt of any of claims 1-6, wherein at least one R⁵ is hydrogen.
33. The compound or salt of any of claims 1-6, wherein one or both R⁶ are C1-C4 alkyl.
34. The compound or salt of any of claims 1-6, wherein one or both R⁶ are hydrogen.

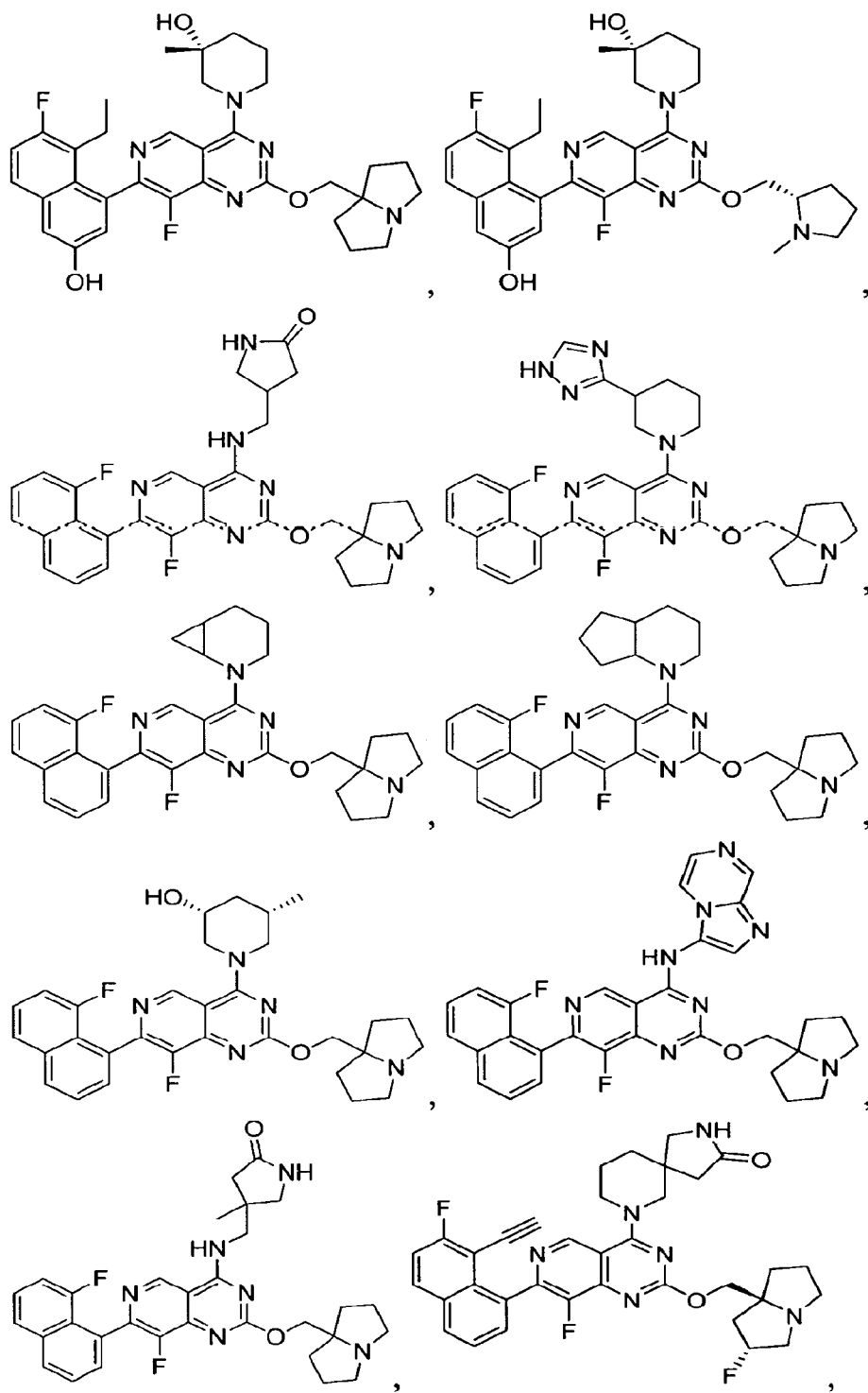
35. The compound or salt of any of claims 1-6, wherein two R⁶ join to form C3-C6 cycloalkyl or heterocycle.
36. The compound or salt of any of claims 1-6, wherein Y¹ is L-C3-C6 cycloalkyl, L-heteroaryl, L-aryl, or L-heterocycle, where L is a bond, C1-C4 alkyl, NH or N(C1-C3) alkyl.
37. The compound or salt of claim 27, wherein Y¹ is L-heteroaryl, where said heteroaryl is thietane dioxide, iso-thiazolidine dioxide, imidazopyrazine, pyridine or pyrimidine.
38. The compound or salt of claim 27, wherein Y¹ is L-C3-C6 cycloalkyl.
39. The compound or salt of claim 30, wherein the cycloalkyl is cyclobutane, cyclopentane, cyclohexane or cycloheptane.
40. The compound or salt of claim 27, wherein Y¹ is L-heterocycle.
41. The compound or salt of claim 32, wherein the heterocycle is pyrrolidinone.
42. In certain embodiments of the invention Y² is hydrogen.
43. The compound or salt of any of claims 1-6, wherein Y² is C1-C4 alkyl;
44. The compound or salt of any of claims 1-6, wherein at least one R⁸ is C1-C4 alkyl.
45. The compound or salt of any of claims 1-6, wherein at least one R⁸ is hydroxy or C1-C3 alkyl-hydroxy.
46. The compound or salt of any of claims 1-6, wherein one or two R⁸ are oxo (=O).
47. The compound or salt of any of claims 1-6, wherein at least one R⁸ is aryl or heteroaryl.
48. The compound or salt of any of claims 1-6, wherein at least one R⁸ is C(O)OH.
49. The compound or salt of any of claims 1-6, wherein at least one R⁸ is -C(O)NH₂, -C(O)NH(C1-C3 alkyl) or -C(O)N(C1-C3 alkyl)₂.
50. The compound or salt of any of claims 1-6, wherein at least one R⁸ is -NH₂, -NH(C1-C3 alkyl); -N(C1-C3 alkyl)₂.

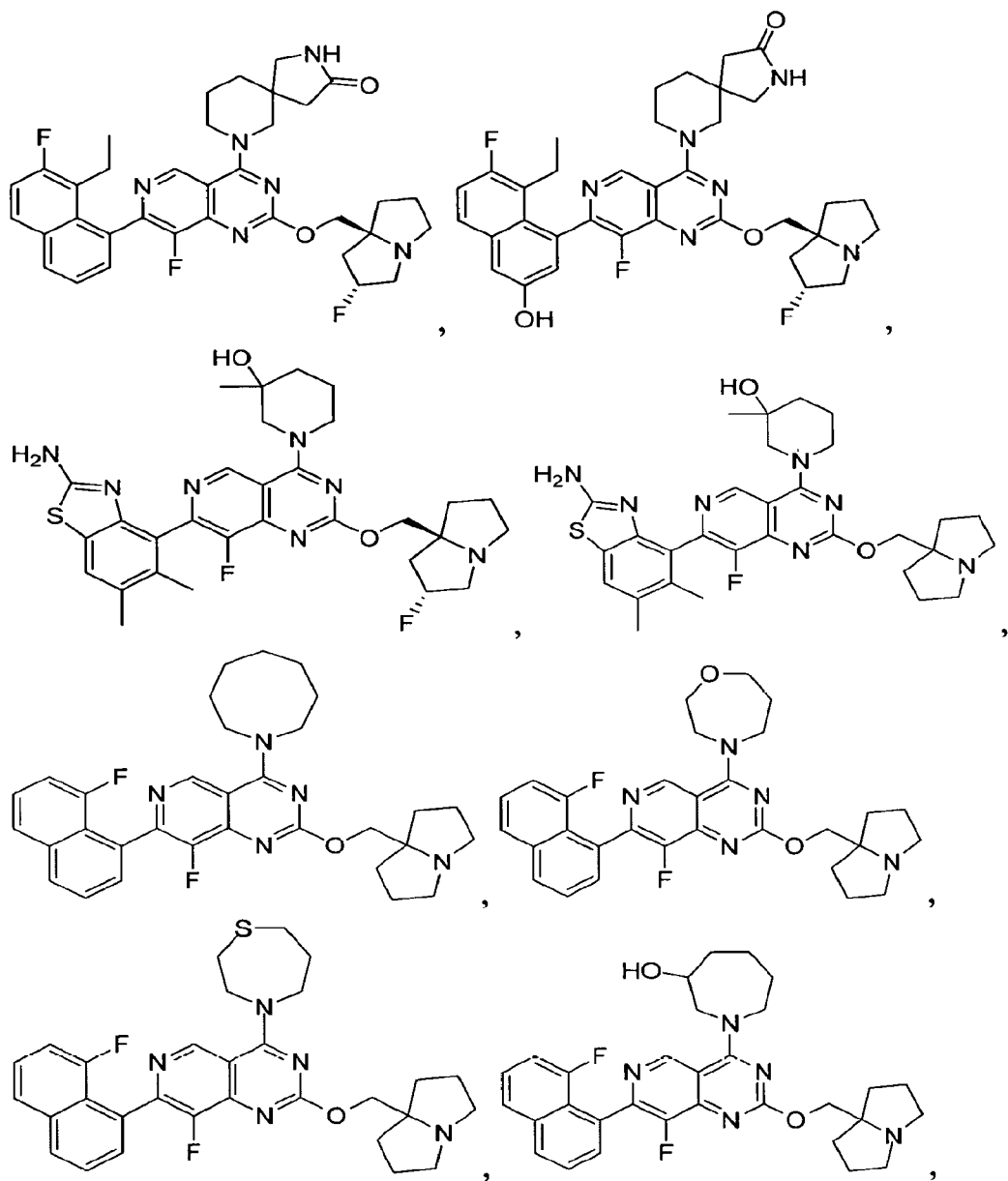
51. The compound or salt of any of claims 1-6, wherein at least one R^9 is C1-C4 alkyl.
52. The compound or salt of any of claims 1-6, wherein at least one R^9 is hydroxy or C1-C3 alkyl-hydroxy.
53. The compound or salt of any of claims 1-6, wherein one or two R^9 is oxo (=O).
54. The compound or salt of any of claims 1-6, wherein at least one R^9 is aryl or heteroaryl.
55. The compound or salt of any of claims 1-6, wherein at least one R^9 is C(O)OH.
56. The compound or salt of any of claims 1-6, wherein at least one R^9 is -C(O)NH₂, -C(O)NH(C1-C3 alkyl) or -C(O)N(C1-C3 alkyl)₂.
57. The compound or salt of any of claims 1-6, wherein Y^1 and Y^2 join to form piperidine, azepane, azocane, thiazepine, diazepane, oxazepane, azetidine, pyrrolidine, piperazine bound to a fused ring via nitrogen or thiomorpholine.
58. The compound or salt of any of claims 1-6, wherein two R^7 on the same atom join to form a spirocyclic ring selected from C3-C6 cycloalkyl and heterocycle, where said spirocyclic ring is optionally substituted with one or more substituents selected from oxo (=O), halogen, hydroxy, C1-C3 alkyl and -O-(C1-C3 alkyl).
59. The compound or salt of any of claims 1-6, wherein two R^7 on adjacent atoms join to form a bond or a fused ring selected from C3-C6 cycloalkyl optionally substituted with 1-4 R^8 ; heteroaryl optionally substituted with 1-4 R^8 ; aryl optionally substituted with 1-4 R^8 , and heterocycle optionally substituted with 1-4 R^8 .
60. The compound or salt of any of claims 1-6, wherein two R^7 on non-adjacent atoms join to form a 1-2 carbon bridge.
61. A compound selected from:

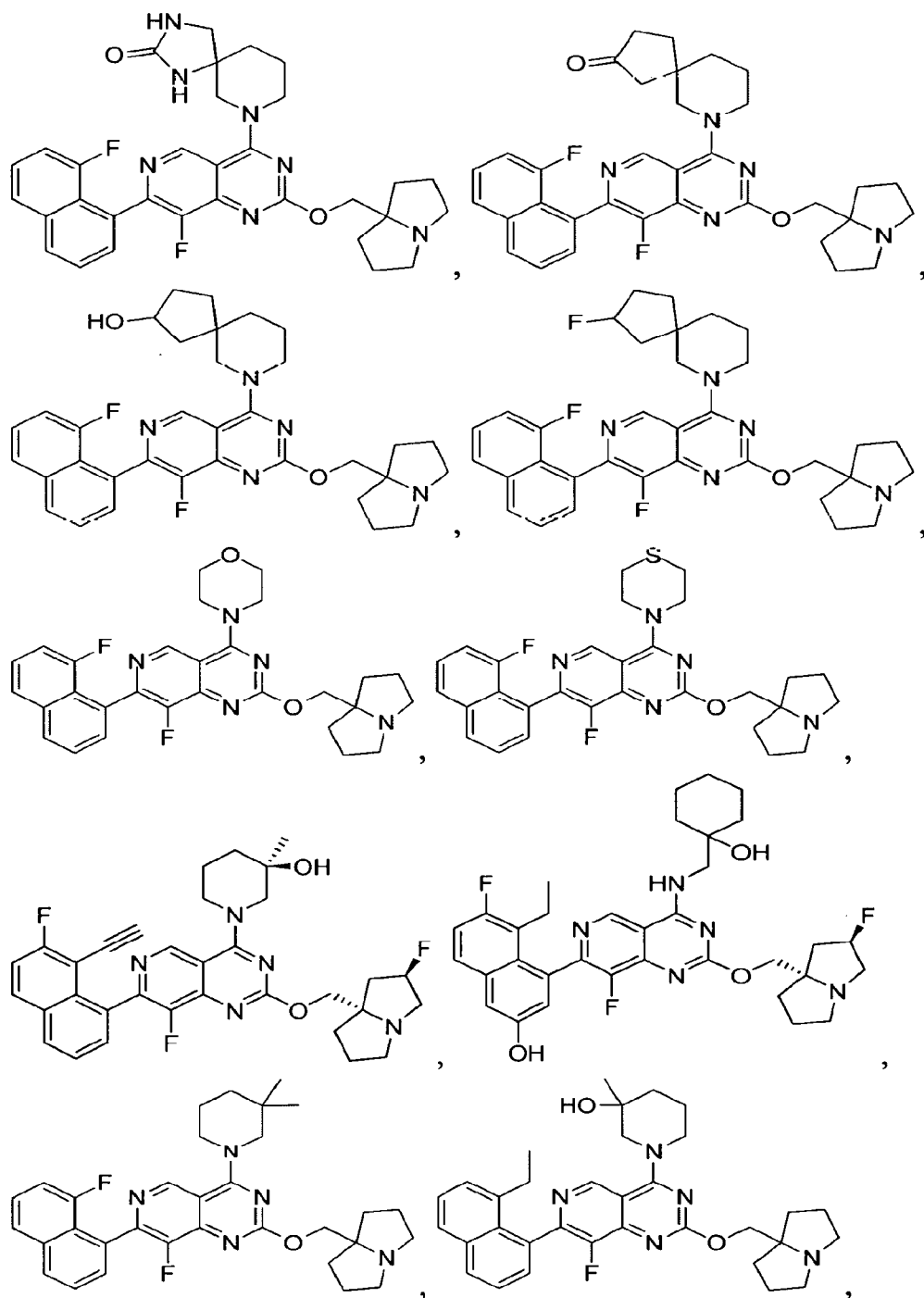


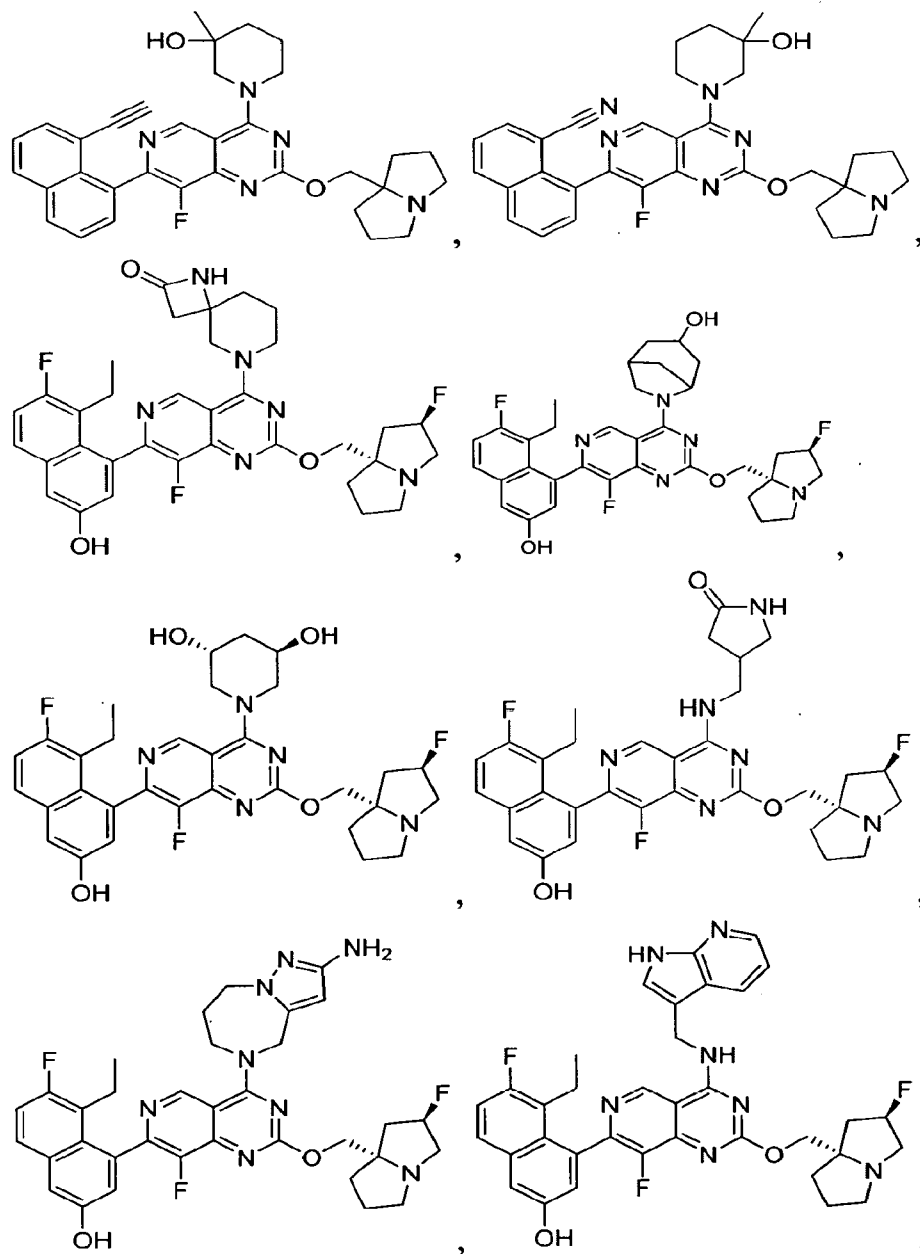


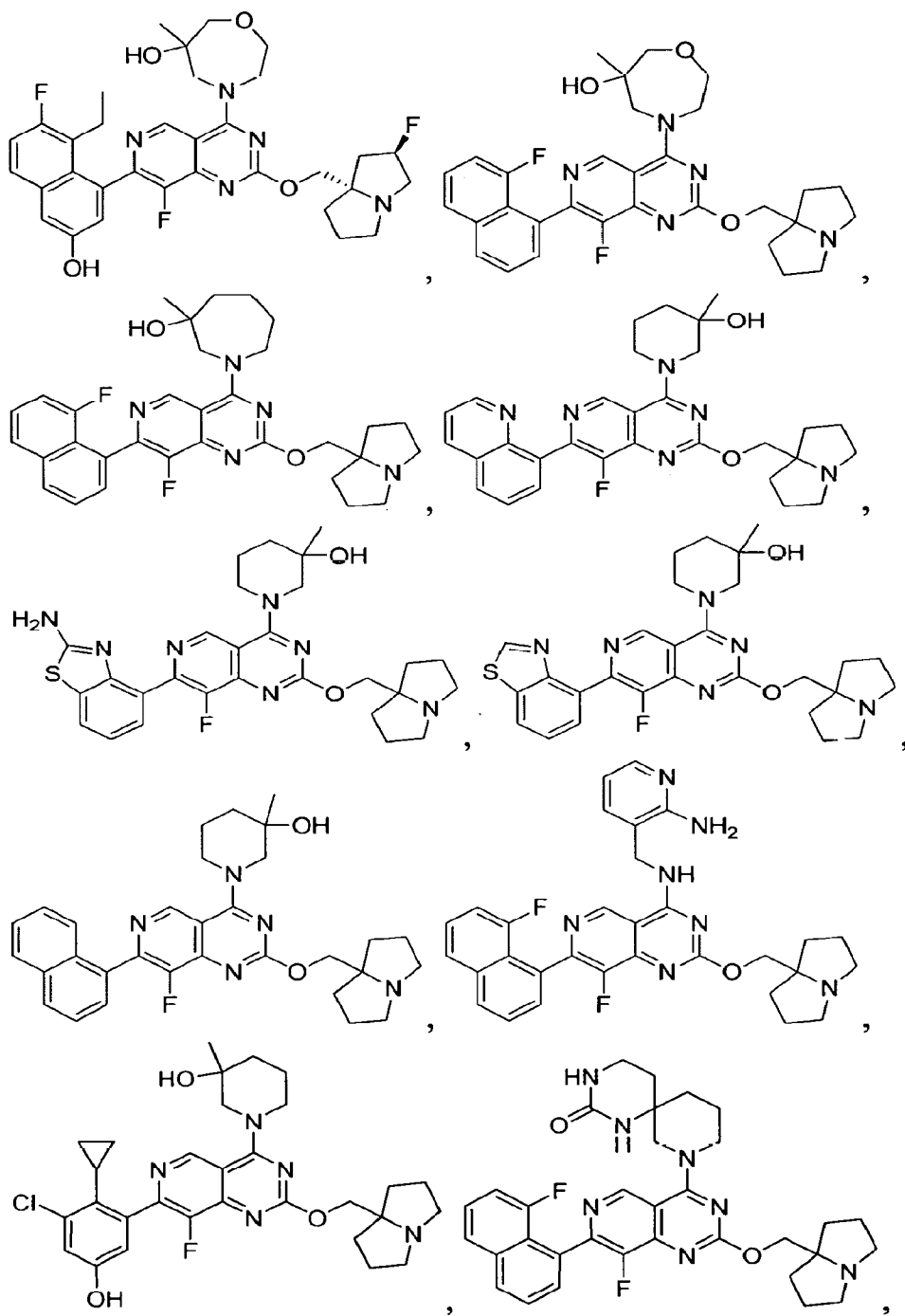


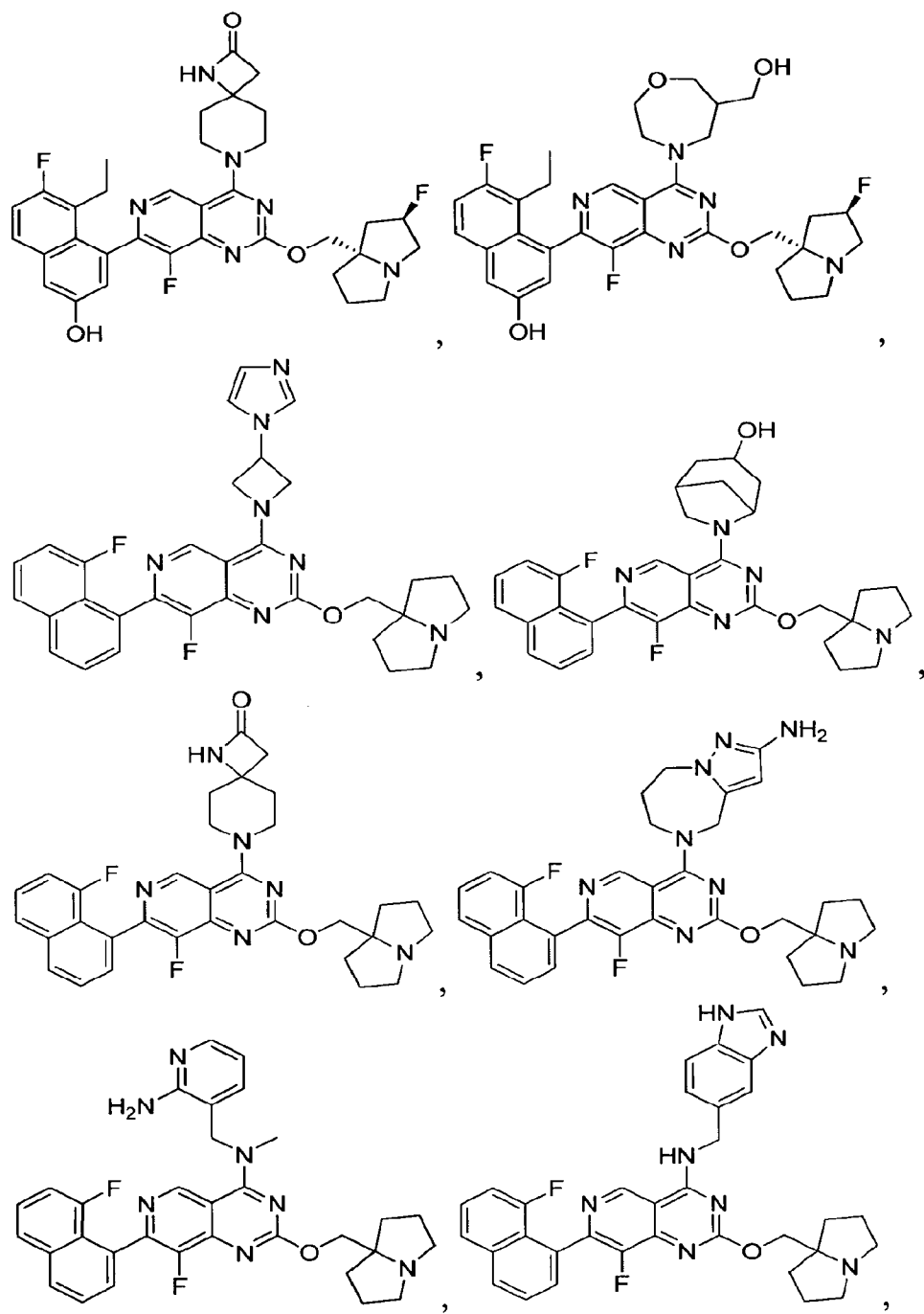


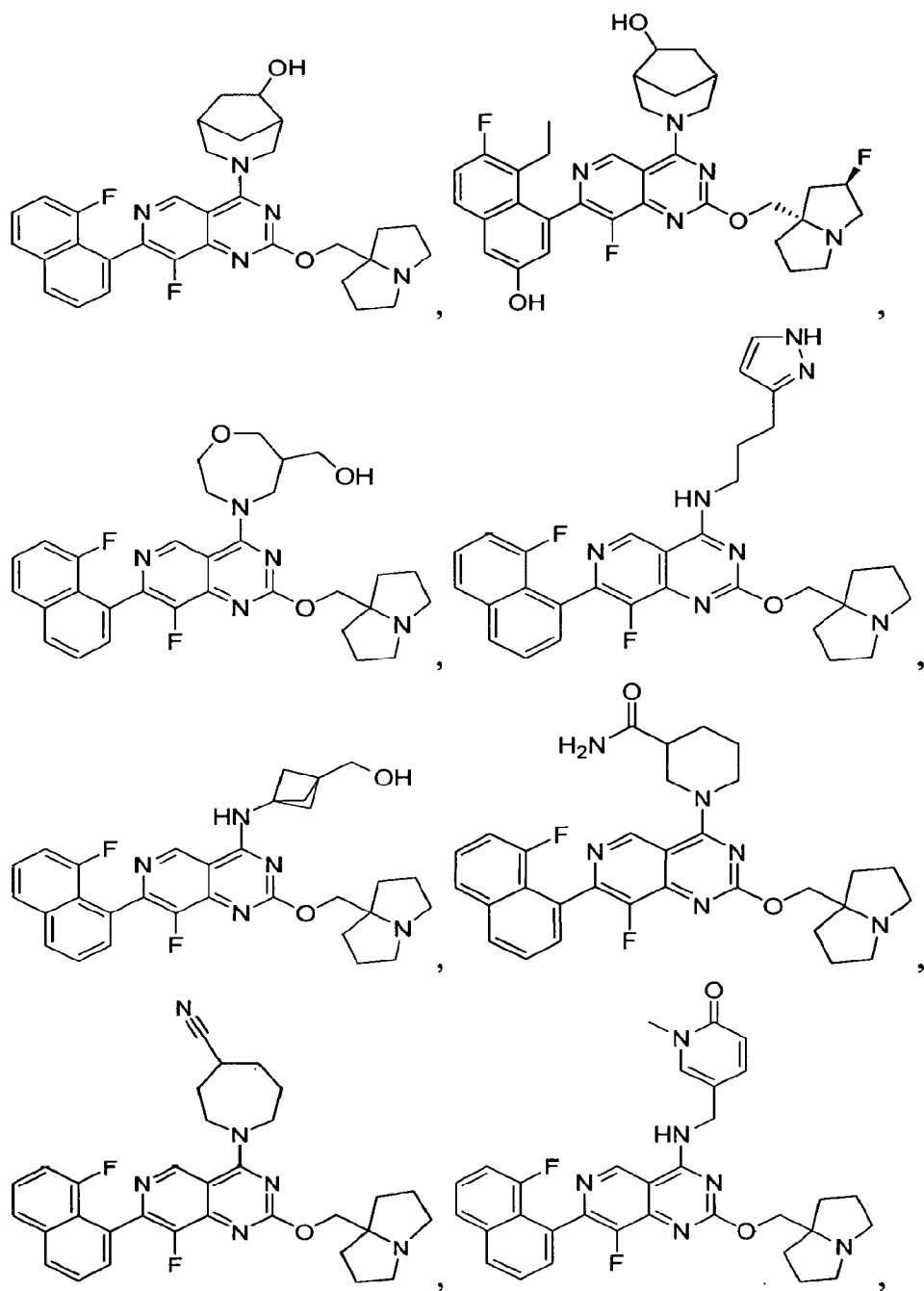


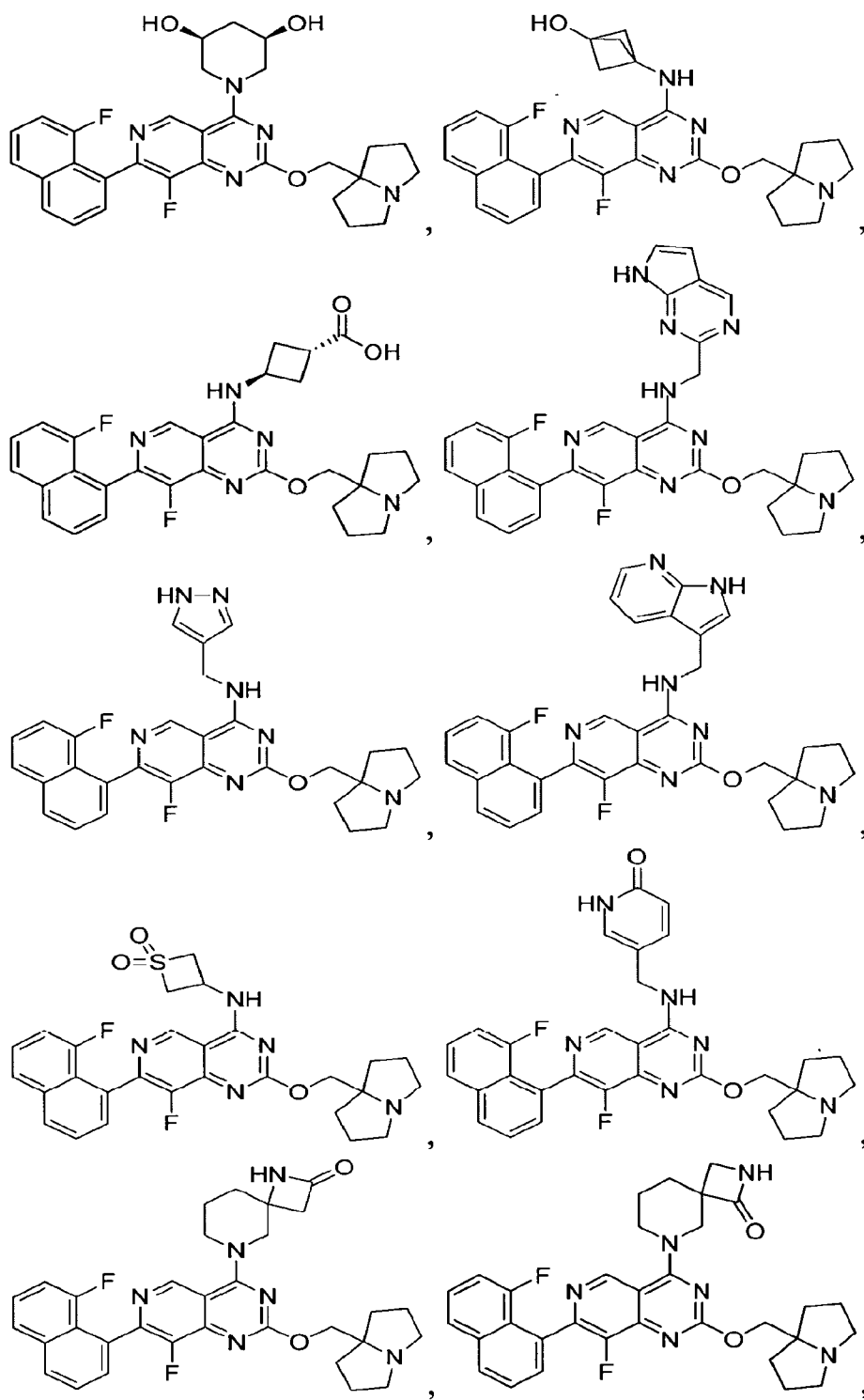


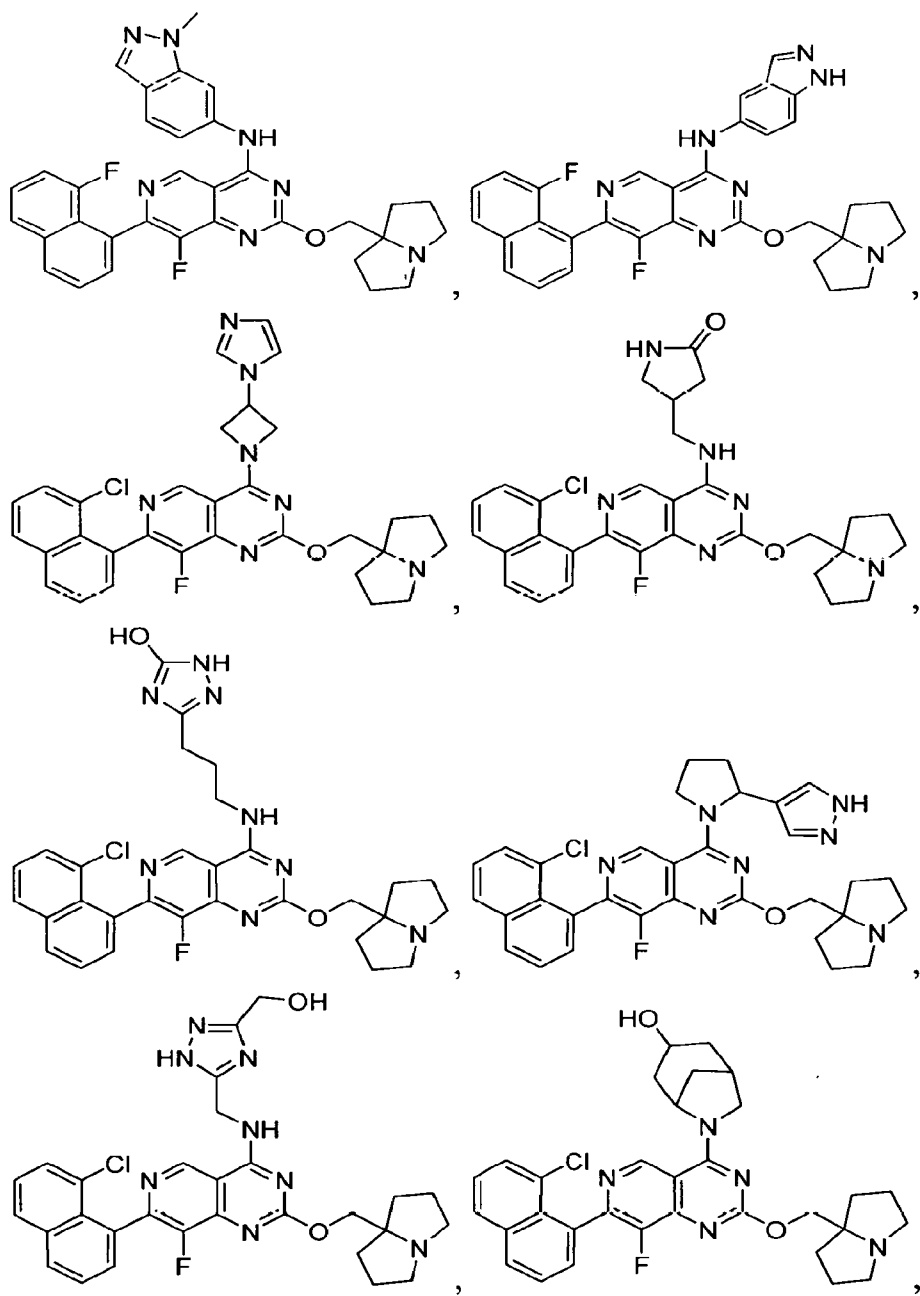


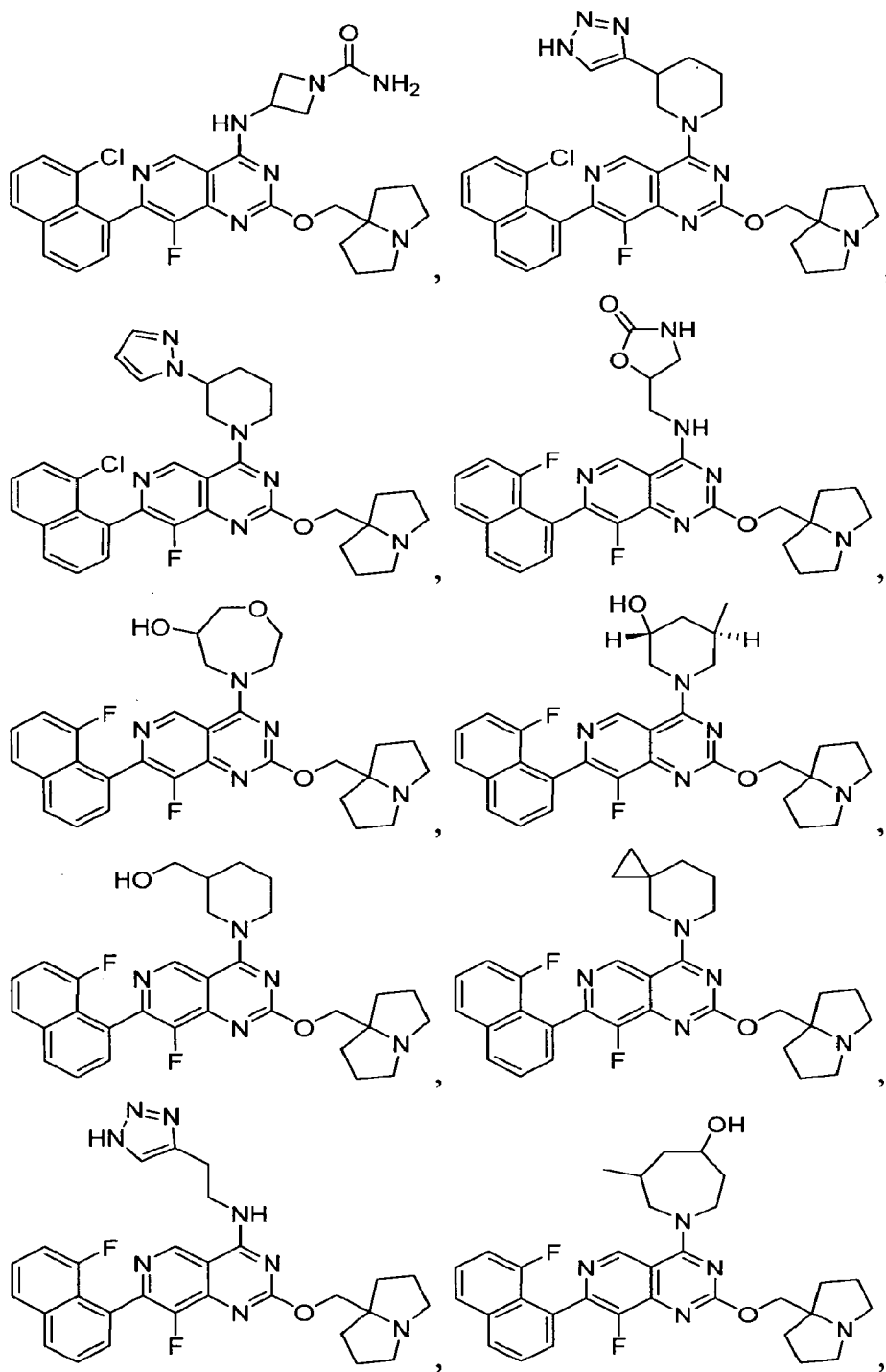


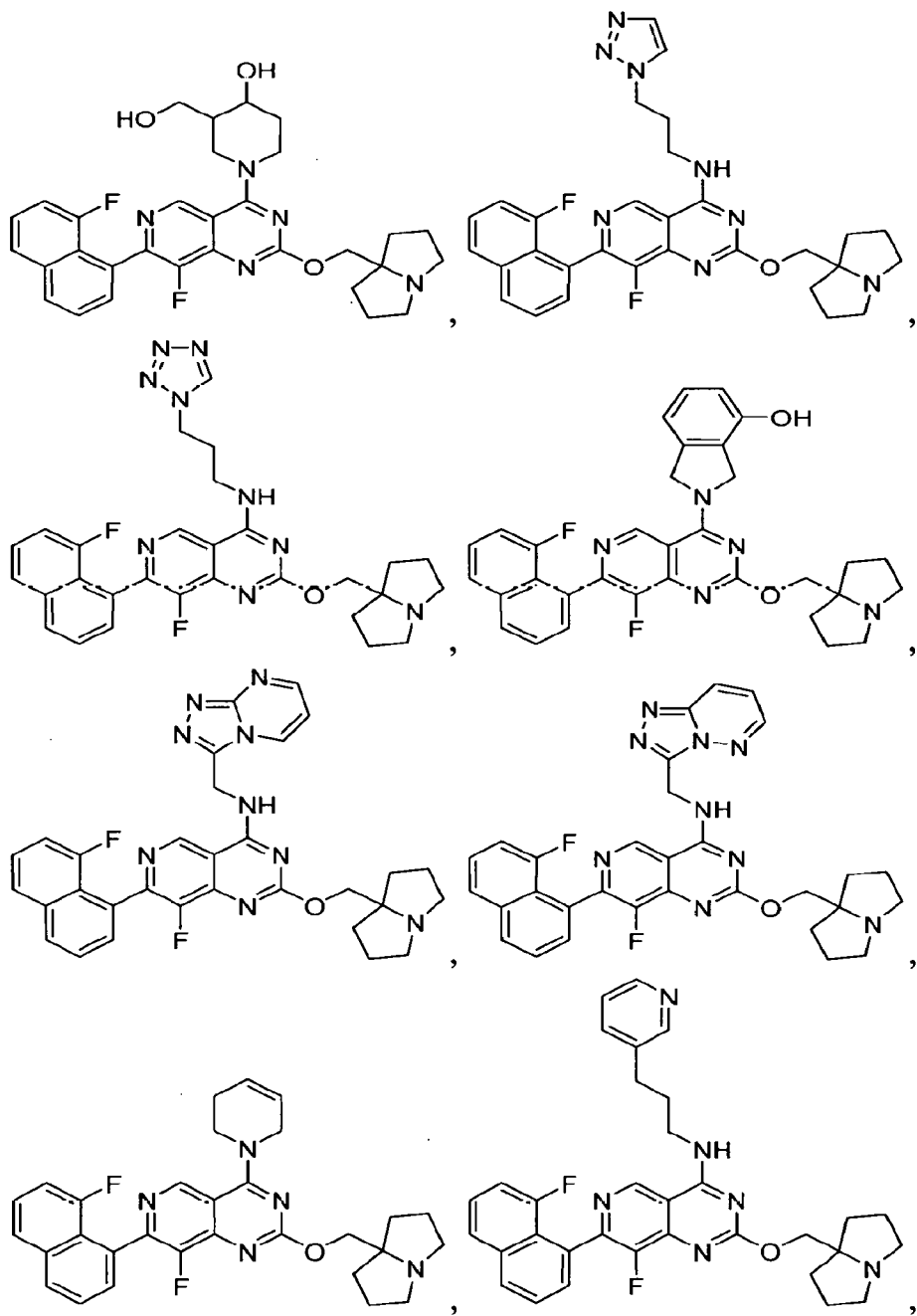


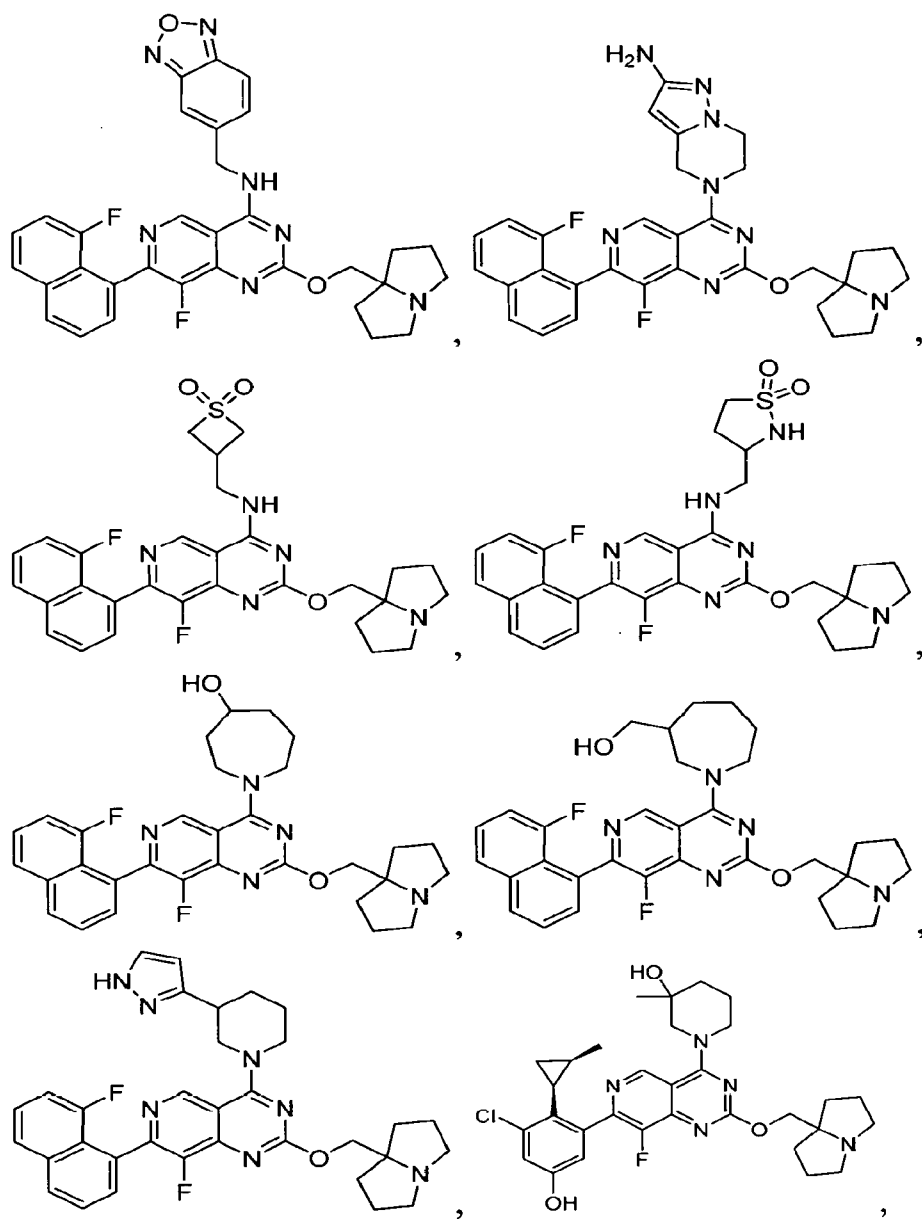


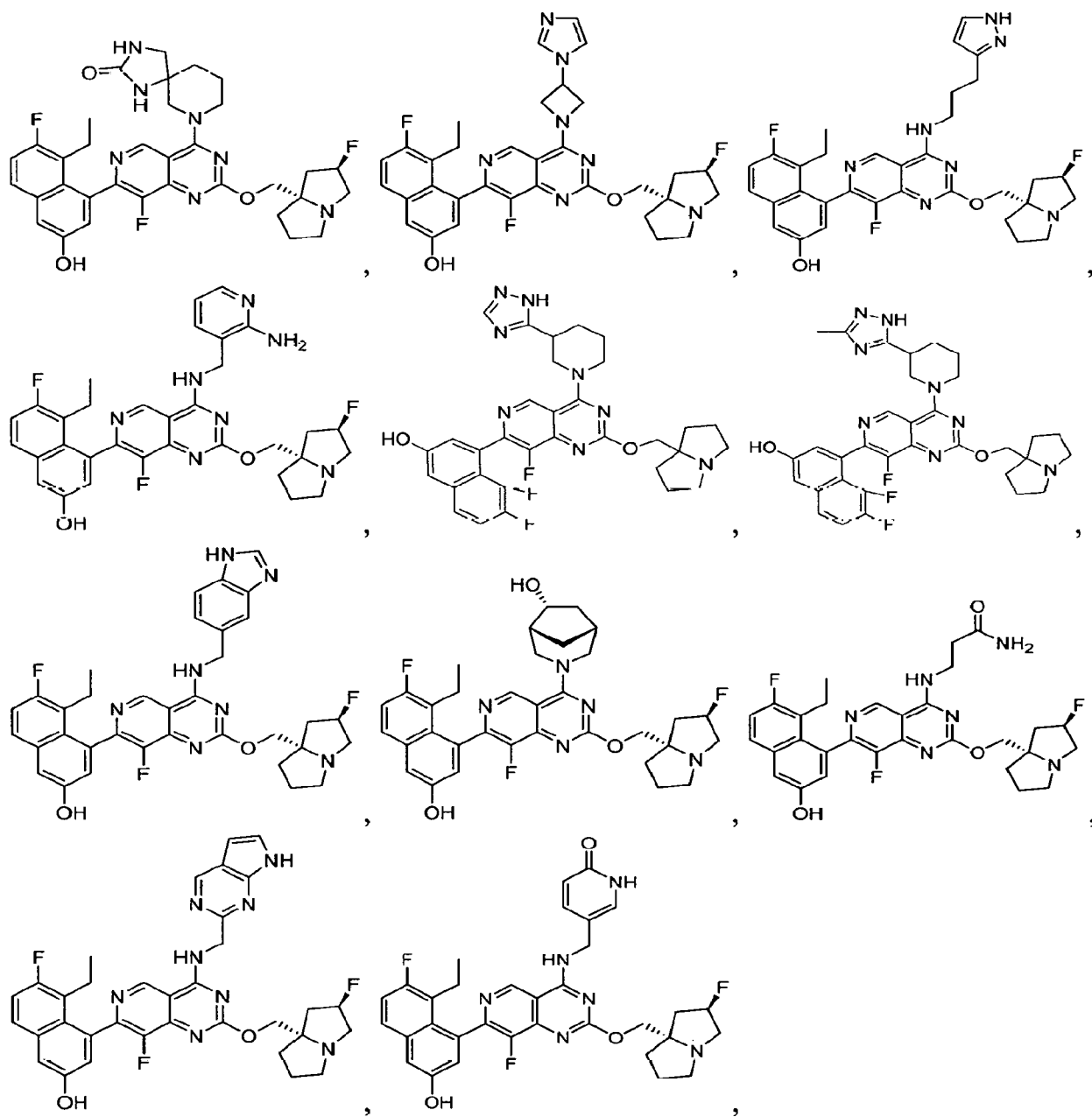


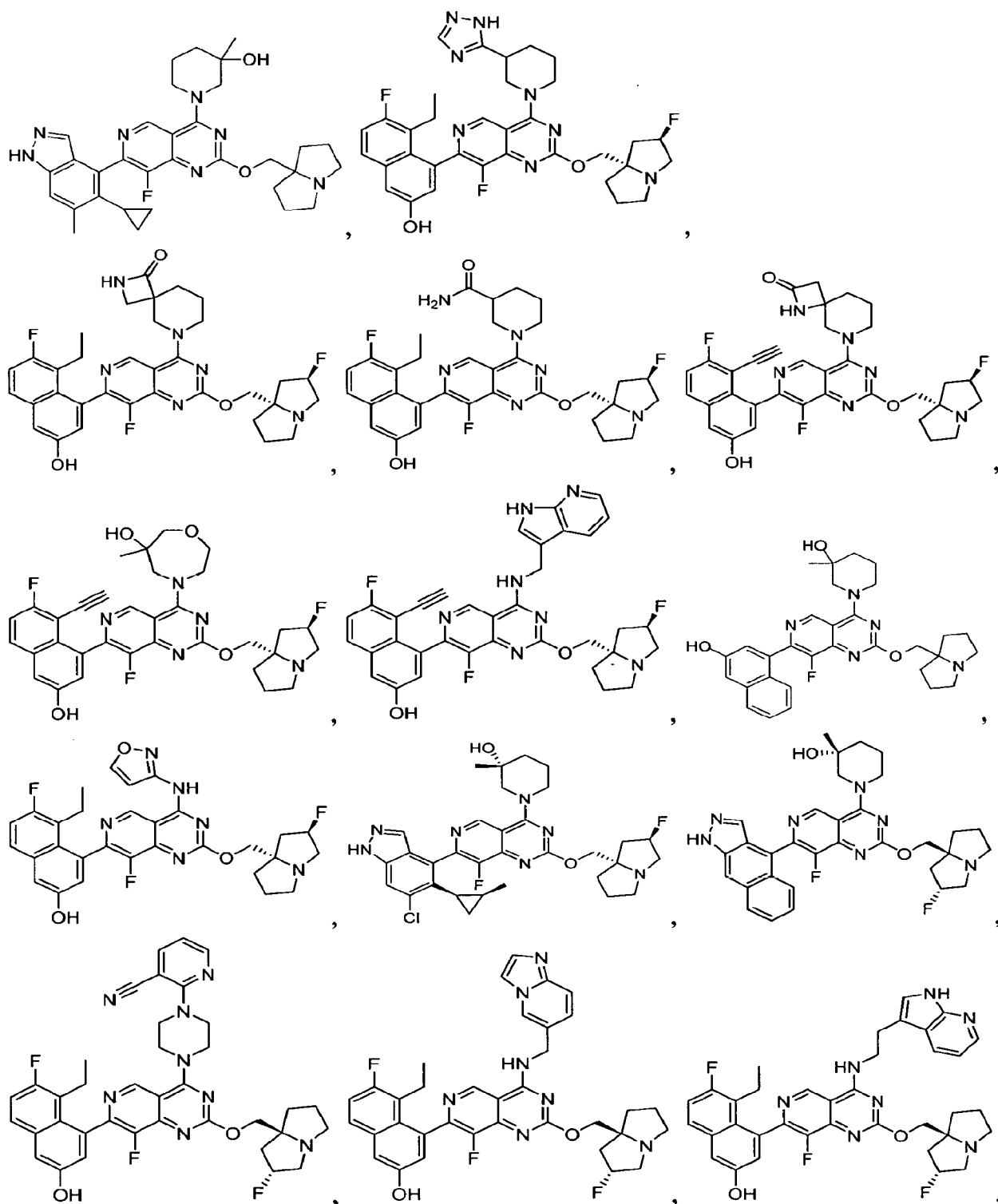


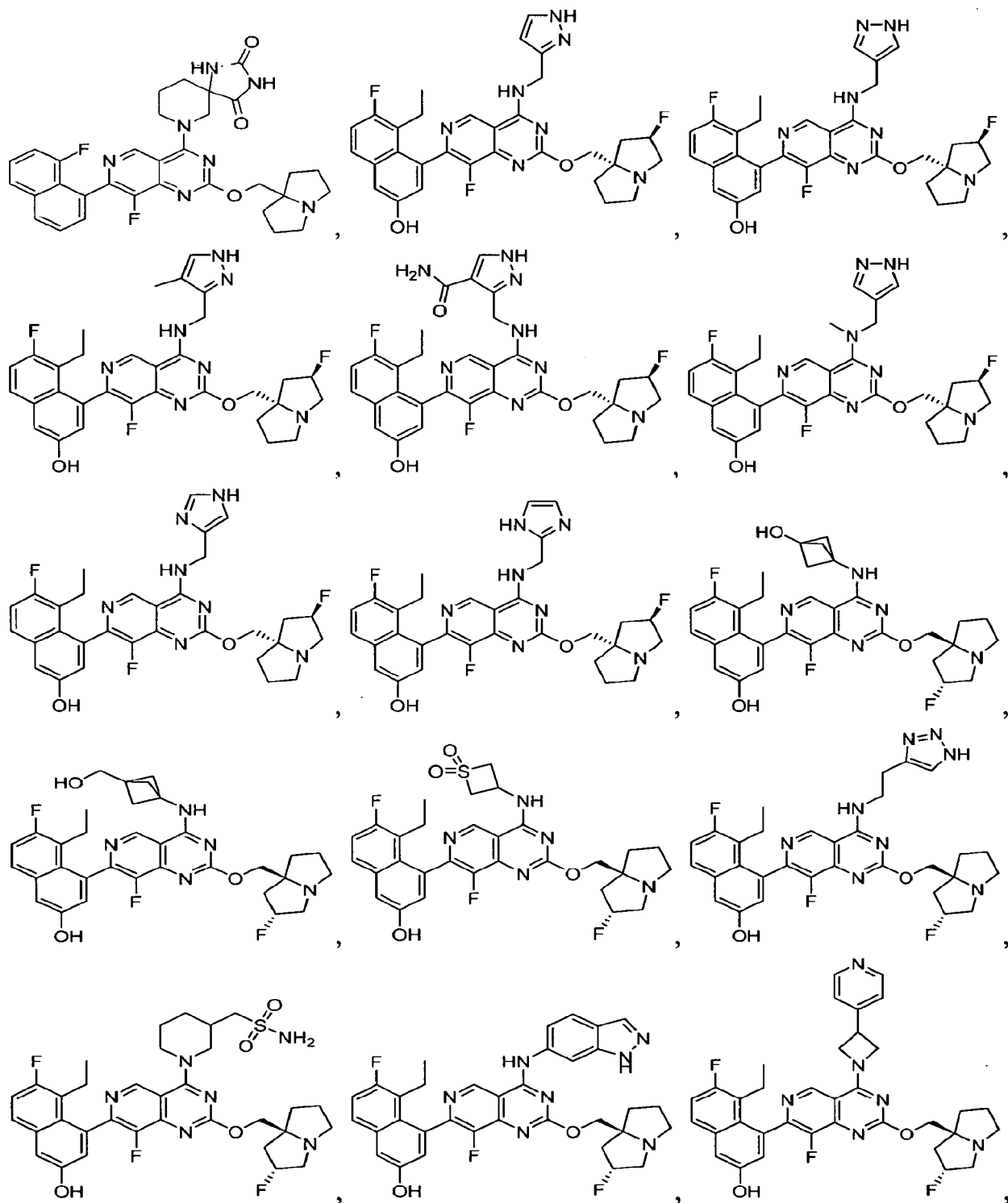


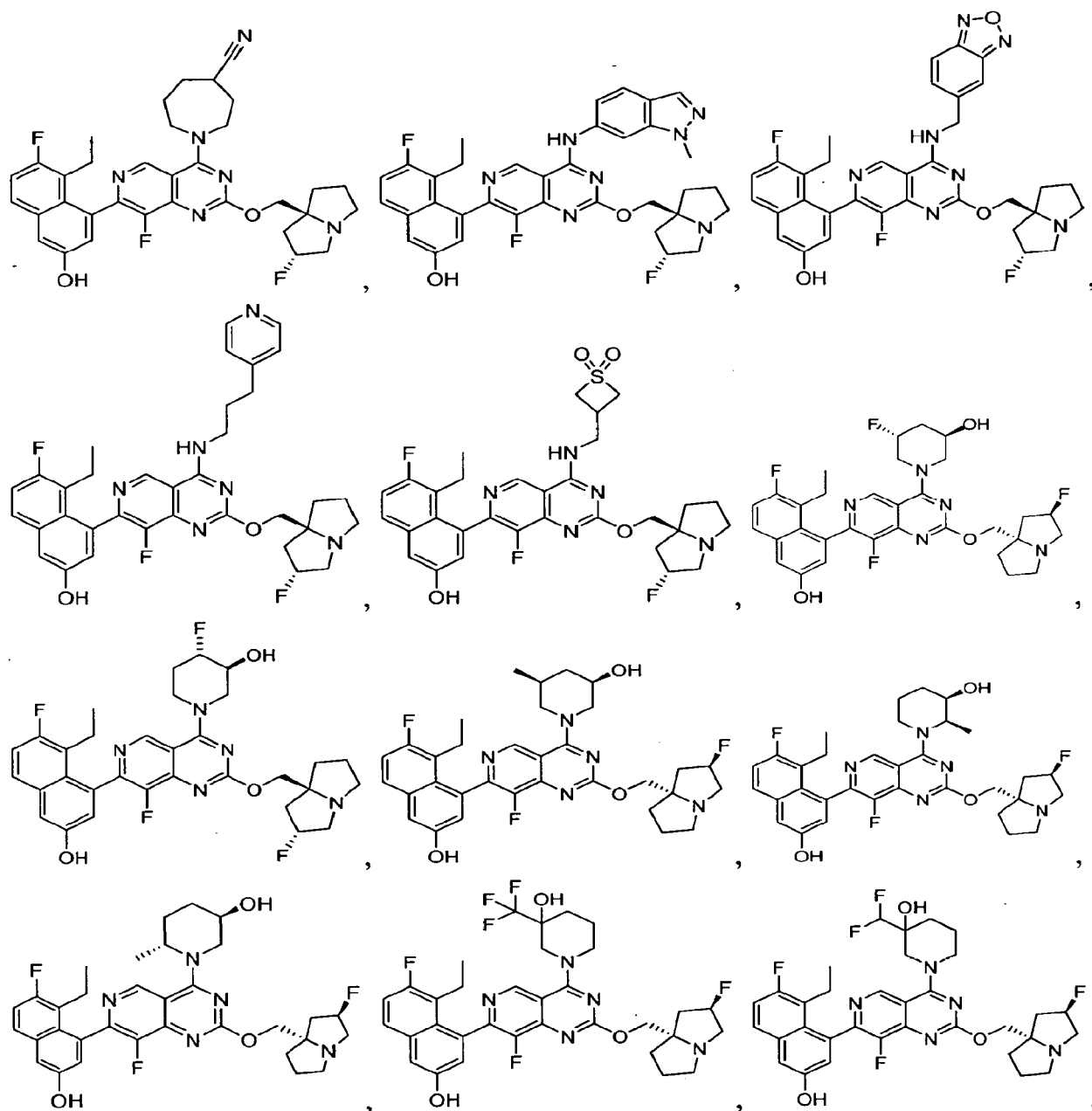


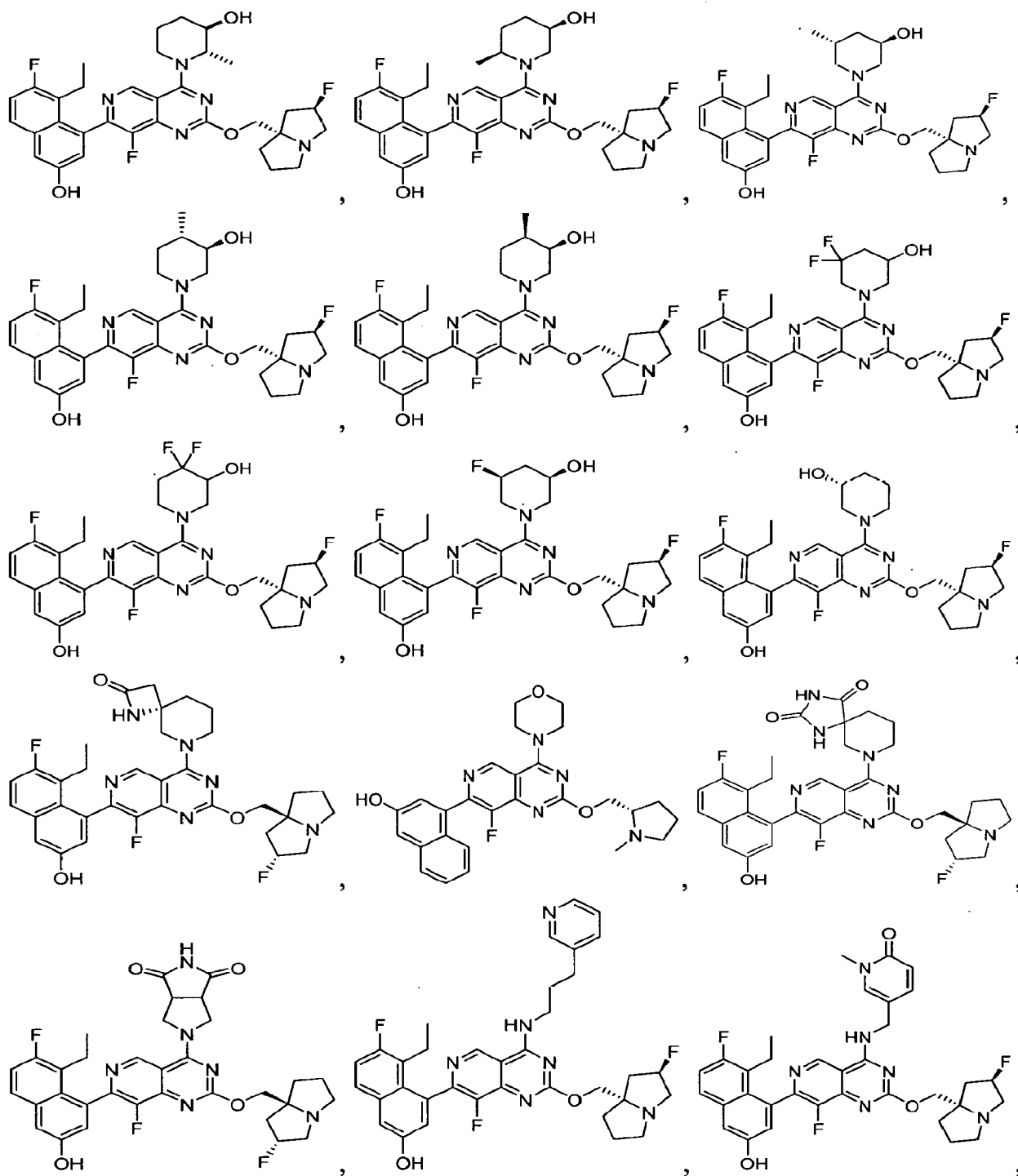


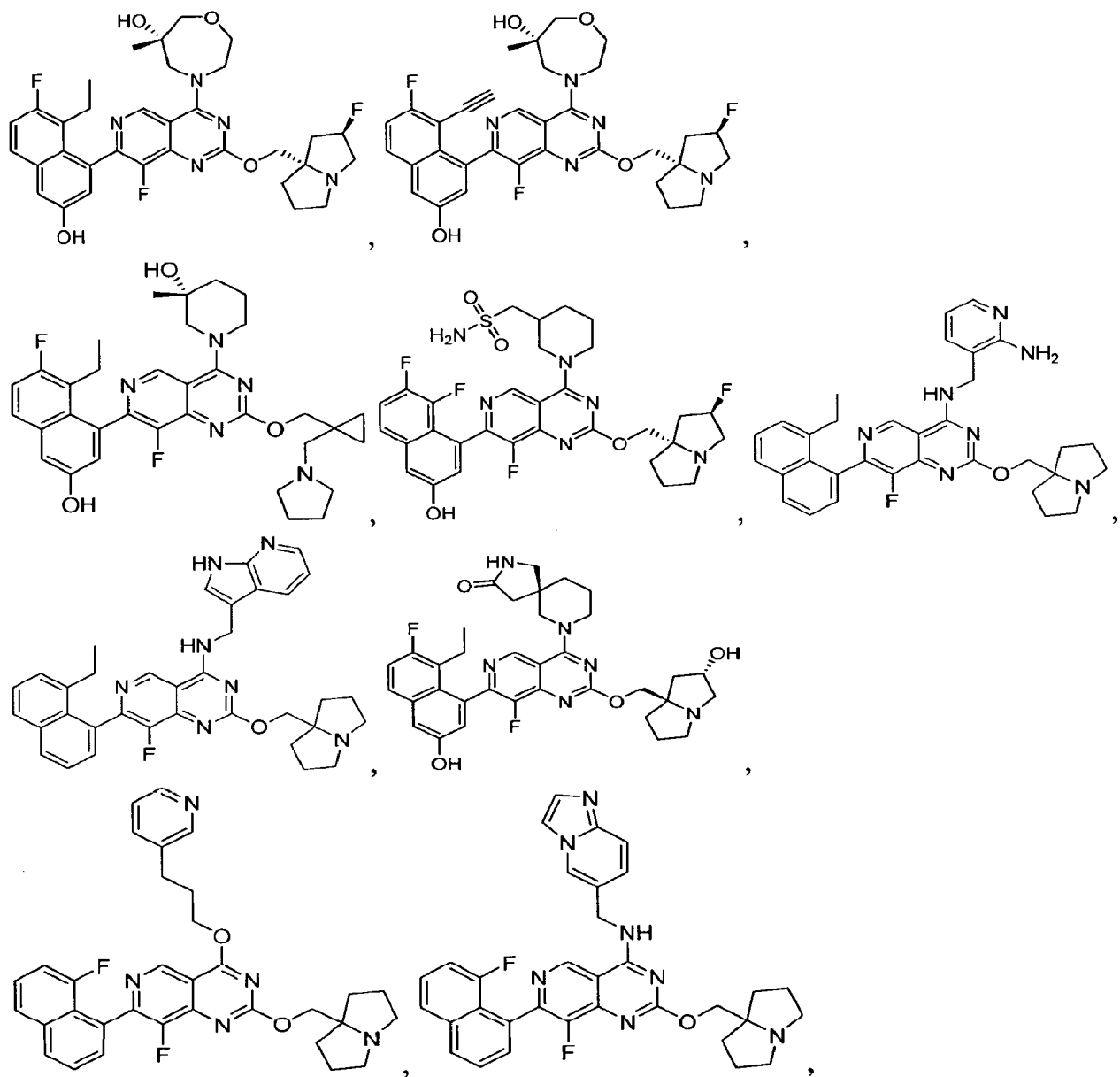


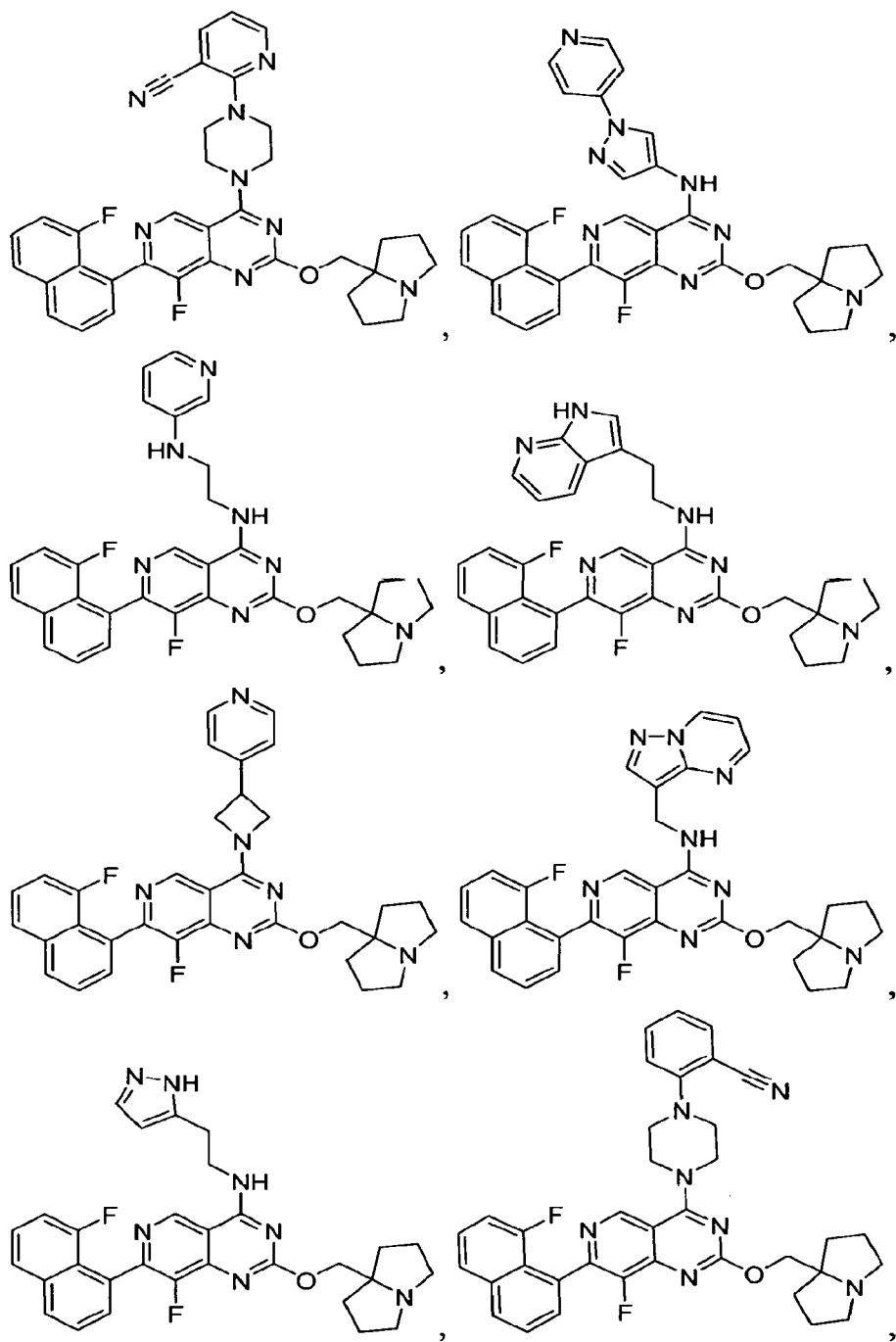


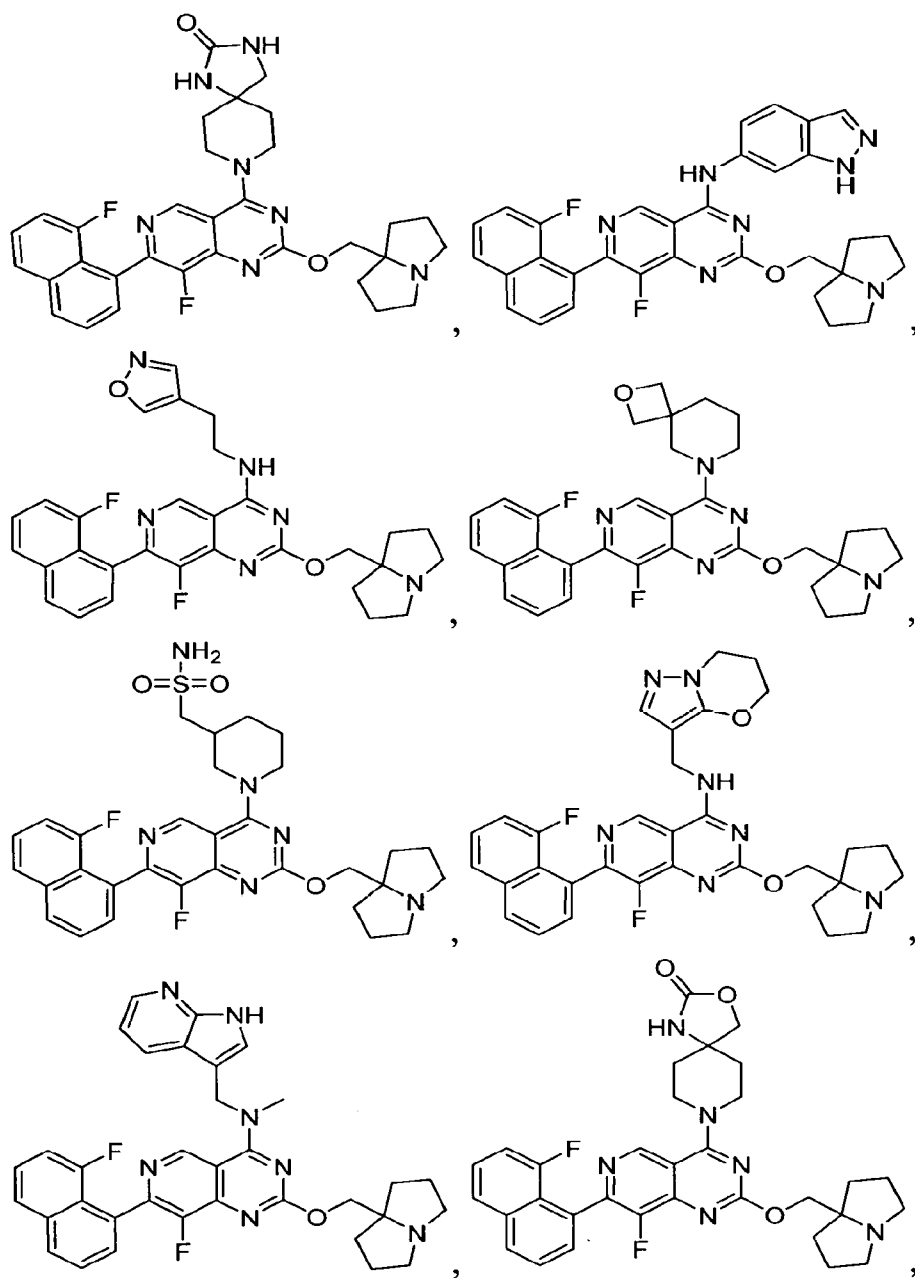


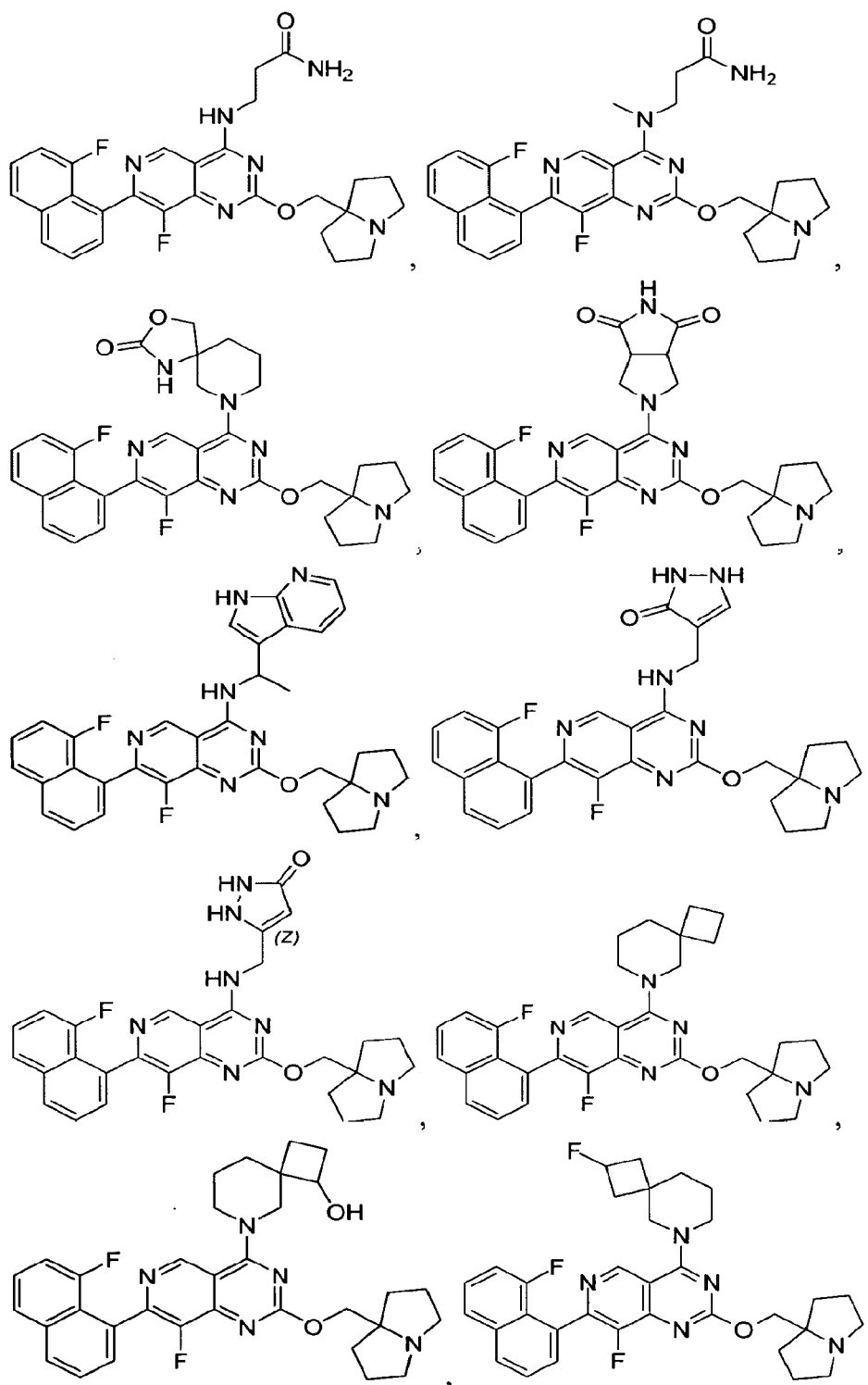


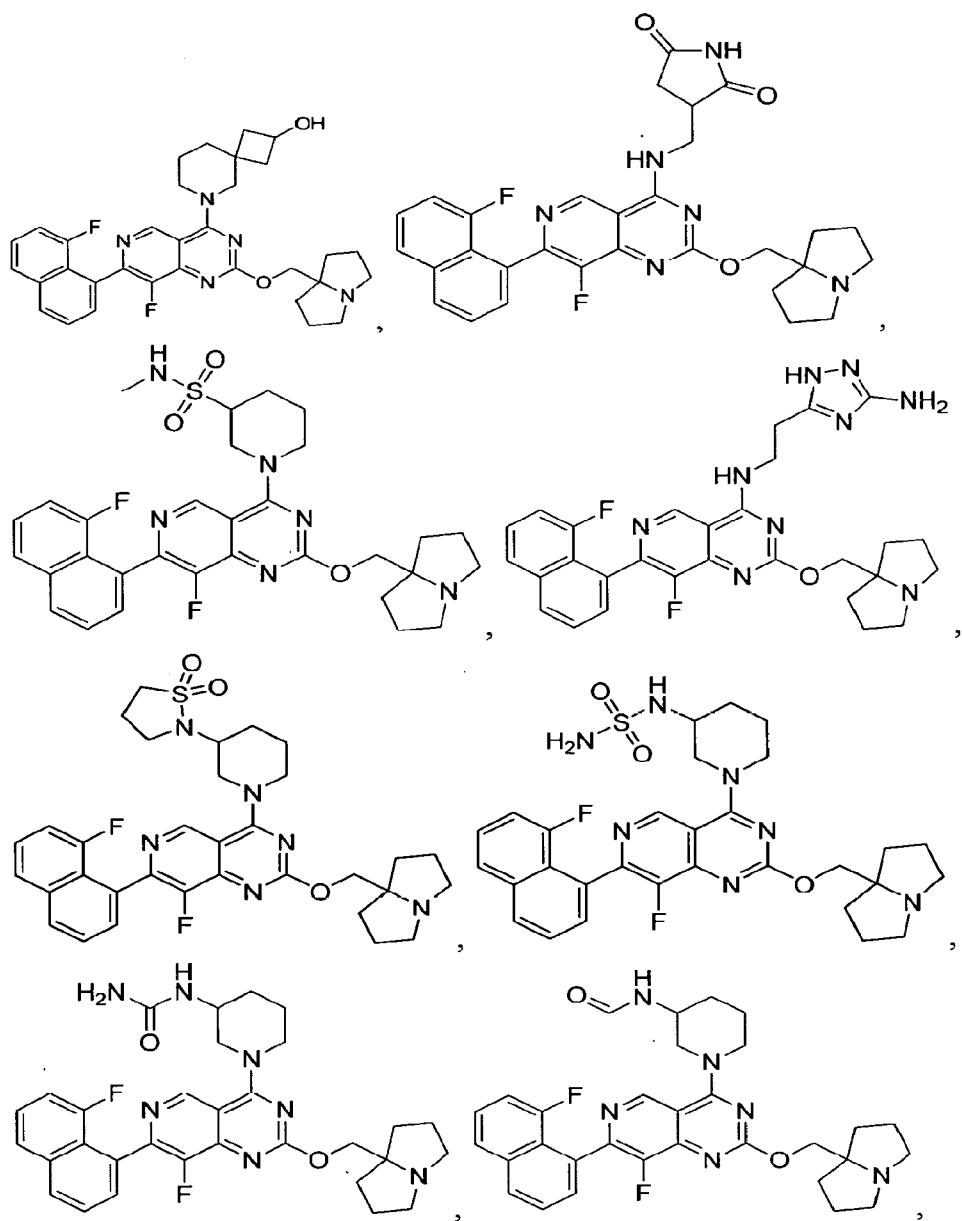


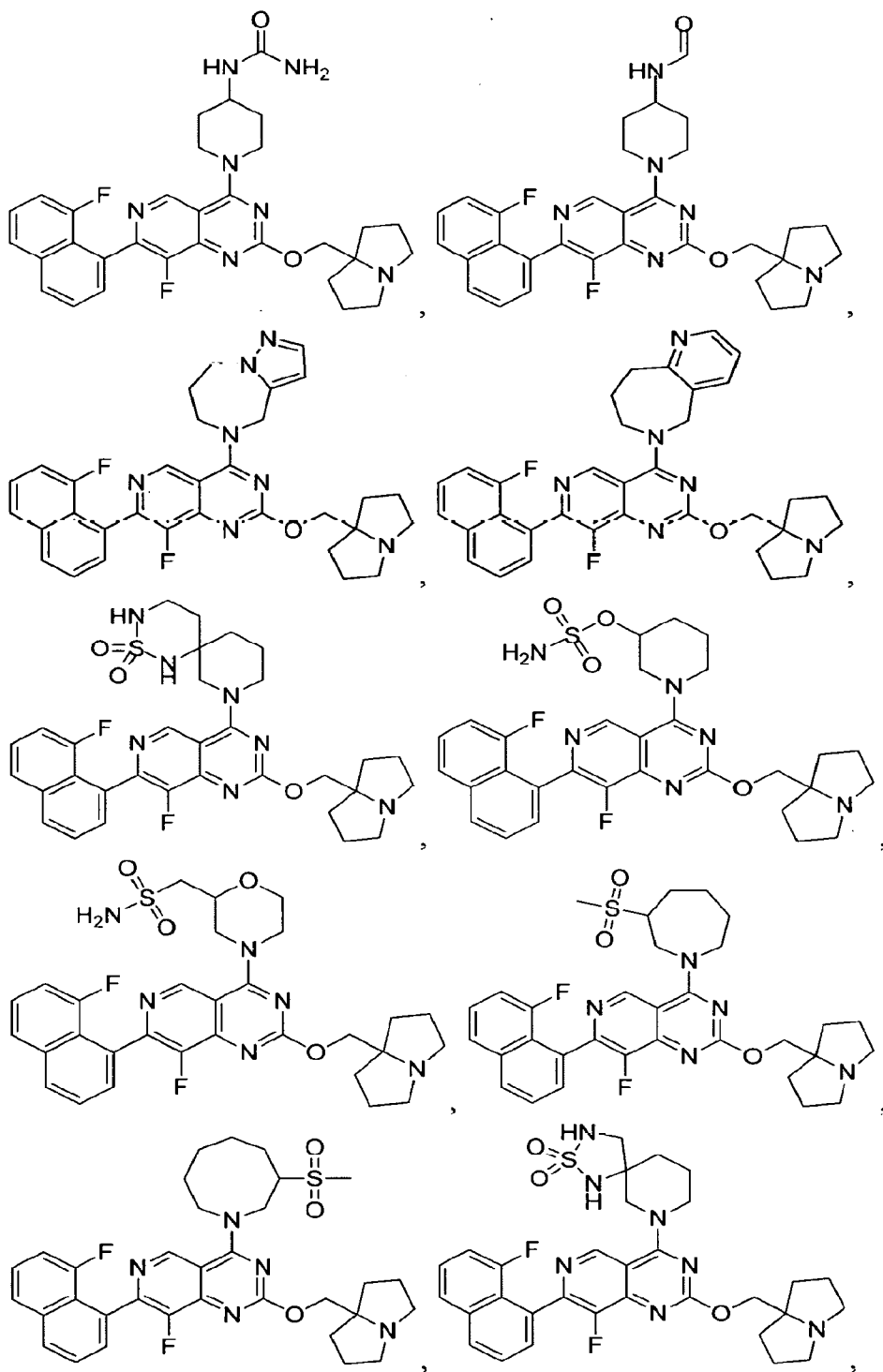


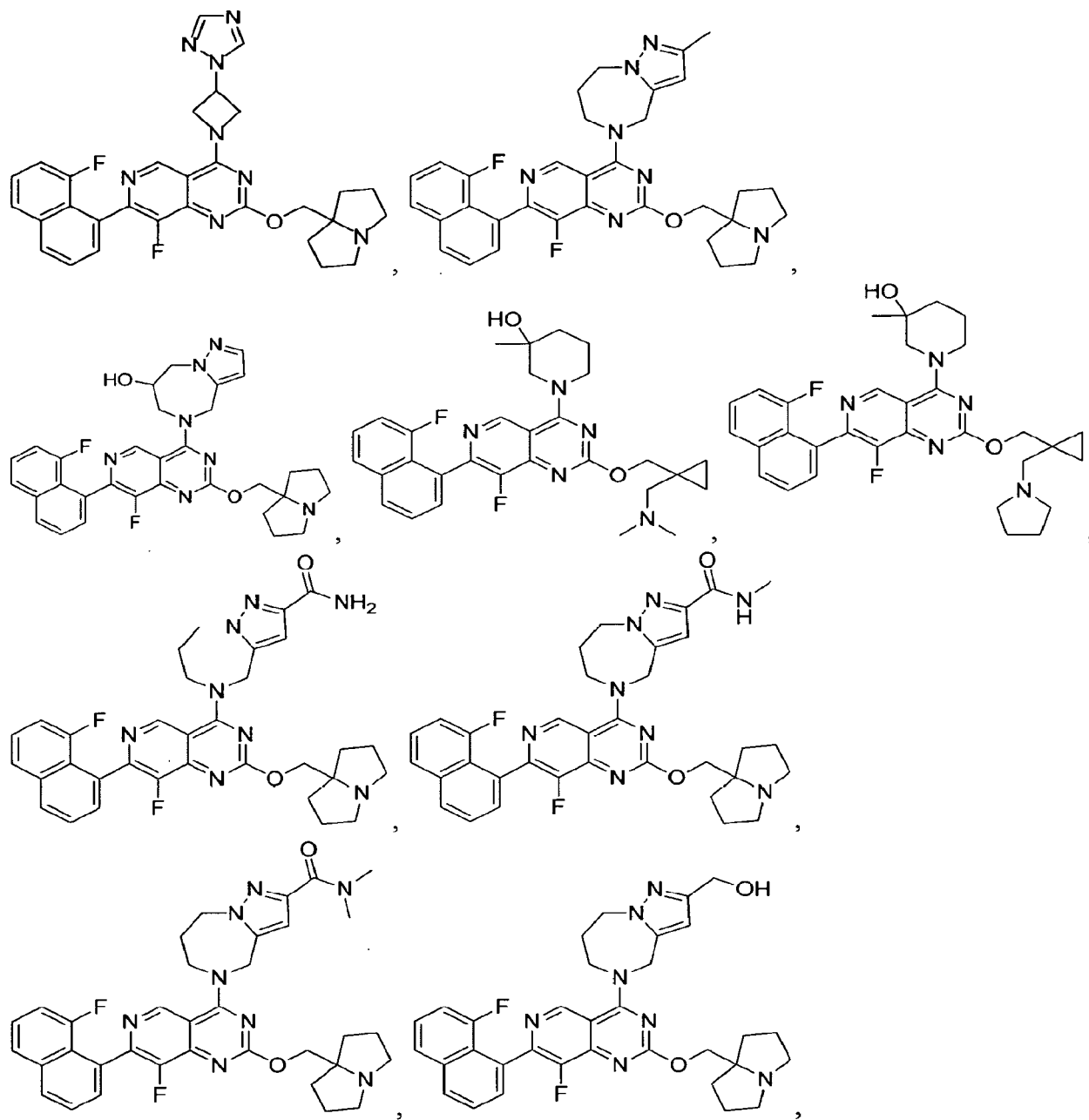


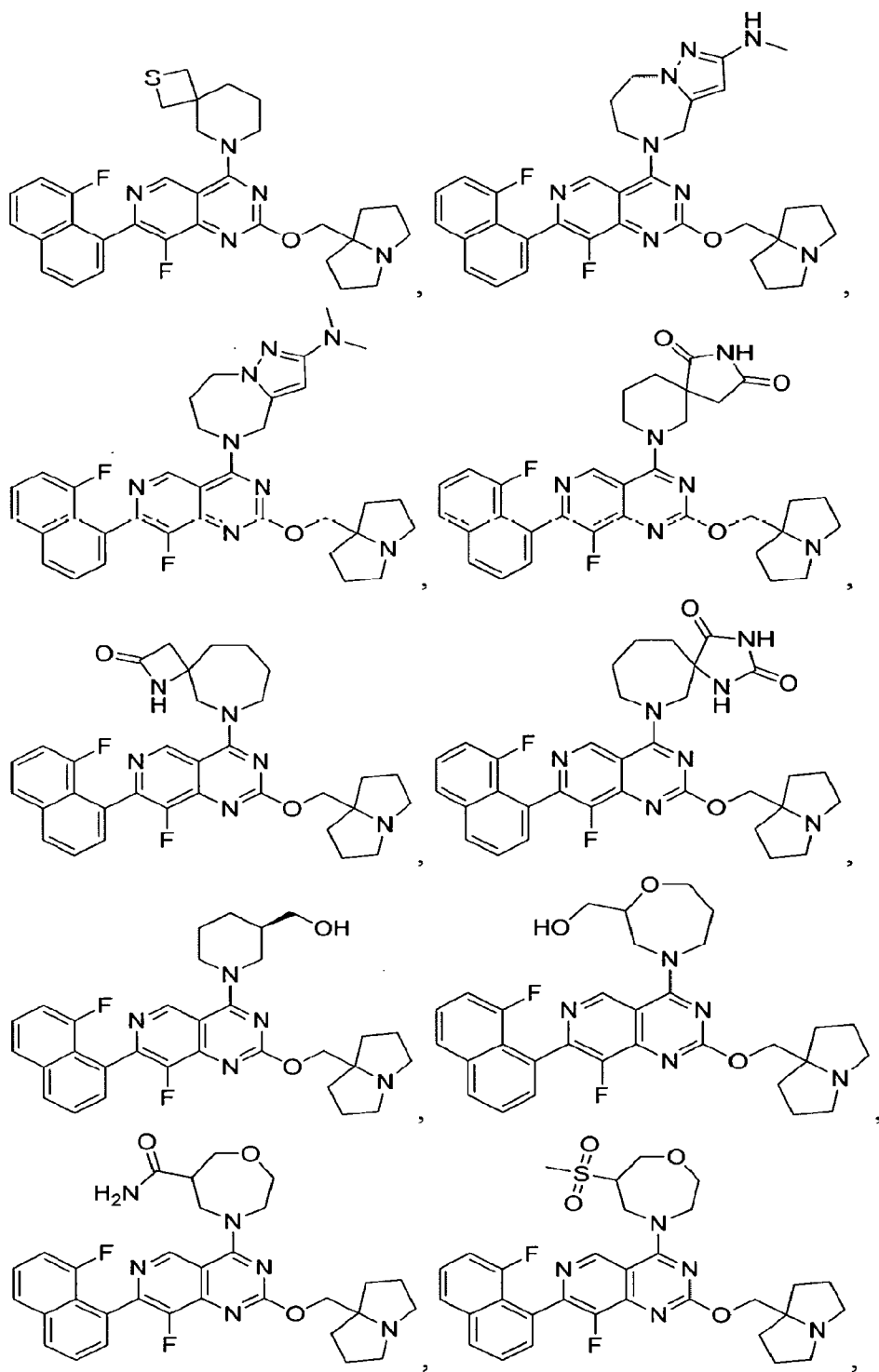


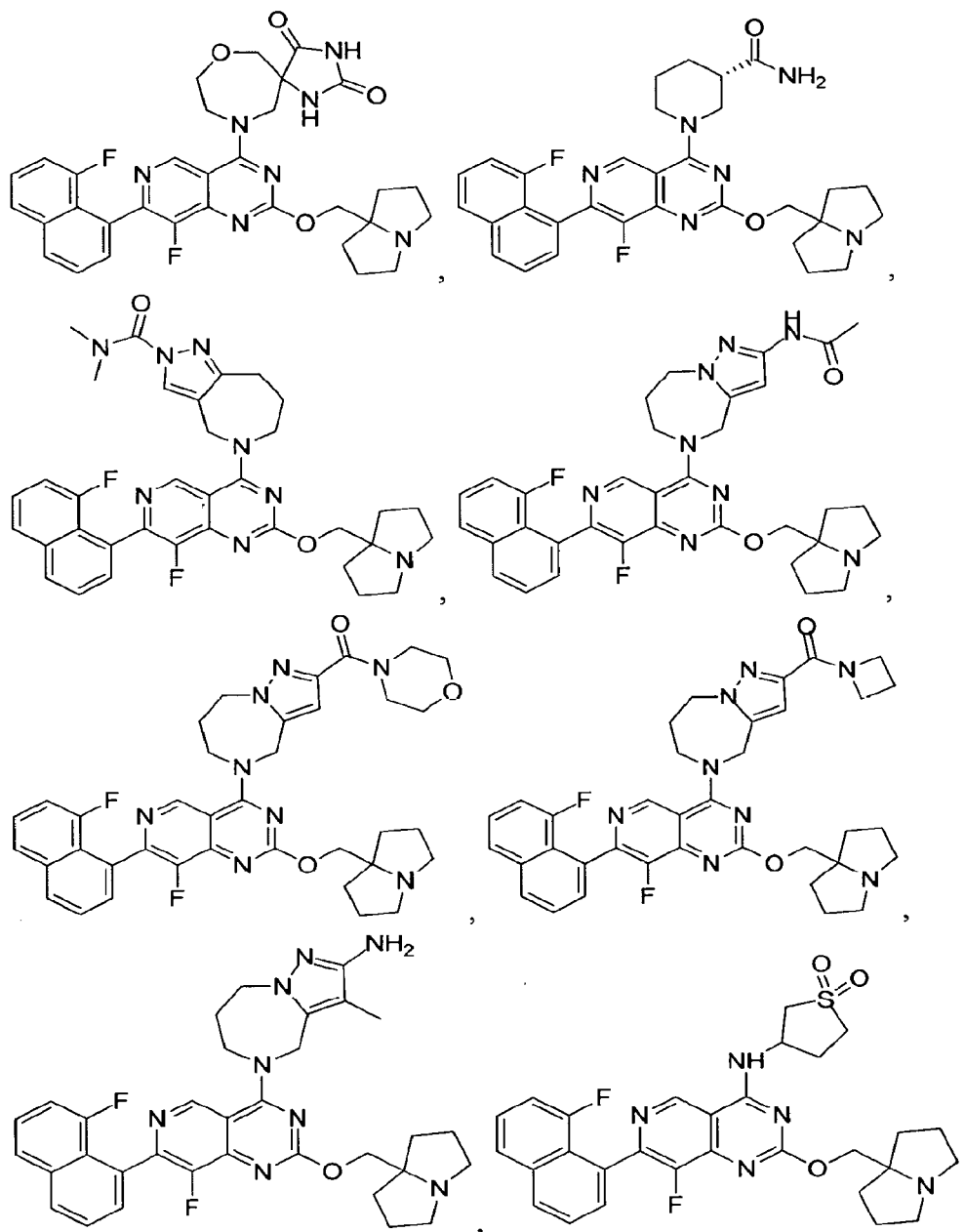


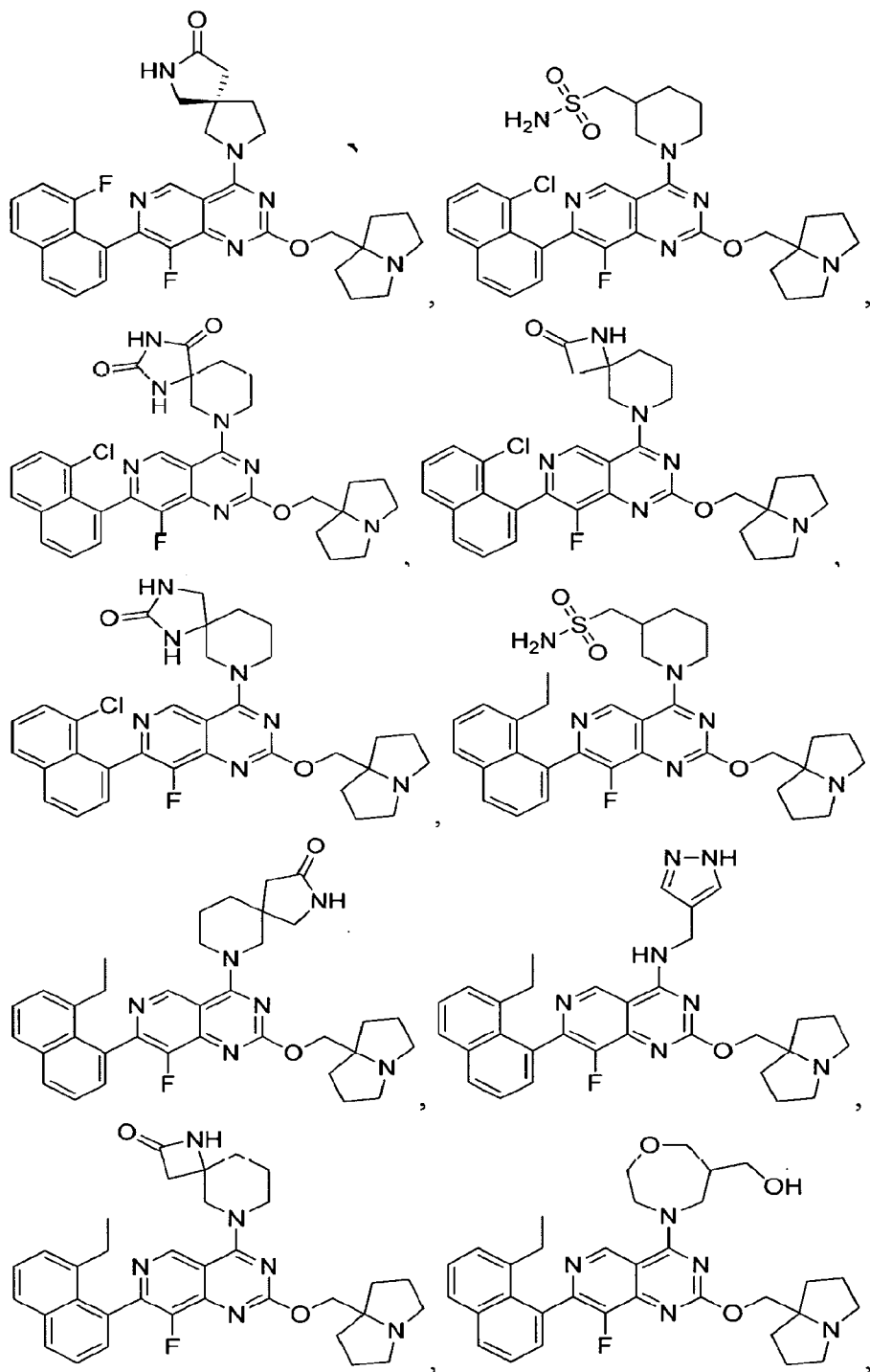


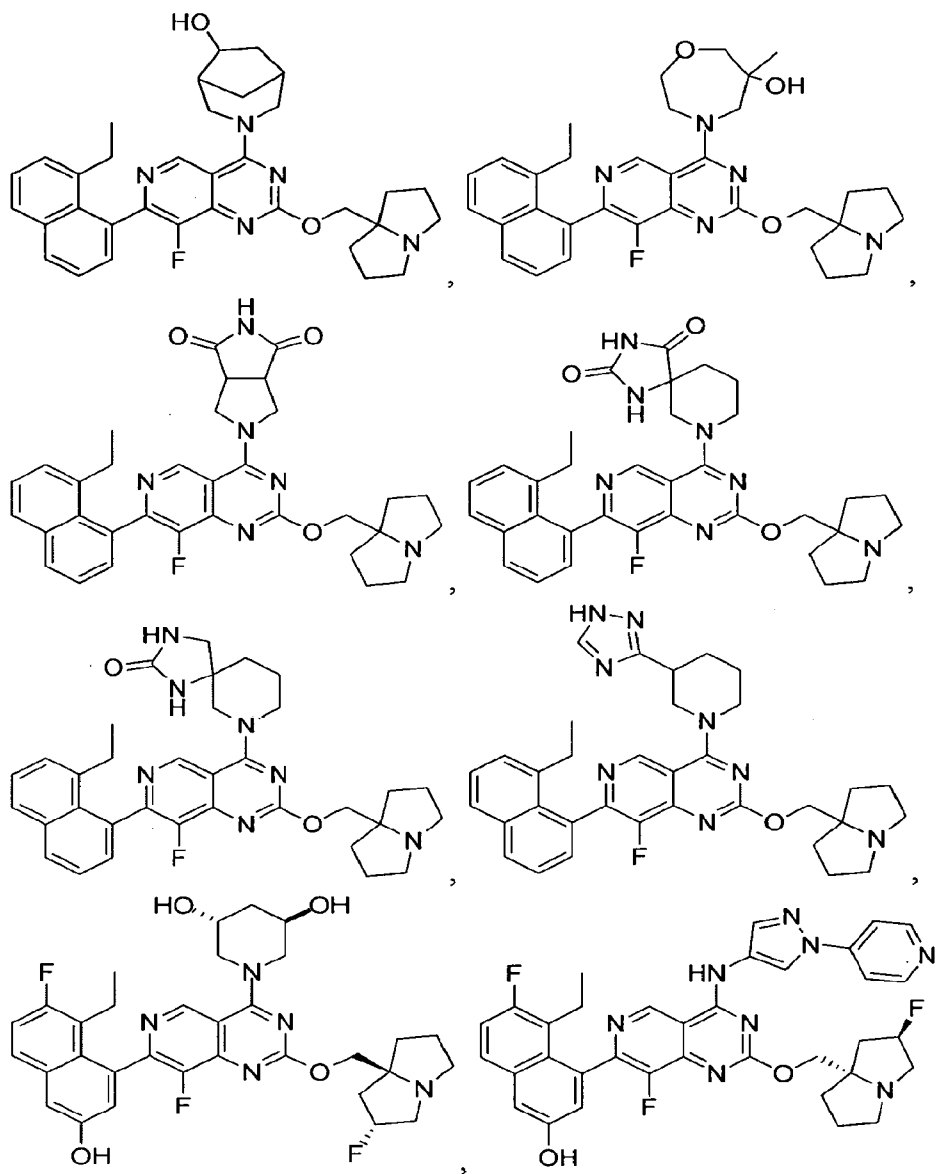


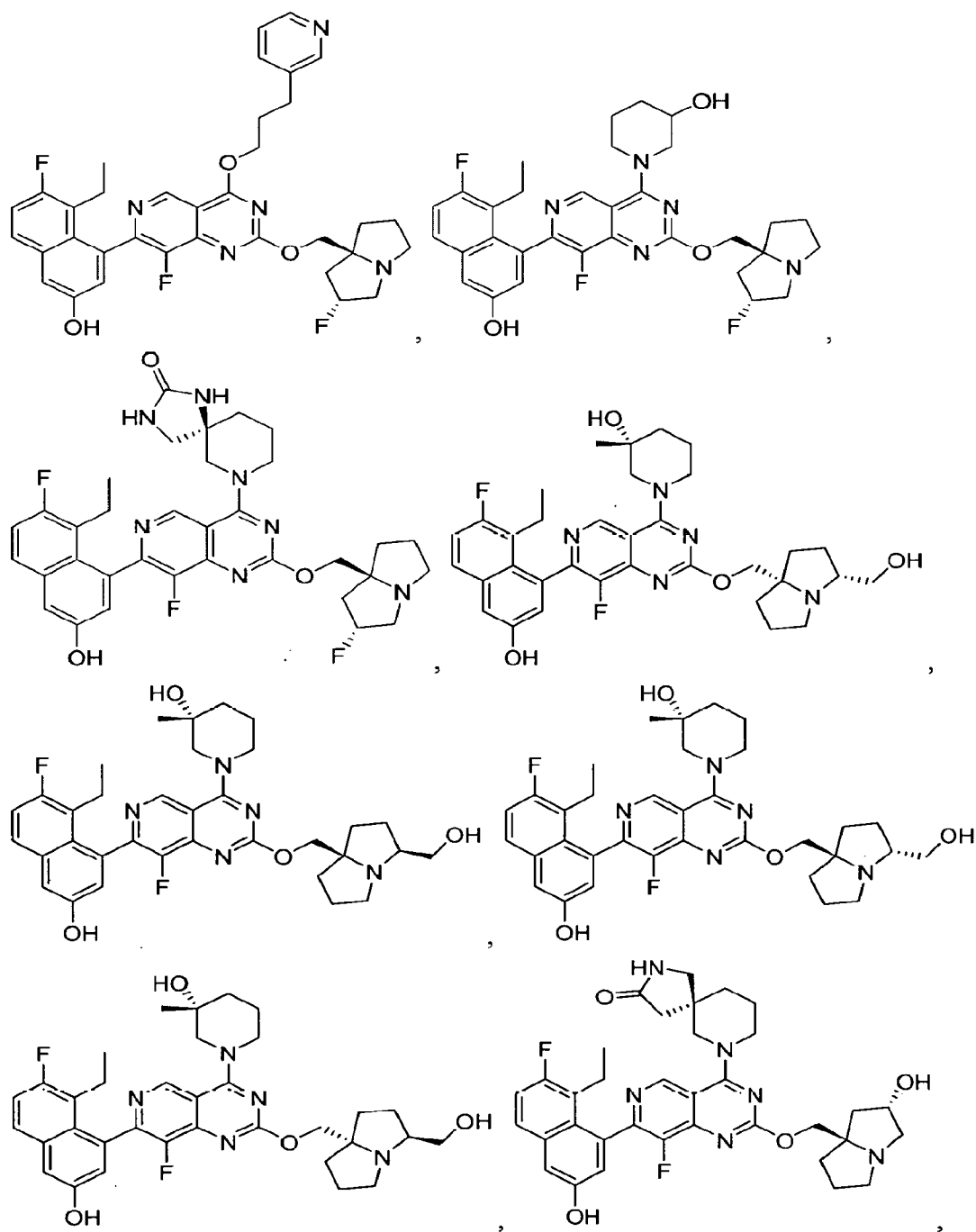


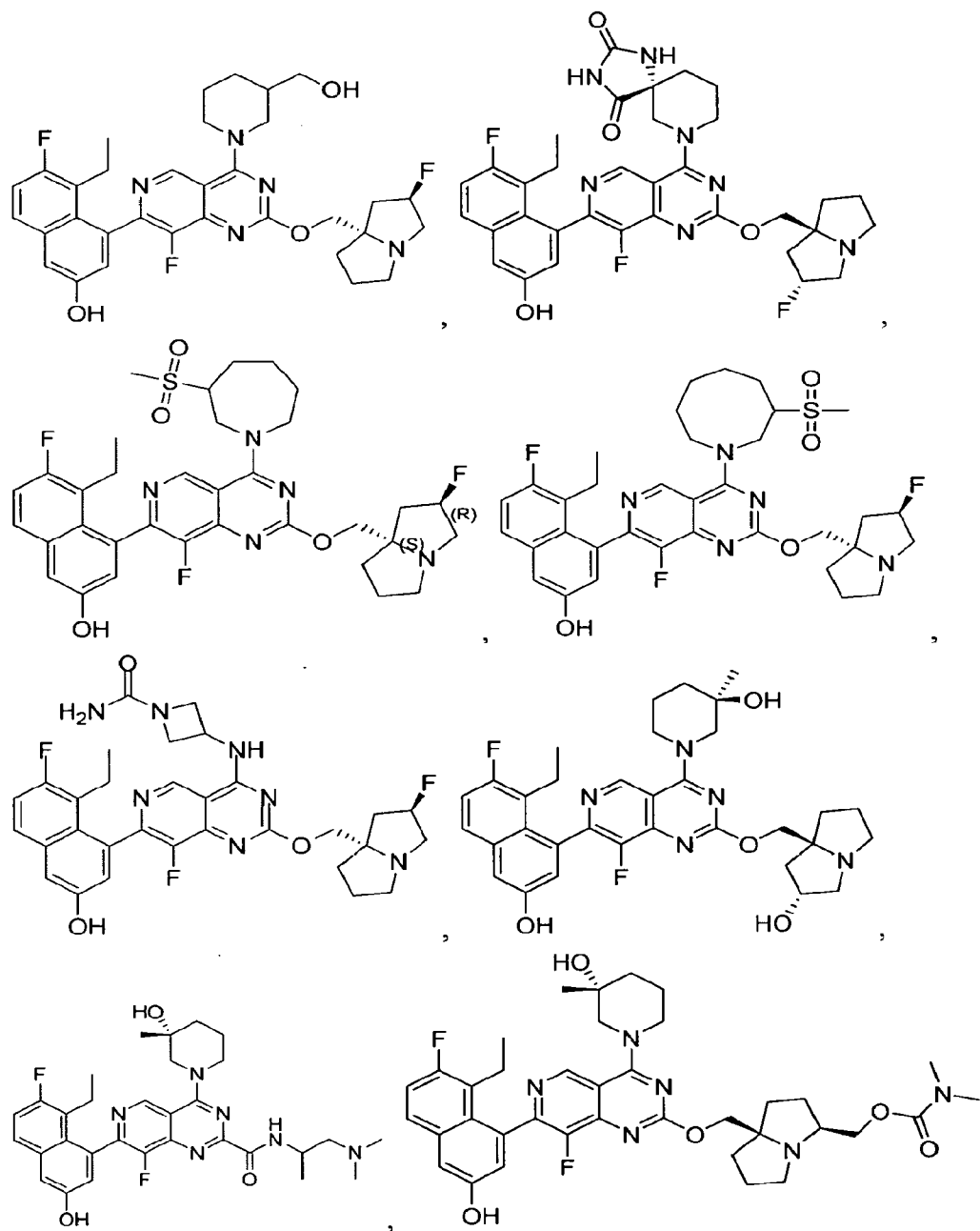


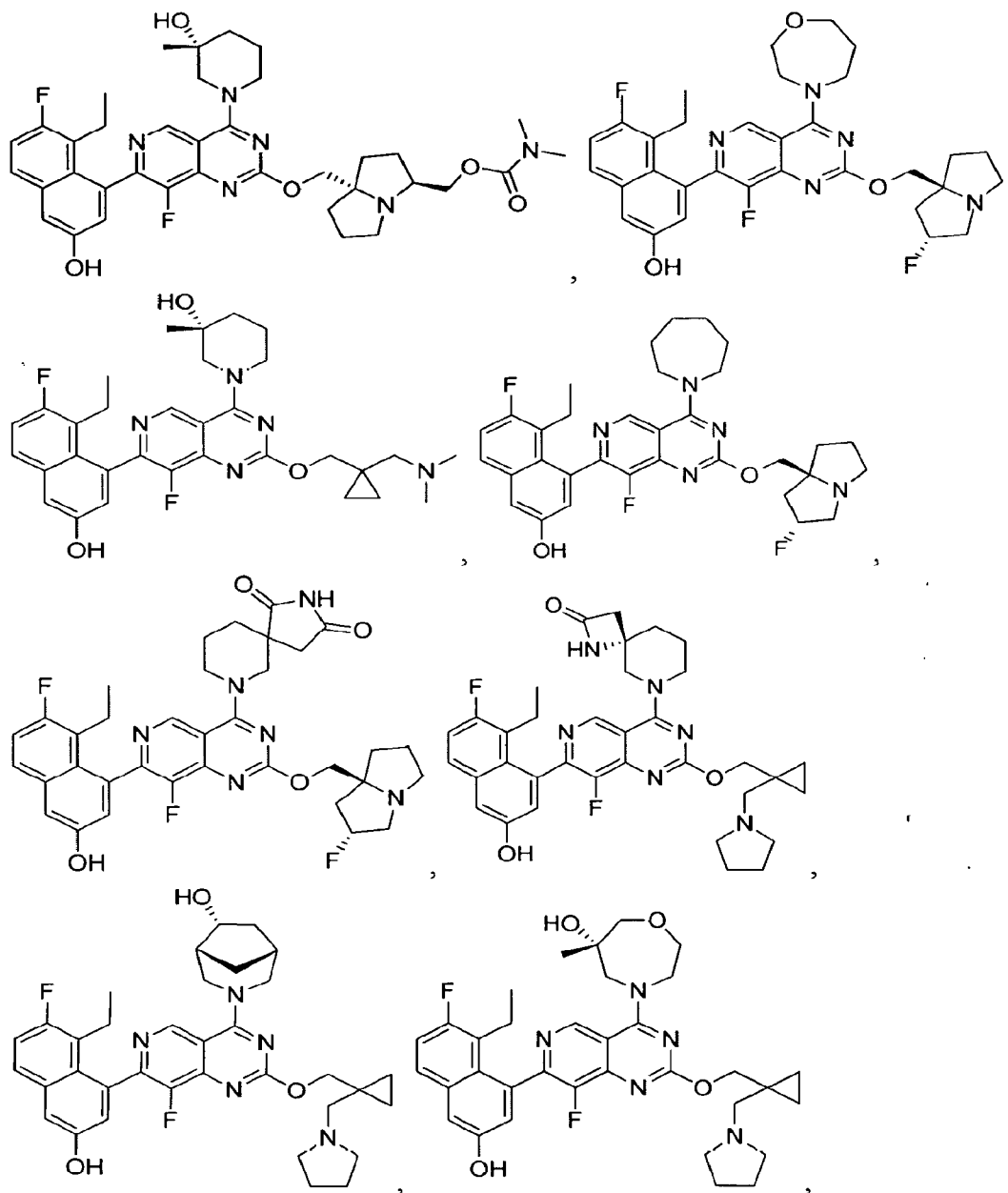


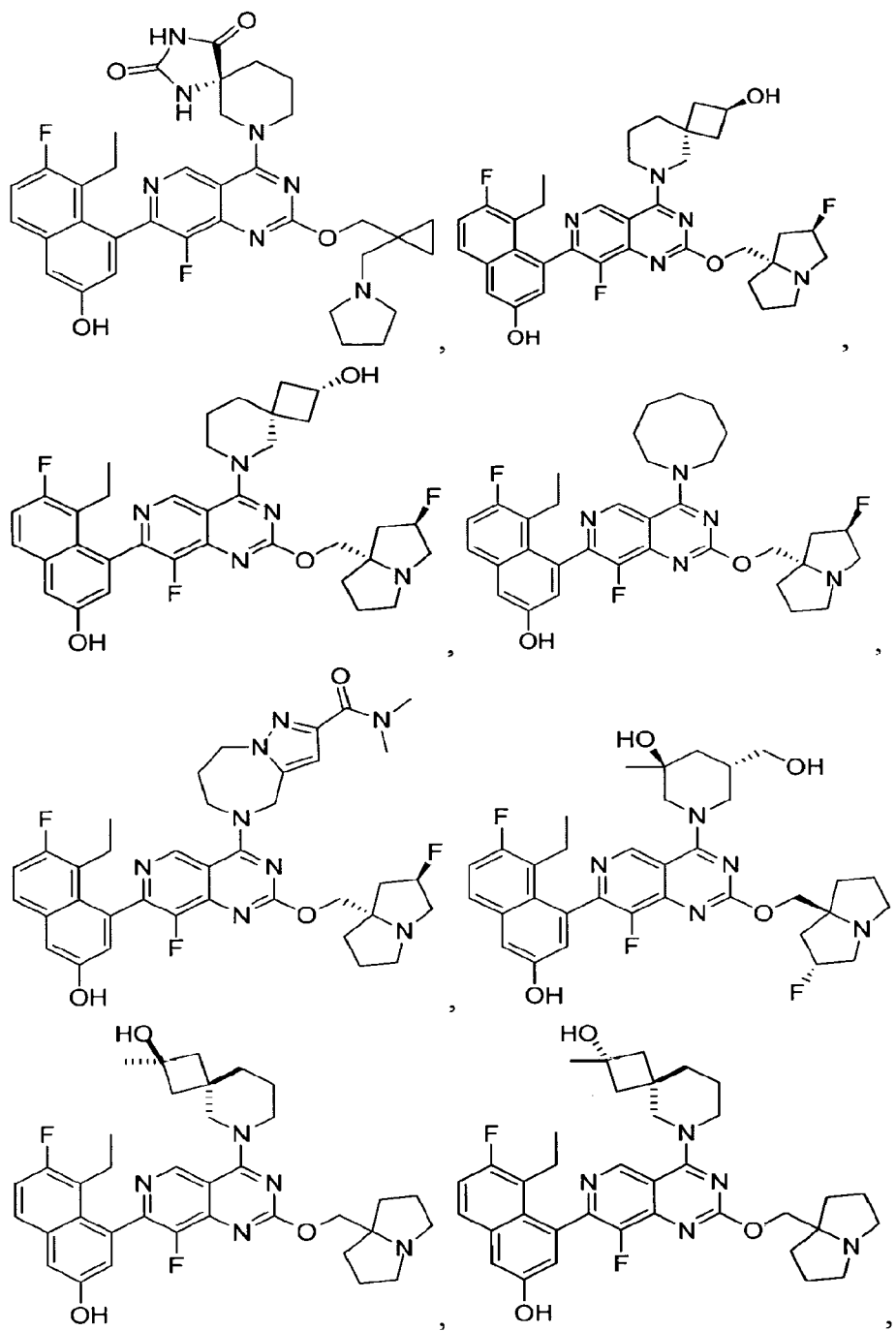


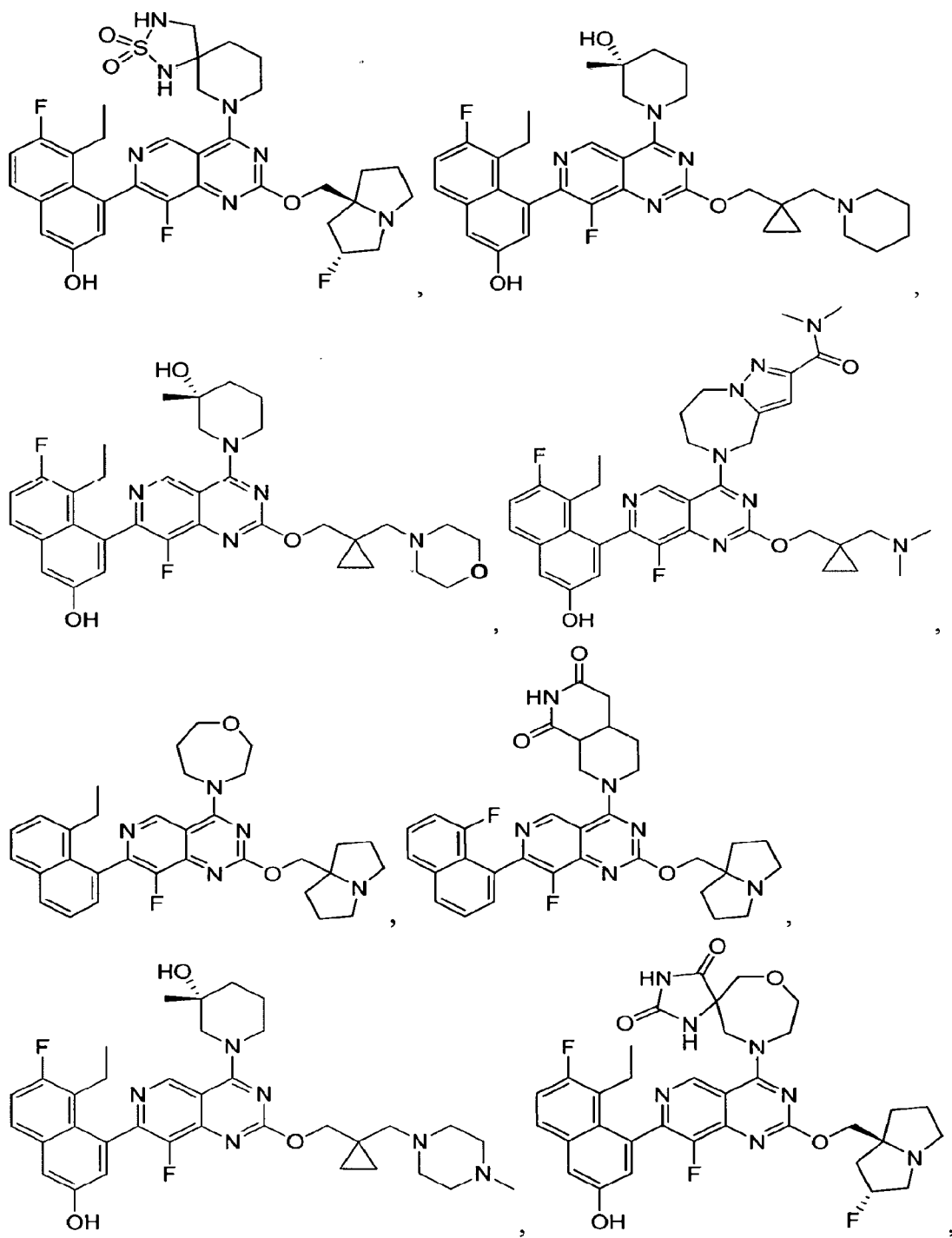


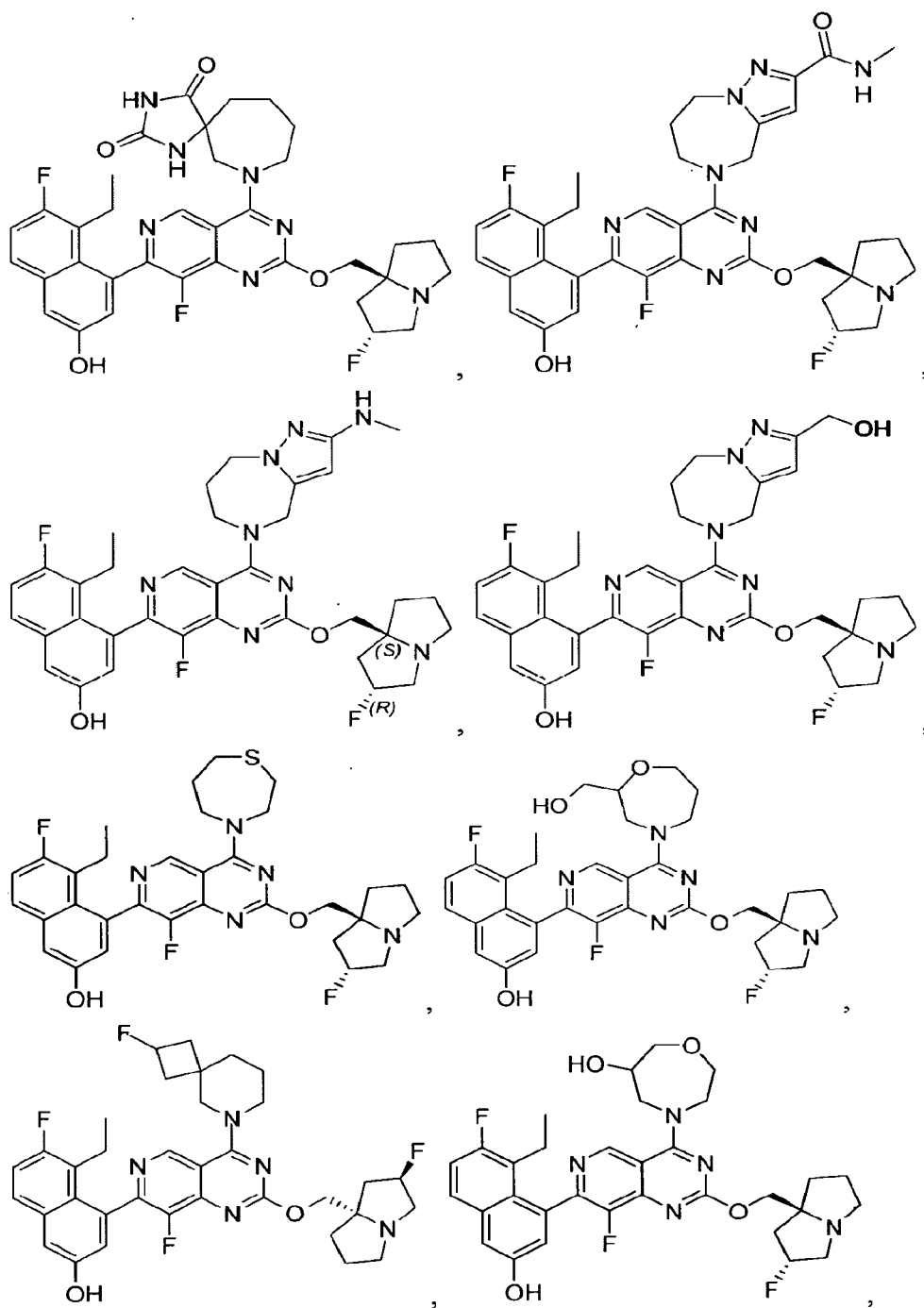


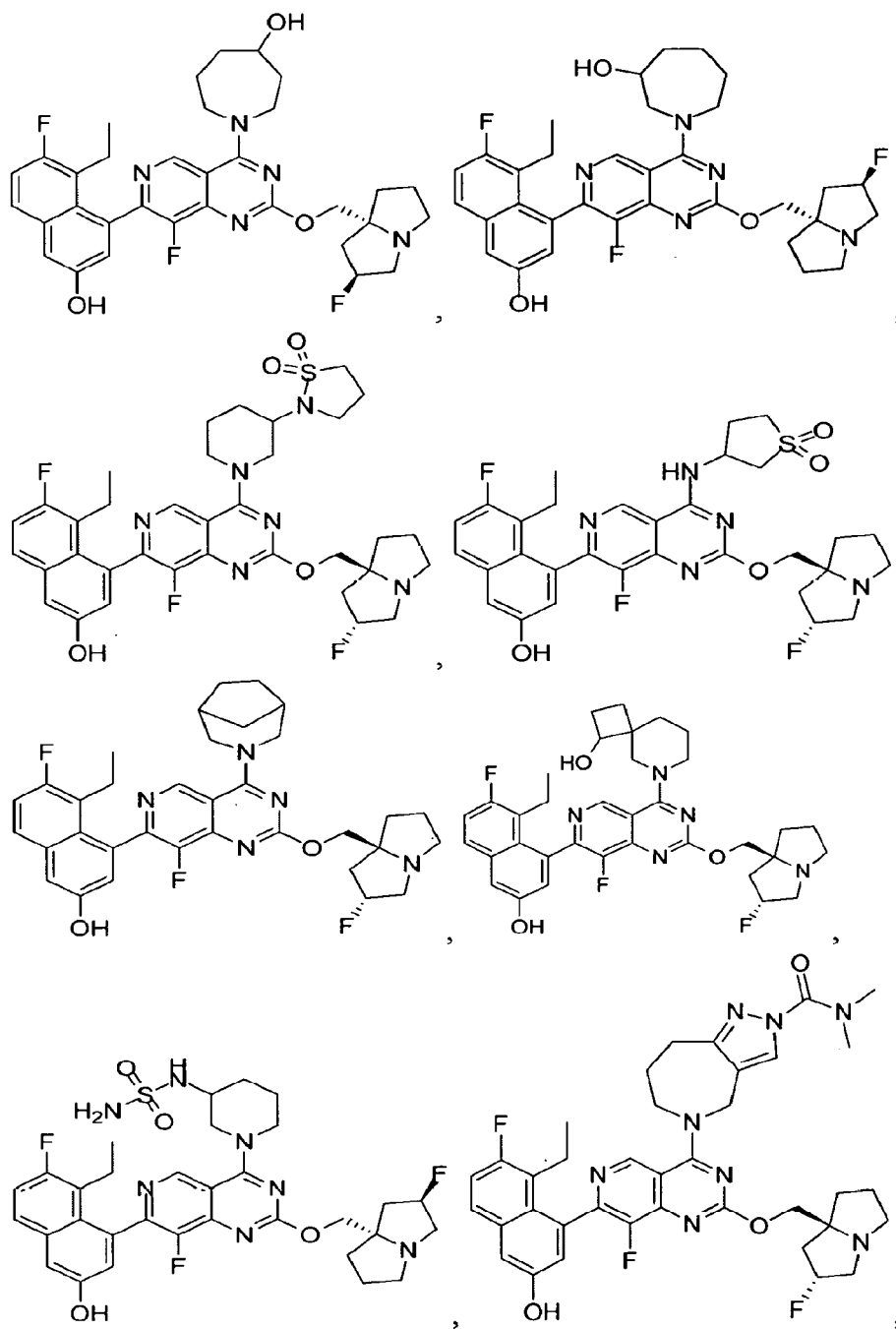


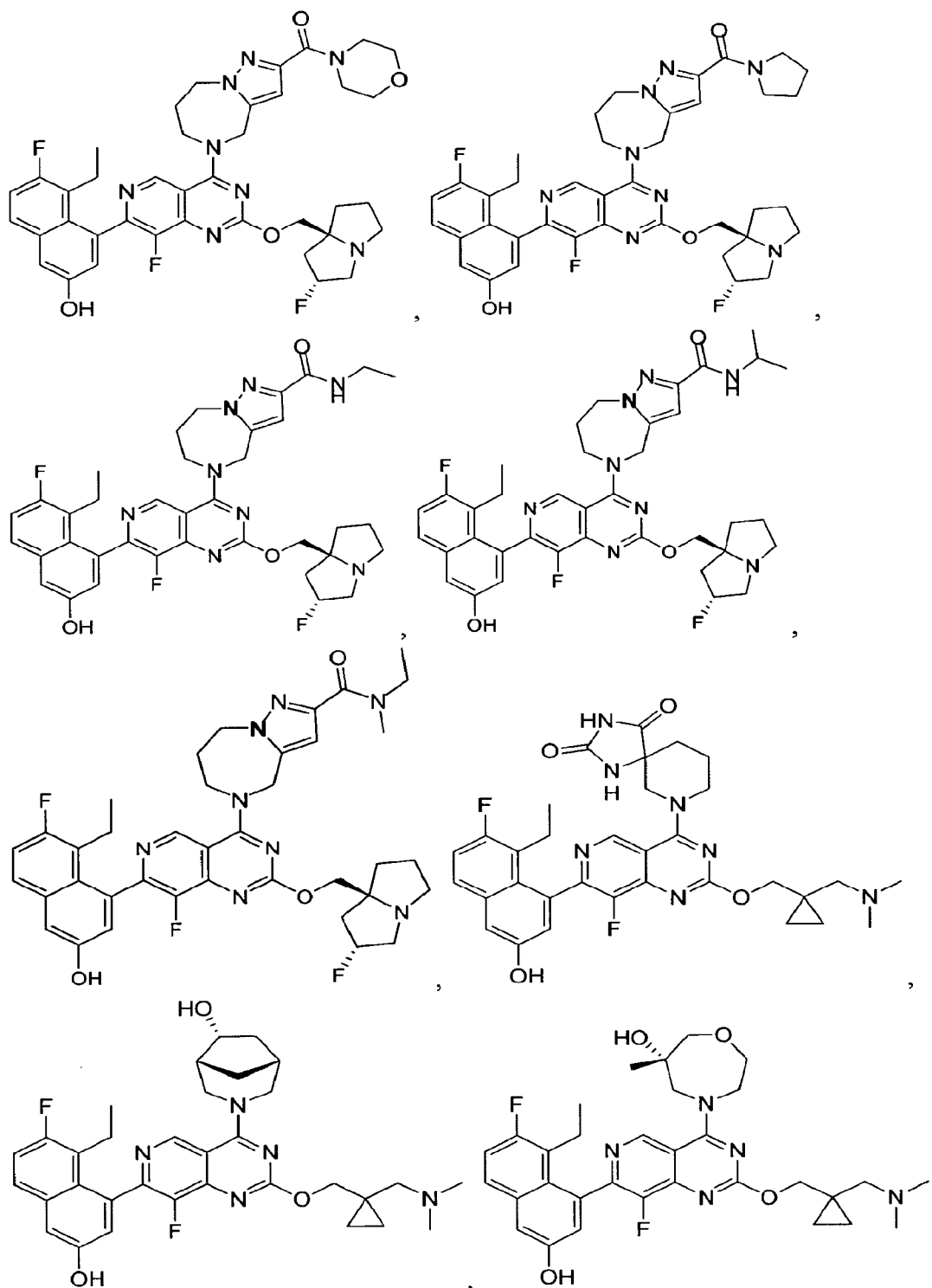


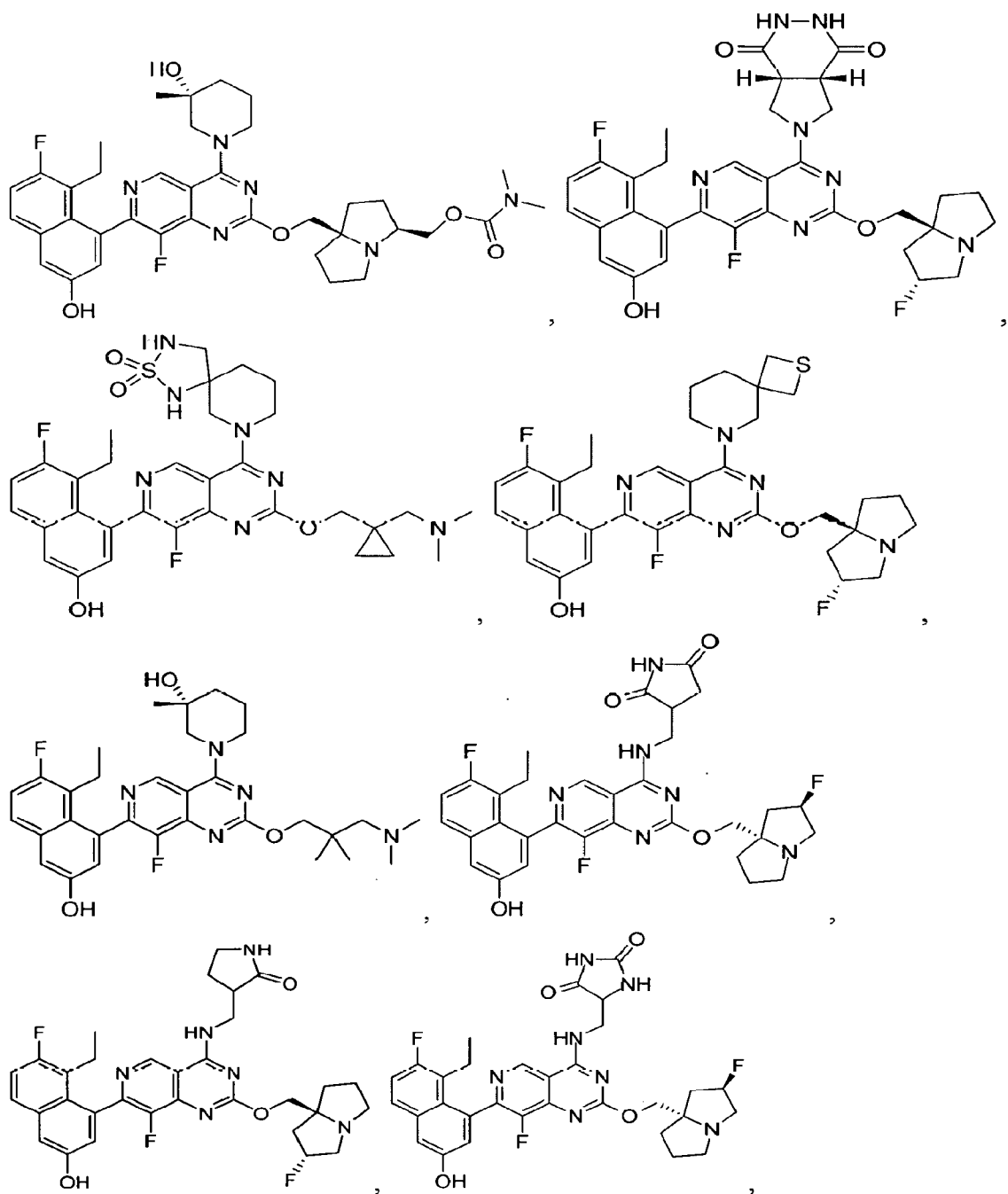


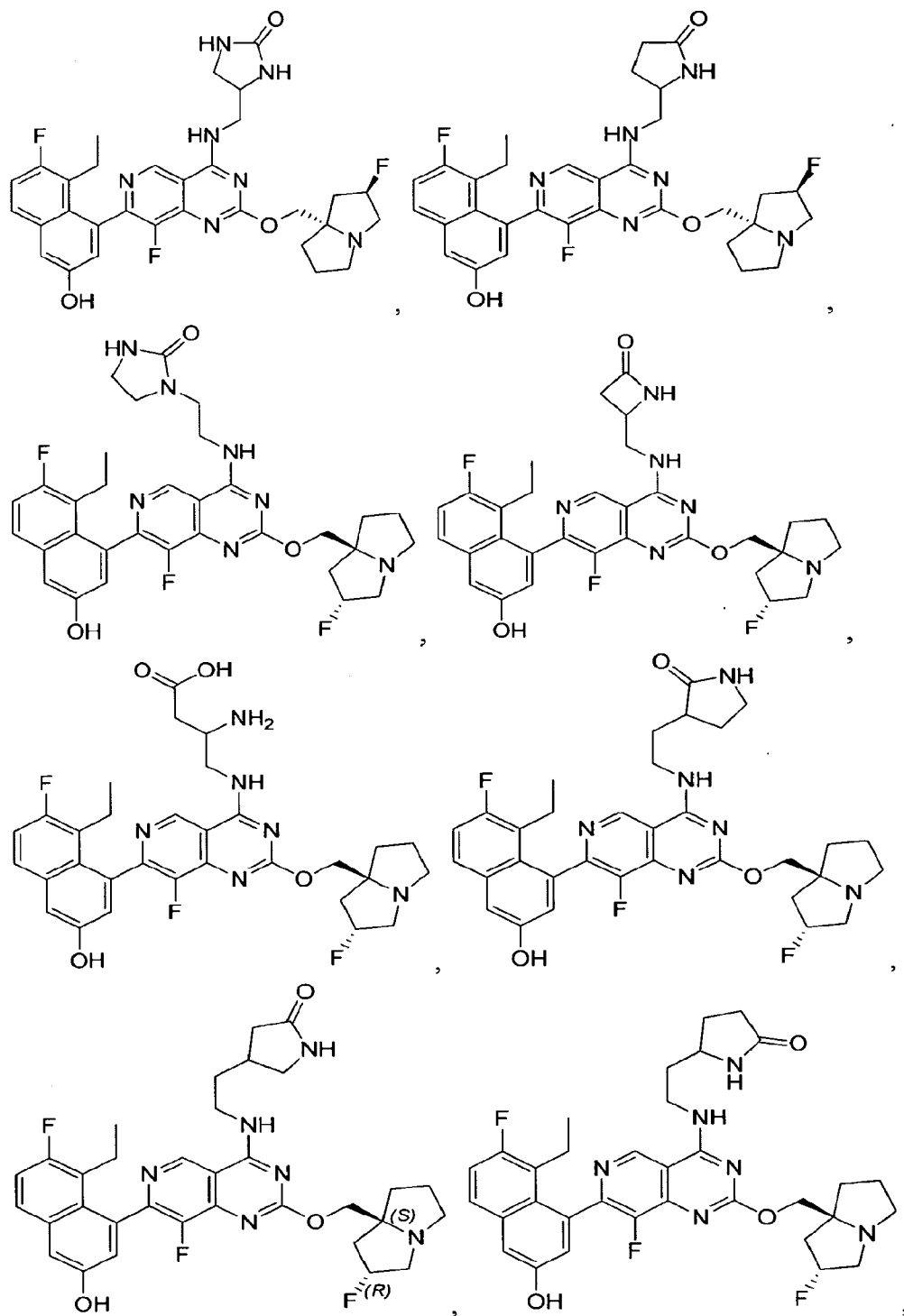


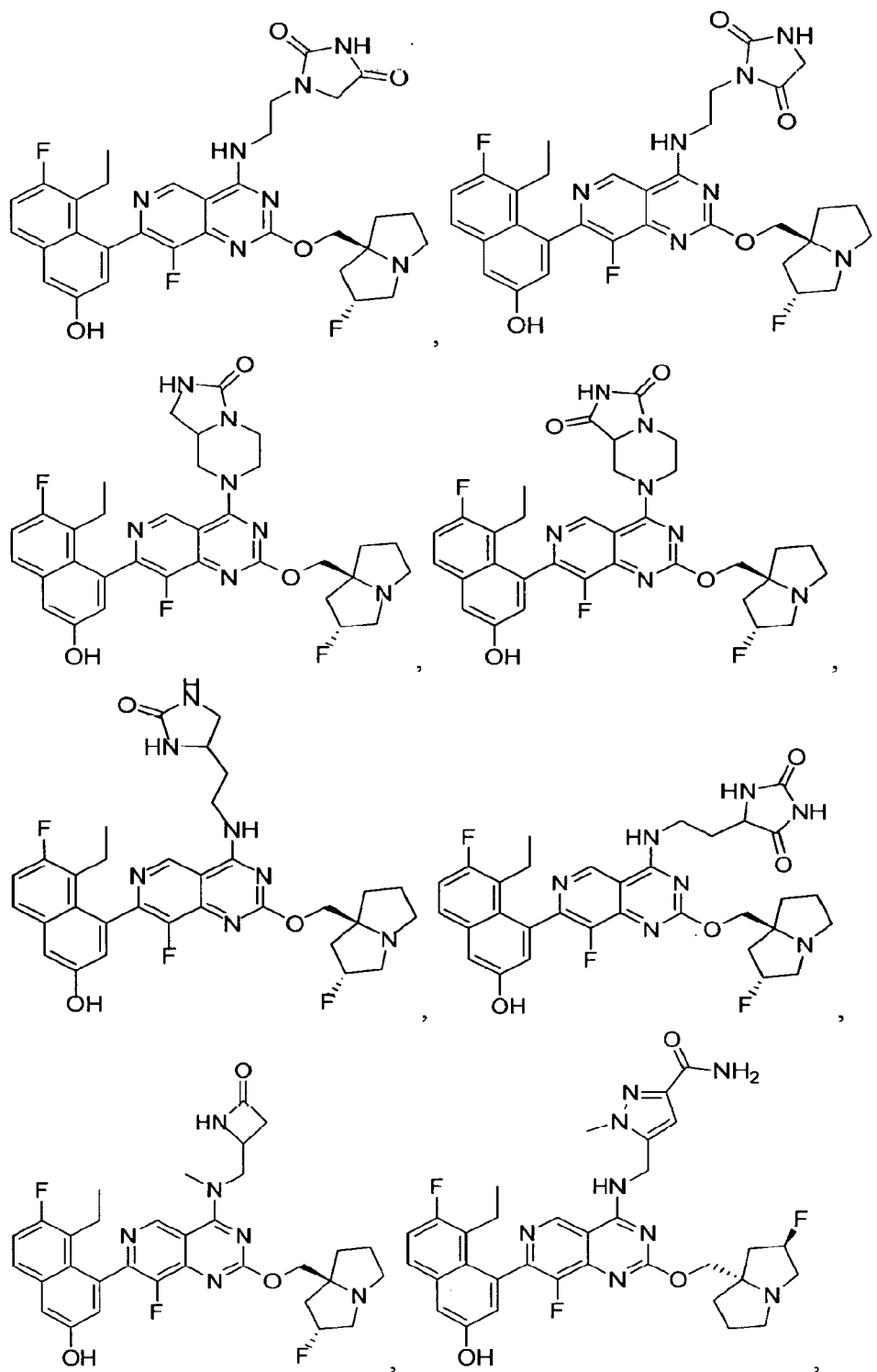


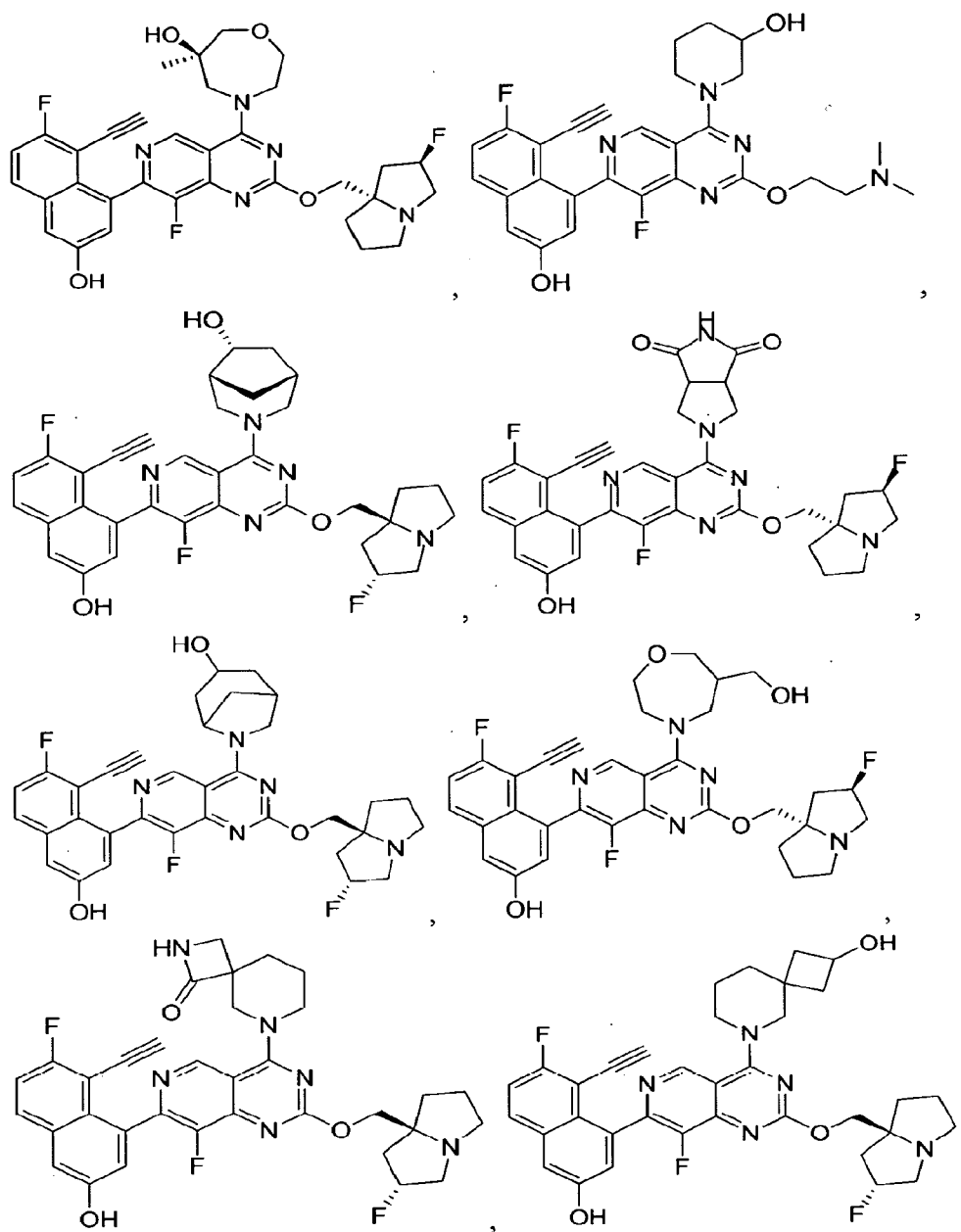


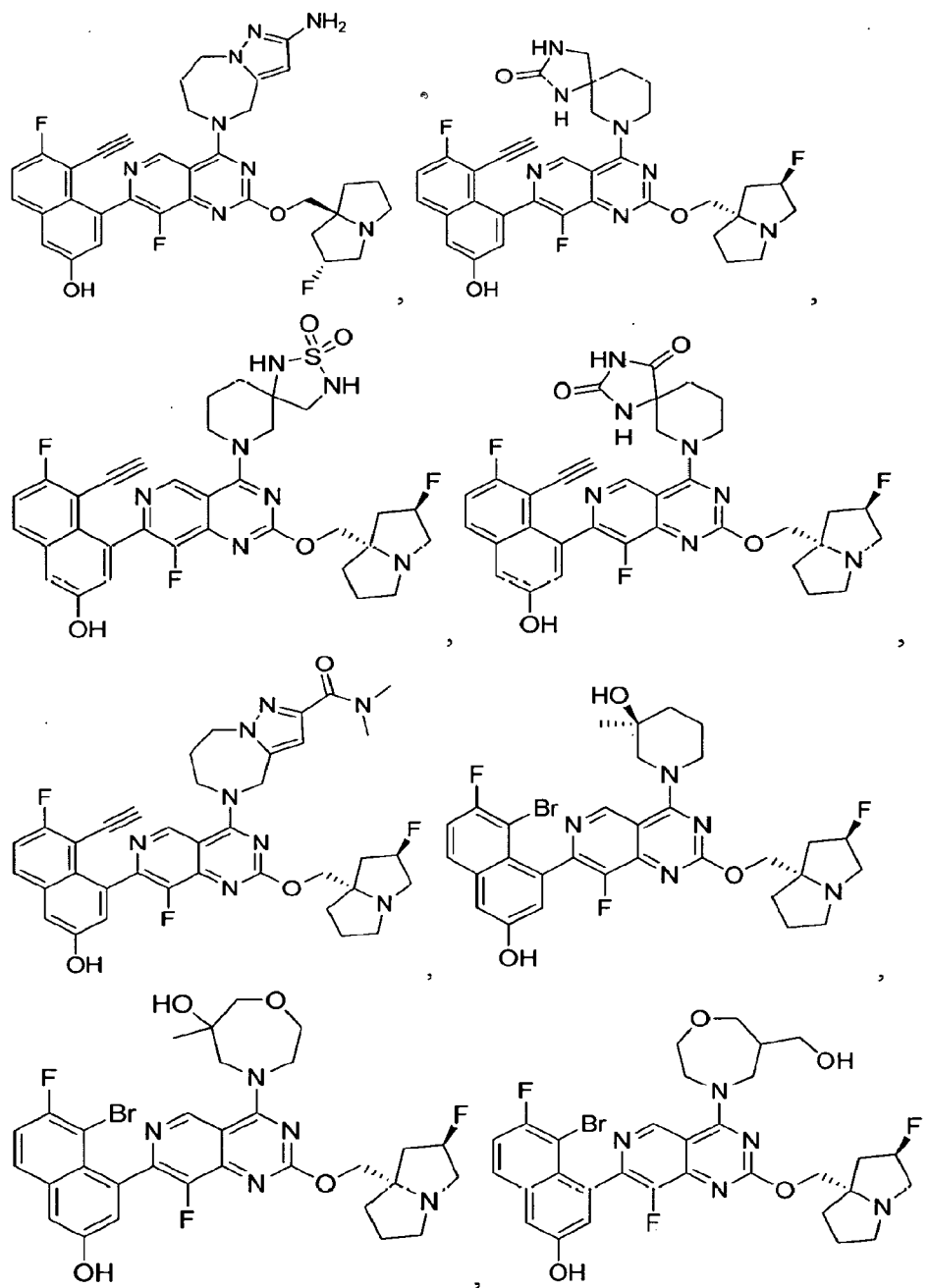


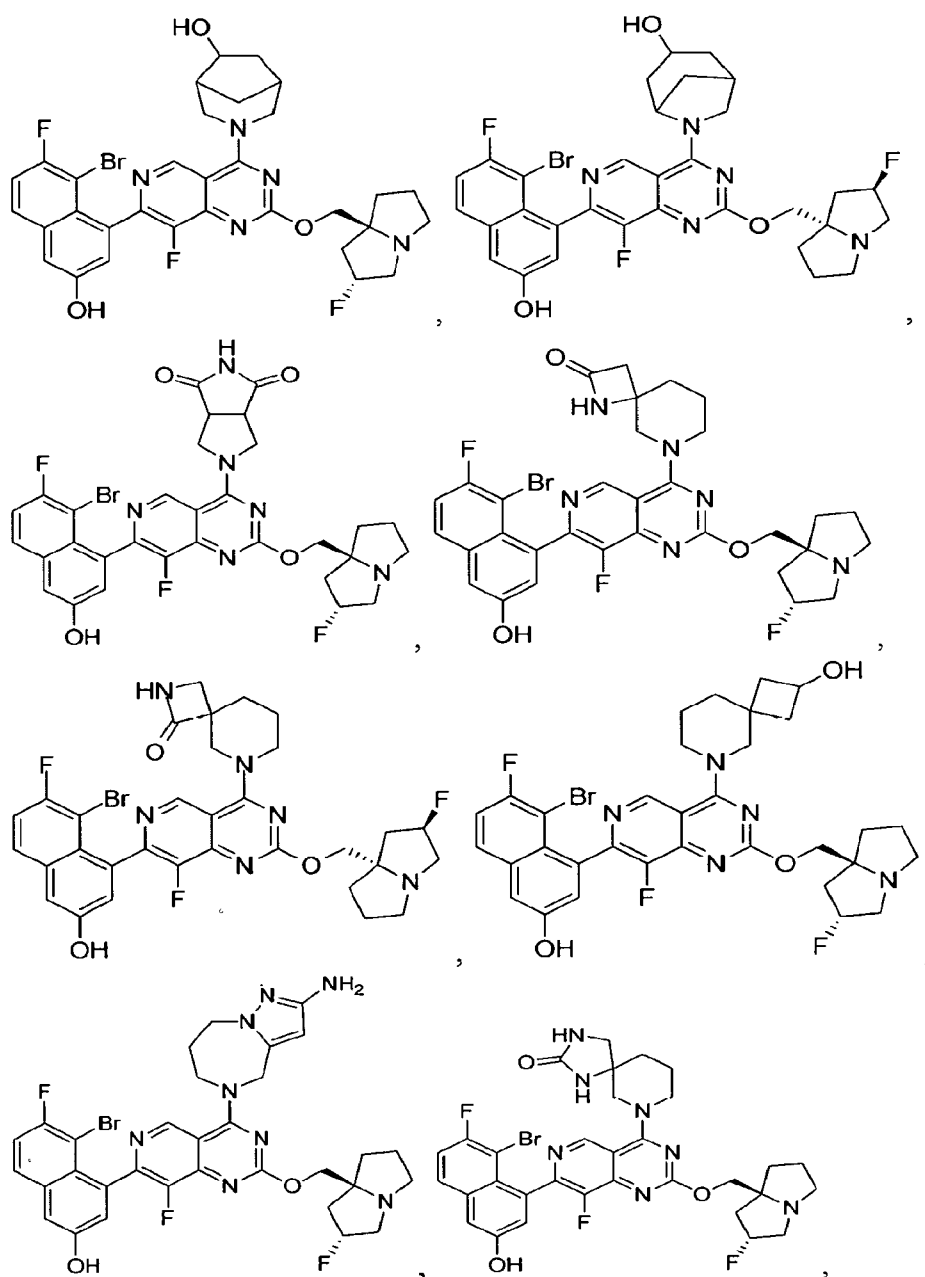


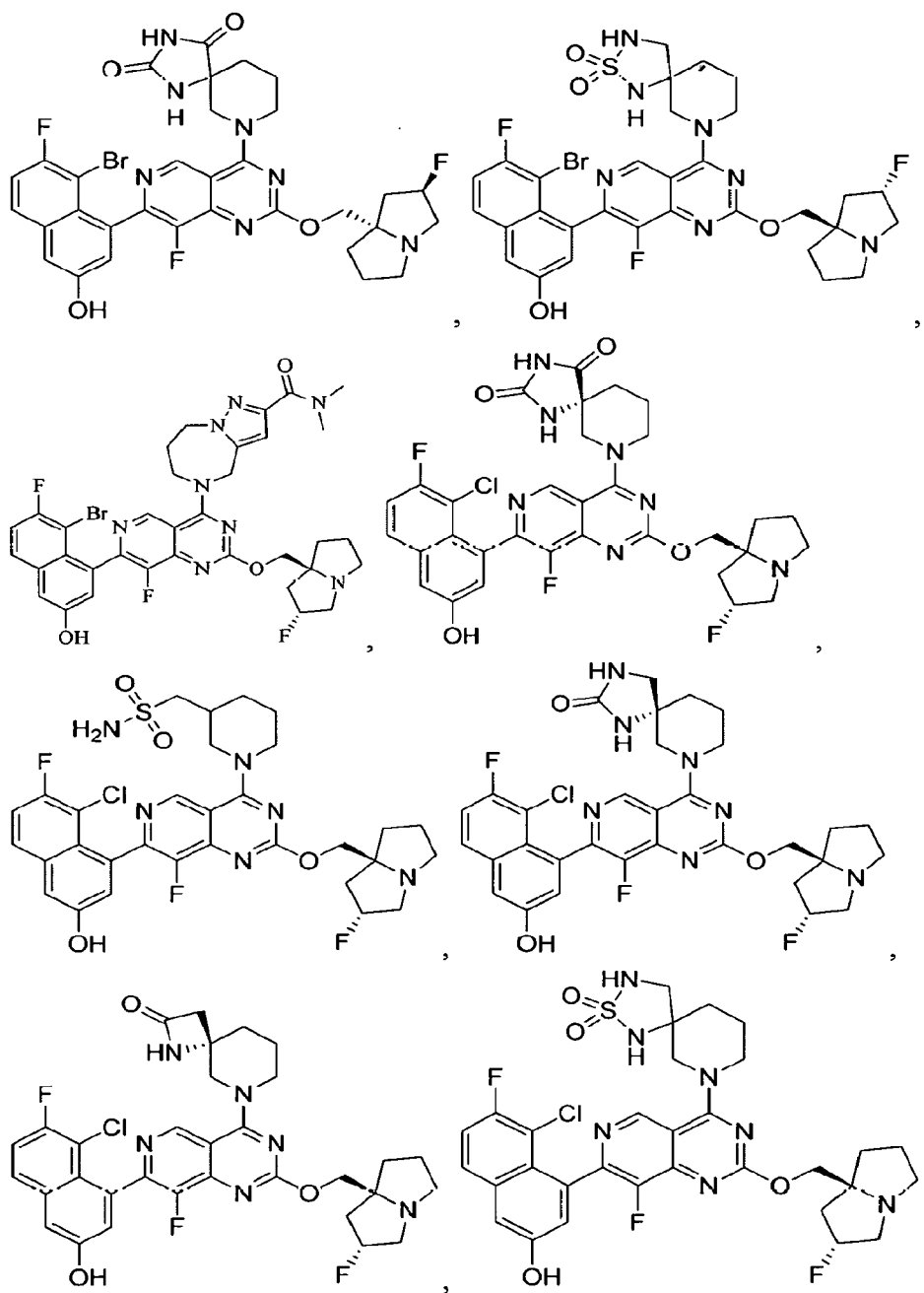


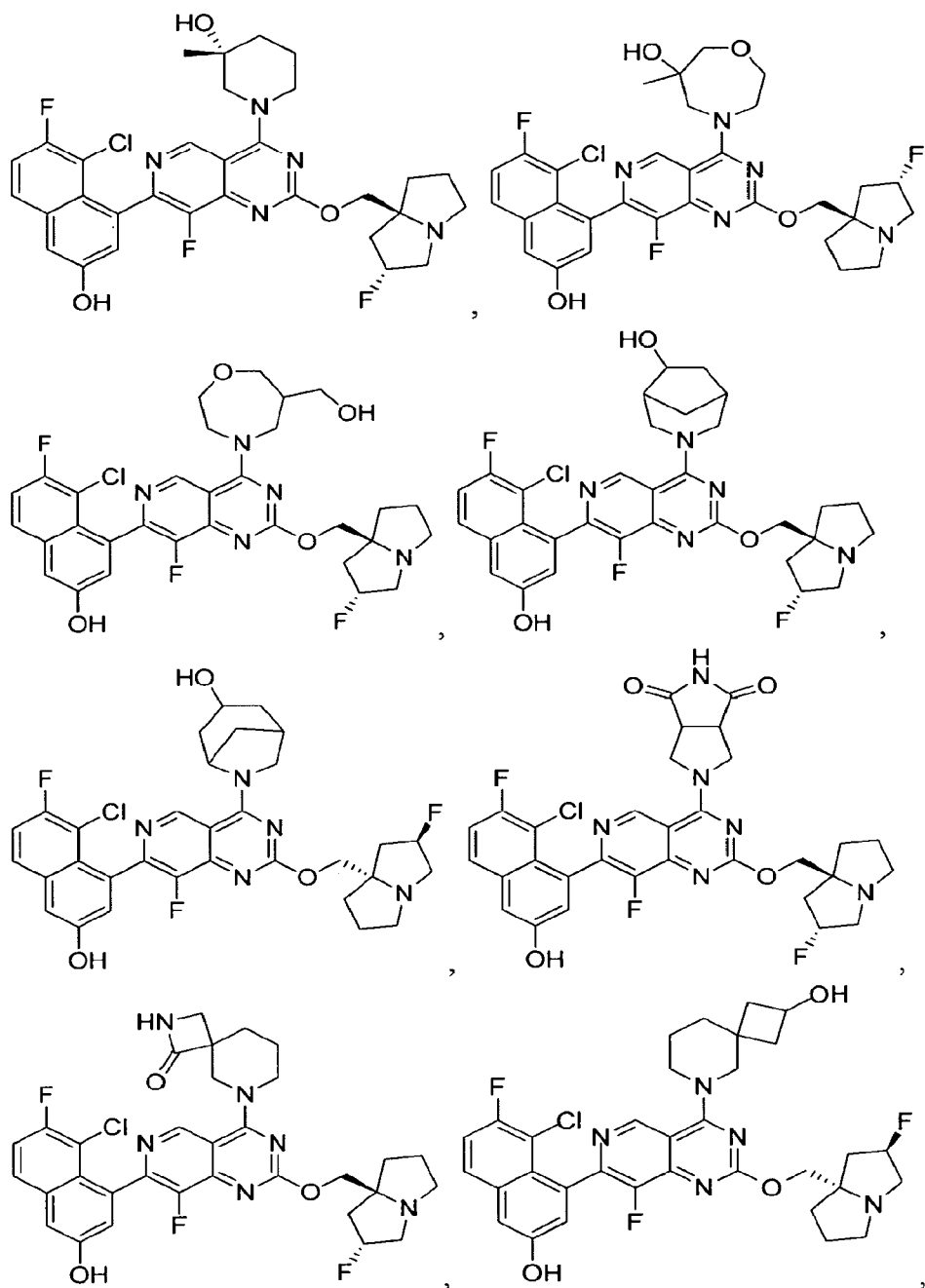


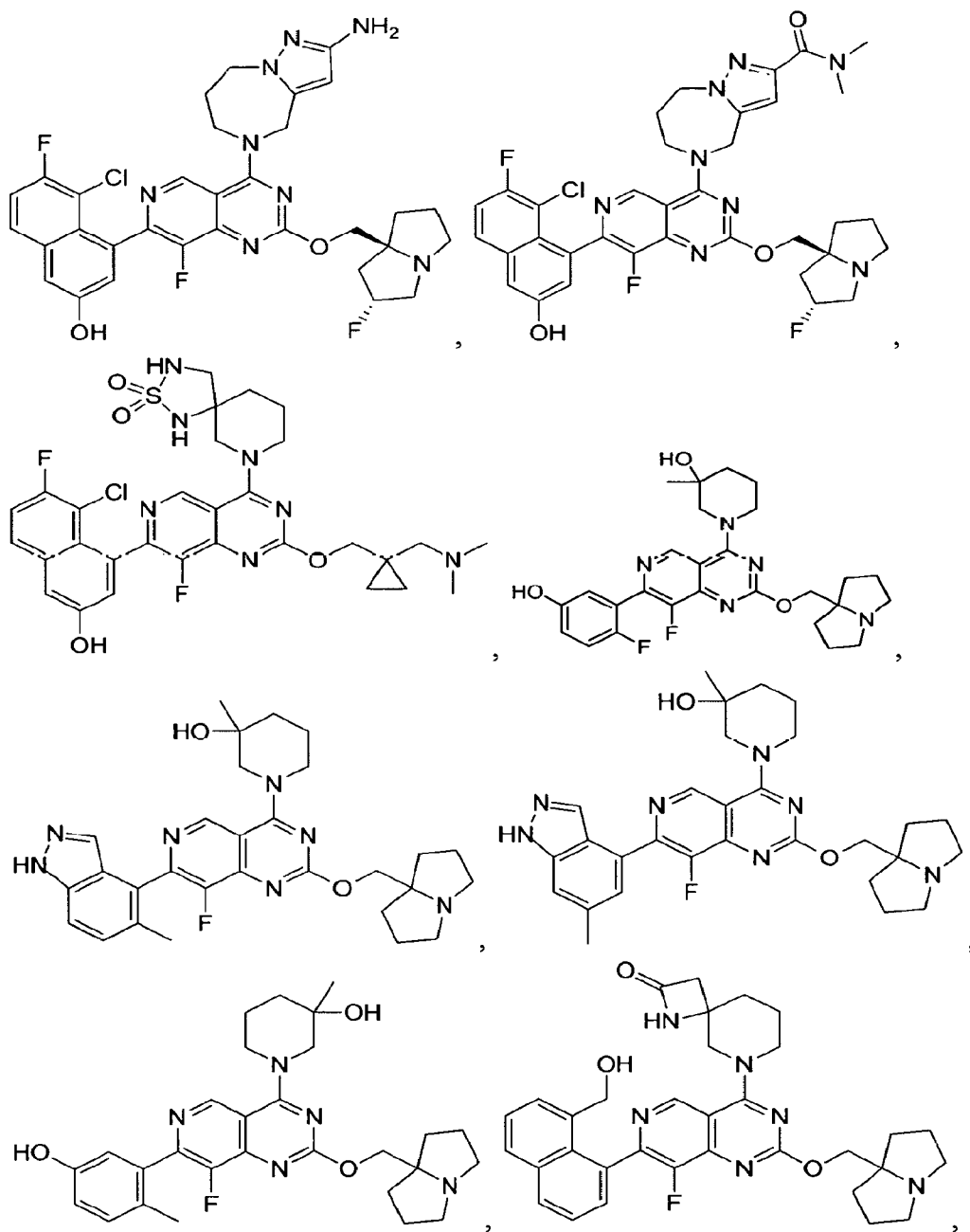


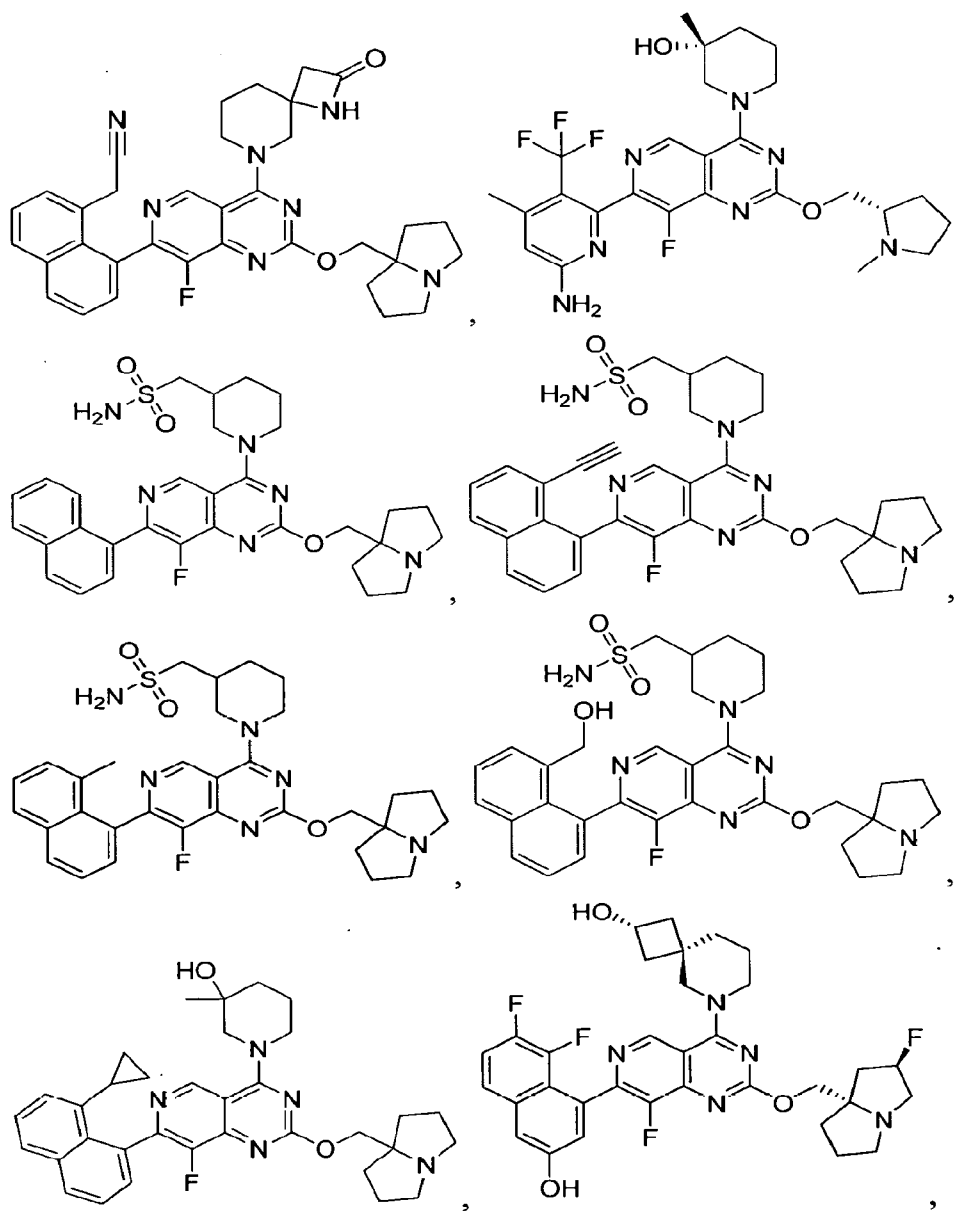


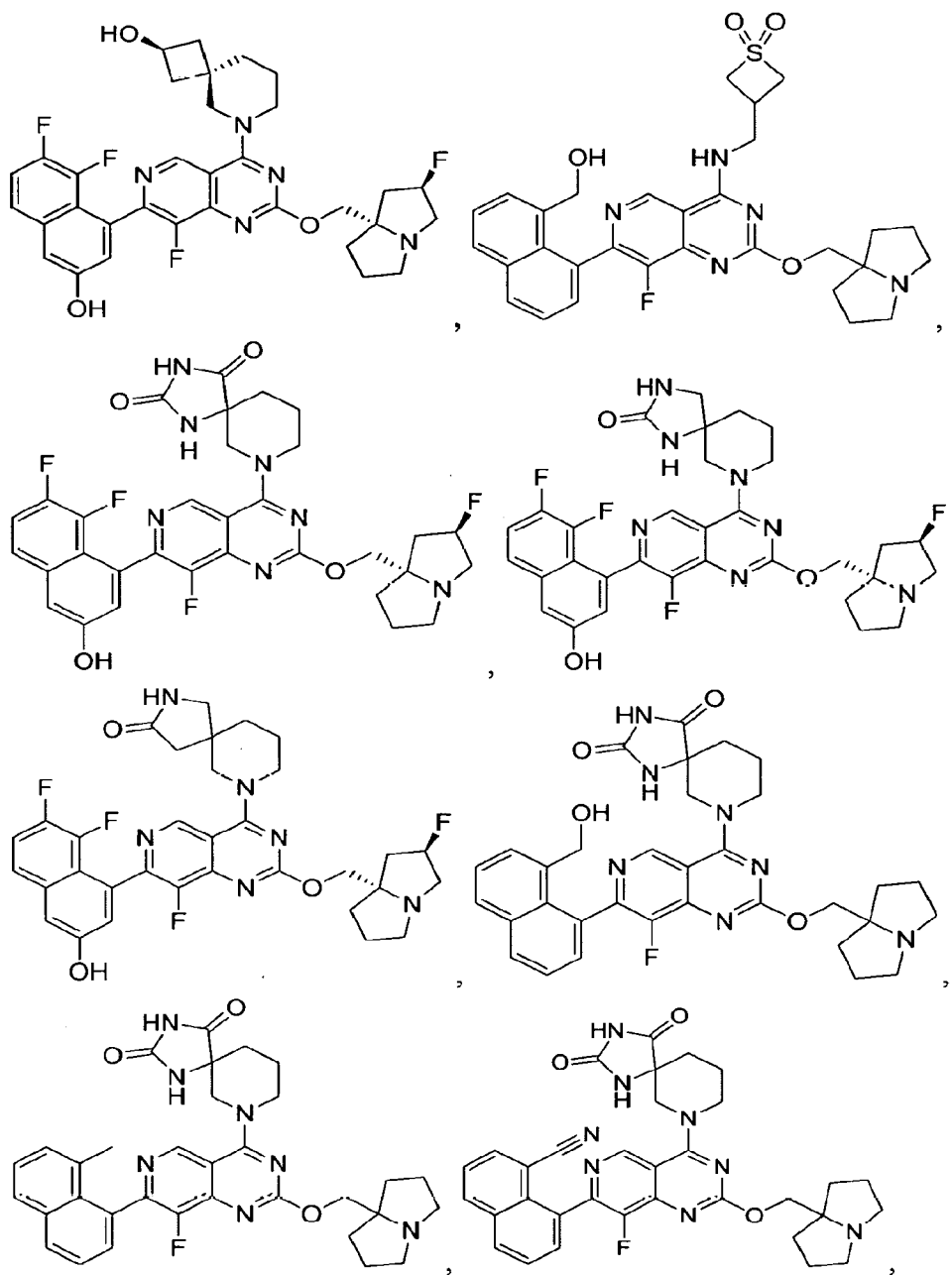


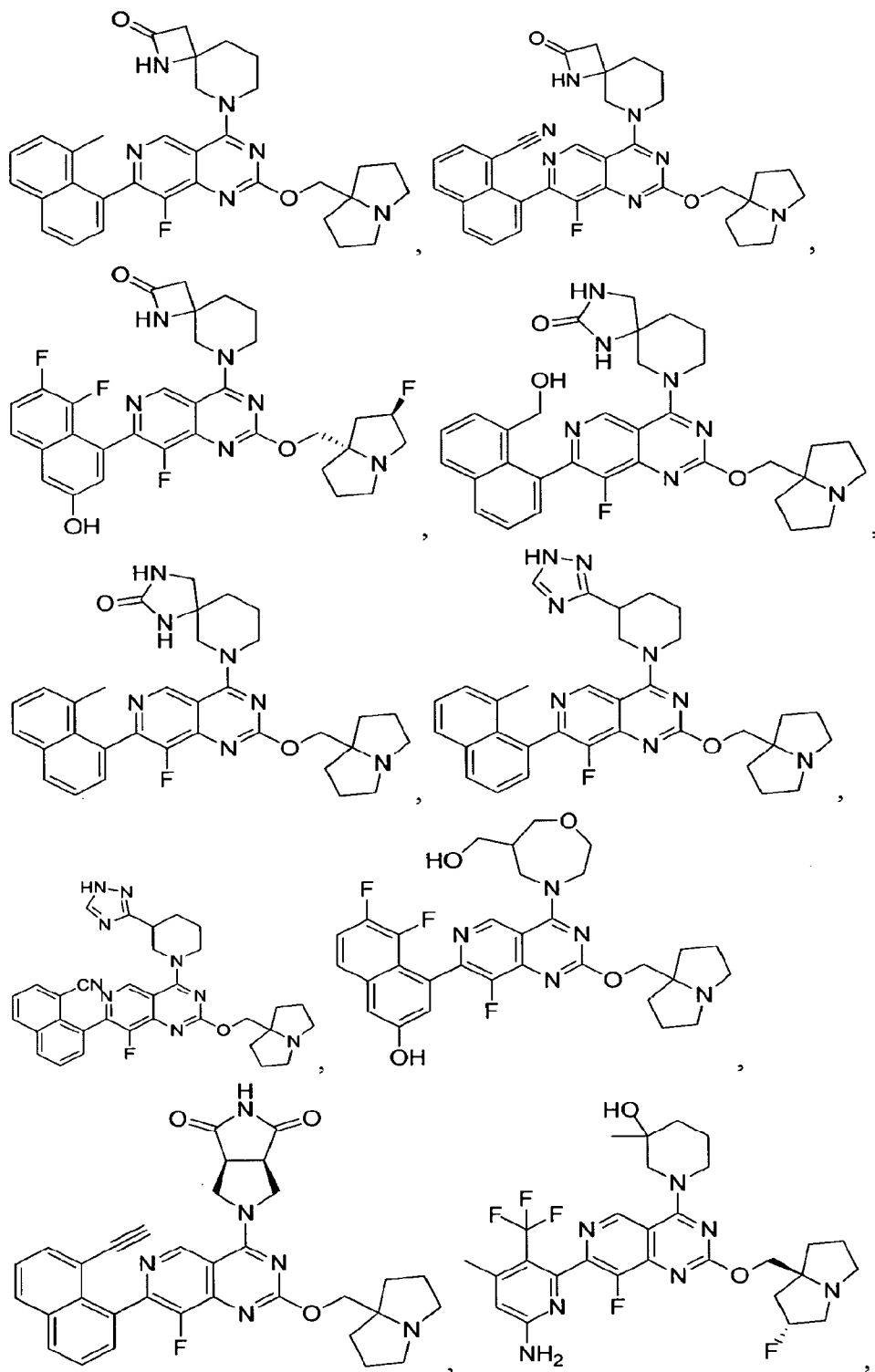


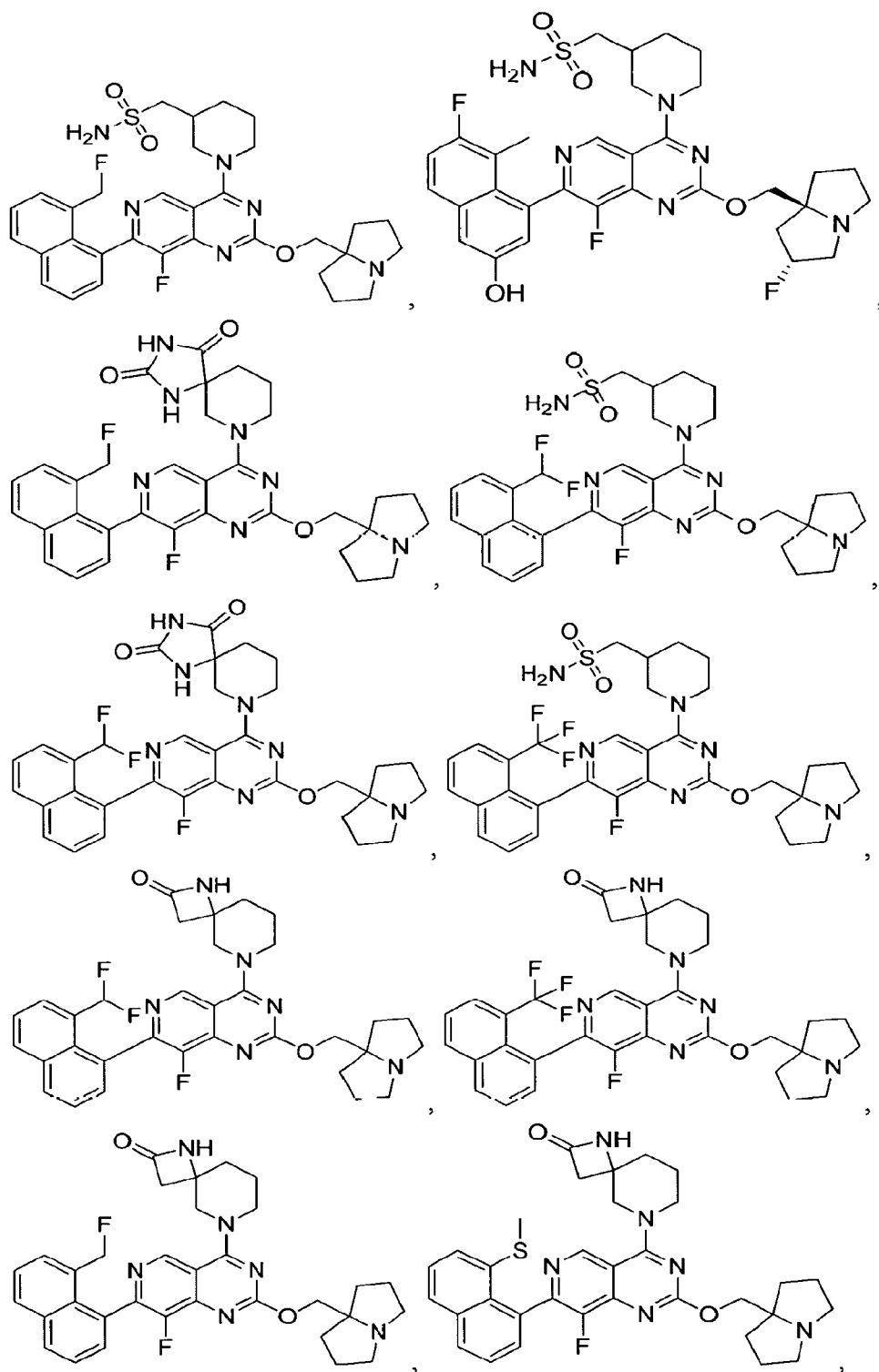


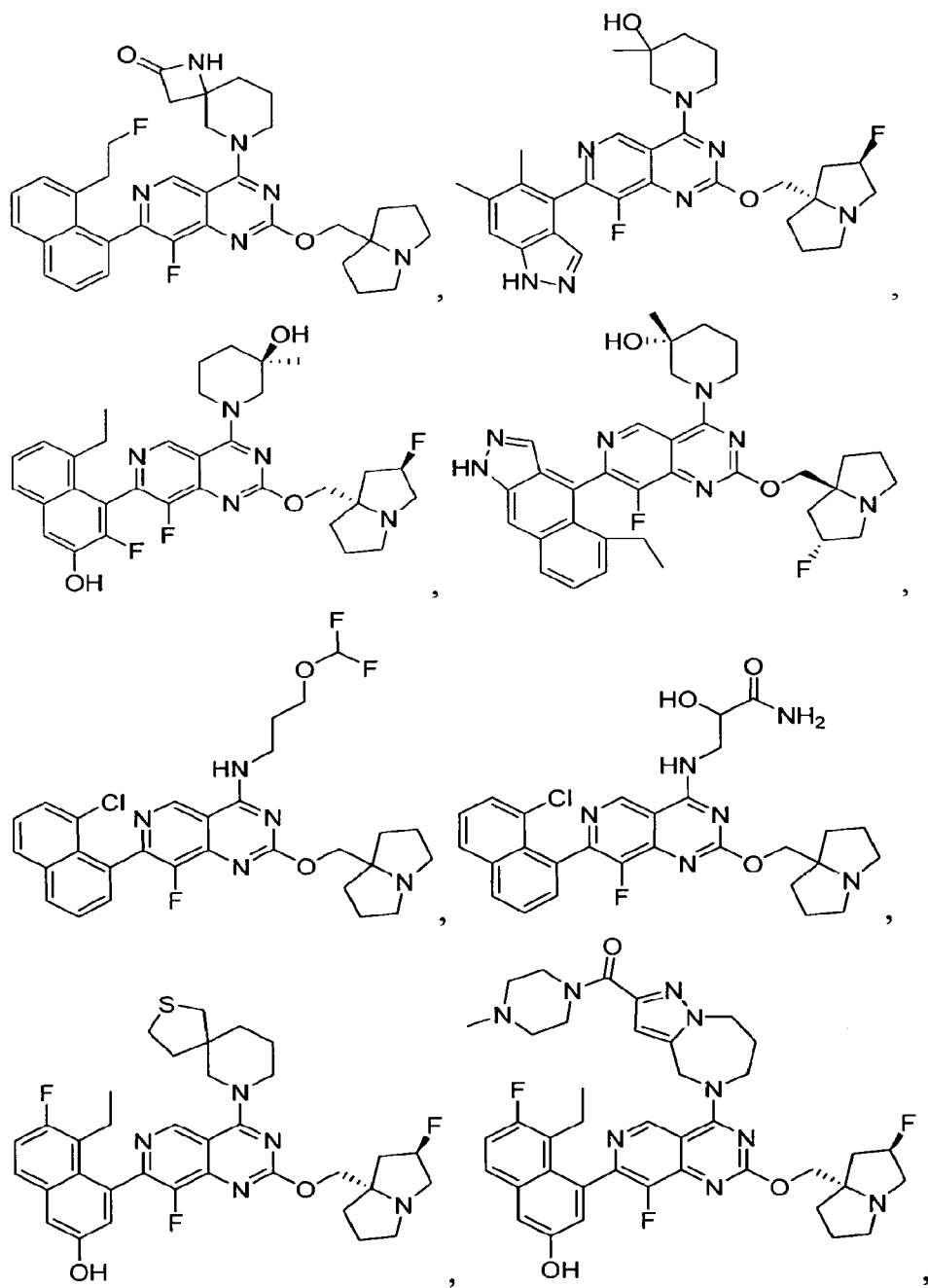


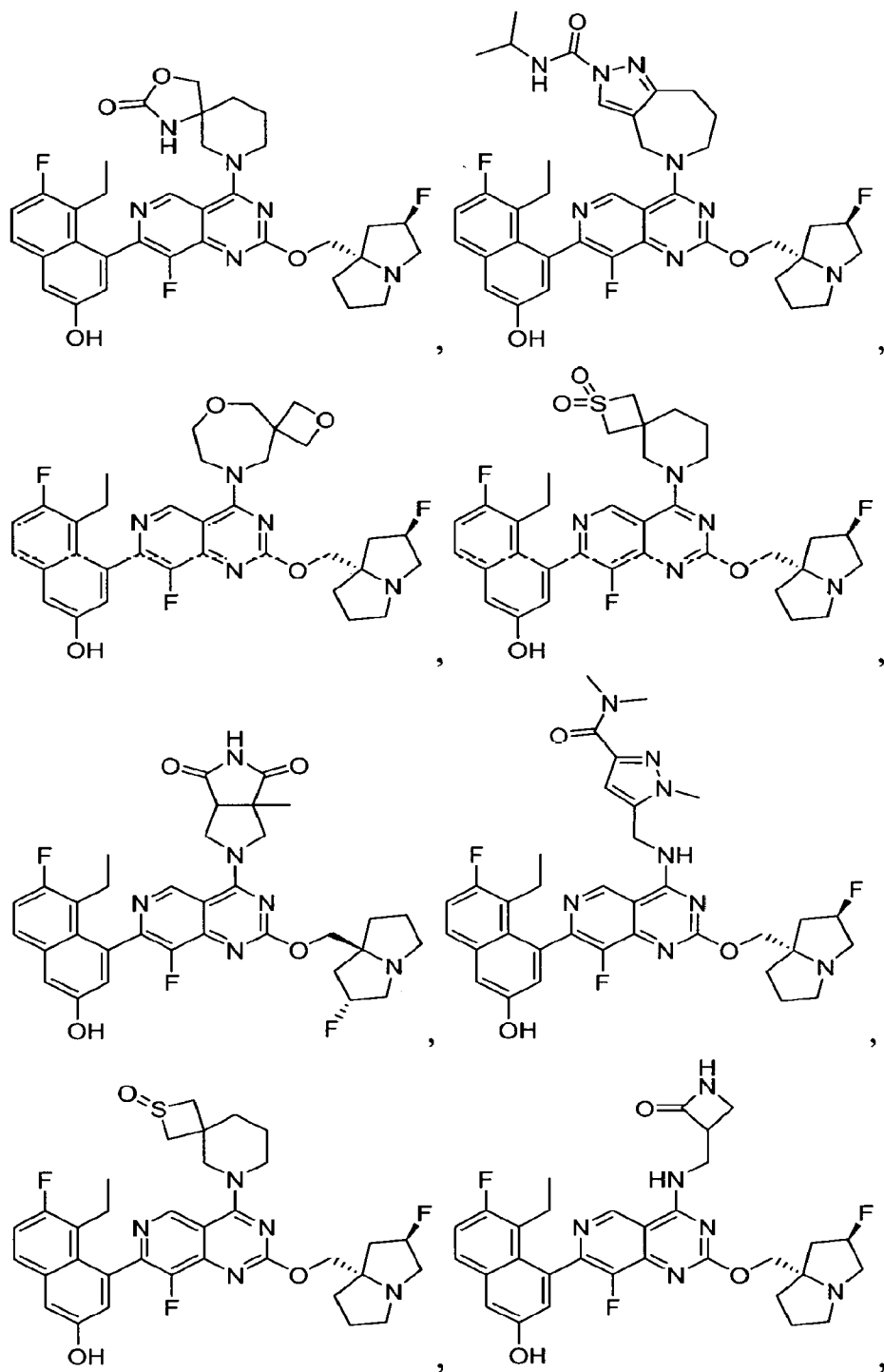


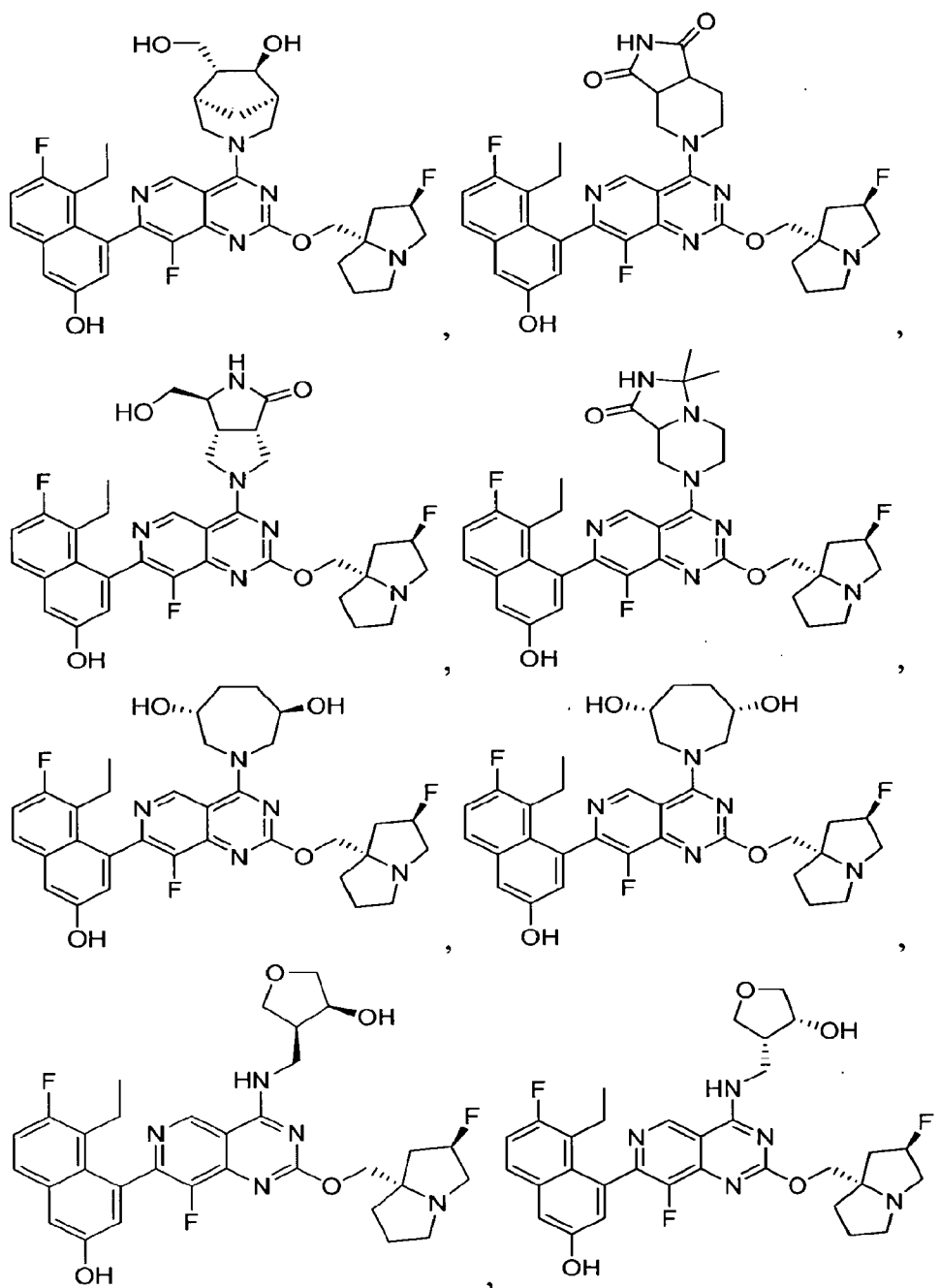


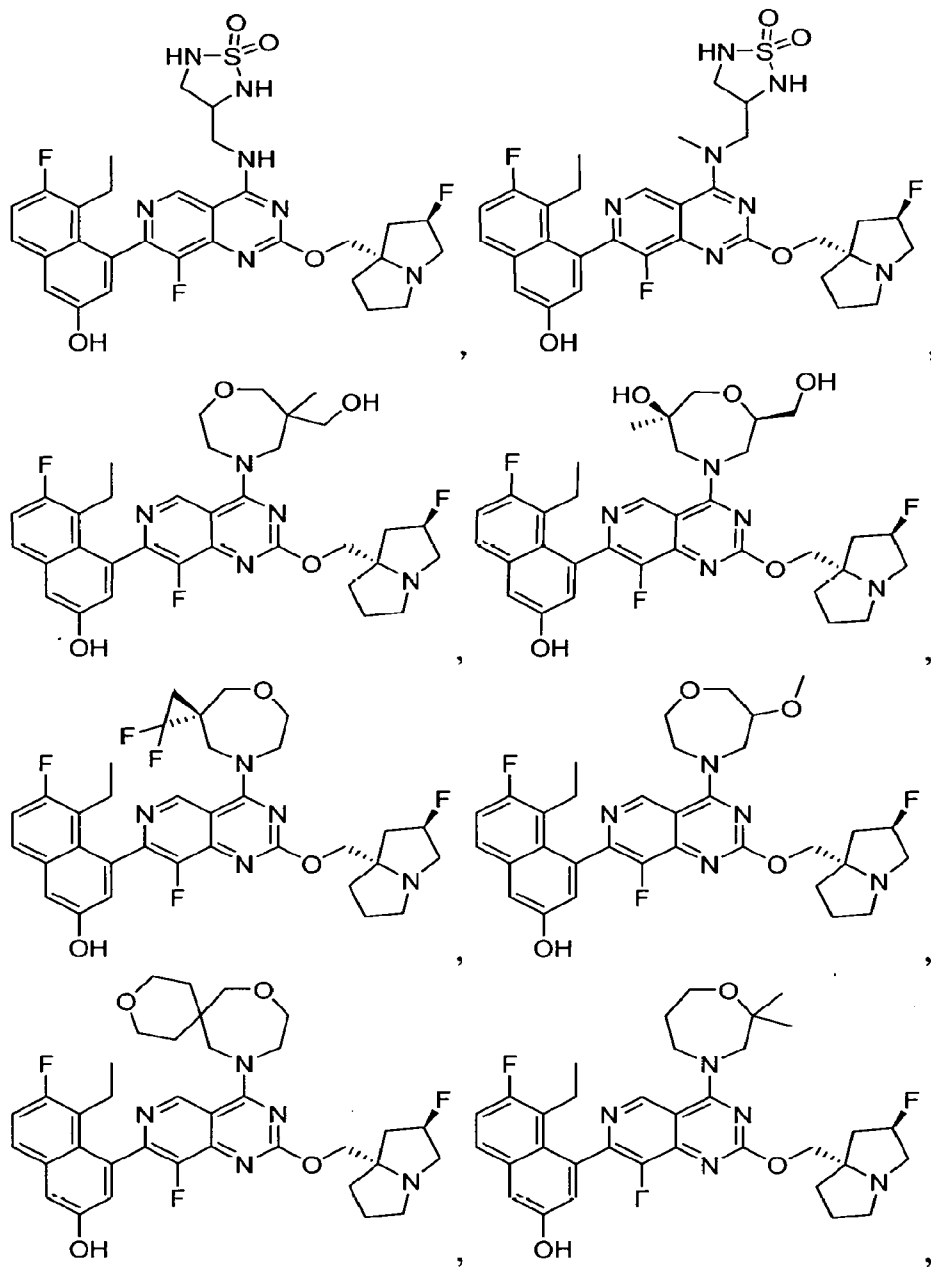


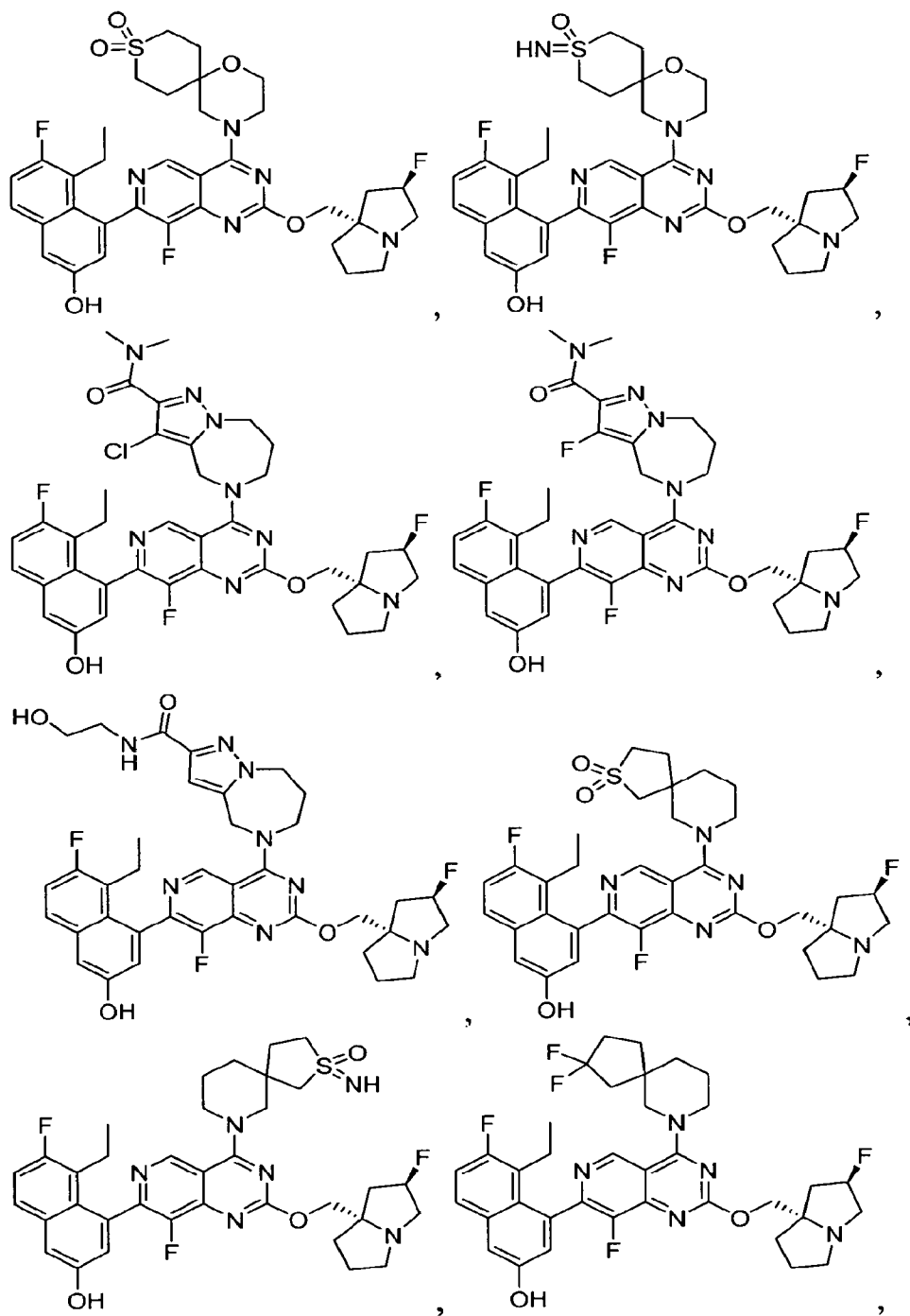


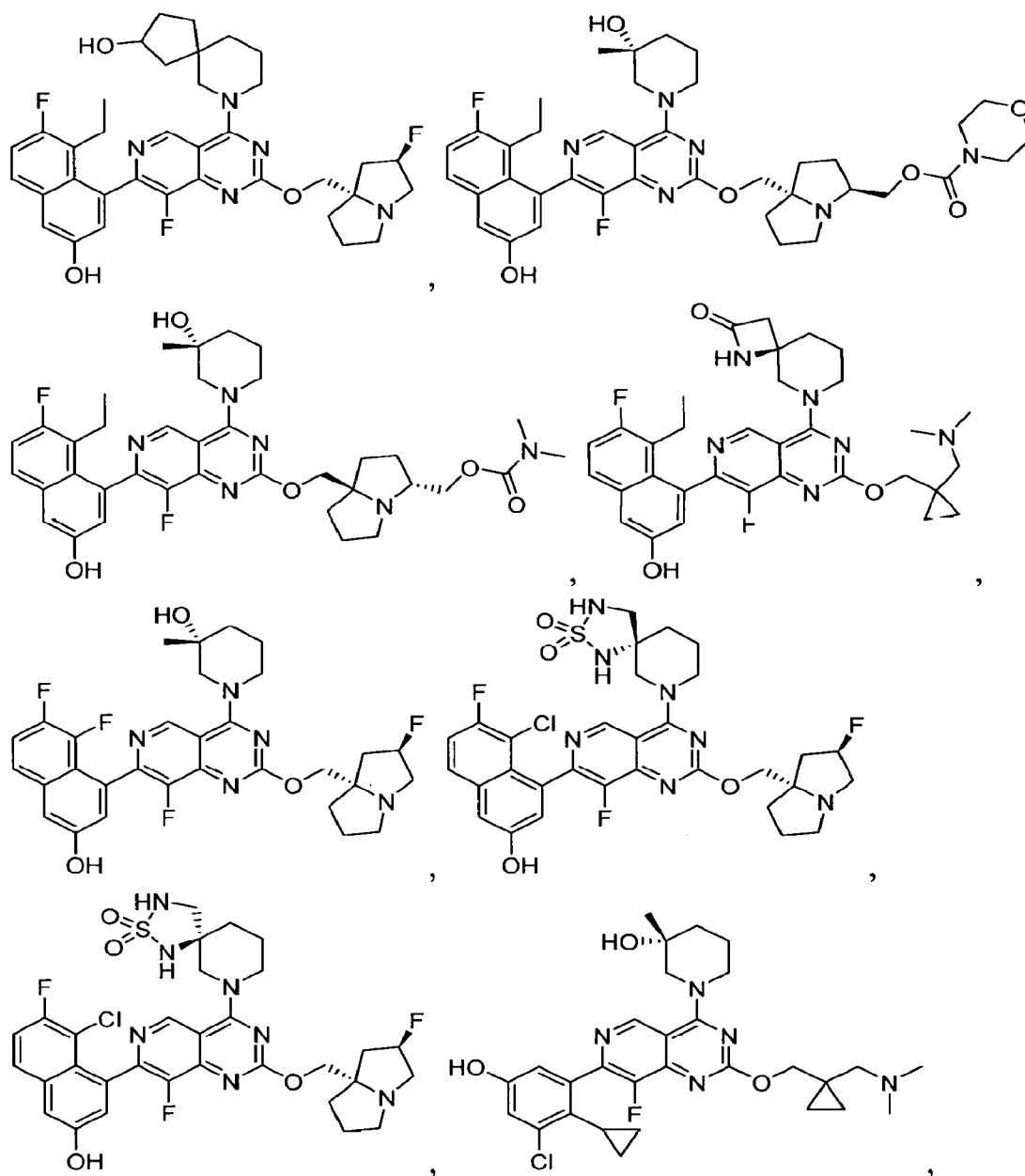


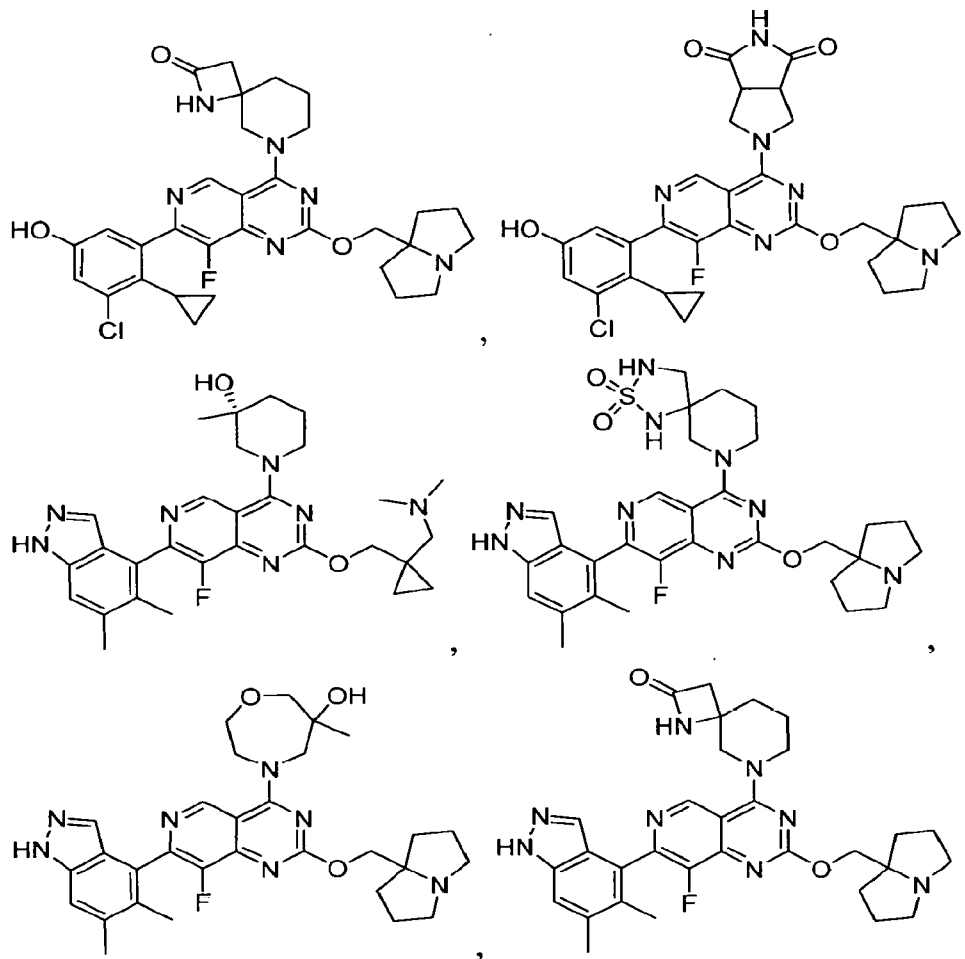












and pharmaceutically acceptable salts thereof.

62. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of any one of claims 1-53 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

63. A method for inhibiting the wild type KRas, KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D or KRas Q61H activity in a cell, comprising contacting the cell in which inhibition of KRas activity is desired with an effective amount of a compound of according to any one of claims 1-53 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 54.

64. A method for treating cancer comprising administering to a patient having cancer a therapeutically effective amount of a compound according to any one of claims 1-53 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 54.

65. The method of claim 56, wherein the therapeutically effective amount of the compound is between about 0.01 to 100 mg/kg per day.

66. The method of claim 57, wherein the therapeutically effective amount of the compound is between about 0.1 to 50 mg/kg per day.

67. The method of claim 56, wherein the cancer is selected from the group consisting of Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Biliary tract: gall bladder carcinoma, ampullary carcinoma, cholangiocarcinoma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma,

osteochondroma (osteochondilagenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma.

68. The method of claim 59, wherein the cancer is a KRas G12A-associated cancer.
69. The method of claim 59, wherein the cancer is a KRas G12C-associated cancer.
70. The method of claim 59, wherein the cancer is a KRas G12D-associated cancer.
71. The method of claim 59, wherein the cancer is a KRas G12R-associated cancer.
72. The method of claim 59, wherein the cancer is a KRas G12S-associated cancer.
73. The method of claim 59, wherein the cancer is a KRas G12V-associated cancer.
74. The method of claim 59, wherein the cancer is a KRas G13D-associated cancer.

75. The method of claim 59, wherein the cancer is a KRas Q61H-associated cancer.
76. The method of claim 59, wherein the cancer is a KRas G12A-associated cancer.
77. The method of claim 59, wherein the cancer is associated with at least one of wild type KRas, KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D or KRas Q61H.
78. The method of any of claims 60-69, wherein the cancer is non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer or pancreatic cancer.
79. A method for treating cancer in a patient in need thereof, the method comprising (a) determining that the cancer is associated with wild type KRas or a KRas G12A, KRas G12C, KRas G12D, KRas G12R, KRas G12S, KRas G12V, KRas G13D or KRas Q61H mutation; and (b) administering to the patient a therapeutically effective amount of a compound according to any one of claims 1-53 or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 54.
80. The method of any one of claims 55-71, wherein the administering is done via a route selected from the group consisting of parenteral, intraperitoneal, intradermal, intracardiac, intraventricular, intracranial, intracerebrospinal, intrasynovial, intrathecal administration, intramuscular injection, intravitreal injection, intravenous injection, intra-arterial injection, oral, buccal, sublingual, transdermal, topical, intratracheal, intrarectal, subcutaneous, and topical administration.
81. The method of claim 72, wherein the administration route is oral.
82. The method of claim 72, wherein the administration is intravenous injection.
83. The method of claim 72, wherein the administration route is intramuscular injection.

84. The method of claim 72, wherein the administration route utilizes a delivery device.
85. The method of claim 72, wherein administration is done in a hospital setting.