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 Pharmcol. 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 all., (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).

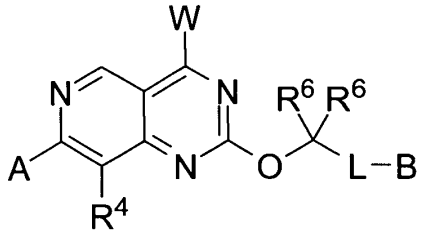
[00004] The well-known role of KRas in malignancy and the discovery of these frequent mutations in KRas in various tumor types made KRas a highly attractive target of the pharmaceutical industry for cancer therapy. Notwithstanding thirty years of large-scale discovery efforts to develop inhibitors of 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) Agnew Chem Int Ed Engl. 51(25):6140-6143 doi: 10.1002/anie201201358) 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

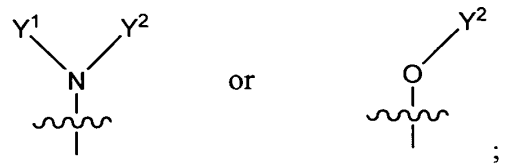
[00007] In one aspect of the invention, compounds are provided that inhibit KRas activity. In certain embodiments, the compounds are represented by Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

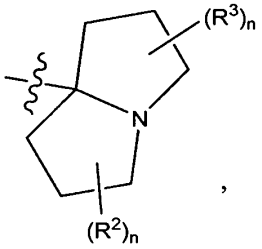
[00008] W is:



;

[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:



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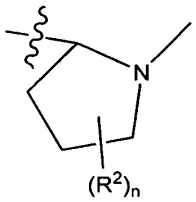
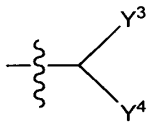


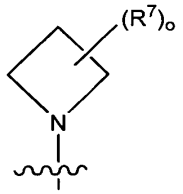
and


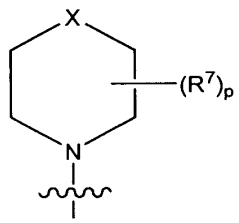
;

[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)-NH_2, 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:



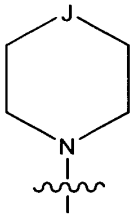
or


[000014] where X is selected from: a bond, -S-, -O-, -N< bound to a fused ring, -CH_2-, -CH_2-N-, -CH_2-N-CH_2-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-, -O-CH_2- and -S-CH_2-;

[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-, -CH_2-, -C(C1-C3 alkyl)$_2$-, -CH(C1-C3alkyl)- and -N(C1-C3 alkyl)-;

[000018] 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, -$CH_2C(=O)N(R^5)_2$, -C3-C4 alkynyl$(NR^5)_2$, -$N(R^5)_2$, deuteroC2-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 R^2 is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-$OC(O)N(R^5)_2$, -CO_2R^5, or -$CO_2N(R^5)_2$;

[000020] each R^3 is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-$OC(O)N(R^5)_2$, -CO_2R^5, or -$CO_2N(R^5)_2$;

[000021] each R^4 is independently hydrogen, halogen or C1 – C3 alkyl;

[000022] each R^5 is independently hydrogen or C1-C3 alkyl, or two R^5 join to form cycloalkyl or heterocycle;

[000023] each R^6 is independently hydrogen, hydroxy, C1-C4 hydroxyalkyl or heteroaryl,

[000024] or two R^6 join to form C3-C6 cycloalkyl or heterocycle;

[000025] each R^7 is independently hydrogen, C1-C3 alkyl, hydroxy, halogen, C1-C3 haloalkyl, -L-NH_2, -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), -$C(O)N(R^{10})_2$, -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 $C(O)NH_2$,

[000026] 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 alkyl),

[000027] 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

[000028] two R^7 on non-adjacent atoms optionally join to form a 1-2 carbon bridge;

[000029] each R^8 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 R^9 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), $-C(O)NH_2$, -C(O)NH(C1-C3 alkyl), $-C(O)N(C1\text{-}C3\ alkyl)_2$ or -CN;

[000031] 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;

[000032] each L is independently a bond, -C1-C4 alkyl-, -C1-C4 alkyl-NH-, -NH-, -N(C1-C3 alkyl)- or cyclopropyl-CH_2-;

[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 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 acccptable 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.

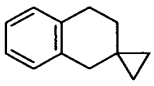
[000073] An "C1-C4 alkylene," group is a C1-C4 alkyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Exemplary alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene.

[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 C_6-C_{14} aromatic moiety comprising one to three aromatic rings, which is optionally substituted with one or more R^8 or R^9 groups as defined herein. As one embodiment, the aryl group is a C_6-C_{10} 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 system: .

[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 (C_6-C_{10})aryl(C_1- C_6)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 SO_2, 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 R^8 or R^9 groups on ring carbon or ring nitrogen at one or more positions, wherein R^6 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, azetidinyl, aziridinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, piperazinyl, imidazolidinyl, imidazopyridinyl, thiazolidinyl, dithianyl, trithianyl, dioxolanyl, oxazolidinyl, oxazolidinonyl, decahydroquinolinyl, piperidonyl, 4-piperidinonyl, quinuclidinyl, thiomorpholinyl, thiomorpholinyl 1,1 dioxide, morpholinyl, azepanyl, oxazepanyl, azabicyclohexanyls, azabicycloheptanyl, azabicyclooctanyls, azabicyclononanyls (e.g., octahydroindolizinyl), azaspiroheptanyls, dihydro-1H,3H,5H-oxazolo[3,4-c]oxazolyl, tetrahydro-

1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizine], hexahydro-1H-pyrrolizinyl, hexahydro-1H-pyrrolo[2,1-c][1,4]oxazinyl, octahydroindolizinyl, oxaazaspirononanyls, oxaazaspirooctanyls, diazaspirononanyls, oxaazabiocycloheptanyls, hexahydropyrrolizinyl 4(1H)-oxide, tetrahydro-2H-thiopyranyl 1-oxide and tetrahydro-2H-thiopyranyl 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 acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole, furanyl, furazanyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 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.

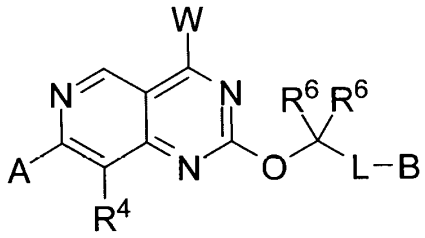
[000083] As used herein, a "therapeutically effective amount" of a compound is an amount that is sufficient to ameliorate, or in some manner reduce a symptom or stop or reverse progression of a condition, or negatively modulate or inhibit the activity of one or more of wild type KRas, KRas G12A, KRas 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

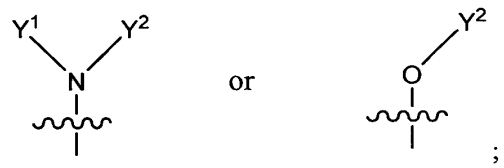
[000086] In certain embodiments of the invention there are provided compounds of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

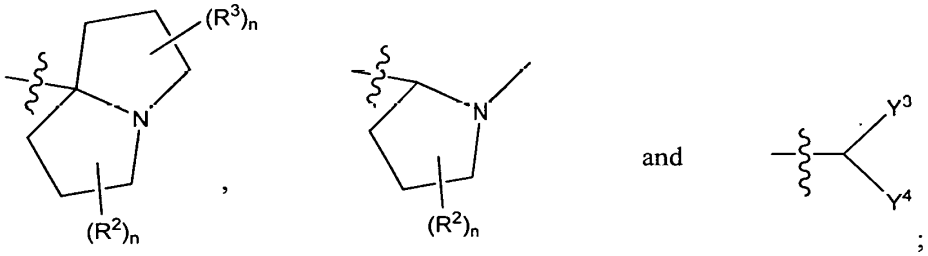
[000087] W is:



;

[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:

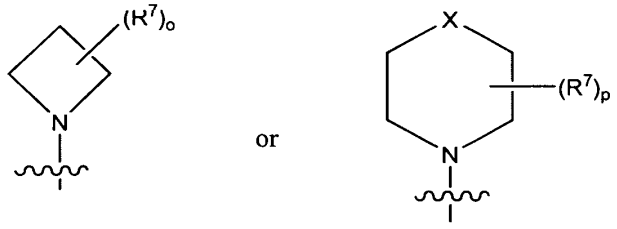


;

[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)-NH_2, 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:

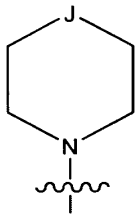


where X is selected from: a bond, -S-, -O-, -N< bound to a fused ring, -CH_2-, -CH_2-N-, -CH_2-N-CH_2-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-, -O-CH_2- and -S-CH_2-;

[000093] Y^3 is hydrogen or C1-C4 alkyl;

[000094] Y^4 is hydrogen or C1-C4 alkyl;

[000095] or Y^3 and Y^4 join to form:



where J is selected from: a bond, -O-, -NH-, -CH_2-, -C(C1-C3 alkyl)$_2$-, -CH(C1-C3alkyl)- and -N(C1-C3 alkyl)-;

[000096] 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, -CH_2C(=O)N(R^5)$_2$, -C3-C4 alkynyl(NR^5)$_2$, -N(R^5)$_2$, deuteroC2-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 R^2 is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-OC(O)N(R^5)$_2$, -CO_2R^5, or -CO_2N(R^5)$_2$;

[000098] each R^3 is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-OC(O)N(R^5)$_2$, -CO_2R^5, or -CO_2N(R^5)$_2$;

[000099] each R^4 is independently hydrogen, halogen or C1 – C3 alkyl;

[0000100] each R^5 is independently hydrogen or C1-C3 alkyl, or two R^5 join to form cycloalkyl or heterocycle;

[0000101] each R^6 is independently hydrogen, hydroxy, C1-C4 hydroxyalkyl or heteroaryl,

[0000102] or two R^6 join to form C3-C6 cycloalkyl or heterocycle;

[0000103] each R^7 is independently hydrogen, C1-C3 alkyl, hydroxy, halogen, C1-C3 haloalkyl, -L-NH_2, -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(R^{10})$_2$, -NHC(O)H , -CN, aryl, -(CH_2)$_{1-2}$S(O)$_2$N(R^{10})$_2$, -NH-S(O)$_2$N(R^{10})$_2$, -O-S(O)$_2$N(R^{10})$_2$, S(O)$_2$$R^{10}$,or heteroaryl or heterocycle optionally independently substituted with 1-2 substituents independently selected from C1-C3 alkyl, -CN and C(O)NH_2,

[0000104] 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 alkyl),

[0000105] 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

[0000106] two R^7 on non-adjacent atoms optionally join to form a 1-2 carbon bridge;

[0000107] each R^8 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 R^9 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)NH_2, -C(O)NH(C1-C3 alkyl), -C(O)N(C1-C3 alkyl)$_2$ or -CN;

[0000109] 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;

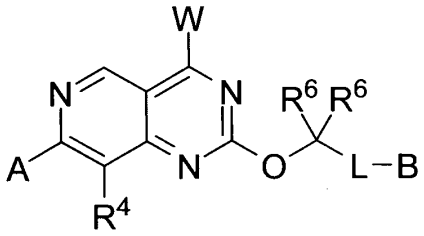
[0000110] each L is independently a bond, -C1-C4 alkyl-, -C1-C4 alkyl-NH-, -NH-, -N(C1-C3 alkyl)- or cyclopropyl-CH_2-;

[0000111] each n is 0-3;

[0000112] o is 1-6; and

[0000113] p is 1-8.

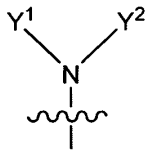
[0000114] Embodiments of the invention also include compounds of Formula (I):



Formula (I)

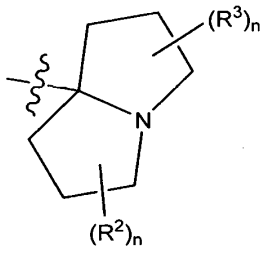
or a pharmaceutically acceptable salt thereof, wherein:

[0000115] W is:



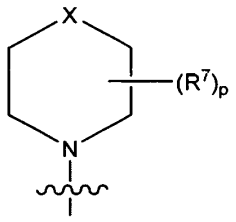
[0000116] A is naphthyl optionally substituted with 1-4 R^1;

[0000117] B is:



;

[0000118] Y^1 and Y^2 join to form:



where X is selected from: -CH_2-, -CH_2-CH_2- and -O-CH_2-;

[0000119] 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, -$CH_2C(=O)N(R^5)_2$, -C3-C4 alkynyl$(NR^5)_2$, -$N(R^5)_2$, deuteroC2-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 R^2 is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-$OC(O)N(R^5)_2$, -CO_2R^5, or -$CO_2N(R^5)_2$;

[0000121] each R^3 is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-$OC(O)N(R^5)_2$, -CO_2R^5, or -$CO_2N(R^5)_2$;

[0000122] each R^4 is independently hydrogen, halogen or C1 – C3 alkyl;

[0000123] each R^5 is independently hydrogen or C1-C3 alkyl, or two R5 join to form cycloalkyl or heterocycle;

[0000124] each R^6 is independently hydrogen, hydroxy, C1-C4 hydroxyalkyl or heteroaryl,

[0000125] or two R^6 join to form C3-C6 cycloalkyl or heterocycle;

[0000126] each R^7 is independently hydrogen, C1-C3 alkyl, hydroxy, halogen, C1-C3 haloalkyl, -L-NH_2, -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), -$C(O)N(R^{10})_2$, -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 $C(O)NH_2$,

[0000127] 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 alkyl),

[0000128] 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

[0000129] two R^7 on non-adjacent atoms optionally join to form a 1-2 carbon bridge;

[0000130] each R^8 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 R^9 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), $-C(O)NH_2$, -C(O)NH(C1-C3 alkyl), $-C(O)N(C1\text{-}C3\ alkyl)_2$ or -CN;

[0000132] 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;

[0000133] each L is independently a bond, -C1-C4 alkyl-, -C1-C4 alkyl-NH-, -NH-, -N(C1-C3 alkyl)- or cyclopropyl-CH_2-;

[0000134] each n is 0-3;

[0000135] o is 1-6; and

[0000136] p is 1-8.

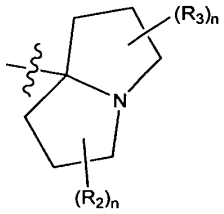
[0000137] Embodiments also include such compounds or salts wherein each R^1 is independently selected from halogen, hydroxy, C1-C3 alkoxy and C1-C4 alkyl.

[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.

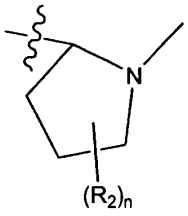
[0000139] Embodiments also include such compounds or salts wherein each R^7 is independently selected from hydrogen, C1-C4 alkyl, hydroxy, C1-C3 alkoxy, and wherein two R^7 on non-adjacent atoms optionally join to form a 1-2 carbon bridge.

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

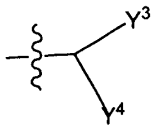
[0000141] Embodiments also include such compounds or salts wherein B is:



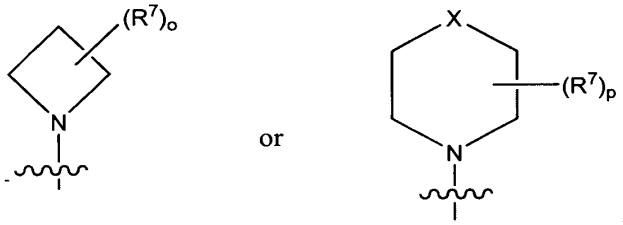
[0000142] Embodiments also include such compounds or salts wherein B is:



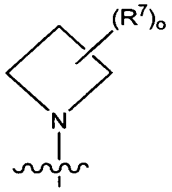
[0000143] Embodiments also include such compounds or salts wherein B is:



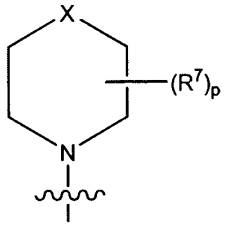
[0000144] Embodiments also include such compounds or salts wherein Y^1 and Y^2 join to form:



[0000145] Embodiments also include such compounds or salts wherein Y^1 and Y^2 join to form:



[0000146] Embodiments also include such compounds or salts wherein Y^1 and Y^2 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 R^1 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 $-C(O)NH_2$, -C(O)NH(C1-C3 alkyl) or $-C(O)N(C1\text{-}C3\ alkyl)_2$.

[0000180] In certain embodiments of the invention R^8 is $-NH_2$, -NH(C1-C3 alkyl); $-N(C1\text{-}C3\ alkyl)_2$.

[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 R^9 is aryl or heteroaryl.

[0000185] In certain embodiments of the invention at least one R^9 is C(O)OH.

[0000186] In certain embodiments of the invention at least one R^9 is $-C(O)NH_2$, -C(O)NH(C1-C3 alkyl) or $-C(O)N(C1\text{-}C3\ alkyl)_2$.

[0000187] In certain embodiments of the invention Y^1 and Y^2 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 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 oxo (=O), halogen, hydroxy, C1-C3 alkyl and -O-(C1-C3 alkyl).

[0000189] In certain embodiments of the invention, 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.

[0000190] In certain embodiments of the invention, two R^7 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-trifluoracetic 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, intravitreous 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, cinnamoate, mandeloate, 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, osteochronfroma (osteocartilaginous 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,

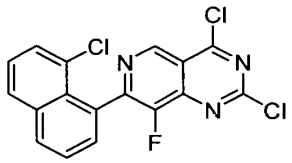
compounds of the present invention may be prepared according to the reaction schemes and examples outlines below.

[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.

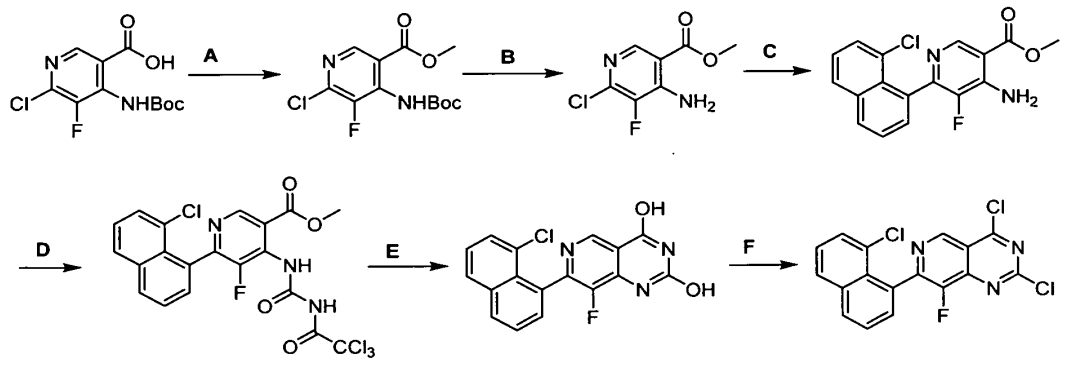
[0000221] The compounds of the present invention may be in anhydrous, solvated or hydrated forms, and all such forms are included within the scope of the invention.

[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-fluoro-pyridine-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 $TMSCHN_2$ (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 $NaHCO_3$ (150 mL), followed by brine (150 mL). The organic layer was dried over Na_2SO_4, 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-fluoro-pyridine-3-carboxylate (15 g, 91%). Colorless oil; Rf = 0.50 (3:1 petroleum ether/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$): 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-fluoro-pyridine-3-carboxylate. To a solution of methyl 4-(tert-butoxycarbonylamino)-6-chloro-5-fluoro-pyridine-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 Na_2CO_3 solution (100 mL) and extracted with ethyl acetate (3 × 200 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuum to give methyl 4-amino-6-chloro-5-fluoro-pyridine-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-fluoro-pyridine-3-carboxylate. A mixture of methyl 4-amino-6-chloro-5-fluoro-pyridine-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.)*, $Pd(dppf)Cl_2$ (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 N_2. 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 Na_2SO_4 and concentrated in vacuum. The residue was purified by chromatography (Al_2O_3, 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; Rf = 0.20 (3:1 petroleum ether/ethyl acetate); LCMS [ESI, M+1]: 331.

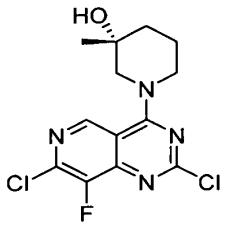
[0000226] Step D. methyl 6-(8-chloro-1-naphthyl)-5-fluoro-4-[(2,2,2-trichloroacetyl)carbamoylamino] pyridine-3-carboxylate. To a solution of methyl 4-amino-6-(8-chloro-1-naphthyl)-5-fluoro-pyridine-3-carboxylate (5.5 g, 16.6 mmol, 1.0 *equiv.)* in THF (82 mL) was added 2,2,2-trichloroacetyl isocyanate (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 NH_3•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.

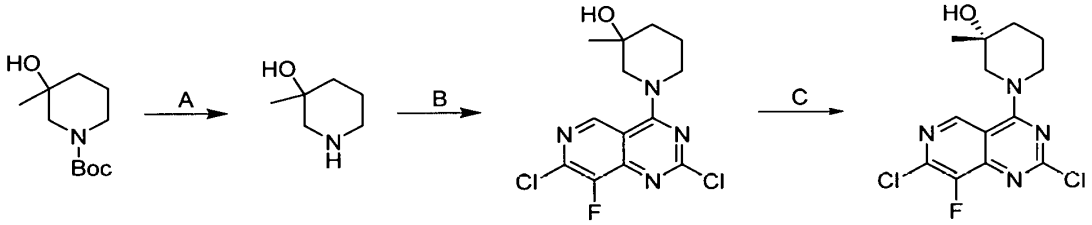
[0000228] Step F. 2,4-dichloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidine. A solution of $POCl_3$ (1.62 g, 10.6 mmol, 985 µL, 36.2 *equiv.)* and N-ethyl-N-isopropylpropan-2-amine (189 mg, 1.46 mmol, 255 µL, 5.0 *equiv.)* was stirred at 0 °C, followed by the addition of 7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol (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

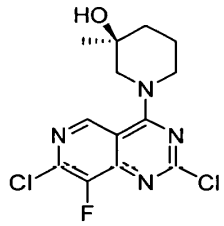


[0000229] Step A. 3-methylpiperidin-3-ol: To the solution of tert-butyl 3-hydroxy-3-methyl-piperidine-1-carboxylate (2.45 g, 11.4 mmol) in acetonitrile (9 mL) was added HCl•dioxane (4 M, 18 mL) at 0°C, and the mixture was stirred at 0°C for 0.5 h. After completion, the reaction mixture was concentrated 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-fluoro-pyrido[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 Na_2SO_4 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 um); mobile phase: [0.1 % NH_3WATER 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.

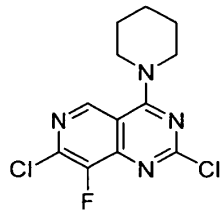
Intermediate 3



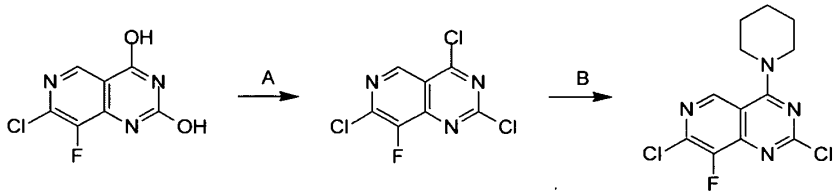
(S)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

[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



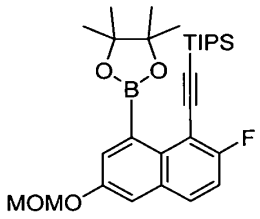
2,7-dichloro-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine



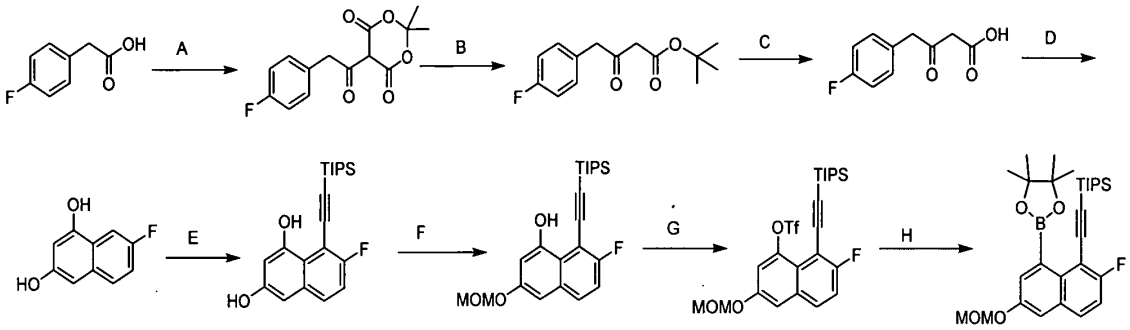
[0000233] Step A. 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine: To a mixture of 7-chloro-8-fluoropyrido[4,3-d]pyrimidine-2,4-diol (2.8 g, 13.0 mmol) in $POCl_3$ (20 mL) was added DIEA (5.04 g, 39.0 mmol, 6.79 mL) in one portion at 25 °C under N_2. The mixture was heated to 110 °C and stirred for 2 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 N_2. 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 CH_3CN (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 CH_3CN/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; ^{1}H NMR (400 MHz, $CDCl_3$-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 CF_3SO_3H (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.

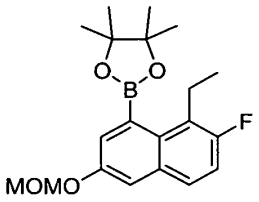
[0000239] Step E. 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol. To the mixture of 7-fluoronaphthalene-1,3-diol (120 g, 673 mmol, 1 *equiv.)*, 2-bromoethynyl(triisopropyl)silane (184 g, 707 mmol, 1.05 *equiv.)*, AcOK (132 g, 1.34 mol, 2 *equiv.)* in dioxane (800 mL) was added dichlororuthenium;1-isopropyl-4-methyl-benzene dimer (41.3 g, 67.4 mmol, 0.1 *equiv.)* under N_2. 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; ^{1}H NMR (400 MHz, $CDCl_3$-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.

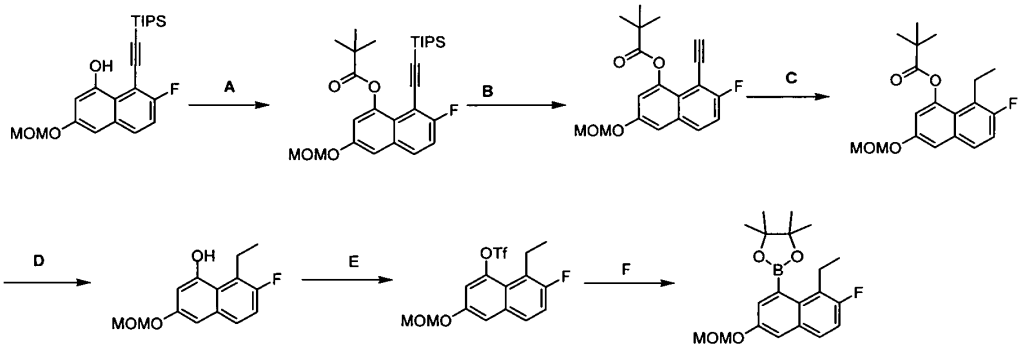
[0000241] Step G: 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate. To the solution of 7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (80 g, 198 mmol, 1 *equiv.)*, DIEA (77.0 g, 596 mmol, 104 mL, 3 *equiv.)* in DCM (1200 mL) was added Tf_2O (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 Na_2SO_4 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 $Pd(dppf)Cl_2$ (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, $CDCl_3$-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 μmol, 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 Na_2SO_4 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 Na_2SO_4 and concentrated to give the title compound (2.20 g, crude). Yellow oil. LCMS [ESI, M+1]:331.1.

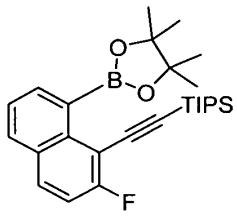
[0000245] Step C. 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl pivalate. To the solution of 8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl pivalate (2.00 g, 6.05 mmol, 1.0 *equiv.)* in MeOH (20 mL) was added Pd/C (200 mg, 10% purity) under N_2. The suspension was degassed in vacuum and purged with H_2 several times. The mixture was stirred under H_2 (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. ^{1}H NMR (400 MHz, $CDCl_3$) 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) .

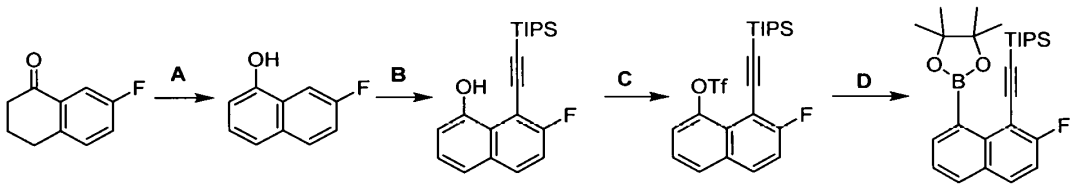
[0000247] Step E. 8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethane sulfonate. To the solution of8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (520 mg, 2.08 mmol, 1.0 *equiv.)*, DIEA (806 mg, 6.24 mmol, 3.0 *equiv.)* in DCM (10 mL), trifluoromethylsulfonyl trifluorometh anesulfonate (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 Na_2SO_4 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. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67-7.59 (m, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.37 (d, *J* = 2.4Hz, 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 $Pd(dppf)Cl_2$ (96.0 mg, 131μmol, 0.1 *equiv.)* under N_2. The mixture was degassed and strirred 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, $CDCl_3$) 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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).

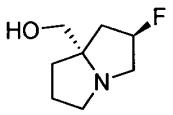
[0000250] Step B. 7-fluoro-8-(2-triisopropylsilylethynyl)naphthalen-1-ol. To a solution of (bromoethynyl)triisopropylsilane (72.0 g, 275 mmol, 1.20 *equiv.)* and 7-fluoronaphthalen-1-ol (37.2 g, 230 mmol, 1.0 *equiv.)* in DCE (500 mL) were added dichlororuthenium;1-isopropyl-4-methyl-benzene (21.1 g, 34.4 mmol, 0.15 *equiv.)*, K_2CO_3(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; ^{1}H NMR (400 MHz, $CDCl_3$) 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 Tf_2O (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; ^{1}H NMR (400 MHz, $CDCl_3$) 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).

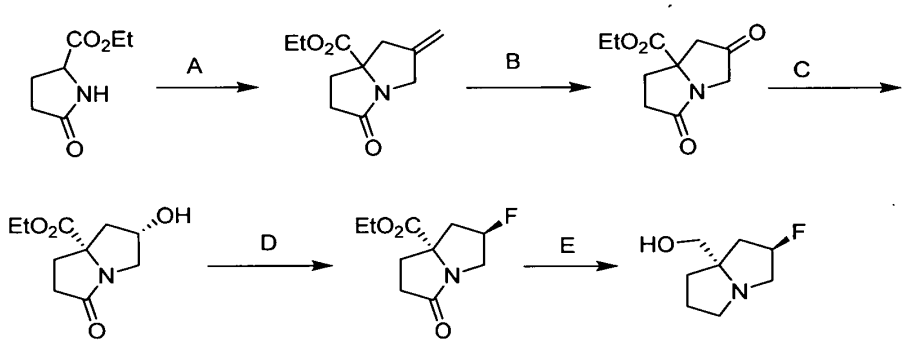
[0000252] Step D. ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane. To a solution of [7-fluoro-8-(2-triisopropylsilylethynyl)-1-naphthyl]

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 $Pd(dppf)Cl_2$ (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, $CDCl_3$) 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 N_2. 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 Na_2SO_4, 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, Rf = 0.40) to afford the title compound (898 g, 3.88

mol, 40.6% yield, 82% purity) as a yellow oil. LCMS: Rt = 0.716 min, m/z = 210.1 (M+H). ^{1}H 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, Rf = 0.50) to afford the title compound (821 g, 3.62 mol, 93.3% yield, 93.1% purity) as a yellow oil. LCMS: Rt = 0.543 min, m/z = 212.1 (M+H). ^{1}H 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).

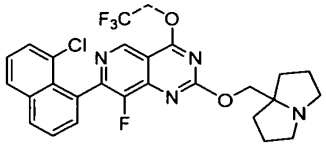
[0000255] Step C. ethyl 2-hydroxy-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate. To a solution of ethyl 2,5-dioxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (257 g, 1.22 mol, 1.00 *equiv.)* in EtOH (1300 mL) was slowly added $NaBH_4$ (13.8 g, 365 mmol, 0.30 *equiv.)* at 0 °C under N_2. The mixture 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. ^{1}H 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

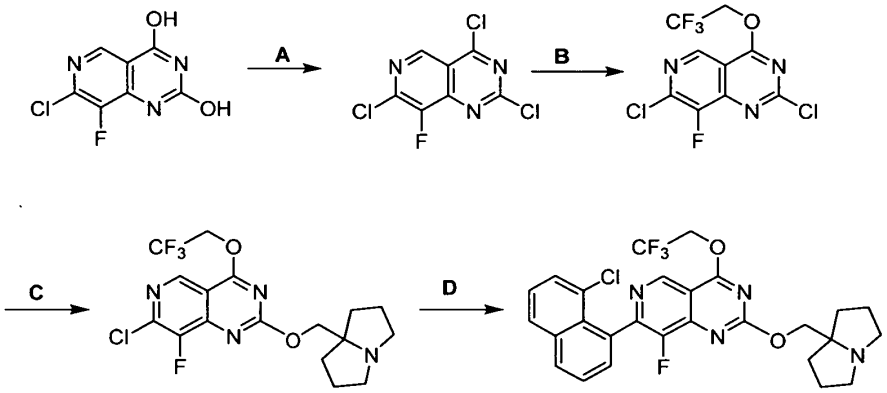
(40.0 mL) at 10°C, then diluted with water (750 mL) and extracted with DCM (750 mL × 3). The combined organic layers were washed with brine (750 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate = 1/0 to 0/1, Rf = 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-NH_2 250*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). ^{1}H NMR: 400 MHz $CDCl_3$ 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; 200minmin, desired product: Peak 2, Rt = 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 $LiAlH_4$ (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 N_2. 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 $MgSO_4$, 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.^{1}H NMR: 400 MHz $CDCl_3$ 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 $POCl_3$ (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

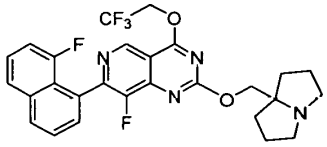
hours. After completion, the mixture was poured onto Silica gel column, purified by column chromatography (Silica gel, petroleum ether/ethyl acetate=30/1 to 10/1), and then further purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) affording 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (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 NH_4Cl aqueous solution (300 mL), and the organic layer was separated and dried over anhydrous Na_2SO_4. The mixture was filtered, and the filtrate was concentrated under reduced pressure at 40 °C to dryness. The crude product was triturated with CH_3CN (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, $CDCl_3$) 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.

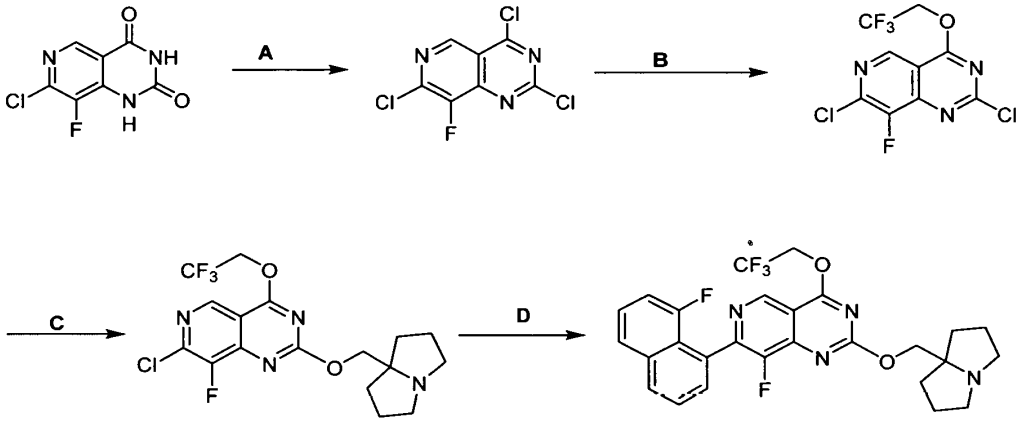
[0000261] Step D. 7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. To a mixture of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (5.00 g, 11.9 mmol, 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.)*, $Pd(dppf)Cl_2$ (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 N_2 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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 $POCl_3$ (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.

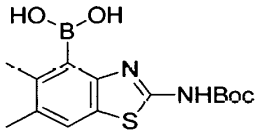
[0000263] Step B. 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (100 g, 396 mmol, 1.00 *equiv.)* and 2, 2, 2-trifluoroethanol (59.4 g, 594 mmol, 42.7 mL, 1.50 *equiv.)* in toluene (2 L) was added t-BuONa (152 g, 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. NH_4Cl solution (1 L × 2), dried over Na_2SO_4, 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.

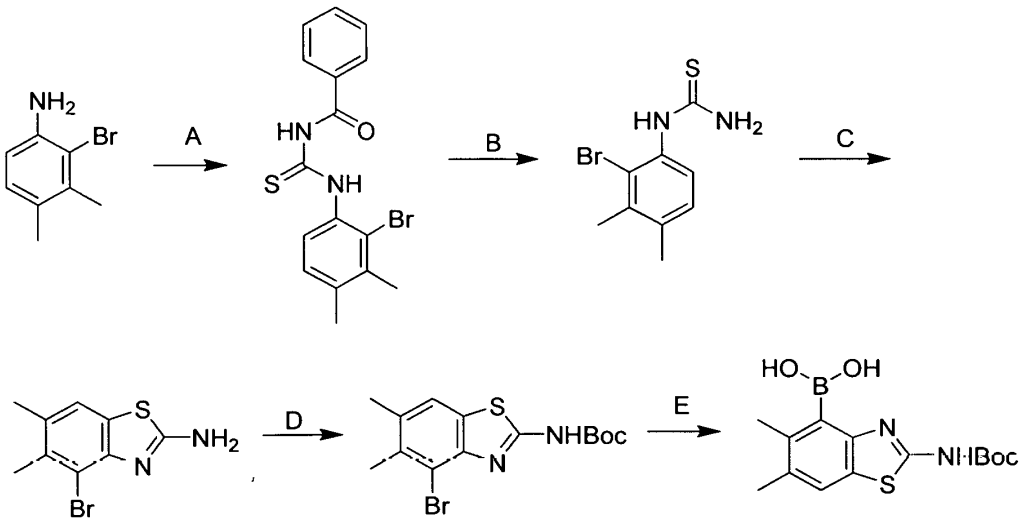
[0000265] Step D. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. A mixture of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (17.0 g, 40.4 mmol, 1.00 *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, 1.16e-1 *equiv.)*, K_3PO_4 (1.5 M, 80.8 mL, 3.00 *equiv.)* in toluene (170 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 65 °C for 4 hrs under N_2 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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.

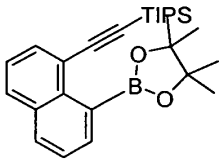
[0000268] Step C. 4-bromo-5,6-dimethylbenzo[d]thiazol-2-amine: To a solution of 1-(2-bromo-3,4-dimethylphenyl)thiourea (2.20 g, 8.49 mmol) in $CHCl_3$ (30 mL) was added drop-wise Br_2 (1.36 g, 8.49 mmol) in $CHCl_3$ (2 mL) at 0 °C. The mixture was stirred at 70 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with ethyl acetate (200 mL), saturated $Na_2S_2O_3$ aqueous (50 mL) and saturated $NaHCO_3$ aqueous solution (50 mL). The mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, 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; ^{1}H 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 Na_2SO_4. The mixture was filtered and concentrated under reduced pressure to give a residue. The

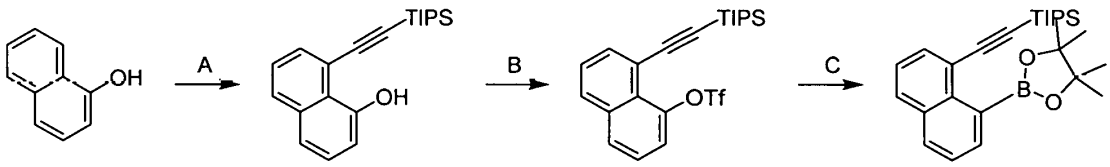
residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=1/19] to give tert-butyl (4-bromo-5,6-dimethylbenzo[d]thiazol-2-yl)carbamate (2.6 g, 91% yield) as a light yellow solid; LCMS (ESI, M-55): m/z 300.9, 302.9.

[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 N_2 for 3 times. Then [2-(2-aminophenyl)phenyl]-chloro-palladium;tricyclohexylphosphane (100 mg, 169 μmol, 0.06 *equiv.)* was added. The mixture was stirred at 80 °C for 40 hours under N_2 atmosphere. After completion, the reaction mixture was diluted with water (1 mL) and brine (1 mL), and extracted with ethyl acetate (2 mL × 4). The combined organic layers were dried over anhydrous Na_2SO_4 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



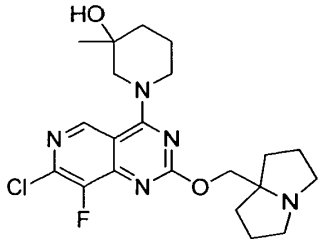
[0000271] Step A. 8-((triisopropylsilyl)ethynyl)naphthalen-1-ol: To a solution of naphthalen-1-ol (500 mg, 3.47 mmol, 1.25 mL), potassium carbonate (479 mg, 3.47 mmol), dichlororuthenium;1-isopropyl-4-methyl-benzene (531 mg, 867 μmol) and sodium acetate (56.9 mg, 694 μmol) in DCE (20.0 mL) was added 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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).

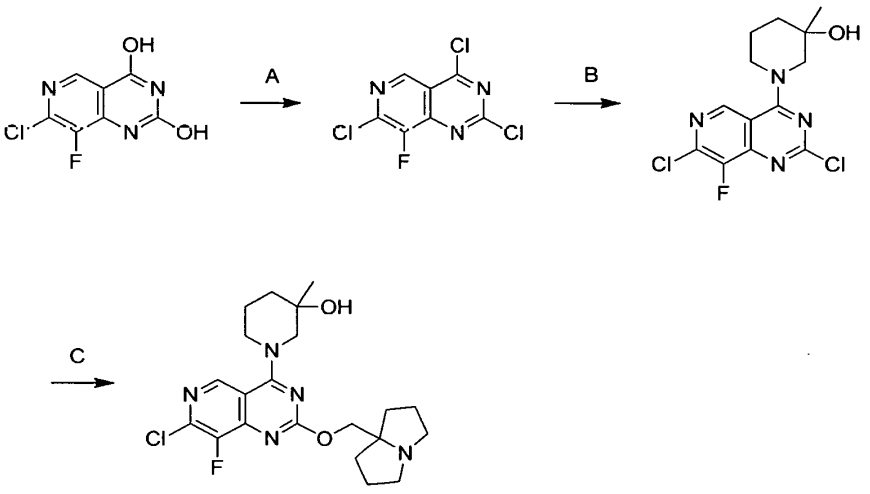
[0000272] Step B. 8-((triisopropylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate: To a solution of 8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (760 mg, 2.34 mmol) and DIEA (605 mg, 4.68 mmol, 816 µL) in DCM (8.00 mL) was added Tf_2O (991 mg, 3.51 mmol, 580 µL) at -40 °C. The reaction was stirred 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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), $Pd(dppf)Cl_2$ (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; ^{1}H NMR (400 MHz, $CDCl_3$) 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



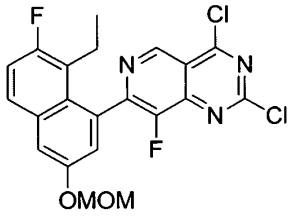
[0000274] Step A. 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine: To a mixture of 7-chloro-8-fluoropyrido[4,3-d]pyrimidine-2,4-diol (2.8 g, 13.0 mmol) in $POCl_3$ (20 mL) was added DIEA (5.04 g, 39.0 mmol, 6.79 mL) in one portion at 25 °C under N_2. The mixture was heated to 110 °C and stirred for 2 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-(2,7-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

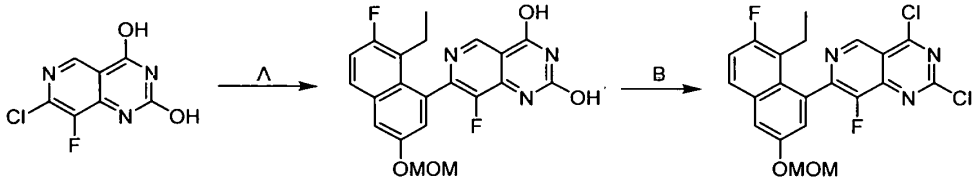
(1.52 g, 13.2 mmol) in portions at -40 °C under N_2. The mixture was stirred at -40 °C for 1 hour. After completion, the mixture was filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Silica gel, Petroleum ether/Ethyl acetate = 1/0, 0/1) affording 1-(2,7-dichloro-8-fluoropyrido[4,3-*d*] pyrimidin-4-yl)-3-methylpiperidin-3-ol (2.81 g, 71% yield) as a yellow solid; ^{1}H 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 N_2. 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; ^{1}H NMR (400 MHz, $CDCl_3$): 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



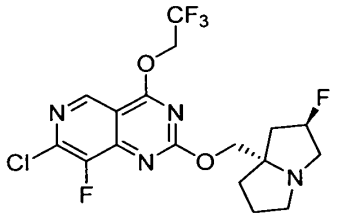
2,4-dichloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidine



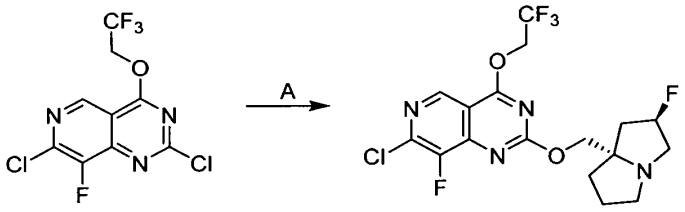
[0000277] Step A. 7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol: To a mixture of 7-chloro-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol, 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (14.0 g, 39.0 mmol) and K_3PO_4 (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 N_2. The mixture was de-gassed and heated to 78 °C for 9.5 hours under N_2. 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 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) 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 $POCl_3$ (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 $NaHCO_3$ solution. Then the mixture was extracted with ethyl acetate (8 mLX2). 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) as a brown oil, which was used in the next step without further purification.

Intermediate 15

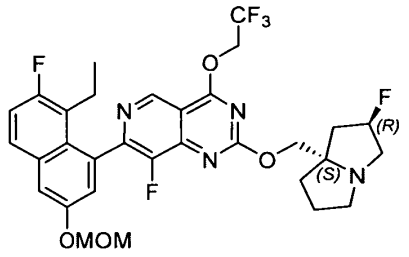


7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine

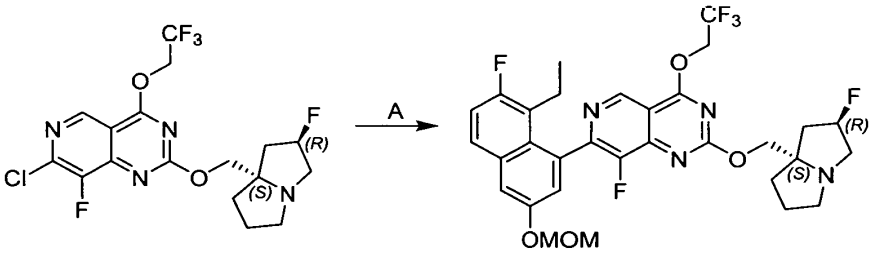


[0000279] Step A. 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a mixture of 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (33.3 g, 1.0 *equiv.*), DIEA (54.5 g, 4.0 *equiv.*) and 4Å molecular 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 Na_2SO_4, 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; ^{1}H 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

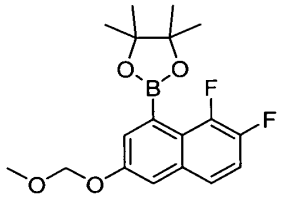


7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine

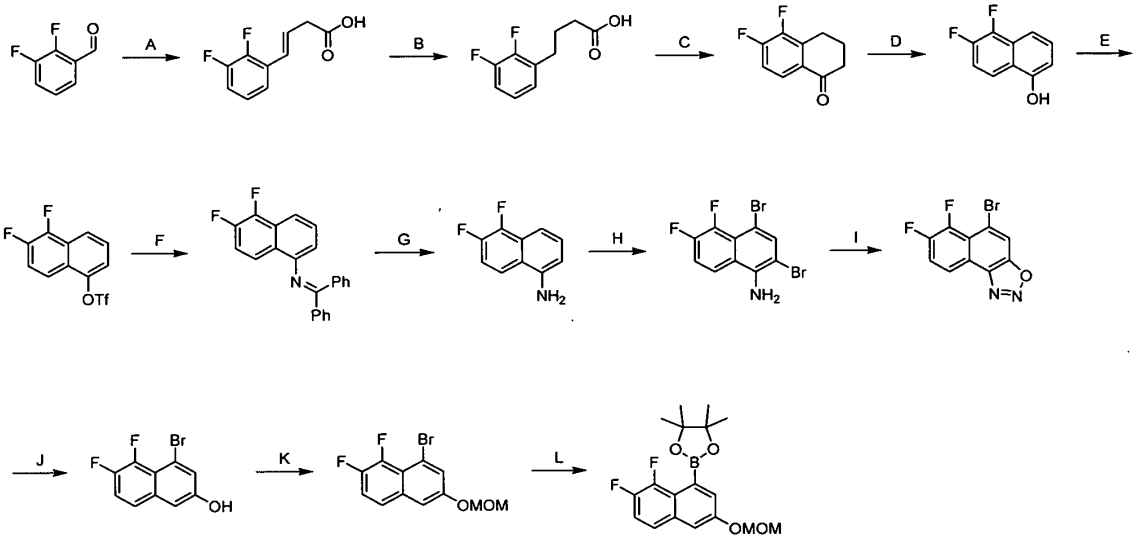


[0000280] Step A. 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a mixture of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (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 Cs_2CO_3 (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 N_2. The suspension was degassed and purged with H_2 several times. The mixture was stirred under H_2 (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(2*H*)-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 $AlCl_3$ (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 Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 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 Br_2 (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.)*, Li_2CO_3 (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 Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 50:1 to 10:1) to afford the title compound (10 g, 90% yield) as a yellow solid; ^{1}H 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 Tf_2O (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 Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 20: 1 to 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.)*, $Pd_2(dba)_3$ (8.80 g, 0.1 *equiv.)*, Xantphos (11.1 g, 0.2 *equiv.)* and Cs_2CO_3 (93.9 g, 3 *equiv.)* in toluene (500 mL) was degassed and stirred at 90 °C for 12 hours under N_2 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 Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 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 $NaHCO_3$ solution and extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 20:1 to 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 Br_2

(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.

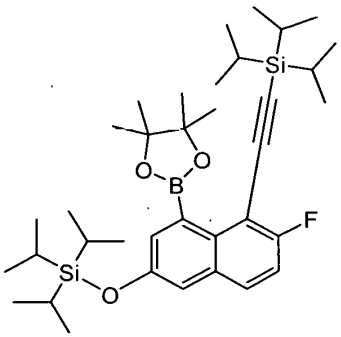
[0000289] Step I. 5-bromo-6,7-difluoronaphtho[1,2-*d*][1,2,3]oxadiazole: 2,4-dibromo-5,6-difluoronaphthalen-1-amine (16 g, 47.5 mmol, 1.0 *equiv.)* was dissolved in AcOH (280 g, 98.2 equiv.) and propionic acid (26.5 g, 7.53 *equiv.)* and cooled to 0 °C. Then $NaNO_2$ (4.91 g, 1.5 *equiv.)* was added 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; ^{1}H 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 $NaBH_4$ (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 Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 20:1 to 3:1) to afford the title compound (6.3 g, 59% yield) as a black solid; LCMS (ESI, M-1): m/z = 257.1.

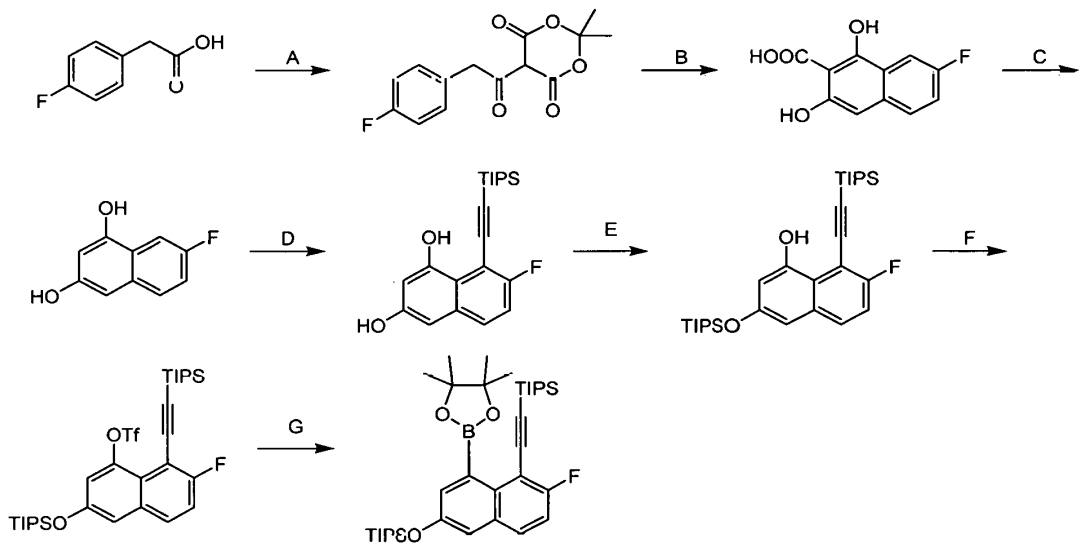
[0000291] Step K. 8-bromo-1,2-difluoro-6-(methoxymethoxy)naphthalene: To a solution of 4-bromo-5,6-difluoronaphthalen-2-ol (6.3 g, 1.0 *equiv.)* in DCM (120 mL) was added DIEA (7.86 g, 2.5 *equiv.)* and MOMCl (3.44 g, 1.76 *equiv.)*. The mixture was stirred at 0 °C for 0.5 hour. The reaction mixture 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 Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 20:1 to 5:1) to afford the title compound (5.5 g, 75% yield) as a yellow solid; ^{1}H 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.)*, Pin_2B_2 (6.28 g, 2.5 *equiv.)*, KOAc (2.91 g, 3.0 *equiv.)*, $Pd(dppf)Cl_2$ (724 mg, 0.1 *equiv.)* in dioxane (60 mL) was degassed and stirred at 110 °C for 1 hour under N_2 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 Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 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 H_2O (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 H_2O 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; ^{1}H 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 CF_3SO_3H (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 H_2O (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 H_2O (1 L) and saturated $NaHCO_3$ aqueous (0.3 L), and then extracted with ethyl acetate (4 × 0.5 L). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (0.5 L), water (0.5 L) and brine (0.5 L), dried over anhydrous Na_2SO_4 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 $NaHCO_3$ aqueous (0.5 L) and brine (0.2 L), dried over anhydrous Na_2SO_4, and concentrated to give a residue. The residue was purified by column chromatography [SiO_2, 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).

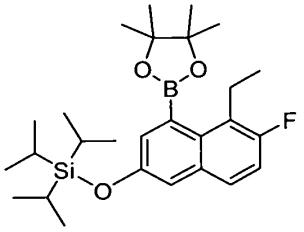
[0000297] Step E. 7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-ol: To a solution of 7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalene-1,3-diol (197 g, 1 *equiv.*) and DIPEA (142 g, 2.0 *equiv.*) in DCM (1 L) was added TIPSCl (122 g, 1.2 *equiv.*) dropwise between 0 and 10 °C for 1 hour. The mixture was stirred 25 °C for 1 hour. The mixture was poured H_2O (2 L). The DCM phase was separated and washed with brine (3 × 1 L). The DCM phase was dried over anhydrous Na_2SO_4

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

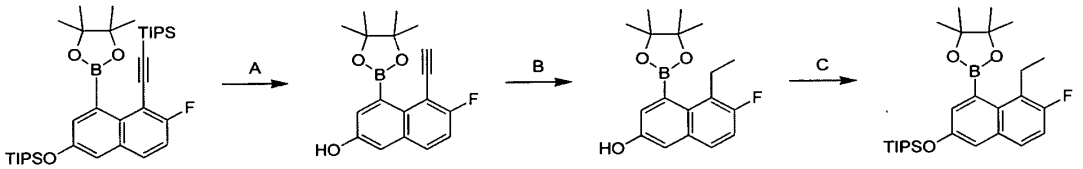
[0000298] Step F. 7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yltrifluoromethanesulfonate: To a solution of 7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-ol (282 g, 1 *equiv.*) and DIPEA (248 g, 3.5 *equiv.*) in DCM (1.7 L) was added Tf_2O (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), H_2O (1.5 L), brine (2 ×1 L), dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by column chromatography [SiO_2, 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); ^{19}F 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 $Pd(dppf)Cl_2$ (16 g, 0.06 *equiv.*) in MeCN (1.5 L) was degassed stirred at 78 °C for 4 hours under N_2 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



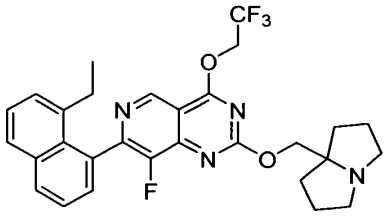
[0000300] Step A. 5-ethynyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol: To a solution of ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane (1.50 kg, 1.0 *equiv.*) in DMSO (15.0 L) was added CsF (2.19 kg, 6.0 *equiv.*) in one portion at 25°C under N_2. 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 Na_2SO_4, 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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 with H_2 three times and stirred at 25 °C under H_2 (15 Psi) for 5 hrs. The mixture was filtered through a diatomite powder pad and washed with THF

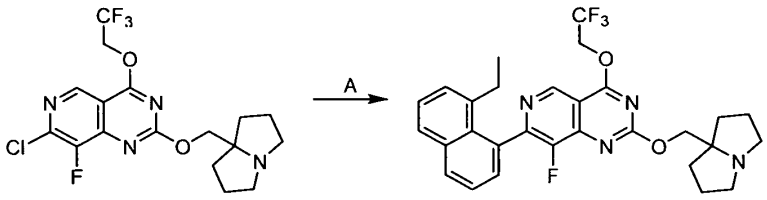
(200 mL × 2), the filtrate was concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether/EtOAc 50:1 to 3:1) to afford the title compound (74.0 g, 88.5% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 1H), 7.41-7.37 (m, 1H), 7.23-7.18 (m, 2H), 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 × 300 mL). The combined organic phase was washed with brine (3 × 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; ^{1}H 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



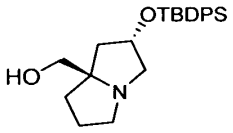
7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine



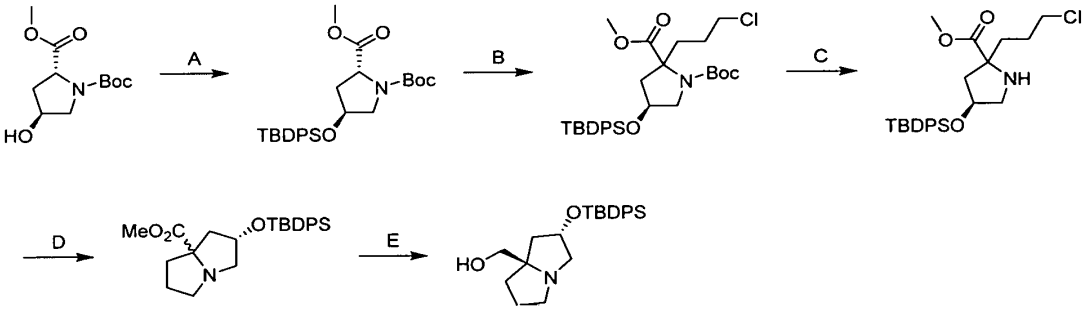
[0000303] Step A. 7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: A mixture of 7-chloro-8-fluoro-2-

((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.*), K_3PO_4 (1.5 M, 3.0 *equiv.*) in THF (2 mL) was degassed and stirred at 60 °C for 12 hours under N_2 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 Na_2SO_4, 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 Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (SiO_2,

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.

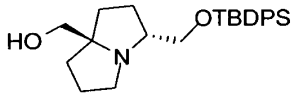
[0000305] Step B. (4S)-1-tert-butyl 2-methyl 4-((tert-butyldiphenylsilyl)oxy)-2-(3-chloropropyl)pyrrolidine-1,2-dicarboxylate: To a solution of (2R,4S)-1-tert-butyl 2-methyl 4-((tert-butyldiphenylsilyl)oxy)pyrrolidine-1,2-dicarboxylate (37.0 g, 1.0 *equiv.*) in THF (400 mL) was added LDA (2 M, 49.7 mL, 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 Na_2SO_4, filtered and concentrated. The residue was purified by reversed phase flash chromatography (C18, 0.1 % formic acid condition) and column chromatography (SiO_2, 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. (2*S*)-methyl 2-((*tert*-butyldiphenylsilyl)oxy)hexahydro-1*H*-pyrrolizine-7*a*-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 $NaHCO_3$ (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 Na_2SO_4, filtered and concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 250*80mm*10 um; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 75%-100%, 20min) to afford the title compound (1.3 g, two steps 18% yield) as a colorless oil.

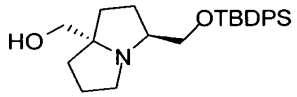
[0000308] Step E. ((2S,7aR)-2-((tert-butyldiphenylsilyl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol: To a solution of (2S)-methyl 2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizine-7a-carboxylate (1.30 g, 1.0 *equiv.*) in THF (15 mL) was added $LiAlH_4$ (349 mg, 3.0 *equiv.*) at -40 °C. The mixture was stirred at -40 °C for 1 hour. Upon completion, the reaction mixture was quenched with saturated aqueous Na_2SO_4 solution (1 mL), filtered and concentrated to afford the title compound (1.1 g, 91% yield)as a yellow oil; ^1H NMR (400 MHz, $CDCl_3$) 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



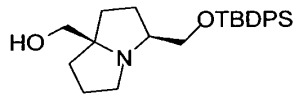
((3R,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol

Intermediate 23



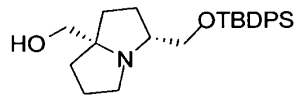
((3S,7aS)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol

Intermediate 24

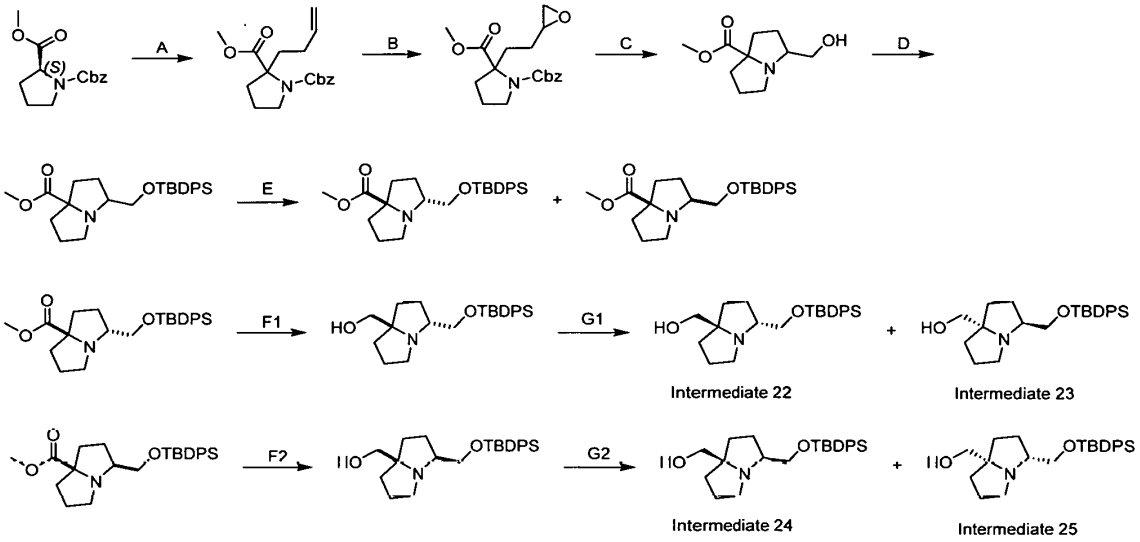


((3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol

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 NH_4Cl (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 [SiO_2, 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 Na_2SO_3 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 [SiO_2, petroleum ether/ethyl acetate 10:1 to 5:1) to afford the title compound (200 g, 62.9% yield) as a yellow oil. ^{1}H 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 N_2 atmosphere. The suspension was degassed under vacuum and purged with H_2 (50 psi) several times. The mixture was stirred at 25 °C under H_2 (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; ^{1}H 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-butyldiphenylsilyl)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 H_2O (2 × 500 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduce pressure to give a residue. The residue was purified by column chromatography (SiO_2, 0.1%NH_3H_2O, 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-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol: To a mixture of rac-(3R,7aR)-methyl 3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizine-7a-carboxylate (160 g, 70% purity, 1 *equiv.*) in THF (2 L) was added $LiAlH_4$ (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 H_2O (13 mL), 15% aqueous NaOH (13 mL), H_2O (39 mL), dried over anhydrous Na_2SO_4 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-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol and ((3S,7aS)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol: The stereoisomers of rac-((3R,7aR)-3-(((tert-butyldiphenylsilyl)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-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol (54 g, 40% yield) as a yellow oil ^{1}H 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.

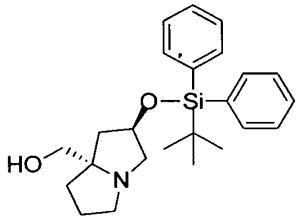
[0000315] and ((3S,7aS)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol (62 g, 48% yield) as a yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.77 - 7.64 (m, 4H), 7.48 - 7.35 (m, 6H), 3.96 - 3.62 (m, 1H), 3.57 - 3.30 (m, 2H), 3.18 - 2.85 (m, 3H), 2.01 - 1.90 (m, 2H), 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-butyldiphenylsilyl)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 H_2O (8.00 mL), NaOH (15%, 8.00 mL) and H_2O (24.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford the title compound (72.0 g, crude) as yellow oil. LCMS [ESI, M+1]: m/z = 410.2.

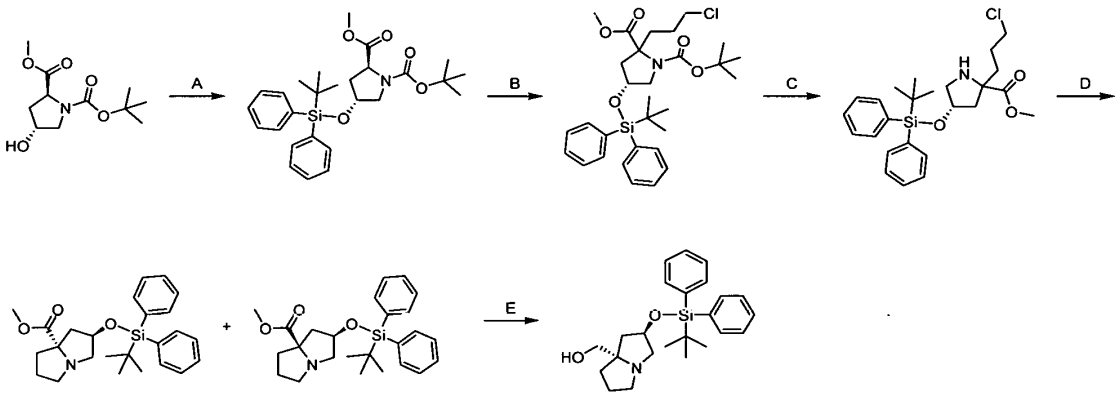
[0000317] Step G2: ((3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol and ((3R,7aS)-3-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol: The stereoisomers of rac-((3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol (110g) were separated by SFC (column: REGIS (s,s) WHELK-O1 (250 mm × 50 mm, 10 um); mobile phase: [0.1%NH_3-H_2O ETOH];B%: 40%-40%, 3.7min) to afford title compounds ((3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a (5H)-yl)methanol (45 g, 40% yield) as yellow oil ^{1}H 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-butyldiphenylsilyl)oxy)methyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (90466-H2B) (45 g, 40% yield) as a yellow oil. ^{1}H 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-butyldiphenylsilyl)oxy)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 H_2O (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 [SiO_2, 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, $CDCl_3$) 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-chloro-propane (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 H_2O (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; ^{1}H 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).

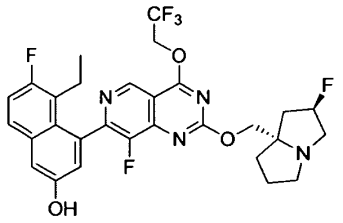
[0000321] Step C. (4R)-methyl 4-((tert-butyldiphenylsilyl)oxy)-2-(3-chloropropyl)pyrrolidine-2-carboxylate: To a solution of (4R)-1-tert-butyl 2-methyl 4-((tert-butyldiphenylsilyl)oxy)-2-(3-chloropropyl)pyrrolidine-1,2-dicarboxylate (36.0 g, 1.0 equiv.) in ACN (200 mL) was added HCl•dioxane (4.0 M, 200 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)-methyl2-((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 × 100 mL). The combined organic phase was dried over anhydrous sodium sulfate, concentrated and purified by prep-HPLC [column: Waters Xbridge C18 150 × 50mm × 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 × 100mm × 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.

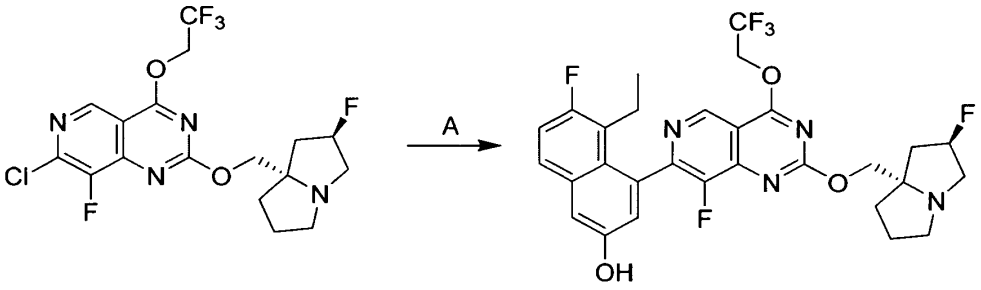
[0000323] Step E. ((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methanol: To a solution of (2R,7aS)-methyl 2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizine-7a- carboxylate (4.50 g, 1.0 equiv.) in THF (100 mL) was added $LiAlH_4$ (1.21 g, 3.0 equiv.) at -40 °C. The mixture 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; ^{1}H 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



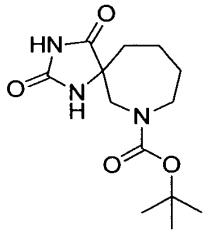
5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol



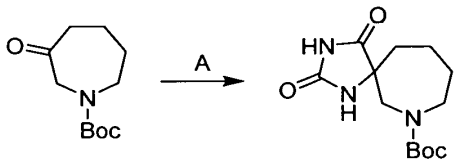
[0000324] Step A. 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol: To a solution of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (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 Cs_2CO_3 (1.5 M in H_2O, 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 N_2. 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; ^{1}H 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

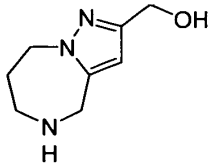


tert-butyl 2,4-dioxo-1,3,7-triazaspiro[4.6]undecane-7-carboxylate

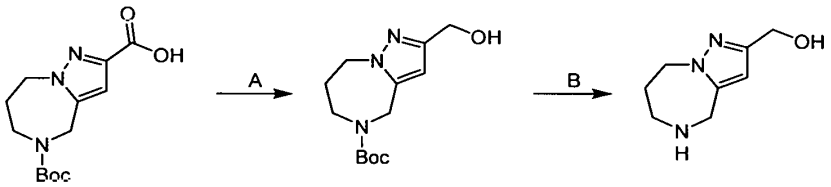


[0000325] Step A. tert-butyl 2,4-dioxo-1,3,7-triazaspiro[4.6]undecane-7-carboxylate: To a solution of tert-butyl 3-oxoazepane-1-carboxylate (2.00 g, 1.0 equiv.) and $(NH_4)_2CO_3$ (2.70 g, 3.0 equiv.) in EtOH (10 mL) and H_2O (10 mL) was added KCN (1.12 g, 1.83 equiv.). The reaction was stirred at 85 °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; ^{1}H 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



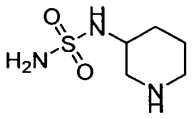
5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-ylmethanol



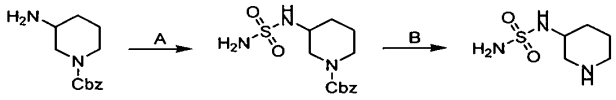
[0000326] Step A. tert-butyl 2-(hydroxymethyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: To a solution of 5-(tert-butoxycarbonyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (500 mg, 1.0 *equiv.*) in THF (10 mL) was added $LiAlH_4$ (135 mg, 2.0 *equiv.*) 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 $NaHCO_3$. 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



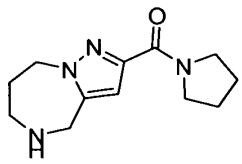
3-(sulfamoylamino)piperidine



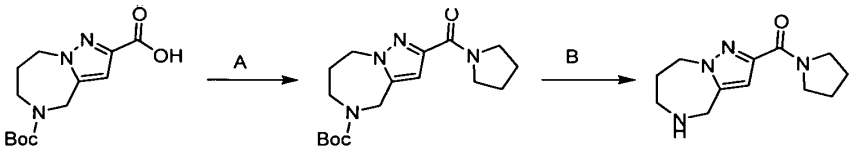
[0000328] Step A. benzyl 3-(sulfamoylamino)piperidine-1-carboxylate: To a solution of benzyl 3-aminopiperidine-1-carboxylate (500 mg, 1.0 *equiv.*) in dioxane (10 mL) was added sulfamide (410 mg, 254 µL, 2.0 *equiv.*). After stirring at 80 °C for 12 hours, another portion of sulfamide (615 mg, 382 µL, 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 N_2 atmosphere. The suspension was degassed and purged with H_2 3 times. The mixture was stirred under H_2 (15 Psi) at 20 °C for 12 hours. The reaction mixture was filtered under N_2 and the filtrate was concentrated to afford the title compound (240 mg, 99% yield) as a colorless oil; ^{1}H 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

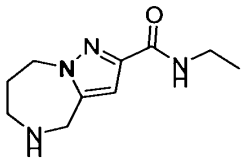


[0000330] Step A. tert-butyl-2-(pyrrolidine-1-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-*a*][1,4]diazepine-5(6H)-carboxylate: To a solution of 5-*tert*-butoxycarbonyl-4,6,7,8-tetrahydropyrazolo[1,5-*a*][1,4]diazepine-2-carboxylic acid (160 mg, 1.0 *equiv.*), pyrrolidine (121 mg, 3.0 *equiv.*) and triethylamine (74.8 mg, 103 μL, 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 × 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 μL, 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.

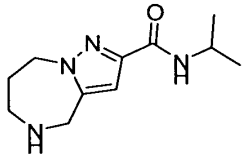
[0000332] Intermediates 32, 33, 34 and 51 were synthesized according to the procedure described for Intermediate 31.

Intermediate 32



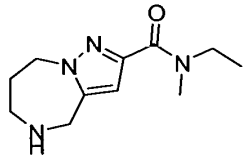
N-ethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

Intermediate 33



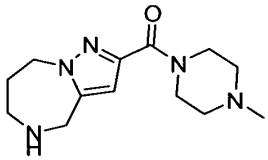
N-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

Intermediate 34



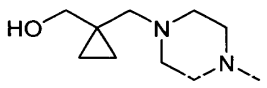
N-ethyl-N-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

Intermediate 51

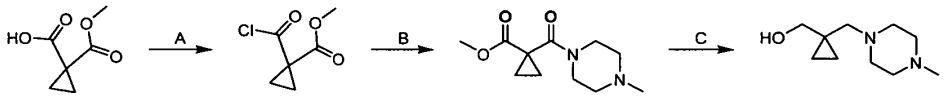


(4-methylpiperazin-1-yl)(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanone

Intermediate 35



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

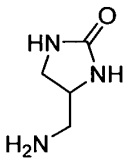


[0000333] Step A. methyl 1-(chlorocarbonyl)cyclopropanecarboxylate: To a mixture of 1-(methoxycarbonyl)cyclopropanecarboxylic acid (2.0 g, 1.0 *equiv.*), DMF (101 mg, 0.1 *equiv.*) in DCM (15 mL) was added $(COCl)_2$ (2.64 g, 1.82 mL, 1.5 *equiv.*). The mixture was stirred at 0-20 °C for 1 hour. The 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.

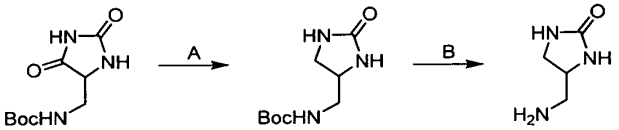
[0000334] Step B. methyl 1-(4-methylpiperazine-1-carbonyl)cyclopropanecarboxylate: To a mixture of methyl 1-chlorocarbonylcyclopropanecarboxylate (2.2 g, 1.0 *equiv.*), TEA (4.11 g, 3.0 *equiv.*) in DCM (15 mL) was added 1-methylpiperazine (1.63 g, 1.2 *equiv.*). The mixture was stirred at 0-20 °C for 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; ^{1}HNMR (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 $LiAlH_4$ (503 mg, 2.0 *equiv.*) portion wise under N_2. The suspension was degassed and purged with N_2 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



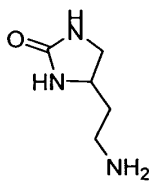
4-(aminomethyl)imidazolidin-2-one



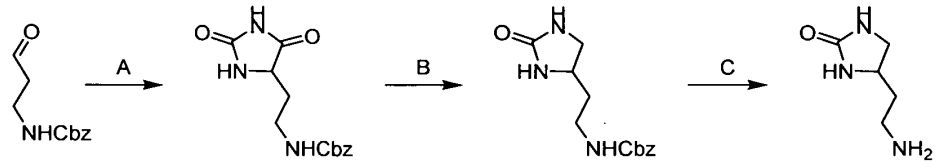
[0000336] Step A. tert-butyl ((2-oxoimidazolidin-4-yl)methyl)carbamate: A mixture of tert-butyl N-[(2,5-dioxoimidazolidin-4-yl)methyl]carbamate (100 mg, 1.0 *equiv.*) and BH_3•Me_2S (10.0 M, 2.0 *equiv.*) in THF (3 mL) at 0 °C was degassed and stirred at 60°C for 1 hour under N_2 atmosphere. The reaction 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-d6) 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



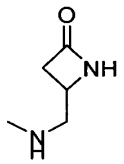
[0000338] Step A. benzyl (2-(2,5-dioxoimidazolidin-4-yl)ethyl)carbamate: Ammonium carbonate (25.5 g, 11.0 *equiv.*) was added to benzyl *N*-(3-oxopropyl)carbamate (5.00 g, 1.00 *equiv.*) in methanol (40.0 mL) and water (36.0 mL) under a flow nitrogen gas. To the reaction mixture was added potassium cyanide (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; ^{1}H 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. ^{1}H 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).

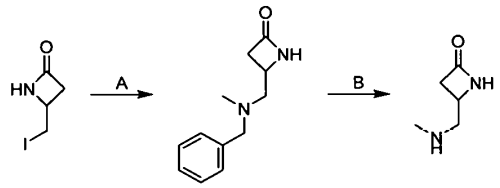
[0000340] Step C. 4-(2-aminoethyl)imidazolidin-2-one: To a solution of benzyl *N*-[2-(2-oxoimidazolidin-4-yl)ethyl]carbamate (80.0 mg, 1.00 *equiv.*) in tetrahydrofuran (5.00 mL) was

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

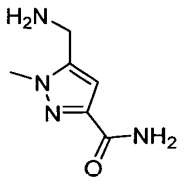


[0000341] Step A. 4-((benzyl(methyl)amino)methyl)azetidin-2-one: To a solution of 4-(iodomethyl)azetidin-2-one (100 mg, 1.0 *equiv.*) and *N*-methyl-1-phenyl-methanamine (86.2 mg, 1.5 *equiv.*) in acetonitrile (1.5 mL) was added potassium carbonate (196 mg, 3.0 *equiv.*). The mixture was stirred at 60 °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.

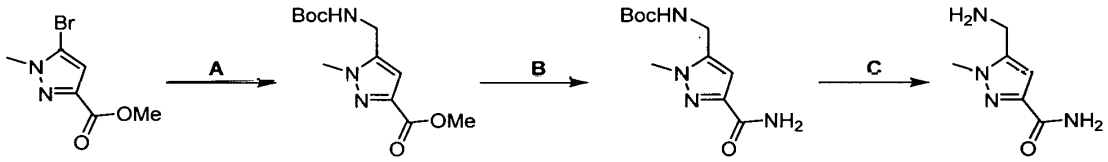
[0000342] Step B. 4-((methylamino)methyl)azetidin-2-one: A mixture of 4-[[benzyl(methyl)amino]methyl]azetidin-2-one (60.0 mg, 1.0 *equiv.*) and Pd/C (20.0 mg, 10% purity) in methyl alcohol (0.5 mL) was degassed and purged with hydrogen for 3 times, and then the mixture was stirred at 25 °C for 2 hours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



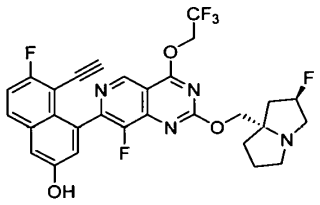
[0000343] Step A. methyl 5-(((tert-butoxycarbonyl)amino)methyl)-1-methyl-1H-pyrazole-3-carboxylate: A mixture of methyl 5-bromo-1-methyl-1H-pyrazole-3-carboxylate (900 mg, 1 *equiv.*), Potassium [[(tert-Butoxycarbonyl)amino]methyl]trifluoroborate (1.46 g, 1.5 *equiv.*), $Pd(OAc)_2$ (73.8 mg, 0.08 *equiv.*) and XPhos (313 mg, 0.16 *equiv.*) and Cs_2CO_3 (4.02 g, 3 *equiv.*) in THF (50 mL) and water (5 mL) was degassed and stirred at 100 °C for 2 hours under N_2 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 $NH_3 \bullet H_2O$ (3.64 g, 4 mL, 25% NH3, 17.48 *equiv.*) was stirred at 20 °C for 2 hours under N_2 atmosphere. The reaction mixture was diluted with water (20 mL) and extracted

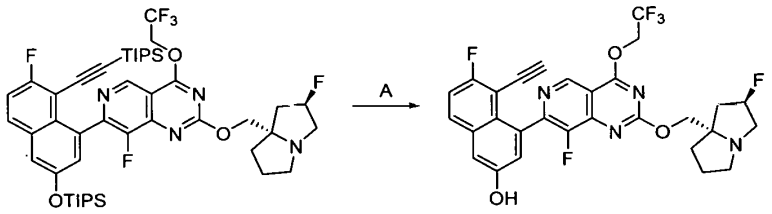
with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (10 mL × 1), dried over anhydrous sodium sulfate, filtered and concentrated to give the title compound (220 mg, 58% yield) as a white solid.

[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 CH_2Cl_2 (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. ^{1}H 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



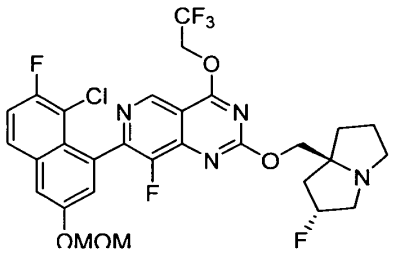
5-ethynyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol



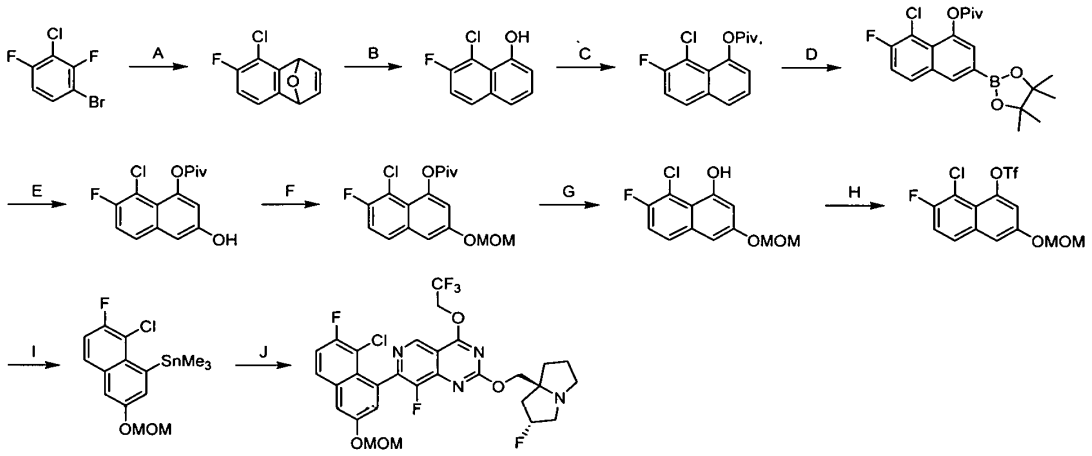
[0000346] Step A. 5-ethynyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol: To a solution of 8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)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 Na_2SO_4, 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 ayellow oil; ^{1}H 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 $NaHCO_3$ and extracted with ethyl acetate (2 × 2 L). The combined organic layers were dried over Na_2SO_4, 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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.), 4Å 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 Na_2SO_4 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; ^{1}H 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 N_2 atmosphere. The mixture was filtered, concentrated and purified by column chromatography [SiO_2, 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 H_2O_2 (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 Na_2SO_4, concentrated and purified by reversed phase flash chromatography (C 18, water (0.1% $NH_3 \cdot H_2O$)- ACN) to afford the title compound (5.4 g, 15% yield) as a gray solid; ^{1}H 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 Na_2SO_4, concentrated and purified by column chromatography [SiO_2, 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, 1.0 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 Na_2SO_4, concentrated and purified by column chromatography [SiO_2, Petroleum ether/Ethyl acetate 10:1 to 5:1] to afford the title compound (5.6 g, 93% yield) as a yellow solid.

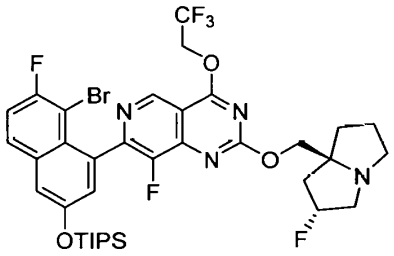
[0000354] Step H. 8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate: To a solution of 8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (5.00 g, 1.0 equiv.) in DCM (60 mL) were added DIEA (2.52 g, 3.39 mL, 1.0 equiv.) and trifluoromethanesulfonic anhydride (8.24 g, 4.82 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 Na_2SO_4, concentrated and purified by column chromatography [SiO_2, Petroleum ether/Ethyl acetate 50:1 to 10:1] to afford the title compound (6.9 g, 91% yield) as a yellow solid; ^{1}H 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 $Pd(PPh_3)_4$ (595 mg, 0.1 equiv.) under N_2. 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 (SiO_2, Petroleum ether/Ethyl acetate 1:0 to 10:1) to afford the title compound (2 g, 96.35% yield) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 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).

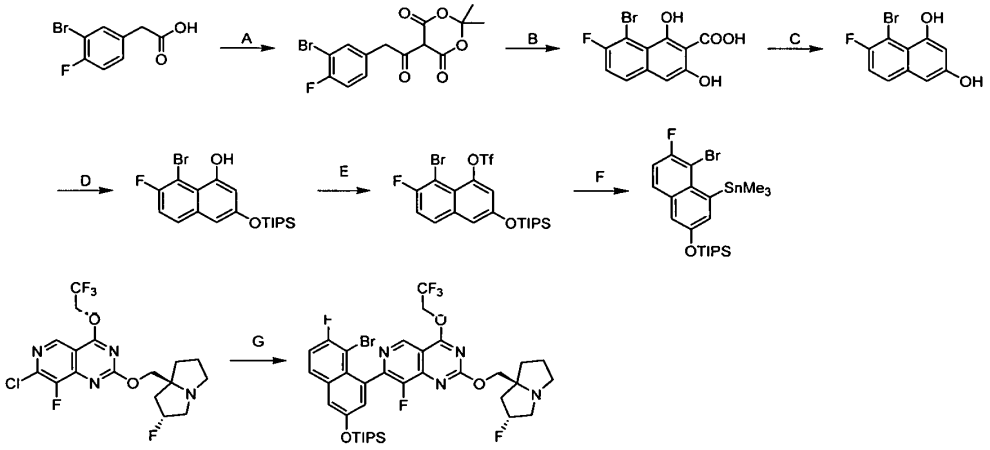
[0000356] Step J. 7-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a to a solution of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (625 mg, 1 equiv.) and [8-chloro-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-trimethyl-stannane (1.72 g, 3 equiv.) in toluene (25 mL) was added $Pd(dppf)Cl_2$ (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 N_2. 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; ^{1}H 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-fluoro-phenyl)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 N_2 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 N_2 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 Na_2SO_4, 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 Na_2SO_4 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.

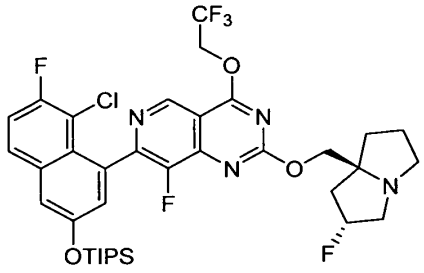
[0000361] Step E. 8-bromo-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl trifluoromethanesulfonate: To a solution of 8-bromo-7-fluoro-3-triisopropylsilyloxy-naphthalen-1-ol (14.7 g, 1.0 *equiv.*) and DIEA (13.8 g, 18.6 mL, 3.0 *equiv.*) in DCM (200 mL) was added Tf_2O (12.0 g, 7.04 mL, 1.2 *equiv.*) 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 Na_2SO_4 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 $Pd(PPh_3)_2Cl_2$ (643 mg, 0.1 *equiv.*) in toluene (50 mL) was added LiCl (1.17 g, 563 µL, 3.0 *equiv.*) under N_2. 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; ^{1}H 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 $Pd(dppf)Cl_2$ (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.

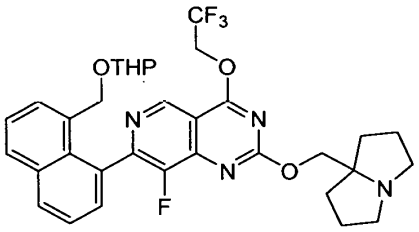
Intermediate 43



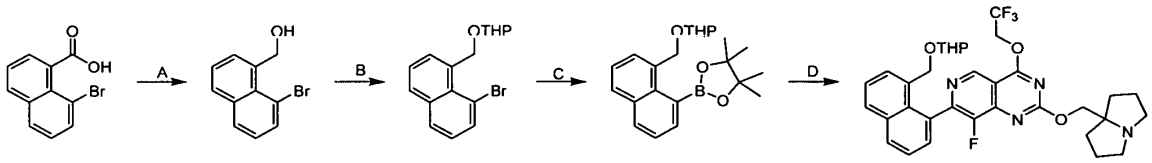
7-(8-chloro-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine

[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 BH_3•Me_2S (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; ^{1}H NMR (400 MHz, DMSO-*d6*) 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).

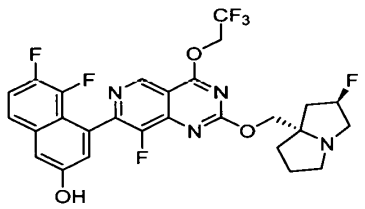
[0000366] Step B. 2-((8-bromonaphthalen-1-yl)methoxy)tetrahydro-2H-pyran: To a solution of 3,4-dihydropyran (1.22 g, 1.0 *equiv.*), 8-bromonaphthalen-1-yl)methanol (3.44 g, 1.0 *equiv.*) and 4-methylbenzenesulfonic acid (514 mg, 0.1 *equiv.*) in DCM (40 mL) was stirred at 25 °C for 5 hours. The reaction 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. ^{1}H NMR (400 MHz, 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-(((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 Pd(dppf)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

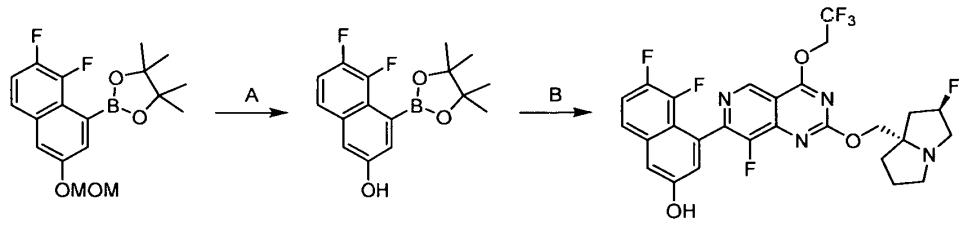
organic phase was washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate 100:1 to 15:1) to afford the title compound (290 mg, 85% yield) as a white solid; ^{1}H NMR (400 MHz, CDCl3) 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; ^{1}H 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, M+1): m/z = 627.2.

Intermediate 45



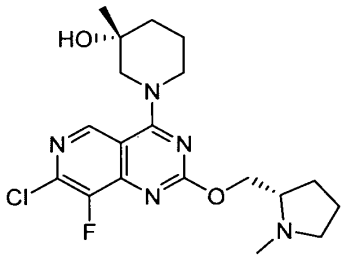
5,6-difluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol



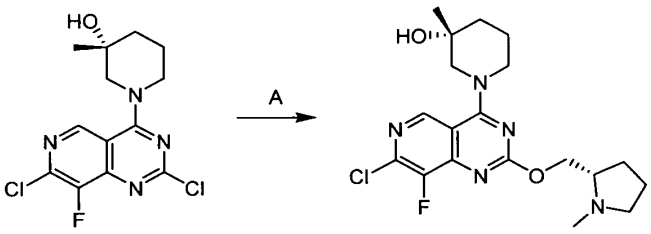
[0000369] Step A. 5,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol: To a solution of 2-[7,8-difluoro-3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (500 mg, 1.0 *equiv.*) in ACN (15 mL) was added HCl•dioxane (4 M, 7.50 mL, 21.0 *equiv.*) at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. The mixture was diluted with saturated aqueous $NaHCO_3$ (15 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, 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 Cs_2CO_3 (1.5 M, 1.39 mL, 3.0 *equiv.*) under N_2. 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 Na_2SO_4, 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

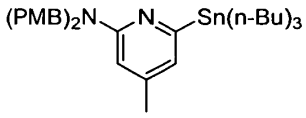


(R)-1-(7-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

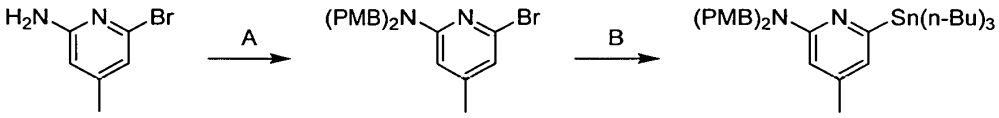


[0000371] Step A. (R)-1-(7-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (2.20 g, 1.0 equiv.) and 4Å molecular sieves (500 mg) in dioxane (15 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 H_2O (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

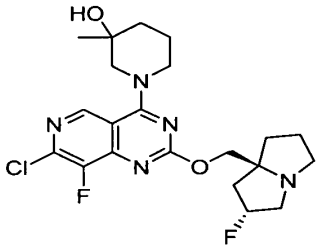


[0000372] Step A. 6-bromo-N,N-bis(4-methoxybenzyl)-4-methylpyridin-2-amine: To a solution of 6-bromo-4-methyl-pyridin-2-amine (180 g, 1.0 equiv.) in DMAC (1.8 L) was added NaH (115 g, 60% purity, 3.0 equiv.) at 0 °C under nitrogen atmosphere. The mixture was stirred at 25°C for 1 hour under nitrogen 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 Na_2SO_4 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; ^{1}H NMR (400 MHz, $CDCl_3$-*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.

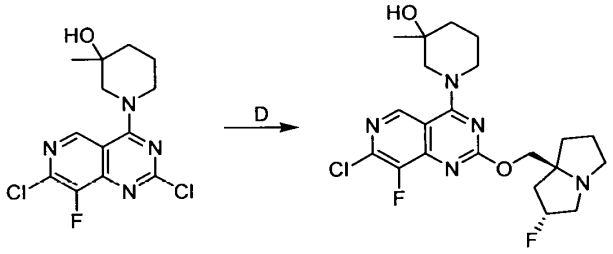
[0000373] Step B. N,N-bis(4-methoxybenzyl)-4-methyl-6-(tributylstannyl)pyridin-2-amine: A mixture of 6-bromo-*N*,*N*-bis[(4-methoxyphenyl)methyl]-4-methyl-pyridin-2-amine (200 g, 1.0 equiv.), tributyl(tributylstannyl)stannane (651 g, 2.4 equiv.), $Pd_2(dba)_3$ (42.9 g, 0.1 equiv.), PCy_3 (26.2 g, 0.2 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 N_2 atmosphere. After reaction completion, the mixture was concentrated in vacuum. The residue was purified by column chromatography (SiO_2, 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. ^{1}H NMR (400 MHz, $CDCl_3$-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

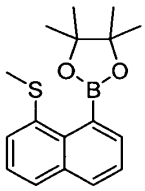


1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

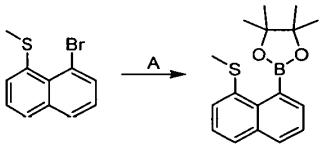


[0000374] Step D. 1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of 1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (2.22 g, 1.0 *equiv.*), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (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 tittle compound (1.90 g, 62% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 454.1.

Intermediate 49

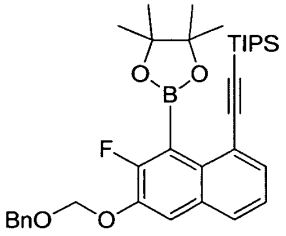


4,4,5,5-tetramethyl-2-(8-(methylthio)naphthalen-1-yl)-1,3,2-dioxaborolane

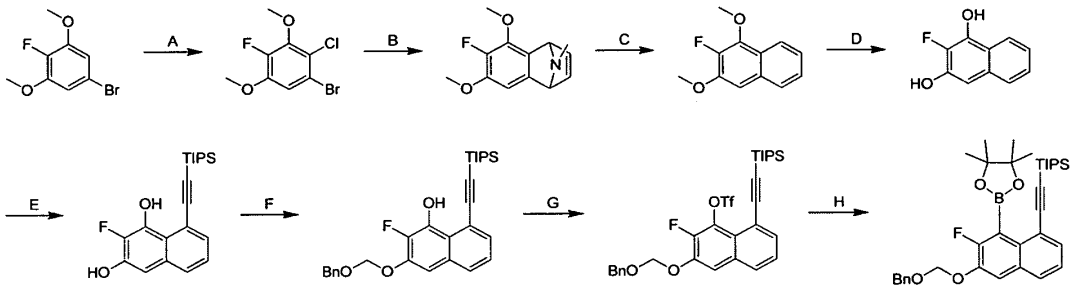


[0000375] Step A. 4,4,5,5-tetramethyl-2-(8-(methylthio)naphthalen-1-yl)-1,3,2-dioxaborolane: To a solution of 1-bromo-8-methylsulfanyl-naphthalene (1.00 g, 1.0 *equiv.*) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.53 g, 5.0 *equiv.*) in ACN (20 mL) were added TEA (1.20 g, 3.0 *equiv.*) and $Pd(dppf)Cl_2$ (433 mg, 0.15 *equiv.*). The mixture was stirred at 80 °C for 5 hours under N_2 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 Na_2SO_4, concentrated and purified by column chromatography [Silica gel, Petroleum ether/Ethyl acetate 1:0 to 30:1] to afford the tittle compound (1.00 g, 84% yield, 99% purity) as a yellow oil; ^1H NMR (400 MHz, CHLOROFOMR-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 tittle compound (85 g, 74% yield)as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) 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 NH_4Cl 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 tittle 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 Na_2SO_3 solution (100 mL). The organic

layer was separated and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 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 BBr_3 (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 (SiO_2, 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, $CDCl_3$) 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-((*triiso*propylsilyl)ethynyl)naphthalene-1,3-diol: To a solution of 2-fluoronaphthalene-1,3-diol (7.6 g, 1.0 equiv.) and 2-bromoethynyl(*triiso*propyl)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 N_2 atmosphere. The mixture was poured into H_2O (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, $CDCl_3$) 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.

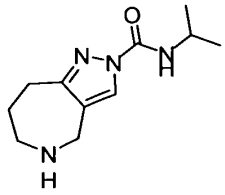
[0000381] Step F. 3-((benzyloxy)methoxy)-2-fluoro-8-((*triiso*propylsilyl)ethynyl)naphthalen-1-ol: To a solution of 2-fluoro-8-((*triiso*propylsilyl)ethynyl)naphthalene-1,3-diol (2.8 g, 1.0 equiv.) and DIEA (1.51 g, 1.5 equiv.) in DCM (24.0 mL) was added ((chloromethoxy)methyl)benzene (1.22 g, 1.0 equiv.) 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 (SiO_2, 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, $CDCl_3$) 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.

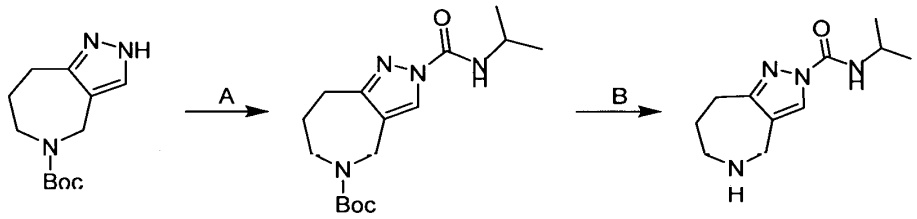
[0000382] Step G. 3-((benzyloxy)methoxy)-2-fluoro-8-((*triiso*propylsilyl)ethynyl)naphthalen-1-yl trifluoromethanesulfonate: To a solution of 3-((benzyloxy)methoxy)-2-fluoro-8-((*triiso*propylsilyl)ethynyl)naphthalen-1-ol (550 mg, 1.0 equiv.) and DIEA (297 mg, 2.0 equiv.) in DCM (3.0 mL) was added Tf_2O (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 tittle compound (650 mg, 92% yield) as a yellow solid; ^{1}H 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-((*triiso*propylsilyl)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 $Pd(dppf)Cl_2$ (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 tittle compound (32 mg, 66% yield) as a yellow oil; ^{1}H 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



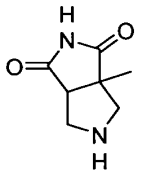
N-isopropyl-5,6,7,8-tetrahydropyrazolo[4,3-c]azepine-2(4H)-carboxamide



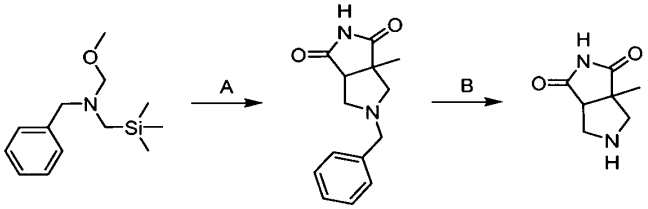
[0000384] Step A. tert-butyl 2-(isopropylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[4,3-c]azepine-5-carboxylate: To a solution of tert-butyl 4,6,7,8-tetrahydro-2H-pyrazolo[4,3-c]azepine-5-carboxylate (4.0 g, 1.0 *equiv.)* in THF (20 mL) was added portion wise CDI (2.73 g, 1 *equiv.)* and isopropylamine (1.1 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 (SiO_2, **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

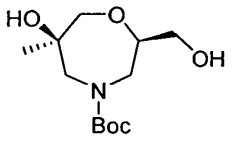


[0000386] Step A. 5-benzyl-3a-methyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione: To a mixture of 3-methylpyrrole-2,5-dione (608 mg, 1.0 equiv.) and N-(methoxymethyl)-1-phenyl-N-(trimethylsilylmethyl)methanamine (1.3 g, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added a solution of TFA (62.4 mg, 40.5uL, 0.1 equiv.) in CH_2Cl_2 (1.0 mL). The mixture was stirred at 25 °C for 1 hour. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (40 mL) and extracted with CH_2Cl_2 (3 × 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.

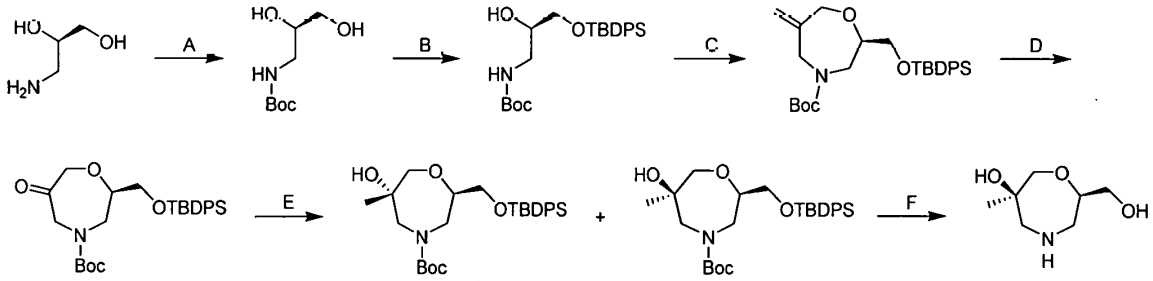
[0000387] Step B. tert-butyl N-[(5-carbamoyl-2-methyl-pyrazol-3-yl)methyl]carbamate: To a mixture of 5-benzyl-3a-methyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (0.8 g, 1.0 equiv.) in THF (30 mL) was added Pd/C (300 mg, 10% purity), the mixture was degassed and purged with H_2 and stirred at 40 °C for 12 hours under H_2 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 Et_3N (84.3 g, 1.52 equiv.) in CH_3OH (1.5 L) was added Boc_2O (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 H_2O (2.0 L) and extracted with ethyl acetate (1.0 L). The organic phase was washed with brine (500 mL), dried over Na_2SO_4, 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 tittle compound (48.0 g, 45% yield) as a colorless oil; ^1H NMR (400 MHz, DMSO-d_6) 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 CH_2Cl_2 (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 CH_2Cl_2 (500 mL) and H_2O (1.0 L). The organic phase was separated and washed with brine 1.0 L (2×500 mL). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash silica gel chromatography (ethyl acetate in petroleum ether 0 - 20%) to afford the tittle compound (42.3 g, 37.9% yield) as a colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6) 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-butyldiphenylsilyl)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 N_2 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 N_2 atmosphere. The mixture was quenched by addition of H_2O (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 Na_2SO_4. 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 tittle compound (1.8 g, 7.64% yield) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 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.

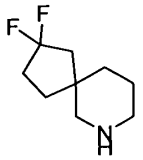
[0000391] Step D. (R)-tert-butyl 2-(((tert-butyldiphenylsilyl)oxy)methyl)-6-oxo-1,4-oxazepane-4-carboxylate: To a solution of tert-butyl (2R)-2-[[tert-butyl(diphenyl)silyl]oxymethyl]-6-methylene-1,4-oxazepane-4-carboxylate (1.8 g, 1 equiv.) in THF (9 mL) and H_2O (9 mL) were added $NaIO_4$ (1.84 g, 2.3 equiv.) and K_2OsO_4•$2H_2O$ (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 Na_2SO_3 (20 mL) at 0 °C and H_2O (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 (SiO_2, Petroleum ether/Ethyl acetate 1:0 to 100:1) to afford the tittle compound (1.1 g, 57% yield) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 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.

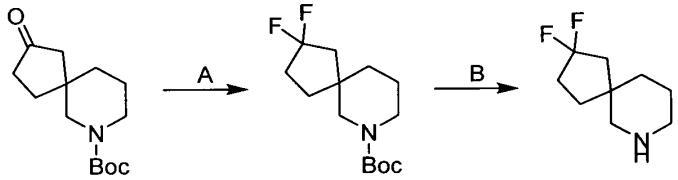
[0000392] Step E. (2R,6S)-tert-butyl 2-(((tert-butyldiphenylsilyl)oxy)methyl)-6-hydroxy-6-methyl-1,4-oxazepane-4-carboxylate and (2R,6R)-tert-butyl 2-(((tert-butyldiphenylsilyl)oxy)methyl)-6-hydroxy-6-methyl-1,4-oxazepane-4-carboxylate: To a solution of tert-butyl (2R)-2-[[tert-butyl(diphenyl)silyl]oxymethyl]-6-oxo-1,4-oxazepane-4-carboxylate (900 mg, 1 equiv.) in THF (13 mL) was added MeMgBr (3 M, 4.04 equiv.) under N_2 atm. at 0 °C. The reaction mixture was stirred at 25 °C for 2 hours under N_2 atmosphere. The mixture was quenched by addition of sat.aq.NH_4Cl (30 mL) at 0 °C and H_2O (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; ^{1}H NMR (400 MHz, $CDCl_3$) 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-butyldiphenylsilyl)oxy)methyl)-6-hydroxy-6-methyl-1,4-oxazepane-4-carboxylate (520 mg, 1 equiv.) in CH_2Cl_2 (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 H_2O (4 mL) and the pH of the mixture was adjusted to 7 with saturated $NaHCO_3$ aqueous. The mixture was extracted with ethyl acetate (2 × 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (70 mg, crude) as a light-yellow oil.

Intermediate 55



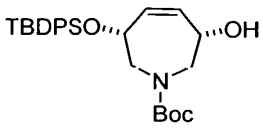
3,3-difluoro-7-azaspiro[4.5]decane



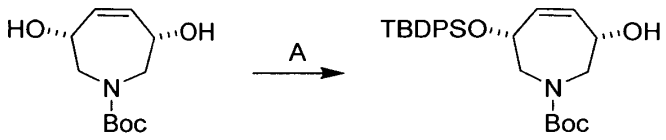
[0000394] Step A. tert-butyl 3,3-difluoro-7-azaspiro[4.5]decane-7-carboxylate: To a solution of tert-butyl 3-oxo-7-azaspiro[4.5]decane-7-carboxylate (500 mg, 1.0 equiv.) in CH_2Cl_2 (8 mL) was added DAST (541 mg, 443 µL, 1.7 equiv.). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography (SiO_2, 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); ^{19}F 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 $NaHCO_3$, 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

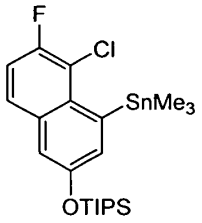


tert-butyl (3R,6S)-3-((tert-butyldiphenylsilyl)oxy)-6-hydroxy-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate

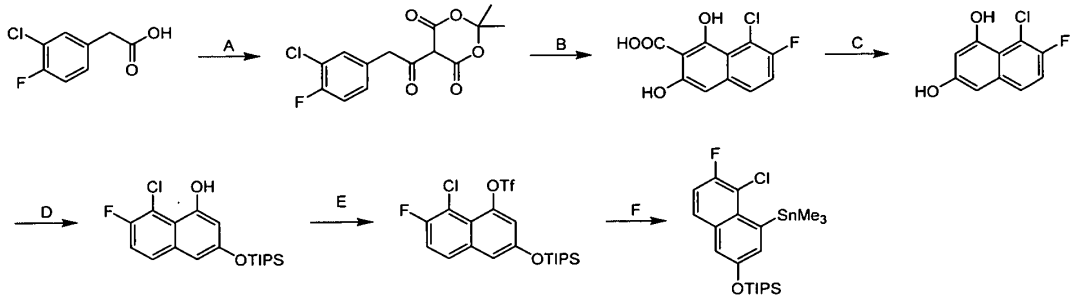


[0000396] Step A. tert-butyl (3R,6S)-3-((tert-butyldiphenylsilyl)oxy)-6-hydroxy-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate: To a solution of tert-butyl 3,6-dihydroxy-2,3,6,7-tetrahydroazepine-1-carboxylate (3.00 g, 1 equiv.) in DMF (20 mL) was added imidazole (2.67 g, 3 equiv.) and TBDPSCl (4.32 g, 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 (SiO_2, Petroleum ether/ Ethyl acetate 10:1 to 5:1) to afford the title compound (1.8 g, 29.4% yield) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) 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



((5-chloro-6-fluoro-4-(trimethylstannyl)naphthalen-2-yl)oxy)triisopropylsilane



[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-fluoro-phenyl)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. ^{1}HNMR (400 MHz, $CDCl_3$) 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 CF_3SO_3H (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 H_2O (700 mL) was stirred at 85 °C for 12 hours under N_2. The mixture was concentrated under vacuum to remove

acetonitrile. The residue was extracted with ethyl acetate (2 L× 2), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, 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 Na_2SO_4 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).

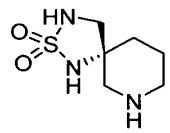
[0000400] Step D. 8-chloro-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-ol: To a solution of 8-chloro-7-fluoronaphthalene-1,3-diol (10 g, 1 equiv.) and DIEA (12.2 g, 2.0 equiv.) in DCM (150 mL) was added TIPSCl (8.16 g, 0.9 equiv.) at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. The mixture was concentrated in vacuum and the residue was purified by column chromatography (SiO_2, 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 Tf_2O (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 (SiO_2, 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 trifluoromethanesulfonatc (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 $Pd(PPh_3)_4$ (1.15 g, 0.1 equiv.) under N_2. The mixture was stirred at 100 °C for 12 hours under N_2. 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 (SiO_2, petroleum ether) and reversed phase flash [water (0.1%, FORMIC ACID)/acetonitrile] to afford the title compound

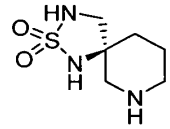
(3 g, 55% yield) as yellow oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ= 7.60 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.31 - 7.26 (m, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 1.35 - 1.30 (m, 3H), 1.15 (d, *J* = 7.2 Hz, 18H), 0.51 - 0.35 (m, 9H)

Intermediate 58

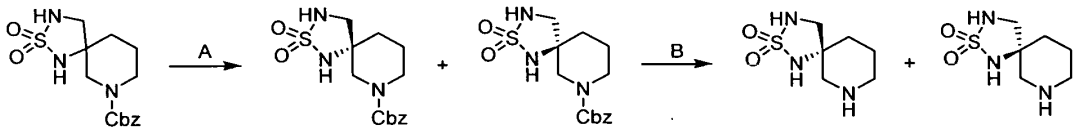


(*R*)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide

Intermediate 59



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

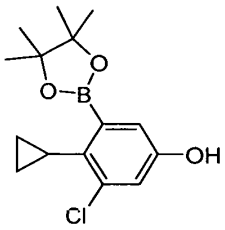


[0000403] Step A. benzyl (*R*)-2-thia-1,3,7-triazaspiro[4.5]decane-7-carboxylate 2,2-dioxide and benzyl (*S*)-2-thia-1,3,7-triazaspiro[4.5]decane-7-carboxylate 2,2-dioxide: Racemic benzyl 2-thia-1,3,7-triazaspiro[4.5]decane-7-carboxylate 2,2-dioxide (46.5 g) was separated by chiral SFC (column: DAICEL CHIRALPAK IC(250mm*50mm,10um); mobile phase: [0.1%NH_3H_2O-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, M+1): m/z = 326.1.

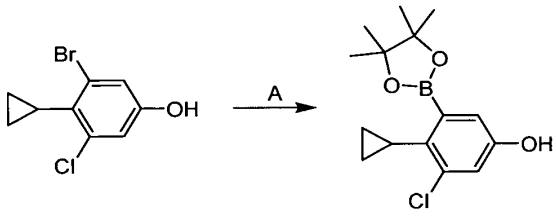
[0000404] Step B. (*R*)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide: To a solution of (*R*)-2-thia-1,3,7-triazaspiro[4.5]decane-7-carboxylate 2,2-dioxide (20.0 g, 1.00 equiv.) in methanol (160 mL) was added Pd/C (10%, 3.00 g) under nitrogen atmosphere. The suspension was degassed and stirred under 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. ^{1}H NMR (400 MHz, MeOD-d$_4$) 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. ^{1}H NMR (400 MHz, MeOD-d$_4$) 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

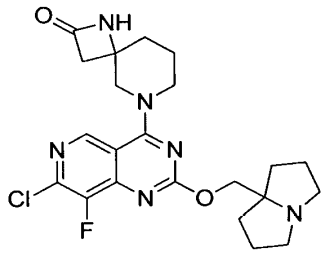


3-chloro-4-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

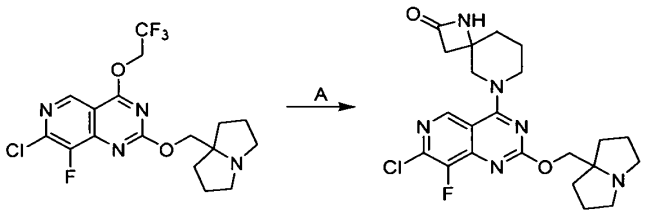


[0000406] Step A. 3-chloro-4-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol: To a solution of 3-bromo-5-chloro-4-cyclopropyl-phenol (2.00 g, 1.0 equiv.) in dioxane (50 mL) was added KOAc (2.38 g, 3.0 equiv.), Pin_2B_2 (4.00 g, 2.0 equiv.) and $Pd(dppf)Cl_2$ (591 mg, 0.1 equiv.). The mixture was stirred at 100 °C for 4 hours under nitrogen atmosphere. The reaction mixture was poured into saturated aqueous NH_4Cl 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

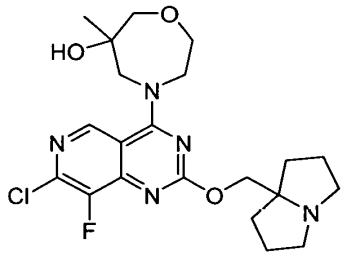


6-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one

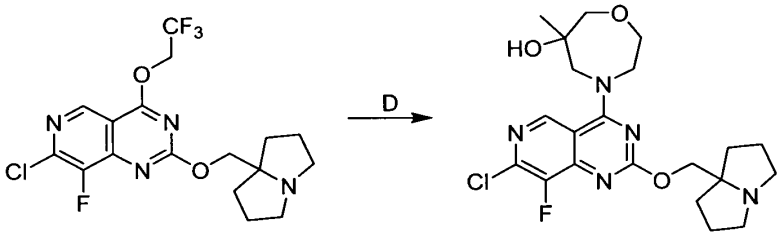


[0000407] Step A. 6-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one: To a mixture of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (200 mg, 475 μmol, 1.0 equiv.), 1,6-diazaspiro[3.5]nonan-2-one (60.0 mg, 428 μmol, 0.9 equiv.), 4Å molecular sieves (10.0 mg) in DMF (2 mL) was added DIEA (184 mg, 1.43 mmol, 248 μL, 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 μmol, 27% yield) as a yellow solid; LCMS (ESI, M+1): m/z= 461.3.

Intermediate 62

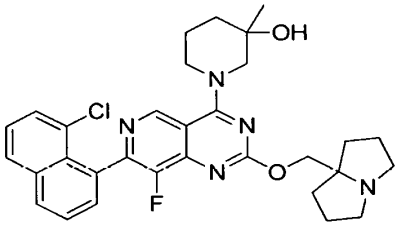


4-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol

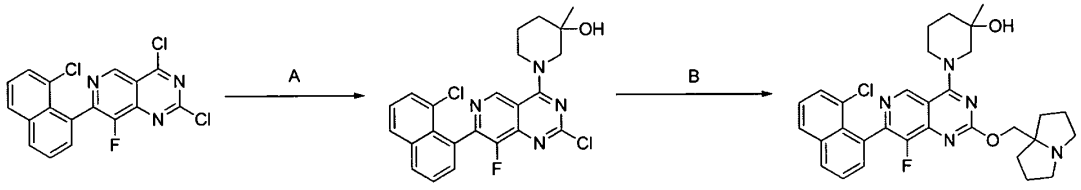


[0000408] Step A. 4-(7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol: A mixture of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (0.45 g, 1 equiv.), 6-methyl-1,4-oxazepan-6-ol (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



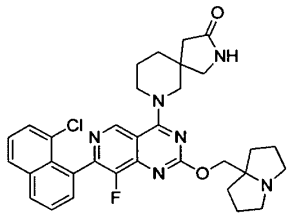
1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



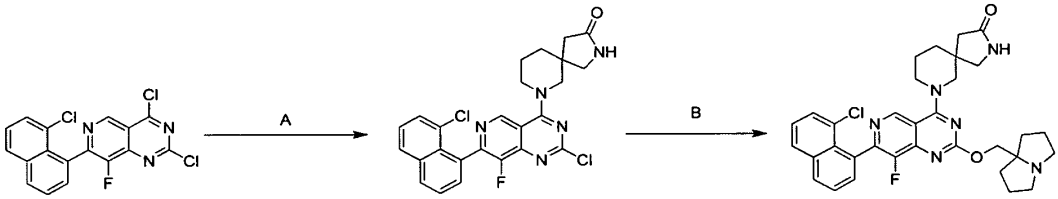
[0000409] Step A. 1-[2-chloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol: To a mixture of 2,4-dichloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidine (1.48 g, 3.90 mmol) in dichloromethane (15 mL) was added DIEA (5.05 g, 39.0 mmol, 6.80 mL) and 3-methylpiperidin-3-ol (270 mg, 2.34 mmol) at - 40 °C under N_2. 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 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)/acetiontrile] 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; ^{1}H 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

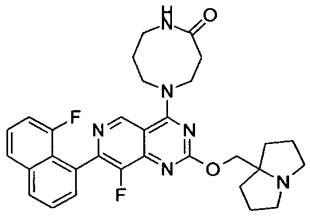


[0000411] Step A. 7-[2-chloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 2,4-dichloro-7-(8-chloro-1 -naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidine (0.15 g, 396 µmol) in dichloromethane (5.0 mL) was added DIEA (512 mg, 3.96 mmol) at - 40 °C. After the mixture was stirred at - 40 °C for 10 minutes, 2,9-diazaspiro[4.5]decan-3-one (73.3 mg, 475 µmol) 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 × 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.

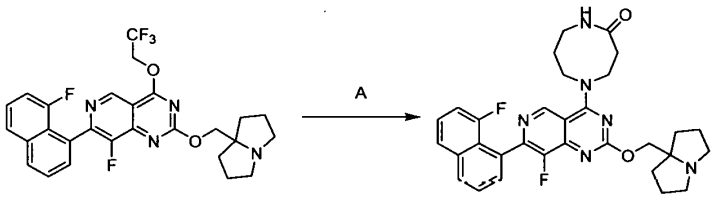
[0000412] Step B. 7-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: A mixture of 7-[2-chloro-7-(8-chloro-1-naphthyl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-2,7-diazaspiro[4.5]decan-3-one (100 mg, 201 µmol),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



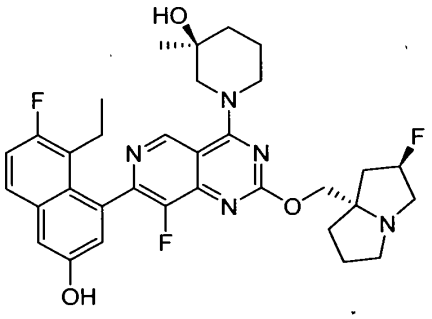
5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,5-diazocan-2-one



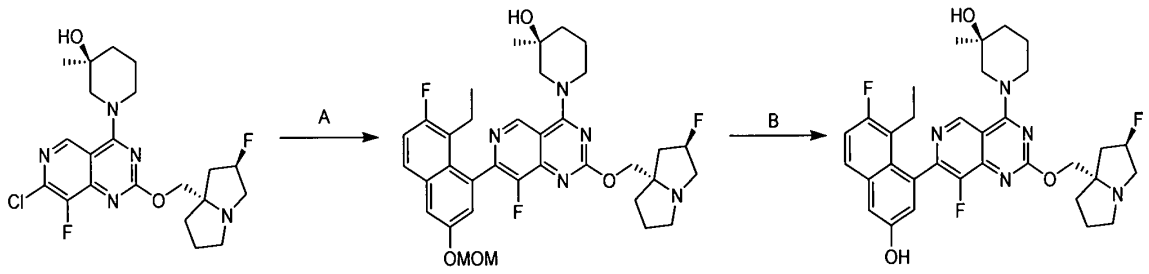
[0000413] Step A. 5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,5-diazocan-2-one: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (100 mg, 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

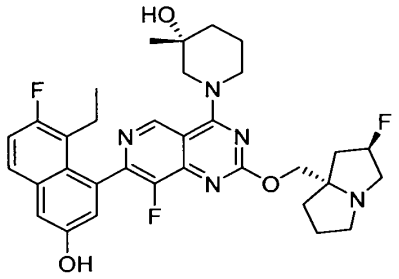


[0000414] Step A. (S)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-

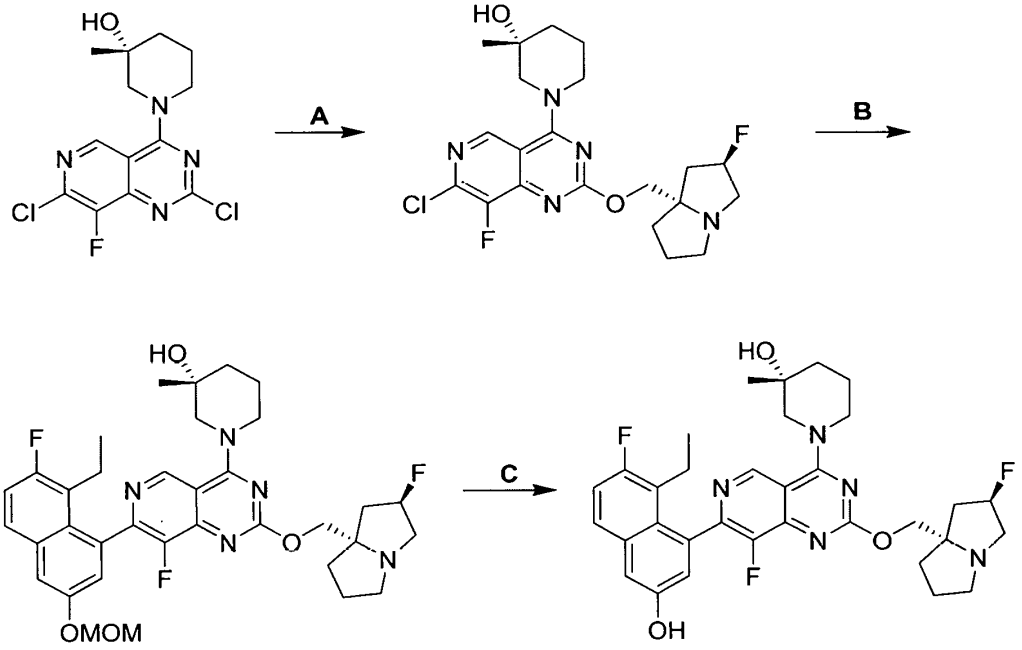
methylpiperidin-3-ol: To a mixture of 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (103 mg, 286 μmol, 1.3 equiv.) and (S)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (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×5um; 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

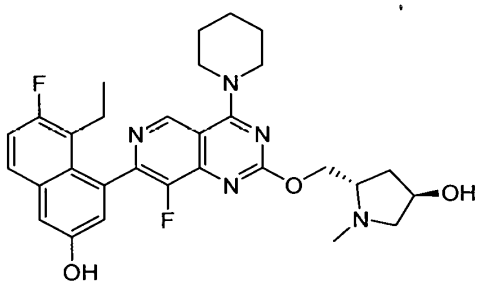
diluted with ethyl acetate (300 mL) and water (200 mL), and aqueous layer was then extracted with ethyl acetate (300 mL). The combined organic phase was washed with brine (200 mL) and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated to give a residue. The residue was purified 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-G3cataCXium-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.

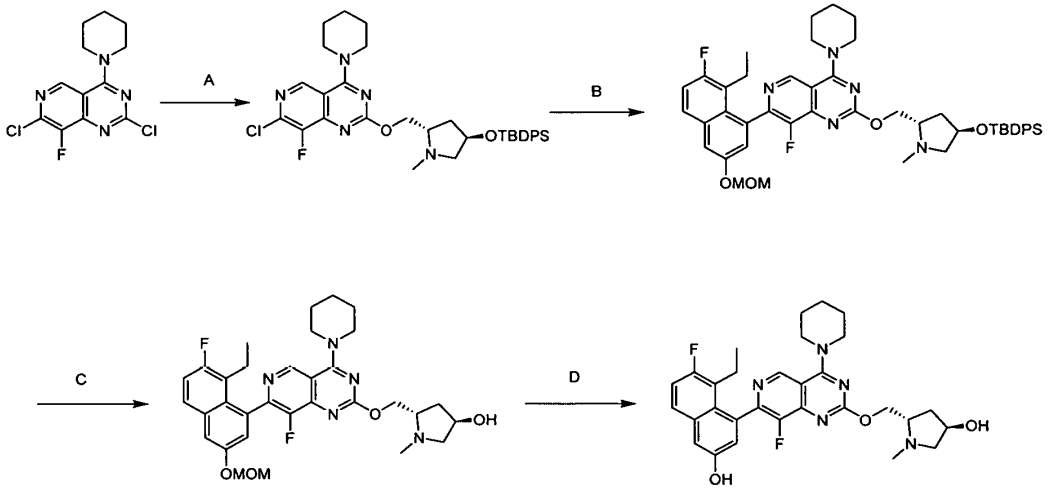
[0000418] Step C. (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To the solution of (R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-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 μmol) and ((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methanol (189 mg, 511 μmol) 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.

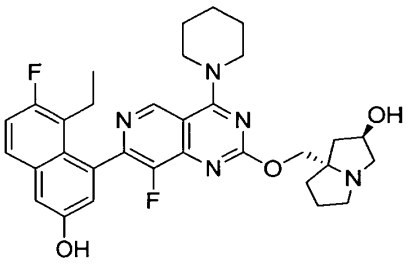
[0000420] Step B. 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine: A mixture of 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-chloro-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine (170 mg, 268 μmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (193 mg, 536 μmol), cataCXium-A-Pd-G3cataCXium-A-Pd-G3 (19.5 mg, 26.8 μmol) and K3PO4 (1.5 M in water , 536 μL) 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 × 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.

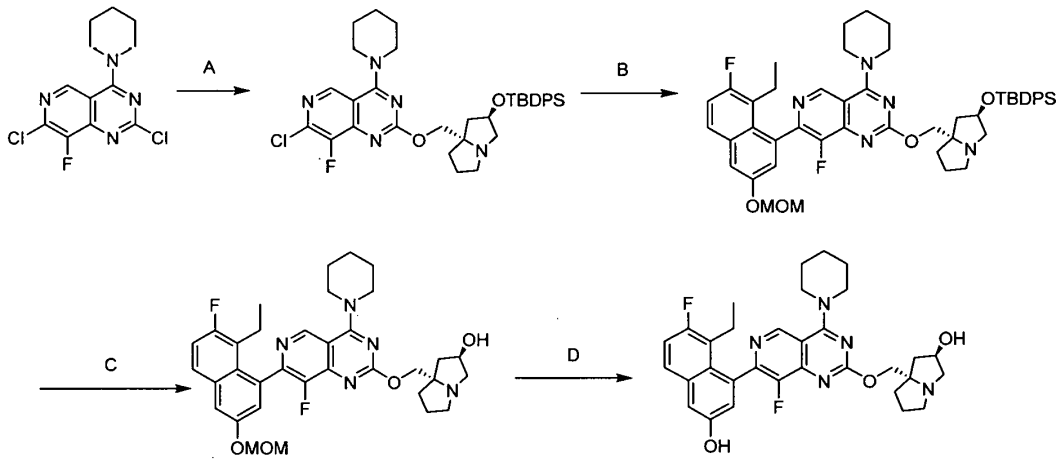
[0000421] Step C. (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol: To a solution of 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine (200 mg, 144 μmol, 60% purity) in DMF (6.0 mL) was added CsF (65.7 mg, 433 μmol, 15.9 μL). 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 × 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 μmol) 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 × 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 100×25mm×5μm; 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 N_2. The reaction mixture was quenched by the addition of water (50.0 mL) at 0 °C, and extracted with DCM (30.0 mL × 3). The combined organic layers were washed with brine (40.0 mL), dried over Na_2SO_4, 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. ^{1}H NMR (400 MHz, $CDCl_3$) 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.

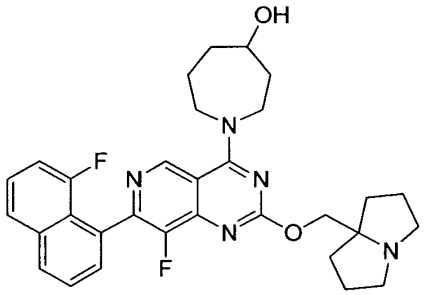
[0000424] Step B. 2-(((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 2-(((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine (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 K_3PO_4 (1.50 M, 727 μL) and cataCXium-A-Pd-G3cataCXium-A-Pd-G3 (26.5 mg, 36.4 μmol) under N_2. The mixture was stirred at 100 °C for 1 hour under N_2. 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 Na_2SO_4, 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 Na_2SO_4, 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.

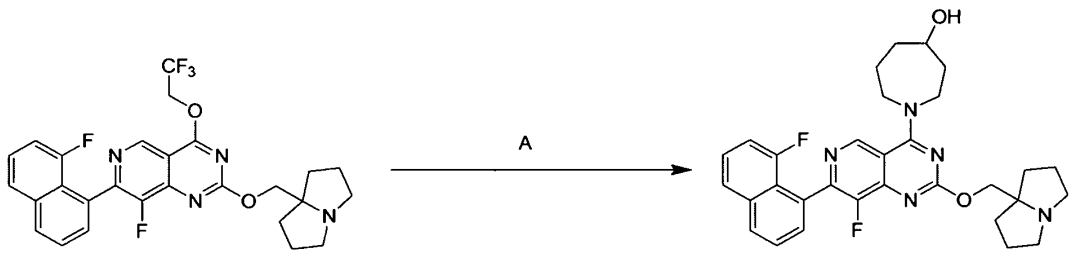
[0000426] Step D. (2R,7aS)-7a-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-2-ol: To a

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 μmol, 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. $NaHCO_3$ (20.0 mL) at 0 °C and then extracted with EtOAc (15.0 mL × 3). The combined organic layers were washed with brine (20.0 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: water s Xbridge BEH C18 100×25mm×5μm;mobile phase: [water (10mM NH_4HCO_3)-ACN];B%: 25%-65%,10min) to give the title compound (19.85 mg, 26% yield, 99.0% purity) as a light-yellow solid.; ^{1}H 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

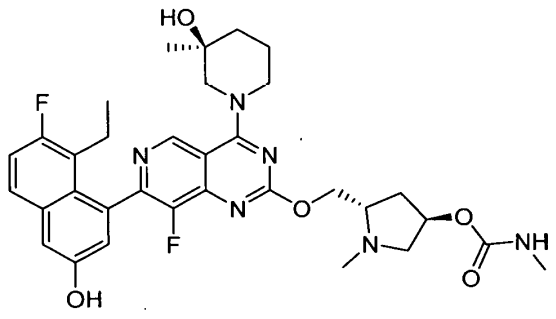


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-ol

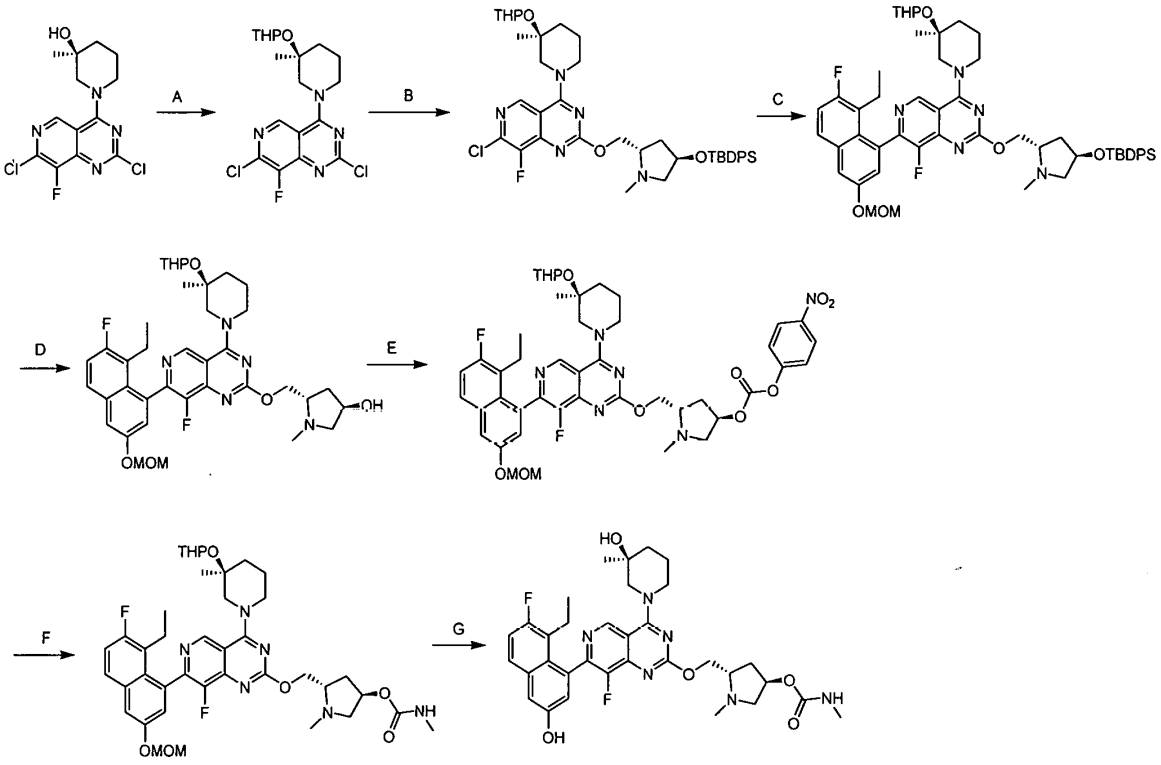


[0000427] Step A. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-ol: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (100 mg, 189 μmol) and azepan-4-ol hydrochloride (42.9 mg, 283 μmol, HCl) in DMF (3.00 mL) was added DIEA (73.1 mg, 566 μmol, 98.5 μL, 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×5μm;mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 20%-60%,10min) and re-purified by prep-HPLC (column: Welch Xtimate C18 150×25mm×5μm;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; ^{1}H 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); ^{1}H 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. $NaHCO_3$ (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; ^{1}H NMR (400 MHz, $CDCl_3$-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), K_3PO_4 (1.50 M, 1.07 mL) in toluene (8 mL) was added [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butyl-phosphane;methanesμlfonate (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-

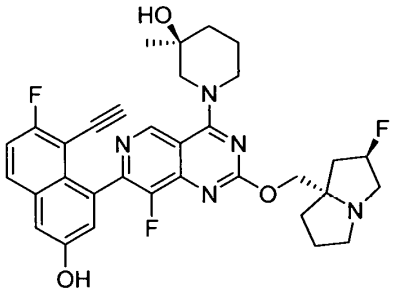
d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol: To the mixture of 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3S)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidine (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.

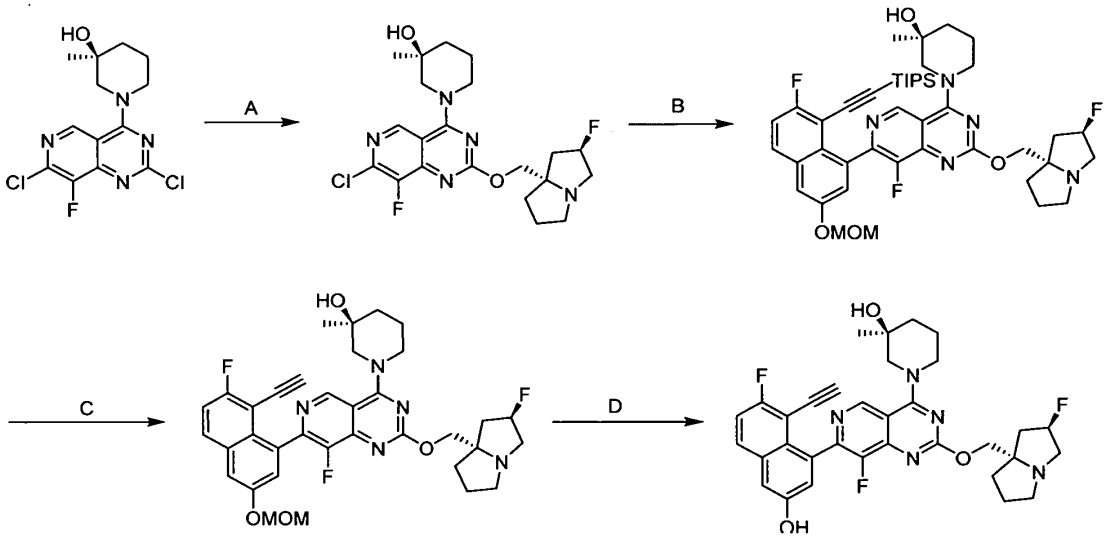
[0000433] Step F. [(3R,5S)-5-[[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-4-[(3S)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] N-methylcarbamate: A mixture of (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3S)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)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 μmol) 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 $NaHCO_3$ solution. The mixture was triturated with methanol (2 × 10 mL) and filtered. The filtrate was concentrated in vacuum. The residue was purified by prep-HPLC (Phenomenex Gemini-NX C18 75*30mm*3um; 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. ^{1}H 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). ^{19}F NMR (400 MHz, METHANOL-d4) δ = -121.268, -139.169. HPLC: >99% ee, Chiralcel OD-3 50 × 4.6mm I.D., 3μm A: 60% MeOH + 40% ACN (w/ 0.05% DEA), B: CO_2, 3mL/min, 220 nm, t_R: 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 μmol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (150 mg, 942 μmol), 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 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 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.

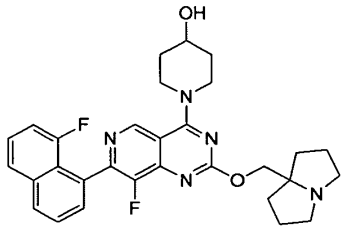
[0000436] Step B. (S)-1-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (S)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (290 mg, 639 μmol), K_3PO_4 (1.5 M in *water* , 1.3 mL) in THF (5.2 mL) was degassed and purged with N_2 for 3 times. cataCXium-A-Pd-G3 (47 mg, 64.5 μmol) 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 μmol) 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.

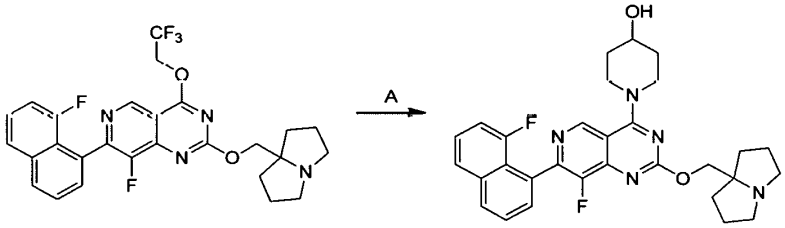
[0000437] Step C. (S)-1-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (S)-1-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)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 $NaHCO_3$ aqueous (5 mL). The mixture was extracted with ethyl acetate (5 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 × 30mm × 3um; 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, 0.5FORMIC ACID). ^{1}H 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). ^{19}F NMR (377 MHz, methanol-d4) δ = -111.68, -140.68, -173.93. LCMS (ESI, M+1): m/z = 604.1.

EXAMPLE 11

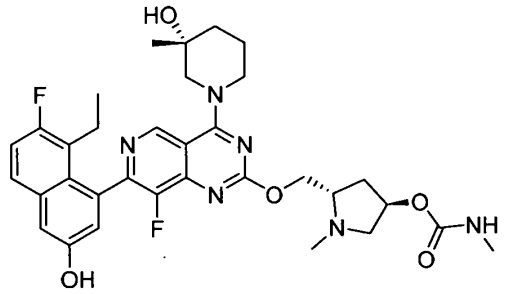


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-4-ol

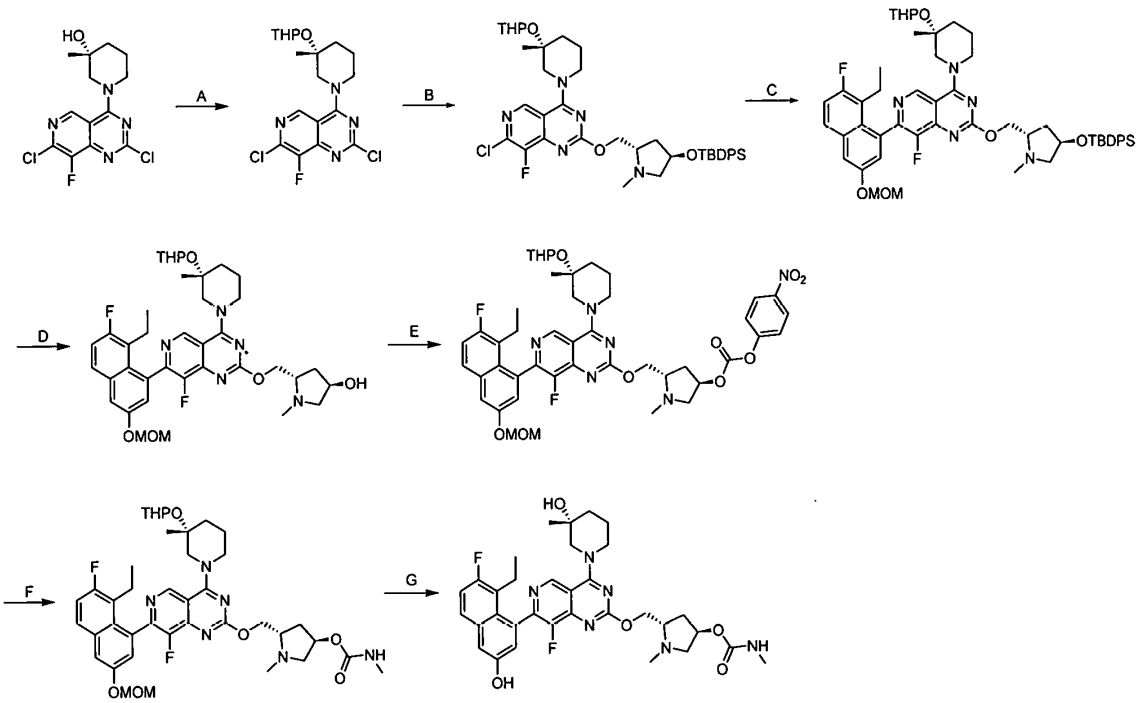


[0000439] Step A: 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-4-ol: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 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 °C for 2 hours. Upon completion, the reaction was filtered and purified by prep-HPLC (column: water s Xbridge BEH C18 100×25mm×5μm; 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. ^{1}H 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, 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 Na_2SO_4, 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-butyldiphenylsilyl)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), K_3PO_4 (1.5 M, 3.21 mL) in toluene (10 mL) was added [cataCXium-A-Pd-G3 (117 mg, 160 μmol) under N_2. 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-butyldiphenylsilyl)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.

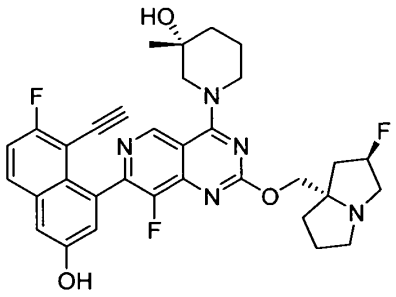
[0000443] Step D. (3R,5S)-5-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((3R)-3-methyl-3-((tetrahydro-2H-pyran-2-yl)oxy)piperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)-1-methylpyrrolidin-3-ol: To a mixture of 2-(((2S,4R)-4-((tert-butyldiphenylsilyl)oxy)-1-methylpyrrolidin-2-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-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 μmol) 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 μmol) and (4-nitrophenyl) carbonochloridate (41.0 mg, 203 μmol) in THF (1 mL) was added t-BuOK (1 M in THF, 170 μL) 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 Na_2SO_4, 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.

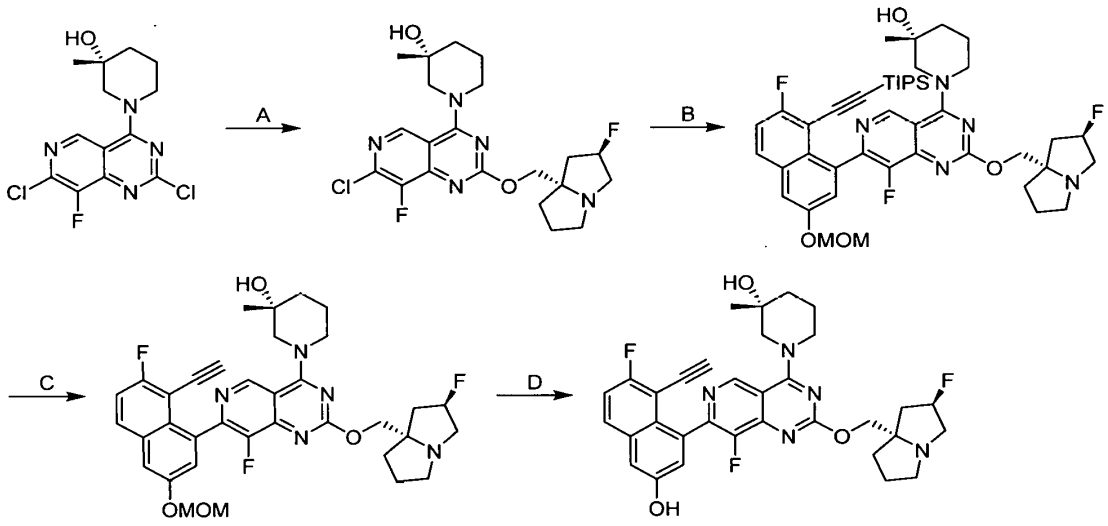
[0000445] Step F. [(3R,5S)-5-[[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-4-[(3R)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] N-methylcarbamate: A mixture of [(3R,5S)-5-[[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-4-[(3R)-3-methyl-3-tetrahydropyran-2-yloxy-1-piperidyl]pyrido[4,3-d]pyrimidin-2-yl]oxymethyl]-1-methyl-pyrrolidin-3-yl] (4-nitrophenyl) carbonate (49.0 mg, 56.1 μmol) and methanamine (2 M in THF, 702 μL) 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 μmol) 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 $NaHCO_3$ solution and the mixture was triturated with methanol (2 × 8 mL) The filtrate was concentrated in vacuum. The residue was purified by prep-HPLC (column: Shim-pack C18 150*25*10μm; 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). ^{19}F 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 μmol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (150 mg, 942 μmol), 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 N_2 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.

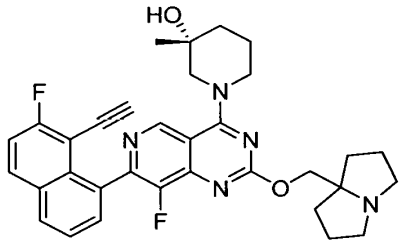
[0000448] Step B. (R)-1-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (150 mg, 330 μmol), and K_3PO_4 (1.5 M in water , 0.7 mL) in THF (3.5 mL) was degassed and purged with N_2 for 3 times. cataCXium-A-Pd-G3 (25 mg, 34.3μmol) 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 μmol). 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 × 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 μmol) 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.

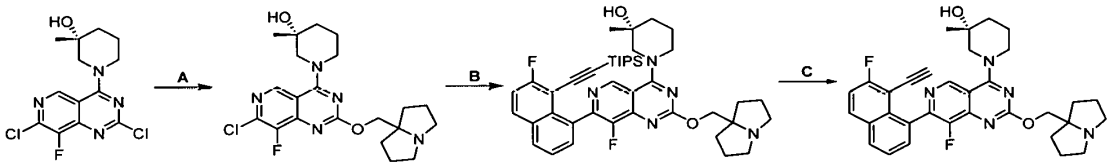
[0000450] Step D. (R)-1-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of (R)-1-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (100 mg, 154 μmol) 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 × 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, 0.4FORMIC ACID). ^1H NMR (400 MHz, methanol-d4) 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-d4) 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

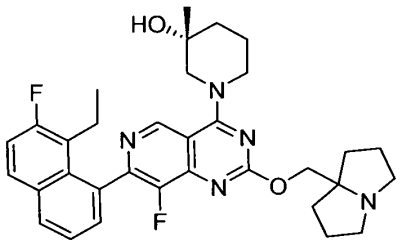
residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (R)-1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (244 mg, 44% yield). Yellow Solid; LCMS (ESI, M+1): m/z 436.3.

[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 μmol), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (291 mg, 642 μmol), K_3PO_4 (1.5 M, 918 μL) in THF (3 mL) was added cataCXium-A-Pd-G3cataCXium-A-Pd-G3 (33.4 mg, 45.9 μmol) 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.

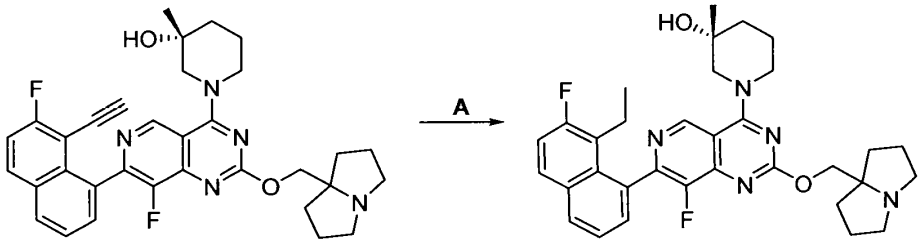
[0000453] Step C. (R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To the solution of (R)-1-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (100 mg, 138 μmol) 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, 0.77FORMIC ACID). Yellow Solid; ^{1}H 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



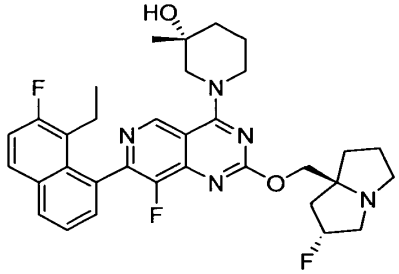
(R)-1-(6-(8-ethyl-7-fluoronaphthalen-1-yl)-5-fluoro-3-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-1-yl)-3-methylpiperidin-3-ol



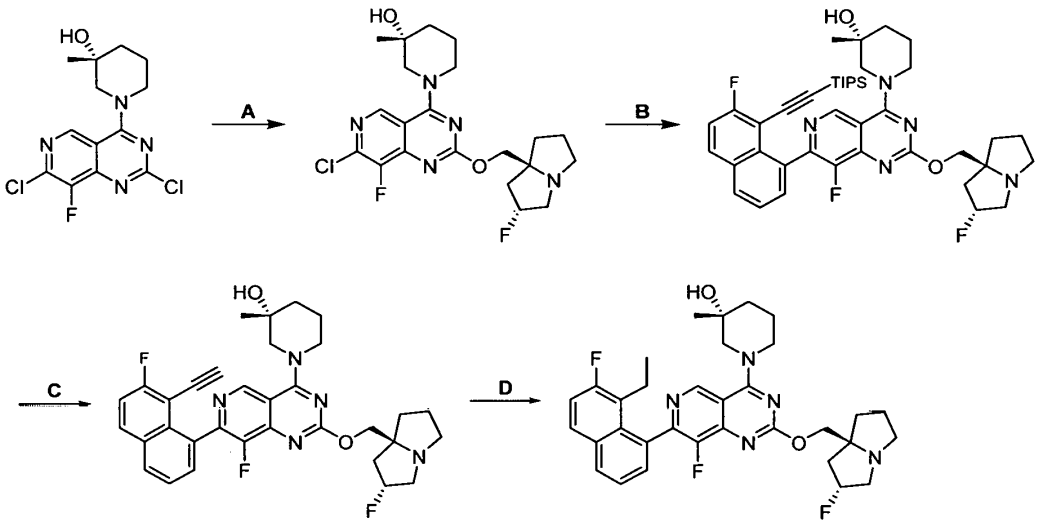
[0000454] Step A. (R)-1-(6-(8-ethyl-7-fluoronaphthalen-1-yl)-5-fluoro-3-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-1-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (50.0 mg, 87.8 μmol) in MeOH (2 mL) was added Pd/C (20 mg, 10% purity) under N_2. The suspension was degassed in vacuum and purged with H_2 several times. The mixture was stirred under H_2 (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 × 25mm × 5 μm; mobile phase: [water (10 mM NH_4HCO_3) - 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; ^{1}H 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 μmol),

((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (145 mg, 911 μmol), 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)pyrído[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (168 mg, 56% yield). Yellow Solid; LCMS (ESI, M+1): m/z 454.3.

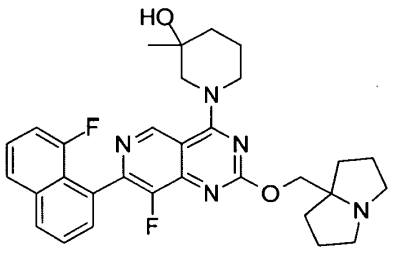
[0000456] Step B. (R)-1-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (180 mg, 397 μmol), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (234 mg, 517 μmol), and K_3PO_4 (1.5 M, 793 μL) in THF (3 mL) was added cataCXium-A-Pd-G3cataCXium-A-Pd-G3 (28.9 mg, 39.7 μmol) under N_2. 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 μmol) 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

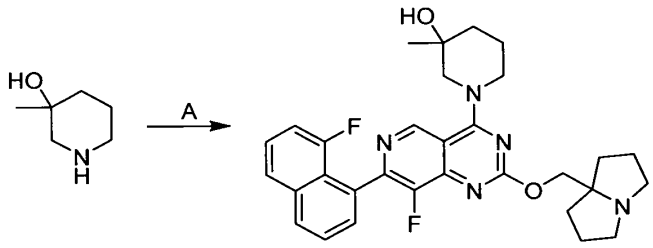
purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give (R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (190 mg, 89% yield). Yellow Solid; LCMS (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 μmol) in MeOH (2.0 mL) was added Pd/C (20 mg, 10% purity) under N_2. The suspension was degassed in vacuum and purged with H_2 several times. The mixture was stirred under H_2 (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 × 25 mm × 5 μm; mobile phase: [water (10 mM NH_4HCO_3) - 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; ^{1}H 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

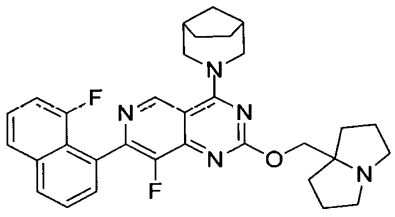


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

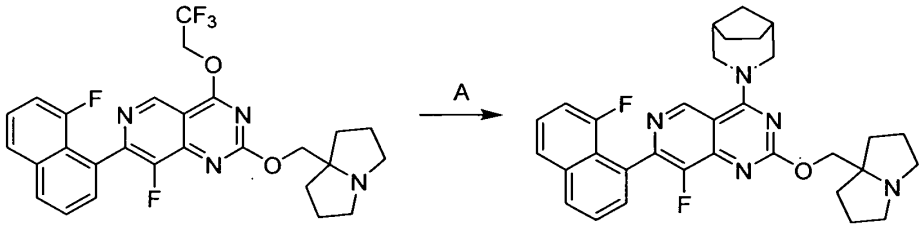


[0000459] Step A. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin- 7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of 3-methylpiperidin-3-ol and DIEA (51.1 mg, 396 μmol) and 4Å molecular sieves (50 mg) in DMF (2 mL) was added 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin- 7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (69.9 mg, 132 μmol) in one portion at 20 °C under N_2. 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*5μm; mobile phase: [water (10mM NH_4HCO_3)-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. ^{1}H NMR (400 MHz, methanol-d_4) 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

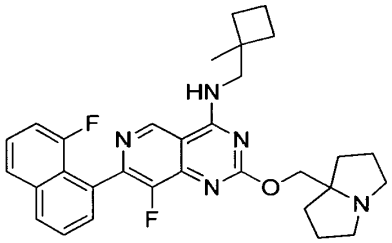


4-((1R,5S)-3-azabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine

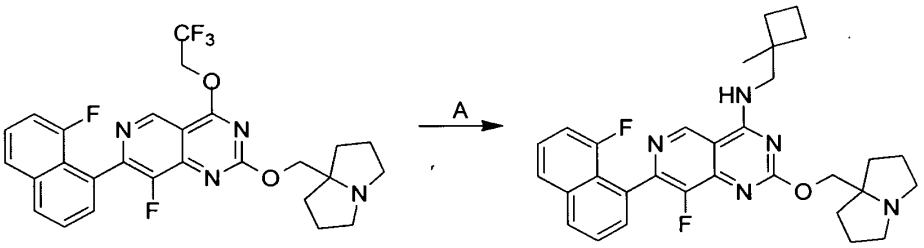


[0000460] Step A. 4-((1R,5S)-3-azabicyclo[3.2.1]octan-3-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μmol) in DMF (1.0 mL) were added DIEA (36.5 mg, 283 μmol, 49.3 μL) and (1R,5S)-3-azabicyclo[3.2.1]octane (31.4 mg, 283 μmol). The mixture was stirred at 40 °C for 1 hour. Upon completion, the residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75×30mm×3μm; 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. ^{1}H NMR (400MHz, $CDCl_3$) 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

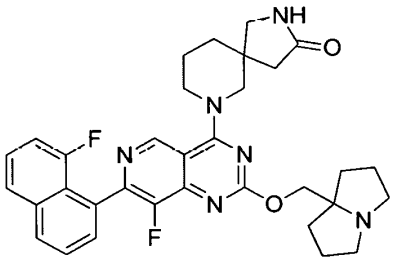


8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-((1-methylcyclobutyl)methyl)pyrido[4,3-d]pyrimidin-4-amine

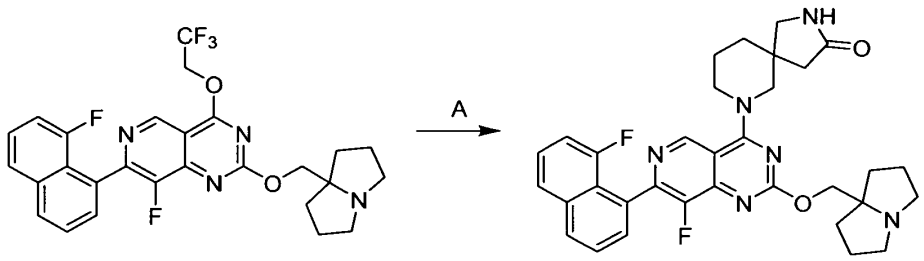


[0000461] Step A. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-((1-methylcyclobutyl)methyl)pyrido[4,3-d]pyrimidin-4-amine: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μmol) in DMF (1.0 mL) were added DIEA (60.9 mg, 471 μmol, 82.1 μL) and (1-methylcyclobutyl)methanamine (38.4 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%, 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. ^{1}H NMR (400MHz, $CDCl_3$) 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

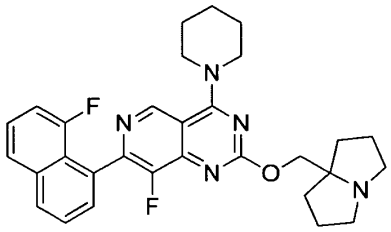


7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one

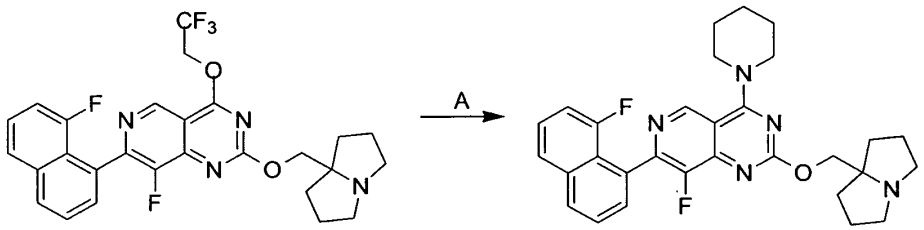


[0000462] Step A. 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl) methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μmol), DIEA (60.9 mg, 471 μmol, 82.1 μL) 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 μmol, 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 × 25 mm × 5 μm; 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; ^{1}H 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, M+1): m/z 585.3.

EXAMPLE 21

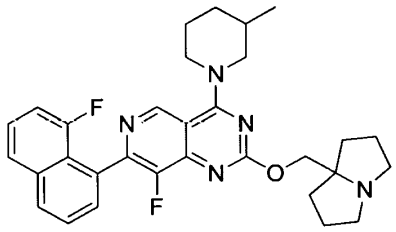


8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine

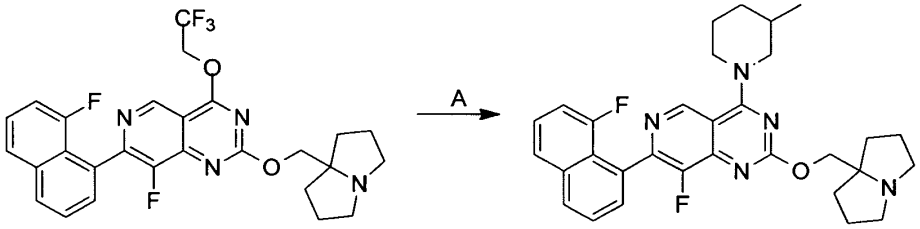


[0000463] Step A. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(piperidin-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μmol) in DMF (1.0 mL) were added DIEA (36.5 mg, 283 μmol, 49.3 μL) and piperidine (12.0 mg, 141 μmol, 14.0 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 100×25mm×5μm; mobile phase: [water (10mM NH_4HCO_3)-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. ^{1}H NMR (400MHz, $CDCl_3$) 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

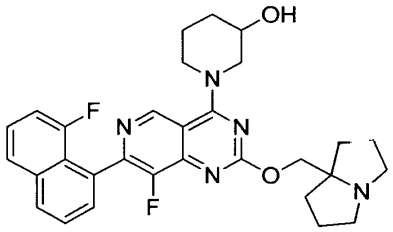


8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine

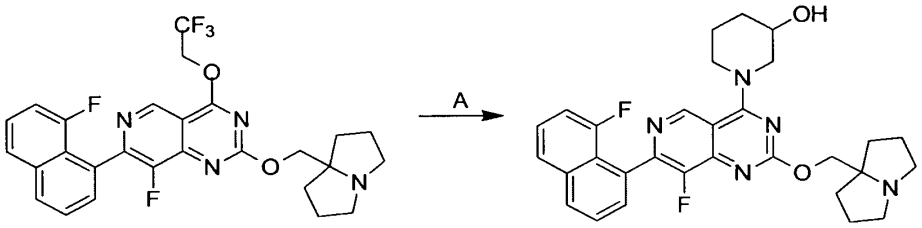


[0000464] Step A. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 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 100×25mm×5μm; 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. ^{1}H 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, M+1]: m/z 530.1.

EXAMPLE 23

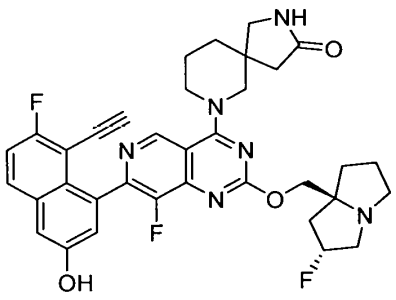


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol

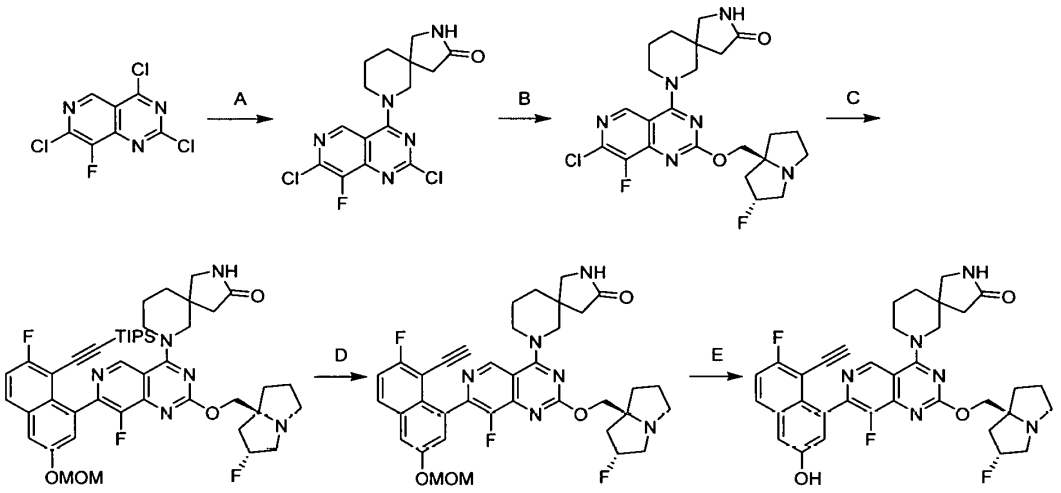


[0000465] Step A. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μmol) in DMF (1.0 mL) were added DIEA (36.5 mg, 283 μmol, 49.3 μL) and piperidin-3-ol (28.6 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 100×25mm×5μm; mobile phase: [water (10mM NH_4HCO_3)-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. ^{1}H NMR (400MHz, $CDCl_3$) 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 Na_2SO_4 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 Na_2SO_4, 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.

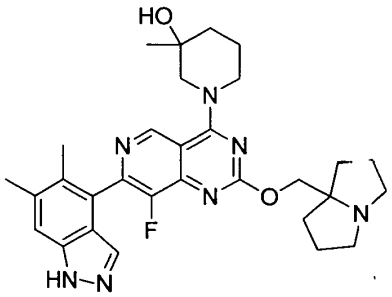
[0000468] Step C. 7-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl) naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 7-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[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 K_3PO_4 (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 Na_2SO_4 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 Na_2SO_4. 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-

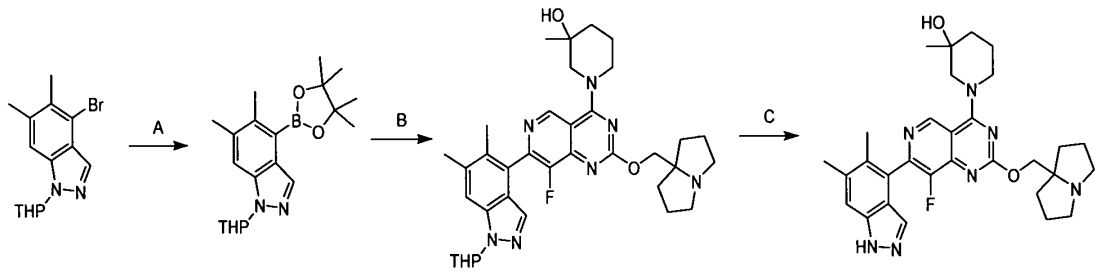
(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (60 mg, 98% yield). Yellow solid; LCMS (ESI, M+1): m/z 687.3.

[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 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 h. After completion, the mixture was concentrated at 20 °C. The residue was purified by prep-HPLC [Water s Xbridge 150 × 25 mm × 5 μm; A: water (10mM NH_4HCO_3), 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; ^{1}H NMR (400 MHz, DMSO-d_6) 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



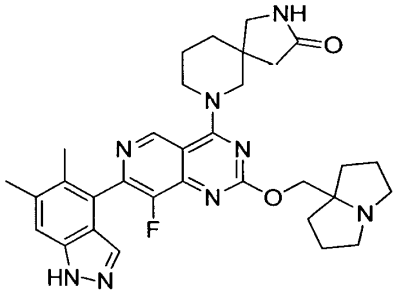
[0000471] Step A. 5,6-dimethyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole: To a solution of 4-bromo-5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (2.00 g, 6.47 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (3.29 g, 12.9 mmol) and KOAc (1.90 g, 19.4 mmol) in dioxane (40 mL) was added $Pd(dppf)Cl_2$ (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 Na_2SO_4. 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 K_3PO_4 (1.5 M, 1.33 mL) in one portion at 25 °C under N_2. 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.

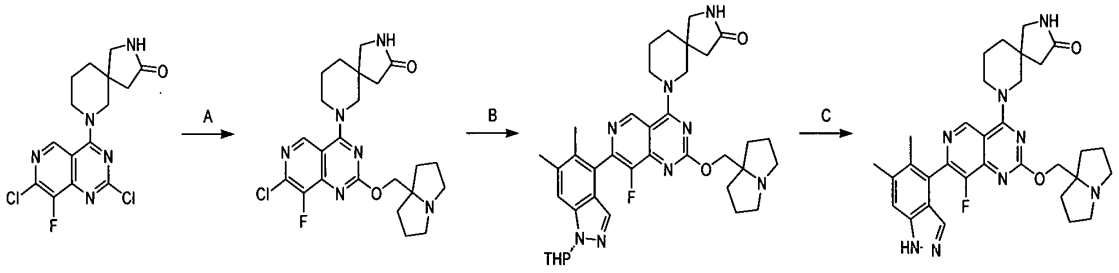
[0000473] Step C. 1-(7-(5,6-dimethyl-1H-indazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of 1-(7-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-8-fluoro-2-((tetrahydro-1H-

pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (290 mg, 460 μmol) and ACN (0.2 mL) was added HCl•dioxane (4 M, 1.98 μL) in one portion at 25°C under N_2. 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). ^{1}H 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 μmol), 4Å molecular sieves (10 mg) and DIEA (314 mg, 2.43 mmol, 423 μL) in dioxane (2 mL) was added (hexahydro-1H-pyrrolizin-7a-yl)methanol (126 mg, 891 μmol). The mixture was stirred at 95 °C

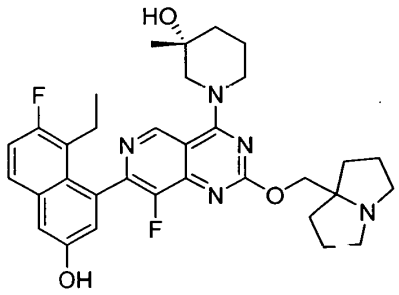
for 16 h. After completion, water (5.0 mL) was added and the mixture was extracted with EtOAc (2 × 5.0 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography (C18, water (0.1 % formic acid)/ACN) to 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 K_3PO_4 (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 Na_2SO_4, 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.

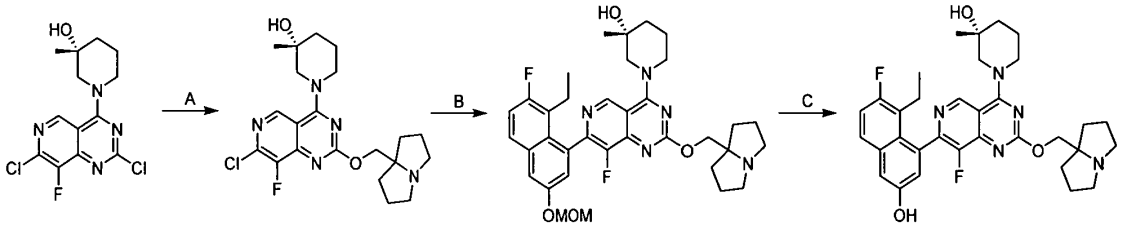
[0000476] Step C. 7-(7-(5,6-dimethyl-1H-indazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of 7-(7-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (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 NH_4HCO_3), B: ACN, B%: 16%-46% over 10 min) to afford the title compound (7.08 mg, 26% yield). White solid; ^{1}H NMR (400 MHz, $CDCl_3$) 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

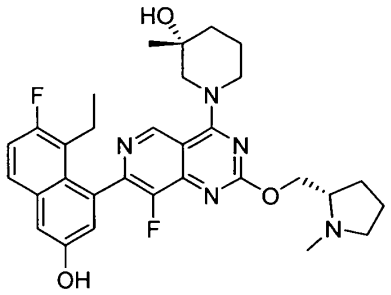


[0000477] Step A. (R)-1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (125 mg, 377 μmol), (hexahydro-1H-pyrrolizin-7a-yl)methanol (56 mg, 396 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.

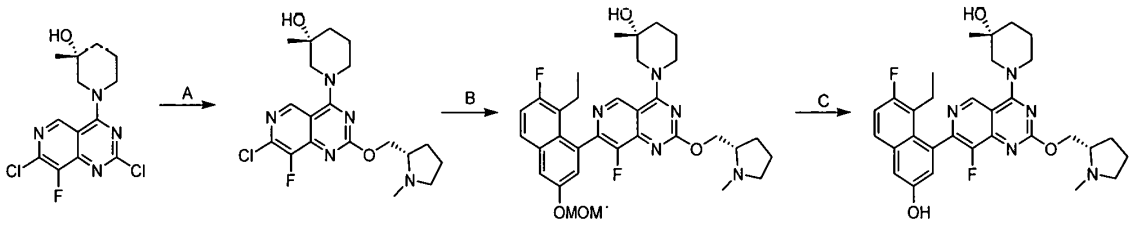
[0000478] Step B. (R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (R)-1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (40 mg, 91.8 μmol), K_3PO_4 (1.5 M in water , 0.2 mL) in THF (1 mL) was degassed and purged with N_2 for 3 times. cataCXium-A-Pd-G3 (14 mg, 19.2 μmol) 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 μmol). 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 × 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 μmol) 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 $NaHCO_3$ aqueous (5 mL). The mixture was extracted with ethyl acetate (5 mL × 4). The combined organic layers were dried over anhydrous 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 um; 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, 0.7FORMIC ACID). ^{1}H 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). ^{19}F 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 μmol), [(2S)-1-methylpyrrolidin-2-yl]methanol (157 mg, 1.36 mmol, 161 μl), DIEA (176 mg, 1.36 mmol, 237 μl) and 4Å molecular sieves (15.0 mg, 453 μmol) 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 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 (3*R*)-1-[7-chloro-8-fluoro-2-[[(2*S*)-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.

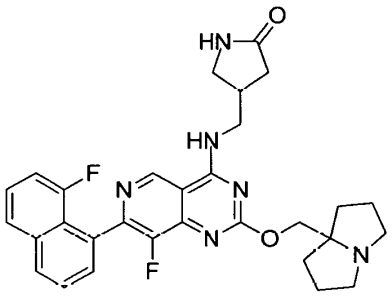
[0000481] Step B. (3R)-1-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol:

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 μmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (237 mg, 659 μmol) and K_3PO_4 (1.5 M, 659 μl) in THF (2.1 mL) was added [2-(2-aminophenyl)phenyl]palladium(1+);bis(1-adamantyl)-butyl-phosphane;methanesμlfonate (24.0 mg, 32.9 μmol) 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.

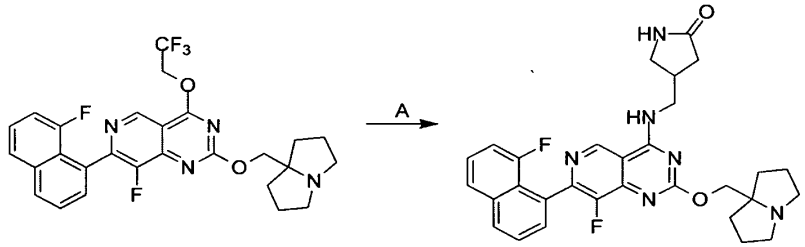
[0000482] Step C. (3R)-1-[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol: To a mixture of (3R)-1-[7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-2-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (40.0 mg, 65.8 μmol) 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 × 8 mL). The mixture was filtered and concentrated in vacuum. The residue was purified by prep-HPLC (Shim-pack C18 150×25×10um; mobile phase: [water (0.225% formic acid) - ACN]; B%: 20% - 40%, 10 min) to afford (3*R*)-1-[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-[[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-*d*]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (14.4 mg, 36% yield, 0.6FORMIC ACID). White solid. ^{1}H NMR (400 MHz, METHANOL-d4): 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-d4) δ =

-121.070, -139.482. HPLC: >99% ee, Chiralcel OJ-3 50×4.6mm I.D., 3μm; Mobile phase: Phase A for CO_2, and Phase B for MeOH (0.05% DEA); Gradient elution: MeOH (0.05% DEA) in CO_2 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



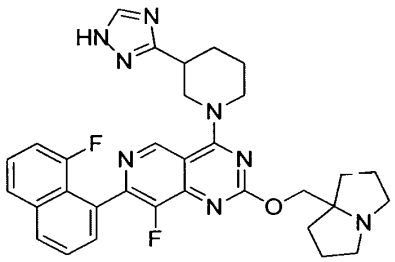
4-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one



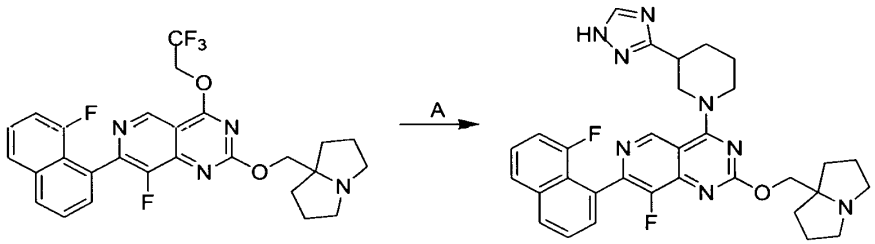
[0000483] Step A. 4-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (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. ^{1}H NMR

(400MHz, $CDCl_3$) 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); ^{1}H NMR (400MHz, MeOD-d_4) 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



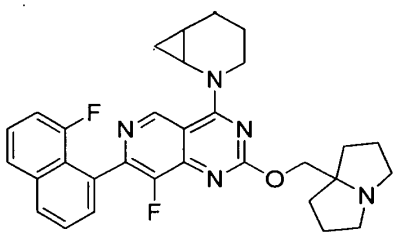
4-(3-(1H-1,2,4-triazol-3-yl)piperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine



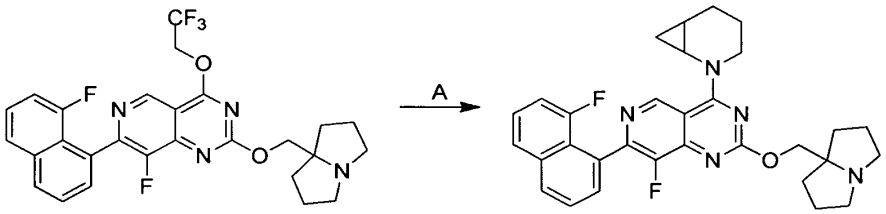
[0000484] Step A. 4-(3-(1H-1,2,4-triazol-3-yl)piperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine: A mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine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

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. ^{1}H 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



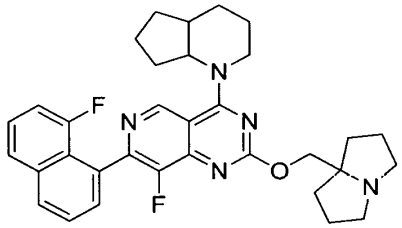
4-(2-azabicyclo[4.1.0]heptan-2-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine



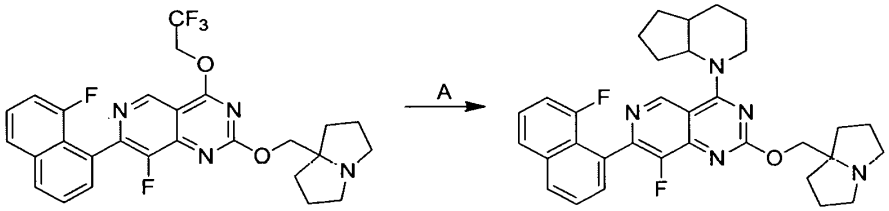
[0000485] Step A. 4-(2-azabicyclo[4.1.0]heptan-2-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine: A mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 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 NH_4HCO_3)-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. ^{1}H 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



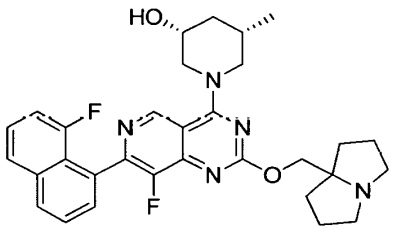
8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(octahydro-1H-cyclopenta[b]pyridin-1-yl)pyrido[4,3-d]pyrimidine



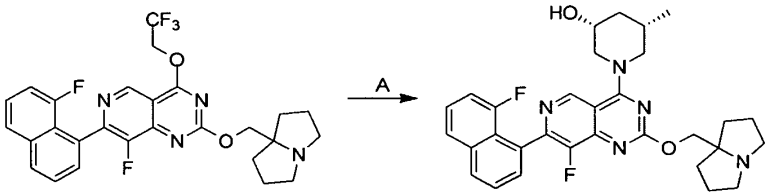
[0000486] Step A. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(octahydro-1H-cyclopenta[b]pyridin-1-yl)pyrido[4,3-d]pyrimidine: A mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (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 NH_4HCO_3)-

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. ^{1}H 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



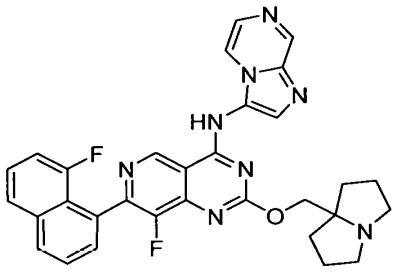
(3R,5S)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol



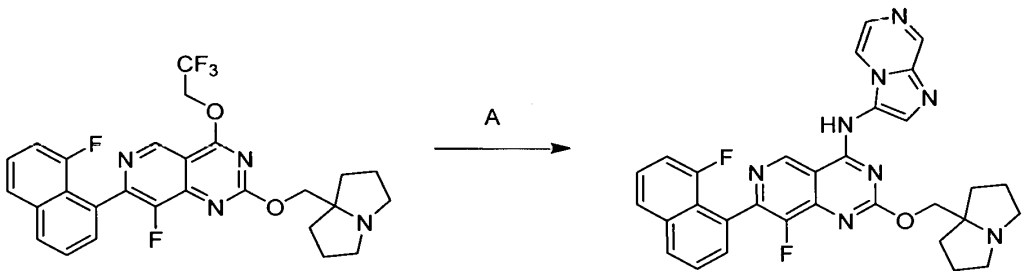
[0000487] Step A. (3R,5S)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol: To a solution of (3R,5S)-5-methylpiperidin-3-ol (15 mg, 98.9 μmol, HCl) and 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (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 Na_2SO_4. 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 NH_4HCO_3)-ACN]; B%: 30%-60%, 8min) to give the title compound (8.92 mg, 16% yield) as a light yellow solid. ^{1}H 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



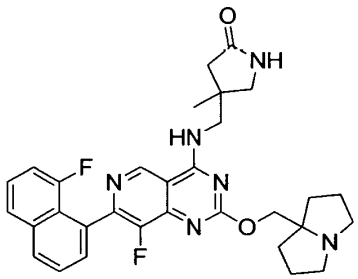
8-fluoro-7-(8-fluoronaphthalen-1-yl)-N-(imidazo[1,2-a]pyrazin-3-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine



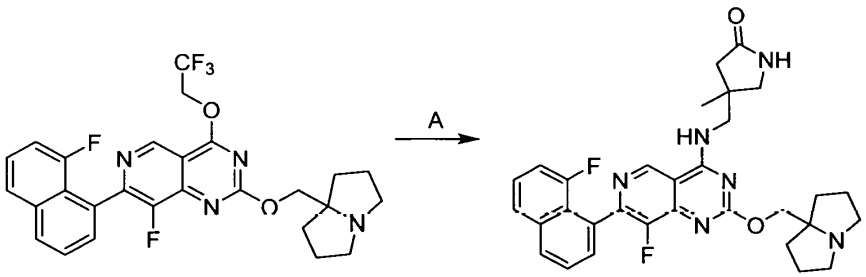
[0000488] Step A: 8-fluoro-7-(8-fluoronaphthalen-1-yl)-N-(imidazo[1,2-a]pyrazin-3-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: To a solution of

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 Na_2SO_4, 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 NH_4HCO_3)-ACN]; B%: 27%-57%, 10 min) to afford the title compound. LCMS (ESI, M+1): m/z 565.3.

EXAMPLE 35



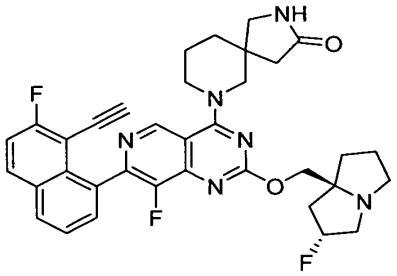
4-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)-4-methylpyrrolidin-2-one



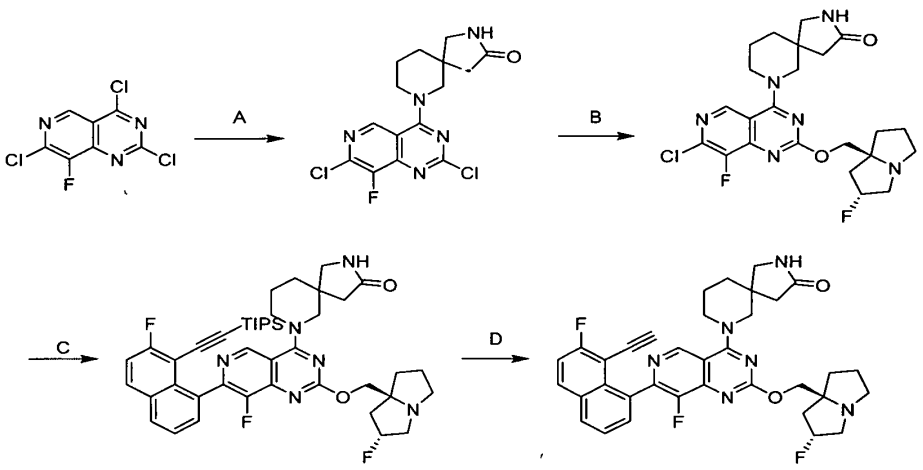
[0000489] Step A. 4-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)-4-methylpyrrolidin-2-one: To a mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine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

methylpyrrolidin-2-one (96.6 mg, 754 μmol) in DMF (2.00 mL) was added DIEA (24.4 mg, 189 μmol) at 25°C under N_2.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 × 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 × 30 mm × 3 μm; 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. ^{1}H NMR (400 MHz, DMSO-d_6): 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 Na_2SO_4, 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

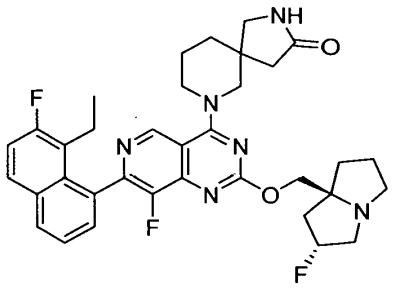
[0000491] Step B. 7-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl) methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 7-(2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (300 mg, 810 μmol), DIEA (314 mg, 2.43 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 Na_2SO_4, 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*,7a*S*)-2-fluorohexahydro-1*H*-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-(((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 μmol), ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (413 mg, 913 μmol) 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 μmol). The mixture was stirred at 60 °C for 2 hours. The mixture was diluted with water (10 mL), extracted with EtOAc (3 × 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*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-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

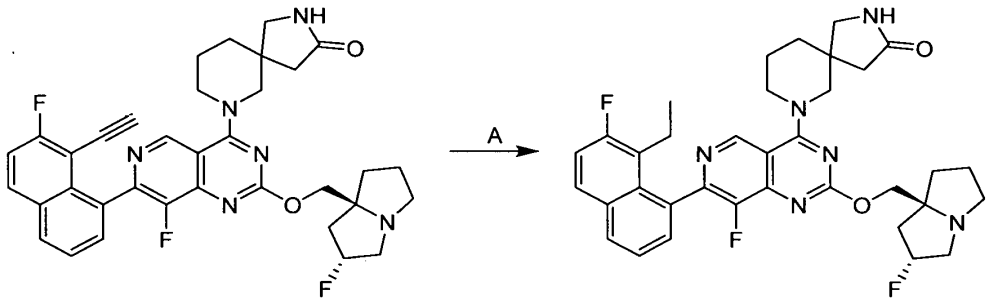
[0000493] Step D. 7-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of 7-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl) ethynyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (350 mg, 447 μmol) 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 × 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 × 25 mm × 10 μm; 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*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-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. ^{1}H 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



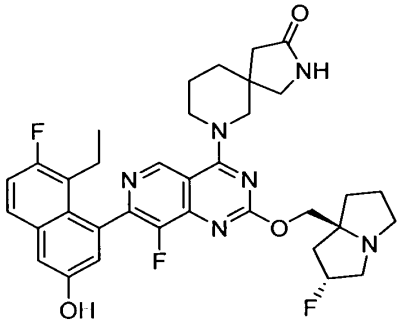
7-(7-(8-ethyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one



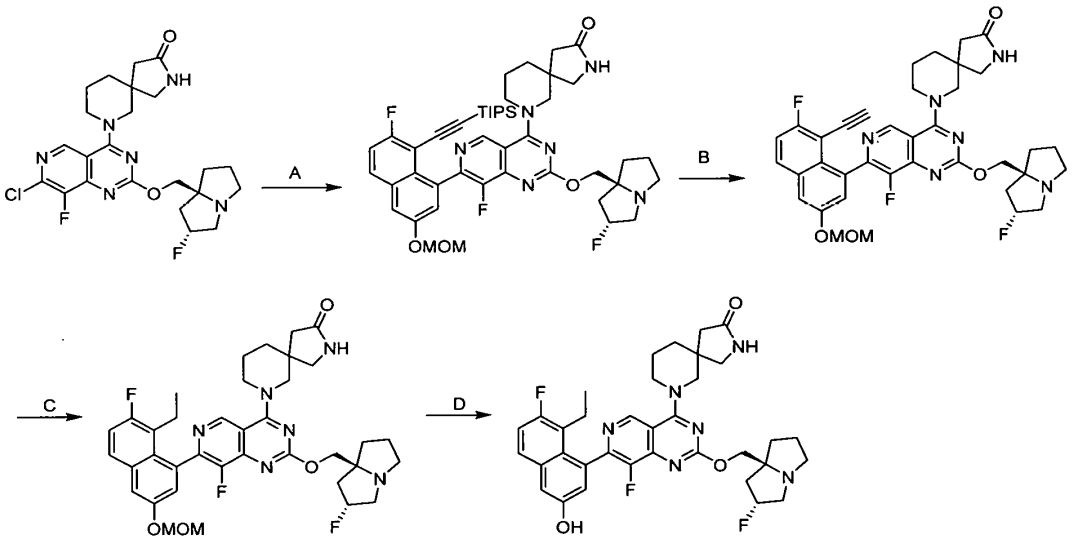
[0000494] Step A. 7-(7-(8-ethyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of 7-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (50.0 mg, 77.0 μmol, 0.5FORMIC ACID) in MeOH (1 mL) was added Pd/C (5.0 mg, 10% purity). The suspension was degassed and purged with H_2 3 times. The mixture was stirred at 25°C for 1 hour under H_2 (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 × 25 mm × 5μm; mobile phase: [water (10mM NH_4HCO_3)-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 μmol) 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 μmol) in THF (2 mL) were added K_3PO_4 (1.5 M, 406 μL) and cataCXium-A-Pd-G3 (22.2 mg, 30.4 μmol). 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 × 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

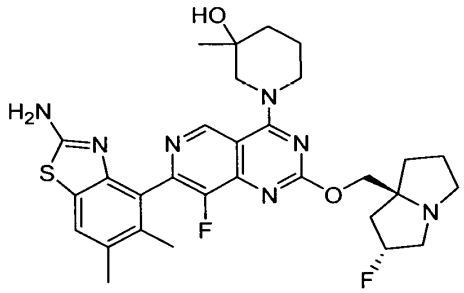
[0000496] Step B. 7-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a mixture of 7-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (110 mg, 130 μmol) 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-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7*a*-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 μmol) and MeOH (2 mL) was added Pd/C (100 mg, 10% purity) in one portion at 25 °C under N_2. The

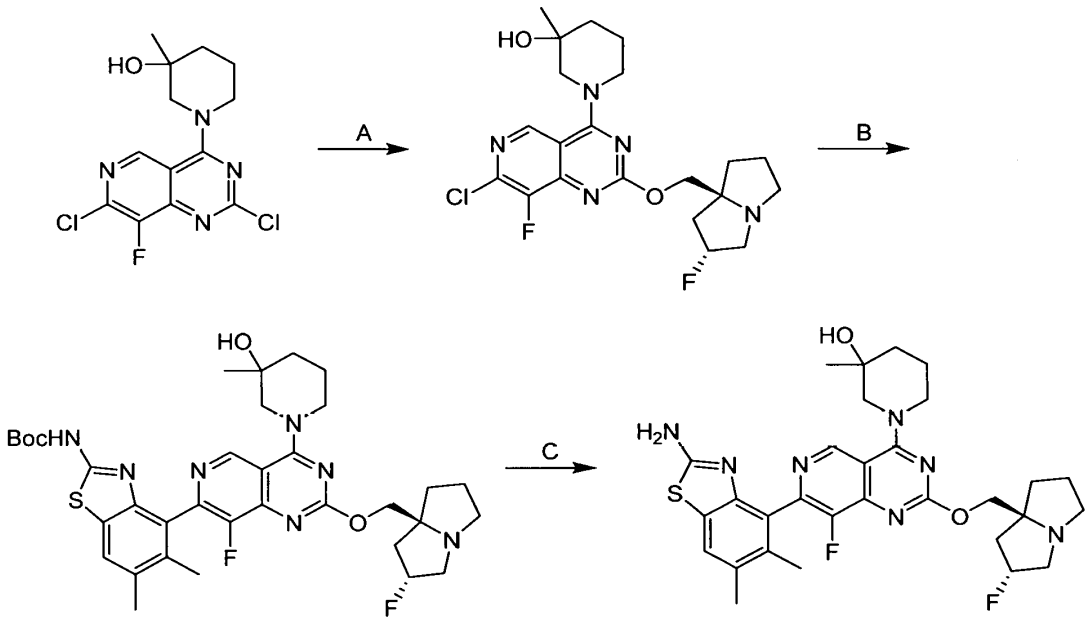
suspension was degassed and purged with H_2 3 times. The mixture was stirred at 25 °C for 1 hour under H_2 (15 psi). The reaction mixture was filtered and concentrated under reduced pressure to afford 7-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[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 N_2. 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, 0.1FORMIC ACID) as white solid. ^{1}H NMR (400 MHz, methanol-d_4): 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



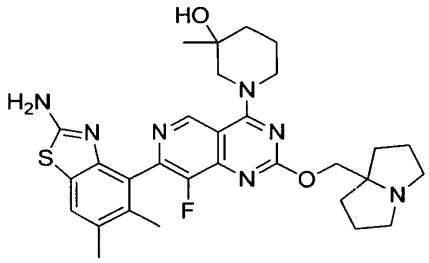
[0000499] Step A. 1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of 1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (0.200 g, 604 μmol), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (144 mg, 906 μmol), DIEA (234 mg, 1.81 mmol, 315μL) 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 μmol), [2-(tert-butoxycarbonylamino)-5,6-dimethyl-1,3-benzothiazol-4-yl]boronic acid (49.7 mg, 154 μmol) and K_3PO_4 (1.5 M in water , 220 μL) 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 μmol) under N_2. The mixture was de-gassed and then heated to 60 °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.

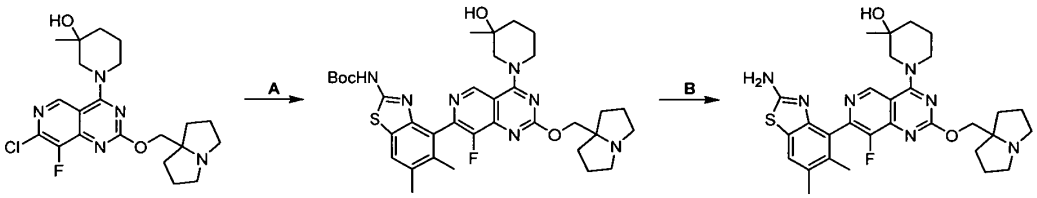
[0000501] Step C. 1-(7-(2-amino-5,6-dimethylbenzo[d]thiazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of tert-butyl (4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-5,6-dimethylbenzo[d]thiazol-2-yl)carbamate (37.0 mg, 53.2 μmol) and dichloromethane (0.7 mL) was added TFA (2.16 g, 18.9 mmol, 1.4 mL) at 0°C and the mixture was stirred at 0 - 28 °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 × 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-d4): 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

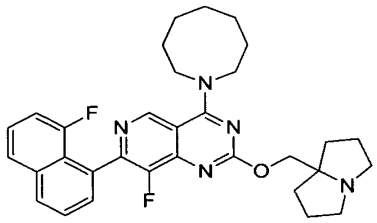


[0000502] Step A. tert-butyl (4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-5,6-dimethylbenzo[d]thiazol-2-yl)carbamate: To the mixture of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (150 mg, 344 μmol), (2-((tert-butoxycarbonyl)amino)-5,6-dimethylbenzo[d]thiazol-4-yl)boronic acid (130 mg, 403 μmol), and K_3PO_4 (1.5 M, 688 μL) in THF (2 mL) was added BrettPhos Pd G3 (31.2 mg, 34.4 μmol) 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-

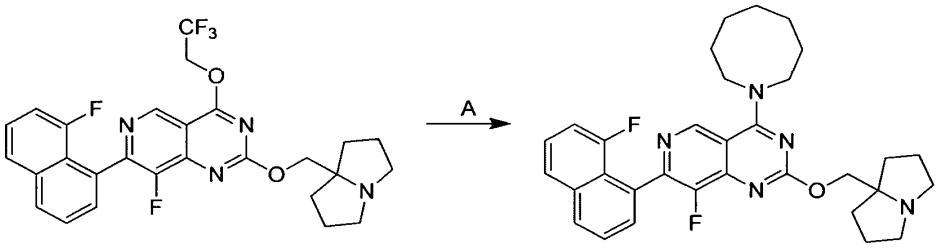
methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-5,6-dimethylbenzo[d]thiazol-2-yl)carbamate (132 mg, 52% yield). White Solid; LCMS (ESI, M+1): m/z 678.3.

[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 μmol) 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. Na_2CO_3 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 × 25 mm × 10 μm; 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; ^{1}H NMR (400 MHz, METHANOL-d_4) 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

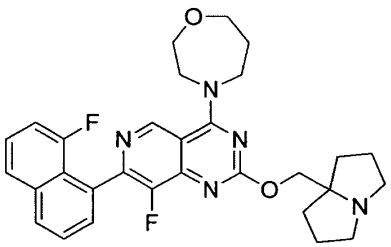


4-(azocan-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine

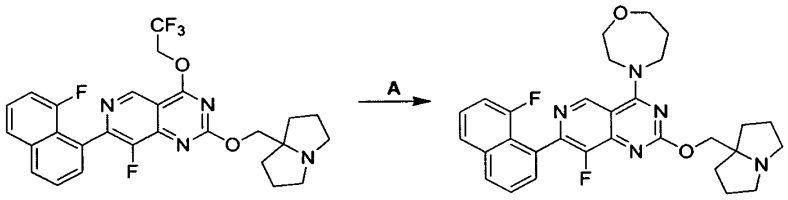


[0000504] Step A 4-(azocan-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine: To a mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.2 μmol) and azocane (21.3 mg, 188 μmol) in DMF (1 mL) were added DIEA (48.7 mg, 377 μmol) and 4Å molecular sieves (30 mg) in one portion at 25 °C under N_2. 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 × 3μm; 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, 16.8μmol, 18% yield, 99% purity, 0.24FORMIC ACID). White solid; ^{1}H 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

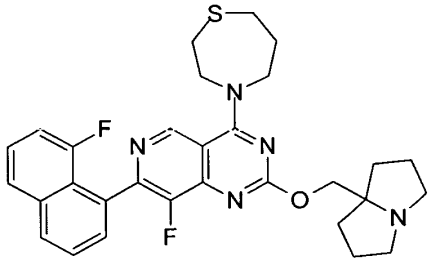


4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane

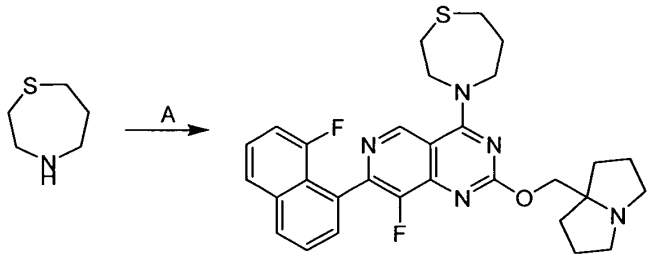


[0000505] Step A. 4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane: To a mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (20.0 mg, 34.7 μmol, formic acid salt), 1,4-oxazepane (5.73 mg, 41.6 μmol, HCl), and 4Å molecular sieves (5 mg) in DMF (0.5 mL) was added DIEA (17.9 mg, 139 μmol), 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 × 25 mm × 10 μm; 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; ^{1}H 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

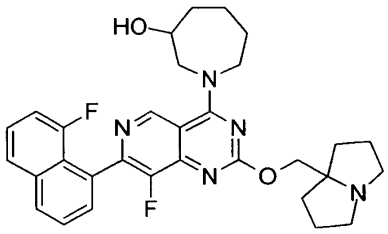


4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-thiazepane

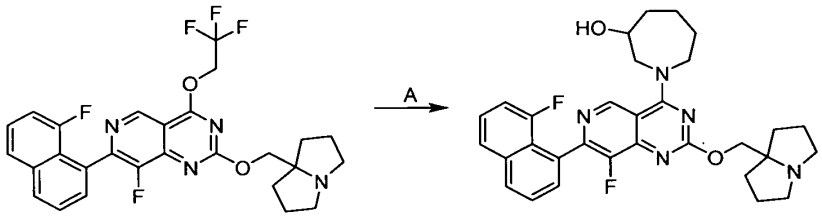


[0000506] Step A. 4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-thiazepane: To a mixture of 8-fluoro-7- (8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50 mg, 94.2 μmol) and 1,4-thiazepane (33.1 mg, 283 μmol) in DMF (1 mL) were added DIEA (48.7 mg, 377 μmol, 65.0 μL) and 4Å molecular sieves (30 mg) in one portion at 25°C under N_2. 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 × 3μm; 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 μmol, 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

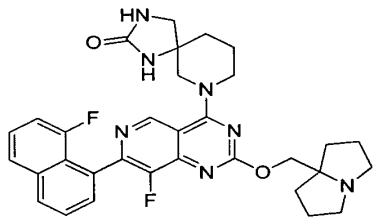


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-ol

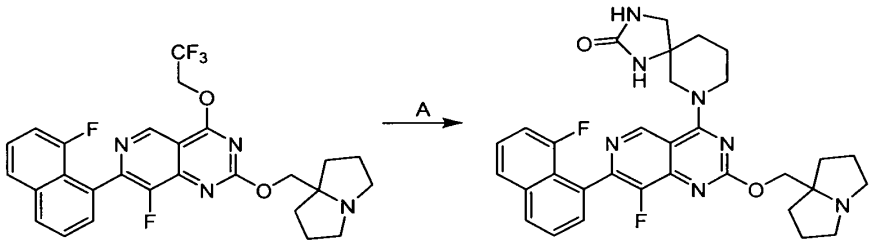


[0000507] Step A. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-ol: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (20.0 mg, 37.7 μmol) and DIEA (14.6 mg, 113 μmol, 19.7 μL) in DMF (1.0 mL) was added azepan-3-ol (8.68 mg, 75.4 μmol). 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 × 50mm × 3um; 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 μmol, 32% yield, 95.5% purity). Yellow solid; ^{1}H 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

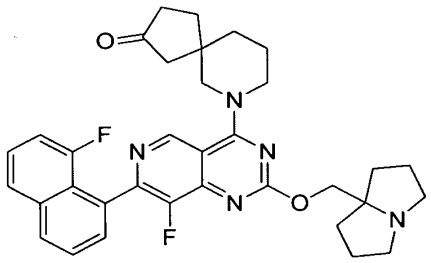


7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one.

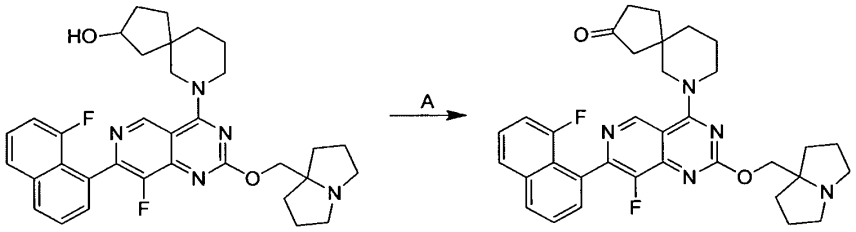


[0000508] Step A. 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (20.0 mg, 37.7 μmol) and 1,3,7-triazaspiro[4.5]decan-2-one (8.78 mg, 56.6 μmol) in DMF (0.2 mL) was added DIEA (48.7 mg, 377 μmol). 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 × 3). The combined organic layers were washed with brine (3 mL × 2), 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: 3_Phenomenex Luna C18 75 × 30 mm × 3 μm; 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; ^{1}H 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



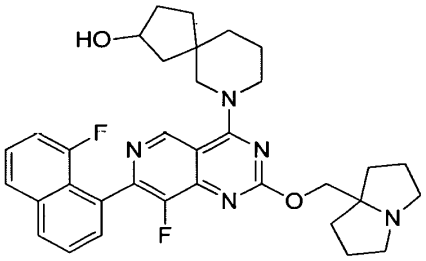
7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-one.



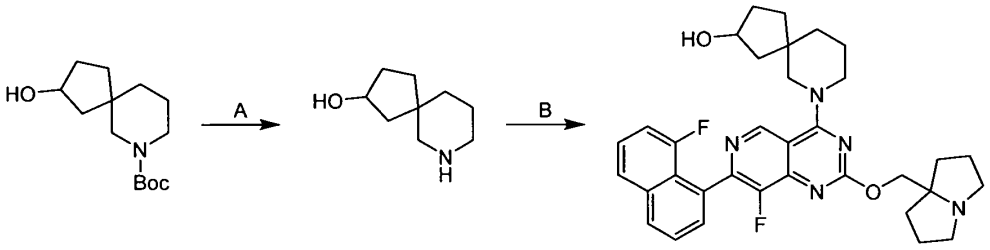
[0000509] Step A. 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-one: To a solution of 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-ol (30.0 mg, 51.2 μmol) in dichloromethane (2.0 mL) was added Dess-Martin Reagent (43.5 mg, 102 μmol). The mixture was stirred at 20 °C for 10 hours. After completion, the reaction mixture was quenched with saturated 10 mL Na_2SO_3 at 20 °C, and then extracted with EtOAc (5 mL × 3). The combined organic layer was washed with saturated $NaHCO_3$ (3 mL × 2) and brine (5 mL). The mixture was dried over anhydrous Na_2SO_4 and filtered. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (Phenomenex Luna C18 75 × 30 mm × 3 um; 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; ^{1}H 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-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-ol

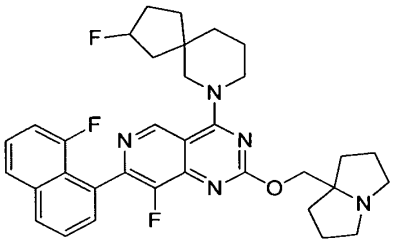


[0000510] Step A. 7-azaspiro[4.5]decan-2-ol hydrochloride: To a solution of tert-butyl 2-hydroxy-7-azaspiro[4.5]decane-7-carboxylate (70 mg, 274.13 μmol) in MeOH (1 mL) was added HCl•MeOH (4 M, 1 mL). The mixture was stirred at 20 °C for 2 hours. The reaction mixture was concentrated under reduced pressure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

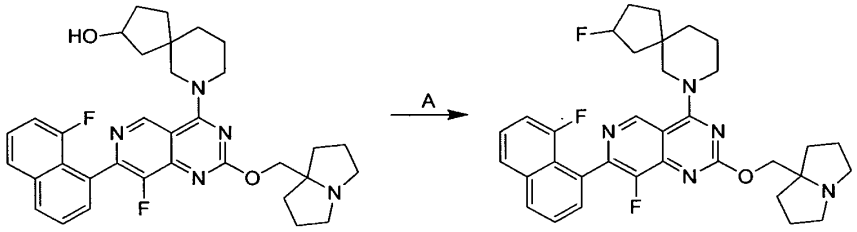
[0000511] Step B. 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-ol: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine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

hydrochloride (8.8 mg, 56.6 μmol) in DMF (0.2 mL) was added DIEA (24.4 mg, 188 μmol, 32.8 μL). 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 × 3). The combined organic layers were washed with brine (3 mL × 2), 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: water s Xbridge BEH C18 100 × 30 mm × 10 um; mobile phase: [water (10 mM NH_4HCO_3)-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%. ^{1}H 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

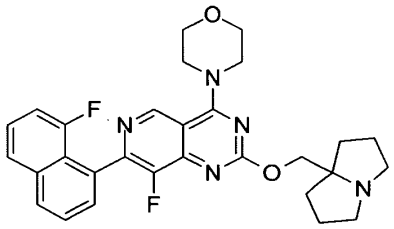


8-fluoro-4-(2-fluoro-7-azaspiro[4.5]decan-7-yl)-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine

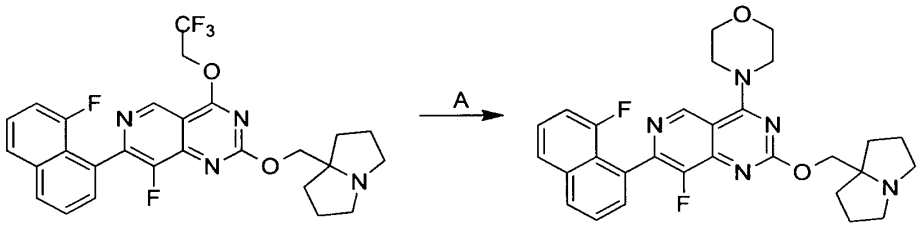


[0000512] Step A. 8-fluoro-4-(2-fluoro-7-azaspiro[4.5]decan-7-yl)-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine: To a solution of 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-azaspiro[4.5]decan-2-ol (30.0 mg, 51.2 μmol) in DCM (2 mL) was added bis(2-methoxyethyl)aminosulfur trifluoride (113 mg, 512 μmol, 112 μL) 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 × 3). The combined organic layers were washed with saturated $NaHCO_3$ (3 mL × 2) and brine (3 mL), 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 75×30mm×3μm; 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; ^{1}H 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). ^{1}H 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

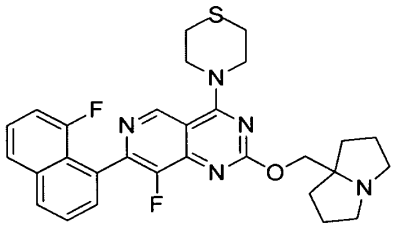


4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)morpholine

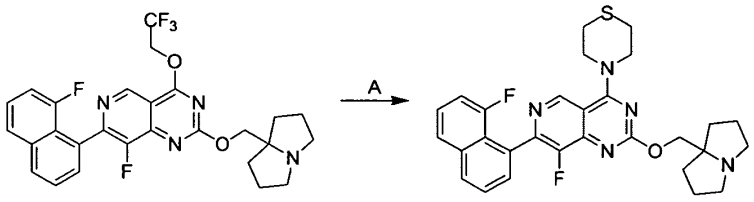


[0000513] Step A. 4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)morpholine: A mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30.0 mg, 52.0 μmol, formic acid salt), morpholine (9.07 mg, 104 μmol, 9.16 μL), DIEA (26.9 mg, 208 μmol, 36.3 μL) 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*10μm; mobile phase: [water (0.225% formic acid) - ACN]; B%: 15% - 45%, 10 min) to afford the title compound (7.45 mg, 27% yield, 0.4FORMIC ACID). Off-white Solid. ^{1}H NMR (400 MHz, $CDCl_3$-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). ^{19}F NMR (400 MHz, $CDCl_3$-d) δ = -112.256. -138.683. LCMS (ESI, M+1): m/z 518.2.

EXAMPLE 50

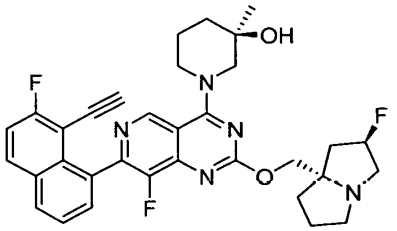


4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)thiomorpholine



[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 N_2 atmosphere. The reaction mixture was filtered and purified by prep-HPLC (column: Shim-pack C18 150 × 25 × 10um; 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, 0.3FORMIC ACID). ^{1}H NMR (400 MHz, DMSO-d_6) 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

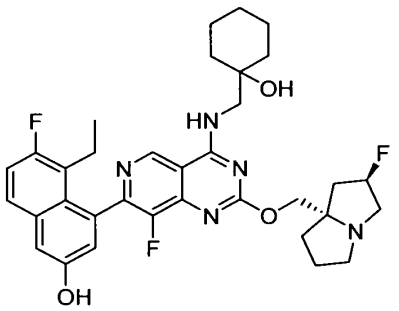


(R)-1-(7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

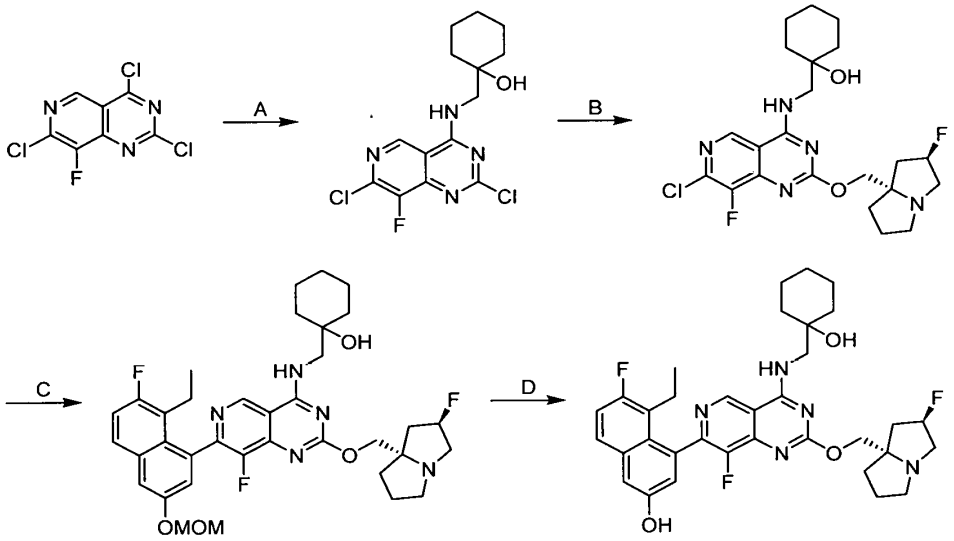
[0000515] Synthesized according to Example 16, step A to C. Yellow Solid; ^{1}H NMR (400 MHz, methanol-d_4) δ 9.24-9.03 (m, 1H), 8.19-8.06 (m, 2H), 7.74-7.58 (m, 2H), 7.51-7.36 (m, 1H),

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 N_2. 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; ^{1}H 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.

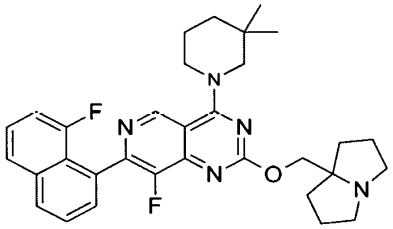
[0000517] Step B 1-(((7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)cyclohexanol: To a mixture of ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (346 mg, 2.17 mmol) and 1-(((2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)amino)methyl)cyclohexanol (500 mg, 1.45 mmol) in dioxane (5 mL) was added DIEA (561 mg, 4.35 mmol) in one portion at 25 °C under N_2. 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 K_3PO_4 (1.5 M, 855 μL) in one portion at 25 °C under N_2. 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.

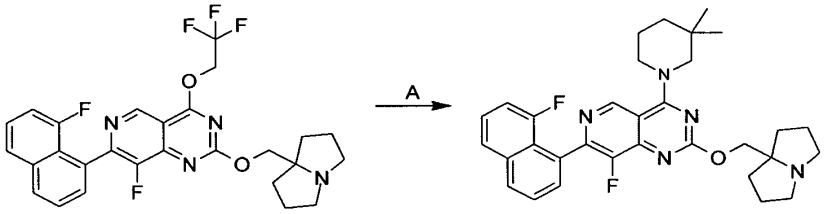
[0000519] Step D 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(((1-hydroxycyclohexyl)methyl)amino)pyrido[4,3-d]pyrimidin-7-

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 μmol) 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 × 30mm × 3μm; 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; ^{1}H 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



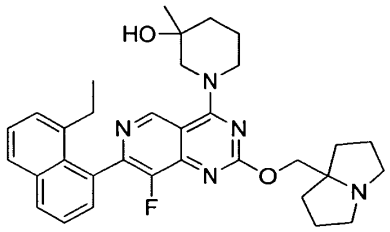
4-(3,3-dimethylpiperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine



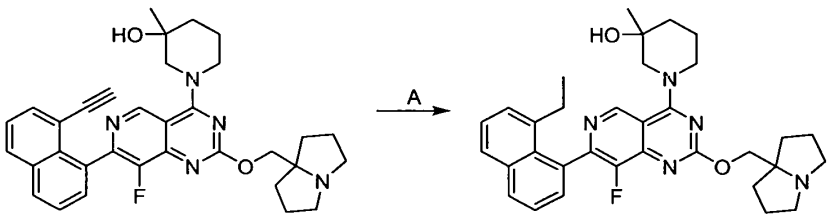
[0000520] Step A. 4-(3,3-dimethylpiperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)- 2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine: To a solution of 8-fluoro-7-

(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (100 mg, 188 μmol) and DIEA (73.1 mg, 565 μmol, 98.5 μL) in DMF (1.5 mL) was added 3,3-dimethylpiperidine (42.7 mg, 377 μmol). 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; ^{1}H NMR (400 MHz, METHANOL-d_4) 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



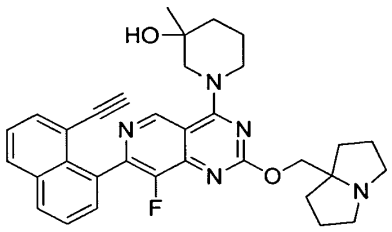
1-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



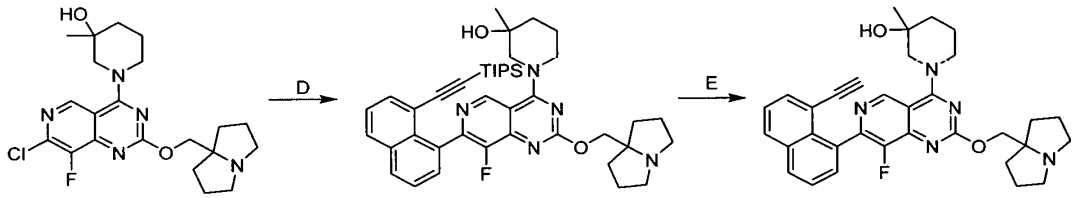
[0000521] Step A. 1-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of 1-(7-(8-ethynylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-

d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (65 mg, 118 μmol) in MeOH (4 mL) was added Pd/C (10 mg, 10% purity) under N_2 atmosphere. The mixture was degassed and purged with H_2 for 3 times and stirred at 25 °C for 18 hours under H_2 atmosphere (15 psi). The reaction mixture was filtered. The filtrate was concentrated under reduced pressure, purified by prep-HPLC (column: Phenomenex luna C18 150 × 25mm × 10um; 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, 0.9FORMIC ACID). ^{1}H NMR (400 MHz, DMSO+D_2O) 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

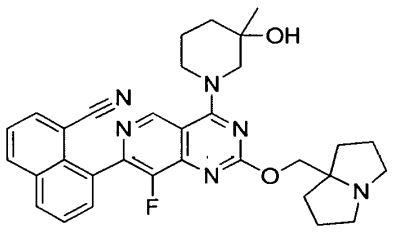


[0000522] Step A. 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (115 mg, 264 μmol) and K_3PO_4 (1.5 M in water , 550 μL) in THF (3 mL) was degassed and purged with N_2 for 3 times. Triisopropyl-[2-[8-(4,4,5,5-

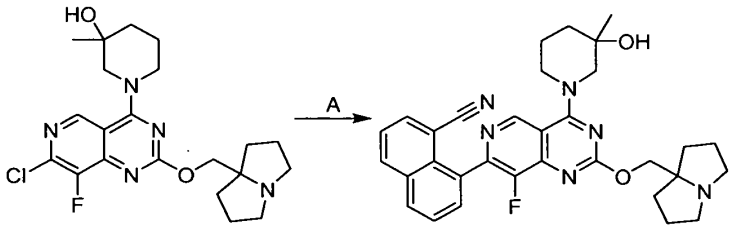
tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthyl]ethynyl]silane (130 mg, 299 μmol) was added, followed by cataCXium-A-Pd-G3 (20 mg, 27.5 μmol). The mixture was stirred at 60 °C for 3 hours under N_2 atmosphere. The combined reaction mixture was diluted with water (15ml), extracted with ethyl acetate (5 mL × 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-ethynylnaphthalen-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 × 25mm × 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%). ^{1}H NMR (400 MHz, 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

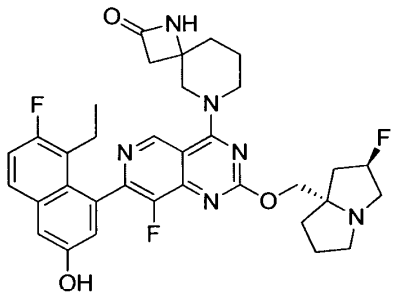


8-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-1-naphthonitrile

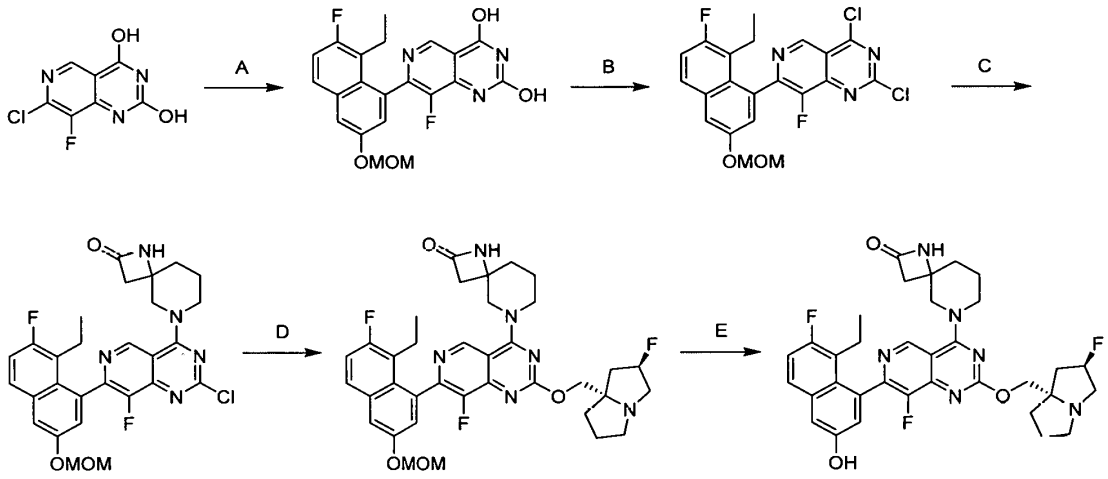


[0000524] Step A. 8-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)-1-naphthonitrile: To a solution of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (50.0 mg, 115 μmol) and 8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthonitrile (48.0 mg, 172 μmol) in toluene (2.0 mL) was added K_3PO_4 (1.5 M, 229 μl) and cataCXium-A-Pd-G3 (12.53 mg, 17.20 μmol). 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 × 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* 10μm; 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. ^{1}H 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, 169μL) in toluene (3 mL) were added DIEA (141 mg, 1.09 mmol, 190 μL) and 7-[8-ethyl-7-fluoro-3-

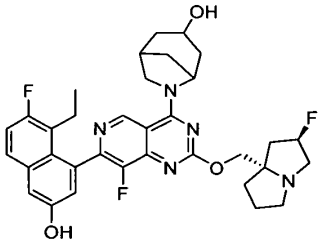
(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine-2,4-diol (150 mg, 363 μmol) and the mixture was stirred at 110 °C for 25 mins. After completion, the mixture was concentrated in vacuum and the pH value was adjusted to 8 with cold saturated $NaHCO_3$ solution. Then the mixture was extracted 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.

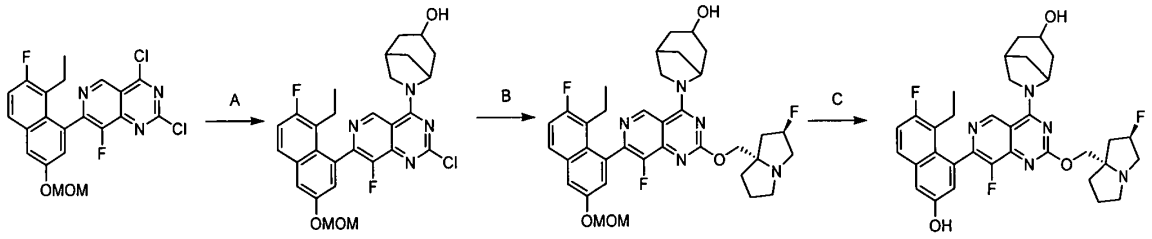
[0000528] Step D. 6-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one. A mixture of 8-[2-chloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-1,8-diazaspiro[3.5]nonan-2-one (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 μmol) 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 $NaHCO_3$ solution and 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 prep-HPLC (Water s Xbridge 150*25mm*5μm; mobile phase: [water (10mM NH_4HCO_3) - 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). ^{19}F 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,7a*S*)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol

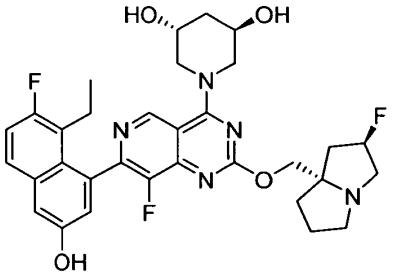


[0000530] Step A. 6-(2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido [4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol: To a solution of 2,4-dichloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidine (163 mg, 362 μmol) and DIPEA (297 mg, 2.30 mmol) in DCM (2 mL) was added 6-azabicyclo[3.2.1]octan-3-ol (33 mg, 259 μmol) 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 (5ml), and extracted with ethyl acetate (10 mL × 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.

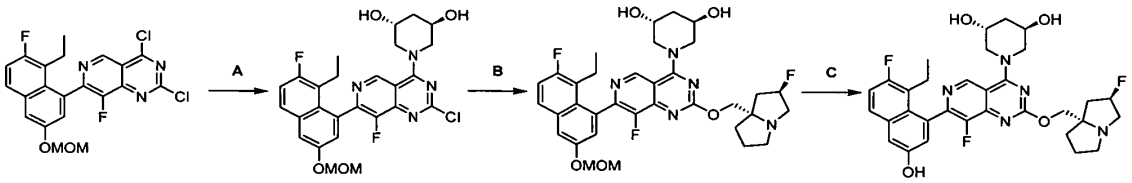
[0000531] Step B. 6-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol: A mixture of 6-(2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol (66 mg, 122 μmol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (78 mg, 490 μmol), DIPEA (52 mg, 402 μmol), and 4Å molecular sieves (40 mg, 40.7 μmol) 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 × 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,7a*S*)-2-fluorohexahydro-1*H*-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 μmol) 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 $NaHCO_3$ aqueous (8 mL) at 0 °C. The residue was washed with DCM (4 mL × 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 × 25 mm × 5 μm;mobile phase: [water (10mM NH_4HCO_3)-ACN];B%: 42%-72%,10min) to give the product as a yellow solid. (10 mg, 18%). ^{1}H NMR (400 MHz, METHANOL-d_4) 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-d_4) 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



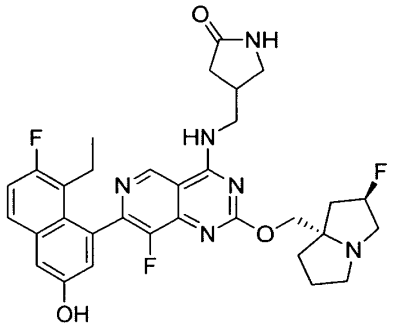
[0000533] Step A. (3R,5R)-1-(2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol: To a mixture of 2,4-dichloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidine (200 mg, 444 μmol), and DIEA (287 mg, 2.22 mmol) in dichloromethane (3 mL) was added (3R,5R)-piperidine-3,5-diol (47.8 mg, 311 μmol, 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 Na_2SO_4. 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 μmol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (45.0 mg, 282 μmol), and 4Å molecular sieves (30.0 mg) in dioxane (1.5 mL) was added DIEA (54.8 mg, 424 μmol), 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.

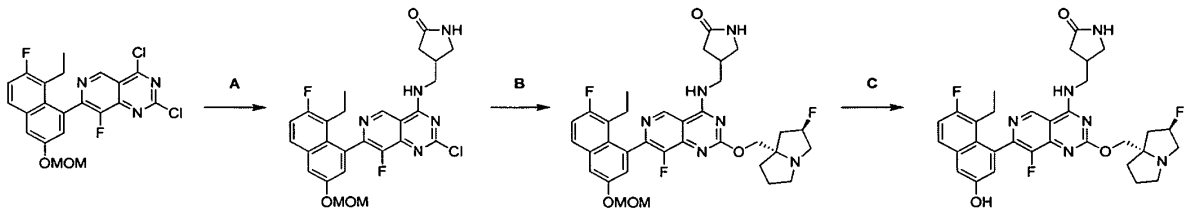
[0000535] Step C. (3R,5R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol. To the solution of (3R,5R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-

yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol (42.0 mg, 64.3 μmol) 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. $NaHCO_3$. The mixture was extracted with ethyl acetate (8 mL × 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 × 25 mm × 5 μm; mobile phase: [water (10 mM NH_4HCO_3) - 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; ^{1}H NMR (400 MHz, METHANOL-d_4) 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



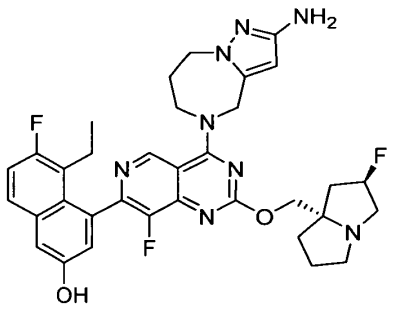
[0000536] Step A. 4-(((2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one: To the mixture of 2,4-dichloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidine (170 mg, 378 μmol), and DIEA (244 mg, 1.89 mmol) in dichloromethane (3 mL) was added 4-(aminomethyl)pyrrolidin-2-one (34.5 mg, 302 μmol) 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 μmol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (66.3 mg, 417 μmol), and 4Å molecular sieves (5.0 mg) in dioxane (1.5 mL) was added DIEA (80.8 mg, 625 μmol), 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.

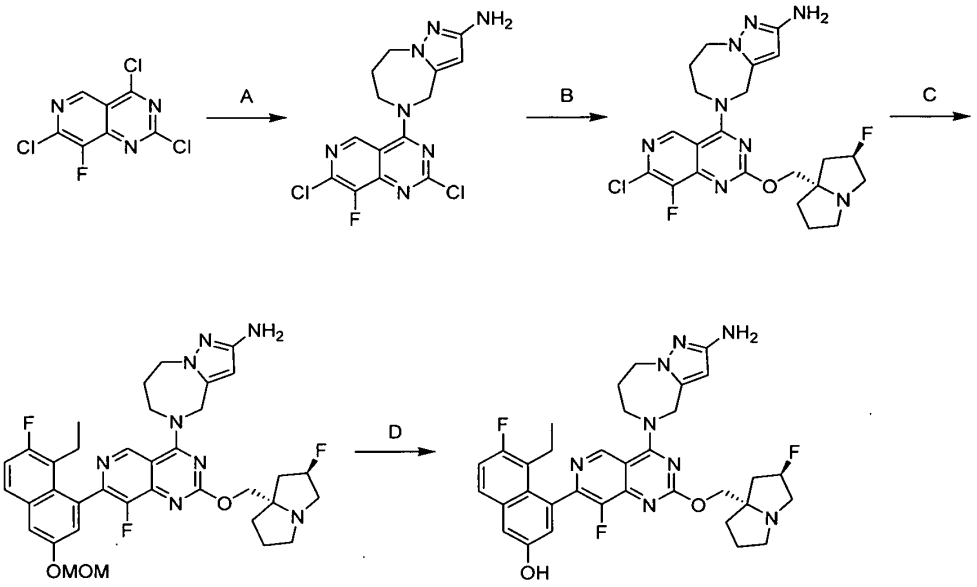
[0000538] Step C. 4-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one: To the solution of 4-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one (78.0 mg, 120 μmol) 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.

$NaHCO_3$ 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 NH_4HCO_3) - 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-d_4) 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 μL) in dichloromethane (1 mL) was added 5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (118 mg, 776 μmol) at -40 °C and the mixture was stirred at -40 °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, 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 μL) and 4Å molecular sieves (400 mg) in dioxane (1 mL) was stirred at 90°C for 16 hours. After completion,

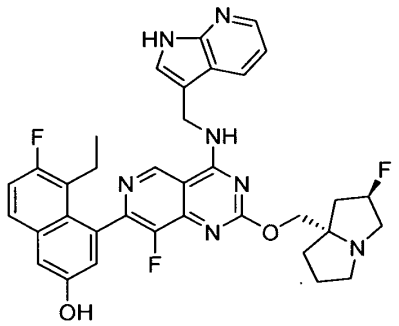
the mixture was filtered and concentrated in vacuum to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to give 5-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (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 μmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (67 mg, 185 μmol), K_3PO_4 (1.5 M, 285 μL) in THF (1 mL) was added cataCXium-A-Pd-G3 (10 mg, 14 μmol) under N2, 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.

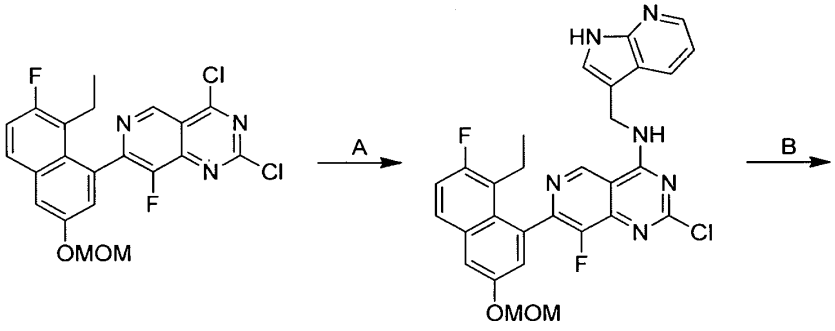
[0000542] Step D. 4-(4-(2-amino-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol. 5-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (14 mg, 20 μmol) was added to HCl•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×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.

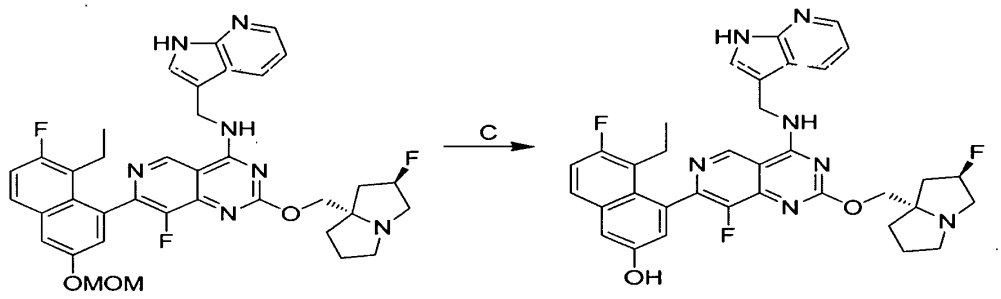
The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; mobile phase: [water (10 mM NH4HCO3)-ACN]; B%: 20%-50%, 10 min) to afford 4-(4-(2-amino-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol (4.58 mg, 34% yield). White solid; ^{1}H 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





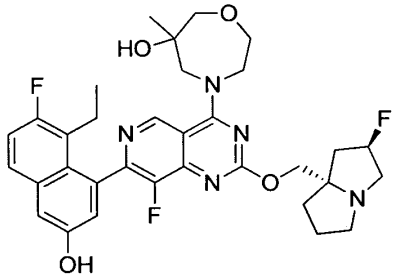
[0000543] Step A. N-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-amine: To a solution of 2,4-dichloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidine (163 mg, 362 μmol) and 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 °C. The mixture was stirred at -40 °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 × 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 °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

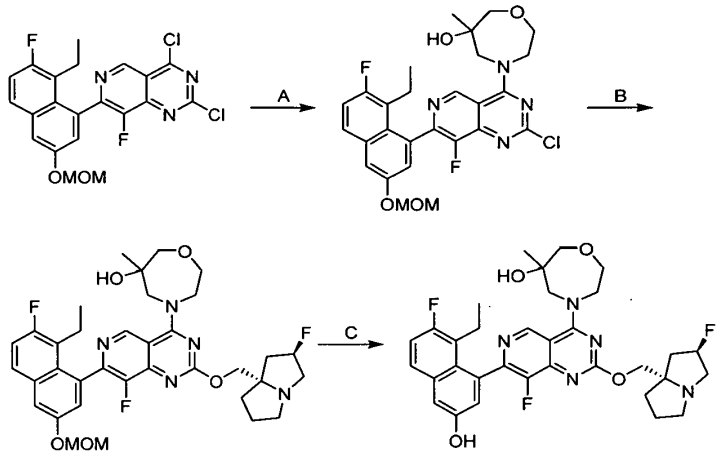
(0.1% formic acid)/acetonitrile=1/1] to afford the product as white solid (100 mg, 54% yield). LCMS (ESI, M+1): m/z 684.3.

[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 μmol) 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 $NaHCO_3$ solid below 5 °C. The mixture was extracted with DCM (10 mL × 4). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: water s Xbridge 150 × 25mm × 5um; A: [water (10mM NH_4HCO_3)]; 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 × 4.6 mm I.D., 3 μm column A: CO_2, B: MeOH (w/ 0.05% DEA), 5% to 40%, 3mL/min, 220 nm, t_R: 2.009 min ; ^{1}H 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); ^{19}F NMR (376 MHz, DMSO-d_6): 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



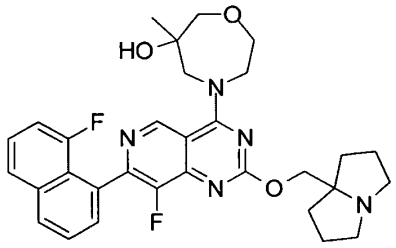
[0000546] Step A. 4-[2-chloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-6-methyl-1,4-oxazepan-6-ol: To a mixture of 2,4-dichloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine (189 mg, 420 μmol) and DIEA (217 mg, 1.68 mmol, 292 μL) in dichloromethane (2 mL) was added 6-methyl-1,4-oxazepan-6-ol (49.5 mg, 378 μmol) 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 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 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 μmol), ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (90.3 mg, 567 μmol), DIEA (73.3 mg, 567 μmol, 98.8 μL) and 4Å molecular sieves (10 mg) in dioxane (1 mL) was

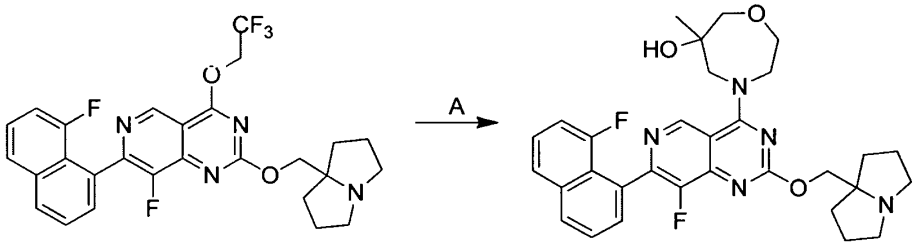
stirred at 90 °C for 21 h. After completion, the mixture was filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to the title compound (92.0 mg, 73% yield). Yellow solid. LCMS (ESI, M+1): m/z 668.3.

[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 μmol) 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 $NaHCO_3$ solution and the mixture was extracted with ethyl acetate twice. The combined organic layer was dried over Na_2SO_4 and filtered. The residue was concentrated in vacuum. The residue was purified by prep-HPLC (Shim-pack C18 150*25*10um; 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. ^{1}H 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

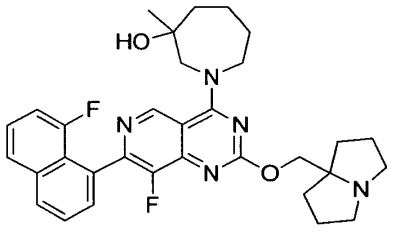


4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol

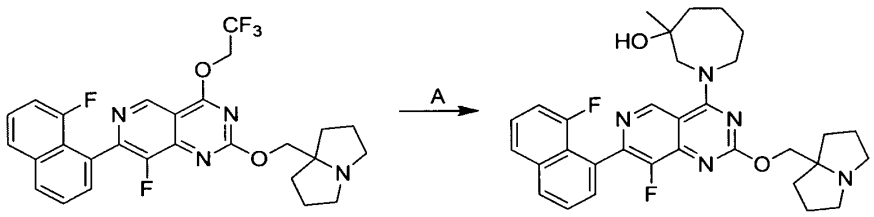


[0000549] Step A. 4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol: To the mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30 mg, 56 μmol), 6-methyl-1,4-oxazepan-6-ol (15 mg, 113 μmol) 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 × 25 mm × 10 μm; mobile phase: [water (0.225% formic acid)-ACN]; B%: 15% - 45%, 10 min) and (column: Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; 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

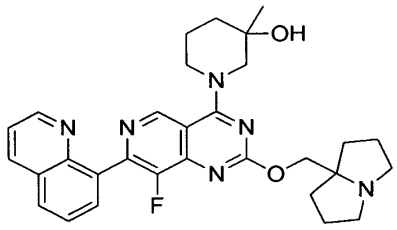


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylazepan-3-ol

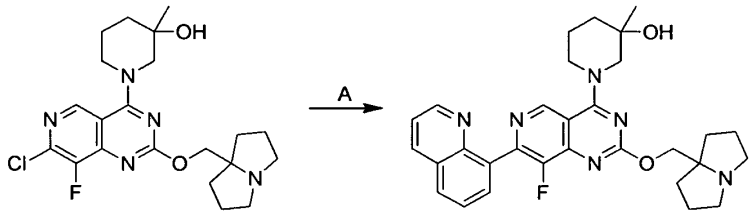


[0000550] Step A. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylazepan-3-ol: 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.3 μmol, 1.0 equiv.), DIEA (60.9 mg, 471 μmol, 82.1 μL, 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 μmol, 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 × 25 mm × 10 μm; 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; ^{1}H 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

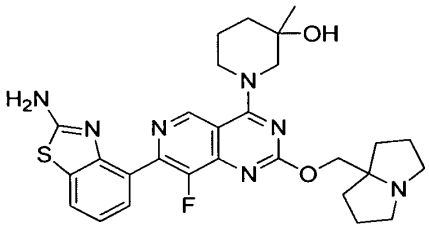


1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(quinolin-8-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

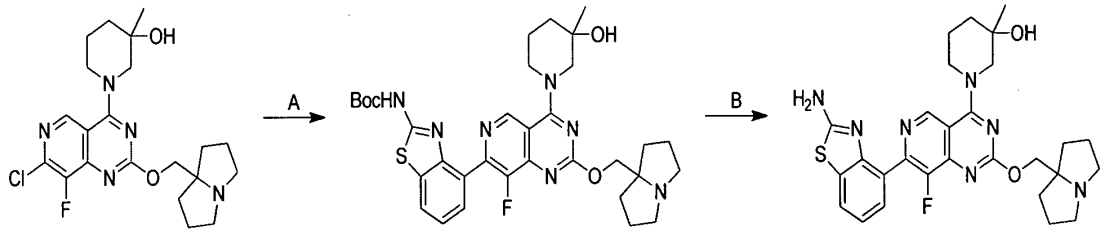


[0000551] Step A. 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(quinolin-8-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (100 mg, 229 μmol), quinolin-8-ylboronic acid (79.4 mg, 459 μmol, 79.4 μL), Na_2CO_3 (72.9 mg, 688 μmol) and tetrabutylammonium bromide (74.0 mg, 229 μmol) in 1,2-dimethoxyethane (3.0 mL), EtOH (3.0 mL) and water (1.0 mL) was added $Pd(PPh_3)_4$ (53.0 mg, 45.9 μmol, 0.2 equiv.). The mixture was stirred at 80 °C for 12 h. Upon completion, the mixture reaction was diluted water (5.0 mL) and was extracted with EtOAc (3 × 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 × 30 mm × 3 μm; 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, 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

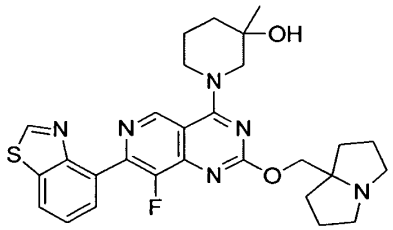


[0000552] Step A. tert-butyl (4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)benzo[d]thiazol-2-yl)carbamate: To a mixture of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (150 mg, 344 μmol), (2-((tert-butoxycarbonyl)amino)benzo[d]thiazol-4-yl)boronic acid (202 mg, 688 μmol) and K_3PO_4 (1.5 M, 688 μL) in THF (2.0 mL) was added BrettPhos Pd G3 (31.2 mg, 34.4 μmol). 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 × 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.

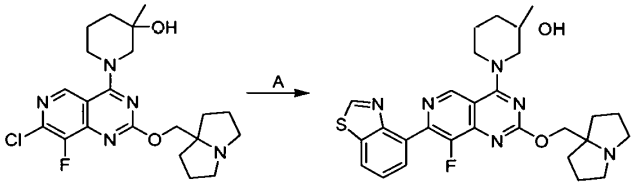
[0000553] Step B. 1-(7-(2-aminobenzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin- 7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of tert-butyl (4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-hydroxy-3-

methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)benzo[d]thiazol-2-yl)carbamate (90.0 mg, 139 μmol) 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 ~ 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 × 10 μm; A: water (0.225% formic acid), B: ACN, B%: 9%-39% over 10min], followed by prep-HPLC [Water s Xbridge 150 × 5 mm × 5 μm; 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; ^{1}H NMR (400 MHz, 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



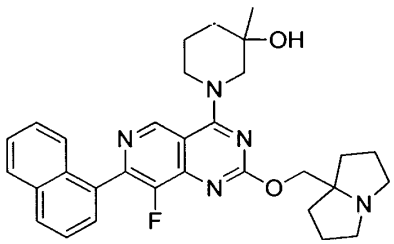
1-(7-(benzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



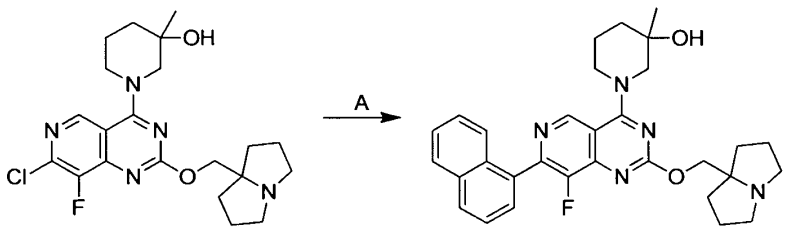
[0000554] Step A. 1-(7-(benzo[d]thiazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of 1-(7-chloro-8-

fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (100 mg, 229 μmol), benzo[d]thiazol-4-ylboronic acid (53.4 mg, 298 μmol), K_3PO_4 (1.5 M, 0.5 mL) and [2-(2-aminophenyl)phenyl]palladium(1+);bis (1-adamantyl)-butyl-phosphane;methanesulfonate (25.1 mg, 34.4 μmol) in THF (2.00 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 60 °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 150×25mm× 10μm; 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; ^{1}H 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

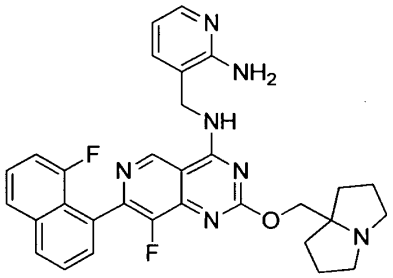


1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

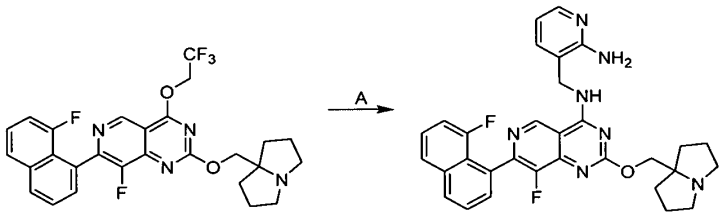


[0000555] Step A. 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (50.0 mg, 115 μmo), naphthalen-1-ylboronic acid (39.5 mg, 229 μmol) and K_3PO_4 (1.50 M in water , 229 μL) in THF (1.0 mL) was added cataCXium-A-Pd-G3 (8.35 mg, 11.5 μmol). 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 × 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 × 25 mm × 10 μm; 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; ^{1}H 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

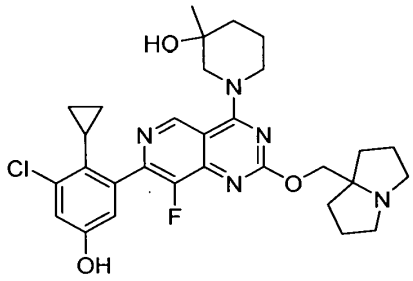


N-((2-aminopyridin-3-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

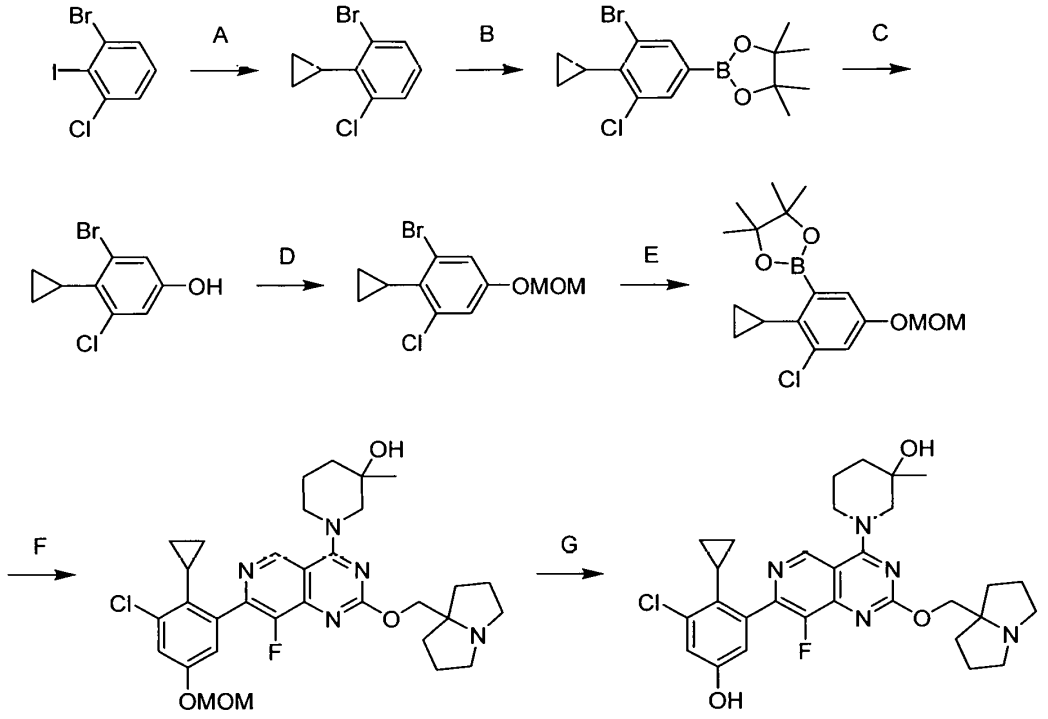


[0000556] Step A. N-((2-aminopyridin-3-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30 mg, 56.55 μmol) and 3-(aminomethyl)pyridin-2-amine (34.8 mg, 283 μmol) in DMF (3 mL) were added DIPEA (21.9 mg, 170 μmol) 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 μm;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. ^{1}H 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), K_3PO_4 (4.82 g, 22.7 mmol), and $Pd(dppf)Cl_2$ (461 mg, 630 μmol) in 1,4-dioxane (12 mL) and water (3 mL) was degassed and purged with N_2 for 3 times. The mixture was stirred at 100 °C for 7 hours under N_2 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 Na_2SO_4. 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, $CDCl_3$) 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 μmol) and 4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine (83.5 mg, 311 μmol) in hexane (10 mL) was degassed and purged with N_2 for 3 times. The reaction mixture was stirred at 60 °C for 3 hours under N_2 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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 water $_2$ (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 $Na_2S_2O_3$ (10 % aq, 40 mL) at 0 °C. The mixture was extracted with ethyl acetate 60 mL (30 mL × 2). 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 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); ^{1}H NMR (400 MHz, $CDCl_3$) 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 × 3). The combined organic layers were washed with brine (30 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 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); ^{1}H NMR (400 MHz, $CDCl_3$) δ

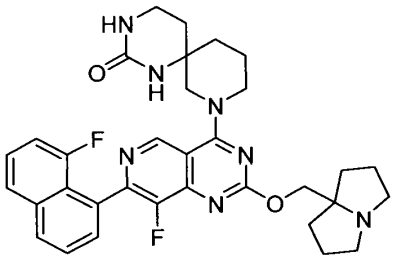
= 7.20 (d, J = 2.6 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 5.12 (s, 2H), 3.47 (s, 3H), 1.70 (tt, J = 5.7, 8.4 Hz, 1H), 1.17-1.11 (m, 2H), 0.76-0.69 (m, 2H).

[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, 1.03mmol), 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)Cl_2 (75.37 mg, 103 μmol). 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 × 5 mL). The organic layer was dried over by anhydrous Na_2SO_4, 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); ^{1}H NMR (400 MHz, $CDCl_3$) 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).

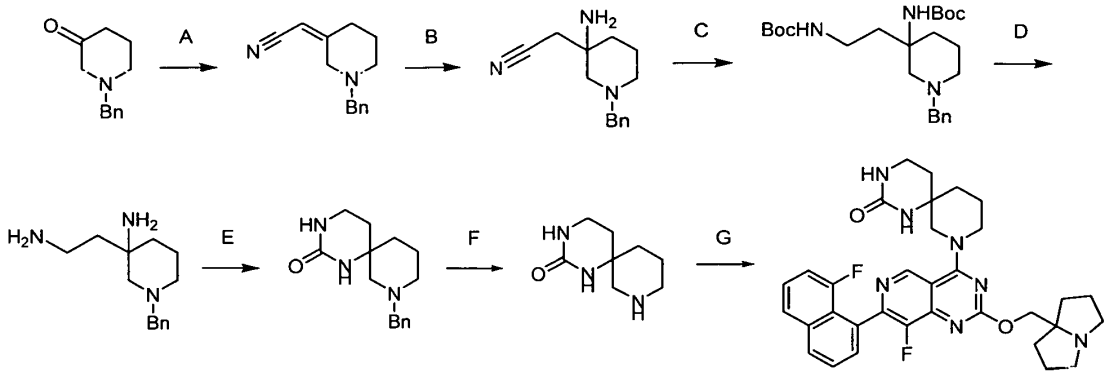
[0000562] Step F. 1-(7-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of 2-[3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl- 1,3,2-dioxaborolane (77.7 mg, 229 μmol), 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 μmol) and K_3PO_4 (1.5 M in water , 229.40 μL) in THF (0.5 mL) was added cataCXium-A-Pd-G3 (8.35 mg, 11.5 μmol). The mixture was degassed and purged with N_2 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 × 5 mL). The organic layer was dried over Na_2SO_4, 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); ^{1}H NMR (400 MHz, $CDCl_3$) 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 μmol) 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 150×25mm×10μm; 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); ^{1}H NMR (400 MHz, METHANOL-d4) 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 (25mL) 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 × 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. ^{1}H 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. ^{1}H 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 $NiCl_2$•6WATER (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 (80mL × 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.

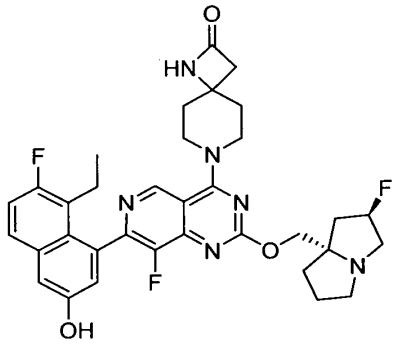
[0000568] Step E. 8-benzyl-1,3,8-triazaspiro[5.5]undecan-2-one: To a mixture of 3-(2-aminoethyl)-1-benzyl-piperidin-3-amine (250 mg, 926 μmol, HCl) in toluene (25 mL) was added TEA (281 mg, 2.78 mmol, 387 μL) and di(imidazol-1-yl)methanone (300 mg, 1.85 mmol). The reaction mixture was stirred at 80 °C 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 × **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 150×25mm×10μm;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. ^{1}H 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.

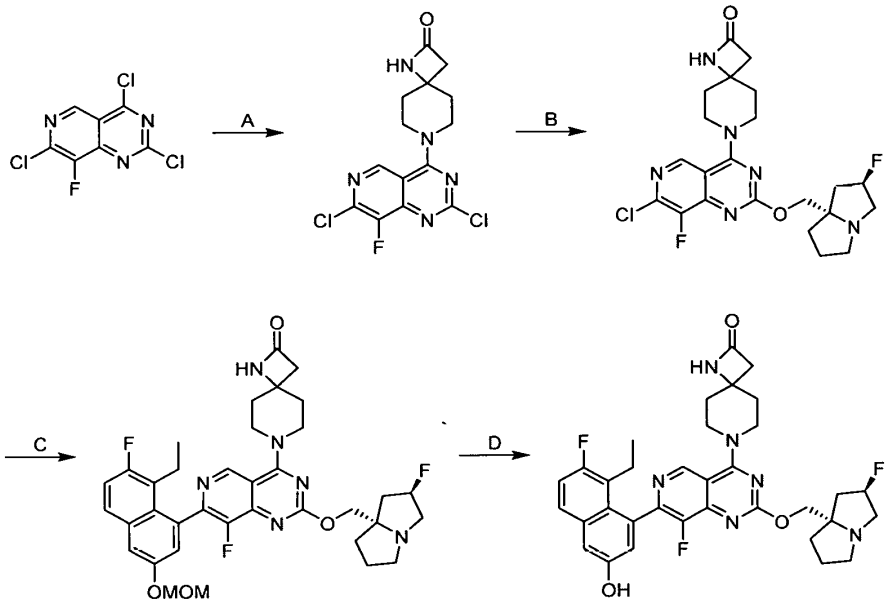
[0000569] Step F. 1,3,8-triazaspiro[5.5]undecan-2-one: To a mixture of 8-benzyl-1,3,8-triazaspiro[5.5]undecan-2-one (70 mg, 270 μmol) in MeOH (1 mL) was added Pd/C (34.5 mg, 32.4 μmol, 10% purity). The reaction mixture was stirred at 25 °C for 16 hours under H_2 (15 psi). The reaction mixture was filtered and concentrated under reduced pressure to give 1,3,8-triazaspiro[5.5]undecan-2-one (45 mg, crude) as a colorless oil. ^{1}H 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×10μm;mobile phase: [water (0.225% formic acid)-ACN];B%: 12%-42%,11min) to give the title compound (9.06 mg, 5.63% yield) as an off-white solid. ^{1}H 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 Na_2SO_4. The mixture was filtered and concentrated under reduced pressure to give 7-

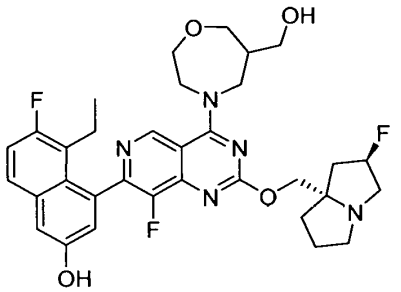
(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)- 1,7-diazaspiro[3.5]nonan-2-one (350 mg, crude) as yellow solid. (M+1). LCMS (ESI, M+1): m/z 356.1.

[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 μmol), 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 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, 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 μmol, 37% yield over two steps, 99.3% purity) as yellow solid. LCMS (ESI, M+1): m/z 479.2.

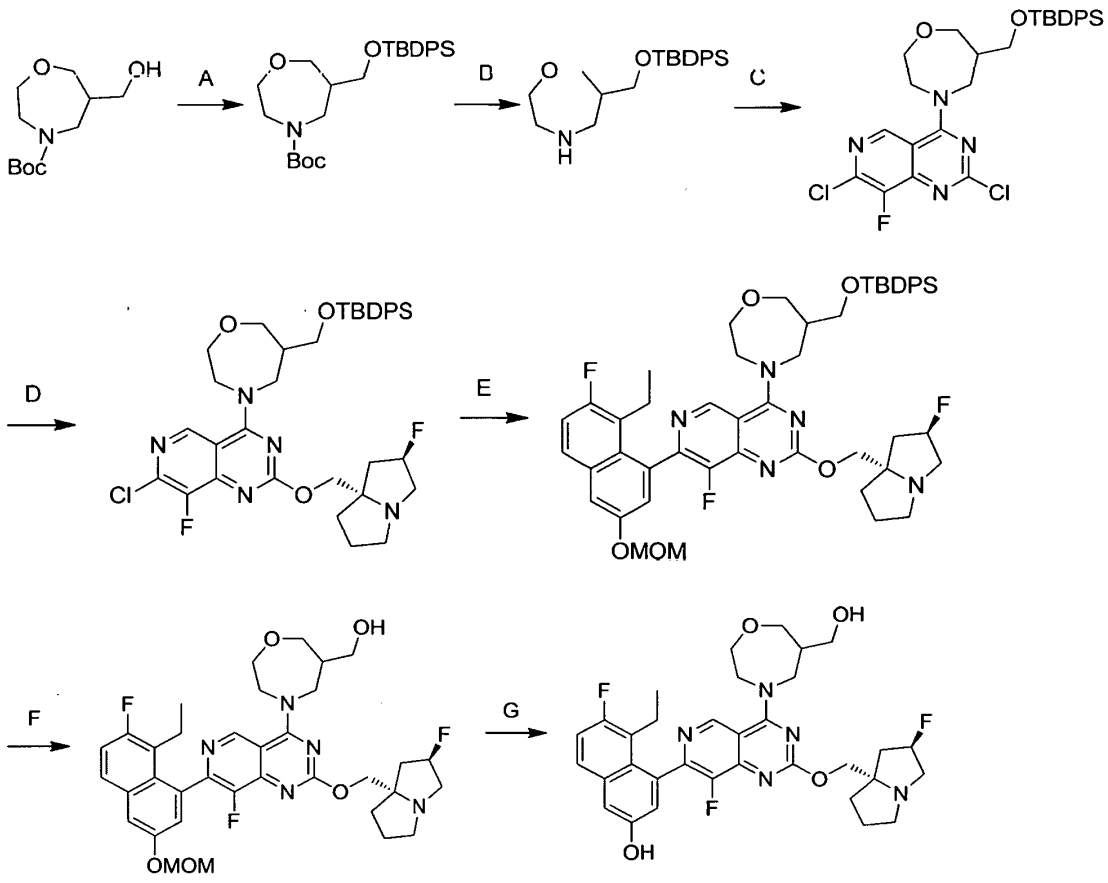
[0000573] Step C. 7-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one: To a mixture of 7-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one (90.0 mg, 188 μmol), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (135 mg, 376 μmol) and Cs_2CO_3 (1.5 M, 376 μL) in methoxycyclopentane (2.0 mL) was added cataCXium-A-Pd-G3 (27.4 mg, 37.6 μmol). The mixture was stirred at 100 °C for 3 hours. The mixture was quenched with water (5 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layer was 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 (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 μmol) 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 × 25 mm × 5 μm; 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. ^{1}H NMR (400 MHz, 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 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 tert-butyl 6-(((tert-butyldiphenylsilyl)oxy)methyl)-1,4-oxazepane-4-carboxylate (1.10 g, 71% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) 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 $NaHCO_3$. The mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 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 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-(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) waere 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.

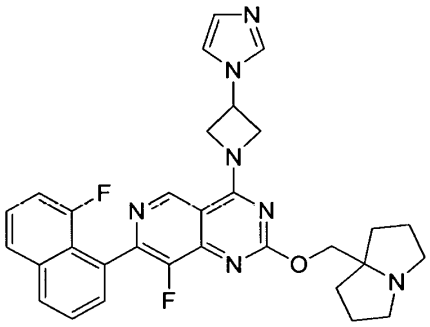
[0000579] Step E. 6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane: To a solution of 6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane (500 mg, 706 μmol) 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 μmol). The mixture was stirred at 90 °C for 2 hours. The reaction mixture was diluted with water (10mL) and extracted with ethyl acetate (3 × 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 μmol, 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.

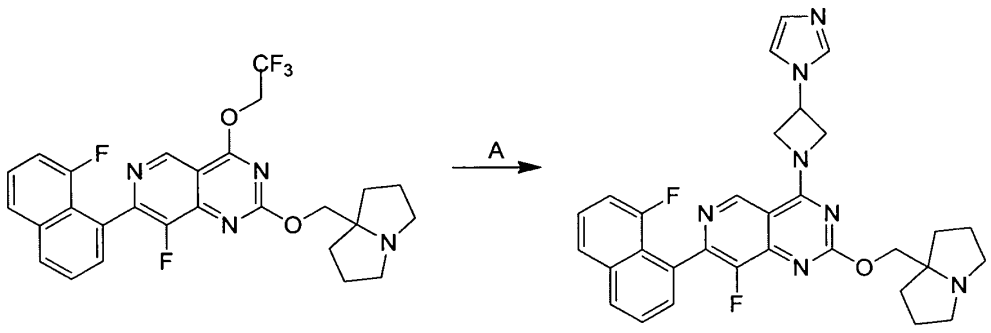
[0000581] Step G. 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(6-(hydroxymethyl)-1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol: To a solution of (4-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-

d]pyrimidin-4-yl)-1,4-oxazepan-6-yl)methanol (100 mg, 150 μmol) 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×5μm; mobile phase: [water (10mM NH_4HCO_3)-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. ^{1}H 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

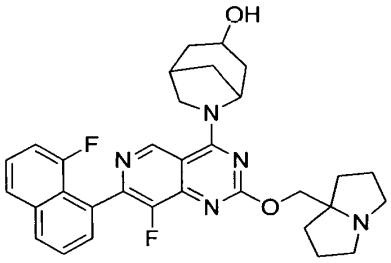


4-(3-(1H-imidazol-1-yl)azetidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine

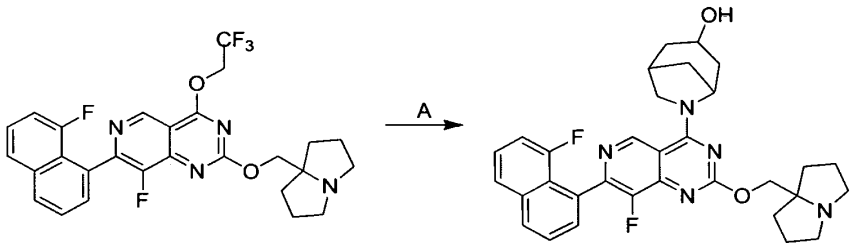


[0000582] Step A. 4-(3-(1H-imidazol-1-yl)azetidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine: A mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 94.0 μmol) in DMF (0.5 mL) was added 4 Å molecular sieves (50.0 mg, 94.0 μmol), DIEA (48.7 mg, 377 μmol), 1-(azetidin-3-yl)imidazole (15.0 mg, 94.0 μmol, HCl salt) and stirred at 40°C for 16 hours under N_2 atmosphere. The mixture solution was filtered and purified by reverse-phase preparatory HPLC (15% to 25% water /ACN with 0.225% formic acid formic acid over 7 minutes) to give 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 (10.81 mg, 20% yield). ^{1}H NMR (400 MHz $CDCl_3$): δ 8.94 (s, 1H), 8.04 - 7.99 (m, 1H), 7.79 - 7.72 (m, 2H), 7.68 - 7.62 (m, 1H), 7.61 - 7.57 (m, 1H), 7.47 (m, 1H), 7.29 (br s, 1H), 7.24 (s, 1H), 7.14 (dd, J = 7.6, 12.8 Hz, 1H), 5.37 - 5.27 (m, 1H), 5.19 (m, 2H), 4.82 (m, 2H), 4.54 (s, 2H), 3.61 - 3.42 (m, 2H), 2.88 - 2.73 (m, 2H), 2.26 (m, 2H), 2.08 - 2.01 (m, 4H), 1.87 - 1.82 (m, 2H); LCMS (ESI, M+1): m/z 554.3

EXAMPLE 76

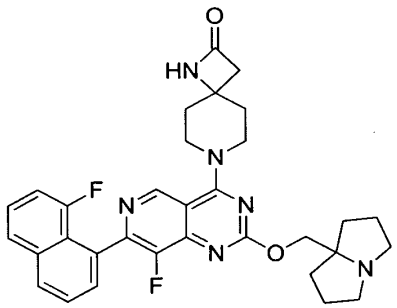


6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol

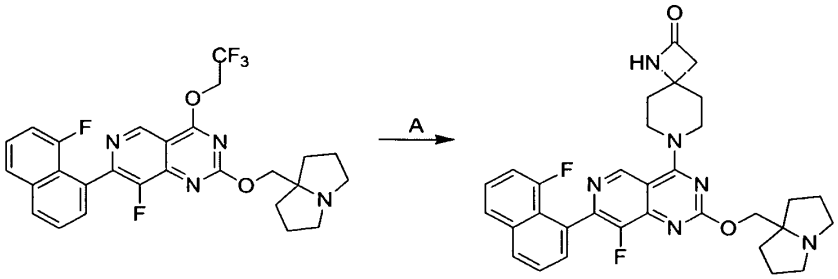


[0000583] Step A. 6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol: 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (100 mg, 189 μmol), DIEA (122 mg, 943 μmol) and 4Å molecular sieves (10.0 mg) in DMF (5.0 mL) was added 6-azabicyclo[3.2.1]octan-3-ol (48.0 mg, 377 μmol). The mixture was stirred at 40 °C for 12 hours. The reaction mixture was diluted water (5.0 mL) and was extracted with EtOAc (3 × 5.0 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The mixture was filtered and concentrated under reduced pressure to give a residue. The reaction was purified by prep-HPLC [Phenomenex Synergi C18 150 × 25 mm × 10 μm; A: water (0.225% formic acid formic acid), B: ACN, B%: 12%-42%] to afford 6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol (3.89 mg, 4% yield) as yellow solid. ^{1}H NMR (400 MHz, METHANOL-d_4): δ 9.43-9.24 (m, 1H), 8.61-8.44 (m, 1H), 8.17-8.03 (m, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.75-7.65 (m, 1H), 7.63-7.48 (m, 2H), 7.23-7.14 (m, 1H), 5.07-4.97 (m, 1H), 4.64-4.59 (m, 2H), 4.55 (br s, 1H), 4.41-4.34 (m, 1H), 4.3 -4.22 (m, 1H), 4.15 (br d, J = 2.0 Hz, 1H), 3.65-3.53 (m, 2H), 3.26-3.10 (m, 2H), 2.81 (br s, 1H), 2.75-2.57 (m, 1H), 2.38-1.97 (m, 11H), 1.90-1.81 (m, 1H); LCMS (ESI, M+1): m/z 558.2

EXAMPLE 77

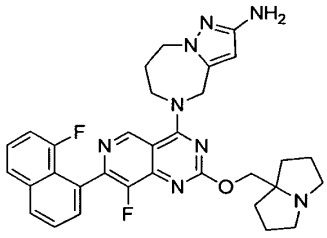


7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one

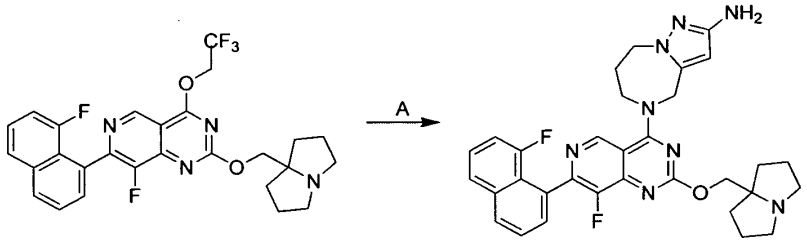


[0000584] Step A. 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one: 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (100 mg, 189 μmol), DIEA (122 mg, 943 μmol) and 4Å molecular sieves (10 mg) in DMF (5 mL) was added 1,7-diazaspiro[3.5]nonan-2-one (50.0 mg, 357 μmol). The mixture was stirred at 40 °C for 12 hours. The reaction mixture was diluted water (5.0 mL) and extracted with EtOAc (3 × 5.0 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The mixture was filtered and concentrated under reduced pressure to give a residue. The reaction was purified by prep-HPLC [Phenomenex Synergi C18 150 × 25 mm × 10 μm; A: water (0.225% formic acid formic acid), B: ACN, B%: 11%-41%] to afford 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,7-diazaspiro[3.5]nonan-2-one (16.0 mg, 14% yield) as yellow solid. ^{1}H NMR (400 MHz, METHANOL-d_4): δ 9.10 (s, 1H), 8.52 (br s, 1H), 8.12 (br d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.74-7.68 (m, 1H), 7.62 (dd, J = 0.8, 7.2 Hz, 1H), 7.57-7.50 (m, 1H), 7.24-7.15 (m, 1H), 4.63 (s, 2H), 4.29-4.14 (m, 2H), 4.12-4.00 (m, 2H), 3.72-3.57 (m, 2H), 3.27-3.17 (m, 2H), 2.87 (s, 2H), 2.36-2.26 (m, 2H), 2.24-2.12 (m, 4H), 2.11-2.01 (m, 6H); LCMS (ESI, M+1): m/z 571.3

EXAMPLE 78

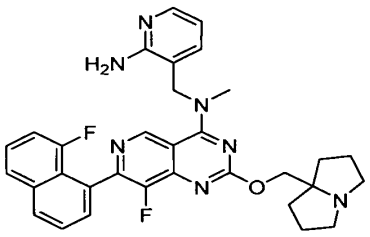


5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine

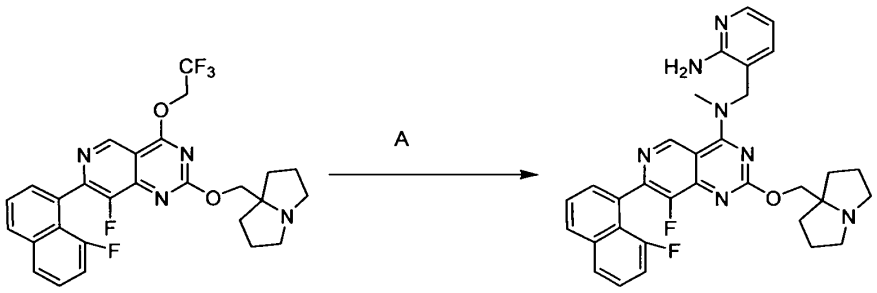


[0000585] Step A. 5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine: To the mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (42 mg, 79 μmol), 5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (18 mg, 119 μmol) and 4Å molecular sieves (40 mg, 79 μmol) in DMF (0.6 mL) was added DIEA (31 mg, 237 μmol). The mixture was stirred at 40 °C for 12 hours. The reaction mixture was filtered and purified by prep-HPLC (column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (0.225% formic acid)-ACN]; B%: 10 % - 40 %, 10 min) to afford 5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-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 (5.57 mg, 11% yield, 0.422FA) as white solid. ^{1}H NMR (400 MHz, METHANOL-d_4): δ 9.23 (s, 1H), 8.55 (s, 1H), 8.13 (br d, J = 8.8 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.71 (dd, J = 7.2, 8.0 Hz, 1H), 7.61 (dd, J = 1.2, 7.2 Hz, 1H), 7.54 (dt, J = 5.2, 8.0 Hz, 1H), 7.24 - 7.13 (m, 1H), 5.79 (s, 1H), 5.17 - 5.06 (m, 2H), 4.49 (s, 2H), 4.38 (br t, J = 5.6 Hz, 2H), 4.28 - 4.19 (m, 2H), 3.48 - 3.39 (m, 2H), 3.10 - 2.96 (m, 2H), 2.43 - 2.32 (m, 2H), 2.25 - 2.16 (m, 2H), 2.15 - 2.02 (m, 4H), 2.00 - 1.89 (m, 2H); LCMS (ESI, M+1): m/z 583.2

EXAMPLE 79

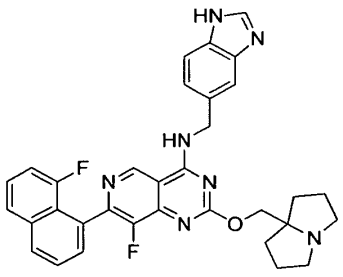


N-((2-aminopyridin-3-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-N-methyl-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

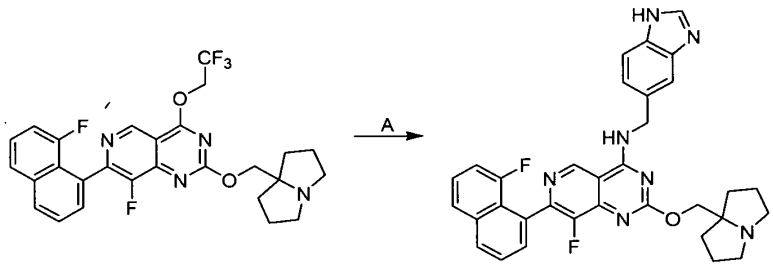


[0000586] Step A: N-((2-aminopyridin-3-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-N-methyl-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (100 mg, 189 μmol, 1.0 equiv.), DIEA (122 mg, 943 μmol, 164 μL, 5.0 equiv.) and 4Å molecular sieves (50 mg) in DMF (1.0 mL) was added 3-((methylamino)methyl)pyridin-2-amine (51.7 mg, 377 μmol, 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 Gemini-NX C18 75 × 30 mm × 3 μm; A: water (0.225% formic acid formic acid), B: ACN, B%: 8%-38% over 7 min] to afford the title compound (6.38 mg, 6% yield, 99% purity). White solid; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.22 (s, 1H), 8.48 (br d, J = 0.4 Hz, 1H), 8.12 (br d, J = 8.2 Hz, 1H), 7.99-7.91 (m, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.75-7.66 (m, 1H), 7.63-7.58 (m, 1H), 7.57-7.50 (m, 2H), 7.24-7.13 (m, 1H), 6.79-6.67 (m, 1H), 5.00 (s, 2H), 4.59 (s, 2H), 3.71-3.61 (m, 5H), 3.30-3.22 (m, 2H), 2.31-2.17 (m, 4H), 2.16-2.01 (m, 4H); LCMS [ESI, M+1]: 568.4.

EXAMPLE 80

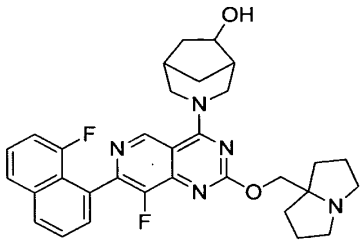


N-((1H-benzo[d]imidazol-5-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

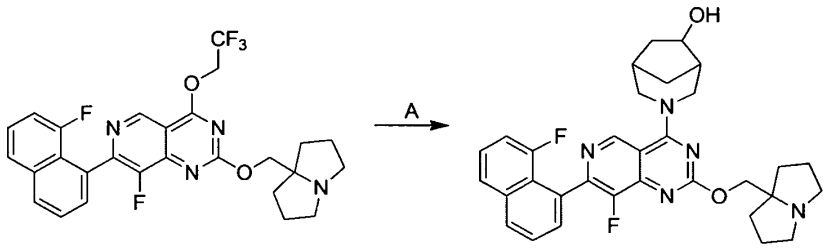


[0000587] Step A. N-((1H-benzo[d]imidazol-5-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (100 mg, 189 μmol), DIEA (122 mg, 943 μmol) and 4Å molecular sieves (10 mg) in DMF (1.0 mL) was added (1H-benzo[d]imidazol-5-yl)methanamine (55.5 mg, 377 μmol). The mixture was stirred at 40 °C for 12 hours. The reaction solution was filtered and purified by prep-HPLC [Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; A: water (0.225% formic acid formic acid), B: ACN, B%: 8%-38% over 7 min] to afford N-((1H-benzo[d]imidazol-5-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine (41.0 mg, 38% yield) as white solid. ^{1}H NMR (400 MHz, METHANOL-d_4): δ 9.27 (s, 1H), 8.55 (br s, 1H), 8.19 (s, 1H), 8.11 (br d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.75-7.67 (m, 2H), 7.64-7.57 (m, 2H), 7.56-7.49 (m, 1H), 7.43-7.38 (m, 1H), 7.23-7.14 (m, 1H), 5.03 (s, 2H), 4.55 (s, 2H), 3.63-3.52 (m, 2H), 3.24-3.13 (m, 2H), 2.26-2.18 (m, 2H), 2.17-2.11 (m, 2H), 2.10-2.02 (m, 2H), 2.01-1.93 (m, 2H); LCMS (ESI, M+1): m/z 578.2

EXAMPLE 81

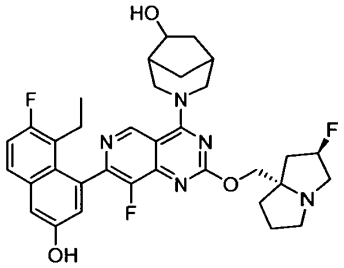


3-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol

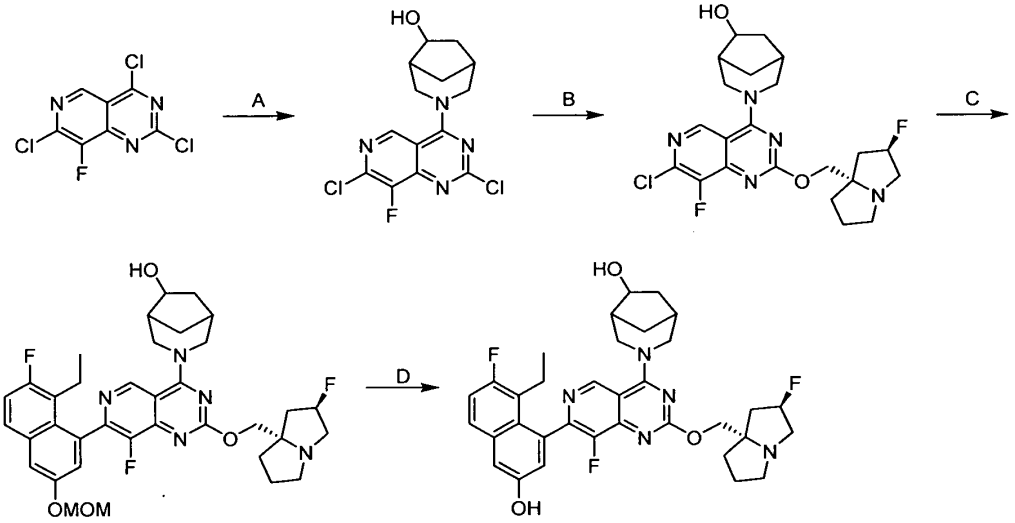


[0000588] Step A. 3-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol: To the mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50 mg, 94 μmol), 3-azabicyclo[3.2.1]octan-6-ol (26 mg, 207 μmol) and 4Å molecular sieves (40 mg) in DMF (1 mL) was added DIEA (49 mg, 377 μmol) The mixture was stirred at 40 °C for 16 hours. The reaction mixture was filtered and purified by prep-HPLC (column: water s Xbridge 150 × 25 mm × 5 μm; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 27%-57%, 10 min) to afford 3-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (12.5 mg, 23% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.32 (d, J = 12.4 Hz, 1H), 8.17 (br d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.73 (dt, J = 3.2, 7.6 Hz, 1H), 7.67 - 7.52 (m, 2H), 7.35 - 7.24 (m, 1H), 4.84 - 4.66 (m, 2H), 4.59 (m, 1H), 4.16 (br d, J = 2.4 Hz, 1H), 4.08 - 3.96 (m, 2H), 3.72 (br t, J = 12.4 Hz, 1H), 2.95 - 2.88 (m, 2H), 2.56 - 2.53 (m, 2H), 2.33 (br s, 1H), 2.17 - 2.04 (m, 2H), 1.88 (m, 2H), 1.83 - 1.70 (m, 5H), 1.69 - 1.61 (m, 1H), 1.61 - 1.49 (m, 2H), 1.26 (br d, J = 13.2 Hz, 1H); LCMS (ESI, M+1): m/z 558.3

EXAMPLE 82



3-(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)-3-azabicyclo[3.2.1]octan-6-ol



[0000589] Step A. 3-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol: To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (150 mg, 594 μmol), DIPEA (231 mg, 1.79 mmol) in DCM (1.5 mL) was added 3-azabicyclo[3.2.1]octan-6-ol (54.0 mg, 330 μmol, HCl). DIPEA (231 mg, 1.79 mmol) in DMF (1.0 mL) was dropwise added at -40 °C. The mixture was stirred at -40 °C for 1.5 h. The reaction mixture was diluted with water (20 mL) and extracted DCM (10 mL × 3). The combined organic phase was dried with anhydrous Na_2SO_4 and filtered. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate=5/1 to 1.5/1). TLC (PE/EA=1/1, Rf = 0.41) to afford 3-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (90 mg, 31% yield) as a yellow solid; LCMS (ESI, M+1): m/z 343.0.

[0000590] Step B. 3-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol: A mixture of 3-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (90 mg, 262 μmol), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (50 mg, 314 μmol,), 4Å molecular sieves (20 mg) ,DIPEA (102 mg, 792 μmol) in dioxane (1.0 mL) was degassed and purged with N_2 for 3 times. The mixture was stirred at 95 °C for 16 h under N_2 atmosphere. After completion,

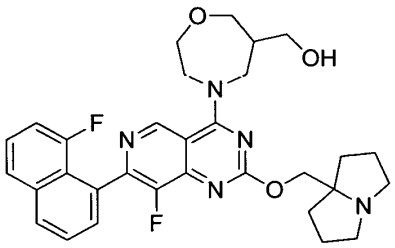
the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile=3/1] to afford 3-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (96 mg, 71% yield) as a yellow gum; LCMS (ESI, M+1): m/z 466.1.

[0000591] Step C. 3-(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-azabicyclo[3.2.1]octan-6-ol: A mixture of 3-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (96 mg, 206 μmol), and K_3PO_4 (1.5 M in water , 412 μL) in THF (2.0 mL) was degassed and purged with N_2 for 3 times. 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (112 mg, 311 μmol) was added. Then CataCXium A Pd G3 (15 mg, 20.6 μmol) was added into the reaction mixture. The mixture was stirred at 65 °C for 4 h under N_2 atmosphere. After completion, the reaction mixture was diluted with water (3.0 mL) and extracted with ethyl acetate (1.0 mL × 4). The combined organic phase was dried over anhydrous Na_2SO_4 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=13/7] to afford 3-(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-azabicyclo[3.2.1]octan-6-ol (104 mg, 75 % yield) as a yellow oil; LCMS (ESI, M+1): m/z 664.3.

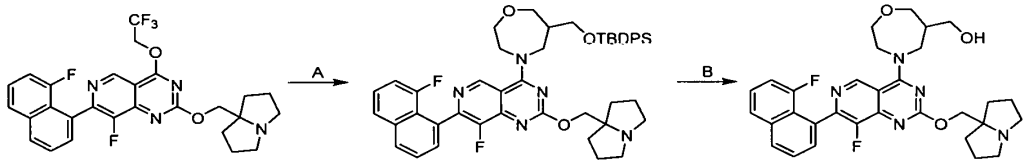
[0000592] Step D. 3-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol: To a solution of 3-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (99 mg, 149 μmol) in MeCN (4.0 mL) was added HCl/dioxane (4 M, 2.0 mL) at 0 °C. The mixture was stirred between 0 °C and 10 °C for 0.5 h. After completion, the reaction mixture was quenched with saturated $NaHCO_3$ aqueous (10 mL). The mixture was extracted with ethyl acetate (10 mL × 4). The combined organic phase was dried over anhydrous Na_2SO_4 and filtered. The mixture was

concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [Water s Xbridge 150 × 25mm × 5 μm; A: water (10 mM NH_4HCO_3), B: ACN, B%: 41%-71% over 10 min] to afford 3-(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-azabicyclo[3.2.1]octan-6-ol (33.5 mg, 36% yield) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ 9.25-9.01 (m, 1H), 7.70-7.62 (m 1H), 7.30 (d, J = 2.8 Hz, 1H), 7.27-7.20 (m, 1H), 7.09-7.01 (m, 1H), 5.41-5.19 (m, 1H), 5.04-4.97 (m, 1H), 4.77-4.73 (m, 1H), 4.38-4.16 (m, 3H), 3.97-3.68 (m, 1H), 3.54-3.39 (m, 1H), 3.29-3.07 (m, 3H), 3.04-2.81 (m, 1H), 2.58-2.28 (m, 3H), 2.28-2.11 (m, 5H), 2.03-1.85 (m, 4H), 1.85-1.76 (m, 1H), 1.40 (br d, J = 13.6 Hz, 1H), 0.83-0.75 (m, 3H). F NMR (376 MHz, METHANOL-d4) δ = -121, -139, -173. LCMS (ESI, M+1): m/z 620.3.

EXAMPLE 83



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

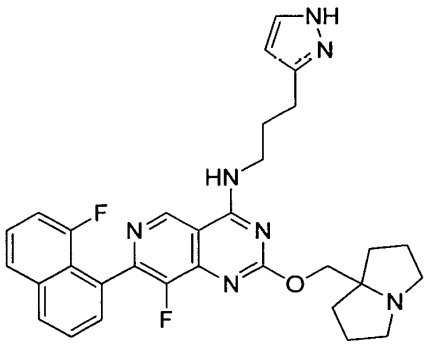


[0000593] Step A. 6-(((tert-butyldiphenylsilyl)oxy)methyl)-4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane: 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (100 mg, 189 μmol), 6-(((tert-butyldiphenylsilyl)oxy)methyl)-1,4-oxazepane (153 mg, 377 μmol, HCl) and 4Å molecular sieves

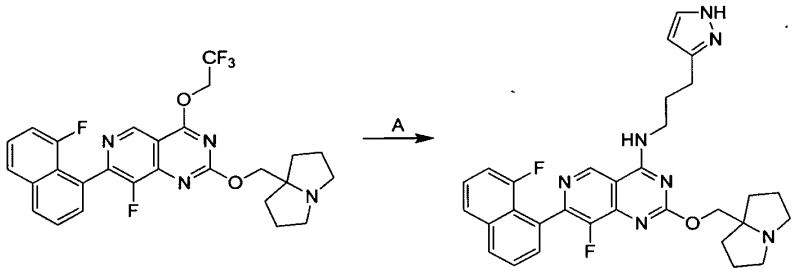
(10.0 mg) in DMF (1 mL) was added DIEA (73.1 mg, 566 μmol). The mixture was stirred at 40 °C for 12 hours. The reaction mixture was diluted water (5 mL) and was extracted with EtOAc (3 × 5.0 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography (C18, water (0.1 % formic acid)/ACN) to afford 6-(((tert-butyldiphenylsilyl)oxy)methyl)-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 (46.0 mg, 29.8% yield) as colorless oil. LCMS (ESI, M+1): m/z 800.4.

[0000594] Step B. (4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepan-6-yl)methanol: 6-(((tert-butyldiphenylsilyl)oxy)methyl)-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 (45.0 mg, 56.3 μmol) in DMF (1 mL) was added CsF (85.4 mg, 562 μmol). The mixture was stirred at 25 °C for 12 hours. The reaction solution was filtered and purified by prep-HPLC [Phenomenex Gemini-NX C18 75 × 30mm × 3μm; A: water (0.225% formic acid), B: ACN; B%: 12%-42% over 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-oxazepan-6-yl)methanol (9.78 mg, 30.7% yield) as yellow solid. ^{1}H NMR (400 MHz, METHANOL-d_4): δ 9.24 (s, 1H), 8.54 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.75-7.67 (m, 1H), 7.66-7.57 (m, 1H), 7.57-7.50 (m, 1H), 7.24-7.15 (m, 1H), 4.66 (br d, J = 14.0 Hz, 1H), 4.55-4.55 (m, 1H), 4.55-4.39 (m, 2H), 4.19-3.92 (m, 4H), 3.84 (dd, J = 10.0, 14.0 Hz, 1H), 3.68-3.55 (m, 3H), 3.52-3.40 (m, 2H), 3.12-2.99 (m, 2H), 2.59-2.44 (m, 1H), 2.28-2.17 (m, 2H), 2.16-2.02 (m, 4H), 2.00-1.92 (m, 2H); LCMS (ESI, M+1): m/z 562.3.

EXAMPLE 84

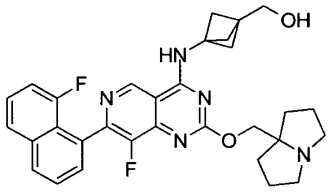


N-(3-(1H-pyrazol-3-yl) propyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl) methoxy) pyrido [4, 3-d] pyrimidin-4-amine

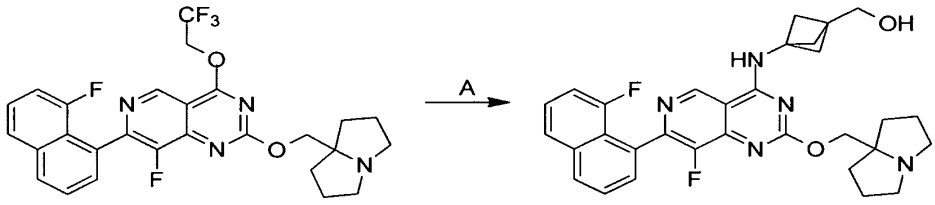


[0000595] Step A. N-(3-(1H-pyrazol-3-yl)propyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50 mg, 94.2 μmol), 3-(1H-pyrazol-3-yl)propan-1-amine (18.7 mg, 94.2 μmol, 2 HCl salt) and 4Å molecular sieves (50 mg) in DMF (0.5 mL) was added DIEA (60.9 mg, 471 μmol). The mixture was stirred at 40 °C for 16 hours under N_2. The mixture was filtered through a pad of Celite. The filtrate was poured into 10 mL water and extracted with ethyl acetate (10 mL × 2). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by reverse-phase preparatory HPLC (20% to 40% water /ACN with 0.225% formic acid formic acid over 10 minutes) to give N-(3-(1H-pyrazol-3-yl)propyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine (2.08 mg, 3.67% yield). LCMS (ESI, M+1): m/z 556.3. ^{1}H NMR (400 MHz, METHANOL-d_4) δ: 9.17 (s, 1H), 8.63-8.47 (m, 1H), 8.13 (br d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.75 - 7.67 (m, 1II), 7.59 (d, J = 6.4 Hz, 1H), 7.57-7.47 (m, 2H), 7.23-7.15 (m, 1H), 6.21 (d, J = 2.0 Hz, 1H), 4.58 (br s, 2H), 3.76 (m, 2H), 3.67-3.57 (m, 2H), 3.27-3.16 (m, 2H), 2.84 (t, J = 7.6 Hz, 2H), 2.66 (s, 1H), 2.35-2.03 (m, 10H).

EXAMPLE 85

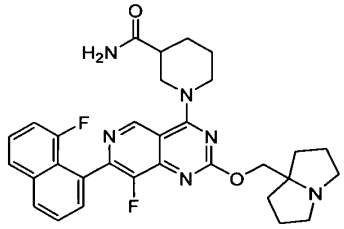


(3-((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)bicyclo[1.1.1]pentan-1-yl)methanol

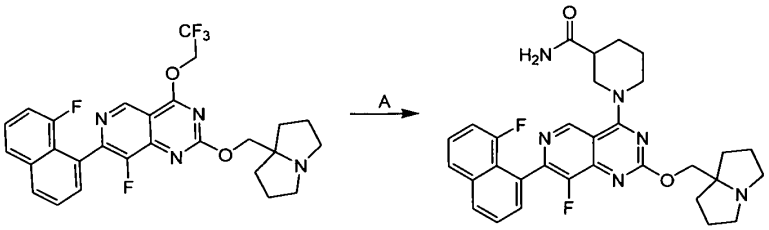


[0000596] Step A. (3-((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)bicyclo[1.1.1]pentan-1-yl)methanol: To a solution of (3-amino-1-bicyclo[1.1.1]pentanyl)methanol (9.60 mg, 84.8 μmol) and 4Å molecular sieves (20 mg) in DMF (1.0 mL) were added DIEA (36.5 mg, 283 μmol, 49.2 μL) 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 (30 mg, 56.5 μmol). The mixture was stirred at 40 °C for 12 hours. Upon completion, The reaction mixture was filtered through Celite and the filtrate was concentrated. The residue was purified by prep-HPLC (column: water s Xbridge 150×25mm× 5μm;mobile phase: [water (10mM NH_4HCO_3)-ACN];B%: 32%-62%,10min) to afford (3-((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)bicyclo[1.1.1]pentan-1-yl)methanol (9.82 mg, 32% yield) as a white solid. LCMS (ESI, M+1): m/z 544.2.

EXAMPLE 86

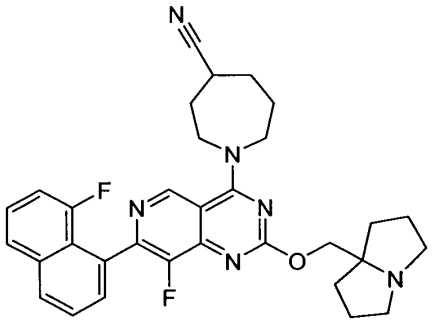


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-carboxamide

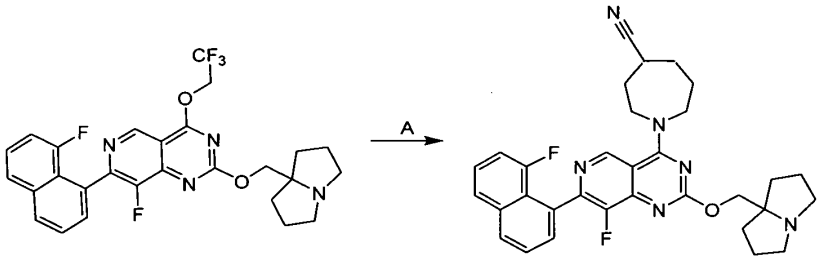


[0000597] Step A. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-carboxamide: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30 mg, 56.6 μmol), DIEA (21.9 mg, 169 μmol, 29.6 μL) and 4Å molecular sieves (1.0 mg) in DMF (1.0 mL) was added (3R)-piperidine-3-carboxamide (14.5 mg, 113 μmol). The mixture was stirred at 40 °C for 2 hours. After completion, the mixture was concentrated at 20 °C. The residue was purified by prep-HPLC [column: Shim-pack C18 Ultra 150 × 25mm × 10um; A: water (0.225% formic acid formic acid), B: ACN, B%: 17%-37% 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)piperidine-3-carboxamide (8.41 mg, 26% yield, 98.2% purity). Yellow solid; LCMS (ESI, M+1): m/z 559.3.

EXAMPLE 87

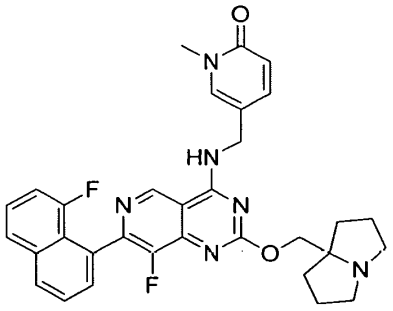


1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepane-4-carbonitrile

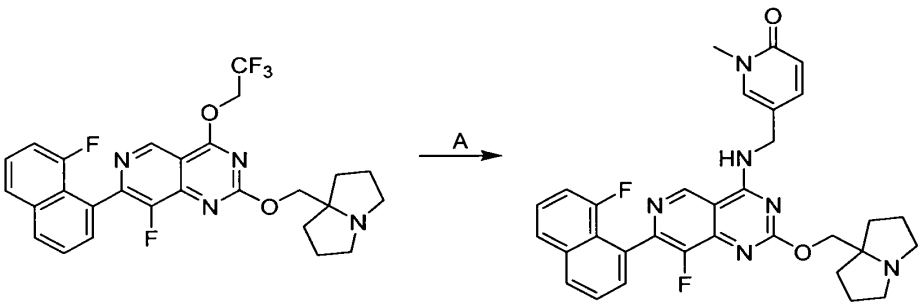


[0000598] Step A. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepane-4-carbonitrile: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30.0 mg, 56.6 μmol), DIEA (21.9 mg, 169 μmol, 29.5 μL) and 4Å molecular sieves (1.0 mg) in DMF (1.0 mL) was added (4R)-azepane-4-carbonitrile (14.1 mg, 113 μmol HCl). The mixture was stirred at 40 °C for 12 hours. After completion, the mixture was concentrated at 20 °C. The residue was purified by prep-HPLC [column: water s Xbridge C18 150 × 25mm × 5 μm; A: water (10mM NH_4HCO_3), B: ACN, B%: 30%-60% over 9min] to afford 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro- 1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepane-4-carbonitrile (3.64 mg, 12% yield, 100% purity). Yellow solid; LCMS (ESI, M+1): m/z 555.2.

EXAMPLE 88

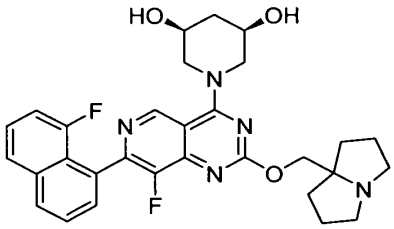


5-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)-1-methylpyridin-2(1H)-one

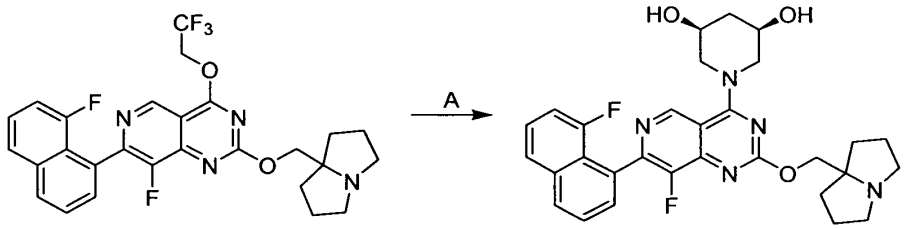


[0000599] Step A. 5-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)-1-methylpyridin-2(1H)-one: To a mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30.0 mg, 56.5 μmol) and 5-(aminomethyl)-1-methyl- pyridin-2-one (19.7 mg, 113 μmol, HCl) in DMF (1.0 mL) was added DIEA (29.2 mg, 226 μmol) and 4Å molecular sieves (30 mg) in one portion at 25 °C under N_2. The mixture was stirred at 40 °C for 12 hours. The reaction mixture was filtered and purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75*30mm*3μm;mobile phase: [water (0.225% formic acid)-ACN]; B%: 15%-45%,7min) to afford 5-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)-1-methylpyridin-2(1H)-one (12.3 mg, 22% yield); Off-white solid. LCMS (ESI, M+1): m/z 569.3.

EXAMPLE 89

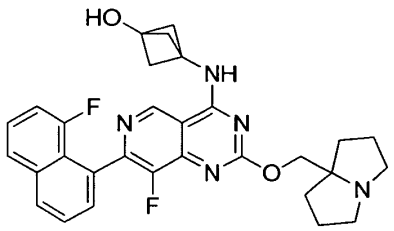


(3S,5R)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol

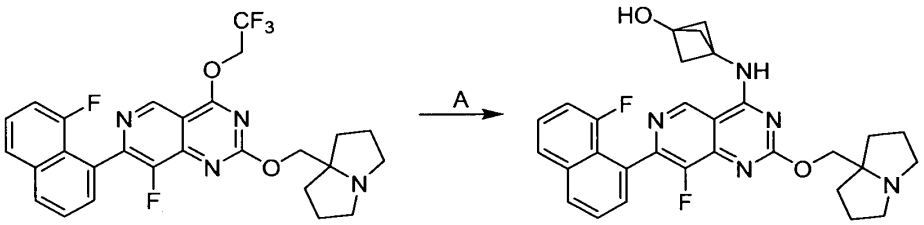


[0000600] Step A. (3S,5R)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol: To a solution of (3S,5R)-piperidine-3,5-diol (9.94 mg, 84.8 μmol) and 4Å molecular sieves (20 mg) in DMF (1.0 mL) were added DIEA (36.5 mg, 283 μmol, 49.2 μL) 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 (30 mg, 56.5 μmol). The mixture was stirred at 40 °C for 12 hours. Upon completion, the reaction mixture was filtered through Celite and the filtrate was concentrated. The residue was purified by prep-HPLC (column: water s Xbridge 150×25mm× 5μm;mobile phase: [water (10mM NH_4HCO_3)- ACN];B%: 25%-55%,10min) to afford (3S,5R)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol (13.03 mg, 42% yield, 100% purity) as a white solid. LCMS (ESI, M+1): m/z 548.2.

EXAMPLE 90

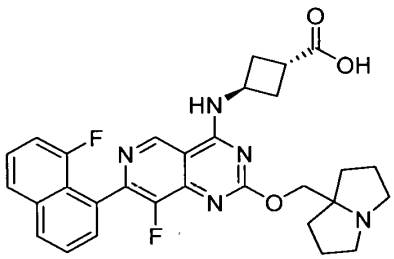


3-((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)bicyclo[1.1.1]pentan-1-ol

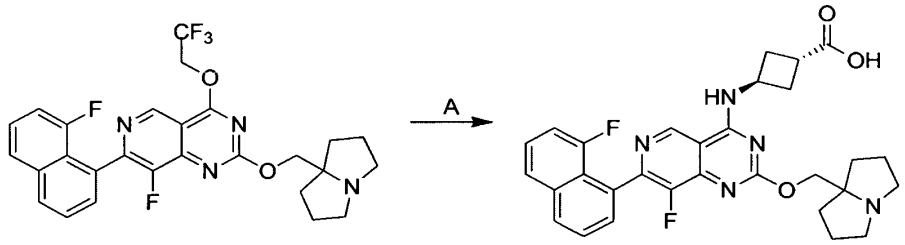


[0000601] Step A. 3-((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl) methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)bicyclo[1.1.1]pentan-1-ol: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30.0 mg, 56.5 μmol) in DMF (1.0 mL) were added DIEA (29.2 mg, 226 μmol, 39.4 μL), 4Å molecular sieves (10 mg), and 3-aminobicyclo[1.1.1]pentan-1-ol (11.2 mg, 113 μmol). The mixture was stirred at 40 °C for 12 hours. The reaction mixture was filtered and purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10μm; mobile phase: [water (0.225% formic acid)-ACN]; B%: 15%-45%, 10min) to afford 3-((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)bicyclo[1.1.1]pentan-1-ol (6.53 mg, 12.3 μmol, 100% purity); White solid. LCMS (ESI, M+1): m/z 530.3.

EXAMPLE 91

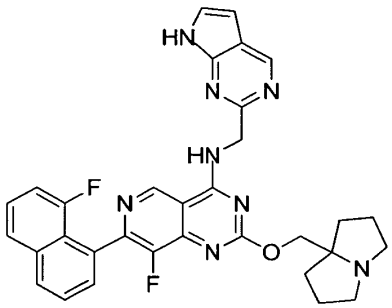


trans-3-((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)cyclobutane-1-carboxylic acid

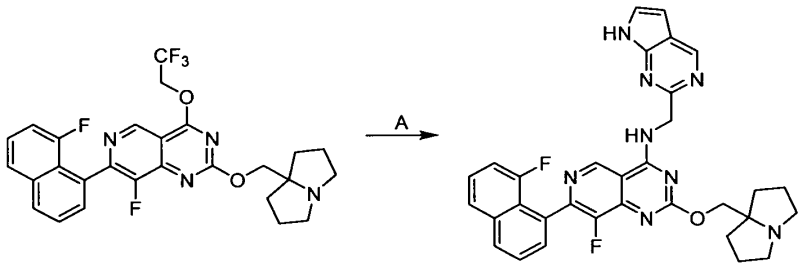


[0000602] Step A. trans-3-((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)cyclobutanecarboxylic acid: To a mixture of trans-3-aminocyclobutanecarboxylic acid (9 mg, 59.4 μmol, HCl), DIPEA (49.0 mg, 379 μmol) and 4Å molecular sieves (10 mg) in DMSO (0.8 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 (20 mg, 37.7 μmol). The mixture was stirred at 40 °C for 39 hours under N_2 atmosphere. The reaction mixture was filtered and purified by prep-HPLC (column: water s Xbridge 150 × 25mm × 5 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 14%-44%, 10 minutes) to give the product as white solid (7.35 mg, 35% yield). LCMS (ESI, M+1): m/z 546.3.

EXAMPLE 92

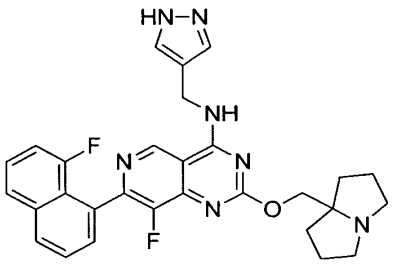


N-((7H-pyrrolo[2,3-d]pyrimidin-2-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

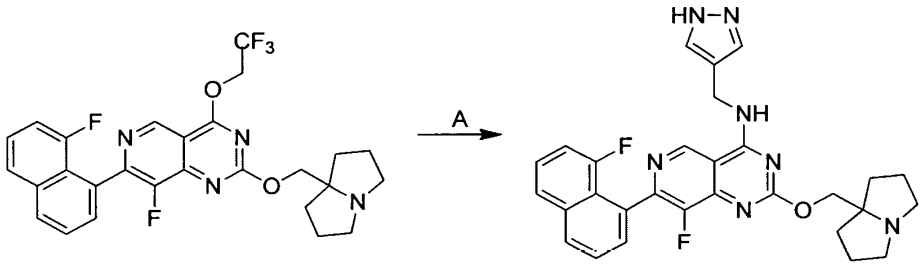


[0000603] Step A. N-((7H-pyrrolo[2,3-d]pyrimidin-2-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: To a solution of 7H-pyrrolo[2,3-d]pyrimidin-2-ylmethanamine (12.6 mg, 84.8 μmol) and 4Å molecular sieves (20 mg) in DMF (1.0 mL) were added DIEA (36.5 mg, 283 μmol, 49.25 μL) 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. The mixture was stirred at 40 °C for 12 hours. Upon completion, the reaction mixture was filtered and purified by prep-HPLC (column: water s Xbridge 150×25mm×5μm;mobile phase: [water (10mM NH4HCO3)-ACN];B%: 30%-60%,10min) to afford N-((7H-pyrrolo[2,3-d]pyrimidin-2-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine (13.53 mg, 41.3% yield, 100% purity) as an off-white solid. 1H NMR (400 MHz, METHANOL-d4) δ = 9.31 (s, 1H), 8.95 (s, 1H), 8.12 (br d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.71 (t, J = 7.7 Hz, 1H), 7.61 (d, J = 6.6 Hz, 1H), 7.54 (dt, J = 5.0, 7.9 Hz, 1H), 7.44 (d, J = 3.5 Hz, 1H), 7.20 (dd, J = 7.8, 13.0 Hz, 1H), 6.64 (d, J = 3.5 Hz, 1H), 5.19-5.08 (m, 2H), 4.24 (s, 2H), 3.29-3.21 (m, 2H), 2.97-2.84 (m, 2H), 2.06-1.92 (m, 4H), 1.90-1.72 (m, 4H). LCMS (ESI, M+1): m/z 579.3.

EXAMPLE 93

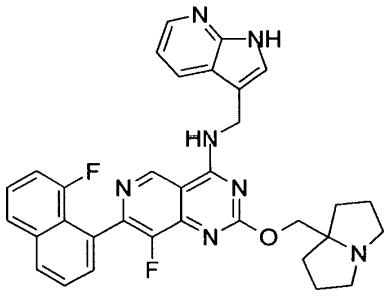


N-((1H-pyrazol-4-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

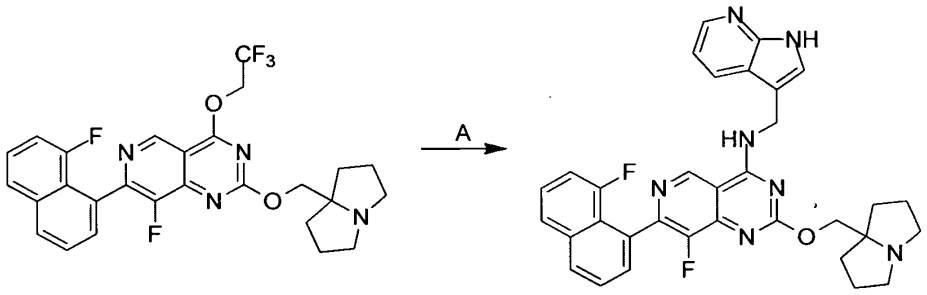


[0000604] Step A. N-((1H-pyrazol-4-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro- 1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: A mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30.0 mg, 56.5 μmol) and 1H-pyrazol-4-ylmethanamine (19.2 mg, 113 μmol, 2 HCl) in DMF (1 mL) was added DIEA (29.2 mg, 226 μmol) and 4Å molecular sieves (30 mg) in one portion at 25 °C under N_2. The mixture was stirred at 40 °C for 12 hours. The reaction mixture was filtered and the filtrate was purified. 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%, 7min) to afford N-((1H-pyrazol-4-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine (2.14 mg, 6.6% yield); Yellow solid. LCMS (ESI, M+1): m/z 528.3.

EXAMPLE 94

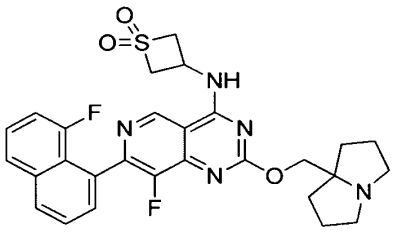


N-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

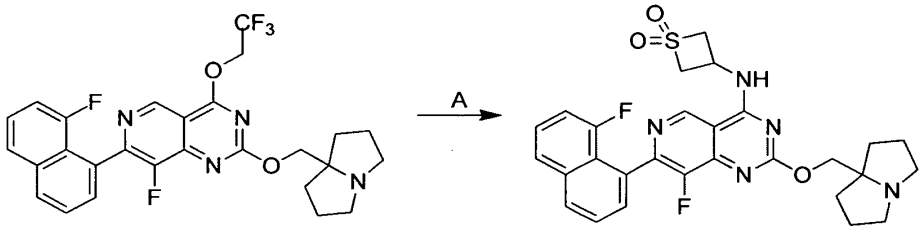


[0000605] Step A. N-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: A mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 86.6 μmol, formic acid salt), 1H-pyrrolo[2,3-b]pyridin-3-ylmethanamine (28.6 mg, 130 μmol, 2 HCl), DIEA (78.3 mg, 606 μmol, 105 μL) and 4Å molecular sieves (10 mg) in DMF (0.5 mL) was stirred at 40 °C for 16 hours. After completion, the mixture was filtered and purified by prep-HPLC (column: water s Xbridge 150×25mm× 5μm; mobile phase: [water (10mM NH_4HCO_3) - ACN]; B%: 33% - 63%, 8 min) to afford the title compound, 18% yield). White Solid. ^{1}H NMR (400 MHz, $CDCl_3$-d): δ 9.33 - 9.22 (m, 1H), 8.83 (s, 1H), 8.33 (br dd, J = 4.0, Hz, 1H), 8.00 (br dd, J = 8.0, 18.8 Hz, 2H), 7.72 (d, J = 7.6 Hz, 1H), 7.62 - 7.57 (m, 1H), 7.56 - 7.52 (m, 1H), 7.46 - 7.40 (m, 2H), 7.13 - 7.06 (m, 2H), 6.54 - 6.37 (m, 1H), 5.09 - 5.01 (m, 2H), 4.33 (s, 2H), 3.19 - 3.09 (m, 2H), 2.71 - 2.61 (m, 2H), 2.18 - 2.09 (m, 2H), 1.93 - 1.86 (m, 4H), 1.73 - 1.69 (m, 2H). LCMS (ESI, M+1): m/z 578.3.

EXAMPLE 95

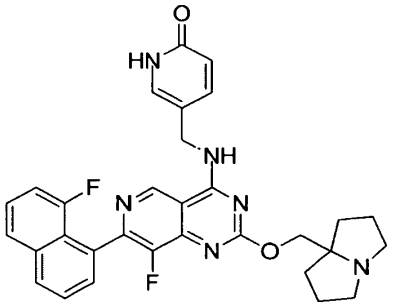


3-((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)thictanc1,1-dioxide

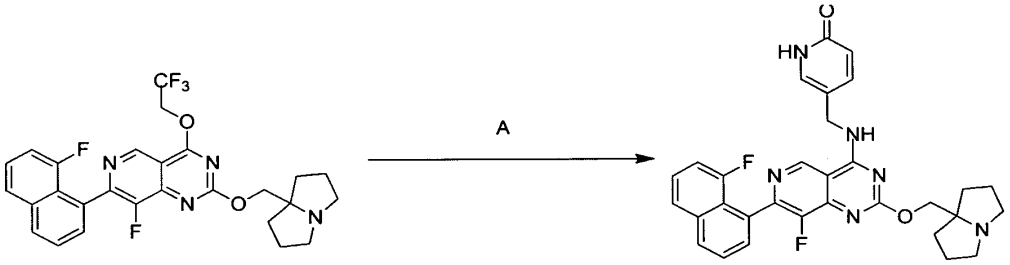


[0000606] Step A. 3-((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)thietane1,1-dioxide: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30.0 mg, 56.5 μmol) in DMF (1 mL) was added DIEA (29.2 mg, 226 μmol,39.4 μL), 4Å molecular sieves (10 mg), 1,1-dioxothietan-3-amine (13.7 mg, 113 μmol). The mixture was stirred at 60 °C for 12 hr. The reaction mixture was filtered and purified by prep-HPLC (column: Phenomenex luna C18 150×25mm×10μm; mobile phase: [water (0.225% formic acid)-ACN]; B%: 11%-47%, 11min) to afford 3-((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)thietane1,1-dioxide (3.25 mg, 5.89 μmol, 10% yield, 100% purity); White solid. LCMS (ESI, M+1): m/z 552.2.

EXAMPLE 96

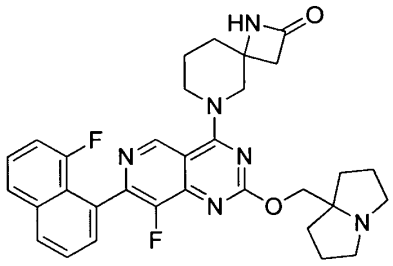


5-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyridin-2(1H)-one

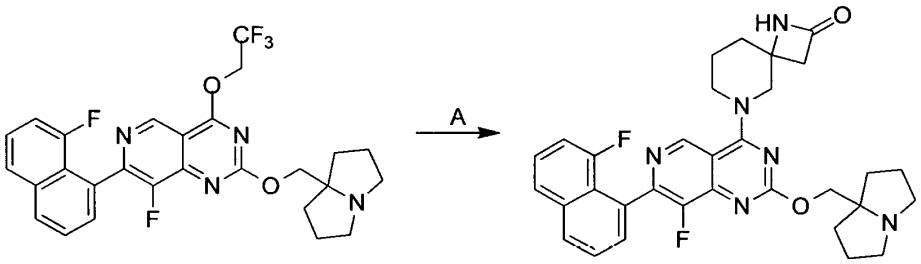


[0000607] Step A. 5-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyridin-2(1H)-one: To a mixture of 5-(aminomethyl)-1H-pyridin-2-one (10.53 mg, 84.83 μmol) and 4Å molecular sieves (20 mg) in DMF (1 mL) were added DIEA (36.54 mg, 282.75 μmol, 49.25 μL) 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 (30 mg, 56.55 μmol). The mixture was stirred at 40 °C for 12 hours. Upon completion, the reaction mixture was filtered. The residue was purified by prep-HPLC (column: water s Xbridge 150×25mm×5μm;mobile phase: [water (10mM NH_4HCO_3)-ACN];B%: 23%-53%,10min) to afford 5-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyridin-2(1H)-one (8.11 mg, 26% yield, 100% purity) as a white solid. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.15 (s, 1H), 8.11 (br d, J = 7.8 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.76 (dd, J = 2.5, 9.4 Hz, 1H), 7.69 (t, J = 7.7 Hz, 1H), 7.64-7.49 (m, 3H), 7.18 (dd, J = 7.6, 13.0 Hz, 1H), 6.57 (d, J = 9.4 Hz, 1H), 4.69 (s, 2H), 4.28 (s, 2H), 3.14-3.05 (m, 2H), 2.72 (td, J = 6.5, 10.4 Hz, 2H), 2.06 (td, J = 6.1, 12.1 Hz, 2H), 1.97-1.82 (m, 4H), 1.80-1.71 (m, 2H). LCMS (ESI, M+1): m/z 555.3.

EXAMPLE 97

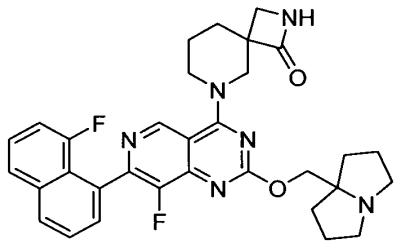


6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one

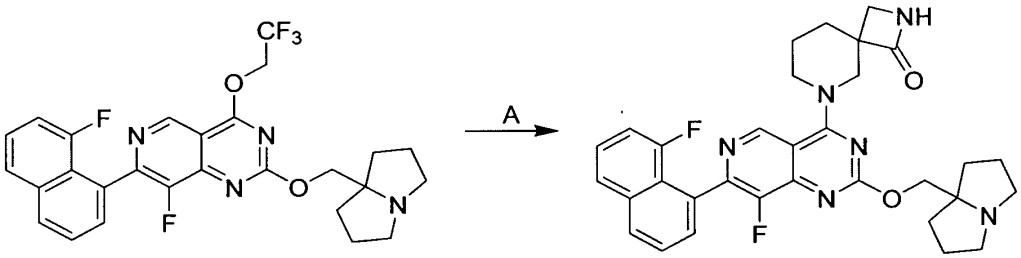


[0000608] Step A. 6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one: A solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30 mg, 56.55 μmol) in DMF (1 mL) was added DIEA (29.3 mg, 226 μmol, 39.4 μL), 4Å molecular sieves (10 mg) and 1,6-diazaspiro[3.5]nonan-2-one (15.8 mg, 113 μmol). The mixture was stirred at 60 °C for 2 hours. After completion, the mixture was filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150×40mm×15μm; mobile phase: [water (0.225% formic acid) - ACN]; B%: 15% - 45%, 10 min) to give 6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one (9.11 mg, 28% yield); White solid. ^{1}H NMR (400 MHz, METHANOL-d4) δ 9.14 (s, 1H), 8.53 (br s, 1H), 8.13 (br d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.58-7.49 (m, 1H), 7.25-7.15 (m, 1H), 4.60-7.57 (m, 2H), 4.48-4.27 (m, 2H), 4.03 (t, J = 12.8 Hz, 1H), 3.95-3.80 (m, 1H), 3.66-3.52 (m, 2H), 3.25-3.10 (m, 2H), 2.97-2.87 (m, 1H), 2.83-2.74 (m, 1H), 2.35-2.23 (m, 2H), 2.23-2.09 (m, 5H), 2.09-1.96 (m, 5H). LCMS (ESI, M+1): m/z 571.2.

EXAMPLE 98

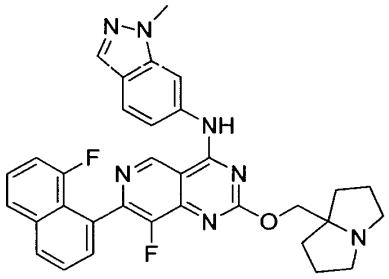


6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,6-diazaspiro[3.5]nonan-1-one

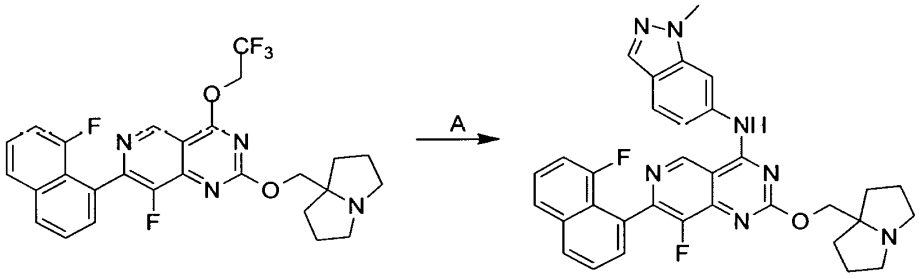


[0000609] Step A. (*S*)-6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,6-diazaspiro[3.5]nonan-1-one: To a solution 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30.0 mg, 56.5 μmol) in DMF (1 mL) was added DIEA (29.2 mg, 226 μmol, 39.4 μL), 4Å molecular sieves (10 mg) and (4*R*)-2,8-diazaspiro[3.5]nonan-3-one (15.8 mg, 113 μmol, 2.0 *equiv.)*. The mixture was stirred at 40 °C for 12 hr. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by prep-HPLC (column: water s Xbridge 150×25mm×5μm;mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 32%-62%, 10min) to afford the title compound (5.18 mg, 8.91 μmol, 16% yield, 98.1% purity); White solid. LCMS (ESI, M+1): m/z 571.3.

EXAMPLE 99

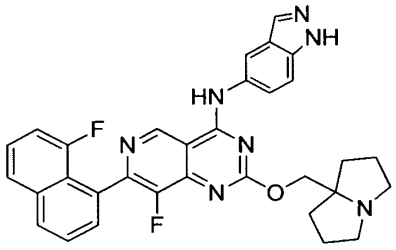


8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-(1-methyl-1H-indazol-6-yl)pyrido[4,3-d]pyrimidin-4-amine

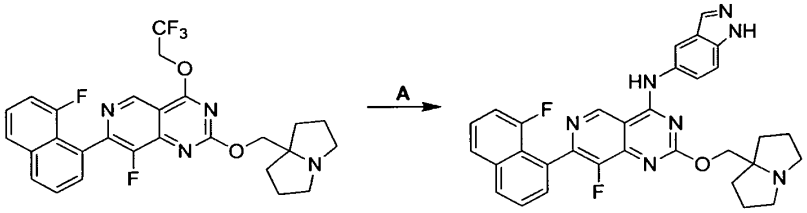


[0000610] Step A. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-(1-methyl-1H-indazol-6-yl)pyrido[4,3-d]pyrimidin-4-amine: To a mixture of 1-methylindazol-6-amine (11.1 mg, 75.4 μmol) in THF (1 mL) was added NaH (4.52 mg, 113 μmol, 60% purity) in one portion at 0 °C under N_2 for 15 minutes. Then 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 (20.0 mg, 37.7 μmol) was added at 0 °C. The mixture was stirred at 0 °C for 15 minutes. The residue was quenched with saturated NH_4Cl aqueous solution (0.1mL) dropwise, and then filtered. The filtrate was concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75×30mm×3μm;mobile phase: [water (0.225% formic acid)-ACN]; B%: 18%-48%,7min) to afford 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-(1-methyl-1H-indazol-6-yl)pyrido[4,3-d]pyrimidin-4-amine (5.29 mg, 22% yield); Off-white solid. LCMS (ESI, M+1): m/z 578.4.

EXAMPLE 100



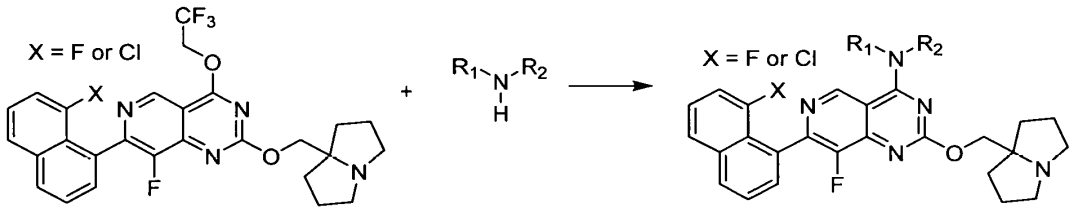
8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-(1H-indazol-5-yl)pyrido[4,3-d]pyrimidin-4-amine



[0000611] Step A. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-(1H-indazol-5-yl)pyrido[4,3-d]pyrimidin-4-amine: To the mixture of 1H-indazol-5-amine (6.93 mg, 52.0 μmol), 4Å MS (5 mg) in THF (0.5 mL) was added LiHMDS (1 M, 105 μL) at 0 °C. After 0.5 hour, to the mixture was added 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 (20.0 mg, 34.7 μmol, formic acid salt). The mixture was stirred at 20 °C for 14 hours. The reaction mixture was diluted with sat. NH_4Cl (3 mL) and extracted with ethyl acetate twice. The combined organic phase was washed with brine (5 mL), dried over anhydrous sodium sulfate. The mixture was filtered and concentrated 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 NH_4HCO_3) - ACN]; B%: 40% - 70%, 8 min) to afford 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-(1H-indazol-5-yl)pyrido[4,3-d]pyrimidin-4-amine (3.98 mg, 20% yield). Yellow Solid; LCMS (ESI, M+1): m/z 564.4.

[0000612] Synthesis of EXAMPLE 101 to 131: 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 or 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 (0.04 mmol, 1 equiv.), amine

(HNR_1R_2, 2 equiv.) and DIEA (3 eq or 5/7 eq for amine hydro/dihydro chlorides) in DMSO (1 mL) was heated with stirring at 40 °C for 16 hours. The resulting solution was cooled to room temperature and subjected to HPLC purification (deionized water /HPLC-grade acetonitrile or methanol, ammonia) to give the product.

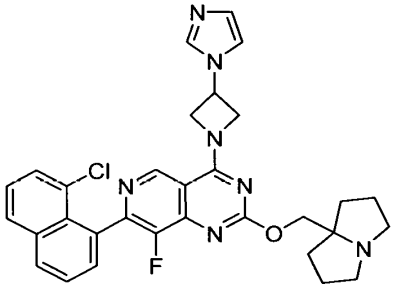


1. Table 1. Mass Spectrum Data of Example 103 to 131

Example No.	Obs. M+1	Example No.	Obs. M+1
101	570	117	562.2
102	561.2	118	557.4
103	589	119	558.2
104	584.1	120	566.2
105	575.1	121	580.2
106	574.2	122	580.2
107	562.2	123	514.2
108	599.2	124	567.2
109	598.1	125	580.2
110	547	126	569.2
111	548.4	127	566

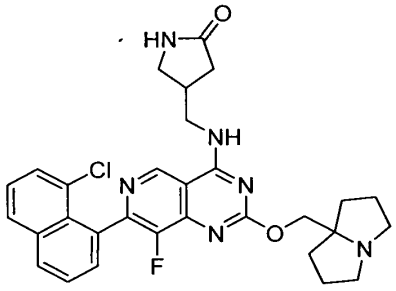
112	546.4	128	581.2
113	546.4	129	546.2
114	542.2	130	560.2
115	543.2	131	582.2
116	560.2		

EXAMPLE 101



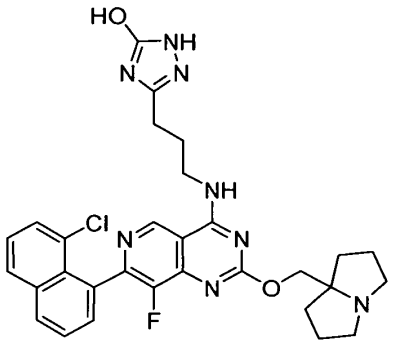
4-(3-(1H-imidazol-1-yl)azetidin-1-yl)-7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine

EXAMPLE 102



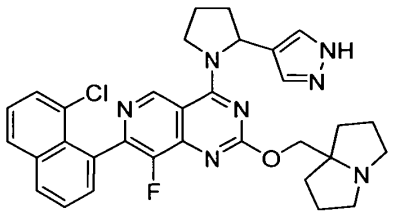
4-(((7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyrrolidin-2-one

EXAMPLE 103



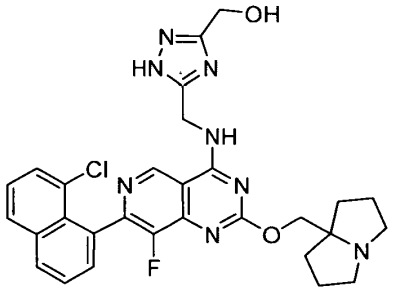
3-(3-((7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)propyl)-1H-1,2,4-triazol-5-ol

EXAMPLE 104



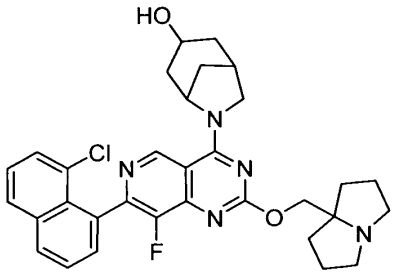
4-(2-(1H-pyrazol-4-yl)pyrrolidin-1-yl)-7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine

EXAMPLE 105



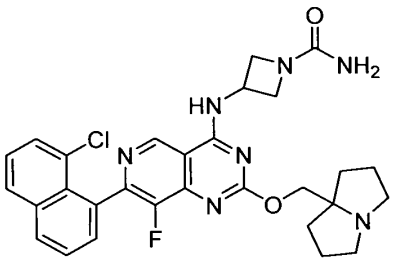
(5-(((7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)-1H-1,2,4-triazol-3-yl)methanol

EXAMPLE 106



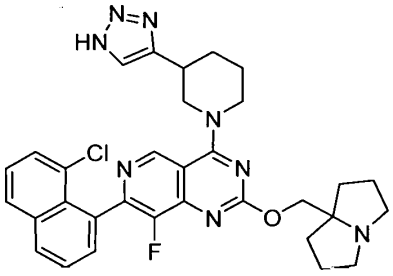
6-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol

EXAMPLE 107



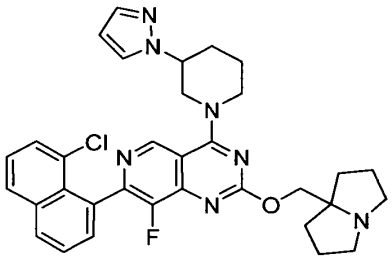
3-((7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)azetidine-1-carboxamide

EXAMPLE 108



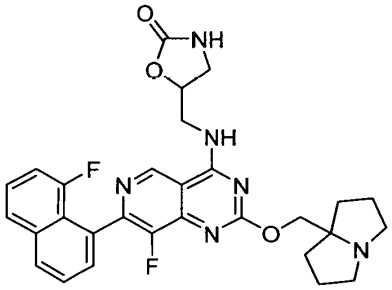
4-(3-(1H-1,2,3-triazol-4-yl)piperidin-1-yl)-7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine

EXAMPLE 109



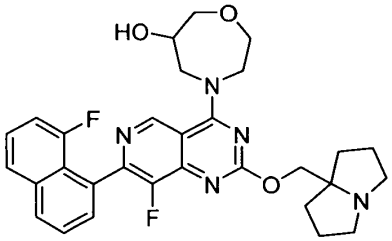
4-(3-(1H-pyrazol-1-yl)piperidin-1-yl)-7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine

EXAMPLE 110



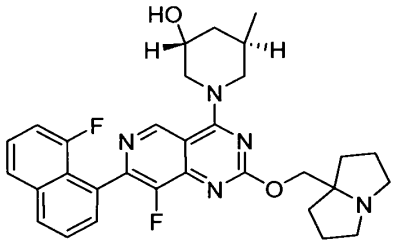
5-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)oxazolidin-2-one

EXAMPLE 111



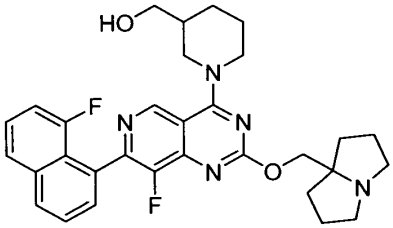
4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepan-6-ol

EXAMPLE 112



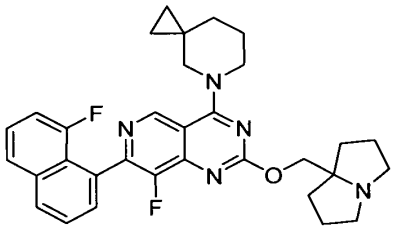
(3R,5R)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-methylpiperidin-3-ol

EXAMPLE 113



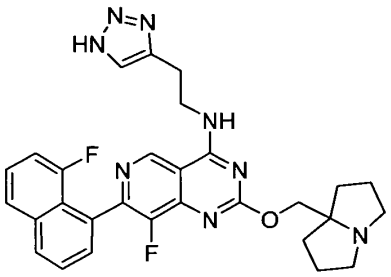
(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanol

EXAMPLE 114



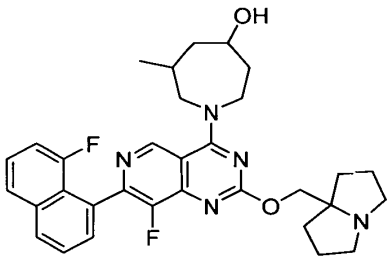
8-fluoro-7-(8-fluoronaphthalen-1-yl)-4-(5-azaspiro[2.5]octan-5-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine

EXAMPLE 115



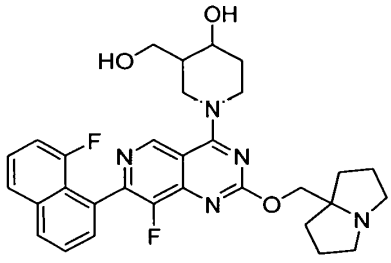
N-(2-(1H-1,2,3-triazol-4-yl)ethyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 116



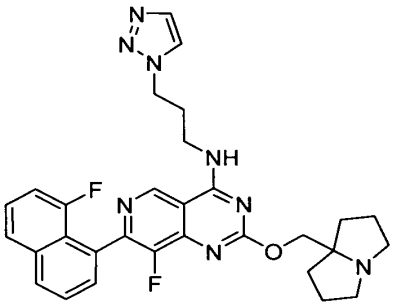
1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methylazepan-4-ol

EXAMPLE 117



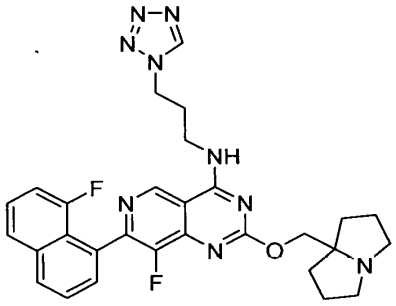
1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-(hydroxymethyl)piperidin-4-ol

EXAMPLE 118



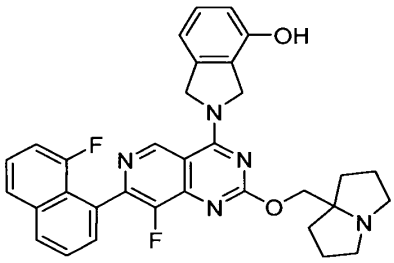
N-(3-(1H-1,2,3-triazol-1-yl)propyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 119



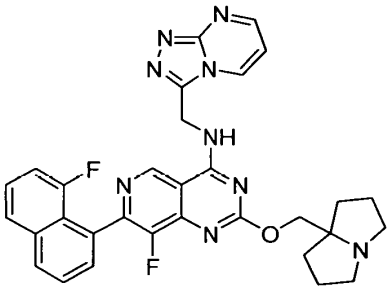
N-(3-(1H-tetrazol-1-yl)propyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 120



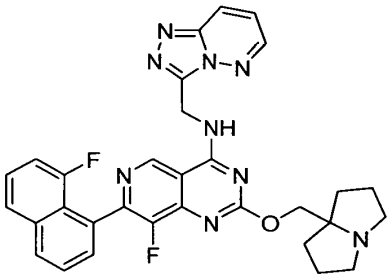
2-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)isoindolin-4-ol

EXAMPLE 121



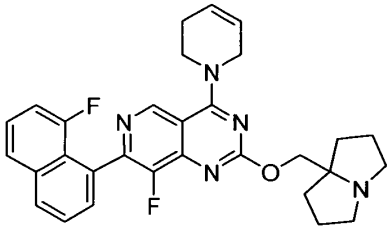
N-([1,2,4]triazolo[4,3-a]pyrimidin-3-ylmethyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 122



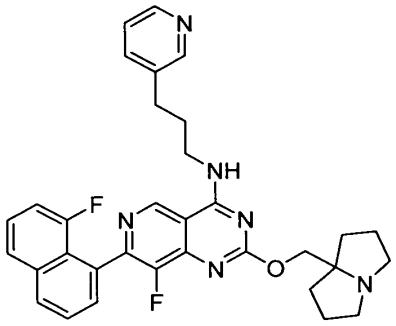
N-([1,2,4]triazolo[4,3-b]pyridazin-3-ylmethyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 123



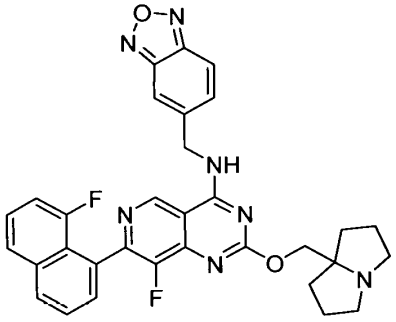
4-(3,6-dihydropyridin-1(2H)-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine

EXAMPLE 124



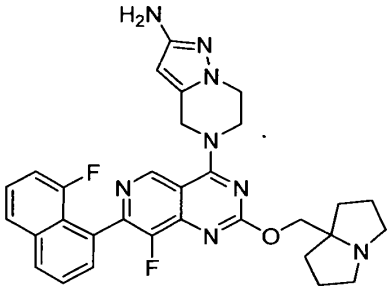
8-fluoro-7-(8-fluoronaphthalen-1-yl)-N-(3-(pyridin-3-yl)propyl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 125



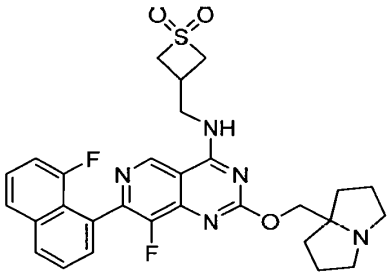
N-(benzo[c][1,2,5]oxadiazol-5-ylmethyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 126



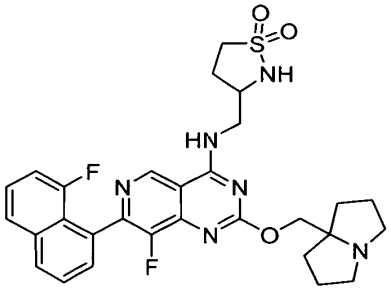
5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-2-amine

EXAMPLE 127



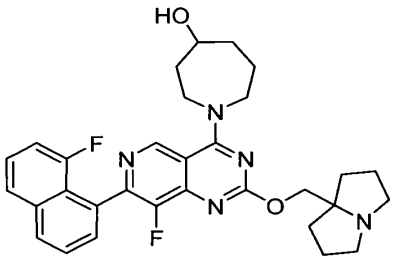
3-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)thietane 1,1-dioxide

EXAMPLE 128



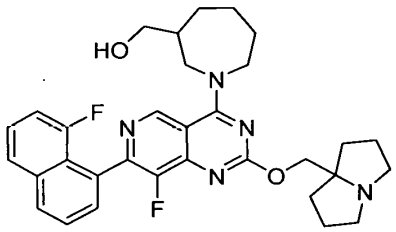
(R)-3-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)isothiazolidine 1,1-dioxide

EXAMPLE 129



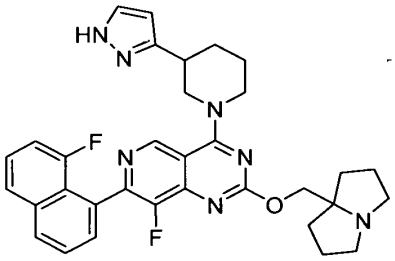
1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-ol

EXAMPLE 130



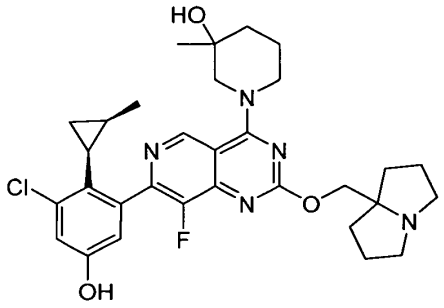
(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-3-yl)methanol

EXAMPLE 131

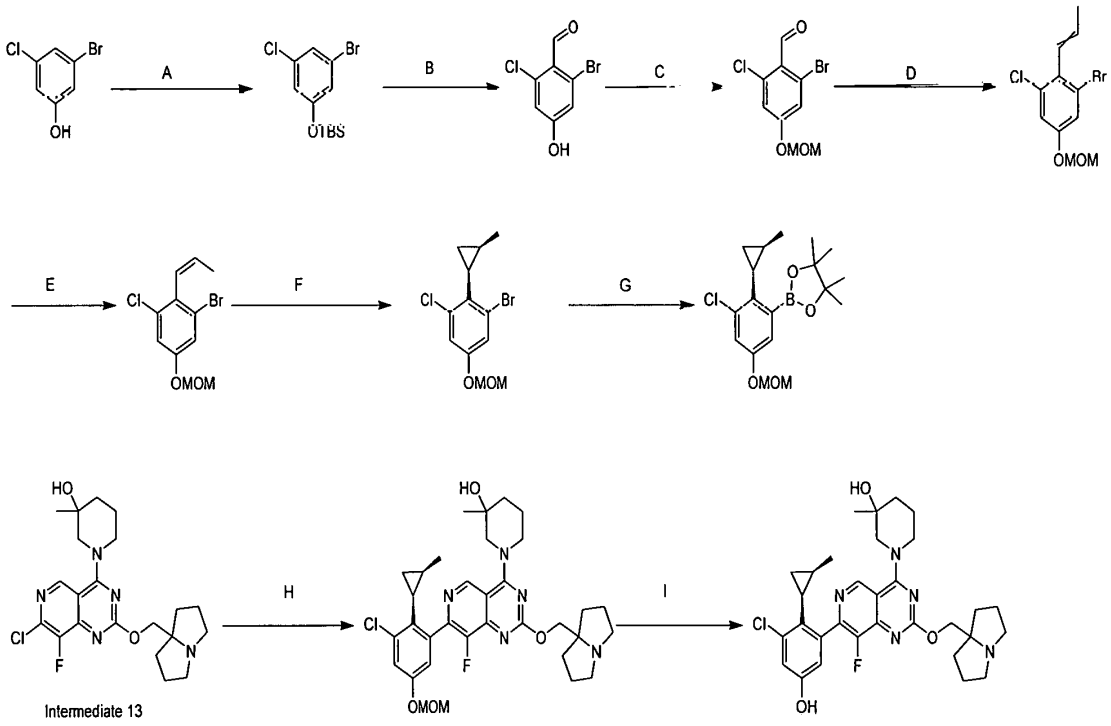


4-(3-(1H-pyrazol-3-yl)piperidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine

EXAMPLE 132



1-(7-(3-chloro-5-hydroxy-2-((1S,2R)-2-methylcyclopropyl)phenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



[0000613] Step A. (3-bromo-5-chloro-phenoxy)-tert-butyl-dimethyl-silane: To the mixture of 3-bromo-5-chlorophenol (50 g, 1.0 *equiv.*) and imidazole (36.1 g, 2.2 *equiv.*) in DMF (250 mL) was added TBSCl (40 g, 1.1 *equiv.*) at 0 °C. The reaction was stirred and allowed to warm up to 25 °C over the course of 15 hours. The mixture was diluted with water (3 L) and extracted with ethyl acetate (400 mL × 2). The combined organic layers were washed with saturated aqueous NH_4Cl solution (150 mL), dried over anhydrous Na_2SO_4, concentrated, and purified by silica gel

column chromatography (petroleum ether) to afford the title compound (89.5 g, crude) as a colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.31 (d, J = 1.6 Hz, 1H), 7.03 (t, J = 1.2 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 0.94 (s, 9H), 0.21 (s, 6H).

[0000614] Step B. 2-bromo-6-chloro-4-hydroxy-benzaldehyde: To the solution of (3-bromo-5-chloro-phenoxy)-tert-butyl-dimethyl-silane (84.5 g, crude) in THF (850 mL) was added LDA (2 M in hexane, 184 mL) dropwise at -65 °C. The reaction was stirred at -65 °C for 2 hours. DMF (40.5 mL) was added dropwise at -65 °C and the reaction was stirred at -65 °C for 0.1 hour. The mixture was quenched with 1.5 N aqueous HCl solution between -65 °C and 0 °C until the pH was 2 ~ 3 and then extracted with ethyl acetate (300 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was dispersed in petroleum ether/ethyl acetate 20:1 (210 mL), stirred for 0.5 hour and filtered. The filter cake was washed with petroleum ether (50 mL) and dried under reduced pressure to afford the title compound (42.7 g, 86% yield over two steps) as a light yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.38 (br s, 1H), 10.13 (s, 1H), 7.11 (d, J = 2.4 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H); LCMS (ESI, M+1): m/z = 236.9.

[0000615] Step C. 2-bromo-6-chloro-4-(methoxymethoxy)benzaldehyde: To the solution of 2-bromo-6-chloro-4-hydroxy-benzaldehyde (49 g, 1 *equiv.*) and DIEA (54.2 g, 2.0 *equiv.*) in DCM (500 mL) was added MOMCl (21.8 g, 1.3 *equiv.*) dropwise at 0 °C under N_2 atmosphere. The reaction was stirred between 0 °C and 15 °C for 1 hour. The mixture was quenched with saturated aqueous $NaHCO_3$ solution (100 mL) and water (100 mL) maintaining the temperature below 10 °C. The organic layer was washed with saturated aqueous NH_4Cl solution (200 mL × 5) and water (100 mL), dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography (petroleum ether / ethyl acetate 5:1 to 9:2) to afford the title compound (56 g, 94% yield) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.18 (s, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 5.36 (s, 2H), 3.40 (s, 3H).

[0000616] Step D. 1-bromo-3-chloro-5-(methoxymethoxy)-2-(prop-1-en-1-yl)benzene: To the mixture of ethyl(triphenyl)phosphonium bromide (59.8 g, 1.5 *equiv.*) in THF (350 mL) was added *t*-BuOK (1 M in THF, 140 mL, 1.3 *equiv.*) dropwise at 0 °C. The mixture was stirred between 0 and 10 °C for 1 hour. A solution of 2-bromo-6-chloro-4-(methoxymethoxy)benzaldehyde (30 g, 1.0 *equiv.*) in THF (300 mL) was added dropwise maintaining the temperature below 10 °C. The mixture was stirred between 0 and 10 °C for 0.5

hour. The mixture was quenched with water (200 mL) maintaining the temperature below 10 °C. The mixture was concentrated and extracted with ethyl acetate (100 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography (petroleum ether) to afford the title compound (30 g, 95% yield) as a light yellow liquid.

[0000617] Step E. 1-bromo-3-chloro-5-(methoxymethoxy)-2-[(Z)-prop-1-enyl]benzene: 1-bromo-3-chloro-5-(methoxymethoxy)-2-(prop-1-en-1-yl)benzene (30 g, 1 *equiv.*) was purified by prep-HPLC [column: Phenomenex luna C18 (250 × 70mm, 10 um); mobile phase: [water (0.225% Formic acid)-ACN] B%: 80%-100%, 13 min) to afford the title compound (11.5 g, 38% yield) as a light yellow liquid; ^{1}H NMR (400 MHz, chloroform-d) δ = 7.24 (d, *J* = 2.4 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 6.20-6.18 (m, 1H), 5.94 (qd, *J* = 6.8, 11.2 Hz, 1H), 5.15 (s, 2H), 3.49 (s, 3H), 1.58-1.56 (m, 3H).

[0000618] Step F. cis-1-bromo-3-chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl)benzene: To a solution of $ZnEt_2$ (1 M in n-hexane, 175 mL, 6 *equiv.*) in DCM (180 mL) was added TFA (20.0 g, 6 *equiv.*) in DCM (20 mL) dropwise at -40 °C. The reaction was stirred at -40 °C for 30 minutes. A solution of CH_2I_2 (46.9 g, 6 *equiv.*) in DCM (10 mL) was added dropwise at -40 °C and the reaction was stirred at -40 °C for 30 minutes. 1-bromo-3-chloro-5-(methoxymethoxy)-2-[(Z)-prop-1-enyl]benzene (8.5 g, 1.0 *equiv.*) in DCM (10 mL) was added dropwise at -40 °C and the reaction was stirred and allowed to warm up to 25 °C for 16 hours. The mixture was quenched with saturated aqueous $NaHCO_3$ solution maintaining the temperature below 10 °C until pH 7 ~ 8. The mixture was filtered through a pad of celite. The filter cake was washed with DCM (100 mL × 2). The layers of the filtrate were separated, and the aqueous layer was extracted with DCM (100 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified reversed phase flash chromatography (mobile phase: [water (0.1% Formic acid)/ACN 1:9]) to afford the title compound (1.5 g, 16% yield) as a yellow oil; ^{1}H NMR (400 MHz, chloroform-d) δ = 7.22 (d, *J* = 2.4 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 5.13 (s, 2H), 3.48 (s, 3H), 1.82 (dt, *J* = 6.8, 8.4 Hz, 1H), 1.58-1.56 (m, 2H), 1.54-1.37 (m, 1H), 0.85 (d, *J* = 6.0 Hz, 3H).

[0000619] Step G. cis-2-[3-chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: To a mixture of cis-1-bromo-3-chloro-5-

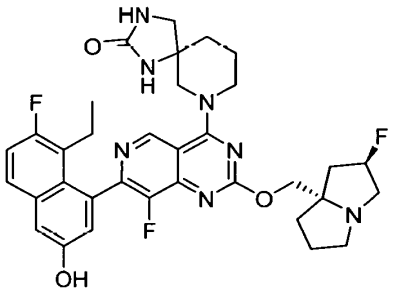
(methoxymethoxy)-2-(2-methylcyclopropyl)benzene (1.4 g, 1.0 *equiv.*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.33 g, 2.0 *equiv.*) and KOAc (1.57 g, 3.5 *equiv.*) in dioxane (22 mL) was added $Pd(dppf)Cl_2$ (336 mg, 0.1 *equiv.*). The reaction was stirred 80 °C for 5 hours under N_2 atmosphere. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (20 mL × 4). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography [petroleum ether / ethyl acetate 30:1 to 10:1]. The crude product was purified again by reversed phase flash chromatography (mobile phase: [water (0.1% Formic acid)]) to afford the title compound (0.4 g, crude) as a light yellow oil; ^1H NMR (400 MHz, chloroform-d) δ = 7.13-7.10 (m, 2H), 5.16-5.15 (m, 2H), 3.48-3.46 (m, 3H), 2.11-2.05 (m, 1H), 1.53-1.51 (m, 1H), 1.39-1.36 (m, 12H), 1.28-1.25 (m, 2H), 0.72 (d, J = 6.0 Hz, 3H); LCMS (ESI, M+1): m/z = 353.2.

[0000620] Step H. cis-1-[7-[3-chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl)phenyl]-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl]-3-methyl-piperidin-3-ol: A mixture of 1-[7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol, Intermediate 13 (65 mg, 1.0 *equiv.*), cis-2-[3-chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (95 mg, crude), cataCXium A Pd G3 (17 mg, 0.15 *equiv.*) and K_3PO_4 (1.5 M in water , 300 μL, 3 *equiv.*) in methoxycyclopentane (1.5 mL) was stirred at 90 °C for 1 hours under N_2 atmosphere. The mixture was diluted with water (1 mL) and extracted with ethyl acetate (2 mL × 4). The combined organic layers were concentrated and purified by reversed phase flash chromatography (Mobile phase: [water (0.1% formic acid) / acetonitrile 1:1] to afford the title compound (69 mg, 70% yield) as a brown solid; LCMS (ESI, M+1): m/z = 626.4.

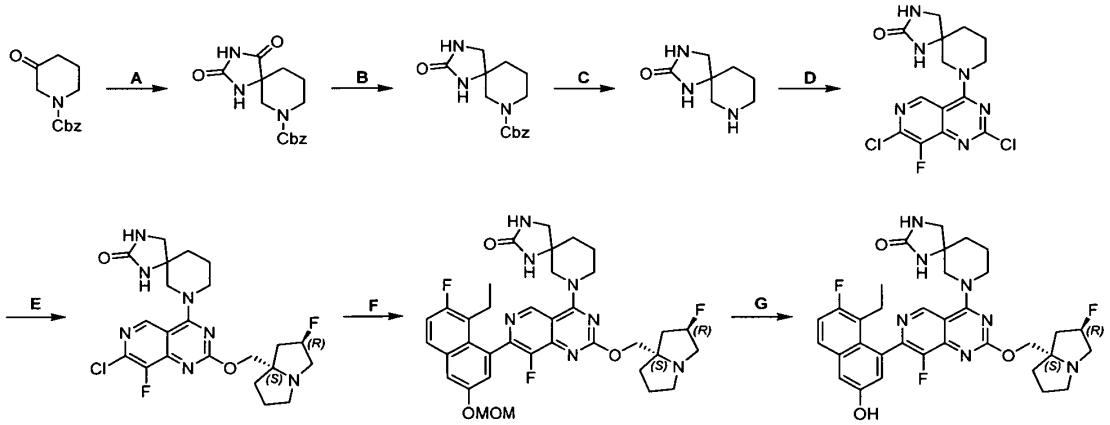
[0000621] Step I. 1-(7-(3-chloro-5-hydroxy-2-((1S,2R)-2-methylcyclopropyl)phenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To the solution of cis-1-[7-[3-chloro-5-(methoxymethoxy)-2-(2-methylcyclopropyl)phenyl]-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (69 mg, 1.0 *equiv.*) in MeCN (2 mL) was added HCl in dioxane (4 M, 1.5 mL) dropwise at 0 °C. The reaction was stirred at 0 °C for 0.5 hour. The mixture was concentrated at room temperature. The residue was dissolved in ethyl acetate (20 mL) and water (5 mL). The pH of the mixture was adjusted to 8 with $NaHCO_3$

solid maintaining the temperature below 5 °C. The mixture was extracted with ethyl acetate (10 mL × 4). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by prep-HPLC (column: water s Xbridge 150 × 25mm × 5um; mobile phase: [water (10mM NH_4HCO_3) / CAN], B%: 29%-59%, 9 min] to afford the title compound (24.9 mg, 37% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.21-9.17 (m, 1H), 7.00-6.94 (m, 1H), 6.81-6.76 (m, 1H), 4.51 (d, J = 12 Hz, 1H), 4.28-4.25 (m, 3H), 3.66-3.59 (m, 1H), 3.46-3.44 (m, 1H), 3.11-3.09 (m, 2H), 2.73 (td, J = 6.4, 10.4 Hz, 2H), 2.09-2.06 (m, 3H), 1.94-1.87 (m, 6H), 1.79-1.74 (m, 4H), 1.28-1.27 (m, 3H), 1.21-1.04 (m, 1H), 0.82 (br s, 1H), 0.65 (br d, J = 5.6 Hz, 3H), 0.52-0.15 (m, 1H); LCMS (ESI, M+1): m/z = 582.4.

yl)-8- EXAMPLE 133



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



[0000622] Step A. benzyl 2,4-dioxo-1,3,7-triazaspiro[4.5]decane-7-carboxylate: To the mixture of benzyl 3-oxopiperidine-1-carboxylate (7.00 g, 1.0 *equiv.*), $(NH_4)_2CO_3$ (8.65 g, 3.0 *equiv.*) in EtOH (35 mL) and water (35 mL) was added KCN (2.93 g, 1.5 *equiv.*), the reaction was stirred at 85 °C for 16 hours. The reaction was cooled to 25 °C and concentrated. The residue was diluted with water (300 mL), extracted with ethyl acetate (300 mL× 3). The combined organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate, concentrated to give the title compound (6.70 g, 63% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.42 - 7.19 (m, 5H), 5.19 - 4.97 (m, 2H), 3.84 (br s, 2H), 3.54 - 3.34 (m, 1H), 3.26 - 3.06 (m, 1H), 2.10 - 1.94 (m, 1H), 1.91 - 1.50 (m, 3H); LCMS (ESI, M+Na): m/z = 326.1.

[0000623] Step B. Benzyl 2-oxo-1,3,7-triazaspiro[4.5]decane-7-carboxylate: To the solution of benzyl 2,4-dioxo-1,3,7-triazaspiro[4.5]decane-7-carboxylate (1.00 g, 1.0 *equiv.*) in THF (20 mL) was added BH_3•THF (1 M in THF, 19.8 mL, 6.0 *equiv.*) at 0 °C. The reaction was then stirred at 80 °C for 2 hours. The mixture was quenched by addition of MeOH (20 mL) slowly at 0 °C and stirred at 20 °C for 0.5 hour and then concentrated. The residue was purified reversed phase flash chromatography (C18, mobile phase: [water (0.1% formic acid)/acetonitrile]) to provide the title compound (800 mg, 82% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 290.1.

[0000624] Step C. 1,3,7-triazaspiro[4.5]decan-2-one: To a solution of benzyl 2-oxo-1,3,7-triazaspiro[4.5]decane-7-carboxylate (480 mg, 1.0 *equiv.*) in *t*-BuOH (8 mL) was added $Pd(OH)_2/C$ (70 mg, 10% purity) under N_2. The suspension was degassed and purged with H_2 several times. The reaction was stirred under H_2 (15 psi) at 20 °C for 2 hours. The mixture was filtered and concentrated to give the title compound (255 mg, crude) as a white solid.

[0000625] Step D. 7-(2,7-dichloro-8-fluoropyrido[4,3-*d*]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one: To a mixture of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (500 mg, 1.0 *equiv.*), DIEA (768 mg, 3.0 *equiv.*) in dichloromethane (8 mL) was added 1,3,7-triazaspiro[4.5]decan-2-one (250 mg, 0.8 *equiv.*) at -40 °C. The reaction was stirred at -40 °C for 0.5 hour. The mixture was diluted with dichloromethane (10 mL) and water (10 mL), extracted with dichloromethane (5 mL). The combined organic phase was washed with brine (8 mL), dried over anhydrous sodium sulfate, concentrated to give the title compound (650 mg, crude) as a yellow solid.

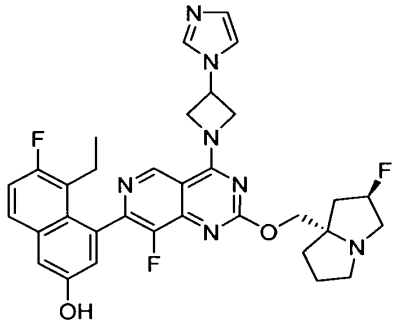
[0000626] Step E. 7-(7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one: To the mixture of 7-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one (650 mg, crude), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (502 mg), 4Å molecular sievess (300 mg) in dioxane (7 mL) was added DIEA (679 mg). The reaction was stirred at 90 °C for 12 hours. The reaction mixture was diluted with ethyl acetate (15 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (15 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated and purified reversed phase flash chromatography (C18, mobile phase: [water (0.1% formic acid)/acetonitrile]) to give the title compound (405 mg, 38% yield over three steps) as a yellow solid; ^{1}H NMR (400 MHz, chloroform-d) δ 8.74 - 8.40 (m, 1H), 5.47 - 5.21 (m, 1H), 4.61 - 4.12 (m, 4H), 3.97 - 2.74 (m, 8H), 2.51 - 2.05 (m, 4H), 2.01 - 1.56 (m, 6H); LCMS (ESI, M+1): m/z = 494.2.

[0000627] Step F. 7-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-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)-1,3,7-triazaspiro[4.5]decan-2-one (210 mg, 1.0 *equiv.*), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (184 mg, 1.2 *equiv.*), K_3PO_4 (1.5 M in water , 3.0 *equiv.*) in THF (3 mL) was added CataCXium A Pd G3 (31.0 mg, 0.1 *equiv.*) under N_2. The reaction was stirred at 60 °C for 28 hours. The reaction mixture was diluted with ethyl acetate (15 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (15 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, concentrated and purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]) and prep-HPLC [column: Phenomenex Gemini-NX C18 75×30mm×3 μm; mobile phase: [water (0.05% ammonia hydroxide v/v))/ACN], B%: 28% - 58%, 10 min] to give the title compound (9.00 mg, 3% yield) as a white solid; LCMS (ESI, M+1): m/z = 692.4.

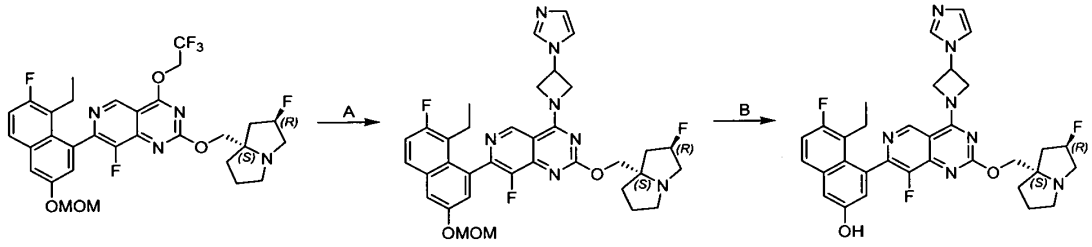
[0000628] Step G. 7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one: To the solution of 7-(7-(8-ethyl-7-fluoro-3-

(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one (8.00 mg, 1.0 *equiv.*) in MeOH (1 mL) was added HCl•dioxane (4 M, 2 mL) at 0 °C, the mixture was stirred at 0 °C for 0.5 hour. The mixture was concentrated, pH was adjusted to 7 by $NaHCO_3$ and MeOH (1 mL) was added. The residue was purified by prep-HPLC [column: Shim-pack C18 150 × 25 × 10 μm; mobile phase: [water (0.225% formic acid formic acid)/ACN], B%: 15% - 45%, 10 min] to afford the title compound (6.07 mg, 78% yield, 0.50 formic acid) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.13 (s, 1H), 7.75 - 7.61 (m, 1H), 7.36 - 7.19 (m, 2H), 7.05 (t, J = 3.2 Hz, 1H), 5.56 - 5.34 (m, 1H), 4.59 - 4.45 (m, 2H), 4.43 - 4.14 (m, 2H), 4.07 - 3.86 (m, 2H), 3.74 - 3.49 (m, 3H), 3.46 - 3.34 (m, 2H), 3.27 - 3.21 (m, 1H), 2.63 - 2.35 (m, 3H), 2.32 - 2.11 (m, 4H), 2.10 - 1.79 (m, 5H), 0.90 - 0.73 (m, 3H); LCMS (ESI, M+1): m/z = 648.3.

EXAMPLE 134



4-(4-(3-(1H-imidazol-1-yl)azetidin-1-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

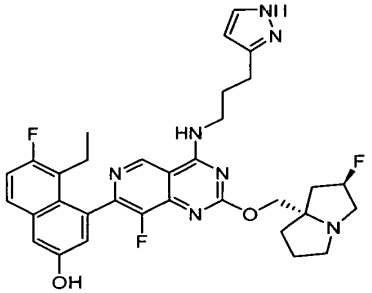


[0000629] Step A. 4-(3-(1H-imidazol-1-yl)azetidin-1-yl)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-

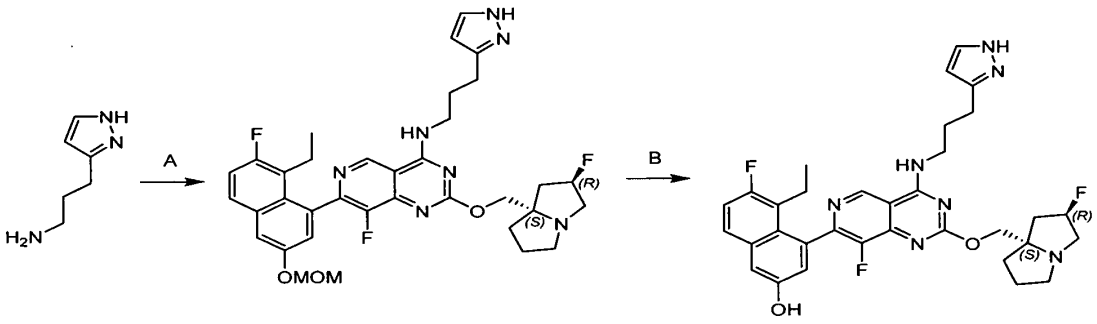
yl)methoxy)pyrido[4,3-d]pyrimidine: To the solution of 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (60.0 mg, 1.0 *equiv.*) and DIEA (60.9 mg, 5.0 *equiv.*) in DMF (2.0 mL) was added 1-(azetidin-3-yl)imidazole (18.1 mg, 1.20 *equiv.*, HCl salt). The mixture was stirred at 40 °C for 12 hours. The mixture treated with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The organic layer was washed with brine (2 × 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound (60 mg, crude) as a yellow liquid; LCMS (ESI, M+1): m/z = 660.3.

[0000630] Step B. 4-(4-(3-(1H-imidazol-1-yl)azetidin-1-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: To the solution of 4-(3-(1H-imidazol-1-yl)azetidin-1-yl)-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]pyrimidine (50.0 mg, 1.0 *equiv.*) in DCM (0.5 mL) was added TFA (7.70 g, 891 *equiv.*). The reaction was stirred at 20 °C for 0.5 hour. The mixture was concentrated. The residue was purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30mm × 3 μm; mobile phase: [water (10mM NH_4HCO_3)/ACN], B%: 34%-64%, 8min] to afford the title compound (9.23 mg, 19% yield over two steps) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ 8.96 (s, 1H), 7.97 (s, 1H), 7.68 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.58 (s, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.6 Hz, 1H), 7.11 (s, 1H), 7.04 (d, J = 2.4 Hz, 1H), 5.55-5.45 (m, 1H), 5.41-4.90 (m, 5H), 4.38-4.23 (m, 2H), 3.29-3.13 (m, 3H), 3.05-2.96 (m, 1H), 2.56-2.43 (m, 1H), 2.39-2.19 (m, 2H), 2.18-2.08 (m, 2H), 2.05-1.83 (m, 3H), 0.79 (t, *J* = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 616.4.

EXAMPLE 135



4-(4-((3-(1H-pyrazol-3-yl)propyl)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

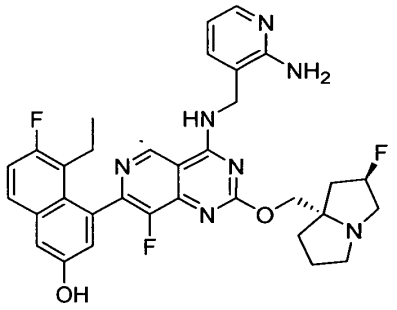


[0000631] Step A. N-(3-(1H-pyrazol-3-yl)propyl)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: To a solution of 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50 mg, 1.0 *equiv.*) and 3-(1H-pyrazol-3-yl)propan-1-amine (14.7 mg, 1.5 *equiv.*) in DMF (2 mL) was added DIEA (50.8 mg, 5 *equiv.*). The mixture was stirred at 40 °C for 16 hours. The mixture was poured into water (10 mL) and extracted with ethyl acetate (10 mL × 2). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford the title compound (40 mg, 77% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 662.4.

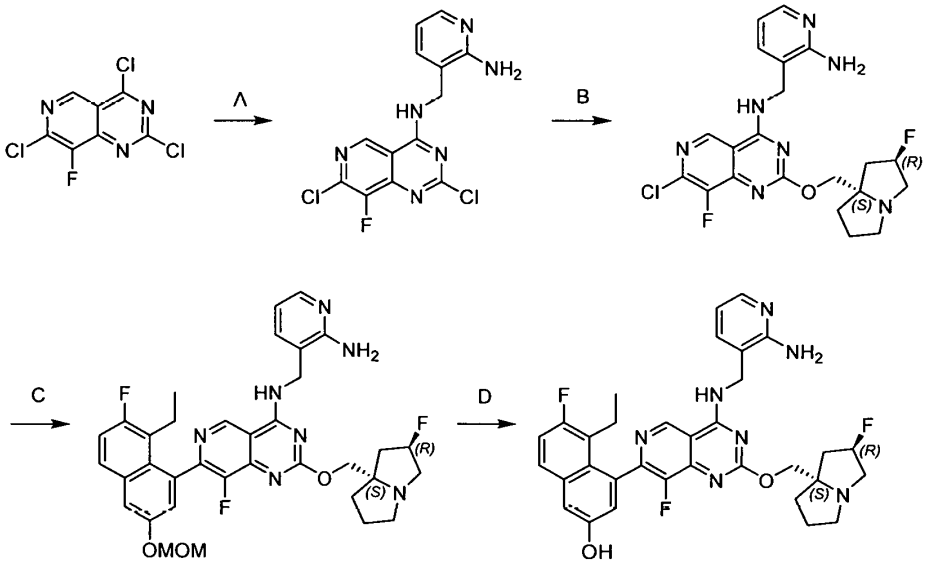
[0000632] Step B. 4-(4-((3-(1H-pyrazol-3-yl)propyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol: To a solution of N-(3-(1H-pyrazol-3-yl)propyl)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine (40 mg, 1.0 *equiv.*) in ACN (2 mL) was added HCl•dioxane (4 M, 1.36 mL, 90 *equiv.*). The mixture was stirred at 0 °C for 1 hour. The mixture was concentrated in vacuum. The residue was purified by Prep-HPLC [column: water s Xbridge 150×25mm×5 μm; mobile phase: [water (10mM NH_4HCO_3)/ACN], B%: 35%-65%, 8min) to afford the title compound (13.7 mg, 34% yield) as a white solid; ^{1}HNMR (400 MHz, methanol-d_4) δ = 9.12 (s, 1H), 7.67 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.50 (br s, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.20 (d, *J* = 1.6 Hz, 1H), 5.43 - 5.24 (m, 1H), 4.38 - 4.24

(m, 2H), 3.75 (t, *J* = 7.2 Hz, 2H), 3.25 (br s, 1H), 3.11 - 3.00 (m, 1H), 2.83 (t, *J* = 7.2 Hz, 2H), 2.54 - 1.86 (m, 12H), 0.79 (t, *J* = 7.2 Hz, 3H). LCMS (ESI, M+1): m/z = 618.3.

EXAMPLE 136



4-(4-(((2-aminopyridin-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



[0000633] Step A. N-((2-aminopyridin-3-yl)methyl)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-amine: To a mixture of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (300 mg, 1.0 *equiv.*), DIEA (461 mg, 3.0 *equiv.*) and 4Å molecular sievess (20 mg) in DCM (5 mL) was added 3-(aminomethyl)pyridin-2-amine (205 mg, 1.4 *equiv.*) at -40 °C. The mixture was stirred at

-40 °C for 1 hour. The mixture was poured into water (10 mL) and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford the title compound (150 mg, 37% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 339.1.

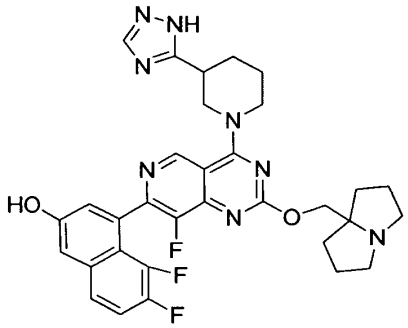
[0000634] Step B. N-((2-aminopyridin-3-yl)methyl)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: To a mixture of N-((2-aminopyridin-3-yl)methyl)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-amine (150 mg, 1.0 *equiv.*), 4Å molecular sievess (15 mg) and DIEA (172 mg, 3.0 *equiv.*) in dioxane (3 mL) was added ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (84.5 mg, 1.2 *equiv.*). The reaction was stirred at 90 °C for 12 hours. The mixture was poured into water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by reversed phase flash column chromatography (C18, mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (50 mg, 24% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 462.2.

[0000635] Step C. N-((2-aminopyridin-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: To a mixture of N-((2-aminopyridin-3-yl)methyl)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine (50 mg, 1.0 *equiv.*), 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (78.0 mg, 2.0 *equiv.*) and Cs_2CO_3 (1.5 M in water , 216 μL, 3.0 *equiv.*) in methoxycyclopentane (2.0 mL) was added cataCXium-A-Pd-G3 (15.8 mg, 0.2 *equiv.*). The reaction was stirred at 100 °C for 3 hours. The mixture was poured into water (5 mL) and extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified reversed phase flash column chromatography (C18, mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (40 mg, 56% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 660.3.

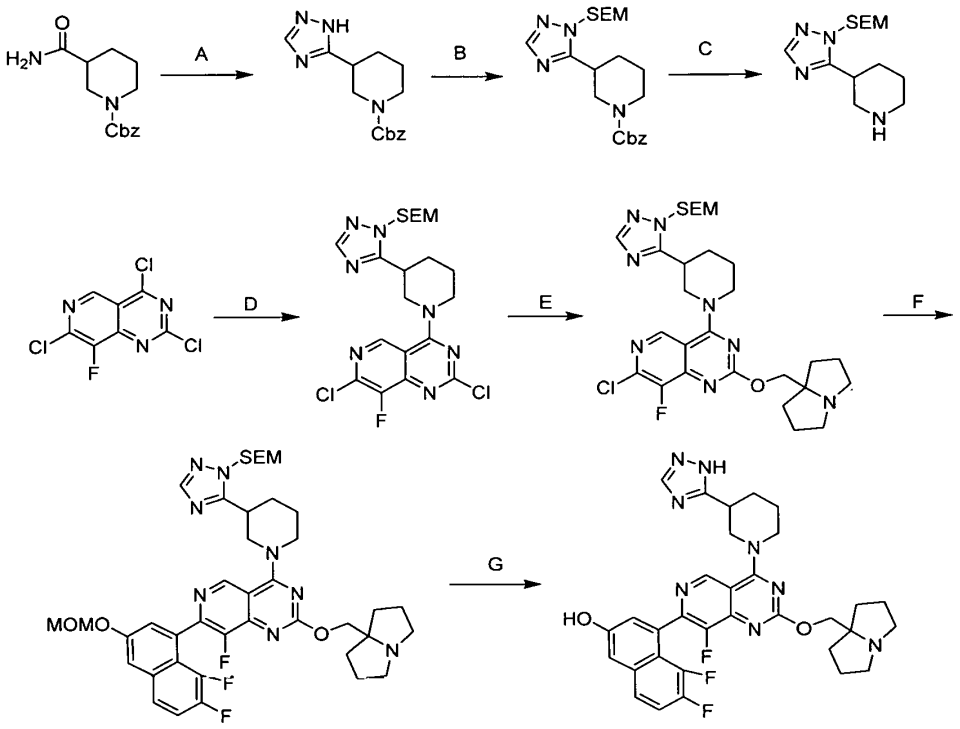
[0000636] Step D. 4-(4-(((2-aminopyridin-3-yl)methyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol: To a mixture of N-((2-aminopyridin-3-yl)methyl)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-

yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine (25.0 mg, 1.0 *equiv.*) in DCM (1 mL) was added TFA (1.54 g, 356 *equiv.*). The reaction was stirred at 20 °C for 1 hour. The mixture was concentrated. The residue was purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30mm × 3μm; mobile phase: [water (0.225% formic acid)/ACN], B%: 8%-38%, 7min] to afford the title compound (7.44 mg, 32% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.22 (s, 1H), 8.55-8.38 (m, 1H), 7.92 (br d, *J* = 5.2 Hz, 1H), 7.68 (dd, *J* = 6.0, 8.8 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.04 (s, 1H), 6.71 (dd, *J* = 5.2, 7.2 Hz, 1H), 5.57-5.32 (m, 1H), 4.76 (br s, 2H), 4.56-4.45 (m, 2H), 3.74-3.58 (m, 3H), 3.29-3.23 (m, 1H), 2.60-2.38 (m, 3H), 2.36-2.24 (m, 1H), 2.23-2.11 (m, 3H), 2.10-1.96 (m, 1H), 0.78 (t, *J* = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 616.4.

EXAMPLE 137



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



[0000637] Step A. benzyl 3-(1H-1,2,4-triazol-5-yl)piperidine-1-carboxylate: A mixture of benzyl 3-carbamoylpiperidine-1-carboxylate (5.0 g, 1.0 *equiv.*) in DMF-DMA (45.4 g, 20.0 *equiv.*) was heated to 110 °C for 2 hours. After removal of the volatiles, the residue was re-dissolved in AcOH (30 mL) and treated with N_2H_4•WATER (1.17 g, 1.20 *equiv.*). The reaction was heated to 90 °C for 1 hour. The mixture was concentrated under reduced pressure to remove AcOH. The residue was diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 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)/ACN, 0-100%]) to afford the title compound (5.30 g, 97% yield) as a white solid; LCMS (ESI, M+1): m/z = 287.2.

[0000638] Step B. benzyl 3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)piperidine-1- carboxylate: To a solution of benzyl 3-(1H-1,2,4-triazol-5-yl)piperidine-1-carboxylate (4.40 g, 1.0 *equiv.*) in THF (40 mL) was added NaH (1.23 g, 60% purity, 2.0 *equiv.*). The mixture was stirred at 0 °C for 0.5 hour before SEM-Cl (3.84 g, 1.50 *equiv.*) was added at 0 °C. The mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched by addition of

water (50 mL) at 0 °C, and extracted with ethyl acetate (3 × 50 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)/ACN, 0-100%]) to afford the title compound (3.30 g, 49% yield) as a yellow liquid; LCMS (ESI, M+1): m/z = 417.3.

[0000639] Step C. 3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)piperidine: To a solution of benzyl 3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)piperidine-1-carboxylate (3.00 g, 1.0 *equiv.*) in MeOH (20 mL) was added Pd/C (300 mg, 10% purity). The suspension was degassed in vacuum and purged with H_2 several times. The reaction was stirred under H_2 (15 psi) at 25 °C for 1 hour. The mixture was filtered and the filtrate was concentrated to afford the title compound (1.80 g, crude) as a colourless liquid.

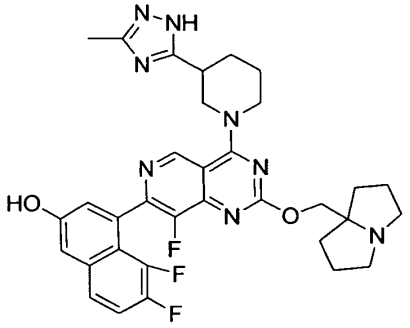
[0000640] Step D. 2,7-dichloro-8-fluoro-4-(3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)piperidine (1.51 g, 0.90 *equiv.*) in DCM (15 mL) was added DIEA (2.30 g, 3.0 *equiv.*) and 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (1.50 g, 1.0 *equiv.*) at -60 °C .The mixture was stirred at -60 °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 anhydrous sodium sulfate, concentrated, and purified by reversed phase flash chromatography (C18, mobile phase: [water (0.1% formic acid)/ACN, 0-100%]) to afford the title compound (2.30 g, 81% yield over two steps) as a yellow solid; LCMS (ESI, M+1): m/z = 498.2.

[0000641] Step E. 7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 2,7-dichloro-8-fluoro-4-(3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidine (2.00 g, 1.0 *equiv.*) in dioxane (8 mL) was added DIEA (1.56 g, 3.0 *equiv.*), 4Å molecular sievess (500 mg) and (hexahydro-1H-pyrrolizin-7a-yl)methanol (1.13 g, 2.0 *equiv.*). The reaction was stirred at 95 °C for 12 hours. The mixture was filtered. The filtrate was concentrated, and purified by reversed phase flash chromatography (C18, mobile phase: [water (0.1% formic acid)/ACN, 0-100%]) to afford the title compound (1.60 g, 66% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 603.3.

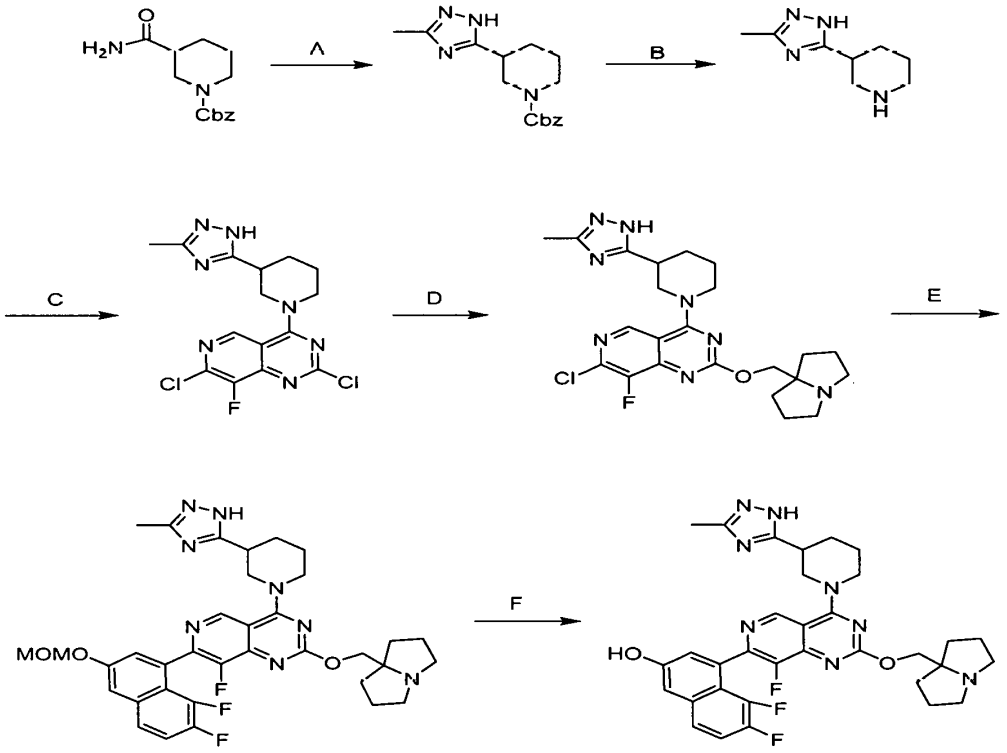
[0000642] Step F. 7-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidine: To a mixture of 7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidine (500 mg, 1.0 *equiv.*) and 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (580 mg, 2.0 *equiv.*) in THF (10 mL) was added K_3PO_4 (1.5 M, 3.0 *equiv.*) and CataCXium A Pd G3 (90.5 mg, 0.15 *equiv.*). 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 × 10 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)/ACN, 0-100%]) to afford the title compound (400 mg, 58% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 791.4.

[0000643] Step G. 4-(4-(3-(1H-1,2,4-triazol-5-yl)piperidin-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5,6-difluoronaphthalen-2-ol: To a solution of 7-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidine (200 mg, 1.0 *equiv.*) in DCM (1.0 mL) was added TEA (1.45 g, 56.8 *equiv.*). The reaction was stirred at 25 °C for 2 hours. 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 aqueous Na_2CO_3. The mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated, and purified by reversed phase flash chromatography [column: Phenomenex Gemini-NX C18 75 × 30mm × 3 μm; mobile phase: [water (0.225% formic acid)/CAN]; B%: 20%-30%, 7min] to afford the title compound (46.8 mg, 27% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ 9.12 (s, 1H), 8.33 (s, 1H), 7.77-7.66 (m, 1H), 7.61-7.50 (m, 1H), 7.43-7.35 (m, 1H), 7.28-7.20 (m, 1H), 4.77-4.63 (m, 1H), 4.51-4.40 (m, 1H), 4.39-4.26 (m, 2H), 3.57-3.51 (m, 1H), 3.30-3.17 (m, 3H), 2.94-2.81 (m, 2H), 2.27-2.17 (m, 1H), 2.08-1.72 (m, 12H). LCMS (ESI, M+1): m/z = 617.3.

EXAMPLE 138



5,6-difluoro-4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol



[0000644] Step A. benzyl 3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidine-1-carboxylate: A mixture of benzyl 3-carbamoylpiperidine-1-carboxylate (1.50 g, 1.0 *equiv.*) in 1,1-dimethoxy-N,N-dimethyl-ethanamine (15.2 g, 20.0 *equiv.*) was heated at 110 °C for 2 hours. After removal of the volatiles, the residue was re-dissolved in AcOH (3 mL). hydrazine hydrate (438 mg, 1.50

equiv.) was added, and the reaction was heated to 90 °C for 1 hour. The mixture was concentrated under reduced pressure to remove AcOH. The residue was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, concentrated, and purified by silica gel column chromatography (petroleum ether/ethyl acetate 10:1 to 1:1) to afford the title compound (1.50 g, 87% yield) as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 5.21-5.07 (m, 2H), 4.40-4.18 (m, 1H), 4.11-3.88 (m, 1H), 3.34-2.82 (m, 3H), 2.39 (s, 3H), 2.18-2.08 (m, 1H), 1.93-1.49 (m, 3H). LCMS (ESI, M+1): m/z = 301.2.

[0000645] Step B. 3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidine: To a solution of benzyl 3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidine-1-carboxylate (1.50 g, 1.0 *equiv.*) in MeOH (20 mL) was added Pd/C (200 mg, 10% purity) under N_2. The suspension was degassed in vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15psi) at 25 °C for 2 hours. The reaction mixture was filtered and the filtrate was concentrated to afford the title compound (800 mg, crude) as a by yellow liquid.

[0000646] Step C. 2,7-dichloro-8-fluoro-4-(3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidine (592 mg, 1.50 *equiv.*) in THF (20 mL) was added DIEA (921 mg, 3.0 *equiv.*) and 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (600 mg, 1.0 *equiv.*) at -60 °C. The mixture was stirred at -60 °C for 0.5 hour. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 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)/ACN, 0-100%]) to afford the title compound (600 mg, 66% yield) as yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 4.65 (br dd, J = 3.2, 13.2 Hz, 1H), 4.50-4.39 (m, 1H), 3.94 (dd, J = 9.2, 13.2 Hz, 1H), 3.74-3.62 (m, 1H), 3.32-3.20 (m, 1H), 2.48 (s, 3H), 2.37-2.26 (m, 1H), 2.19-2.10 (m, 1H), 2.04-1.98 (m, 1H), 1.92-1.79 (m, 1H); LCMS (ESI, M+1): m/z = 382.1.

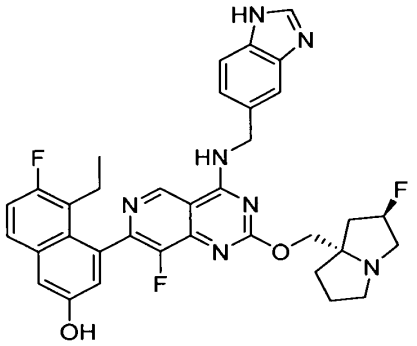
[0000647] Step D. 7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 2,7-dichloro-8-fluoro-4-(3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidine (600 mg, 1.0 *equiv.*) in dioxane (6 mL) was added DIEA (609 mg, 3.0 *equiv.*) and (hexahydro-1H-

pyrrolizin-7a-yl)methanol (665 mg, 3.0 *equiv.*). The reaction was stirred at 95 °C for 3 hours. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 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)/ACN, 0-20%]) to afford the title compound (400 mg, 47% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 487.3.

[0000648] Step E. 7-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidine (200 mg, 1.0 *equiv.*) and 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (288 mg, 2.0 *equiv.*) in methoxycyclopentane (6.0 mL) was added K_3PO_4 (1.5 M, 3.0 *equiv.*) and CataCXium A Pd G3 (44.9 mg, 0.15 *equiv.*). The reaction was stirred at 90 °C for 2 hours. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 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)/ACN, 0-20%]) to afford the title compound (80 mg, 29% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 675.4.

[0000649] Step F. 5,6-difluoro-4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol: To a solution of 5,6-difluoro-4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(3-methyl-1H-1,2,4-triazol-5-yl)piperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol (80.0 mg, 1.0 *equiv.*) in ACN (1 mL) was added HCl•dioxane (4.0 M, 72.0 *equiv.*). The reaction was stirred at 25 °C for 0.5 hour. The mixture was concentrated and purified by reversed phase HPLC [column: Phenomenex Luna C18 150 × 25mm × 10 μm; mobile phase: water (0.225% formic acid)/ACN; B%: 12%-42%, 10min] to afford the title compound (29.5 mg, 39% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.14 (s, 1H), 8.54 (s, 1H), 7.66-7.59 (m, 1H), 7.45-7.37 (m, 1H), 7.36-7.31 (m, 1H), 7.29-7.22 (m, 1H), 4.62-4.51 (m, 3H), 3.79-3.66 (m, 2H), 3.65-3.56 (m, 2H), 3.28-3.15 (m, 3H), 2.41 (s, 3H), 2.34-2.25 (m, 3H), 2.24-2.00 (m, 9H), 1.97-1.86 (m, 1H). LCMS (ESI, M+1): m/z = 631.3.

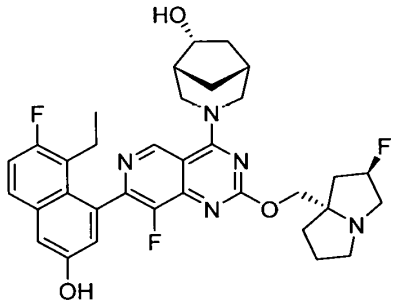
EXAMPLE 139



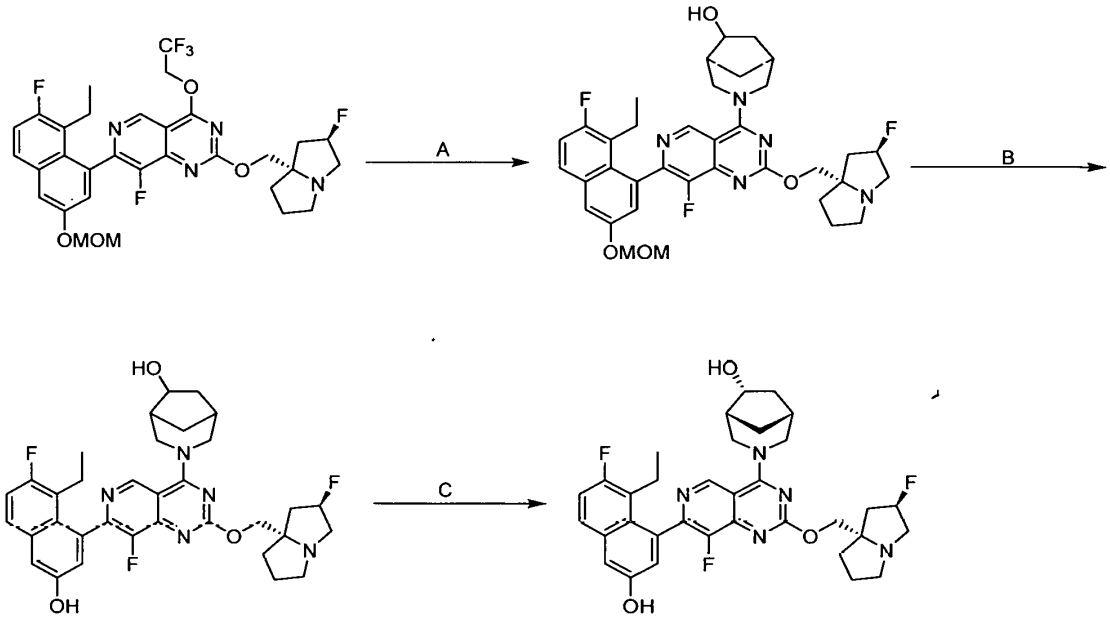
4-(4-(((1H-benzo[d]imidazol-5-yl)methyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol

[0000650] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.23 (s, 1H), 8.52 (br d, J = 1.2 Hz, 1H), 8.18 (s, 1H), 7.72 (s, 1H), 7.70-7.60 (m, 2H), 7.41 (dd, J = 1.2, 8.4 Hz, 1H), 7.32-7.22 (m, 2H), 7.04 (d, J = 2.8 Hz, 1H), 5.40-5.22 (m, 1H), 5.03 (br d, J = 1.2 Hz, 2H), 4.42-4.28 (m, 2H), 3.51-3.34 (m, 3H), 3.18-2.99 (m, 1H), 2.50-2.38 (m, 1H), 2.30-2.09 (m, 4H), 2.07-1.99 (m, 2H), 1.96-1.81 (m, 1H), 0.79 (t, J = 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 640.3.

EXAMPLE 140



3-(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-azabicyclo[3.2.1]octan-6-ol



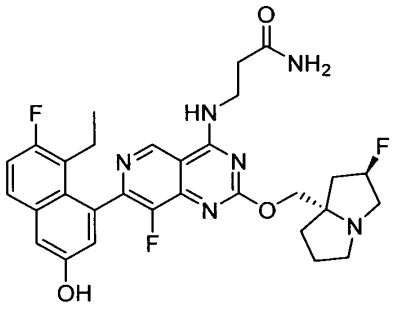
[0000651] Step A. 3-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol: A mixture of 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (130 mg, 1.0 *equiv.*, 1.7FORMIC ACID), 3-azabicyclo[3.2.1]octan-6-ol (60 mg, 2.0 *equiv.*, HCl), DIPEA (200 μL, 6.3 *equiv.*), 4Å molecular sieves (30 mg) in DMF (1.0 mL) was degassed and stirred at 40 °C for 15 hours. The mixture was filtered. The filtrate was purified reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile 11:9]) to afford the title compound (115 mg, 89% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 664.3.

[0000652] Step B. 3-(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-azabicyclo[3.2.1]octan-6-ol: To a solution of 3-(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-azabicyclo[3.2.1]octan-6-ol (142 mg, 1.0 *equiv.*) in MeCN (3.0 mL) was added HCl•dioxane (4 M, 1.5 mL). The reaction was stirred at 0 °C for 0.5 hour. The mixture was quenched with saturated aqueous $NaHCO_3$ (15 mL) and extracted with

ethyl acetate (15 mL × 4). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated and purified by prep-HPLC [column: Water s Xbridge 150 × 25 mm × 5 μm; mobile phase: [water (10mM NH_4HCO_3)/ACN]; B%: 41%-71%, 9 min] to afford the title compound (49.1 mg, 36% yield) as a white solid.

[0000653] Step C 3-(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-azabicyclo[3.2.1]octan-6-ol: 3-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7aS)-2-fluorohexahydro-1*H*-pyrrolizin-7*a*-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (72 mg, 1 *equiv.*) was purified by SFC (column: DAICEL CHIRALPAK AD (250 mm × 30 mm, 10 μm); mobile phase: [IPA-ACN]; B%: 35%-35%, 30 minutes) to give the crude product as the second eluting peak. The crude product was further re-purified by prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: [water (10mM NH_4HCO_3) /ACN]; B%: 43%-73%, 10 min] to afford the title compound (13.6 mg, 18% yield) as a white solid; SFC: >99% ee, Chiralpak AD-3 50 × 4.6 mm I.D., 3 μm column A: IPA+ACN (0.05% DEA), B: CO2, 3mL/min, tR: 0.900 min; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.24 (d, J = 19.6 Hz, 1H), 7.67 (dd, J = 6.0, 2.8 Hz, 1H), 7.31-7.30 (m, 1H), 7.26-7.21 (m, 1H), 7.09-7.03 (m, 1H), 5.39 (d, J = 53.2 Hz, 1H), 5.00-4.78 (m, 1H), 4.45-4.42 (m, 1H), 4.35-4.31 (m, 3H), 3.80 (br dd, J = 12.8, 18.8 Hz, 1H), 3.57-3.50 (m, 1H), 3.49-3.34 (m, 3H), 3.22-3.09 (m, 1H), 2.51-2.36 (m, 3H), 2.34-2.18 (m, 4H), 2.16-1.88 (m, 5H), 1.86-1.75 (m, 1H), 1.45-1.26 (m, 1H), 0.83-0.76 (m, 3H); LCMS (ESI, M+1): m/z = 620.3.

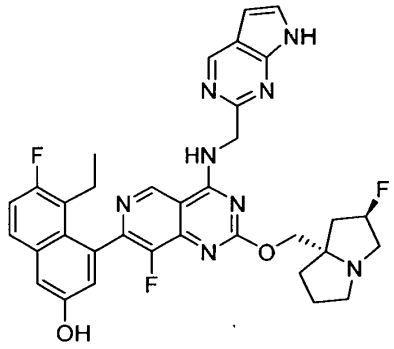
EXAMPLE 141



3-((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)amino)propenamide

[0000654] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.13 (s, 1H), 7.67 (dd, J = 6.0, 9.2 Hz, 1H), 7.30 (d, J = 2.8 Hz, 1H), 7.24 (t, J = 9.6 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 5.42-5.22 (m, 1H), 4.41-4.24 (m, 2H), 4.02-3.90 (m, 2H), 3.27-3.13 (m, 3H), 3.05-2.98 (m, 1H), 2.71 (t, J = 6.4 Hz, 2H), 2.50 (br s, 1H), 2.39-2.19 (m, 2H), 2.18-2.10 (m, 2H), 2.04-1.90 (m, 3H), 0.78 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 581.3.

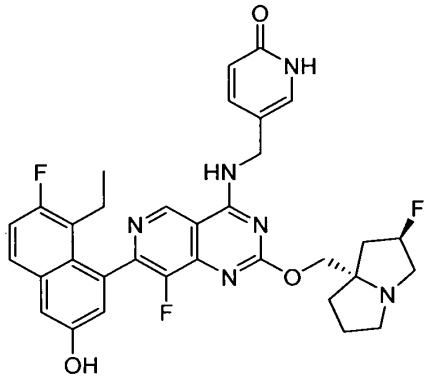
EXAMPLE 142



4-(4-(((7H-pyrrolo[2,3-d]pyrimidin-2-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

[0000655] The title compound was synthesized according to the procedure described for example 61. ^{1}H NMR (400 MHz, methanol-d$_4$): δ = 9.31 (s, 1H), 8.95 (s, 1H), 8.51 (br s, 1H), 7.69 (dd, J = 5.6, 8.8 Hz, 1H), 7.49 - 7.43 (m, 1H), 7.35 - 7.30 (m, 1H), 7.26 (t, J = 9.6 Hz, 1H), 7.06 (s, 1H), 6.65 (d, J = 3.6 Hz, 1H), 5.35 - 5.19 (m, 1H), 5.13 (s, 2H), 4.16 - 4.08 (m, 1H), 4.24 - 4.06 (m, 1H), 3.49 - 3.34 (m, 2H), 3.14 - 3.00 (m, 1H), 2.57 - 2.44 (m, 1H), 2.07 - 1.91 (m, 4H), 2.35 - 1.89 (m, 3H), 1.86 - 1.73 (m, 1H), 0.82 (br t, J = 6.8 Hz, 3H); LCMS (ESI, M+1): m/z = 641.3.

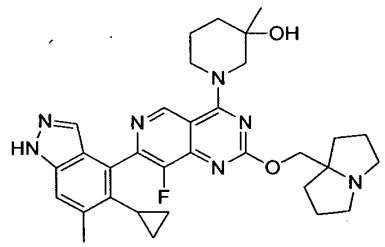
EXAMPLE 143



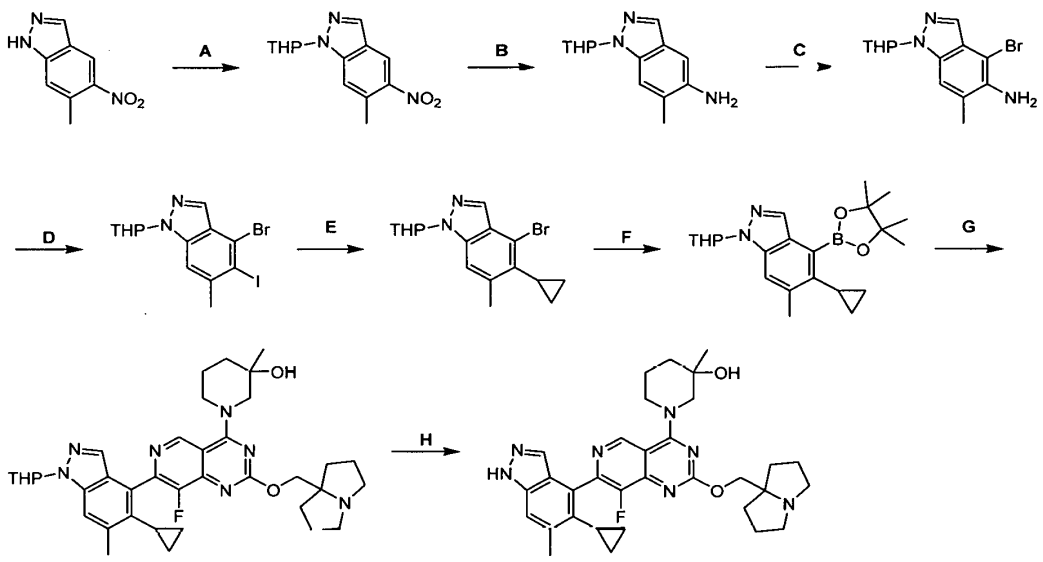
5-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)pyridin-2(1H)-one

[0000656] The title compound was synthesized according to the procedure described for example 135. ^{1}HNMR (400 MHz, methanol-d4) δ = 9.23 (s, 1H), 7.77 (dd, *J* = 2.4, 9.2 Hz, 1H), 7.69 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.26 (t, *J* = 9.2 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.58 (d, *J* = 9.2 Hz, 1H), 5.70 - 5.49 (m, 1H), 4.78 - 4.65 (m, 4H), 4.12 - 3.84 (m, 3H), 3.53 - 3.43 (m, 1H), 2.80 - 2.53 (m, 2H), 2.51 - 2.30 (m, 4H), 2.24 - 2.07 (m, 2H), 0.78 (t, *J* = 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 617.3.

EXAMPLE 144



1-(7-(5-cyclopropyl-6-methyl-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



[0000657] Step A. 6-methyl-5-nitro-1-tetrahydropyran-2-yl-indazole: To a solution of 6-methyl-5-nitro-1*H*-indazole (8.60 g, 1 *equiv.*) in DCM (86 mL) was added THP (12.5 g, 3 *equiv.*), TsOH (834 mg, 0.1 *equiv.*) and resulting mixture was stirred at 20°C for 2 hours under N_2 atmosphere. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine (1 × 100 mL), dried over anhydrous sodium sulfate, concentrated and purified by flash silica gel chromatography (ethyl acetate / petroleum 0 to 20%) to afford the title compound (12 g, 95% yield) as a yellow solid; ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.12 (s, 1H), 7.49 (s, 1H), 5.73 (dd, J = 2.7, 9.2 Hz, 1H), 4.08 - 3.95 (m, 1H), 3.81 - 3.72 (m, 1H), 2.74 (s, 3H), 2.59 - 2.46 (m, 1H), 2.21 - 2.06 (m, 2H), 1.85 - 1.69 (m, 3H).

[0000658] Step B. 6-methyl-1-tetrahydropyran-2-yl-indazol-5-amine: To a mixture of 6-methyl-5-nitro-1-tetrahydropyran-2-yl-indazole (6.00 g, 1 *equiv.*) and NH_4Cl (4.91 g, 91.9 mmol, 4 *equiv.*) in EtOH (50 mL) and water (10 mL) was added iron powder (6.41 g, 5 *equiv.*). The reaction was stirred at 80 °C for 3 hours. The mixture was filtered to remove solids. The filtrate was concentrated in vacuum. The residue was diluted with water (30 mL) and filtered. Then the filter cake was triturated with petroleum ether/ethyl acetate 50:1 (20 mL) at 25 °C for 30 min to afford the title compound (3.7 g, 70% yield) as a light red solid; ^{1}HNMR (400 MHz, CDCl3) δ 7.81 (s, 1H), 7.32 (s, 1H), 6.94 (s, 1H), 5.64 (dd, J = 2.8, 9.2 Hz, 1H), 4.10 - 3.97 (m, 1H), 3.81 -

3.70 (m, 1H), 3.69 - 3.45 (m, 2H), 2.64 - 2.47 (m, 1H), 2.35 (s, 3H), 2.22 - 2.01 (m, 2H), 1.83 - 1.72 (m, 2H), 1.70 - 1.61 (m, 1H).

[0000659] Step C. 4-bromo-6-methyl-1-tetrahydropyran-2-yl-indazol-5-amine: To a solution of 6-methyl-1-tetrahydropyran-2-yl-indazol-5-amine (4.50 g, 1 *equiv.*) in THF (130 mL) was added NBS (3.81 g, 1.1 *equiv.*). The reaction was stirred at 25°C for 2 hours under N_2 atmosphere. The mixture was diluted with water (150 mL) and extracted with ethyl acetate (2 × 150 mL). The combined organic layers were washed with brine (1 × 150 mL), dried over anhydrous sodium sulfate, concentrated and purified by flash silica gel chromatography (ethyl acetate/petroleum ether 0 to 50%) to afford the title compound (3.5 g, 57% yield) as a yellow solid; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.29 (s, 1H), 5.63 (dd, J = 2.8, 9.2 Hz, 1H), 4.07 -3.90 (m, 3H), 3.82 - 3.67 (m, 1H), 2.60 - 2.47 (m, 1H), 2.38 (d, J = 0.8 Hz, 3H), 2.20 - 2.02 (m, 2H), 1.83 - 1.63 (m, 3H).

[0000660] Step D. 4-bromo-5-iodo-6-methyl-1-tetrahydropyran-2-yl-indazole: To a solution of 4-bromo-6-methyl-1-tetrahydropyran-2-yl-indazol-5-amine (1.80 g, 1 *equiv.*) in THF (20 mL) was added CuI (1.33 g, 1.2 *equiv.*), CH_2I_2 (77.7 g, 50 *equiv.*) and isopentyl nitrite (2.04 g, 3 *equiv.*). The reaction was stirred at 70 °C for 2 hours. The mixture was diluted with water (100 mL), extracted with ethyl acetate (2 × 200 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, concentrated and purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]). The desired fractions were collected, neutralized with solid $NaHCO_3$ (5 g), concentrated in vacuum to remove acetonitrile, and extracted with dichloromethane (2 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (Silica gel, ethyl acetate/petroleum ether 3/1) to afford the title compound (1.4 g, 53% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 421.0.

[0000661] Step E. 4-bromo-5-cyclopropyl-6-methyl-1-tetrahydropyran-2-yl-indazole: A mixture of 4-bromo-5-iodo-6-methyl-1-tetrahydropyran-2-yl-indazole (500 mg, 1 *equiv.*), cyclopropylboronic acid (112 mg, 1.1 *equiv.*), K_2CO_3 (492 mg, 3 *equiv.*) and $Pd(dppf)Cl_2$ (86.9 mg, 0.1 *equiv.*) in dioxane (10 mL) and water (3 mL) was stirred at 90 °C for 24 hours under N_2. The mixture was diluted with ethyl acetate (40 mL), washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated and purified by reversed phase flash chromatography

(mobile phase: [water (0.1% formic acid)/acetonitrile]) twice to afford the title compound (350 mg, 80% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 337.0.

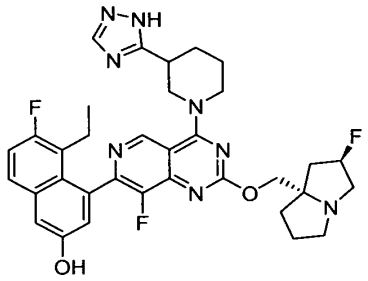
[0000662] Step F. 5-cyclopropyl-6-methyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl)indazole: A mixture of 4-bromo-5-cyclopropyl-6-methyl-1-tetrahydropyran-2-yl-indazole (140 mg, 1 *equiv.*), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (107 mg, 2 *equiv.*), PCy3 Pd G2 (24.7 mg, 0.1 *equiv.*), TEA (169 mg, 4 *equiv.*) in dioxane (1 mL) was stirred at 70 °C for 1 hour under N_2. The mixture was concentrated in vacuum. The residue was purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (35 mg, 19% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 383.3.

[0000663] Step G. 1-[7-(5-cyclopropyl-6-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-8-fluoro-2- ((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl]-3-methyl-piperidin-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 (40 mg, 1 *equiv.*), 5-cyclopropyl-6-methyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (28.1 mg, 0.8 *equiv.*), CataCXium A Pd G3 (6.68 mg, 0.1 *equiv.*), K_3PO_4 (1.5 M in water , 3 *equiv.*) in THF (1 mL) was stirred at 60 °C for 8 hours. The mixture was concentrated and purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (16 mg, 23% yield) as a yellow oil.

[0000664] Step H. 1-(7-(5-cyclopropyl-6-methyl-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 solution of 1-[7-(5-cyclopropyl-6-methyl-1-tetrahydropyran-2-yl-indazol-4-yl)-8-fluoro -2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (14 mg, 1 *equiv.*) in McCN (0.5 mL) was added HCl•dioxane (4 M, 131 *equiv.*). The reaction was stirred at 20 °C for 0.5 hour. The mixture was concentrated in vacuum, neutralized with saturated $NaHCO_3$ solution (0.5 mL), purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]) and then prep-HPLC [column: Phenomenex Synergi C18 150 × 25mm × 10 μm; mobile phase: [water (0.225% formic acid)/ACN] B%: 9% - 39%, 10min] to afford the title compound (2.89 mg, 23% yield) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 9.36 (br d, J = 4.4 Hz, 1H), 8.55 (br s, 1H), 7.74 (br s, 1H), 7.52 (s, 1H), 4.69 -

4.54 (m, 3H), 4.38 (br dd, J = 4.4, 12.8 Hz, 1H), 3.72 - 3.61 (m, 1H), 3.58 - 3.45 (m, 3H), 3.13 (br dd, J = 4.0, 4.8 Hz, 2H), 2.69 (s, 3H), 2.27 (br dd, J = 6.0, 12.0 Hz, 2H), 2.22 - 1.97 (m, 8H), 1.94 - 1.77 (m, 3H), 1.33 (br d, J = 7.6 Hz, 3H), 0.92 - 0.53 (m, 2H), 0.25 - -0.02 (m, 2H); LCMS (ESI, M+1): m/z = 572.4.

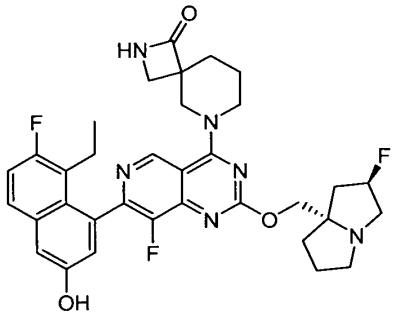
EXAMPLE 145



4-(4-(3-(1H-1,2,4-triazol-5-yl)piperidin-1-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.

[0000665] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400MHz, $CDCl_3$) δ = 13.99 - 13.61 (m, 1H), 10.16 - 9.75 (m, 1H), 9.16 - 9.02 (m, 1H), 7.83 - 7.69 (m, 1H), 7.41 - 7.26 (m, 2H), 7.09 - 6.96 (m, 1H), 5.38 - 5.16 (m, 1H), 4.82 - 4.61 (m, 1H), 4.53 - 4.34 (m, 1H), 4.23 - 4.00 (m, 2H), 3.78 - 3.53 (m, 2H), 3.13 - 2.99 (m, 3H), 2.88 - 2.79 (m, 1H), 2.45 - 2.29 (m, 2H), 2.27 - 1.69 (m, 12H), 0.81 - 0.66 (m, 3H). LCMS (ESI, M+1): m/z = 645.3.

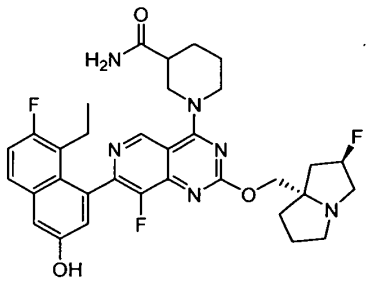
EXAMPLE 146



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)-2,6-diazaspiro[3.5]nonan-1-one

[0000666] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, methanol-d_4) δ 9.07 (s, 1H), 7.68 (dd, J = 5.6, 8.8 Hz, 1H), 7.30 (d, J = 2.8 Hz, 1H), 7.25 (t, J = 9.2 Hz, 1H), 7.06 (t, J = 2.0 Hz, 1H), 5.40 - 5.23 (m, 1H), 4.41 - 4.32 (m, 2H), 4.31 - 4.18 (m, 2H), 4.16 - 3.96 (m, 2H), 3.38 - 3.33 (m, 1H), 3.29 - 3.25 (m, 2H), 3.24 - 3.18 (m, 2H), 3.08 - 3.00 (m, 1H), 2.52 - 2.41 (m, 1H), 2.40 - 2.27 (m, 1H), 2.25 - 1.99 (m, 8H), 1.95 - 1.86 (m, 2H), 0.80 (br t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, methanol-d_4) δ -121.158, -138.976, -173.778; LCMS (ESI, M+1): m/z = 633.4.

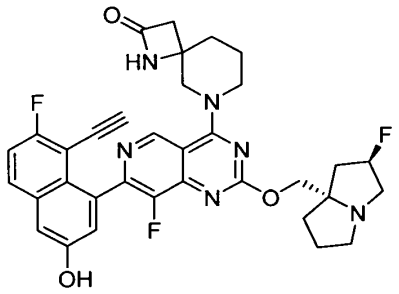
EXAMPLE 147



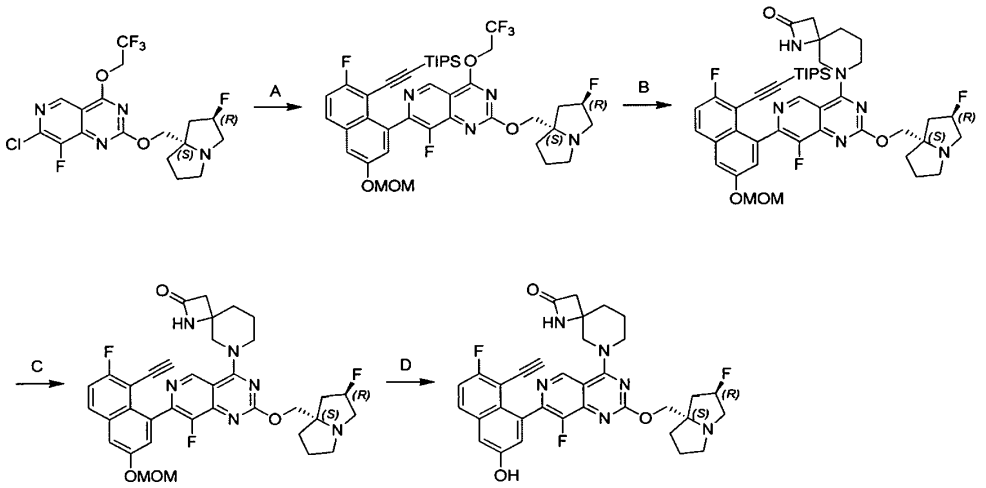
1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-carboxamide

[0000667] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.93 (br s, 1H), 9.09 (s, 1H), 7.76 (dd, J = 6.0, 9.2 Hz, 1H), 7.45 (br d, J = 4.4 Hz, 1H), 7.39-7.29 (m, 2H), 7.03 (d, J = 2.4 Hz, 1H), 6.97 (br s, 1H), 5.40-5.15 (m, 1H), 4.55-4.42 (m, 1H), 4.41-4.31 (m, 1H), 4.19-4.10 (m, 1H), 4.09-4.01 (m, 1H), 3.58-3.42 (m, 2H), 3.17-3.04 (m, 1H), 3.16-3.03 (m, 1H), 3.01 (s, 1H), 2.88-2.76 (m, 1H), 2.66-2.54 (m, 2H), 2.22-2.09 (m, 2H), 2.08-1.95 (m, 3H), 1.93-1.82 (m, 2H), 1.81-1.66 (m, 4H), 0.72 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 621.3.

EXAMPLE 148



6-(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)-1,6-diazaspiro[3.5]nonan-2-one



[0000668] Step A: 8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-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 (410 mg, 1.0 *equiv.*, formic acid salt), ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (563 mg, 1.3 *equiv.*) and Cs_2CO_3 (1.5 M in water , 1.69 mL, 3.0 *equiv.*) in methoxycyclopentane (5.1 mL) was added CataCXium A Pd G3 (61.6 mg, 0.1 *equiv.*) under N_2. The reaction was de-gassed and then heated to 100 °C for 1 hour under N_2. The mixture was poured into saturated NH_4Cl solution (10 mL). Then the mixture was diluted with ethyl acetate

(10 mL) and layers were separated. The aqueous phase was extracted with ethyl acetate (10 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to afford the title compound (547 mg, 76% yield, formic acid salt) as a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ = 9.31 - 9.27 (m, 1H), 7.81 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.55 (d, *J* = 2.4 Hz, 1H), 7.37 - 7.28 (m, 2H), 5.69 - 5.43 (m, 1H), 5.36 - 5.23 (m, 3H), 5.01 - 4.79 (m, 2H), 4.30 - 4.17 (m, 1H), 3.70 - 3.56 (m, 1H), 3.54 - 3.50 (m, 3H), 3.32 (br s, 1H), 2.92 - 2.72 (m, 2H), 2.68 - 2.55 (m, 2H), 2.42 - 2.29 (m, 4H), 0.95 - 0.80 (m, 18H), 0.70 - 0.44 (m, 3H); LCMS (ESI, M+1): m/z = 789.3.

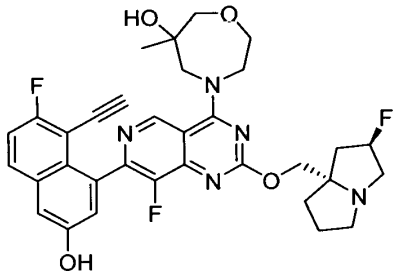
[0000669] Step B: 6-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one: A mixture of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (0.1 g, 1.0 *equiv.*, formic acid salt), 1,8-diazaspiro[3.5]nonan-2-one (58.8 mg, 3.5 *equiv.*), DIEA (46.4 mg, 3.0 *equiv.*) and 4Å molecular sievess (10 mg) in DMF (1 mL) was stirred at 40 - 60 °C for 105 hours. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (27 mg, 26% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 829.5.

[0000670] Step C: 6-(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)-1,6-diazaspiro[3.5] nonan-2-one: A mixture of 6-(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)-1,6-diazaspiro[3.5]nonan-2-one (27.0 mg, 1.0 *equiv.*) and CsF (74.2 mg, 15 *equiv.*) in DMF (0.5 mL) was stirred at 25 °C for 1 hour. The mixture was purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (15.0 mg, 68% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 673.3.

[0000671] Step D: 6-(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)-1,6-

diazaspiro[3.5] nonan-2-one: A mixture of 6-(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)-1,6-diazaspiro[3.5]nonan-2-one (15.0 mg, 1.0 *equiv.*) and TFA (462 mg, 182 *equiv.*) in dichloromethane (0.3 mL) was stirred at 25 °C for 0.5 hour. The mixture was concentrated in vacuum and the pH value was adjusted to around 8 with ice-cold saturated Na_2CO_3 solution. The mixture was diluted with ethyl acetate/methanol 7:1 (8 mL) and the layers were separated. The aqueous phase was extracted with ethyl acetate (6 mL). The combined organic layers were washed with brine (8 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC [column: water s Xbridge 150 × 25mm × 5 μm; mobile phase: [water (10 mM NH_4HCO_3)/ACN] B%: 29% - 59%, 9 min] to afford the title compound (4.50 mg, 31% yield) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.03 (d, *J* = 6.4 Hz, 1H), 7.87 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.37 - 7.30 (m, 2H), 7.22 (d, *J* = 2.4 Hz, 1H), 5.41 - 5.25 (m, 1H), 4.46 - 4.23 (m, 4H), 4.05 - 3.96 (m, 1H), 3.88 - 3.64 (m, 1H), 3.41 - 3.32 (m, 3H), 3.26 - 3.02 (m, 2H), 2.92 - 2.73 (m, 2H), 2.41 - 2.23 (m, 2H), 2.19 - 2.09 (m, 2H), 2.04 - 1.92 (m, 6H); ^{19}F NMR (376 MHz, methanol-*d*4) δ = -111.662, -139.984, -173.693; LCMS (ESI, M+1): m/z = 629.3.

EXAMPLE 149

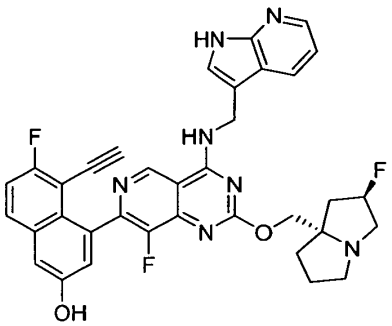


4-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol

[0000672] The title compound was synthesized according to the procedure described for example 24. ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.49 - 9.36 (m, 1H), 7.88 - 7.83 (m, 1H), 7.36 - 7.29 (m, 2H), 7.22 (dd, *J* = 2.4, 10.0 Hz, 1H), 5.39 - 5.22 (m, 1H), 4.64 - 4.45 (m, 2H), 4.35 - 4.16 (m, 3H), 4.05 - 3.84 (m, 3H), 3.74 - 3.61 (m, 2H), 3.47 - 3.41 (m, 1H), 3.29 - 3.11 (m, 3H),

3.06 - 2.98 (m, 1H), 2.40 - 2.18 (m, 2H), 2.17 - 2.09 (m, 1H), 2.05 - 1.95 (m, 2H), 1.94 - 1.85 (m, 1H), 1.27 (d, J = 13.6 Hz, 3H); ^{19}F NMR (376 MHz, methanol-d_4) δ = -111.763, -139.876, -173.658; LCMS (ESI, M+1): m/z = 620.3.

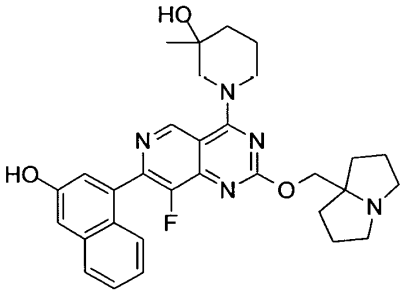
EXAMPLE 150



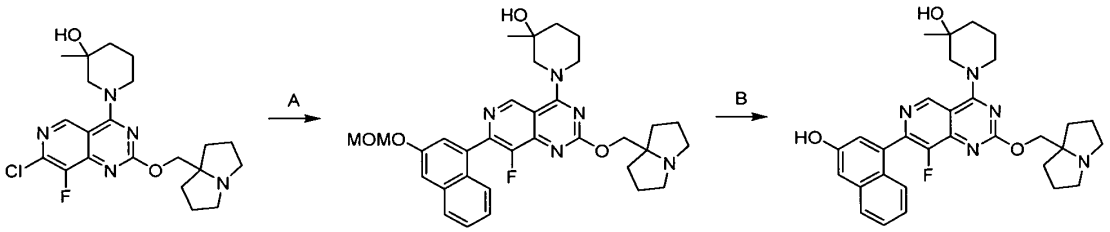
4-(4-(((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethynyl-6-fluoronaphthalen-2-ol

[0000673] The title compound was synthesized according to the procedure described for example 24. ^{1}H NMR (400 MHz, CD_3OD) δ 9.12 (s, 1H), 8.22 (s, 1H), 8.21–8.19 (m, 1H), 7.87–8.82 (m, 1H), 7.54 (s, 1H), 7.35–7.28 (m, 2H), 7.21–7.09 (m, 2H), 5.39–5.20 (d, J = 56.4 Hz,1H), 5.12–5.00 (m, 2H), 4.38–4.26 (m, 2H), 3.30–3.11 (m, 4H), 3.09–2.92 (m, 1H), 2.39–2.25 (m, 1H), 2.24–2.18 (m, 1H), 2.17–2.08 (m, 1H), 2.04–1.93 (m, 2H), 1.93–1.82 (m, 1H); LCMS (ESI, M+1): m/z = 636.4.

EXAMPLE 151



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

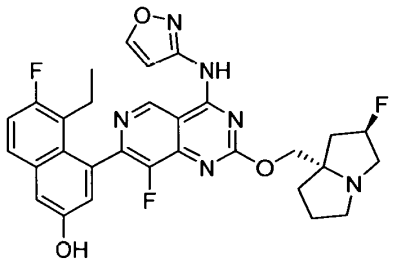


[0000674] Step A. 1-[8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-[4-(methoxymethoxy)-2-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol: To a solution of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (50 mg, 1.0 *equiv.*), 2-[3-(methoxymethoxy)-1-naphthyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (72.1 mg, 2.0 *equiv.*) and K_3PO_4 (1.5 M in water , 3.0 *equiv.*) in THF (0.5 mL) was added CataCXium A Pd G3 (8.35 mg, 0.1 *equiv.*). The mixture was degassed and stirred at 60 °C for 2 hours. Upon reaction completion, the mixture was diluted with water (5 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine 20 mL, dried over Na_2SO_4, filtered, concentrated and purified by silica gel column chromatography (ethyl acetate and then NH_4OH / MeOH 1:1000) to afford the title compound as a brown liquid (45 mg, 67% yield); LCMS (ESI, M+1): m/z = 588.3.

[0000675] Step B. 1-(8-fluoro-7-(3-hydroxynaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of 1-[8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-[4-(methoxymethoxy)-2-naphthyl]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (45 mg, 76.57 μmol, 1 *equiv.)* in MeCN (0.5 mL) was added HCl/dioxane (4 M, 0.5 mL, 26.12 *equiv.)* at 0 °C. The reaction was stirred at 0 °C for 0.5 hour. The mixture was concentrated under reduced pressure and purified by prep-HPLC (column: Phenomenex Luna C18 150×25mm×10μm; mobile phase: [water (0.225% formic acid)/ACN]; B%: 7%-37%, 11.5min) to afford the title compound as a yellow oil (26.86 mg, 59% yield, formic acid salt); ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.33 (s, 1H), 8.55 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.56 (br d, *J* = 8.0 Hz, 1H), 7.46 (dt, *J* = 1.0, 7.6 Hz, 1H), 7.32 (d, *J*

= 2.4 Hz, 1H), 7.30 - 7.24 (m, 2H), 4.66 (s, 3H), 4.38 (br d, J = 13.5 Hz, 1H), 3.72 - 3.62 (m, 3H), 3.53 - 3.40 (m, 1H), 3.28 - 3.21 (m, 2H), 2.33 (ddd, J = 3.2, 6.7, 12.4 Hz, 2H), 2.25 - 2.07 (m, 7H), 1.89 - 1.76 (m, 3H), 1.34 - 1.28 (m, 3H), 1.31 (s, 3H); ^{19}F NMR (377 MHz, METHANOL-d4) δ = -140.42; LCMS (ESI, M+1): m/z = 544.5.

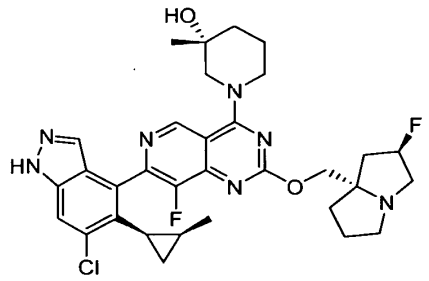
EXAMPLE 152



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

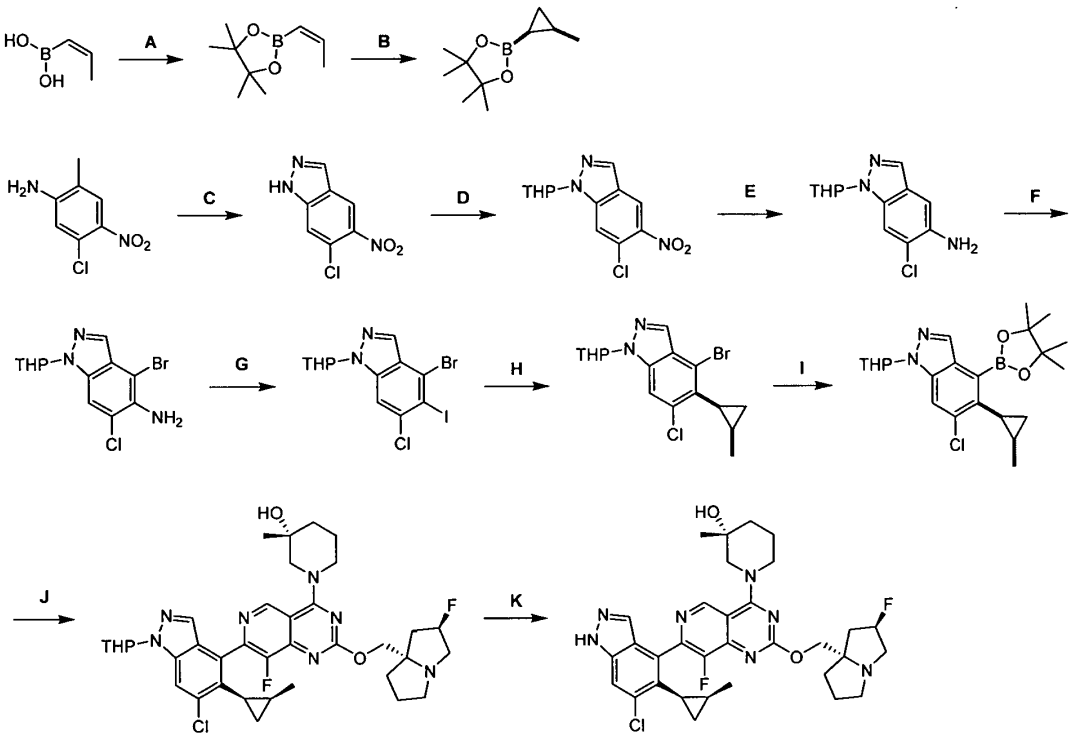
[0000676] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.50 (s, 1H), 8.70 (d, J = 1.6 Hz, 1H), 8.47 (br s, 1H), 7.69 (dd, J = 6.0, 9.2 Hz, 1H), 7.32 (d, J = 2.8 Hz, 1H), 7.30-7.22 (m, 2H), 7.07 (d, J = 2.4 Hz, 1H), 5.56-5.31 (m, 1H), 4.60-4.45 (m, 2H), 3.67-3.47 (m, 3H), 3.28-3.17 (m, 1H), 2.60-2.37 (m, 3H), 2.36-2.24 (m, 1H), 2.23-2.11 (m, 3H), 2.09-1.96 (m, 1H), 0.80 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 577.2.

EXAMPLE 153



(3R)-1-(7-(6-chloro-5-(2-methylcyclopropyl)-1H-indazol-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



[0000677] Step A. 4,4,5,5-tetramethyl-2-[(Z)-prop-1-enyl]-1,3,2-dioxaborolane: A mixture of [(Z)-prop-1-enyl]boronic acid (3.00 g, 1 *equiv.*), pinacol (4.13 g, 1 *equiv.*) and $MgSO_4$ (12.6 g, 3 *equiv.*) in DCM (30 mL) was stirred at 20 °C for 12 hours. After reaction completion, the mixture was filtered and concentrated in vacuum to afford the title compound (5 g, 85% yield) as a yellow liquid. ^1H NMR (400 MHz, $CDCl_3$-d) δ 6.59 - 6.39 (m, 1H), 5.39 - 5.27 (m, 1H), 1.97 (dd, J = 1.6, 6.8 Hz, 3H), 1.32 - 1.25 (m, 12H).

[0000678] Step B. *rac*-4,4,5,5-tetramethyl-2-[2-methylcyclopropyl]-1,3,2-dioxaborolane: To a solution of $ZnEt_2$ (2 M in hexane, 3 *equiv.*) in DCM (10 mL) was added TFA (4.07 g, 3 *equiv.*) at -40 °C. After stirred at -40 °C for 10 mins, CH_2I_2 (9.56 g, 3 *equiv.*) was added into the mixture. The reaction was stirred at -40 °C for 10 mins, 4,4,5,5-tetramethyl-2-[(Z)-prop-1-enyl]-1,3,2-dioxaborolane (2.00 g, 1 *equiv.*) was added into the mixture. The reaction was stirred at 25 °C for 16 hours. After reaction completion, the mixture was diluted with DCM (100 mL) and filtered.

The filtrate was washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to afford the title compound (2.00 g, 92% yield) as a yellow oil and used into next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 1.23 (d, J = 7.6 Hz, 12H), 1.15 - 1.11 (m, 3H), 1.10 - 1.03 (m, 1H), 0.80 - 0.71 (m, 1H), 0.40 - 0.30 (m, 1H), -0.10 (dt, J = 6.8, 9.2 Hz, 1H).

[0000679] Step C. 6-chloro-5-nitro-1*H*-indazole: To a solution of 5-chloro-2-methyl-4-nitro-aniline (10.0 g, 1 *equiv.*) in AcOH (300 mL) was added dropwise the solution of $NaNO_2$ (4.07 g, 1.1 *equiv.*) in water (40 mL) at 0°C. The reaction was stirred at 25°C for 2 hours. After completion, the mixture was poured into 1000 mL water and filtered. The filter cake was washed by 1000 mL water, then dried in vacuum to afford the title compound (8 g, 76% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.25 (s, 1H), 7.71 (s, 1H).

[0000680] Step D. 6-chloro-5-nitro-1-tetrahydropyran-2-yl-indazole: To a solution of 6-chloro-5-nitro-1*H*-indazole (6.6 g, 1 *equiv.*) in DCM (60 mL) was added $TsOH•H_2O$ (635 mg, 0.1 *equiv.*), then 3,4-dihydro-2*H*-pyran (8.43 g, 3 *equiv.*) slowly at 25°C. The mixture was stirred at 25°C for 1 hour before being concentrated in vacuum and purified by flash silica gel chromatography (ethyl acetate in petroleum ether 0-30%) to afford the title compound (7.20 g, 76% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.15 (s, 1H), 7.81 (s, 1H), 5.73 (dd, J = 2.4, 8.9 Hz, 1H), 4.06 - 3.97 (m, 1H), 3.82 - 3.71 (m, 1H), 2.55 - 2.41 (m, 1H), 2.22 - 2.08 (m, 2H), 1.90 - 1.64 (m, 4H).

[0000681] Step E. 6-chloro-1-tetrahydropyran-2-yl-indazol-5-amine: To a solution of 6-chloro-5-nitro-1-tetrahydropyran-2-yl-indazole (7.2 g, 1 *equiv.*) in EtOH (80 mL) and water (16 mL) was added NH_4Cl (5.74 g, 4.2 *equiv.*) and iron powder (5.99 g, 4.2 *equiv.*). The reaction was stirred at 80°C for 6 hours. After completion, the mixture was filtered, the filtrate was concentrated and purified by flash silica gel chromatography (ethyl acetate in petroleum ether 0-30%) to afford the title compound (6 g, 93% yield) as a yellow solid. ^{1}H NMR (400 MHz, CDCl3) δ 7.80 (s, 1H), 7.59 (s, 1H), 7.00 (s, 1H), 5.59 (dd, J = 2.4, 9.3 Hz, 1H), 4.06 - 3.92 (m, 3H), 3.80 - 3.69 (m, 1H), 2.58 - 2.44 (m, 1H), 2.18 - 2.05 (m, 2H), 1.81 - 1.57 (m, 4H).

[0000682] Step F. 4-bromo-6-chloro-1-tetrahydropyran-2-yl-indazol-5-amine: To a solution of 6-chloro-1-tetrahydropyran-2-yl-indazol-5-amine (6.10 g, 1 *equiv.*) in THF (120 mL) was added

NBS (5.18 g, 1.2 *equiv.*). The reaction was stirred at 25°C for 2 hours. After completion, the mixture was filtered and the filtrate was concentrated in vacuum and purified by flash silica gel chromatography (ethyl acetate in petroleum ether 0-30%) to afford the title compound (3 g, 34% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 0.8 Hz, 1H), 7.59 (s, 1H), 5.60 (dd, J = 2.8, 9.2 Hz, 1H), 4.37 (br s,2H), 4.04 - 3.96 (m, 1H), 3.80 - 3.66 (m, 1H), 2.52 - 2.41 (m, 1H), 2.22 - 2.09 (m, 2H), 1.84 - 1.66 (m, 4H).

[0000683] Step G. 4-bromo-6-chloro-5-iodo-1-tetrahydropyran-2-yl-indazole: A reaction mixture of 4-bromo-6-chloro-1-tetrahydropyran-2-yl-indazol-5-amine (2.40 g, 1 *equiv.*), CuI (1.80 g, 1.3 *equiv.*), isopentyl nitrite (2.55 g, 3 *equiv.*) and CH_2I_2 (97.2 g, 50 *equiv.*) in THF (20 mL) was stirred at 70 °C for 2 hours. After completion, the mixture was diluted with water (100 mL), extracted with ethyl acetate (2 × 200 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, concentrated in vacuum and purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]). The desired fractions were collected, neutralized with solid $NaHCO_3$ (5 g), concentrated in vacuum to remove acetonitrile, and extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography (ethyl acetate in petroleum ether 30%) to afford the title compound (1.05 g, 32% yield) as a yellow solid. LCMS (ESI, M-84): m/z = 358.8.

[0000684] Step H. 4-bromo-6-chloro-5-[2-methylcyclopropyl]-1-tetrahydropyran-2-yl-indazole: To a solution of 4-bromo-6-chloro-5-iodo-1-tetrahydropyran-2-yl-indazole (500 mg, 1 *equiv.*), 4,4,5,5-tetramethyl-2-[2-methylcyclopropyl]-1,3,2-dioxaborolane (309 mg, 1.5 *equiv.*) in dioxane (10 mL) and water (3 mL) was added K_2CO_3 (469 mg, 3 *equiv.*) and $Pd(dppf)Cl_2$ (82.9 mg, 0.1 *equiv.*). The reaction was stirred at 90 °C for 12 hours. After completion, the mixture was diluted with ethyl acetate (40 mL), washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated and purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (90 mg, 21% yield) as a yellow oil. LCMS (ESI, M-84): m/z = 286.9.

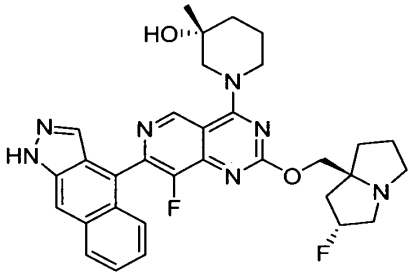
[0000685] Step I. 6-chloro-5-[2-methylcyclopropyl]-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole: A reaction mixture of 4-bromo-6-chloro-5-[2-methylcyclopropyl]-1-tetrahydropyran-2-yl-indazole (80 mg, 1 *equiv.*), 4,4,5,5-tetramethyl-1,3,2-

dioxaborolane (83.1 mg, 3 *equiv.*), TEA (131 mg, 6 *equiv.*), $Pd(OAc)_2$ (4.86 mg, 0.1 *equiv.*) in dioxane (2 mL) was stirred at 70 °C for 5 hours. After completion, the mixture was concentrated in vacuum and purified by reversed phase flash chromatography (C18, mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (70 mg, 78% yield) as a yellow liquid. LCMS (ESI, M+1): m/z = 417.1.

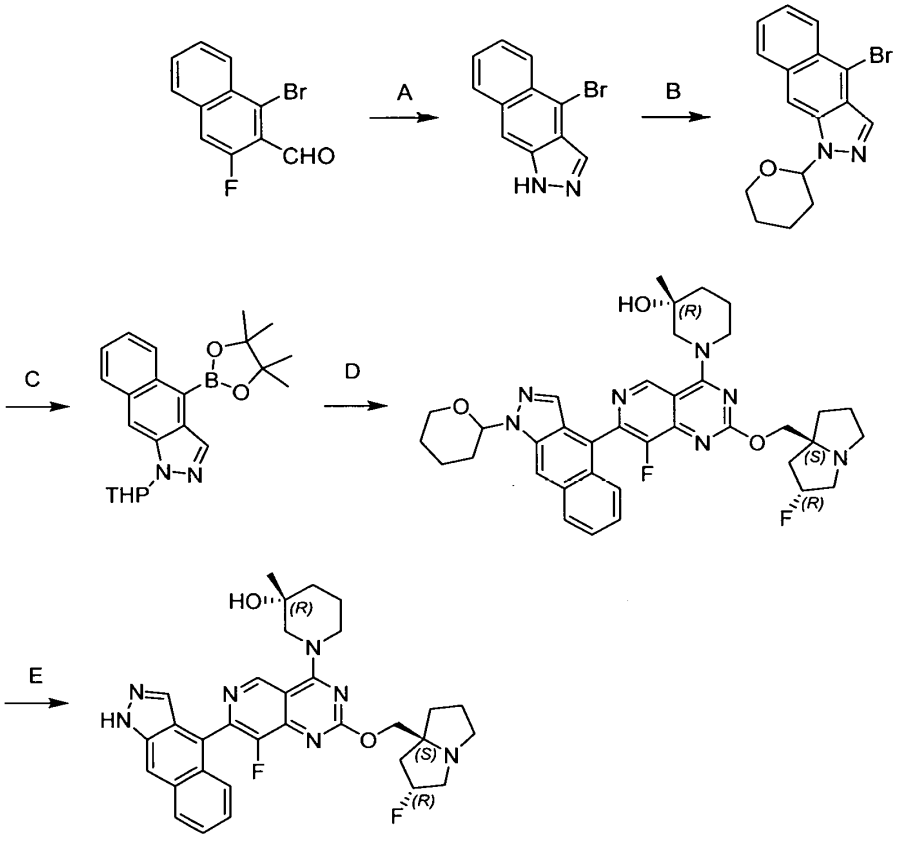
[0000686] Step J. (3R)-1-(7-(6-chloro-5-(2-methylcyclopropyl)-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A reaction mixture of (*R*)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (40 mg, 1 *equiv.*), 6-chloro-5-[2-methylcyclopropyl]-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (36.7 mg, 1 *equiv.*), CataCXium A Pd G3 (6.42 mg, 0.1 *equiv.*) and K_3PO_4 (1.5 M in water , 3 *equiv.*) in THF (1 mL) was stirred at 60 °C for 2 hours. After completion, the mixture was concentrated and purified by reversed phase flash chromatography (C18, mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (7 mg, 11% yield) as a yellow solid. LCMS (ESI, M+1): m/z = 708.3.

[0000687] Step K. (3R)-1-(7-(6-chloro-5-(2-methylcyclopropyl)-1H-indazol-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: A reaction mixture of (3*R*)-1-(7-(6-chloro-5-(2-methylcyclopropyl)-1-(tetrahydro-2*H*-pyran-2-yl)-1H-indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (7 mg, 1 *equiv.*) in HCl/dioxane (4 M, 142 *equiv.*) and MeCN (0.1 mL) was stirred at 15 °C for 10 mins. After reaction completion, the mixture was concentrated in vacuum and purified by reversed phase flash chromatography (C18, mobile phase: [water (0.1% formic acid)/acetonitrile]) and then re-purified by prep-HPLC: [column: Phenomenex luna C18 150 x 25mm x 10um; mobile phase: [water (0.225% formic acid)/CAN]; B%: 18%-48%, 10min] to afford the title compound (1.75 mg, 27% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 9.36 - 9.25 (m, 1H), 8.57 - 8.46 (m, 1H), 8.17 - 7.68 (m, 2H), 5.46 - 5.28 (m, 1H), 4.91 (br d, J = 1.2 Hz, 1H), 4.64 - 4.52 (m, 1H), 4.46 - 4.23 (m, 3H), 3.70 - 3.63 (m, 1H), 3.63 - 3.57 (m, 1H), 3.55 - 3.34 (m, 4H), 3.17 - 3.09 (m, 1H), 2.49 - 2.27 (m, 2H), 2.26 - 2.03 (m, 5H), 2.02 - 1.75 (m, 5H), 1.36 - 1.22 (m, 4H), 1.18 (t, J = 7.2 Hz, 2H), 0.71 - 0.64 (m, 3H). LCMS (ESI, M+1): m/z = 624.3.

EXAMPLE 154



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



[0000688] Step A. 4-bromo-1H-benzo[f]indazole: To a mixture of 1-bromo-3-fluoro-2-naphthaldehyde (500 mg, 1.00 *equiv.*) in dimethyl sulfoxide (5.00 mL) was added hydrazine hydrate (0.60 g, 582 µL, 98.0% purity, 5.9 *equiv.*) and diisopropylethylamine (2.04 g, 2.75 mL, 8.00 *equiv.*) in one portion under nitrogen. The reaction was stirred at 130 °C for 8 hours. The reaction mixture was concentrated under reduced pressure and purified by prep-HPLC (column: Phenomenex luna C18 150 × 25 mm × 10 µm; mobile phase: [water (0.225% formic acid)/ACN]; B%: 44%-74%, 10 min) to give the title compound (150 mg, 30% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.32 - 8.25 (m, 2H), 8.03 (s, 1H), 8.00 - 7.93 (m, 1H), 7.51 - 7.44 (m, 2H); LCMS (ESI, M+1): m/z = 247.1.

[0000689] Step B. 4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[f]indazole: To a solution of 4-bromo-1H-benzo[f]indazole (150 mg, 1.0 *equiv.*) and 3,4-dihydro-2H-pyran (153 mg, 167 µL, 3.0 *equiv.*) in dichloromethane (2.00 mL) was added 4-methylbenzenesulfonic acid hydrate (5.23 mg, 0.05 *equiv.*) in one portion at 25 °C under nitrogen. The reaction was stirred at 25 °C for 12 hours. The reaction mixture was concentrated under reduced pressure and purified by prep-TLC (silica gel, petroleum ether / ethyl acetate 4:1) to give the title compound (180 mg, 543 µmol, 89.5% yield, 100% purity) as a yellow solid. LCMS (ESI, M+1): m/z = 330.9.

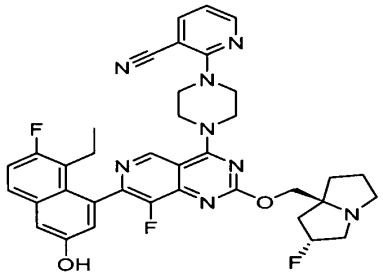
[0000690] Step C. 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[f]indazole: To a solution of 4-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[f]indazole (180 mg, 1.0 *equiv.*) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (166 mg, 1.2 *equiv.*) in dioxane (3.00 mL) was added potassium acetate (160 mg, 3.00 *equiv.*), $Pd(dppf)Cl_2$ (39.8 mg, 0.1 *equiv.*), then the mixture was degassed and stirred at 90 °C for 1 hour under nitrogen. After completion, the reaction mixture was concentrated under reduced pressure and purified by prep-TLC (silica gel, petroleum ether / ethyl acetate 4:1) to give the title compound (150 mg, 54% yield) as a yellow solid. LCMS (ESI, M+1): m/z = 379.3.

[0000691] Step D. (3R)-1-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[f]indazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[f]indazole (150 mg, 1.0 *equiv.*) and (*R*)-1-(7-

chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (180 mg, 1.0 *equiv.*) in toluene (3.00 mL) was added CataCXium A Pd G3 (43.3 mg, 0.15 *equiv.*), potassium phosphate (1.5 M, 793 µL, 3.0 *equiv.*), the reaction mixture was degassed and purged with nitrogen for 3 times, then it was stirred at 90 °C for 2 hours under nitrogen. The reaction mixture was concentrated under reduced pressure and purified by prep-TLC (silica gel, petroleum ether / ethyl acetate 4:1) to give the title compound (200 mg, 36% yield) as a yellow solid. LCMS (ESI, M+1): m/z = 670.5.

[0000692] Step E. (3R)-1-(7-(1H-benzo[f]indazol-4-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 (3R)-1-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[f]indazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (200 mg, 47.5% purity, 1.0 *equiv.*) in dichloromethane (4.00 mL) was added trifluoroacetic acid (6.16 g, 4.00 mL, *equiv.*) in one portion at 0 °C under nitrogen. The reaction was stirred at 20 °C for 10 min. The reaction mixture was concentrated under reduced pressure and purified by prep-HPLC (column: Phenomenex luna C18 150 × 25 mm × 10 um; mobile phase: [water (0.225% formic acid)/ACN]; B%: 8%-38%, 10 min) to give the title compound (27.9 mg, 32% yield, formic acid salt) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 9.41 (d, J = 9.2 Hz, 1H), 8.45 (s, 1H), 8.21 (s, 1H), 8.11 - 8.00 (m, 2H), 7.80 (d, J = 8.8 Hz, 1H), 7.54 - 7.46 (m, 1H), 7.41 - 7.32 (m, 1H), 5.67 - 5.33 (m, 1H), 4.72 - 4.62 (m, 1H), 4.62 - 4.48 (m, 2H), 4.39 (d, J = 13.6 Hz, 1H), 3.84 - 3.54 (m, 4H), 3.52 - 3.39 (m, 1H), 3.29 - 3.25 (m, 1H), 2.68 - 2.38 (m, 2H), 2.37 - 2.28 (m, 1H), 2.28 - 2.13 (m, 3H), 2.12 - 1.98 (m, 1H), 1.94 - 1.72 (m, 3H), 1.31 (s, 3H); ^{19}F NMR (377 MHz, CD_3OD) δ = -139.13, δ = -173.98; LCMS (ESI, M+1): m/z = 586.3.

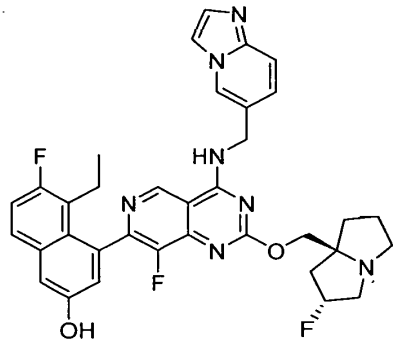
EXAMPLE 155



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

[0000693] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.17 (s, 1H), 8.40 (dd, *J* = 1.6, 4.8 Hz, 1H), 7.98 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.66 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.33 - 7.18 (m, 2H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.91 (dd, *J* = 4.8, 7.6 Hz, 1H), 5.41 - 5.18 (m, 1H), 4.40 - 4.20 (m, 6H), 4.08 - 3.95 (m, 4H), 3.29 - 3.11 (m, 3H), 3.05 - 2.91 (m, 1H), 2.55 - 2.43 (m, 1H), 2.40 - 2.28 (m, 1H), 2.27 - 2.11 (m, 4H), 2.05 - 1.96 (m, 2H), 0.80 (br t, *J* = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 681.4.

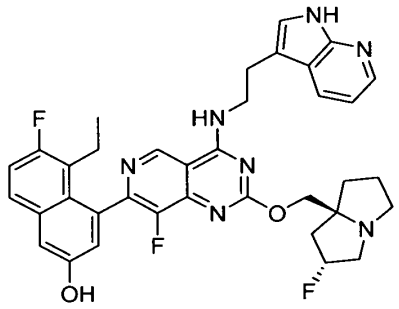
EXAMPLE 156



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

[0000694] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, METHANOL-d4): δ = 9.20 (s, 1H), 8.60 (s, 1H), 8.55 (s, 1H), 7.85 (s, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.60 - 7.53 (m, 2H), 7.45 (dd, *J* = 1.6, 9.2 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 5.34 - 5.16 (m, 1H), 4.92 (br d, *J* = 4.4 Hz, 3H), 4.59 (br s, 2H), 4.32 - 4.19 (m, 2H), 3.26 - 3.12 (m, 3H), 2.98 (dt, *J* = 6.0, 9.6 Hz, 1H), 2.54 - 2.42 (m, 1H), 2.34 - 1.89 (m, 7H), 1.87 - 1.73 (m, 1H), 0.79 (t, *J* = 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 640.3.

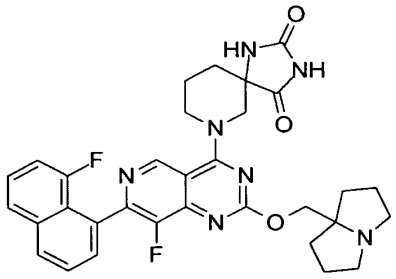
EXAMPLE 157



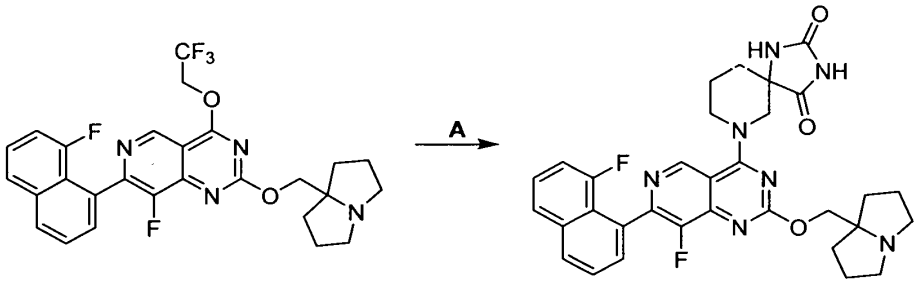
4-(4-((2-(1H-pyrrolo[2,3-b]pyridin-3-yl)ethyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol

[0000695] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, CD_3OD): δ 9.07 (s, 1H), 8.20–8.16 (dd, J = 1.6, 4.8 Hz, 1H), 8.13–8.07 (dd, J = 1.6, 7.6 Hz, 1H), 7.71–7.66 (dd, J = 5.6, 8.8 Hz, 1H), 7.33–7.29 (m, 2H), 7.26 (t, J = 9.2 Hz, 1H), 7.10–7.01 (m, 2H), 5.43–5.20 (m, 1H), 4.31–4.18 (m, 2H), 4.09–3.94 (m, 2H), 3.29–3.12 (m, 5H), 3.07–2.97 (m, 1H), 2.54–2.41 (m, 1H), 2.38–2.25 (m, 1H), 2.25–2.19 (m, 1H), 2.18–2.08 (m, 2H), 2.05–1.95 (m, 2H), 1.95–1.84 (m, 1H), 0.84–0.76 (dt, J = 2.0, 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 654.3.

EXAMPLE 158

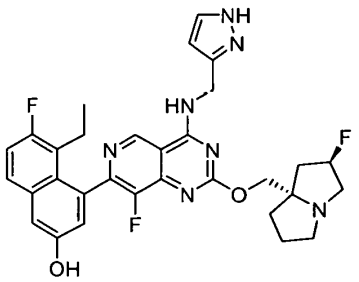


7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione



[0000696] 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]decane-2,4-dione: 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 (150 mg, 1.0 *equiv.*), 1,3,7-triazaspiro[4.5]decane-2,4-dione (76.5 mg, 1.6 *equiv.*) in DMF (1 mL) was added DIEA (183 mg, 5.0 *equiv.*). The reaction was stirred at 40 °C for 10 hours. The mixture was filtered to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75×30 mm×3 um; mobile phase: [water (10 mM NH_4HCO_3)/ACN]; B%: 20% - 50%, 8 min) and lyophilized to afford the title compound (75.13 mg, 42 % yield) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.10 (s, 1H), 8.11 (br d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.73 - 7.65 (m, 1H), 7.63 - 7.58 (m, 1H), 7.56 - 7.48 (m, 1H), 7.23 - 7.14 (m, 1H), 4.62 (br d, *J* = 13.2 Hz, 1H), 4.53 - 4.41 (m, 1H), 4.35 - 4.20 (m, 2H), 3.85 - 3.62 (m, 2H), 3.18 - 3.05 (m, 2H), 2.78 - 2.66 (m, 2H), 2.31 - 2.17 (m, 1H), 2.13 - 1.99 (m, 4H), 1.98 - 1.83 (m, 5H), 1.80 - 1.67 (m, 2H); LCMS (ESI, M+1): m/z = 600.3.

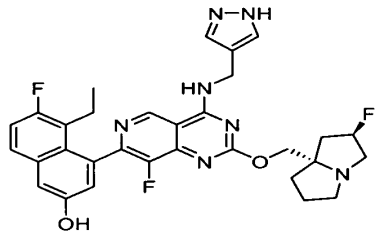
EXAMPLE 159



4-(4-(((1H-pyrazol-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

[0000697] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.18 (s, 1H), 7.70-7.60 (m, 2H), 7.30 (d, J = 2.8 Hz, 1H), 7.25 (t, J = 9.6 Hz, 1H), 7.04 (d, J = 2.8 Hz, 1H), 6.39 (br s, 1H), 5.37-5.21 (m, 1H), 4.94 (s, 2H), 4.29 (q, J = 10.4 Hz, 2H), 3.25-3.12 (m, 3H), 3.04-2.97 (m, 1H), 2.53-2.42 (m, 1H), 2.27-2.20 (m, 1H), 2.16-2.08 (m, 2H), 2.03-1.83 (m, 4H), 0.79 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 590.3.

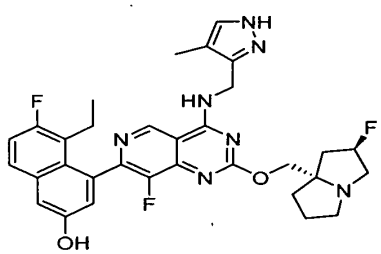
EXAMPLE 160



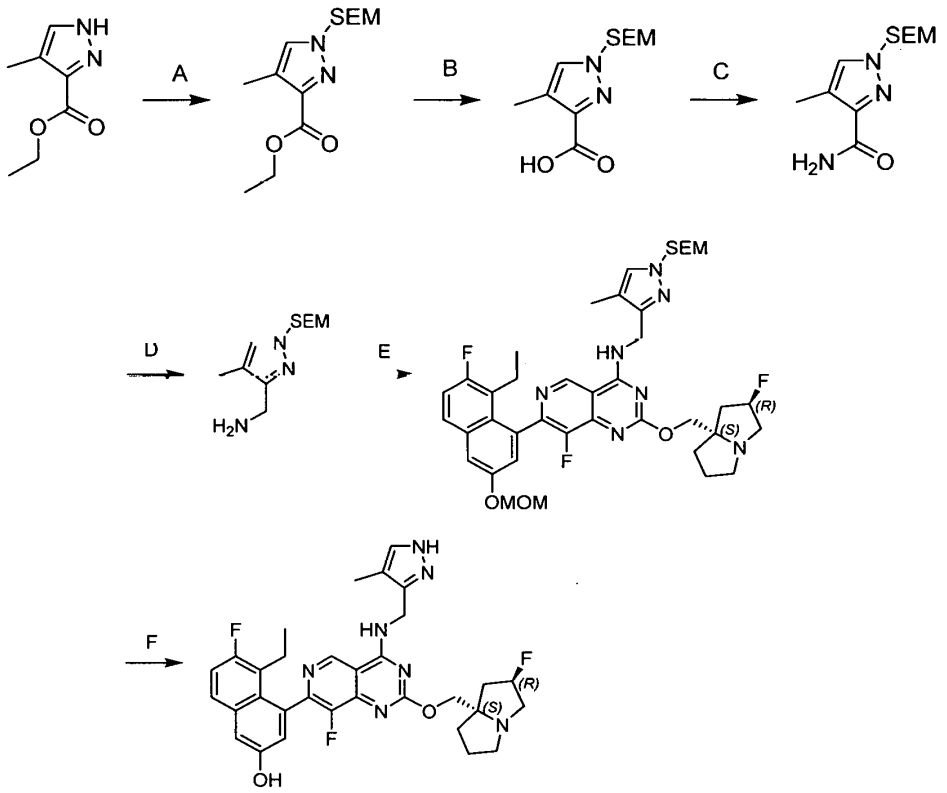
4-(4-(((1H-pyrazol-4-yl)methyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol

[0000698] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.13 (s, 1H), 7.73 (br s, 2H), 7.67 (dd, J = 5.6, 8.8 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.24 (t, J = 9.2 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 5.46-5.16 (m, 1H), 4.80 (s, 2H), 4.44-4.22 (m, 2H), 3.29-3.13 (m, 3H), 3.05-2.97 (m, 1H), 2.53-2.40 (m, 1H), 2.39-2.19 (m, 2H), 2.18-2.07 (m, 2H), 2.05-1.94 (m, 2H), 1.94-1.82 (m, 1H), 0.78 (t, J = 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 590.3.

EXAMPLE 161



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



[0000699] Step A. ethyl 4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-3-carboxylate: To a solution of ethyl 4-methyl-1H-pyrazole-3-carboxylate (1.50 g, 1.0 *equiv.*) in THF (15 mL) was added NaH (428 mg, 60% purity, 1.1 *equiv.*) at 0 °C. The mixture was stirred at 0 °C for 30 minutes. Then SEMCl (1.92 g, 1.2 *equiv.*) was added to the mixture. The reaction was stirred at 20 °C for 1 hour. Upon reaction completion, the mixture was quenched by addition of water (20 mL) at 0 °C, then extracted with ethyl acetate (40 mL × 3). The combined organic layers were washed with brine (80 mL), dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography (petroleum ether/ethyl acetate 20:1 to 5:1) to afford the title compound (2.15 g, 65% yield) as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–

7.39 (d, J = 0.8 Hz, 1H), 5.42 (s, 2H), 4.46–4.32 (dd, J = 7.2, 14.0 Hz, 2H), 3.58–3.48 (m, 2H), 2.31–2.27 (d, J = 0.8 Hz, 3H), 1.42–1.35 (t, J = 7.2 Hz, 3H), 0.93–0.85 (m, 2H), -0.02—0.08 (m, 9H); LCMS (ESI, M+1): m/z = 285.2.

[0000700] Step B. 4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-3-carboxylic acid: To a solution of ethyl 4-methyl-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-pyrazole-3-carboxylate (2.0 g, 1.0 *equiv.*) in EtOH (18.0 mL) was added LiOH hydrate (885 mg, 3.0 *equiv.*) and water (6.0 mL),The reaction was stirred at 20 °C for 2 hours. Upon completion, the reaction mixture was concentrated under reduced pressure to remove EtOH. The residue was diluted with HCl (30 mL, 1 M) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the title compound (1.70 g, 93% yelid) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (s, 1H), 5.46 (s, 2H), 3.62–3.51 (m, 2H), 2.38–2.27 (m, 3H), 0.97–0.83 (m, 2H), 0.04—0.09 (m, 9H).

[0000701] Step C. 4-methyl-1-((2-(trimethylsilyl) ethoxy) methyl)-1H-pyrazole-3-carboxamide: To a solution of 4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-3-carboxylic acid (1.50 g, 1.0 *equiv.*) and NH_4Cl (1.5 g, 5.0 *equiv.*) in DMF (20.0 mL) was added HATU (4.50 g, 2.0 *equiv.*) and DIEA (6.12 g, 8.0 *equiv.*). The reaction was stirred at 40 °C for 2 hours. Upon completion, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, concentrated and purified by reversed phase flash chromatography [C18, mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (1.40 g, 81% yield) as a yellow liquid; ^{1}H NMR (400 MHz, DMSO-D_6): δ 7.71 (d, J = 0.8 Hz, 1H), 7.35–7.06 (m, 2H), 5.35 (s, 2H), 3.56–3.47 (m, 2H), 2.22–2.14 (d, J = 0.4 Hz, 3H), 0.88–0.75 (m, 2H), -0.02—0.11 (m, 9H).

[0000702] Step D. (4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)methanamine: A mixture of 4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-3-carboxamide (1.30 g, 1.0 *equiv.*) and THF (15 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 0 °C for 5 minutes under N_2 atmosphere. Following that $LiAlH_4$ (386 mg, 2.0 *equiv.*) was added into the mixture in portions during a period of 10 minutes. The mixture was stirred at 40 °C for 2 hours. Upon completion, the mixture was quenched by addition

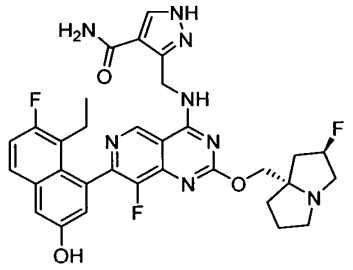
of saturated sodium sulfate (386 μL) at 0°C, filtered and the filtrate was diluted with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated and purified by reversed phase flash chromatography (C18, mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (1.10 g, 87% yield) as a yellow solid; ^{1}H NMR (400 MHz, CD_3OD): δ 7.47 (s, 1H), 5.31 (s, 2H), 3.75 (s, 2H), 3.56–3.50 (m, 2H), 2.07 (s, 3H), 0.89–0.84 (m, 2H), -0.01—0.07 (m, 9H).

[0000703] Step E. 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-((4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)methyl)pyrido[4,3-d]pyrimidin-4-amine: To a solution of (4-methyl-1-((2-(trimethylsilyl)ethoxy) methyl)-1H-pyrazol-3-yl) methanamine (150 mg, 1.0 *equiv.*) and 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 (395 mg, 1.0 *equiv.*) in DMF (3 mL) was added DIEA (401 mg, 541 μL, 5.0 *equiv.*) and 4Å molecular sieves (50 mg). The reaction was stirred at 40 °C for 2 hours. Upon completion, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate. The mixture was filtered and concentrated and purified by reversed phase flash chromatography (C18, mobile phase: [water (0.1% formic acid)/acetonitrile)] to afford the title compound (100 mg, 20.2 % yield) as a yellow oil; LCMS (ESI, M+1): m/z = 778.5.

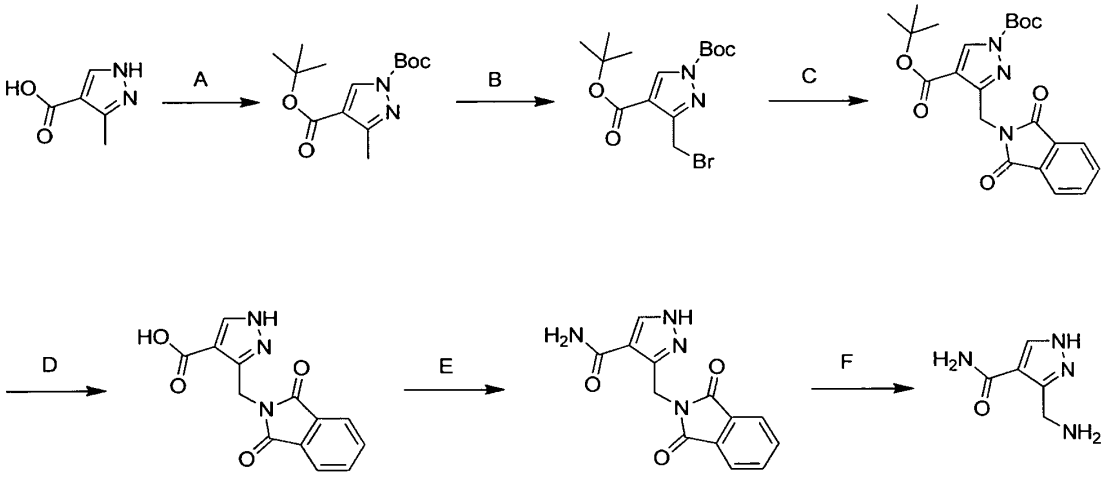
[0000704] Step F. 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(((4-methyl-1H-pyrazol-3-yl)methyl)amino)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol: To a solution of 7-(8-ethyl-7-fluoro-3-(methoxymethoxy) naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-((4-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)methyl)pyrido[4,3-d]pyrimidin-4-amine (90.0 mg, 1.0 *equiv.*) in DCM (1 mL) was added TFA (769 mg, 499 μL, 58 *equiv.*).The mixture was stirred at 20 °C for 0.5 hour. Upon reaction completion, the mixture was concentrated under reduced pressure to remove DCM, the residue was diluted with water (10 mL) and pH was adjusted to 9 with solid Na_2CO_3. Then the mixture was extracted with ethyl acetate (10 mL × 3) and the combined organic layers were washed with brine (20 mL), dried over anhydrous sodium

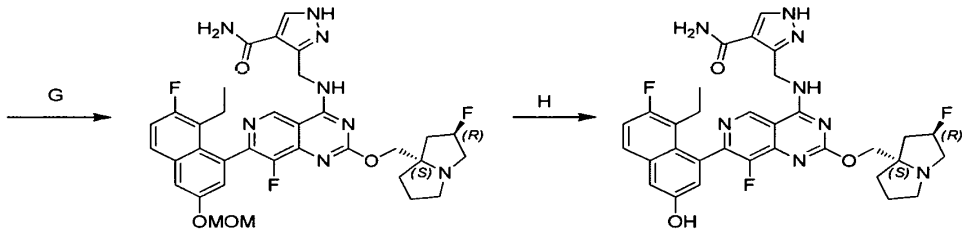
sulfate, concentrated and purified by prep-HPLC [column: waters Xbridge 150 × 25 mm × 5 μm; mobile phase: [water (10 mM NH_4HCO_3)/ACN]; B%: 42% - 72%, 10 minutes] to afford the title compound (16 mg, 52.6 % yield, 98.2 % purity) as a yellow solid; ^{1}H NMR (400 MHz, CD_3OD): δ 9.22–9.15 (d, J = 0.8 Hz, 1H), 7.71–7.64 (dd, J = 5.6, 9.2 Hz, 1H), 7.41 (s, 1H), 7.31–7.26 (d, J = 2.4 Hz, 1H), 7.26–7.20 (t, J = 9.2 Hz, 1H), 7.06–7.03 (d, J = 2.0 Hz, 1H), 5.38–5.17 (m, 1H), 4.89 (s, 2H), 4.34–4.23 (m, 2H), 3.29–3.11 (m, 3H), 3.04–2.94 (m, 1H), 2.53–2.39 (m, 1H), 2.37–2.06 (m, 7H), 2.02–1.83 (m, 3H), 0.78 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 604.4.

EXAMPLE 162



3-(((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)-1H-pyrazole-4-carboxamide





[0000705] Step A. di-tert-butyl 3-methyl-1H-pyrazole-1,4-dicarboxylate: To a solution of 3-methyl-1H-pyrazole-4-carboxylic acid (4.50 g, 1.0 *equiv.*) in 2-methylpropan-2-ol (34.9 g, 13.2 *equiv.*) was added DMAP (872 mg, 0.2 *equiv.*) and Boc_2O (31.1 g, 4.0 *equiv.*) under nitrogen. The reaction was stirred at 40 °C for 12 hours. The reaction mixture was filtered, concentrated and purified by reversed phase flash chromatography (C18, mobile phase: [water (0.1% formic acid)/ACN], 0-70% ACN) to afford the title compound (6.0 g, 59% yield) as a white solid; ^1H NMR (400 MHz, METHANOL-d_4) δ = 8.44 (s, 1H), 2.44 (s, 3H), 1.65 (s, 9H), 1.57 (s, 9H). LCMS (ESI, M-55): m/z = 227.2.

[0000706] Step B. di-tert-butyl 3-methyl-1H-pyrazole-1,4-dicarboxylate: To a solution of ditert-butyl 3-methylpyrazole-1,4-dicarboxylate (3.0 g, 1.0 *equiv.*) in CCl_4 (20 mL) was added NBS (2.27 g, 1.20 *equiv.*) and AIBN (523 mg, 0.3 *equiv.*) under nitrogen. The mixture was stirred at 80 °C for 12 hours. The reaction mixture was filtered, concentrated and purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate 1:0 to 50:1) to afford the title compound (3.0 g, 65% purity, 51% yield) as a colorless liquid; LCMS (ESI, M-99): m/z = 261.0.

[0000707] Step C. di-tert-butyl 3-((1,3-dioxoisoindolin-2-yl)methyl)-1H-pyrazole-1,4-dicarboxylate: To a solution of *di-tert*-butyl 3-(bromomethyl)pyrazole-1,4-dicarboxylate (2.80 g, 65% purity, 1.0 *equiv.*) in DMF (20 mL) was added (1,3-dioxoisoindolin-2-yl)potassium (1.87 g, 2.0 *equiv.*). The reaction was stirred at 100 °C for 2 hours. The reaction mixture was filtered, concentrated and purified by reversed phase flash chromatography (C18, mobile phase: [water (0.1% formic acid)/ACN], 0-40% ACN) to afford the title compound (1.10 g, 55% yield) as a red solid; LCMS (ESI, M-155): m/z = 272.1.

[0000708] Step D. 3-((1,3-dioxoisoindolin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid: To a solution of *di-tert*-butyl 3-[(1,3-dioxoisoindolin-2-yl)methyl]pyrazole-1,4-dicarboxylate (1.10 g, 1.0 *equiv.*) in DCM (10 mL) was added TFA (15.4 g, 52.5 *equiv.*) under nitrogen. The mixture was

stirred at 20 °C for 2 hours. The reaction mixture was filtered and concentrated to afford the title compound (0.9 g, crude, TFA salt) as a yellow solid; LCMS (ESI, M+1): m/z = 272.1.

[0000709] Step E. 3-((1,3-dioxoisoindolin-2-yl)methyl)-1H-pyrazole-4-carboxamide: To a solution of 3-[(1,3-dioxoisoindolin-2-yl)methyl]-1H-pyrazole-4-carboxylic acid (100 mg, 1.0 *equiv.*) in DMF (2 mL) was added DIEA (476 mg, 10.0 *equiv.*), HATU (420 mg, 3.0 *equiv.*) and NH_4Cl (98.6 mg, 5.0 *equiv.*) under nitrogen. The reaction was stirred at 40 °C for 12 hours. The reaction mixture was filtered, the filtrate was concentrated and purified by reversed phase flash chromatography (C18, mobile phase: [water (0.1% formic acid)/ACN], 0-40% ACN) to afford the title compound (30 mg, 30% yield) as a red solid; LCMS (ESI, M+1): m/z = 271.1.

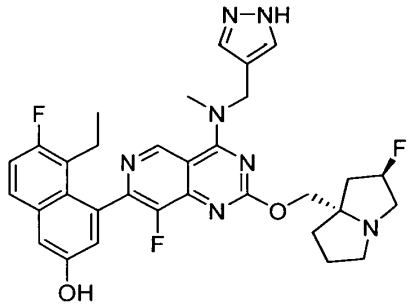
[0000710] Step F. 3-(aminomethyl)-1H-pyrazole-4-carboxamide: To a solution of 3-[(1,3-dioxoisoindolin-2-yl)methyl]-1H-pyrazole-4-carboxamide (20.0 mg, 1.0 *equiv.*) in EtOH (0.5 mL) was added hydrazine hydrate (37.8 mg, 10.0 *equiv.*). The reaction was stirred at 40 °C for 1 hour. The reaction mixture was filtered and the filtrate was concentrated to afford the title compound (5.0 mg, crude) as a yellow solid; LCMS (ESI, M+23): m/z = 163.1.

[0000711] Step G. 3-(((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)-1H-pyrazole-4-carboxamide: To a solution of 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 (60.0 mg, 1.0 *equiv.*, 0.5 formic acid salt) and DIEA (35.3 mg, 3.0 *equiv.*) in DMF (1 mL) was added 4Å MS (20.0 mg) and 3-(aminomethyl)-1H-pyrazole-4-carboxamide (12.7 mg, 1.0 *equiv.*). The reaction was stirred at 40 °C for 12 hours. The reaction mixture was filtered, concentrated and purified by prep-TLC [Silica gel, DCM/MeOH 10:1] to afford the title compound (50.0 mg, 80% yield) as a light yellow solid; LCMS (ESI, M+1): m/z = 677.1.

[0000712] Step H. 3-(((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)-1H-pyrazole-4-carboxamide: To a solution of 3-(((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)-1H-pyrazole-4-carboxamide (40.0 mg,

1.0 *equiv.*) in MeOH (0.5 mL) was added HCl in MeOH (4 M, 0.5 mL).The reaction was stirred at 20 °C for 0.5 hour. The reaction mixture filtered, concentrated and purified by reversed phase flash chromatography [column: Phenomenex Gemini-NX C18 75*30mm*3um; mobile phase: [water (0.225% formic acid)/ACN]; B%: 12%-42%, 7min] to afford the title compound (8.14 mg, 20% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ 9.20 (d, J = 1.6 Hz, 1H), 8.51 (br s, 1H), 8.16 (br s, 1H), 7.68 (dd, J = 6.0, 9.2 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.25 (t, J = 9.2 Hz, 1H), 7.05 (t, J = 2.8 Hz, 1H), 5.50 - 5.33 (m, 1H), 5.19 (s, 2H), 4.54 - 4.35 (m, 2H), 3.69 - 3.43 (m, 3H), 3.21 (br d, J = 5.4 Hz, 1H), 2.57 - 2.32 (m, 3H), 2.30 - 2.10 (m, 4H), 2.05 - 1.94 (m, 1H), 0.78 (dt, J = 2.0, 7.2 Hz, 3H). LCMS (ESI, M+1): m/z = 633.3.

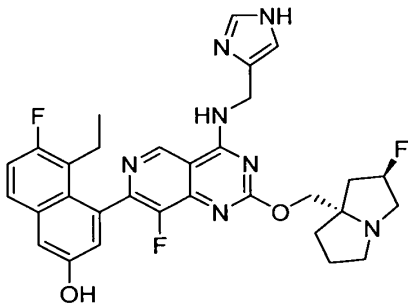
EXAMPLE 163



4-(4-(((1H-pyrazol-4-yl)methyl)(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

[0000713] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.21 (s, 1H), 7.77 (br d, J = 2.0 Hz, 2H), 7.67 (dd, J = 6.0, 9.2 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.24 (t, J = 9.4 Hz, 1H), 7.05 (d, J = 2.8 Hz, 1H), 5.39-5.21 (m, 1H), 5.06 (s, 2H), 4.39-4.23 (m, 2H), 3.59 (s, 3H), 3.27-3.12 (m, 3H), 3.06-2.93 (m, 1H), 2.53-2.42 (m, 1H), 2.38-2.20 (m, 2H), 2.19-2.09 (m, 2H), 2.03-1.85 (m, 3H), 0.80 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z =604.3.

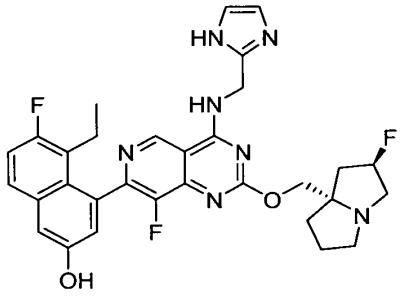
EXAMPLE 164



4-(4-(((1H-imidazol-4-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

[0000714] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.18 (s, 1H), 7.70-7.64 (m, 2H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.24 (t, *J* = 9.2 Hz, 1H), 7.15 (s, 1H), 7.04 (d, *J* = 2.8 Hz, 1H), 5.38-5.21 (m, 1H), 4.77-4.45 (m, 2H), 4.36-4.26 (m, 2H), 3.28-3.13 (m, 3H), 3.06-2.96 (m, 1H), 2.51-2.41 (m, 1H), 2.38-2.19 (m, 2H), 2.18-2.10 (m, 2H), 2.03-1.86 (m, 3H), 0.78 (t, *J* = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 590.2.

EXAMPLE 165

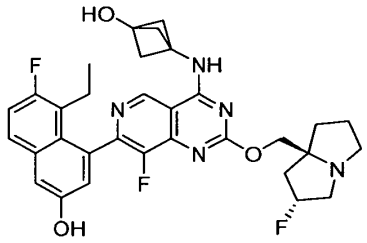


4-(4-(((1H-imidazol-2-yl)methyl)amino)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol

[0000715] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400MHz, METHANOL-d4) δ = 9.20 (s, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.30 (d, *J* = 2.8Hz, 1H), 7.25 (t, *J* = 9.6 Hz, 1H), 7.09 - 6.97 (m, 3H), 5.38 - 5.19 (m, 1H), 4.94 (d, *J* = 4.4 Hz, 2H), 4.28 - 4.15 (m, 2H), 3.29 - 3.12 (m, 3H), 3.06 - 2.95 (m, 1H), 2.54 - 2.41

(m, 1H), 2.35 - 2.06 (m, 4H), 2.03 - 1.83 (m, 3H), 0.79 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 590.3.

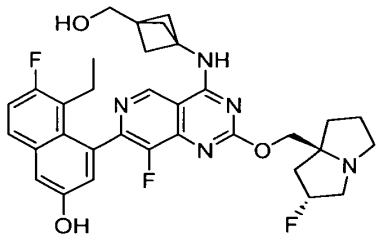
EXAMPLE 166



3-((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)bicyclo[1.1.1]pentan-1-ol

[0000716] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-d4) δ 9.24 (s, 1H), 7.68 (dd, J = 5.6, 8.8 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.25 (t, J = 9.2 Hz, 1H), 7.04 (d, J = 2.0 Hz, 1H), 5.67 - 5.51 (m, 1H), 4.71 (qd, J = 4.4, 12.0 Hz, 2H), 4.10 - 3.85 (m, 3H), 3.54 - 3.44 (m, 1H), 2.80 - 2.56 (m, 2H), 2.45 (s, 6H), 2.43 - 2.31 (m, 4H), 2.28 - 2.07 (m, 2H), 0.77 (br t, J = 6.4 Hz, 3H); LCMS (ESI, M+1): m/z = 592.3.

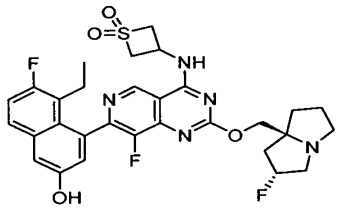
EXAMPLE 167



5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-((3-(hydroxymethyl)bicyclo[1.1.1]pentan-1-yl)amino)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol

[0000717] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, METHANOL-d4): δ = 9.24 (s, 1H), 7.69 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.32 (d, *J* = 2.8 Hz, 1H), 7.26 (t, *J* = 9.6 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 5.66 - 5.51 (m, 1H), 4.76 - 4.62 (m, 2H), 4.11 - 3.86 (m, 3H), 3.73 (s, 2H), 3.54 - 3.43 (m, 1H), 2.79 - 2.59 (m, 2H), 2.49 - 2.30 (m, 5H), 2.28 (s, 5H), 2.21 - 2.07 (m, 2H), 0.78 (br t, *J* = 6.8 Hz, 3H); LCMS (ESI, M+1): m/z = 606.3.

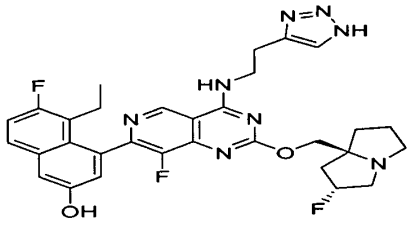
EXAMPLE 168



3-((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)amino)thietane 1,1-dioxide

[0000718] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, CD_3OD) δ 9.28 (s, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 1H), 7.25 (t, *J* = 9.6 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 5.43 - 5.18 (m, 1H), 4.98 - 4.91 (m, 1H), 4.79 - 4.67 (m, 2H), 4.53 - 4.40 (m, 2H), 4.38 - 4.22 (m, 2H), 3.29 - 3.19 (m, 3H), 3.03 (dt, *J* = 5.6, 9.2 Hz, 1H), 2.50 - 2.39 (m, 1H), 2.38 - 2.20 (m, 2H), 2.19 - 2.09 (m, 2H), 2.06 - 1.87 (m, 3H), 0.78 (t, *J* = 7.2 Hz, 3H). LCMS (ESI, M+1): m/z = 614.3.

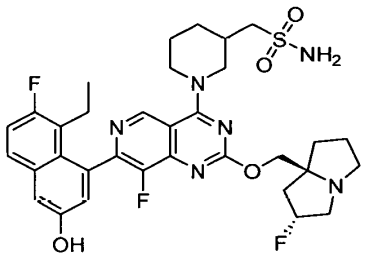
EXAMPLE 169



4-(4-((2-(1H-1,2,3-triazol-4-yl)ethyl)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

[0000719] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, METHANOL-d4): δ = 9.10 (s, 1H), 7.69 (s, 1H), 7.68 - 7.63 (m, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.24 (t, *J* = 9.2 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 5.40 - 5.22 (m, 1H), 4.34 - 4.23 (m, 2H), 4.05 - 3.95 (m, 2H), 3.28 - 3.10 (m, 5H), 3.07 - 2.95 (m, 1H), 2.49 - 2.12 (m, 5H), 2.03 - 1.88 (m, 3H), 0.79 (t, *J* = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 605.2.

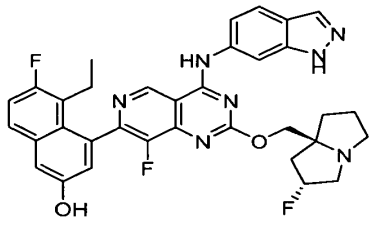
EXAMPLE 170



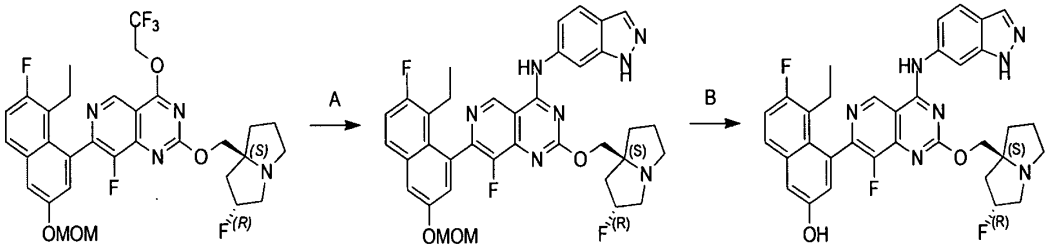
1-(1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide

[0000720] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-*d*4) δ 9.08 (s, 1H), 7.67 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.24 (t, *J* = 9.2 Hz, 1H), 7.05 (dd, *J* = 2.4, 6.0 Hz, 1H), 5.40 - 5.23 (m, 1H), 5.03 - 4.93 (m, 1H), 4.60 - 4.50 (m, 1H), 4.41 - 4.26 (m, 2H), 3.68 - 3.55 (m, 1H), 3.43 - 3.34 (m, 1H), 3.30 - 3.07 (m, 5H), 3.06 - 2.97 (m, 1H), 2.56- 2.43 (m, 2H), 2.41 - 2.08 (m, 5H), 2.04 - 1.89 (m, 4H), 1.86 - 1.74 (m, 1H), 1.68 - 1.55 (m, 1H), 0.80 (q, *J* = 6.8 Hz, 3H); ^{19}F NMR (376 MHz, methanol-*d*4) δ = -121.192, -138.964, -173.392; LCMS (ESI, M+1): m/z = 671.3.

EXAMPLE 171



4-(4-((1H-indazol-6-yl)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

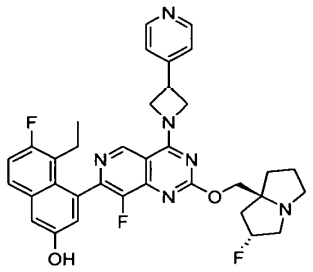


[0000721] Step A. 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-(1H-indazol-6-yl)pyrido[4,3-d]pyrimidin-4-amine: To a solution of 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (200 mg, 1.0 *equiv.*) and 1*H*-indazol-6-amine (41.8 mg, 1.0 *equiv.*) in DMF (2 mL) was added 4Å MS (50 mg) and t-BuONa (60.4 mg, 2.0 *equiv.*). The mixture was stirred at 0 °C for 0.5 hour. Upon reaction completion, the mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated, and purified by reversed phase flash chromatography (C18, mobile phase: [water (0.1% formic acid)/ACN]) to afford the title compound (80 mg, 29% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 670.3.

[0000722] Step B. 4-(4-((1H-indazol-6-yl)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 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-(1H-indazol-6-yl)pyrido[4,3-d]pyrimidin-4-amine (90 mg, 1.0 *equiv.*) in DCM (1 mL) was added TFA (1.15 g, 750 μL, 90 *equiv.*). The mixture was stirred at 0 °C for 0.5 hour. The reaction mixture was concentrated under reduced pressure to remove TFA. The residue was dissolved in water (5 mL), neutralized with solid Na_2CO_3, then extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated and purified by prep-HPLC [column: waters Xbridge 150 × 25mm × 5μm; mobile phase: [water (10mM NH_4HCO_3)/ACN]; B %: 39 %-69 %, 9min] to afford the title compound (12 mg, 17% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 9.65 (s, 1H), 8.42 (s, 1H), 8.13 (s, 1H), 7.91–7.87 (d, J = 8.4 Hz, 1H), 7.82–7.76 (dd,

J = 6.0, 10.2 Hz, 1H), 7.64–7.57 (dd, J = 0.8, 8.4 Hz, 1H), 7.43–7.31 (m, 2H), 7.16–7.13 (d, J = 2.4 Hz, 1H), 5.49–5.20 (m, 1H), 4.41–4.22 (m, 3H), 3.27–3.15 (m, 3H), 3.06–2.93 (m, 1H), 2.55–2.45 (m, 1H), 2.35–2.11 (m, 4H), 2.03–1.82 (m, 3H), 0.86 (t, J = 7.2 Hz, 3H). LCMS (ESI, M+1): m/z = 626.3.

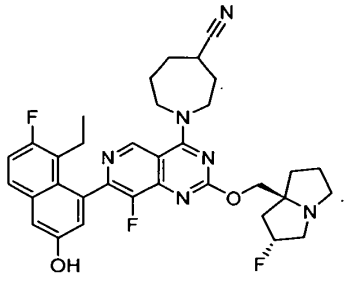
EXAMPLE 172



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

[0000723] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.94 (s, 1H), 9.01 (s, 1H), 8.58 (br d, J = 4.8 Hz, 2H), 7.77 (dd, J = 6.4, 8.6 Hz, 1H), 7.55 (br d, J = 4.8 Hz, 2H), 7.39 - 7.30 (m, 2H), 7.00 (s, 1H), 5.40 - 5.15 (m, 2H), 5.03 - 4.72 (m, 2H), 4.47 - 4.27 (m, 1H), 4.24 - 4.11 (m, 2H), 4.09 - 4.00 (m, 1H), 3.08 (br d, J = 9.2 Hz, 2H), 3.01 (br s, 1H), 2.87 - 2.76 (m, 1H), 2.41 - 2.31 (m, 1H), 2.15 - 2.07 (m, 2H), 2.06 - 1.95 (m, 2H), 1.87 - 1.73 (m, 3H), 0.73 (br t, J = 7.2 Hz, 3H); LCMS [ESI, M+1]: 627.4

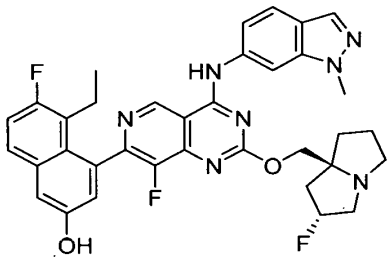
EXAMPLE 173



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)azepane-4-carbonitrile

[0000724] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.15 (s, 1H), 7.67 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.06 (dd, *J* = 2.8, 5.2 Hz, 1H), 5.40-5.22 (m, 1H), 4.40-3.95 (m, 6H), 3.29-3.12 (m, 4H), 3.10-2.95 (m, 1H), 2.55-2.44 (m, 1H), 2.41-2.20 (m, 5H), 2.19-2.06 (m, 3H), 2.05-1.86 (m, 5H), 0.87-0.71 (m, 3H); LCMS (ESI, M+1): m/z = 617.3.

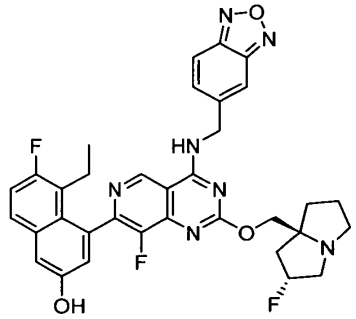
EXAMPLE 174



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

[0000725] The title compound was synthesized according to the procedure described for example 171. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.49 (s, 1H), 8.31 (s, 1H), 8.02 (d, *J* = 0.8 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.69 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.51 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.26 (t, *J* = 9.2 Hz, 1H), 7.09 (d, *J* = 2.8 Hz, 1H), 5.37-5.18 (m, 1H), 4.41-4.24 (m, 2H), 4.11 (s, 3H), 3.26-3.14 (m, 3H), 2.99 (dt, *J* = 5.6, 9.6 Hz, 1H), 2.58-2.44 (m, 1H), 2.37-2.20 (m, 2H), 2.18-2.03 (m, 2H), 2.02-1.82 (m, 3H), 0.82 (t, *J* = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 640.2.

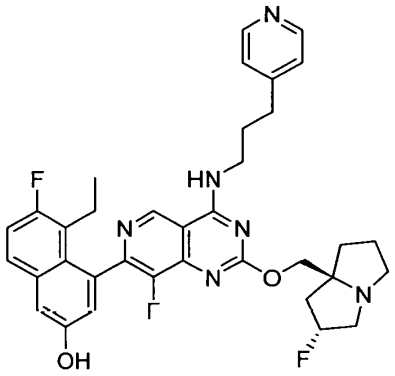
EXAMPLE 175



4-(4-((benzo[c][1,2,5]oxadiazol-5-ylmethyl)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

[0000726] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-d4) δ 9.23 (s, 1H), 7.97 - 7.88 (m, 2H), 7.71 - 7.61 (m, 2H), 7.30 (d, J = 2.8 Hz, 1H), 7.25 (t, J = 9.2 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 5.34 - 5.13 (m, 1H), 5.04 - 4.94 (m, 2H), 4.27 - 4.14 (m, 2H), 3.25 - 3.08 (m, 3H), 3.01 - 2.90 (m, 1H), 2.55 - 2.40 (m, 1H), 2.30 - 2.11 (m, 3H), 2.10 - 1.89 (m, 3H), 1.84 - 1.70 (m, 1H), 0.80 (br t, J = 7.2 Hz, 3H); LCMS [ESI, M+1]: 642.3.

EXAMPLE 176

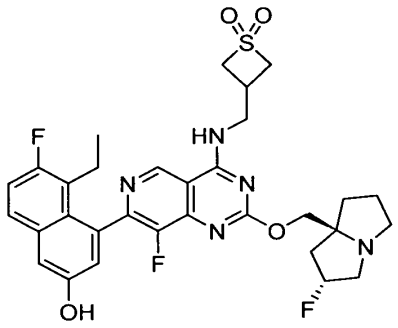


5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-((3-(pyridin-4-yl)propyl)amino)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol

[0000727] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.09 (s, 1H), 8.41 (d, J = 6.0 Hz, 2H),

7.67 (dd, J = 6.0, 9.2 Hz, 1H), 7.37 (d, J = 6.0 Hz, 2H), 7.30 (d, J = 2.8 Hz, 1H), 7.24 (t, J = 9.2 Hz, 1H), 7.04 (d, J = 2.8 Hz, 1H), 5.39-5.22 (m, 1H), 4.32-4.21 (m, 2H), 3.80-3.72 (m, 2H), 3.27-3.13 (m, 3H), 3.05-2.97 (m, 1H), 2.86 (t, J = 7.6 Hz, 2H), 2.53-2.42 (m, 1H), 2.38-2.20 (m, 2H), 2.19-2.09 (m, 4H), 2.03-1.85 (m, 3H), 0.79 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 629.3.

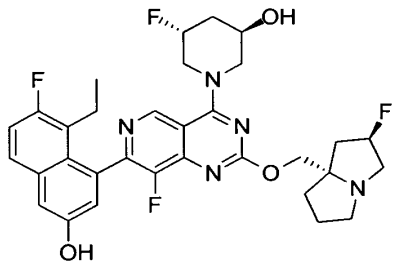
EXAMPLE 177



3-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)amino)methyl)thietane1,1-dioxide

[0000728] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 9.27 (s, 1H), 9.23 - 9.11 (m, 1H), 8.18 (s, 1H), 7.76 (dd, J = 6.0, 8.8 Hz, 1H), 7.41 - 7.28 (m, 2H), 6.99 (d, J = 2.4 Hz, 1H), 5.38 - 5.19 (m, 1H), 4.35 (br t, J = 11.2 Hz, 2H), 4.19 - 4.03 (m, 4H), 3.94 - 3.76 (m, 2H), 3.15 - 3.08 (m, 2H), 3.05 - 2.95 (m, 2H), 2.89 - 2.79 (m, 1H), 2.28 - 1.96 (m, 5H), 1.90 - 1.70 (m, 3H), 0.81 - 0.64 (m, 3H); LCMS (ESI, M+1): m/z = 628.

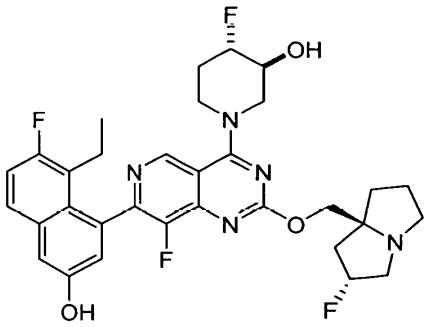
EXAMPLE 178



(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)-5-fluoropiperidin-3-ol

[0000729] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, CD3OD): δ 9.14–9.12 (d, J = 6.8 Hz, 1H), 7.71–7.63 (dd, J = 6.0, 9.2 Hz, 1H), 7.32–7.29 (d, J = 2.8 Hz, 1H), 7.28–7.21 (t, J = 9.6 Hz, 1H), 7.08–7.01 (m, 1H), 5.54 (s, 1H), 5.40 (s, 1H), 5.37 (s, 1H), 5.24 (s, 1H), 4.98 (s, 1H), 4.46–4.15 (m, 5H), 3.82–3.76 (dd, J = 2.0, 11.6 Hz, 1H), 3.29–3.10 (m, 3H), 3.08–2.96 (m, 1H), 2.56–2.40 (m, 3H), 2.40–2.10 (m, 4H), 2.05–1.85 (m, 3H), 0.86–0.74 (td, J = 7.4, 19.2 Hz, 3H); LCMS (ESI, M+1): m/z = 612.3.

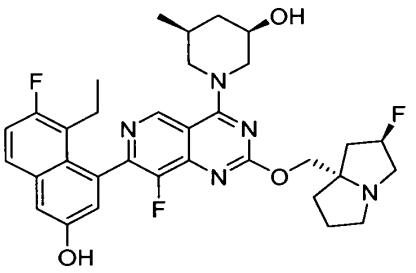
EXAMPLE 179



(3S,4S)-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)-4-fluoropiperidin-3-ol

[0000730] The title compound was synthesized according to the procedure described for example 135 except for HCl•MeOH (4 M, 49.2 *equiv.*) was used in the deprotection step. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.24 (dd, J = 1.2, 6.4 Hz, 1H), 8.49 (s, 1H), 7.68 (dd, J = 6.0, 9.2 Hz, 1H), 7.35-7.19 (m, 1H), 7.06 (t, J = 2.8 Hz, 1H), 5.55-5.28 (m, 1H), 4.79-4.60 (m, 1H), 4.55-4.38 (m, 2H), 4.32-4.12 (m, 2H), 4.11-3.88 (m, 3H), 3.69-3.41 (m, 3H), 3.21 (dt, J = 5.6, 9.6 Hz, 1H), 2.56-2.23 (m, 5H), 2.22-2.08 (m, 3H), 2.07-1.92 (m, 2H), 0.80 (br t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 612.2.

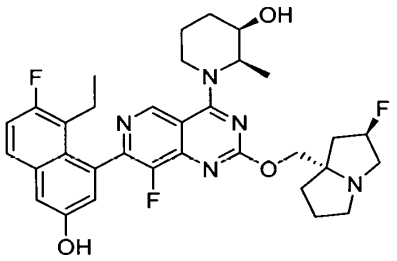
EXAMPLE 180



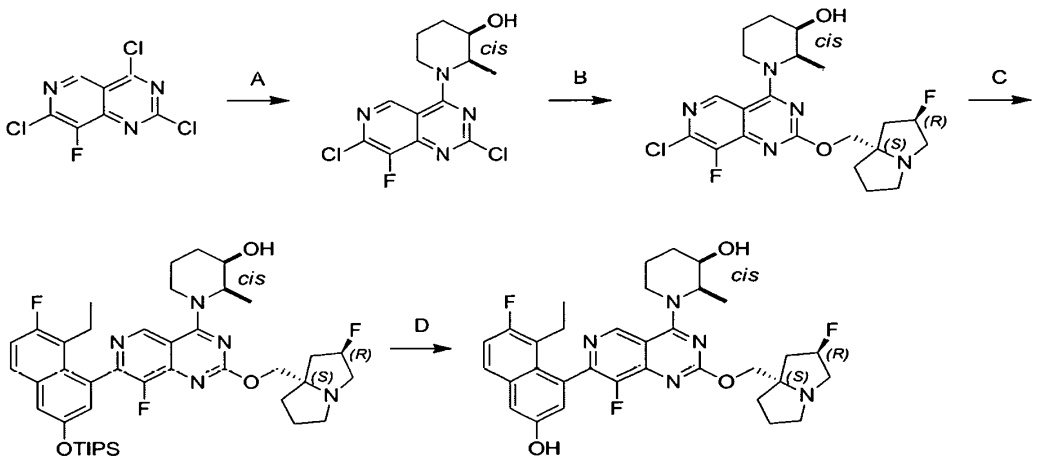
(3*R*,5*S*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7aS)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-5-methylpiperidin-3-ol

[0000731] The title compound was synthesized according to the procedure described for example 135 except for HCl/EtOAc (4 M, 1.0 mL, 27 *equiv.*) was used in the deprotection step. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.05 (d, J = 1.6 Hz, 1H), 7.68 (dd, J = 6.0, 9.2 Hz, 1H), 7.38 - 7.15 (m, 2H), 7.06 (s, 1H), 5.44 - 5.15 (m, 1H), 4.81 - 4.72 (m, 1H), 4.55 (br d, J = 12.8 Hz, 1H), 4.38 - 4.18 (m, 2H), 3.88 (br dd, J = 4.4, 10.4 Hz, 1H), 3.29 - 3.12 (m, 3H), 3.09 - 2.90 (m, 3H), 2.54 - 2.10 (m, 6H), 2.06 - 1.86 (m, 4H), 1.35 - 1.21 (m, 1H), 1.06 (d, J = 6.5 Hz, 3H), 0.80 (br t, J = 7.3 Hz, 3H); LCMS (ESI, M+1): m/z = 608.4.

EXAMPLE 181



(2R,3R)-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)-2-methylpiperidin-3-ol



[0000732] Step A. (2R,3R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-3-ol: To a mixture of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (450 mg, 1.0 *equiv.*), DIEA (2.30 g, 10 *equiv.*) and 4Å molecular sieves (45 mg) in DMAc (4 mL) was added (2*R*,3*R*)-2-methylpiperidin-3-ol (135 mg, 0.5 *equiv.*, HCl) at 15 °C. The reaction was stirred at 15 °C for 1 hour. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]). The desired fractions were collected, neutralized with $NaHCO_3$ solid, concentrated in vacuum to remove acetonitrile, and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine (15 mL) dried over anhydrous sodium sulfate, concentrated in vacuum to afford the title compound (265 mg, 44% yield) as a red solid; ^{1}H NMR (400 MHz, DMSO-*d6*) δ = 8.90 (s, 1H), 5.12 (d, *J* = 4.0 Hz, 1H), 4.92 (br s, 1H), 4.25 (br d, *J* = 11.6 Hz, 1H), 3.77 - 3.67 (m, 1H), 3.46 (br s, 1H), 1.82 - 1.58 (m, 4H), 1.31 (br d, *J* = 6.8 Hz, 3H); LCMS (ESI, M+1): m/z = 331.0.

[0000733] Step B. (2R,3R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-3-ol: A mixture of (2R,3R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-3-ol (257 mg, 1.0 *equiv.*), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (371 mg, 3.0 *equiv.*), DIEA (501 mg, 5.0 *equiv.*) and 4Å molecular sieves (30 mg) in dioxane (3 mL) was stirred at 90 °C for 14 hours. The mixture was filtered and the filtrate was concentrated, purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]). The desired fractions were collected, neutralized with $NaHCO_3$ solid, extracted with ethyl acetate (2 × 40 mL).

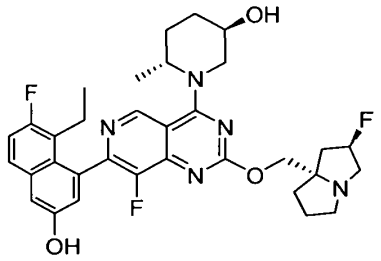
The combined organic layer was washed with brine (40 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum to afford the title compound (296 mg, 74% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 454.1.

[0000734] Step C. (2R,3R)-1-(7-(8-ethyl-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-3-ol: To a mixture of (2R,3R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-3-ol (100 mg, 1.0 *equiv.*), ((5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)triisopropylsilane (156 mg, 1.5 *equiv.*) and Cs_2CO_3 (144 mg, 2.0 *equiv.*) in dioxane (1.5 mL) and water (0.5 mL) was added $Pd(PPh_3)_4$ (25.5 mg, 0.1 *equiv.*) under N_2. The mixture was de-gassed and stirred at 100 °C for 8 hours under N_2. The mixture was diluted with water (3 mL) and extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, concentrated in vacuum. The residue was purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]). The desired fractions were collected neutralized with $NaHCO_3$ solid, concentrated in vacuum to remove acetonitrile, and extracted with ethyl acetate (15 mL). The combined organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to afford the title compound (53.0 mg, 31% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 764.3.

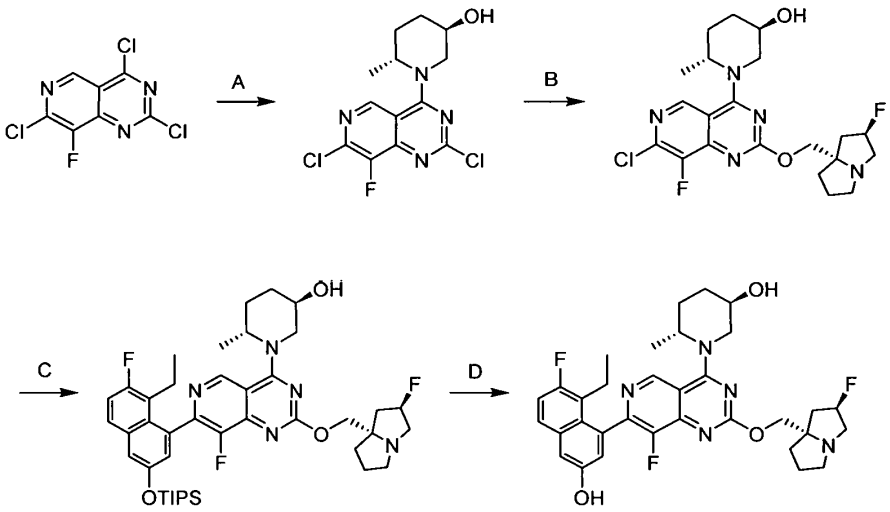
[0000735] Step D. (2R,3R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-3-ol: A mixture of (2R,3R)-1-(7-(8-ethyl-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-methylpiperidin-3-ol (50.0 mg, 1.0 *equiv.*) and CsF (99.4 mg, 10 *equiv.*) in DMF (0.6 mL) was stirred at 15 °C for 1 hour. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]). The desired fractions were collected, neutralized with solid $NaHCO_3$, concentrated in vacuum to remove acetonitrile and extracted with ethyl acetate (2 × 10 mL). The combined organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by prep-HPLC [Waters Xbridge 150 × 25mm × 5 μm; mobile phase: [water (10mM NH_4HCO_3)/ACN]; B%: 39% - 69%, 9 min] twice to afford

the title compound (22.0 mg, 55% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 8.97 (d, J = 2.8 Hz, 1H), 7.67 (dd, J = 5.6, 8.8 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.24 (t, J = 9.2 Hz, 1H), 7.05 (dd, J = 2.4, 6.8 Hz, 1H), 5.30 (d, J = 54.4 Hz,1H), 5.11 - 5.02 (m, 1H), 4.40 (br d, J = 13.6 Hz, 1H), 4.34 - 4.21 (m, 2H), 3.96 - 3.88 (m, 1H), 3.58 - 3.47 (m, 1H), 3.29 - 3.13 (m, 3H), 3.06 - 2.96 (m, 1H), 2.55 - 2.43 (m, 1H), 2.38 - 2.10 (m, 4H), 2.03 - 1.95 (m, 2H), 1.94 - 1.79 (m, 5H), 1.45 (t, J = 6.0 Hz, 3H), 0.85 - 0.75 (m, 3H); ^{19}F NMR (376 MHz, methanol-d_4) δ = -121.191, -138.888, -173.675; LCMS (ESI, M+1): m/z = 608.3.

EXAMPLE 182



(3R,6R)-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)-6-methylpiperidin-3-ol



[0000736] Step A. (3R,6R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-6-methylpiperidin-3-ol: To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (200 mg, 1.0 *equiv.*) and (3R,6R)-6-methylpiperidin-3-ol (84.1 mg, 0.7 *equiv.*, HCl) in DMAc (4 mL) was added DIEA (307 mg, 414 μL, 3 *equiv.*) and 4Å molecular sieves (300 mg). The reaction was stirred at 20 °C for 2 hours. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated in vacuum. The residue was purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]). to afford the title compound (205 mg, 78% yield) as a yellow solid; ^{1}H NMR (400 MHz, DMSO-D$_6$): δ 9.32 (s, 1H), 5.13 - 4.96 (m, 2H), 4.28 – 4.21 (d, J = 13.6 Hz, 1H), 4.00 (s, 1H), 3.76 – 3.68 (d, J = 14.0 Hz, 1H), 2.24 – 2.14 (m, 1H), 2.03 - 1.92 (m, 1H), 1.64 – 1.55 (d, J = 12.8 Hz, 1H), 1.47 – 1.40 (m, 1H), 1.37 – 1.30 (d, J = 6.8 Hz, 3H); LCMS (ESI, M+1): m/z = 331.1.

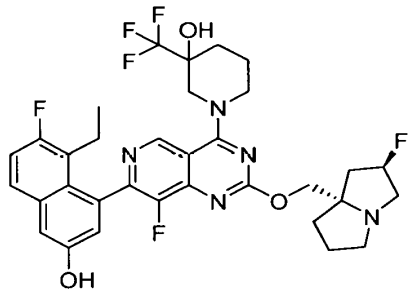
[0000737] Step B. (3R,6R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methylpiperidin-3-ol: To a solution of (3R,6R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-6-methylpiperidin-3-ol (205 mg, 1.0 *equiv.*) and ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (296 mg, 3.0 *equiv.*) in DMF (5 mL) was added DIEA (400 mg, 539 μL, 5.0 *equiv.*) and 4Å molecular sieves (400 mg). The reaction was stirred at 90 °C for 12 hours. The mixture was purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (210 mg, 71.0 % yield) as a yellow solid; LCMS (ESI, M+1): m/z = 454.1.

[0000738] Step C. (3R,6R)-1-(7-(8-ethyl-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methylpiperidin-3-ol: A mixture of (3R,6R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methylpiperidin-3-ol (190 mg, 1.0 *equiv.*), ((5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)triisopropylsilane (395 mg, 2.0 *equiv.*), K$_3$PO$_4$ (1.5 M, 3.0 *equiv.*) and CataCXium A Pd G3 (30.5 mg, 0.1 *equiv.)* in THF (3 mL) was degassed and stirred at 60 °C for 2 hours under N$_2$ atmosphere. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure. The residue was purified by

reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (210 mg, 63% yield) as a black solid; LCMS (ESI, M+1): m/z = 764.4.

[0000739] Step D. (3R,6R)-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)-6-methylpiperidin-3-ol: To a solution of (3R,6R)-1-(7-(8-ethyl-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methylpiperidin-3-ol (100 mg, 1.0 *equiv.*) in DMF (2 mL) was added CsF (199 mg, 10 *equiv.*). The reaction was stirred at 40 °C for 1 hour. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30mm × 3μm; mobile phase: [water (10 mM NH_4HCO_3)/ACN]; B %: 34-64%, 8 minutes] to afford the title compound (72 mg, 90% yield) as a white solid; ^{1}H NMR (400 MHz, CD3OD): δ 9.41 – 9.32 (d, J = 4.4 Hz, 1H), 7.69 – 7.64 (dd, J = 5.6, 8.8 Hz, 1H), 7.32 – 7.29 (d, J = 2.0 Hz, 1H), 7.27 – 7.21 (t, J = 9.6 Hz, 1H), 7.07 – 7.03 (dd, J = 2.4, 6.8 Hz, 1H), 5.42 - 5.21 (d, *J* = 54.4 Hz, 1H), 5.20 - 5.12 (m, 1H), 4.86 (s, 9H), 4.52 – 4.44 (d, *J* = 14.4 Hz, 1H), 4.34 – 4.23 (m, *J* = 10.5 Hz, 2H), 4.13 (s, 1H), 3.84 – 3.76 (m, 1H), 3.29 - 3.16 (m, 3H), 3.05 – 2.97 (m, 1H), 2.57 - 2.08 (m, 7H), 2.04 - 1.73 (m, 4H), 1.59 – 1.52 (m, 1H), 1.48 – 1.44 (m, 3H), 0.84 – 0.77 (t, *J* = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 608.3.

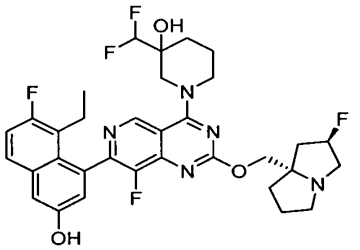
EXAMPLE 183



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

[0000740] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.21 (dd, *J* = 3.2, 14.8 Hz, 1H), 7.67 (dd, *J* = 5.8, 8.9 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.07 (t, *J* = 2.4 Hz, 1H), 5.30 (d, *J* = 54.4 Hz, 1H), 4.72-4.64 (m, 2H), 4.35-4.25 (m, 2H), 3.72 (t, *J* = 14.4 Hz, 1H), 3.37 (t, *J* = 12.8 Hz, 1H), 3.28-3.18 (m, 3H), 3.01 (dt, *J* = 5.2, 9.2 Hz, 1H), 2.24-2.20 (m, 6H), 2.07-1.90 (m, 6H), 0.80 (dt, *J* = 3.2, 7.2 Hz, 3H); F NMR (400 MHz, methanol-d4) δ = -84.2, -121, -139, -174; LCMS (ESI, M+1): m/z = 662.4.

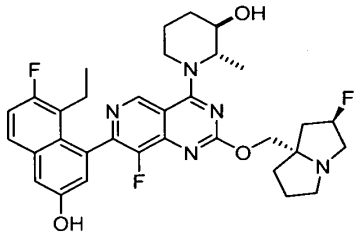
EXAMPLE 184



3-(difluoromethyl)-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)piperidin-3-ol

[0000741] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.25 (dd, *J* = 2.4, 6.8 Hz, 1H), 8.50 (br s, 1H), 7.68 (dd, *J* = 6.0, 8.8 Hz, 1H), 7.32-7.22 (m, 2H), 7.06 (d, *J* = 2.4 Hz, 1H), 5.96-5.60 (m, 1H), 5.52-5.31 (m, 1H), 4.69 (br d, *J* = 13.2 Hz, 1H), 4.57-4.40 (m, 3H), 3.78-3.64 (m, 1H), 3.64-3.45 (m, 3H), 3.45-3.37 (m, 1H), 3.25-3.15 (m, 1H), 2.54-2.31 (m, 3H), 2.29-2.09 (m, 5H), 2.06-1.85 (m, 4H), 0.85-0.74 (m, 3H); LCMS (ESI, M+1): m/z = 644.3.

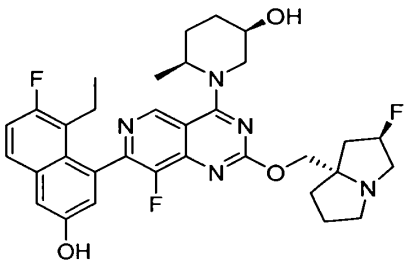
EXAMPLE 185



(2S,3R)-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)-2-methylpiperidin-3-ol

[0000742] The title compound was synthesized according to the procedure described for example 182. ^{1}H NMR (400 MHz, methanol-*d*4): δ ppm 0.74 - 0.86 (m, 3 H) 1.55 (m, 3 H) 1.61 - 1.72 (m, 1 H) 1.77 - 2.04 (m, 4 H) 2.04 - 2.39 (m, 6 H) 2.41 - 2.56 (m, 1 H) 2.96 - 3.05 (m, 1 H) 3.12 - 3.29 (m, 3 H) 3.14 - 3.27 (m, 3 H) 3.47 - 3.63 (m, 1 H) 3.82 - 3.96 (m, 1 H) 4.18 - 4.39 (m, 2 H) 4.49 - 4.59 (m, 1 H) 4.88 - 5.11 (m, 1 H) 5.21 - 5.39 (m, 1 H) 7.05 (dd, *J*=16.8, 2.8 Hz, 1 H) 7.21 - 7.28 (m, 1 H) 7.29 - 7.32 (m, 1 H) 7.67 (dd, *J*=8.8, 6.4 Hz, 1 H) 9.03 (t, *J*=2.4 Hz, 1 H); LCMS (ESI, M+1): m/z = 608.2.

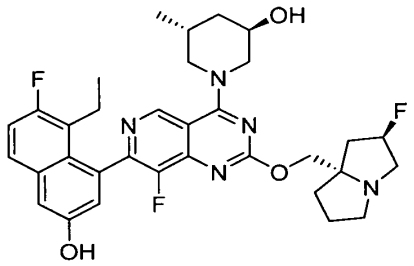
EXAMPLE 186



(3R,6S)-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)-6-methylpiperidin-3-ol

[0000743] The title compound was synthesized according to the procedure described for example 182 except for BrettPhos-Pd-G3 (0.1 *equiv.*) was used instead of cataCXium A Pd G3 in step C. ^{1}H NMR (400 MHz, CHLOROFORM-d): δ = 8.99 - 8.72 (m, 1H), 8.54 (s, 1H), 7.59 - 7.43 (m, 1H), 7.25 - 6.78 (m, 3H), 5.50 - 5.26 (m, 1H), 4.84 - 4.64 (m, 2H), 4.61 - 4.40 (m, 2H), 3.91 - 3.60 (m, 3H), 3.49 - 3.34 (m, 1H), 3.21 - 2.96 (m, 2H), 2.64 - 2.33 (m, 4H), 2.22 - 2.03 (m, 4H), 1.92 (br s, 4H), 1.51 (br t, *J* = 6.8 Hz, 3H), 0.85 - 0.73 (m, 3H); LCMS (ESI, M+1): m/z = 608.2.

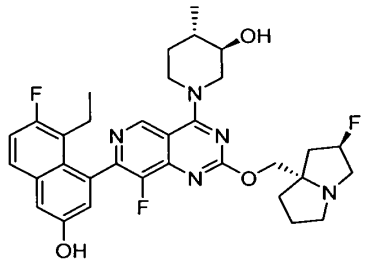
EXAMPLE 187



(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)-5-methylpiperidin-3-ol

[0000744] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-d_4) δ 9.22 (dd, J = 2.8, 8.4 Hz, 1H), 7.67 (dd, J = 6.0, 8.8 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.24 (t, J = 9.2 Hz, 1H), 7.08 - 7.04 (m, 1H), 5.39 - 5.19 (m, 1H), 4.69 - 4.50 (m, 2H), 4.37 - 4.21 (m, 2H), 4.15 (br s, 1H), 3.64 (br d, J = 14.0 Hz, 1H), 3.29 - 3.16 (m, 3H), 3.06 - 2.92 (m, 2H), 2.51 - 2.33 (m, 2H), 2.29 - 2.10 (m, 4H), 2.04 - 1.86 (m, 4H), 1.63 - 1.51 (m, 1H), 1.03 (br d, J = 6.4 Hz, 3H), 0.85 - 0.76 (m, 3H); ^{19}F NMR (400 MHz, methanol-d_4) δ -121.176, -139.194, -173.708; LCMS (ESI, M+1): m/z = 608.3.

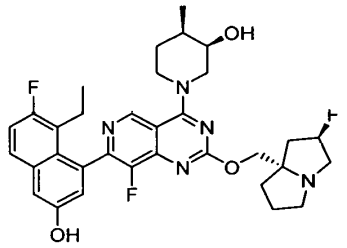
EXAMPLE 188



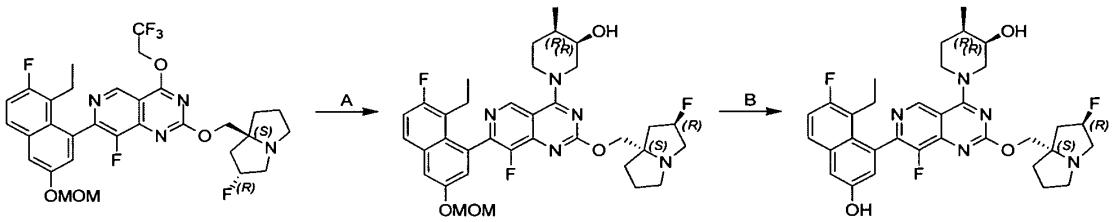
(3R,4S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4-methylpiperidin-3-ol

[0000745] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.06 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 6.0, 9.2 Hz, 1H), 7.34 - 7.19 (m, 2H), 7.05 (t, J = 2.4 Hz, 1H), 5.42 - 5.19 (m, 1H), 4.75 - 4.63 (m, 1H), 4.57 (br d, J = 13.6 Hz, 1H), 4.36 - 4.19 (m, 2H), 3.54 - 3.35 (m, 2H), 3.28 - 3.12 (m, 4H), 3.01 (dt, J = 5.6, 9.2 Hz, 1H), 2.54 - 2.40 (m, 1H), 2.39 - 2.09 (m, 4H), 2.05 - 1.84 (m, 4H), 1.78 - 1.65 (m, 1H), 1.55 - 1.40 (m, 1H), 1.14 (d, J = 6.4 Hz, 3H), 0.87 - 0.72 (m, 3H); LCMS (ESI, M+1): m/z = 608.4.

EXAMPLE 189

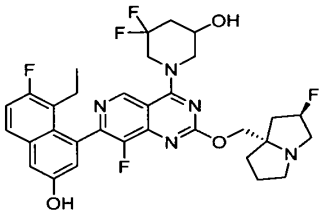


(3R,4R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4-methylpiperidin-3-ol

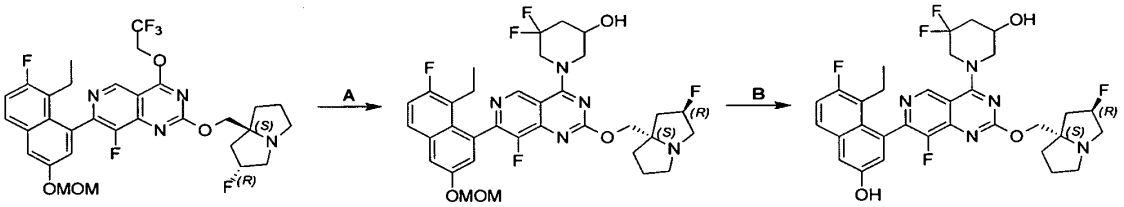


[0000746] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.30 (dd, *J* = 2.8, 9.2 Hz, 1H), 8.50 (s, 1H), 7.68 (dd, *J* =6.0, 9.2 Hz, 1H), 7.37-7.18 (m, 2H), 7.13-6.99 (m, 1H), 5.52-5.33 (m, 1H), 4.81-4.69 (m, 2H), 4.53-4.38 (m, 2H), 3.91 (br s, 1H), 3.67-3.45 (m, 4H), 3.35 (br d, *J* = 3.6 Hz, 1H), 3.21 (dt, *J* = 5.6, 10.0 Hz, 1H), 2.56-2.32 (m, 3H), 2.30-2.10 (m, 4H), 2.07-1.83 (m, 3H), 1.66 (br d, *J* = 12.2 Hz, 1H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.85-0.75 (m, 3H); LCMS (ESI, M+1): m/z = 608.4.

EXAMPLE 190

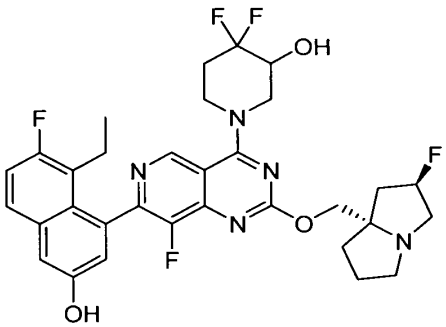


1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,5-difluoropiperidin-3-ol



[0000747] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, METHANOL-d4): δ = 9.26 (dd, *J* = 1.2, 10.8 Hz, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 1H), 7.25 (t, *J* = 9.6 Hz, 1H), 7.07 (t, *J* = 2.4 Hz, 1H), 5.40 - 5.21 (m, 1H), 4.46 - 4.32 (m, 3H), 4.31 - 4.13 (m, 3H), 3.78 - 3.59 (m, 1H), 3.28 - 3.13 (m, 3H), 3.01 (dt, *J* = 5.6, 9.6 Hz, 1H), 2.63 - 2.38 (m, 2H), 2.33 - 2.10 (m, 5H), 2.05 - 1.89 (m, 3H), 0.80 (t, *J* = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 630.2.

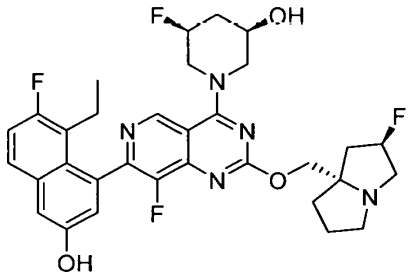
EXAMPLE 191



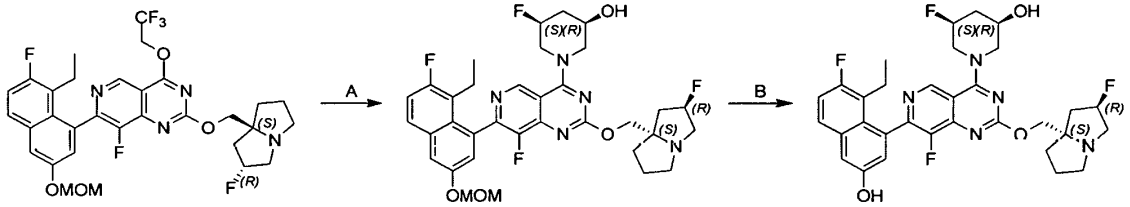
1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-4,4-difluoropiperidin-3-ol

[0000748] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-d_4) δ 0.79 (t, J=7.2 Hz, 3 H) 1.87 - 2.04 (m, 3 H) 2.11 - 2.38 (m, 5 H) 2.41 - 2.62 (m, 2 H) 3.01 (m, 1 H) 3.16 - 3.29 (m, 3 H) 3.61 - 3.70 (m, 1 H) 3.96 - 4.07 (m, 2 H) 4.25 - 4.37 (m, 2 H) 4.38 - 4.60 (m, 2 H) 5.21 - 5.39 (m, 1 H) 7.06 (dd, J=4.4, 2.4 Hz, 1 H) 7.25 (t, J=9.2 Hz, 1 H) 7.30 (d, J=2.8 Hz, 1 H) 7.68 (dd, J=8.8, 5.6 Hz, 1 H) 9.28 (dd, J=9.6, 2.0 Hz, 1 H); ^{19}F NMR (400 MHz, DMSO-d6) δ -110.901, -121.183, -138.993, 173.712. LCMS (ESI, M+1): m/z = 630.3.

EXAMPLE 192



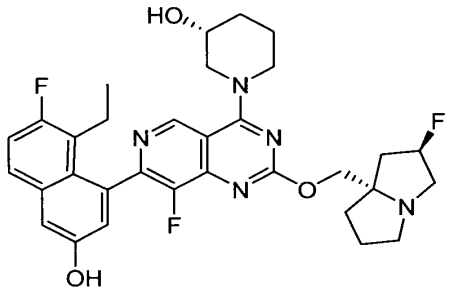
(3R,5S)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5-fluoropiperidin-3-ol



[0000749] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.36 (d, J = 5.8 Hz, 1H), 8.48 (br s, 1H), 7.68 (dd, J = 5.8, 9.2 Hz, 1H), 7.35-7.19 (m, 1H), 7.06 (t, J = 2.8 Hz, 1H), 5.55-5.32 (m, 1H), 5.08-4.91 (m, 1H), 4.58-4.43 (m, 2H), 4.43-4.28 (m, 1H), 4.25-3.95 (m, 4H), 3.72-3.46 (m, 3H), 3.24

(dt, J = 5.6, 10.0 Hz, 1H), 2.60-2.24 (m, 5H), 2.23-1.95 (m, 5H), 0.80 (dt, J = 2.0, 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 612.3.

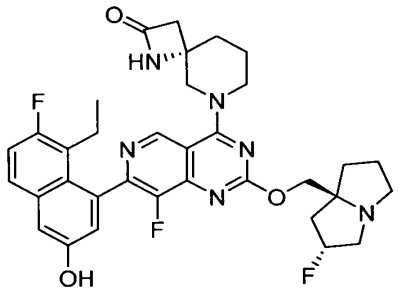
EXAMPLE 193



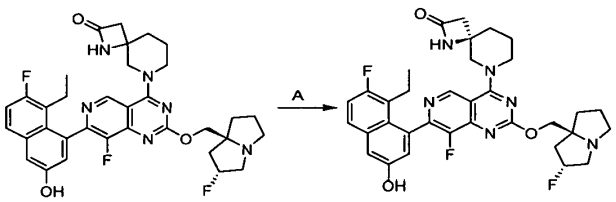
(*R*)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol

[0000750] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-*d*4) δ = 9.18 - 9.08 (m, 1H), 7.73 - 7.61 (m, 1H), 7.32 - 7.28 (m, 1H), 7.27 - 7.19 (m, 1H), 7.08 - 7.03 (m, 1H), 5.39 - 5.20 (m, 1H), 4.36 - 4.29 (m, 1H), 4.28 - 4.19 (m, 2H), 4.08 - 3.91 (m, 3H), 3.87 - 3.74 (m, 1H), 3.29 - 3.12 (m, 3H), 3.06 - 2.95 (m, 1H), 2.56 - 2.41 (m, 1H), 2.40 - 1.84 (m, 10H), 1.82 - 1.67 (m, 2H), 0.86 - 0.74 (m, 3H). LCMS (ESI, M+1): m/z = 594.2.

EXAMPLE 194



(S)-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

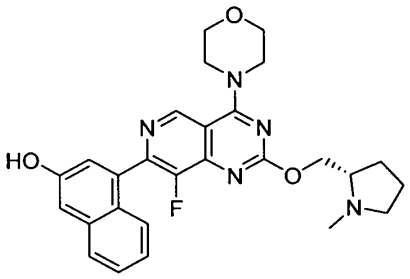


[0000751] 6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one: The title compound was synthesized according to the procedure described for example 134. LCMS (ESI, M+1): m/z = 633.3.

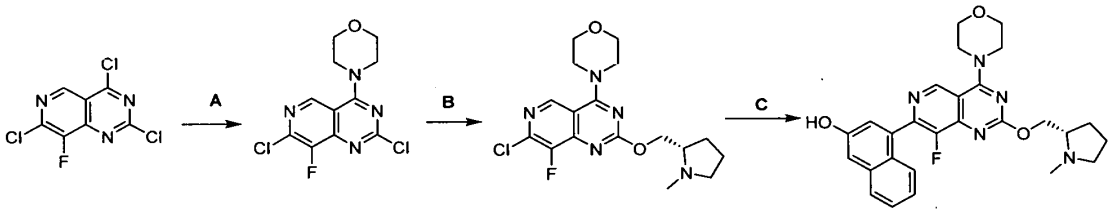
[0000752] Step A. (S)-6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one: Stereoisomeric mixture 6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one (70 mg, 1.0 *equiv.*) was separated by SFC [column: Daicel Chiralpak as (250 mm × 30 mm, 10 um); mobile phase: [CO2 / 0.1%NH_3•H_2O in MeOH] 45%-45%; 25 min]. The desired fractions of product (2nd eluting peak) were collected and concentrated in vacuum to give an impure product. The impure product was purified by prep-HPLC [column: Unisil 3-100 C18 Ultra 150 × 50mm × 3 um; mobile phase: [water (0.225% formic acid)/ACN]; B%: 15%-45%, 10 min]. The desired fractions were collected and concentrated in vacuum to remove ACN. The aqueous layer was lyophilized to afford title compound (8.09 mg, 11% yield, 0.1 formic acid salt) as a white solid; LCMS (ESI, M+1): m/z = 633.4; SFC: 97.2% ee Chiralpak AS-3 50×4.6mm I.D., 3um column A: 60% MeOH + 40% ACN (w/ 0.05% DEA), B: CO_2, 3mL/min, 220 nm, t_R: 2.070 min; ^{1}H NMR (400 MHz, MeOD): δ 9.09 (s, 1H), 7.68 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.6 Hz, 1H), 7.08 - 7.04 (m, 1H), 5.44 - 5.23 (m, 1H), 4.47 - 4.23 (m, 4H), 3.99 (t, *J* = 11.6 Hz, 1H), 3.90 - 3.68 (m,

1H), 3.42 - 3.35 (m, 1H), 3.28 - 3.20 (m, 1H), 3.16 - 3.00 (m, 1H), 2.95 - 2.84 (m, 1H), 2.80 - 2.71 (m, 1H), 2.56 - 2.24 (m, 3H), 2.24 - 1.86 (m, 10H), 0.79 (t, J = 7.6 Hz, 3H).

EXAMPLE 195



(S)-4-(8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)-4-morpholinopyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol



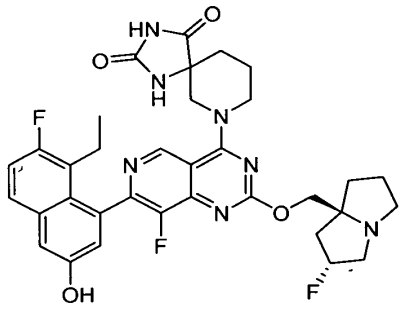
[0000753] Step A. 4-(2,7-dichloro-8-fluoro-pyrido[4,3-*d*]pyrimidin-4-yl)morpholine: To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (600 mg, 2.38 mmol, 1.0 *equiv.*.) in DCM (10.0 mL) were added DIEA (921 mg, 7.13 mmol, 1.24 mL, 3.0 *equiv.*.) and 4Å molecular sieves (200 mg). The mixture was stirred at 25 °C for 10 minutes. Then a solution of morpholine (103 mg, 1.19 mmol, 104 µL, 0.5 *equiv.*.) in DCM (2.0 mL) was added dropwise at -40 °C. The mixture was stirred at -40 °C for 0.5 h. After completion, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 30:1 to 1:1) to afford the title compound (310 mg, 84% yield) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (s, 1H), 4.13-4.07 (m, 4H), 3.92-3.86 (m, 4H); LCMS [ESI, M+1]: 303.1.

[0000754] Step B. 4-[7-chloro-8-fluoro-2-[[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-*d*]pyrimidin-4-yl]morpholine: To a solution of 4-(2,7-dichloro-8-fluoro-

pyrido[4,3-*d*]pyrimidin-4-yl)morpholine (530 mg, 1.75 mmol, 1.0 *equiv.*.) in dioxane (10.0 mL) were added DIEA (678 mg, 5.25 mmol, 914 µL, 3.0 *equiv.*.) and [(2*S*)-1-methylpyrrolidin-2-yl] methanol (604 mg, 5.25 mmol, 623 µL, 3.0 *equiv.*.). The mixture was stirred at 60 °C for 1.5 hrs. After completion, water (10.0 mL) was added and the mixture was extracted with ethyl acetate (3 × 10.0 mL). The combined the organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]) to afford the title compound (480 mg, 67% yield) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H), 4.52 (dd, *J* = 4.8, 10.8 Hz, 1H), 4.33 (dd, *J* = 6.8, 10.8 Hz, 1H), 4.01-3.95 (m, 4H), 3.88-3.81 (m, 4H), 3.13-3.06 (m, 1H), 2.74-2.64 (m, 1H), 2.48 (s, 3H), 2.31-2.25 (m, 1H), 2.09-2.03 (m, 1H), 1.88-1.71 (m, 3H); LCMS [ESI, M+1]: 382.1.

[0000755] Step C. 4-[8-fluoro-2-[[(2*S*)-1-methylpyrrolidin-2-yl]methoxy]-4-morpholino-pyrido[4,3-*d*]pyrimidin-7-yl]naphthalen-2-ol: To a solution of 4-[7-chloro-8-fluoro-2-[[(2S)-1-methylpyrrolidin-2-yl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]morpholine (150 mg, 393 µmol, 1.0 *equiv.*.) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (127 mg, 471 µmol, 1.2 *equiv.*.) in THF (3.0 mL) was added CataCXium A Pd G3 (28.6 mg, 39.3 µmol, 0.1 *equiv.*.) and K_3PO_4 (1.5 M in water , 786 µL, 3.0 *equiv.*.). The mixture was stirred at 60 °C for 2 hrs. After reaction completion, water (5.0 mL) was added and the mixture was extracted with ethyl acetate (3 × 5.0 mL). Combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]). The desired fractions were collected, neutralized with solid $NaHCO_3$, and concentrated in vacuum to remove ACN. The aqueous phase was extracted with ethyl acetate (2 × 10.0 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. Then the residue was purified by prep-HPLC (column: Phenomenex Gemini-NX C18 75 x 30mm x 3µm, mobile phase: [water (10 mM NH_4HCO_3)/ACN]; B%: 22%-52%, 8min) to afford the title compound (51.1 mg, 26% yield) as a yellow solid; ^{1}H NMR (400 MHz, DMSO-d^6): δ 10.21-10.00 (m, 1H), 9.22 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.54 (br d, *J* = 8.4 Hz, 1H), 7.47-7.40 (m, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 7.26-7.21 (m, 2H), 4.41 (dd, *J* = 4.4, 10.8 Hz, 1H), 4.23 (dd, *J* = 6.4, 10.8 Hz, 1H), 4.05-3.97 (m, 4H), 3.84-3.75 (m, 4H), 2.99-2.90 (m, 1H), 2.64-2.54 (m, 1H), 2.35 (s, 3H), 2.17 (q, *J* = 8.8 Hz, 1H), 2.02-1.88 (m, 1H), 1.74-1.57 (m, 3H); HRMS (ESI+) calcd for $C_{27}H_{29}FN_5O_3^+$(M+H$^+$): 490.2249, found 490.2235.

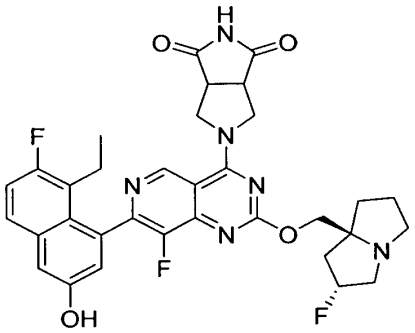
EXAMPLE 196



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

[0000756] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, CD_3OD) δ (ppm) = 9.18-9.04 (m, 1H), 7.67 (dd, J = 5.6, 8.8 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.24 (t, J = 9.6 Hz, 1H), 7.06 (d, J = 2.8 Hz, 1H), 5.40 - 5.15 (m, 1H), 4.69-4.57 (m, 1H), 4.55 - 4.39 (m, 1H), 4.35 - 4.17 (m, 2H), 3.88 - 3.63 (m, 2H), 3.29 - 3.12 (m, 3H), 3.06 - 2.94 (m, 1H), 2.56 - 2.30 (m, 2H), 2.29 - 2.07 (m, 5H), 2.05 - 1.87 (m, 5H), 0.79 (q, J = 7.8 Hz, 3H). LCMS (ESI, M+1): 662.4.

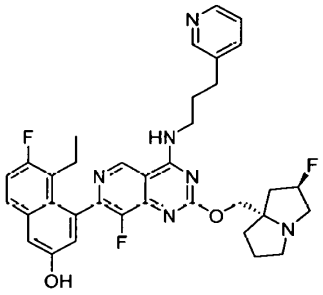
EXAMPLE 197



5-(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)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione

[0000757] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, MeOD) δ 9.29 (s, 1H), 7.68 (dd, J = 6.0, 9.2 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.25 (t, J = 9.2 Hz, 1H), 7.06 (d, J = 2.8 Hz, 1H), 5.57 - 5.37 (m, 1H), 4.68 - 4.60 (m, 2H), 4.59 - 4.48 (m, 2H), 4.40 - 4.30 (m, 2H), 3.80 - 3.55 (m, 5H), 2.67 - 1.97 (m, 9H), 0.78 (br t, J = 7.2 Hz, 3H). LCMS (ESI, M+1): m/z = 633.3.

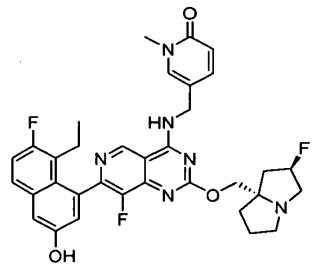
EXAMPLE 198



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

[0000758] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, CD_3OD-d_4) δ 9.10 (s, 1H), 8.46 (d, J = 2.0 Hz, 1H), 8.36 (dd, J = 1.6, 5.2 Hz, 1H), 7.79 (br d, J = 8.0 Hz, 1H), 7.66 (dd, J = 6.0, 9.2 Hz, 1H), 7.37 (dd, J = 4.8, 8.0 Hz, 1H), 7.28 (d, J = 2.8 Hz, 1H), 7.25 (s, 1H), 7.03 (d, J = 2.8 Hz, 1H), 5.45-5.18 (m, 1H), 4.35-4.19 (m, 2H), 3.76 (br t, J = 7.2 Hz, 2H), 3.28-3.12 (m, 3H), 3.01 (dt, J = 5.6, 9.4 Hz, 1H), 2.85 (t, J = 7.6 Hz, 2H), 2.52-2.38 (m, 1H), 2.38-2.19 (m, 2H), 2.19-2.07 (m, 4H), 2.03-1.82 (m, 3H), 0.79 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 629.3.

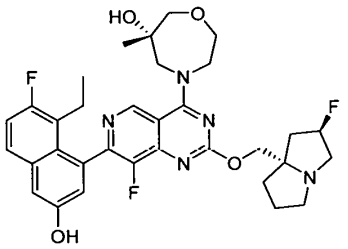
EXAMPLE 199



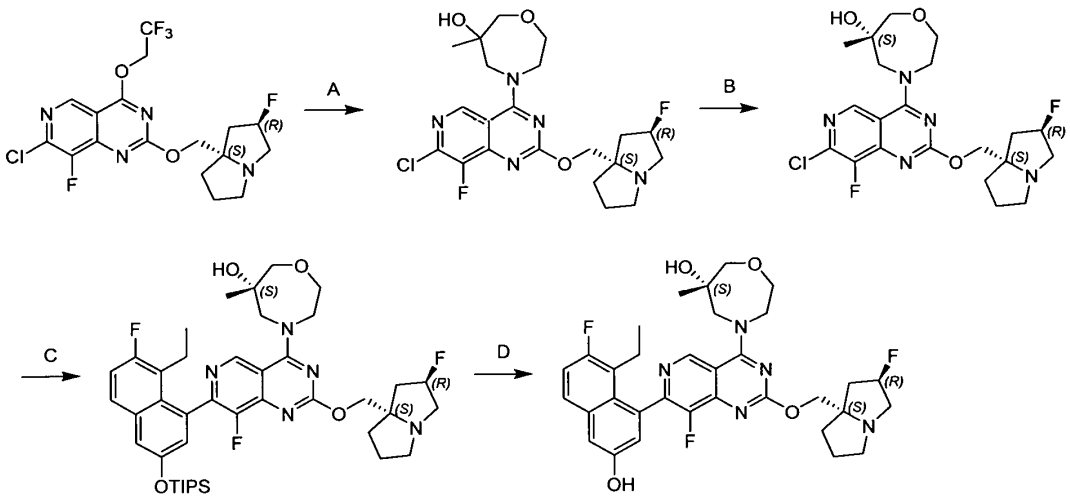
5-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)amino)methyl)-1-methylpyridin-2(1*H*)-one

[0000759] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, CD_3OD-d_4) δ 9.15 (s, 1H), 7.81 (s, 1H), 7.74-7.61 (m, 2H), 7.34-7.17 (m, 2H), 7.03 (d, J = 2.4 Hz, 1H), 6.57 (d, J = 9.2 Hz, 1H), 5.41-5.17 (m, 1H), 4.67 (s, 2H), 4.37-4.19 (m, 2H), 3.59 (s, 3H), 3.28-3.15 (m, 3H), 3.01 (dt, J = 6.0, 9.2 Hz, 1H), 2.53-2.39 (m, 1H), 2.37-2.18 (m, 2H), 2.18-2.07 (m, 2H), 2.04-1.94 (m, 2H), 1.93-1.81 (m, 1H), 0.78 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 631.3.

EXAMPLE 200



(S)-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)-6-methyl-1,4-oxazepan-6-ol



[0000760] Step A. 4-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol: A mixture of 6-methyl-1,4-oxazepan-6-ol (2.66 g, 1.0 *equiv.*), 4Å molecular sieves (850 mg) and DIEA (10.5 g, 4.0 *equiv.*) in DMF (90 mL) was stirred at 15 °C for 0.5 hour. Then 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (8.90 g, 1.0 *equiv.*) was added into the above mixture and the mixture was stirred at 40 °C for 4 hours. The mixture was filtered. The filtrate was diluted with ethyl acetate (120 mL) and water (200 mL), extracted with ethyl acetate (2 × 50 mL) and dichloromethane/methanol = 10/1 (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]) twice. The desired fractions were collected, neutralized with solid $NaHCO_3$, concentrated in vacuum to remove acetonitrile, and extracted with ethyl acetate (3 × 500 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuum to afford the title compound (6.63 g, 68% yield) as a yellow solid; ^{1}H NMR (400 MHz, methanol-*d*4) δ = 9.34 (d, *J* = 2.0 Hz, 1H), 5.38 - 5.21 (m, 1H), 4.52 (td, *J* = 5.2, 14.4 Hz, 1H), 4.43 (dd, *J* = 3.6, 14.8 Hz, 1H), 4.33 - 4.19 (m, 2H), 4.17 - 4.09 (m, 1H), 3.98 (ddd, *J* = 3.6, 6.0, 12.4 Hz, 1H), 3.91 (d, *J* = 15.2 Hz, 1H), 3.86 - 3.78 (m, 1H), 3.71 - 3.60 (m, 2H), 3.28 - 3.16 (m, 3H), 3.05 - 2.97 (m, 1H), 2.36 - 2.23 (m, 1H), 2.23 - 2.17 (m, 1H), 2.16 - 2.08 (m, 1H), 2.03 - 1.94 (m, 2H), 1.93 - 1.83 (m, 1H), 1.25 (s, 3H); LCMS (ESI, M+1): m/z = 470.1.

[0000761] Step B. (S)-4-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol: 4-(7-chloro-8-fluoro-2- (((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol (7.38 g) was separated by SFC [column: DAICEL CHIRALPAK IG (250mm × 50mm, 10 um); mobile phase: [0.1%NH_3xH_2O in EtOH / CO2]; 45% - 45%, 8.7; 300 min]. The first peak was collected and concentrated in vacuum to afford the title compound (3.24 g, 43% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-*d*4) δ = 9.33 (s, 1H), 5.39 - 5.21 (m, 1H), 4.52 (td, *J* = 5.2, 14.4 Hz, 1H), 4.43 (d, *J* = 14.8 Hz, 1H), 4.31 - 4.21 (m, 2H), 4.17 - 4.09 (m, 1H), 3.98 (ddd, *J* = 4.0, 6.4, 12.8 Hz, 1H), 3.90 (d, *J* = 14.8 Hz, 1H), 3.82 (ddd, *J* = 4.0, 7.2, 14.4 Hz, 1H), 3.65 (q, *J* = 12.8 Hz, 2H), 3.29 - 3.15 (m, 3H), 3.05 - 2.95 (m, 1H), 2.36 - 2.23 (m, 1H), 2.23 - 2.17 (m, 1H), 2.16 - 2.07 (m, 1H), 2.03 - 1.93 (m, 2H), 1.93 - 1.82 (m, 1H), 1.25 (s, 3H);

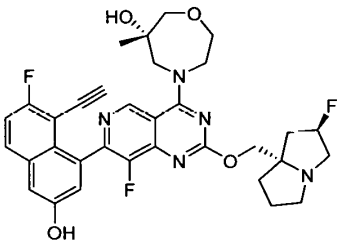
SFC: >99% ee, Chiralpak IG-3 50 × 4.6mm I.D., 3 μm column; A: 60% EtOH + 40% ACN (w/ 0.05% DEA), B: CO_2, 3mL/min, 220 nm, t_R: 1.072 min; LCMS (ESI, M+1): m/z = 470.1.

[0000762] Step C. (S)-4-(7-(8-ethyl-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2- (((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol: To a mixture of (S)-4-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol (1.47 g, 1.0 *equiv.*), ((5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)triisopropylsilane (1.92 g, 1.3 *equiv.*) and K_3PO_4 (1.5 M in water , 6.26 mL, 3.0 *equiv.*) in methoxycyclopentane (19 mL) was added CataCXium A Pd G3 (228 mg, 0.1 *equiv.*) under N_2. The reaction was de-gassed and stirred at 90 °C for 3 hours under N_2. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (20 mL). The organic layer was concentrated in vacuum and purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]). The desired fractions were collected and neutralized with $NaHCO_3$ solid, concentrated in vacuum to remove acetonitrile, and extracted with ethyl acetate (2 × 80 mL). The combined organic layer was washed with brine (60 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuum to afford the title compound (2.08 g, 77% yield) as a white solid; LCMS (ESI, M+1): m/z = 780.5.

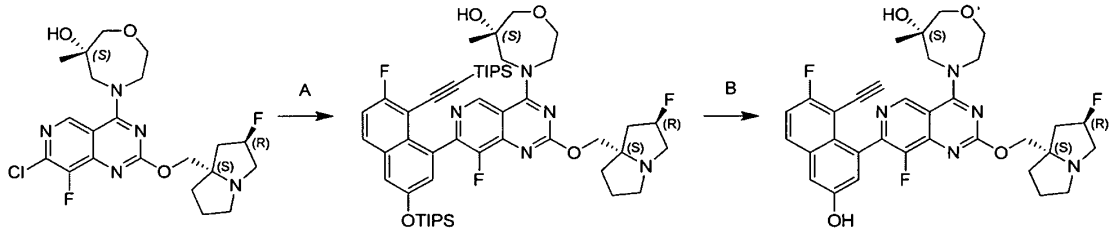
[0000763] Step D. (S)-4-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2- fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol: A mixture of (S)-4-(7-(8-ethyl-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1 -yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol (1.97 g, 1.0 *equiv.*) and CsF (5.75 g, 15 *equiv.*) in DMF (10 mL) was stirred at 15 °C for 1 hour. After completion, the mixture was filtered and the filtrate was purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]). The desired fractions were collected and lyophilized to afford the title compound (1.28 g, 75% yield, formic acid salt) as a white solid; ^{1}H NMR (400 MHz, methanol-*d*4) δ = 9.58 (s, 1H), 7.67 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.32 - 7.29 (m, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.06 (dd, *J* = 2.4, 18.4 Hz, 1H), 5.46 (br d, *J* = 52.8 Hz, 1H), 4.62 - 4.50 (m, 4H), 4.24 - 4.14 (m, 1H), 4.06 - 3.82 (m, 3H), 3.80 - 3.54 (m, 5H), 3.30 - 3.23 (m, 1H), 2.63 - 2.27 (m, 4H), 2.26 - 2.01 (m, 4H), 1.27 (s, 3H), 0.80 (q, *J* = 8.0 Hz, 3H); ^{19}F

NMR (376 MHz, methanol-*d*4) δ = -121.041, -139.083, -173.810; SFC: >99% ee, Chiralpak IG-3 50 × 4.6mm I.D., 3 μm column, A: 60% IPA + 40% ACN (w/ 0.05% DEA), B: CO_2, 3mL/min, 220 nm, t_R: 2.337 min; LCMS (ESI, M+1): m/z = 624.3.

EXAMPLE 201



(S)-4-(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)-6-methyl-1,4-oxazepan-6-ol

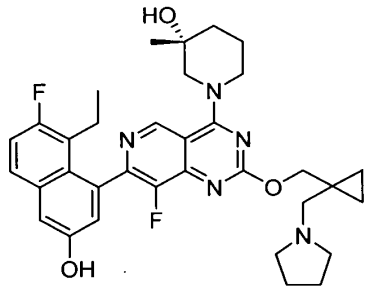


[0000764] Step A. (S)-4-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy) naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol: To a mixture of (S)-4-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol (1.47 g, 1.0 *equiv.*), ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane (2.54 g, 1.3 *equiv.*) and K_3PO_4 (1.5 M in water, 6.26 mL, 3.0 *equiv.*) in THF (19 mL) was added CataCXium A Pd G3 (228 mg, 0.1 *equiv.*) under N_2. The reaction was de-gassed and stirred at 60 °C for 3 hours under N_2. The mixture was diluted with water (20 mL), extracted with ethyl acetate (20 mL), concentrated in vacuum, and purified by reversed phase flash

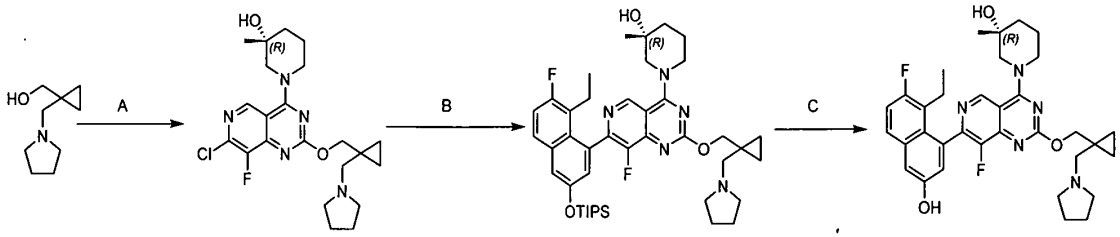
chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]). The desired fractions were collected and concentrated in vacuum to afford the title compound (2.12 g, 70% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 932.6.

[0000765] Step B. (S)-4-(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)-6-methyl-1,4-oxazepan-6-ol: A mixture of (S)-4-(8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol (1.87 g, 1.0 *equiv.*) and CsF (4.57 g, 15 *equiv.*) in DMF (10 mL) was stirred at 15 °C for 7 hours. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography (mobile phase: [water (0.1% formic acid)/acetonitrile]). The desired fractions were collected and lyophilized to afford the title compound (1.19 g, 89% yield, formic acid salt) as a yellow solid; ^{1}H NMR (400 MHz, methanol-*d*4) δ = 9.56 - 9.43 (m, 1H), 7.86 (ddd, *J* = 1.6, 5.6, 8.8 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.23 (dd, *J* = 2.4, 9.6 Hz, 1H), 5.56 - 5.39 (m, 1H), 4.69 - 4.51 (m, 4H), 4.29 - 4.17 (m, 1H), 4.05 - 3.85 (m, 3H), 3.81 - 3.59 (m, 5H), 3.45 (d, *J* = 11.6 Hz, 1H), 3.30 - 3.25 (m, 1H), 2.64 - 2.40 (m, 2H), 2.36 - 2.28 (m, 1H), 2.26 - 2.16 (m, 2H), 2.13 - 2.01 (m, 1H), 1.28 (d, *J* = 14.0 Hz, 3H); ^{19}F NMR (376 MHz, methanol-*d*4) δ = -111.749, -140.066, -173.900; SFC: >99% ee, Chiralpak IE-3 50 × 4.6mm I.D., 3um; A: heptane (0.05% DEA); B: EtOH (0.05% DEA); Gradient: 25% B in A; 1 mL/min, 254 nm, t_R: 4.443 min; LCMS (ESI, M+1): m/z = 620.1.

EXAMPLE 202



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

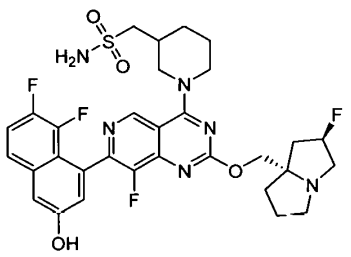


[0000766] Step A. (3R)-1-[7-chloro-8-fluoro-2-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methoxy]pyrido[4,3-*d*]pyrimidin-4-yl]-3-methyl-piperidin-3-ol: A mixture of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (150 mg, 1 *equiv.*), [1-(pyrrolidin-1-ylmethyl)cyclopropyl]methanol (141 mg, 2.0 *equiv.*), DIPEA (178 mg, 3 *equiv.*) and 4Å molecular sieves (50 mg) in dioxane (1.5 mL) was stirred at 95 °C for 12 hours under N_2 atmosphere. The reaction mixture was filtered. The filter cake was washed with DCM (20 mL). The filtrate was concentrated and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile 7:3] to afford the title compound (130 mg, 62% yield) as a light yellow gum; LCMS (ESI, M+1): m/z = 450.2.

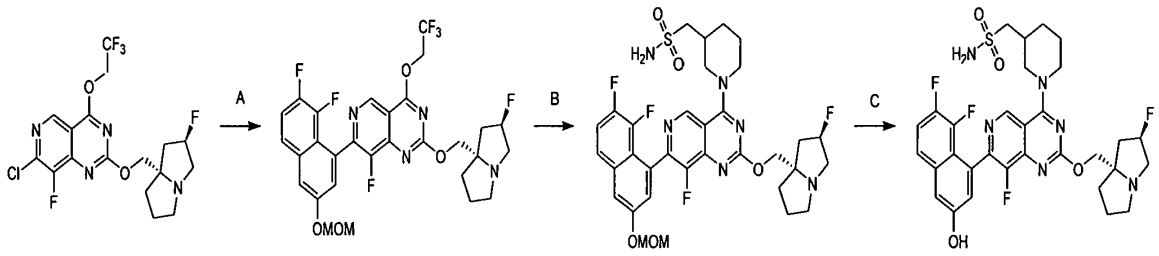
[0000767] Step B. (3R)-1-[7-(8-ethyl-7-fluoro-3-triisopropylsilyloxy-1-naphthyl)-8-fluoro-2-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol: A mixture of (3R)-1-[7-chloro-8-fluoro-2-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methoxy]pyrido[4,3-*d*]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (130 mg, 1 *equiv.*), ((5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)triisopropylsilane (165 mg, 1.2 *equiv.*), CataCXium A (22 mg, 0.1 *equiv.*) and K_3PO_4 (1.5 M in water , 0.6 mL, 3.1 *equiv.*) in methoxycyclopentane (2.4 mL) was degassed and purged with N_2 for 3 times. The mixture was stirred at 90 °C for 2.5 hours. The reaction mixture was diluted with water (1 mL), extracted with ethyl acetate (3 mL × 4), dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (300 mg, crude) as a red gum; LCMS (ESI, M+1): m/z = 760.5.

[0000768] Step C. (3R)-1-[7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol: A mixture of (3R)-1-[7-(8-ethyl-7-fluoro-3-triisopropylsilyloxy-1-naphthyl)-8-fluoro-2-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methoxy]pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (300 mg, crude) and CsF (300 mg) in DMF (2.5 mL) was stirred at 25 °C for 13 hours. The reaction mixture was filtered. The filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile 13:7] and prep-HPLC [column: water s Xbridge 150 × 25mm × 5um; mobile phase: [water (10mM NH_4HCO_3)/CAN]; B%: 33%-66%, 9 minutes] to give a crude product. The crude product was purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30mm ×3um; mobile phase: [water (0.225%formic acid)/ACN]; B%: 20%-50%, 7 minutes] to afford the title compound (60.7 mg, 33% yield over two steps, 0.58 formic acid salt) as a white solid; ^{1}H NMR (400 MHz, methanol-d4) δ = 9.23 (d, J = 3.2 Hz, 1H), 7.68 (dd, J = 6.0, 9.2 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.25 (t, J = 9.6 Hz, 1H), 7.06 (s, 1H), 4.54 (br d, J = 12.4 Hz, 1H), 4.48-4.42 (m, 2H), 4.29 (t, J = 11.2 Hz, 1H), 3.61 (q, J = 13.6 Hz, 1H), 3.45-3.43 (m, 1H), 3.17-3.08 (m, 6H), 2.45-2.42 (m, 1H), 2.19-2.17 (m, 2H), 1.98 (br s, 4H), 1.85-1.76 (m, 3H), 1.29 (d, J = 9.2 Hz, 3H), 0.85-0.75 (m, 7H); LCMS (ESI, M+1): m/z = 604.3.

EXAMPLE 203



1-(1-(7-(7,8-difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide



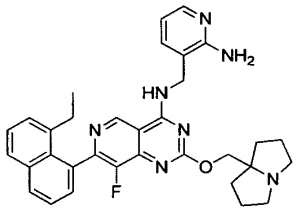
[0000769] Step A. 7-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a mixture of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (300 mg, 1.0 *equiv.*), 2-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (359 mg, 1.5 *equiv.*) and K_3PO_4 (1.5 M in water , 1.37 mL, 3.0 *equiv.*) in THF (5 mL) was added CataCXium A Pd G3 (49.8 mg, 0.1 *equiv.*) under N_2. The reaction was de-gassed and tirred at 60 °C for 1 hour under N_2. The mixture was diluted with water (10 mL), extracted with ethyl acetate (2 × 8 mL), washed with brine (10 mL), dried over Na_2SO_4, concentrated, and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, neutralized with $NaHCO_3$ solid, and extracted with ethyl acetate (2 × 25 mL). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to afford the title compound (323 mg, 73% yield, 0.5 formic acid salt) as a yellow solid; ^{1}H NMR (400 MHz, chloroform-*d*) δ = 9.29 (s, 1H), 7.59 (br dd, *J* = 4.4, 9.2 Hz, 1H), 7.56 - 7.52 (m, 1H), 7.41 - 7.38 (m, 1H), 7.37 - 7.31 (m, 1H), 5.69 - 5.43 (m, 1H), 5.36 - 5.28 (m, 2H), 5.20 - 5.06 (m, 2H), 5.04 - 4.95 (m, 1H), 4.87 - 4.69 (m, 1H), 4.23 - 4.15 (m, 1H), 4.12 - 3.96 (m, 1H), 3.64 - 3.49 (m, 4H), 3.35 - 3.26 (m, 1H), 2.91 - 2.69 (m, 1H), 2.63 - 2.36 (m, 3H), 2.35 - 2.28 (m, 2H); LCMS (ESI, M+1): m/z = 627.1.

[0000770] Step B. (1-(7-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide: A mixture of piperidin-3-ylmethanesulfonamide (65.9 mg, 2.0 *equiv.*), DIEA (95.5 mg, 4.0 *equiv.*) and 4Å molecular sieves (20 mg) in DMF (1.5 mL) was stirred at 15 °C for 0.5 hour. Then 7-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-

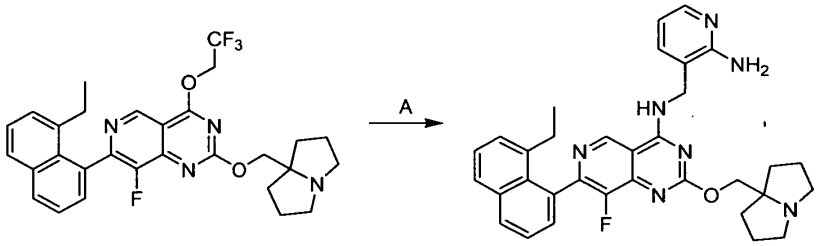
trifluoroethoxy)pyrido[4,3-d]pyrimidine (120 mg, 0.5 formic acid salt) was added into the above mixture and the resulting was stirred at 40 °C for 14 hours. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, neutralized with $NaHCO_3$ solid, concentrated in vacuum to remove acetonitrile, and extracted with ethyl acetate (2 × 15 mL). The combined organic phase was washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to afford the title compound (120 mg, 90% yield) as a yellow solid; LCMS (ESI, M+1, M/2+1): m/z = 705.3, 353.2.

[0000771] Step C. 1-(1-(7-(7,8-difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide: To a mixture of (1-(7-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1 -yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide (60.0 mg, 1.0 *equiv.*) in MeCN (0.5 mL) was added HCl•dioxane (4 M, 1.0 mL, 47 *equiv.*) at 0 °C and the mixture was stirred at 0 °C for 0.5 hour. The mixture was concentrated in vacuum, neutralized with saturated $NaHCO_3$ solution, extracted with ethyl acetate (2 × 8 mL), concentrated in vacuum and purified by prep-HPLC [column: PhenomenexSynergi C18 150 × 25mm × 10um; mobile phase: [water (0.225% formic acid)/ACN]; B%: 8% - 38%, 10 min]. The desired fraction was collected and lyophilized to afford the title compound (30.4 mg, 51% yield, 0.6 formic acid salt) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.13 (s, 1H), 7.62 (br dd, J = 4.4, 8.8 Hz, 1H), 7.44 - 7.36 (m, 1H), 7.34 (s, 1H), 7.25 (dd, J = 2.0, 15.2 Hz, 1H), 5.48 (br d, J = 52.8 Hz, 1H), 5.18 - 5.05 (m, 1H), 4.73 - 4.47 (m, 3H), 3.85 - 3.55 (m, 4H), 3.36 (br s, 1H), 3.29 - 3.10 (m, 3H), 2.68 - 2.36 (m, 4H), 2.25 - 2.01 (m, 4H), 1.96 - 1.87 (m, 1H), 1.83 - 1.54 (m, 2H); ^{19}F NMR (376 MHz, methanol-d_4) δ = -141.320, -145.127, -146.874, -173.734; LCMS (ESI, M+1, M/2+1): m/z = 661.3, 331.2.

EXAMPLE 204

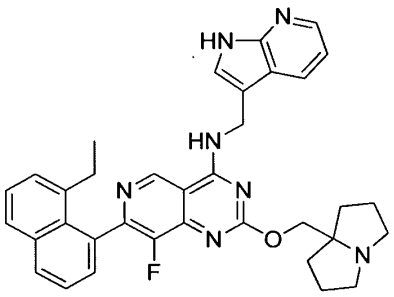


N-((2-aminopyridin-3-yl)methyl)-7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine



[0000772] Step A. N-((2-aminopyridin-3-yl)methyl)-7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine: To a solution of 7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (60.0 mg, 1.0 *equiv.*), 3-(aminomethyl)pyridin-2-amine (27.3 mg, 2.0 *equiv.*) and 4Å molecular sieves (10 mg) in DMF (0.5 mL) was added DIEA (71.7 mg, 5.0 *equiv.*). The reaction was stirred at 40 °C for 72 hours. The mixture was filtered and the filter cake was washed with DMF (1 mL). The filtrate was purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; mobile phase: [water (0.225% formic acid), ACN]; B%: 18%-28%, 7min] to afford title compound (24.2 mg, 39% yield) as an off-white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.24 (s, 1H), 8.61 -8.29 (m, 1H), 8.06 (d, *J* = 7.2 Hz, 1H), 7.94-7.90 (m, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.64 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.52-7.46 (m, 1H), 7.45-7.38 (m, 2H), 6.72 (dd, *J* = 5.2, 7.2 Hz, 1H), 4.77 (s, 2H), 4.65 (s, 2H), 3.72-3.62 (m, 2H), 3.30-3.22 (m, 2H), 2.45-2.37 (m, 1H), 2.36-2.26 (m, 3H), 2.26-2.12 (m, 4H), 2.11-2.04 (m, 2H), 0.91 (t, *J* = 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 564.2.

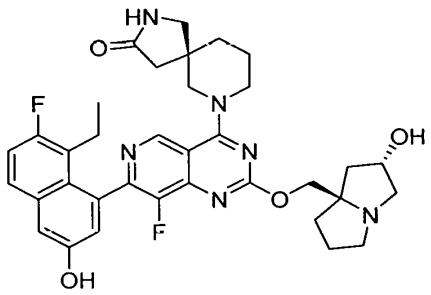
EXAMPLE 205



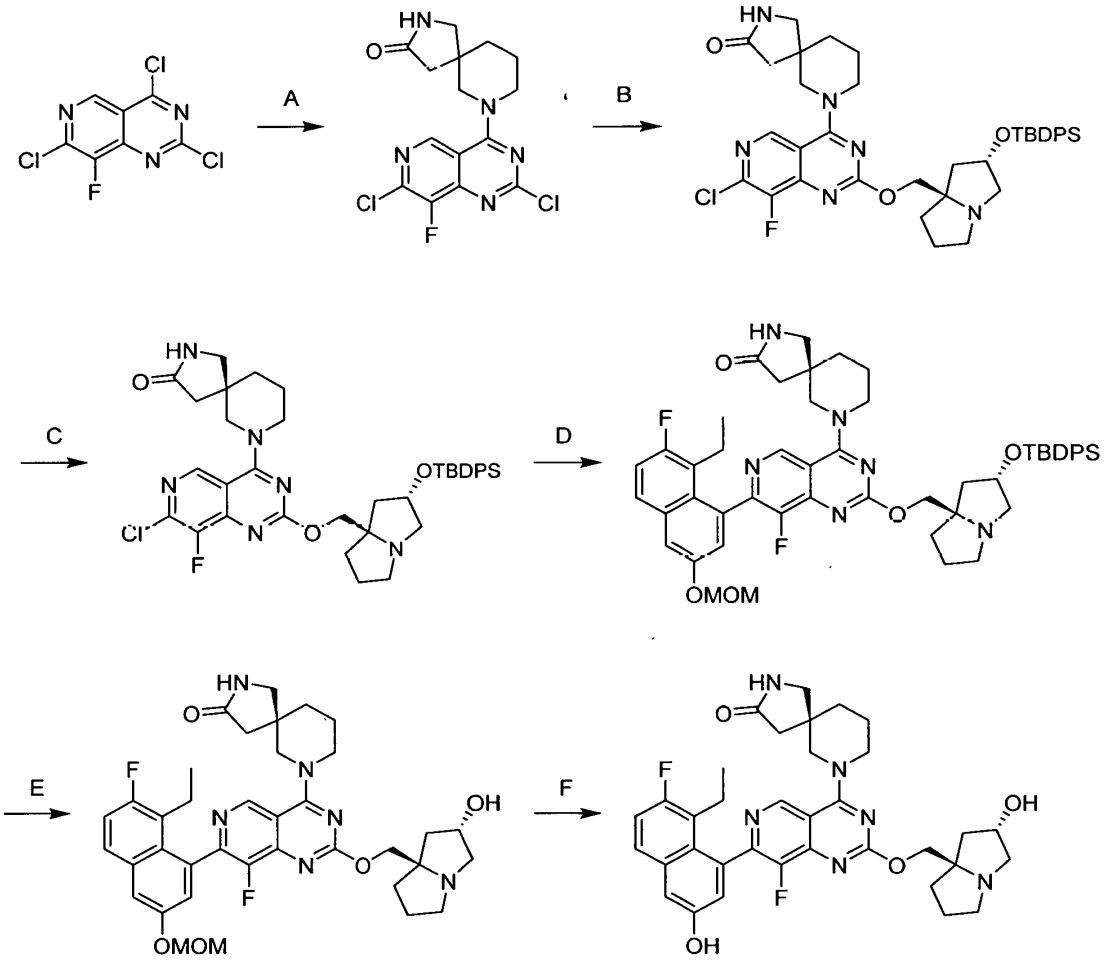
N-((1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-amine

[0000773] The title compound was synthesized according to the procedure described for example 204. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.15 (s, 1H), 8.23-8.17 (m, 2H), 8.06-8.00 (m, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.57-7.52 (m, 2H), 7.50-7.45 (m, 1H), 7.43-7.36 (m, 2H), 7.15-7.11 (m, 1H), 5.13-5.02 (m, 2H), 4.39 (s, 2H), 3.15 (br dd, J = 5.6, 9.6 Hz, 2H), 2.84-2.73 (m, 2H), 2.44-2.23 (m, 2H), 2.10 (ddd, J = 2.4, 6.4, 12.4 Hz, 2H), 2.00-1.87 (m, 4H), 1.84-1.76 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H); LCMS (ESI, M+1): m/z = 588.4.

EXAMPLE 206



(S)-7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2S,7aR)-2-hydroxyhexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one



[0000774] 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 2,9-diazaspiro[4.5]decan-3-one (3.36 g, 1.0 *equiv.*) in DMF (50 mL) was added DIEA (8.45 g, 11.38 mL, 3.0 *equiv.*) and 2,4,7-trichloro-8-fluoro-pyrido[4,3-d]pyrimidine (5.5 g, 1.0 *equiv.*). The reaction was stirred at -40 °C for 3 hours. The mixture was diluted with water 50 mL and extracted with ethyl acetate 150 mL (50 mL × 3). The combined organic layers were washed with brine 300 mL, dried over Na_2SO_4, concentrated, and purified by reversed phase flash chromatography (Silica gel, DCM/MeOH 10:1) to afford the title compound (7.00 g, 87% yield) as a yellow solid.

[0000775] Step B. 7-(2-(((2S,7aR)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of 7-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (3.00 g, 1.0 *equiv.*) and DIPEA (5.24 g, 7.06 mL, 5.0 *equiv.*) in dioxane (30 mL) was added ((2S,7aR)-2-((tert-butyldiphenylsilyl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (3.21 g, 1.0 *equiv.*). The reaction was stirred at 100 °C for 6 hours. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated, and purified by prep-HPLC (mobile phase: [water (0.1% formic acid)/acetonitrile]; 5-70%) to afford the title compound (1.63 g, 15% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.76 (d, J = 4.8 Hz, 1H), 7.66 - 7.64 (m, 1H), 7.66 - 7.58 (m, 3H), 7.51 - 7.36 (m, 6H), 4.74 - 4.52 (m, 2H), 4.35 (dd, J = 18.8, 10.9 Hz, 1H), 4.27 - 3.66 (m, 6H), 3.61 - 3.27 (m, 3H), 3.19 - 2.96 (m, 2H), 2.53 - 2.09 (m, 8H), 1.91 - 1.65 (m, 4H), 1.09 (s, 9H); LCMS (ESI, M+1): m/z = 729.3.

[0000776] Step C. (S)-7-(2-(((2S,7aR)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: 7-(2-(((2S,7aR)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (3.80 g) was purified by chiral prep-HPLC (column: DAICEL CHIRALCEL OD (250mm×30mm,10μm); mobile phase: [0.1% NH_3•H2O/MeOH]; B%: 50%-50%,4.5; 180min) to give the title compound (1.7 g, 32 % yield, 98.9% ee) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.62 (s, 1H), 7.59 - 7.54 (m, 4H), 7.34 - 7.24 (m, 6H), 4.49 - 4.40 (m, 1H), 4.13 - 3.83 (m, 6H), 3.65 - 3.59 (m, 1H), 3.30 (d, J = 7.0 Hz, 3H), 3.04 (s, 3H), 2.18 - 1.98 (m, 8H), 1.80 - 1.71 (m, 4H), 0.98 (s, 9H); LCMS (ESI, M+1): m/z = 729.3.

[0000777] Step D. (S)-7-(2-(((2S,7aR)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: A mixture of 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (356 mg, 2.0 *equiv.*), (S)-7-(2-(((2S,7aR)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (500 mg, 1.0 *equiv.*), CataCXium A Pd G3 (35.95 mg, 0.1 *equiv.*) and K_3PO_4 (1.5 M, 987 μL, 3.0

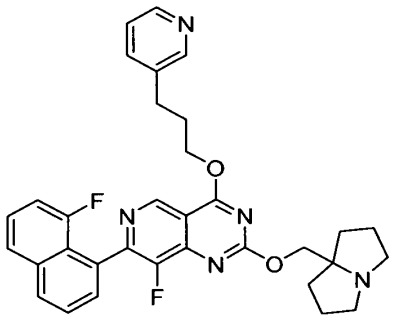
equiv.) in THF (1 mL) was degassed and stirred at 60 °C for 2 hours under nitrogen atmosphere. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (5 mL × 2). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, concentrated and purified by column chromatography (silica gel, DCM/MeOH 1:1) to afford (349 mg, 76% yield) as an orange oil. LCMS (ESI, M+1): m/z = 927.8.

[0000778] Step E. (S)-7-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2S,7aR)-2-hydroxyhexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of (S)-7-(2-(((2S,7aR)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (100 mg, 1.0 *equiv.*) in DMF (1 mL) was added CsF (246 mg, 15 *equiv.*), the reaction was stirred at 40 °C for 16 hours. The mixture was diluted with ethyl acetate (5 mL), washed with brine (15 mL), dried over Na_2SO_4, concentrated, and purified by column chromatography (Silica gel, Ethyl acetate / MeOH (0.1% NH_4OH) 0-100%) to afford the title compound (51 mg, 69% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 9.03 - 8.90 (m, 1H), 7.67 (dd, J = 8.8, 6.0 , Hz, 1H), 7.51 (d, J = 2.8 Hz, 1H), 7.25 - 7.17 (m, 2H), 5.31 - 5.26 (m, 2H), 4.68 (d, J = 5.2 Hz, 1H), 4.49 - 4.34 (m, 1H), 4.22 (d, J = 7.2 Hz, 1H), 4.09 (s, 1H), 3.89 (br s, 1H), 3.76 (t, J = 14.4 Hz, 2H), 3.50 (s, 3H), 3.50 - 3.40 (m, 2H), 3.22 (d, J = 9.6 Hz, 1H), 3.05 - 2.91 (m, 1H), 2.84 - 2.69 (m, 1H), 2.55 - 2.42 (m, 2H), 2.41 - 2.14 (m, 5H), 1.94 - 1.82 (m, 7H), 0.84 (dt, J = 7.4, 2.8 Hz, 4H); LCMS (ESI, M+1): m/z = 689.6.

[0000779] Step F. (S)-7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2S,7aR)-2-hydroxyhexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one: To a solution of (S)-7-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2S,7aR)-2-hydroxyhexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one (37.00 mg, 1.0 *equiv.*) in MeCN (0.4 mL) was added HCl/dioxane (4 M, 376 µL, 28 *equiv.*). The mixture was stirred at 0 °C for 0.5 hour. The mixture was concentrated and purified by prep-HPLC (column: Phenomenex luna C18 150×25mm× 10µm; mobile phase: [water (0.225% formic acid)/ACN]; B%: 14%-44%, 11.5min) to afford the title compound (16.7 mg, 47% yield, 96.7 % ee, formic acid salt) as a yellow solid. ^1H NMR (400 MHz, CD_3OD) δ = 9.12 (s, 1H), 8.58 - 8.48 (m, 1H), 7.73 -

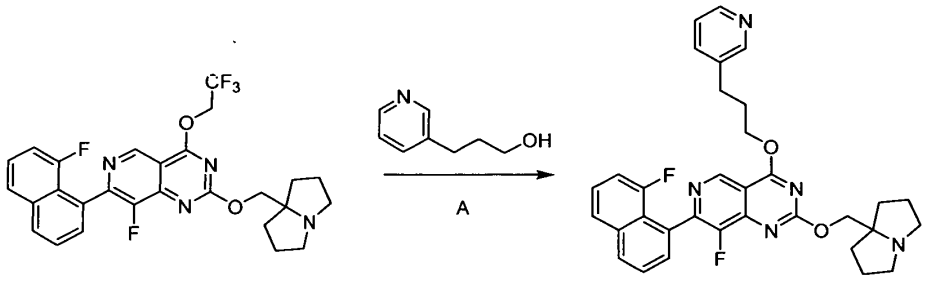
7.64 (m, 1H), 7.31 (d, J = 2.8 Hz, 1H), 7.26 (t, J = 9.2 Hz, 1H), 7.05 (t, J = 3.2 Hz, 1H), 4.66 (s, 1H), 4.56 (dd, J = 11.8, 2.4 Hz, 1H), 4.51 - 4.37 (m, 2H), 4.36 - 4.20 (m, 1H), 4.12 - 3.95 (m, 1H), 3.83 - 3.59 (m, 3H), 3.57 - 3.43 (m, 1H), 3.29 - 3.19 (m, 3H), 2.51 - 2.09 (m, 10H), 1.94 - 1.83 (m, 4H), 0.85 - 0.75 (m, 3H); ^{19}F NMR (377 MHz, CD_3OD) δ = -121.09, -139.15; LCMS (ESI, M+1): m/z = 645.5.

EXAMPLE 207



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

[0000780] Step A: 8-fluoro-7-(8-fluoronaphthalen-1-yl)-4-(3-(pyridin-3-yl)propoxy)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine: To a mixture of 3-(pyridin-3-yl)propan-1-ol (1.5 equiv.) and 4 Å molecular sieves (20 mg) in THF (2 mL) was added LiHMDS (1 M, 141 µL, 1.5 equiv.) at 0 °C. After addition, the mixture was stirred at 0 °C for 20 minutes, and then 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 (50 mg, 1 equiv.) was added at 0 °C. The resulting mixture was stirred at 20 °C for 40 minutes. The reaction mixture was quenched with saturated aqueous NH_4Cl (3 mL) and extracted with ethyl acetate (3×5 mL) 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 prep-HPLC (column: Shim-pack C18 150×25×10um; mobile phase: [water (0.225% formic acid)/ACN]; B%: 31%-51%, 10 min) and lyophilized to afford the title compound. LCMS (ESI, M+1): m/z 568.4.

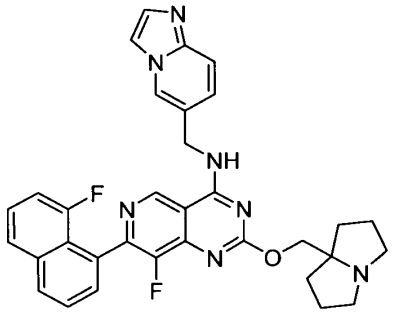


[0000781] Example 208 to 223 were synthesized according to the procedure described for example 34.

[0000782] Table 2. Mass Spectrum Data of Example 208 to 223

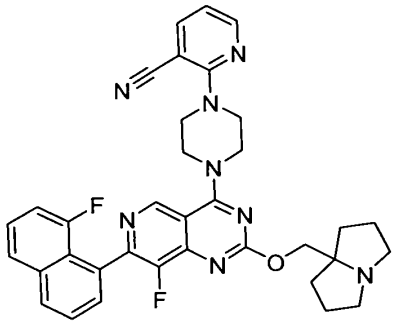
Example No.	Obs. M+1	Example No.	Obs. M+1
208	578.3	216	618.3
209	619.3	217	586.3
210	591.2	218	564.3
211	568.3	219	543.2
212	592.3	220	558.3
213	565.3	221	609.2
214	579.2	222	584.3
215	542.3	223	592.2

EXAMPLE 208



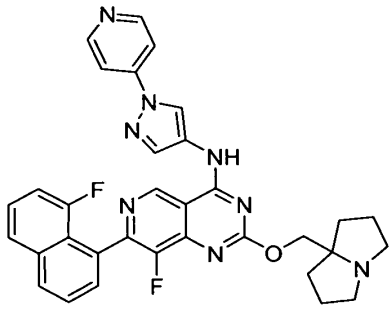
8-fluoro-7-(8-fluoronaphthalen-1-yl)-N-(imidazo[1,2-a]pyridin-6-ylmethyl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 209



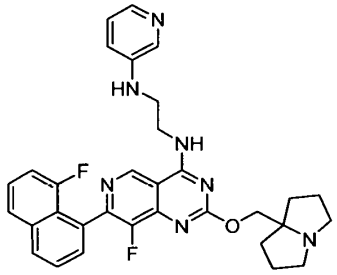
2-(4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperazin-1-yl)nicotinonitrile

EXAMPLE 210



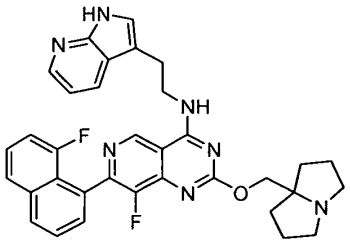
8-fluoro-7-(8-fluoronaphthalen-1-yl)-N-(1-(pyridin-4-yl)-1H-pyrazol-4-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 211



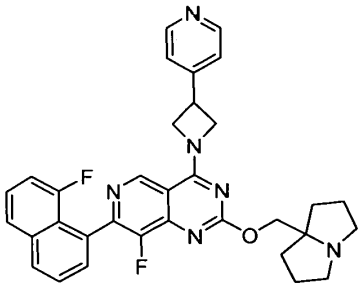
N1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N2-(pyridin-3-yl)ethane-1,2-diamine

EXAMPLE 212



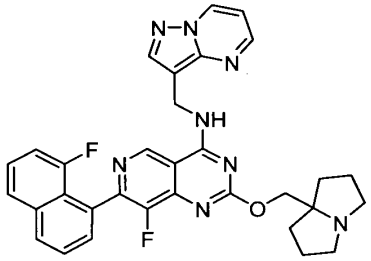
N-(2-(1H-pyrrolo[2,3-b]pyridin-3-yl)ethyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 213



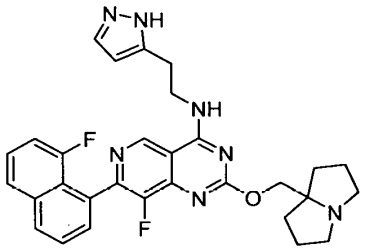
8-fluoro-7-(8-fluoronaphthalen-1-yl)-4-(3-(pyridin-4-yl)azetidin-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine

EXAMPLE 214



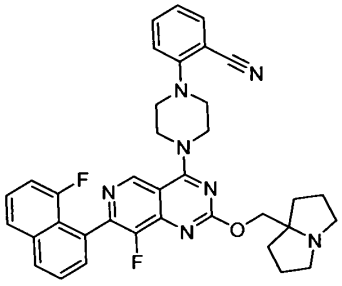
8-fluoro-7-(8-fluoronaphthalen-1-yl)-N-(pyrazolo[1,5-a]pyrimidin-3-ylmethyl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 215



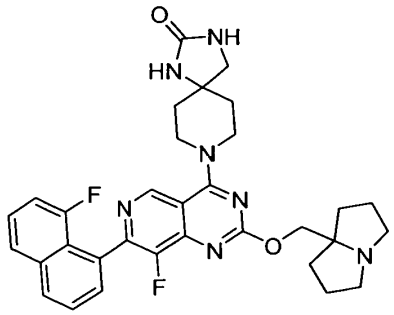
N-(2-(1H-pyrazol-5-yl)ethyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 216



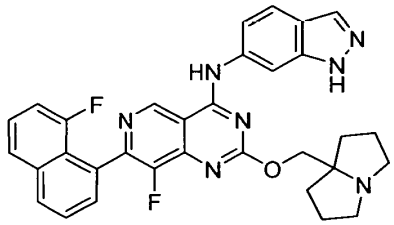
2-(4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4 yl)piperazin-1-yl)benzonitrile

EXAMPLE 217



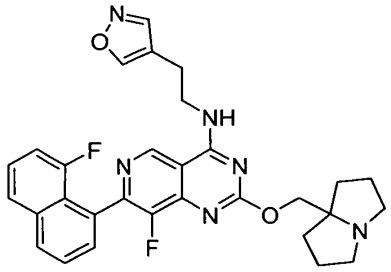
8-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,8-triazaspiro[4.5]decan-2-one

EXAMPLE 218



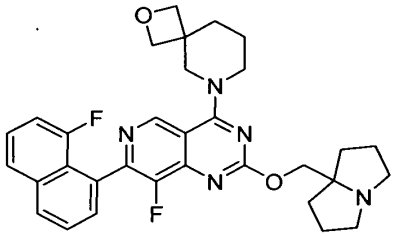
8-fluoro-7-(8-fluoronaphthalen-1-yl)-N-(1H-indazol-6-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 219



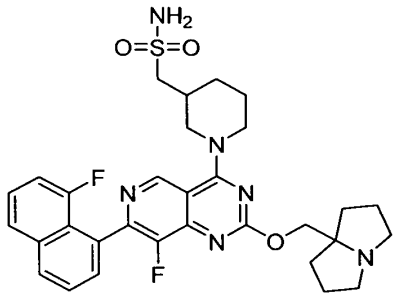
8-fluoro-7-(8-fluoronaphthalen-1-yl)-N-(2-(isoxazol-4-yl)ethyl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 220



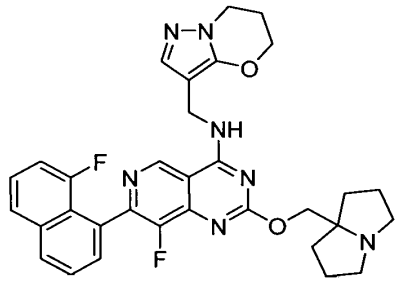
6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-oxa-6-azaspiro[3.5]nonane

EXAMPLE 221



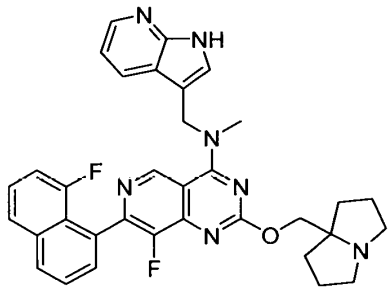
1-(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide

EXAMPLE 222



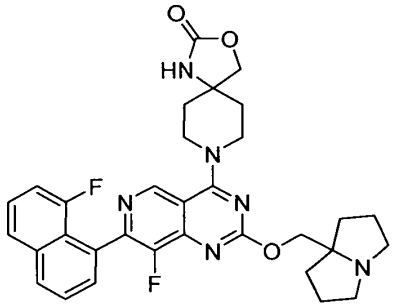
N-((6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-3-yl)methyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

EXAMPLE 223



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

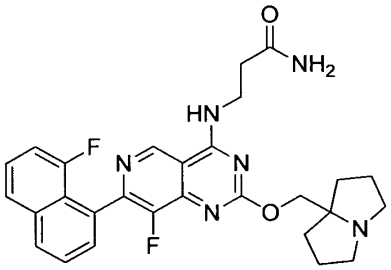
EXAMPLE 224



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

[0000783] The title compound was synthesized according to the procedure described for example 85. LCMS (ESI, M+1): m/z 587.3.

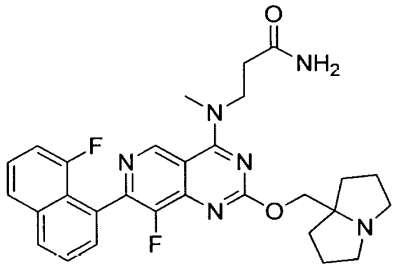
EXAMPLE 225



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

[0000784] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400MHz, MeOD-*d*4) δ 9.17 (s, 1H), 8.12 (br d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 6.6 Hz, 1H), 7.57-7.50 (m, 1H), 7.19 (dd, *J* = 7.6, 13.0 Hz, 1H), 4.66-4.54 (m, 2H), 4.07-3.89 (m, 2H), 3.60-3.48 (m, 2H), 3.19-3.07 (m, 2H), 2.71 (t, *J* = 6.8 Hz, 2H), 2.33-2.23 (m, 2H), 2.21-2.06 (m, 4H), 2.05-1.95 (m, 2H); LCMS (ESI, M+1): m/z = 519.1.

EXAMPLE 226

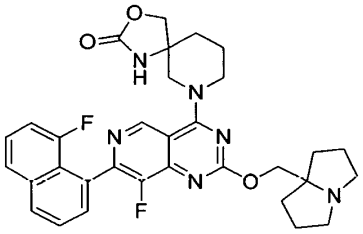


3-((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)(methyl)amino)propanamide

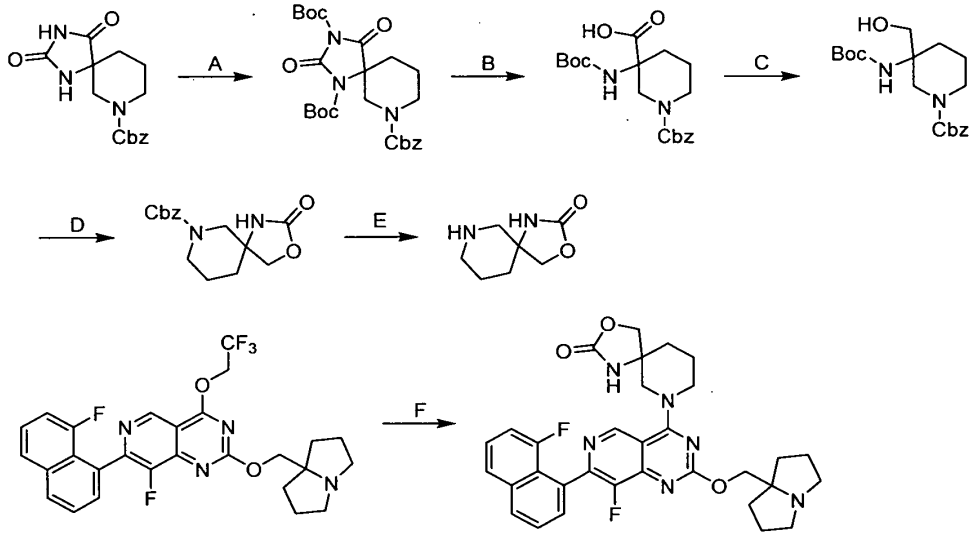
[0000785] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400MHz, DMSO-d6) δ 9.26 (s, 1H), 8.20 (s, 1H), 8.18 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.78-7.68 (m, 1H), 7.65-7.54 (m, 2H), 7.52-7.42 (m, 1H), 7.33-7.28 (m, 1H), 7.01-6.88 (m, 1H), 4.13 (s, 2H), 4.06-4.05 (d, J=6.2 Hz, 2H), 3.53 (s, 3H), 3.02-2.97 (m, 2H),

2.63-2.61 (m, 3H), 1.93-1.89 (dd, J = 5.5, 11.5 Hz, 3H), 1.87-1.74 (m, 5H), 1.68-1.57 (m, 2H); LCMS (ESI, M+1): m/z = 533.2.

EXAMPLE 227



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



[0000786] Step A. 7-benzyl 1,3-di-tert-butyl 2,4-dioxo-1,3,7-triazaspiro[4.5]decane-1,3,7-tricarboxylate: A mixture of benzyl 2,4-dioxo-1,3,7-triazaspiro[4.5]decane-7-carboxylate (3 g, 1 *equiv.*), $(Boc)_2O$ (8.63 g, 4 *equiv.*), TEA (1.0 g, 1 *equiv.*) and DMAP (31 mg, 0.03 *equiv.*) in DME (100 mL) was stirred at 25 °C for 18 hours. The reaction mixture was concentrated to give a yellow solid. The solid was dispersed in isopropyl ether (20 mL) and the mixture was stirred for 10 minutes. The mixture was filtered and the solid was dried under reduced pressure to afford the tittle compound (4 g, crude) as a light-yellow solid; LCMS [ESI, M+H]: m/z = 504.3.

[0000787] Step B. 1-((benzyloxy)carbonyl)-3-((tert-butoxycarbonyl)amino)piperidine-3-carboxylic acid: To a solution of 7-benzyl 1,3-di-tert-butyl 2,4-dioxo-1,3,7-triazaspiro[4.5]decane-1,3,7-tricarboxylate (2 g, 1 *equiv.*) in THF (20 mL) was added $LiOH•H_2O$ (1 M in water , 31.8 mL, 8 *equiv.*) at 25 °C. The mixture was stirred at 25 °C for 18 hours. The pH of the reaction mixture was adjusted to 10 with 2N HCl while maintaining the reaction mixture temperature below 5 °C. $(Boc)_2O$ (4 mL) was added and the mixture was stirred at 25 °C for 18 hours. The pH of the reaction mixture was adjusted to 3 ~ 4 with 2N HCl while maintaining the reaction mixture temperature below 5 °C. The mixture was extracted with ethyl acetate (4 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile 1:1] to afford the tittle compound (1.9 g, crude) as a brown gum; LCMS [ESI, M-55]: m/z = 323.3.

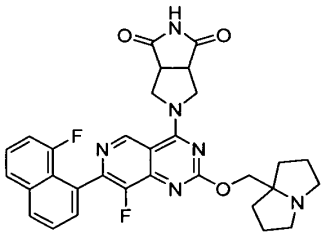
[0000788] Step C. benzyl 3-((tert-butoxycarbonyl)amino)-3-(hydroxymethyl)piperidine-1-carboxylate: To a solution of 1-((benzyloxy)carbonyl)-3-((tert-butoxycarbonyl)amino)piperidine-3-carboxylic acid (1.9 g, crude) in THF (30 mL) was added $LiAlH_4$ (250 mg, 1.3 *equiv.*) at 0 °C under N_2 atmosphere. The mixture was stirred at 20 °C for 15 hours. The reaction mixture was quenched with $Na_2SO_4•10H_2O$ (2 g) and saturated aqueous $NaHCO_3$ (0.1 mL) at 0 °C. Na_2SO_4 (3 g) was added and the mixture was stirred for 5 minutes. The mixture was filtered through a pad of Celite and the filter cake was washed with ethyl acetate/ methanol 10:1 (20 mL) and methanol (100 mL). The filtrate was concentrated and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile 1:4] to afford the tittle compound (0.69 g, crude) as a white gum; LCMS [ESI, M-55]: m/z = 309.2.

[0000789] Step D. benzyl 2-oxo-3-oxa-1,7-diazaspiro[4.5]decane-7-carboxylate: To a solution of benzyl 3-((tert-butoxycarbonyl)amino)-3-(hydroxymethyl)piperidine-1-carboxylate (0.69 g, crude) in DMF (10 mL) was added NaH (60% in mineral oil, 114 mg, 1.5 *equiv.*) in portions at 0 °C. The mixture was stirred at 20 °C for 16 hours. The mixture was quenched with water (150 mL) at 0 °C and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile 1:1] to afford the tittle compound (270 mg, crude) as a white gum; LCMS [ESI, M-55]: m/z =291.2.

[0000790] Step E. 3-oxa-1,7-diazaspiro[4.5]decan-2-one: To a solution of benzyl 2-oxo-3-oxa-1,7-diazaspiro[4.5]decane-7-carboxylate (270 mg, 1 *equiv.*) in CF_3COOH (9 mL) was added $Pd(OH)_2$ (40 mg, 10% purity) under N_2 atmosphere. The mixture was degassed and purged with H_2 for 3 times. The mixture was stirred at 20 °C for 2 hours under H_2 atmosphere (15 psi). The reaction mixture was filtered through a pad of Celite. The filter cake was washed with THF/MeOH 1:1 (30 mL). The combined organic phase was concentrated under reduced pressure. The residue was washed with THF (5 mL × 5) and the combined THF phase was concentrated to afford the tittle compound (145 mg, 36 % yield over five steps) as a colorless oil.

[0000791] Step F. 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-oxa-1,7-diazaspiro[4.5]decan-2-one: 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 (200 mg, 1 *equiv.*), 3-oxa-1,7-diazaspiro[4.5]decan-2-one (145 mg, 2.5 *equiv.*), DIPEA (171 mg, 3.5 *equiv.*) and 4Å molecular sieves (40 mg) in DMF (2 mL) was stirred at 40 °C for 18 hours under N_2 atmosphere. The reaction mixture was filtered. The filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile 7:3] and then prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: [water (10mM NH_4HCO_3)/ACN]; B%: 13%-43%, 10 minutes] to afford the tittle compound (82.6 mg, 36 % yield) as a white solid; ^1H NMR (400 MHz, DMSO-d6) δ = 9.09 (d, *J* = 1.6 Hz, 1H), 8.41 (br s, 1H), 8.18 (br d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.74-7.62 (m, 1H), 7.59-7.58 (m, 2H), 7.31 (dd, *J* = 7.2, 12.8 Hz, 1H), 4.29-4.05 (m, 6H), 3.69-3.66 (m, 2H), 2.94-2.89 (m, 2H), 2.59-2.51 (m, 2H), 1.89-1.77 (m, 10H), 1.61-1.58 (m, 2H); LCMS [ESI, M+H]: m/z = 587.4.

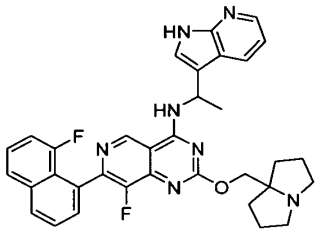
EXAMPLE 228



5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione

[0000792] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.29 (s, 1H), 8.12 (br d, *J* = 7.6 Hz, 1H), 7.85 (br d, *J* = 8.0 Hz, 1H), 7.70 (br t, *J* = 7.6 Hz, 1H), 7.61 (br d, *J* = 7.2 Hz, 1H), 7.57 - 7.48 (m, 1H), 7.18 (br dd, *J* = 7.6, 12.8 Hz, 1H), 4.64 (br d, *J* = 13.2 Hz, 2H), 4.56 (s, 2H), 4.35 (br d, *J* = 3.6 Hz, 2H), 3.78 - 3.76 (m, 2H), 3.60 - 3.47 (m, 2H), 3.20 - 3.07 (m, 2H), 2.26 (td, J = 6.4, 12.4 Hz, 2H), 2.11 (ddd, *J* = 6.4, 12.4, 18.8 Hz, 4H), 2.01 (br dd, *J* = 6.4, 12.8 Hz, 2H) LCMS [ESI, M+1]: m/z = 571.2

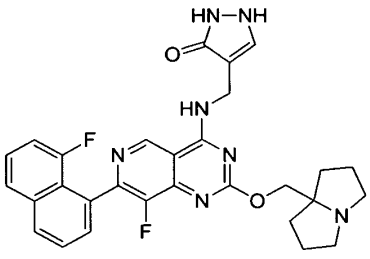
EXAMPLE 229



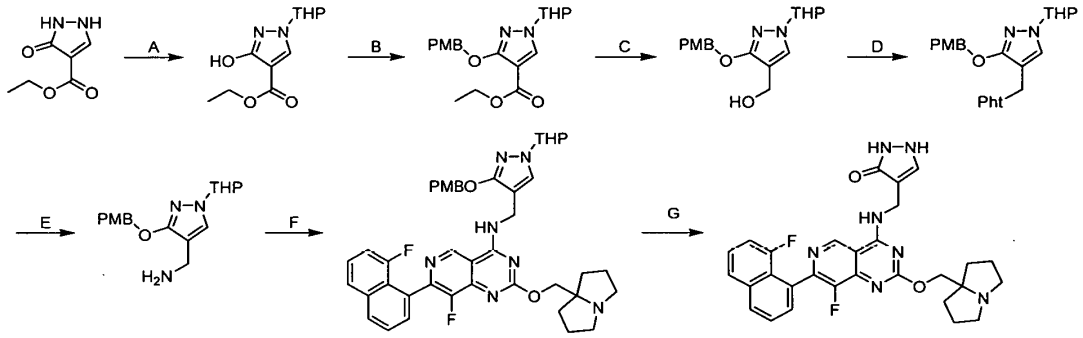
N-(1-(1H-pyrrolo[2,3-b]pyridin-3-yl)ethyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-amine

[0000793] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, methanol-*d*4) δ 9.29 (d, *J* = 3.2 Hz, 1H), 8.23 - 8.09 (m, 3H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.70 (td, *J* = 4.4, 7.6 Hz, 1H), 7.62 - 7.49 (m, 2H), 7.23 - 7.07 (m, 2H), 6.10 - 6.00 (m, 1H), 4.64 - 4.51 (m, 2H), 3.64 - 3.52 (m, 2H), 3.24 - 3.14 (m, 2H), 2.29 - 1.95 (m, 8H), 1.86 (dd, *J* = 3.2, 6.8 Hz, 3H); ^{19}F NMR (376 MHz, methanol-*d*4) δ = -115.427, -141.83; LCMS [ESI, M+1, M/2+1]: m/z = 592.3, 296.7.

EXAMPLE 230



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



[0000794] Step A. ethyl 3-hydroxy-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-4-carboxylate: A mixture of ethyl 3-oxo-2,3-dihydro-1H-pyrazole-4-carboxylate (2 g, 1 *equiv.*) in DCM (20 mL), DHP (3.31 g, 3 *equiv.*), TosOH (220 mg, 0.1 *equiv.*) was stirred at 25 °C for 2 hours under N_2 atmosphere. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, concentrated and purified by silica gel column chromatography [petroleum ether / ethyl acetate] to afford the title compound (2.5 g, 80% yield) as a yellow solid; ^{1}H NMR (400 MHz, DMSO-d6) δ = 10.42 (s, 1H), 8.10 (s, 1H), 5.20 (dd, J = 2.4, 9.6 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.92 (m, 1H), 3.65-3.50 (m, 1H), 1.99 (br s, 1H), 1.93-1.79 (m, 2H), 1.60 (m, 1H), 1.55-1.45 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+Na): m/z = 263.0.

[0000795] Step B. ethyl 3-((4-methoxybenzyl)oxy)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-4-carboxylate: To a mixture of ethyl 3-hydroxy-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-4-carboxylate (800 mg, 1 *equiv.*), K_2CO_3 (920 mg, 2 *equiv.*) in DMF (12 mL) was added PMBCl (626 mg, 1.2 *equiv.*). The mixture was stirred at 60 °C for 16 hours under N_2 atmosphere. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, concentrated and purified by silica gel column chromatography [petroleum ether / ethyl acetate] to afford the title compound (1.0 g, 75.6 % yield) as a white solid; ^{1}H NMR (400 MHz, DMSO-d6) δ = 8.25 (s, 1H), 7.40 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 5.28 (dd, J = 2.4, 10.0 Hz, 1H), 5.16 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.97-3.89 (m, 1H), 3.76 (s, 3H), 3.64-3.56 (m, 1H), 2.13-2.02 (m,

1H), 1.96-1.83 (m, 2H), 1.70-1.57 (m, 1H), 1.56-1.48 (m, 2H), 1.25-1.19 (m, 3H); LCMS (ESI, M+1): m/z = 361.1.

[0000796] Step C. (3-((4-methoxybenzyl)oxy)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)methanol: To a solution of ethyl 3-((4-methoxybenzyl)oxy)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-4-carboxylate (1 g, 1 *equiv.*) in THF (20 mL) was added $LiAlH_4$ (316 mg, 3 *equiv.*) at 0°C and the mixture was stirred at 25 °C for 30 minutes. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to afford the title compound (0.7 g, 69.4% yield) as a white solid; ^{1}HNMR (400 MHz, DMSO-d6) δ = 7.60 (s, 1H), 7.38 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 5.18-5.12 (m, 1H), 5.08 (s, 2H), 4.68 (s, 1H), 4.19 (d, J = 5.2 Hz, 2H), 3.88 (br s, 1H), 3.75 (s, 3H), 3.61-3.53 (m, 1H), 2.09-2.00 (m, 1H), 1.91 (br d, J = 1.6 Hz, 1H), 1.86 -1.77 (m, 1H), 1.70-1.56 (m, 1H), 1.54-1.47 (m, 2H); LCMS (ESI, M+1): m/z = 319.2.

[0000797] Step D. 2-((3-((4-methoxybenzyl)oxy)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)methyl)isoindoline-1,3-dione: A solution of DIAD (381 mg, 1.5 *equiv.*), PPh_3 (494 mg, 1.5 *equiv.*) in THF (8 mL) was stirred at 0 °C for 30 minutes. A solution of (3-((4-methoxybenzyl)oxy)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)methanol (400 mg, 1 *equiv.*) and isoindoline-1,3-dione (277 mg, 1.5 *equiv.*) in THF (8 mL) was added at 0°C and the mixture was stirred at 25°C for 1 hour. The filtrate was diluted with water (15 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulfate, concentrated and purified by silica gel column chromatography [petroleum ether / ethyl acetate] to afford the title compound (150 mg, 22.1 % yield) as a colorless oil; LCMS (ESI, M+Na): m/z = 447.9.

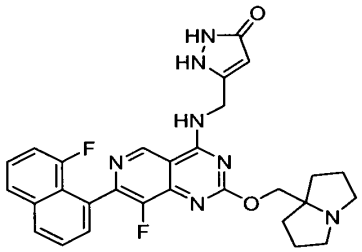
[0000798] Step E. (3-((4-methoxybenzyl)oxy)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)methanamine: A solution of 2-((3-((4-methoxybenzyl)oxy)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)methyl)isoindoline-1,3-dione (50 mg, 1 *equiv.*) and N_2H_4•H_2O (237 mg, 98% purity, 41 *equiv.*) in EtOH (1 mL) was stirred at 40 °C for 16 hours. The mixture was concentrated and triturated with ethyl acetate (10 mL) for 10 minutes to afford the title compound (30 mg, 82.1 % yield) as a colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.92 (br s, 2H), 7.55 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 5.15-5.11 (m, 1H), 5.07 (s, 2H), 3.87 (br d, J = 1.6 Hz,

1H), 3.75 (s, 3H), 3.61-3.52 (m, 1H), 3.40 (s, 2H), 2.07-1.92 (m, 2H), 1.86-1.79 (m, 1H), 1.69-1.58 (m, 1H), 1.54-1.45 (m, 2H); LCMS (ESI, M+1): m/z = 318.2.

[0000799] Step F. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-((3-((4-methoxybenzyl)oxy)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)methyl)pyrido[4,3-d]pyrimidin-4-amine: 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 (40 mg, 1 *equiv.*), DIEA (39.0 mg, 4 *equiv.*), (3-((4-methoxybenzyl)oxy)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)methanamine (23.9 mg, 1 *equiv.*) and 4Å molecular sieves (50 mg) in DMF (0.5 mL) was stirred at 40°C for 16 hours under N_2 atmosphere. The mixture was filtered and purified by reverse phase flash chromatography to afford the title compound (25 mg, 35.1% yield) as a yellow oil; LCMS [ESI, M+1]: m/z = 748.3.

[0000800] Step G. 4-(((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)-1H-pyrazol-3(2H)-one: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-((3-((4-methoxybenzyl)oxy)-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)methyl)pyrido[4,3-d]pyrimidin-4-amine (20 mg, 1 *equiv.*) in DCM (1 mL) was added TFA (770 mg, 252 *equiv.*) at 0°C and the mixture was stirred at 20°C for 16 hours under N_2 atmosphere. The mixture was concentrated and purified by prep-HPLC [column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (0.225% formic acid) / ACN]; B%: 14%-44%, 10 minutes] to afford the title compound (10.5 mg, 63.6% yield) as a white solid.^{1}HNMR (400 MHz, METHANOL-d4) δ = 9.19 (s, 1H), 8.11 (br d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.59 (dd, J = 1.2, 7.2 Hz, 1H), 7.56-7.47 (m, 2H), 7.18 (dd, J = 7.6, 13.2 Hz, 1H), 4.71 (s, 2H), 4.56 (s, 2H), 3.75 (m, 2H), 3.31-3.26 (m, 2H), 2.40-2.31 (m, 2H), 2.29-2.16 (m, 4H), 2.11 (m, 2H); LCMS (ESI, M+1): m/z = 544.2.

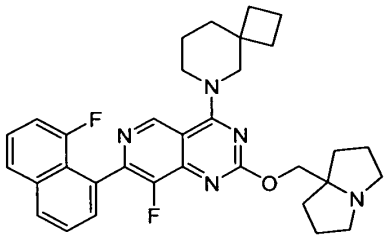
EXAMPLE 231



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

[0000801] The title compound was synthesized according to the procedure described for example 85. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.78-11.35 (m, 1H), 9.79-9.16 (m, 3H), 8.17 (br d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.76-7.70 (m, 1H), 7.63-7.55 (m, 2H), 7.30 (dd, J = 7.6, 13.2 Hz, 1H), 5.65-5.23 (m, 1H), 4.70 (br s, 2H), 4.06 (s, 2H), 2.95-2.89 (m, 2H), 2.56-2.52 (m, 2H), 1.92-1.84 (m, 2H), 1.82-1.71 (m, 4H), 1.60-1.52 (m, 2H); ^{19}F NMR (400 MHz, DMSO-d_6) δ -113.230, -141.701; LCMS (ESI, M+1): m/z = 544.3.

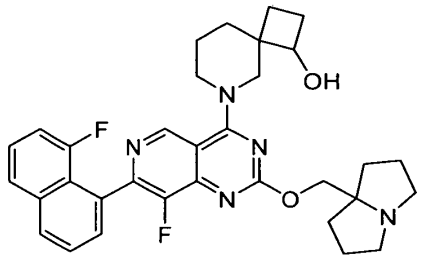
EXAMPLE 232



8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)-4-(6-azaspiro[3.5]nonan-6-yl)pyrido[4,3-*d*]pyrimidine

[0000802] The title compound was synthesized according to the procedure described for example 84. ^{1}HNMR (400 MHz, METHANOL-d4) δ = 9.10 (s, 1H), 8.12 (br d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.74 - 7.67 (m, 1H), 7.62 (d, J = 7.2 Hz, 1H), 7.57 - 7.50 (m, 1H), 7.19 (dd, J = 7.6, 13.2 Hz, 1H), 4.56 (s, 2H), 4.13 - 3.93 (m, 4H), 3.51 (br s, 2H), 3.18 - 3.06 (m, 2H), 2.30 - 2.21 (m, 2H), 2.20 - 2.05 (m, 4H), 2.04 - 1.93 (m, 4H), 1.90 - 1.76 (m, 8H) LCMS [ESI, M+1]: m/z = 556.4

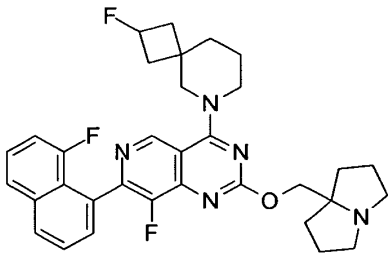
EXAMPLE 233



6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-1-ol

[0000803] The title compound was synthesized according to the procedure described for example 85. ^{1}H NMR (400 MHz, methanol-d4) δ 9.13 - 9.02 (m, 1H), 8.11 (br d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.73 - 7.67 (m, 1H), 7.61 (br d, J = 7.2 Hz, 1H), 7.53 (dt, J = 4.8, 8.0 Hz, 1H), 7.19 (br dd, J = 7.6, 13.2 Hz, 1H), 4.49 - 4.37 (m, 0.5H), 4.35 - 4.27 (m, 2H), 4.21 – 3.80 (m, 4.5H),3.16 - 3.06 (m, 2H), 2.79 - 2.66 (m, 2H), 2.31 - 2.21 (m, 1H), 2.13 - 1.82 (m, 10H), 1.81 - 1.59 (m, 4H), 1.53 - 1.31 (m, 1H); LCMS [ESI, M+1]: 572.3.

EXAMPLE 234

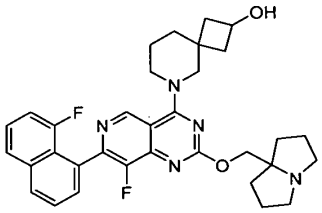


8-fluoro-4-(2-fluoro-6-azaspiro[3.5]nonan-6-yl)-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidine

[0000804] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.05 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.54-7.49 (m, 1H), 7.25-7.21 (m, 1H), 5.26-5.00 (m, 1H), 4.34 (d, J = 16.0 Hz, 2H), 4.11-3.95 (m, 4H), 3.40-

3.12 (m, 2H), 2.85-2.70 (m, 2H), 2.50-2.35 (m, 1H), 2.27-2.22 (m, 1H), 2.18-2.05 (m, 3H), 2.04-1.75 (m, 11H); LCMS (ESI, M+1): m/z = 574.4.

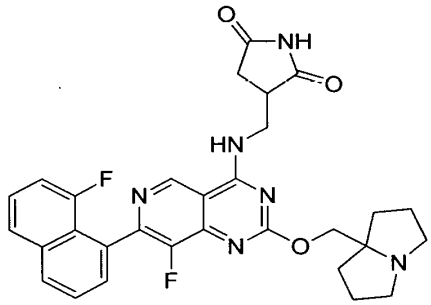
EXAMPLE 235



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

[0000805] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.09 (d, J = 6.8 Hz, 1H), 8.54 (s, 1H), 8.12 (br d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.74-7.67 (m, 1H), 7.62 (d, J = 6.8 Hz, 1H), 7.53 (dt, J = 5.2, 8.0 Hz, 1H), 7.19 (dd, J = 7.6, 12.8 Hz, 1H), 4.54 (d, J = 8.0 Hz, 2H), 4.40-4.20 (m, 1H), 4.17-3.92 (m, 4H), 3.60-3.42 (m, 2H), 3.21-2.98 (m, 2H), 2.38-2.19 (m, 4H), 2.10 (tdd, J = 6.8, 13.2, 19.6 Hz, 4H), 2.03-1.94 (m, 2H), 1.88-1.77 (m, 5H), 1.77-1.66 (m, 1H); LCMS [ESI, M+1]: m/z = 572.2.

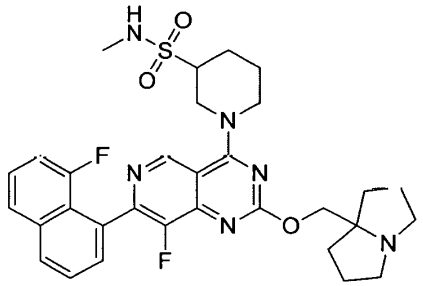
EXAMPLE 236



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

[0000806] The title compound was synthesized according to the procedure described for example 85. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ =9.19 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.54-7.52 (m, 1H), 7.21-7.18 (m, 1H),4.61-4.59 (m, 2H), 4.24-4.12 (m, 1H),, 4.05-3.90 (m, 1H), 3.60-3.40 (m, 3H), 3.20-3.08 (m, 2H), 3.00-2.88 (m, 1H), 2.80-2.62 (m, 1H), 2.40-2.27 (m, 2H), 2.21-2.07 (m, 4H), 2.04-1.90 (m, 2H); LCMS (ESI, M+1): m/z = 559.2.

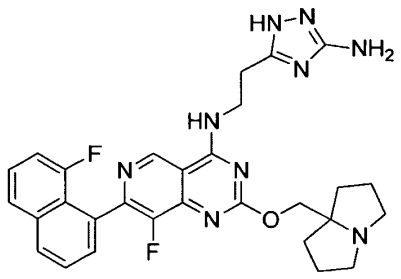
EXAMPLE 237



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

[0000807] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.13 (s, 1H), 8.12 (br d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.70-7.68 (m, 1H), 7.63-7.60 (m, 1H), 7.53 (dt, J = 5.2, 8.0 Hz, 1H), 7.21-7.18 (m, 1H), 4.95 (br d, J = 12.4 Hz, 1H), 4.56 (s, 3H), 3.69-3.68 (m, 3H), 3.47-3.45 (m, 2H), 3.09-3.06 (m, 2H), 2.79 (d, J = 2.4 Hz, 3H), 2.24-2.22 (m, 3H), 2.12-1.97 (m, 8H), 1.86-1.75 (m, 1H). LCMS [ESI, M+1]: m/z = 609.3.

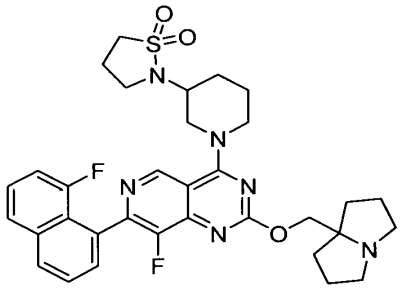
EXAMPLE 238



N-(2-(3-amino-1*H*-1,2,4-triazol-5-yl)ethyl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-amine

[0000808] The title compound was synthesized according to the procedure described for example 84. ^{1}NMR (400 MHz, METHANOL-d4) δ = 9.16 (s, 1H), 8.53 (br s, 1H), 8.12 (br d, *J* = 8.8 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.70 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.61 - 7.49 (m, 2H), 7.19 (ddd, *J* = 1.2, 7.6, 13.2 Hz, 1H), 4.63 (d, *J* = 1.2 Hz, 2H), 4.01 (dt, *J* = 2.8, 6.8 Hz, 2H), 3.71 - 3.60 (m, 2H), 3.27 - 3.19 (m, 2H), 3.00 (t, *J* = 6.8 Hz, 2H), 2.33 (br dd, *J* = 6.4, 12.4 Hz, 2H), 2.25 - 2.13 (m, 4H), 2.09 (br dd, *J* = 6.4, 12.4 Hz, 2H) LCMS [ESI, M+1]: m/z = 558.4

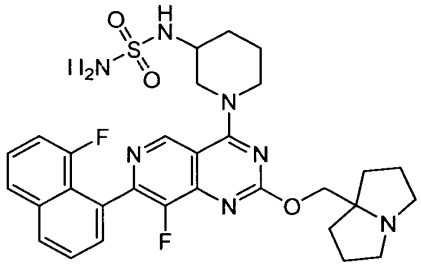
EXAMPLE 239



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

[0000809] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, METHANOL-d4) *δ* = 9.13 (d, *J* = 3.2 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.70 (dt, *J* = 8.0, 3.6 Hz, 1H), 7.66 - 7.57 (m, 1H), 7.53 (dt, *J* = 8.0, 4.8 Hz, 1H), 7.19 (ddd, *J* = 12.4 Hz,7.6, 4.8, 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 4.69 - 4.56 (m, 2H), 4.47 (dd, *J* = 11.6, 6.6 Hz, 1H), 3.88 - 3.77 (m, 1H), 3.69 - 3.58 (m, 1H), 3.53 - 3.37 (m, 5H), 3.28 - 3.17 (m, 2H), 3.06 - 2.97 (m, 2H), 2.39 (quin, *J* = 7.0 Hz, 2H), 2.31 - 2.22 (m, 2H), 2.13 - 2.03 (m, 5H), 2.00 (d, *J* = 11.6 Hz, 2H), 1.97 - 1.87 (m, 2H), 1.84 - 1.70 (m, 1H); ^{19}F NMR (377 MHz, CD_3OD) δ = -115.32, -141.27; LCMS: [ESI, M+1] $^+$: 635.5.

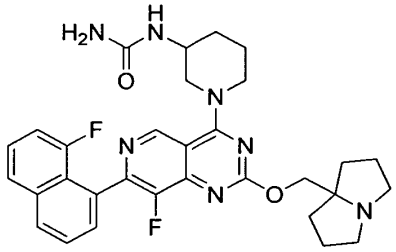
EXAMPLE 240



8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-[3-(sulfamoylamino)piperidin-1-yl]pyrido[4,3-d]pyrimidine

[0000810] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.18 (s, 1H), 8.56 (s, 1H), 8.14 (br d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.78 - 7.69 (m, 1H), 7.63 (dd, *J* = 7.2, 10.2 Hz, 1H), 7.55 (dt, *J* = 5.2, 8.0 Hz, 1H), 7.21 (ddd, *J* = 2.8, 7.6, 12.8 Hz, 1H), 4.78 (br d, *J* = 16.4 Hz, 1H), 4.68 - 4.54 (m, 2H), 4.53 - 4.40 (m, 1H), 3.80 - 3.63 (m, 2H), 3.61 - 3.45 (m, 3H), 3.19 - 3.04 (m, 2H), 2.35 - 2.23 (m, 2H), 2.22 - 2.05 (m, 5H), 2.05 - 1.93 (m, 3H), 1.84 - 1.70 (m, 2H); LCMS (ESI, M+1): m/z= 610.4.

EXAMPLE 241

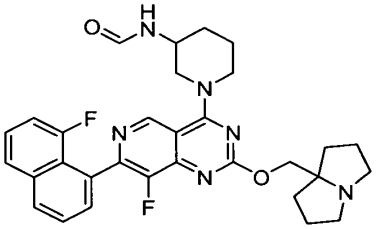


1-(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)urea

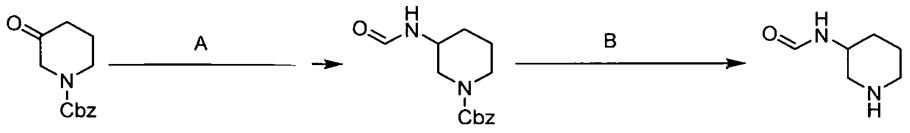
[0000811] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.18 (d, *J* = 1.6 Hz, 1H), 8.12 (br d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.73 - 7.67 (m, 1H), 7.65 - 7.59 (m, 1H), 7.53 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.19 (dd, *J* = 7.6, 12.8 Hz, 1H), 4.72 - 4.64 (m, 1H), 4.63 - 4.56 (m, 1H), 4.55 - 4.43

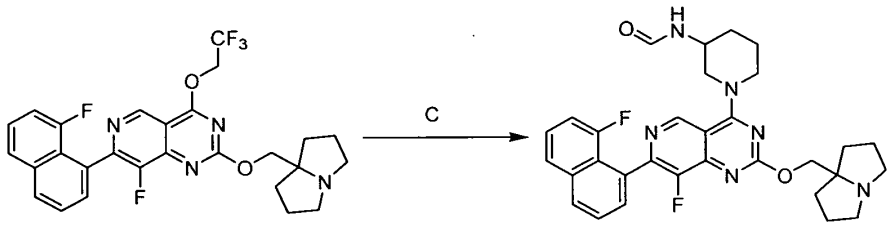
(m, 1H), 4.42 - 4.29 (m, 1H), 3.96 - 3.74 (m, 2H), 3.73 - 3.54 (m, 3H), 3.25 - 3.15 (m, 2H), 2.37 - 2.26 (m, 2H), 2.24 - 2.11 (m, 4H), 2.11 - 1.93 (m, 4H), 1.89 - 1.66 (m, 2H); LCMS [ESI, M+1]: m/z = 574.4.

EXAMPLE 242



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





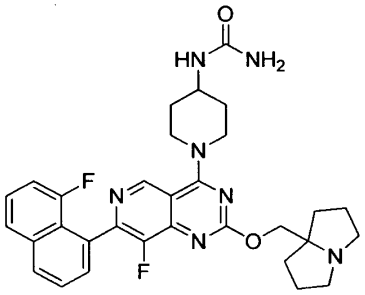
[0000812] Step A. benzyl 3-formamidopiperidine-1-carboxylate: A mixture of benzyl 3-oxopiperidine-1-carboxylate (500 mg, 1.0 *equiv.*), formamide (2.49 g, 25.7 *equiv.*), ammonium formate (3.30 g, 24.4 *equiv.*) and formic acid (2.44 g, 2 mL, 98% purity, 24.2 *equiv.*) was stirred at 160 °C for 7 hours. The reaction mixture was diluted with water (20.0 mL), and then was extracted with ethyl acetate (30 mL × 2). The combined organic layers were 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 (198 mg, 34% yield) as a yellow oil; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ = 8.12 (br d, *J* = 6.4 Hz, 1H),

7.96 (s, 1H), 7.47-7.25 (m, 5H), 5.16-4.99 (m, 2H), 3.85-3.45 (m, 3H), 3.16-2.74 (m, 2H), 1.87-1.60 (m, 2H), 1.52-1.30 (m, 2H); LCMS (ESI, M+1): m/z = 263.0.

[0000813] Step B. N-(piperidin-3-yl)formamide: To a solution of benzyl 3-formamidopiperidine-1-carboxylate (140 mg, 1.0 *equiv.*) in MeOH (10 mL) was added NH_3•MeOH (1 mL, 20% purity) and Pd/C (10.0 mg, 10% purity) under N_2. The suspension was degassed in vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 15 °C for 1 hour. The mixture was filtered and the filtrate was concentrated in vacuum to afford the title compound (77.0 mg, crude) as a colorless solid.

[0000814] Step C. N-(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)formamide: A mixture of N-(piperidin-3-yl)formamide (72.5 mg, 2.0 *equiv.*), DIEA (110 mg, 3.0 *equiv.*) and 4Å molecular seives (100 mg) in DMF (5 mL) was stirred at 15 °C for 0.5 hour. Then to the mixture 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 (150 mg, 1.0 *equiv.*) at 15 °C. The mixture was stirred at 40 °C for 14 hours. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (15 mL). The organic layer was washed with water (2 × 10 mL), dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150 × 25 mm × 10 μm; mobile phase: water (0.225% formic acid, v/v)/ACN] B%: 16% - 46%, 10 min) and lyophilized to afford the title compound (66.2 mg, 38% yield) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.16 (d, J = 3.2 Hz, 1H), 8.35 (br d, J = 7.6 Hz, 1H), 8.26 (s, 1H), 8.18 (br d, J = 8.4 Hz, 1H), 8.02 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.74 (dt, J = 2.4, 8.0 Hz, 1H), 7.68-7.55 (m, 2H), 7.36-7.25 (m, 1H), 4.32-4.13 (m, 4H), 4.09-3.99 (m, 1H), 3.68-3.44 (m, 2H), 3.08-2.97 (m, 2H), 2.72-2.59 (m, 2H), 2.02-1.89 (m, 4H), 1.88-1.73 (m, 5H), 1.71-1.59 (m, 3H); LCMS (ESI, M+1): m/z = 559.3.

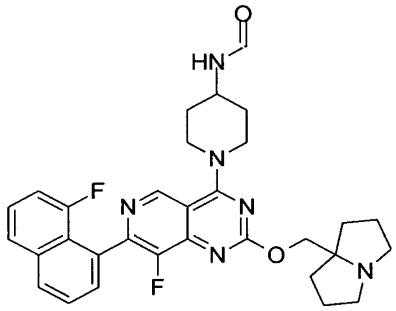
EXAMPLE 243



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

[0000815] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.09 (s, 1H), 8.12 (br d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.75-7.67 (m, 1H), 7.61 (d, J = 6.8 Hz, 1H), 7.53 (dt, J = 5.2, 8.0 Hz, 1H), 7.19 (dd, J = 7.6, 13.2 Hz, 1H), 4.70-4.53 (m, 4H), 3.99-3.85 (m, 1H), 3.68-3.51 (m, 4H), 3.18 (td, J = 6.0, 11.6 Hz, 2H), 2.37-2.22 (m, 2H), 2.20-1.96 (m, 8H), 1.68 (q, J = 11.2 Hz, 2H); LCMS [ESI, M+1]: m/z =574.4.

EXAMPLE 244

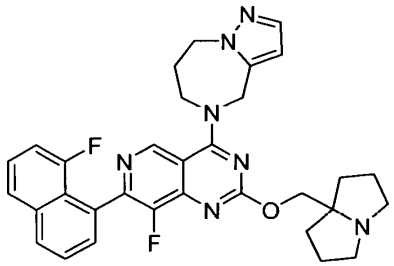


N-(1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-4-yl)formamide

[0000816] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.09 (s, 1H), 8.27-8.16 (m, 3H), 8.02 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.78-7.70 (m, 1H), 7.66-7.55 (m, 2H), 7.31 (dd, J = 7.6, 13.2 Hz, 1H), 4.53-4.39 (m, 2H), 4.20 (s, 2H), 4.13-4.00 (m, 1H), 3.57 (br t, J = 11.2 Hz, 2H), 3.18-3.02 (m, 2H),

2.77-2.64 (m, 2H), 2.04-1.93 (m, 4H), 1.92-1.77 (m, 4H), 1.72-1.55 (m, 4H); LCMS (ESI, M+1): m/z = 559.3

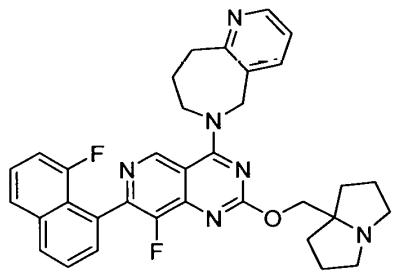
EXAMPLE 245



4-(7,8-dihydro-4*H*-pyrazolo[1,5-a][1,4]diazepin-5(6*H*)-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidine

[0000817] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, CD_3OD-d_6) δ = 9.19 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.73 - 7.67 (m, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.53 (dt, *J* = 8.0, 5.2 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.19 (dd, *J* = 13.2, 8.0 Hz, 1H), 6.48 (d, *J* = 1.6 Hz, 1H), 5.34 - 5.18 (m, 2H), 4.55 - 4.49 (m, 2H), 4.42 (t, *J* = 5.2 Hz, 2H), 4.32 (s, 2H), 3.21 - 3.13 (m, 2H), 2.85 - 2.74 (m, 2H), 2.45 - 2.37 (m, 2H), 2.08 (dd, *J* = 12.4, 6.8 Hz, 2H), 2.01 - 1.87 (m, 4H), 1.84 - 1.75 (m, 2H); ^{19}F NMR (377 MHz, CD_3OD) δ = -115.18, -140.71; LCMS (ESI, M+1): m/z = 568.3.

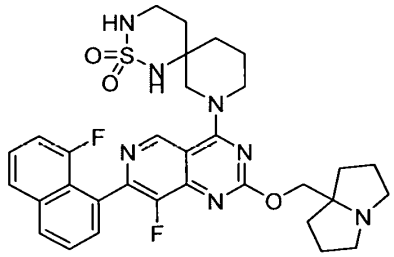
EXAMPLE 246



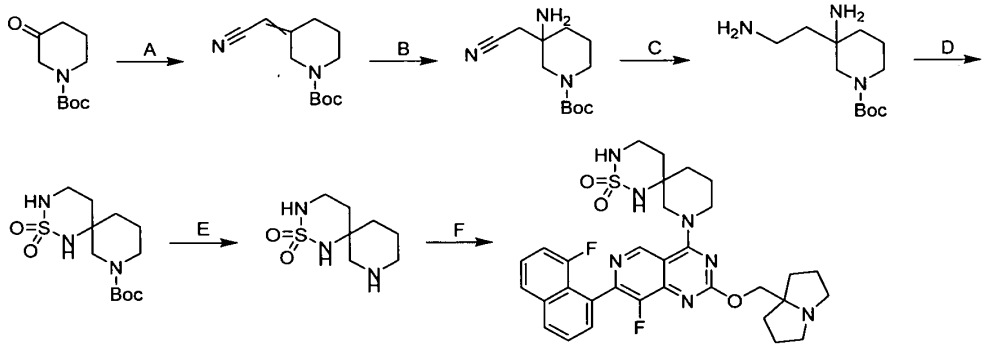
6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepine

[0000818] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, CD_3OD) δ = 9.14 (s, 1H), , 8.36 (dd, J = 4.8, 1.2 Hz, 1H), 8.11 (br d, J = 8.4 Hz, 1H), 7.99 (d, J = 6.8 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.73 - 7.64 (m, 1H), 7.64 - 7.57 (m, 1H), 7.53 (dt, J = 7.6, 4.8 Hz, 1H), 7.32 (dd, J = 7.6, 4.8 Hz, 1H), 7.19 (dd, J = 12.8, 7.6 Hz, 1H), 5.34 - 5.14 (m, 2H), 4.49 - 4.37 (m, 2H), 4.33 - 4.22 (m, 2H), 3.29 - 3.20 (m, 4H), 2.93 - 2.84 (m, 2H), 2.41 - 2.31 (m, 2H), 2.15 - 1.81 (m, 8H); ^{19}F NMR (377 MHz, CD_3OD) δ = -115.23. -140.94; LCMS (ESI, M+1): m/z = 579.2.

EXAMPLE 247



8-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy) pyrido[4,3-d]pyrimidin-4-yl)-2-thia-1,3,8-triazaspiro[5.5]undecane 2,2-dioxide



[0000819] Step A. tert-butyl 3-(cyanomethylene)piperidine-1-carboxylate: To a solution of 2-diethoxyphosphorylacetonitrile (10.7 g, 1.20 *equiv.*) in 2-MeTHF (45 mL) was added K_2CO_3 (8.32 g, 1.20 *equiv.*). The mixture was stirred at 20 °C for 1 hours, then *tert*-butyl 3-oxopiperidine-1-

carboxylate (10.0 g, 50.2 mmol, 1.0 *equiv.*) was added to the mixture. The mixture was stirred at 70 °C for 13 hours. After completion, the reaction mixture was diluted with water (40 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20.00 mL × 2), dried over Na_2SO_4, concentrated and purified by silica gel column chromatography [Petroleum ether / Ethyl acetate 5:1 to 4:1] to afford the title compound (9.0 g, 81% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.24-5.15 (m, 1H), 4.25-3.97 (m, 2H), 3.51-3.47 (m, 2H), 2.64-2.38 (m, 2H), 1.76-1.71 (m, 2H), 1.48-1.44 (m, 9H).

[0000820] Step B. tert-butyl 3-amino-3-(cyanomethyl)piperidine-1-carboxylate: The mixture of tert-butyl 3-(cyanomethylene)piperidine-1-carboxylate (4.0 g, 1.0 *equiv.*) and NH_4OH (20.0 g, 21.98 mL, 30% purity, 9.51 *equiv.*) in MeOH (6.00 mL) was stirred at 90 °C for 4 hours in a sealed tube. After completion, the mixture was concentrated to remove MeOH and then the residue was extracted with ethyl acetate (120 mL×3). The combined organic phase was washed with brine (100 mL × 3), dried with anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography [petroleum ether / ethyl acetate 1:0 to 1:10 then dichloromethane / methyl alcohol 10:1] to afford the title compound (550 mg, 13% yield) as a yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ = 3.56-3.52 (m, 2H), 3.32-3.00 (m, 2H), 2.65-2.54 (m, 2H), 1.80-1.71 (m, 2H), 1.66-1.53 (m, 2H), 1.49 (s, 9H).

[0000821] Step C. tert-butyl 3-amino-3-(2-aminoethyl)piperidine-1-carboxylate: A mixture of tert-butyl 3-amino-3-(cyanomethyl)piperidine-1-carboxylate (200 mg, 1.0 *equiv.*), NH_4OH (97.6 mg, 107 µL, 30% purity, 1.0 *equiv.*) and Raney Nickel (7.16 mg, 0.10 *equiv.*) in MeOH (5 mL) was stirred at 35 °C for 12 hours under H_2 (50 psi). After completion, the mixture was filtered and concentrated to afford the title compound (160 mg, 79% yield) as a yellow gum; ^{1}H NMR (400 MHz, CD_3OD) δ = 3.32-3.21 (m, 2H), 3.20-2.95 (m, 2H), 2.69-2.66 (m, 2H), 1.39-1.36 (m, 15H).

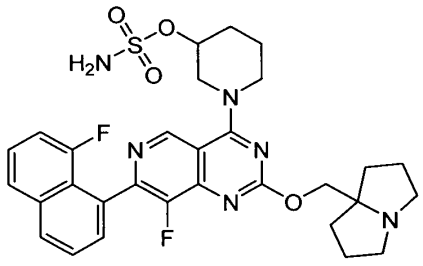
[0000822] Step D. tert-butyl 2-thia-1,3,8-triazaspiro[5.5]undecane-8-carboxylate 2,2-dioxide: A mixture of tert-butyl 3-amino-3-(2-aminoethyl)piperidine-1-carboxylate (160 mg, 1.00 *equiv.*) and sulfamide (94.8 mg, 1.50 *equiv.*) in pyridine (0.30 mL) was stirred at 110 °C for 12 hours under N_2 atmosphere. After completion, the mixture was concentrated and purified by prep-HPLC [column: Phenomenex luna C18 150 × 25mm × 10um; mobile phase: [water (0.225% formic acid)/ACN]; B%: 22%-52%, 10min] to afford the title compound (80.0 mg, 40% yield) as a yellow

gum; ^{1}H NMR (400 MHz, CD_3OD) δ = 4.22-4.12 (m, 1H), 3.62-3.56 (m, 2H), 3.48-3.42 (m, 1H), 3.16-3.12 (m, 2H), 1.95-1.41 (m, 15H).

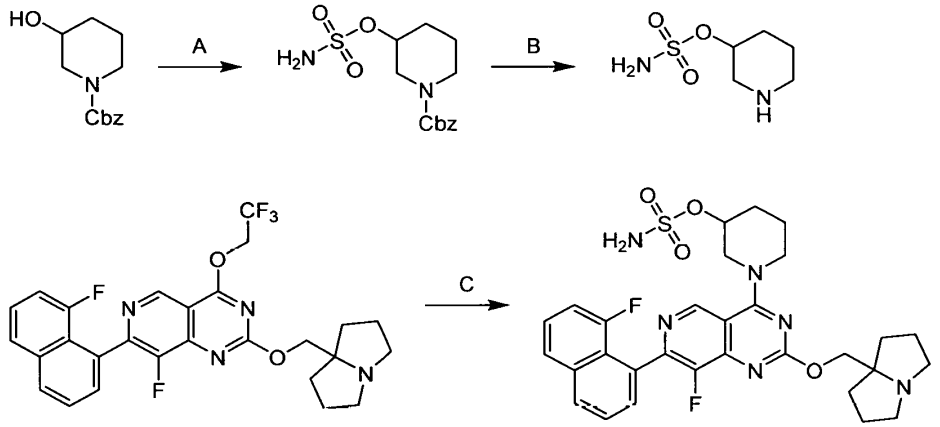
[0000823] Step E. 2-thia-1,3,8-triazaspiro[5.5]undecane 2,2-dioxide: A mixture of tert-butyl 2-thia-1,3,8-triazaspiro[5.5]undecane-8-carboxylate 2,2-dioxide (20.0 mg, 1.00 *equiv.*) and TFA (231 mg, 30.9 *equiv.*) in DCM (0.5 mL) was stirred at 20 °C for 1 hour. After reaction completion, the mixture was concentrated to remove DCM to afford the title compound (20.0 mg, crude, TFA salt) as a yellow oil.

[0000824] Step E. 8-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-thia-1,3,8-triazaspiro[5.5]undecane 2,2-dioxide: A mixture of 2-thia-1,3,8-triazaspiro[5.5]undecane 2,2-dioxide (20.0 mg, 1.00 *equiv.*, TFA), 8-fluoro-7-(8-fluoro-1-naphthyl)-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(2,2,2-trifluoroethoxy) pyrido[4,3-d]pyrimidine (33.2 mg, 1.00 *equiv.*), DIPEA (32.4 mg, 4.00 *equiv.*) and 4Å molecular sieves (10.0 mg, 1.00 *equiv.*) in DMF (1.00 mL) was stirred at 40 °C for 12 hours under N_2. After reaction completion, the mixture was concentrated and purified by prep-HPLC [column: Phenomenex Luna C18 150 × 25mm × 10um; mobile phase: [water (0.225% formic acid)/ACN]; B%: 13%-43%, 10min] to afford the title compound (2.50 mg, 5.7% yield) as an off-white solid; ^{1}H NMR (400 MHz, CD_3OD) δ = 9.15 (d, J = 2.8 Hz, 1H), 8.14 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.73-7.69 (m, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.57-7.55 (m, 1H), 7.22-7.20 (m, 1H), 4.66-4.53 (m, 3H), 4.42-4.20 (m, 2H), 4.01-3.81 (m, 1H), 3.75-3.45 (m, 4H), 3.23-3.13 (m, 2H), 2.37-2.02 (m, 10H), 1.90-1.72 (m, 3H), 1.61-1.50 (m, 1H); LCMS (ESI, M+1): m/z = 636.0.

EXAMPLE 248



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



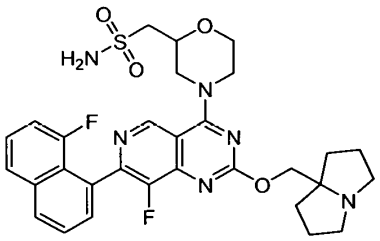
[0000825] Step A. benzyl 3-(sulfamoyloxy)piperidine-1-carboxylate: To a solution of benzyl 3-hydroxypiperidine-1-carboxylate (500 mg, 1.0 *equiv.*) and sulfamoyl chloride (442 mg, 1.8 *equiv.*) in DCM (10 mL) was added TEA (1.08 g, 1.48 mL, 5.0 *equiv.*), the mixture was stirred at 15 °C for 8 hours. After completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge C18 150 × 50 mm × 10 μm; mobile phase: [water (10mM NH_4HCO_3)/ACN], B%: 24% - 54%, 11 min) to afford the title compound (230 mg, 33% yield) as a light yellow oil; LCMS [ESI, M+1]: m/z = 315.2.

[0000826] Step B. piperidin-3-yl sulfamate: To a mixture of benzyl 3-(sulfamoyloxy)piperidine-1-carboxylate (100 mg, 1.0 *equiv.*) in MeOH (2 mL) was added Pd/C (100 mg, 10% purity), the reaction was stirred at 15 °C for 2 hours under H_2 atmosphere (15psi). After completion, the reaction mixture was filtered and concentrated under reduced pressure to afford the title compound (59 mg, crude) as a light yellow solid.

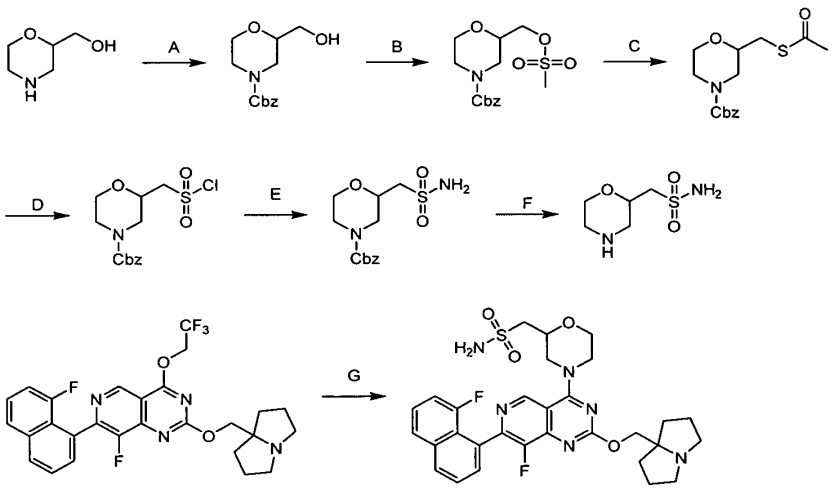
[0000827] Step C. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl sulfamate: To a solution of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 1.0 *equiv.*), piperidin-3-yl sulfamate (25.5 mg,

1.5 *equiv.*) in DMF (1 mL) was added DIEA (36.5 mg, 49.2 µL, 3.0 *equiv.*), the reaction was stirred at 40 °C for 4 hours. After completion, the reaction mixture was filtered to give a residue and the residue was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) and then prep-HPLC (column: Phenomenex Synergi C18 150 × 25 mm × 10 µm; mobile phase: water (0.225% formic acid)/ACN] , B%: 13% - 43%, 10 min) and lyophilized to afford the title compound (3.85 mg, 6% yield over two steps) as a white solid; ^{1}H NMR (400 MHz, methanol-d4): δ = 9.15 (s, 1H), 8.53 (s, 1H), 8.13 (br d, *J* = 8.8 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.74 - 7.68 (m, 1H), 7.64 - 7.59 (m, 1H), 7.57 - 7.50 (m, 1H), 7.24 - 7.15 (m, 1H), 4.62 (br s, 2H), 4.39 - 3.99 (m, 3H), 3.52 - 3.37 (m, 4H), 3.16 - 3.00 (m, 2H), 2.31 - 2.17 (m, 3H), 2.10 (br dd, *J* = 6.0, 12.4 Hz, 8H), 1.87 - 1.74 (m, 1H); LCMS [ESI, M+1]: m/z = 611.3.

EXAMPLE 249



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



[0000828] Step A. benzyl 2-(hydroxymethyl)morpholine-4-carboxylate: A mixture of morpholin-2-ylmethanol (1 g, 1 *equiv.*, HCl salt) and $NaHCO_3$ (1.37 g, 2.5 *equiv.*) in water (10 mL) and THF (10 mL) was stirred at 20 °C for 0.1 hour. Benzyl carbonochloridate (1.20 g, 1.1 *equiv.*) was added dropwise and the mixture was stirred at 20 °C for 16 hours. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (10 mL × 4). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile 3:1] to afford the tittle compound (1.18 g, 71% yield) as a yellow oil; ^{1}H NMR (400 MHz, methanol-d4) δ = 7.37-7.31 (m, 5H), 5.14 (s, 2H), 4.02 (br d, J = 13.2 Hz, 1H), 3.91 (br d, J = 12.8 Hz, 2H), 3.56-3.43 (m, 4H), 3.01 (br s, 1H), 2.78 (br s, 1H); LCMS [ESI, M+Na]: m/z = 274.2.

[0000829] Step B. benzyl 2-(((methylsulfonyl)oxy)methyl)morpholine-4-carboxylate: To a solution of benzyl 2-(hydroxymethyl)morpholine-4-carboxylate (1.18 g, 1 *equiv.*) and TEA (1.02 g, 2.1 *equiv.*) in DCM (15 mL) was added MsCl (1.03 g, 1.9 *equiv.*) dropwise at 0 °C. The mixture was stirred at 10 °C for 1 hour. The mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) at 0 °C. The DCM phase was separated. The aqueous phase was extracted with DCM (20 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated to afford the title compound (1.65 g, crude) as a light yellow oil.

[0000830] Step C. benzyl 2-((acetylthio)methyl)morpholine-4-carboxylate: A mixture of benzyl 2-(((methylsulfonyl)oxy)methyl)morpholine-4-carboxylate (1.65 g, crude) and acetylsulfanylpotassium (660 mg, 1.2 *equiv.*) in DMF (20 mL) was stirred at 95 °C for 1.5 hours. The mixture was diluted with ethyl acetate (30 mL), water (300 mL) and brine (30 mL). The mixture was extracted with ethyl acetate (4 × 20 mL). The organic layer was washed with brine (3 × 20 mL), dried over Na_2SO_4, concentrated and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile 1:9] to afford the title compound (1.15 g, 79% yield over two steps) as a light-yellow liquid; LCMS (ESI, M+Na): m/z = 332.1.

[0000831] Step D. benzyl 2-((chlorosulfonyl)methyl)morpholine-4-carboxylate: To a solution of benzyl 2-((acetylthio)methyl)morpholine-4-carboxylate (1.15 g, 1 *equiv.*) in AcOH (18 mL) and water (2 mL) was added NCS (1.62 g, 3.3 *equiv.*) portion wise. The mixture was poured into water (100 mL). The mixture was extracted with ethyl acetate (4 × 20 mL). The combined organic layers

were washed with water (50 mL), saturated aqueous $NaHCO_3$ (3 × 30 mL), brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated to afford the title compound (1.4 g, crude) as a light-yellow oil.

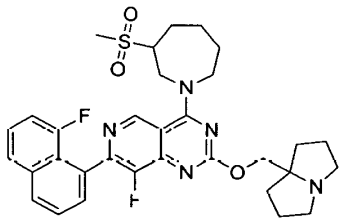
[0000832] Step E. benzyl 2-(sulfamoylmethyl)morpholine-4-carboxylate: Benzyl 2-((chlorosulfonyl)methyl)morpholine-4-carboxylate (1.4 g, crude) in THF (15 mL) was added into $NH_3•H_2O$ (20 mL, 25% purity) dropwise maintaining the temperature below 5 °C. The mixture was stirred between 5 and 15 °C for 0.5 hour. The mixture was diluted with water (150 mL) and extracted with DCM (4 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile 8:17] to afford the title compound (1 g, 85% yield over two steps) as a white solid; ^{1}H NMR (400 MHz, chloroform-d) δ = 7.40-7.32 (m, 5H), 5.15 (br s, 2H), 4.96 (br s, 2H), 4.14-3.94 (m, 4H), 3.63 (br t, J = 10.8 Hz, 1H), 3.31-3.25 (m, 2H), 3.05 (br s, 1H), 2.83 (br s, 1H); LCMS [ESI, M+Na]: m/z = 315.1.

[0000833] Step F. morpholin-2-ylmethanesulfonamide: To a solution of benzyl 2-(sulfamoylmethyl)morpholine-4-carboxylate (300 mg, 1 *equiv.*) in MeOH (10 mL) was added Pd/C (60 mg, 10% purity) under N_2 atmosphere. The mixture was degassed and purged with H_2. The mixture was stirred at 10 °C for 2.5 hours under H_2 atmosphere (15 psi) before being filtered through a pad of Celite. The filter cake was washed with THF/MeOH 1:1 (20 mL). The combined filtrate was concentrated to afford the title compound (180 mg, 100% yield, crude) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.79 (br s, 2H), 3.80-3.71 (m, 1H), 3.70 (td, *J* = 2.4, 11.2 Hz, 1H), 3.45 (dt, *J* = 3.2, 10.8 Hz, 1H), 3.34 (br s, 1H), 3.10-3.06 (m, 2H), 2.90 (dd, *J* = 2.0, 12.0 Hz, 1H), 2.64-2.62 (m, 2H), 2.41 (br dd, *J* = 10.0, 12.0 Hz, 1H).

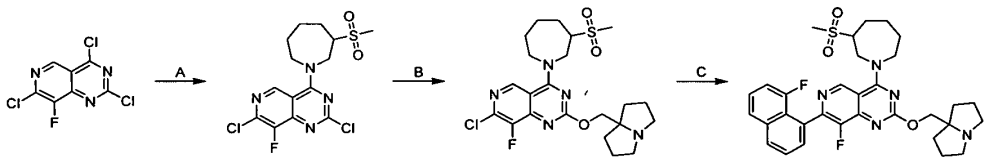
[0000834] Step G. 1-(4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)morpholin-2-yl)methanesulfonamide: A mixture of 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (80 mg, 1 *equiv.*), morpholin-2-ylmethanesulfonamide (55 mg, crude), DIPEA (58.6 mg, 3.0 *equiv.*) and 4Å molecular sieves (20 mg) in DMF (1 mL) was stirred at 40 °C for 14 hours under N_2 atmosphere. The mixture was filtered. The filtrate was purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; mobile phase: [water (0.225% formic acid)-ACN]; B%: 12%-42%, 7 minutes] to afford the title compound (29.7

mg, 30% yield, 0.5 formic acid salt) as a white solid; ^{1}H NMR (400 MHz, methanol-d4) δ = 9.16 (s, 1H), 8.12 (br d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.71-7.64 (m, 1H), 7.61 (dd, *J* = 7.2, 14.8 Hz, 1H), 7.53 (dt, *J* = 5.6, 7.6 Hz, 1H), 7.19 (br dd, *J* = 7.6, 13.2 Hz, 1H), 5.02 (br t, *J* = 14.0 Hz, 1H), 4.63 (br dd, *J* = 6.4, 12.0 Hz, 1H), 4.55-4.46 (m, 2H), 4.31-4.18 (m, 1H), 4.05 (br d, *J* = 10.8 Hz, 1H), 3.82-3.73 (m, 2H), 3.54-3.43 (m, 5H), 3.17-3.03 (m, 2H), 2.29 (td, *J* = 6.4, 12.8 Hz, 2H), 2.14-2.10 (m, 4H), 2.04-1.99 (m, 2H); LCMS [ESI, M+1]: m/z = 611.4.

EXAMPLE 250



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



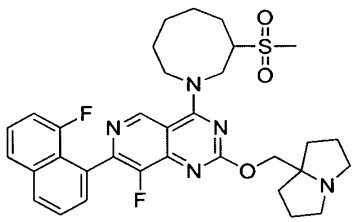
[0000835] Step A. 2,7-dichloro-8-fluoro-4-(3-(methylsulfonyl)azepan-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 2,4,7-trichloro-8-fluoro-pyrido[4,3-d]pyrimidine (215 mg, 1.0 *equiv.*), 3-methylsulfonylazepane (200 mg, 1.1 *equiv.*, HCl) in THF (1 mL) was added DIEA (550 mg, 5.0 *equiv.*) at -40°C. The mixture was stirred at -40 °C for 2 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated to afford the title compound (500 mg, crude) as a yellow solid; LCMS (ESI, M+1): m/z = 393.3.

[0000836] Step B. 7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(methylsulfonyl)azepan-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 2,7-dichloro-8-fluoro-4-(3-methylsulfonylazepan-1-yl)pyrido[4,3-d]pyrimidine (470 mg, 1.0 *equiv.*), 1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethanol (337 mg, 2.0 *equiv.*) and 4Å molecular sieves (200 mg) in

dioxane (2.5 mL) was added DIEA (463 mg, 3.0 *equiv.*). The reaction was stirred at 95 °C for 16 hours. The mixture was diluted with water (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 (180 mg, 29.9% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 498.1.

[0000837] Step C. 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(methylsulfonyl)azepan-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 7-chloro-8-fluoro-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)-4-(3-methylsulfonylazepan-1-yl)pyrido[4,3-d]pyrimidine (100 mg, 1.0 *equiv.*), Cs_2CO_3 (1.5 M, 402 μL, 3.0 *equiv.*) and cataCXium® A Pd G3 (14.6 mg, 0.1 *equiv.*) in methoxycyclopentane (1.5 mL) was added 2-(8-fluoro-1-naphthyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (71.0 mg, 1.3 *equiv.*). The reaction was stirred at 90 °C for 3 hours. The mixture was diluted with water (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 give a crude product. The crude product was purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; mobile phase: [water (0.225% formic acid)/ACN]; B%: 18%-48% , 7 min] and lyophilized to afford the title compound (21.4 mg, 17% yield) as a light yellow solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.22 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.75-7.65 (m, 1H), 7.65-7.49 (m, 2H), 7.25-7.10 (m, 1H), 4.93 (br d, *J* = 13.6 Hz, 1H), 4.57-4.44 (m, 2H), 4.33-4.21 (m, 1H), 4.20-4.05 (m, 1H), 3.91-3.71 (m, 2H), 3.36-3.31 (m, 1H), 3.30-3.26 (m, 1H), 3.15 (d, *J* = 2.0 Hz, 3H), 2.99-2.85 (m, 2H), 2.40-2.28 (m, 1H), 2.27-2.14 (m, 3H), 2.14-2.02 (m, 3H), 2.02-1.92 (m, 3H), 1.91-1.78 (m, 3H), 1.52-1.36 (m, 1H); LCMS (ESI, M+1): m/z = 608.0.

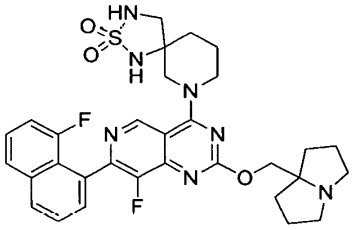
Example 251:



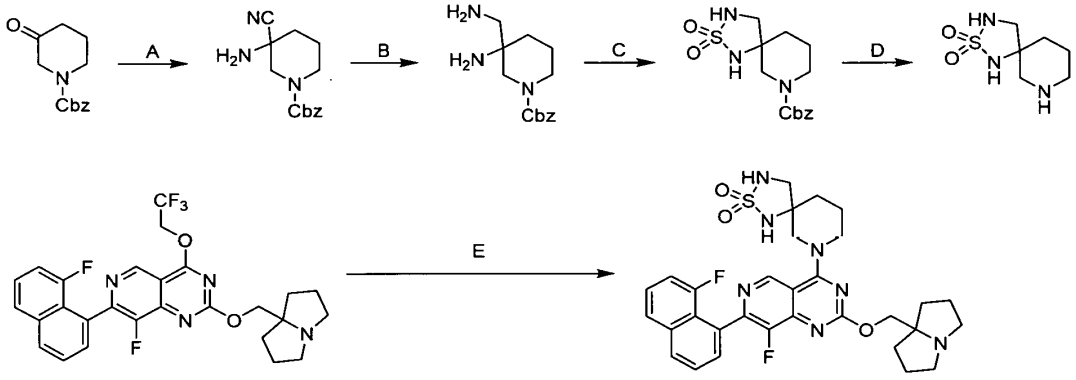
8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(methylsulfonyl)azocan-1-yl)pyrido[4,3 d]pyrimidine

[0000838] The title compound was synthesized according to the procedure described for example 250. ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.25 (d, *J* = 0.8 Hz, 1H), 8.12 (br d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.75-7.67 (m, 1H), 7.61 (dd, *J* = 4.4, 6.8 Hz, 1H), 7.53 (dt, *J* = 5.2, 8.0 Hz, 1H), 7.25-7.12 (m, 1H), 5.12 (br d, *J* = 12.4 Hz, 1H), 4.64-4.51 (m, 3H), 3.98-3.79 (m, 3H), 3.47-3.36 (m, 2H), 3.12 (s, 3H), 3.07-2.97 (m, 2H), 2.52-2.38 (m, 1H), 2.27-2.18 (m, 2H), 2.16-2.08 (m, 3H), 2.07-2.00 (m, 4H), 2.00-1.88 (m, 3H), 1.88-1.69 (m, 2H), 1.59-1.45 (m, 1H); LCMS (ESI, M+1): m/z = 622.2.

EXAMPLE 252



7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide



[0000839] Step A. benzyl 3-amino-3-cyano-piperidine-1-carboxylate: A mixture of benzyl 3-oxopiperidine-1-carboxylate (10.0 g, 1.0 *equiv.*) and NH$_4$Cl (9.17 g, 4.0 *equiv.*) in isopropyl alcohol (60 mL) and NH$_3$•H$_2$O (120 mL) was added KCN (10.1 g, 3.61 *equiv.*) in one portion at

25 °C under N_2. The mixture was stirred at 25 °C for 12 hours. The reaction mixture was poured into water (150 mL), and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine (100 mL), and dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate 20:1 to 0:1) to afford the title compound (10.0 g, 89% yield) as a yellow oil; LCMS (ESI, 2M+1): m/z = 519.2.

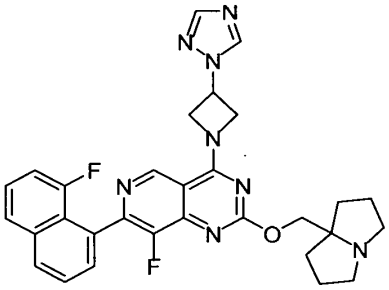
[0000840] Step B. benzyl 3-amino-3-(aminomethyl)piperidine-1-carboxylate : A mixture of benzyl 3-amino-3-cyano-piperidine-1-carboxylate (200 mg, 1.0 *equiv.*), NH_3•MeOH (1.00 mL, 20% purity, 1.0 *equiv.*) in MeOH (5 mL) and Raney Ni (30.0 mg) was stirred at 25 °C for 5 hours under H_2 atmosphere (15 psi). The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: [water (10 mM NH_4HCO_3)/ACN], B%: 9% - 39%, 10 min] and lyophilized to afford the title compound (100 mg, 45% yield) as a colorless oil; ^{1}H NMR (400 MHz, chloroform-d_4) δ = 7.38-7.30 (m, 5H), 5.23-5.03 (m, 2H), 3.45 (br s, 3H), 3.19 (br d, *J* = 13.2 Hz, 1H), 2.78-2.63 (m, 1H), 2.49 (d, *J* = 13.2 Hz, 1H), 1.66-1.40 (m, 4H).

[0000841] Step C. benzyl 2-thia-1,3,7-triazaspiro[4.5]decane-7-carboxylate 2,2-dioxide: To a refluxing solution of sulfamide (109 mg, 10.0 *equiv.*) in Pyridine (2 mL) was added benzyl 3-amino-3-(aminomethyl)piperidine-1-carboxylate (30.0 mg, 1.0 *equiv.*). The resulting mixture was stirred at 120 °C for further 12 hours under nitrogen. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; mobile phase: water (0.225% formic acid), / ACN], B%: 22% - 52%, 7 min] and lyophilized to afford the title compound (15.0 mg, 40% yield) as a yellow solid; ^{1}H NMR (400 MHz, chloroform-d_4) δ = 7.35 (s, 5H), 5.62 (br d, *J* = 0.8 Hz, 1H), 5.13 (br s, 2H), 5.03 (br s, 1H), 3.65 (br d, *J* = 12.0 Hz, 1H), 3.58-3.31 (m, 4H), 3.22-3.11 (m, 1H), 1.95-1.84 (m, 1H), 1.81-1.67 (m, 2H), 1.54 (br dd, *J* = 2.8, 7.2 Hz, 1H).

[0000842] Step D. $2\lambda^6$-thia-1,3,9-triazaspiro[4.5]decane 2,2-dioxide: To a mixture of benzyl 2,2-dioxo-$2\lambda^6$- thia-1,3,9-triazaspiro[4.5]decane-9-carboxylate (15.0 mg, 1.0 *equiv.*) in MeOH (2 mL) was added Pd/C (3.00 mg, 10% purity) and then the mixture was stirred at 25 °C for 1 hour under H_2 atmosphere (15 psi). The mixture was filtered and concentrated under reduced pressure to afford the title compound (17.0 mg, crude) as a yellow solid.

[0000843] Step E. 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide: 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 (15.0 mg, 1.0 *equiv.*) in DMF (1.0 mL) was added DIEA (11.0 mg, 3.0 *equiv.*) and 2λ^6-thia-1,3,9-triazaspiro[4.5]decane 2,2-dioxide (16.2 mg, 3.0 *equiv.*). The mixture was stirred at 45 °C for 12 hours. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC [column: Phenomenex C18 75 × 30 mm × 3 μm; mobile phase: [water (0.1% formic acid)/ACN] B%: 15%-45%, 7 min] and lyophilized to afford the title compound (4.74 mg, 26% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.14 (s, 1H), 8.12 (br d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.76-7.66 (m, 1H), 7.61 (t, *J* = 5.2 Hz, 1H), 7.54 (dt, *J* = 4.8, 7.6 Hz, 1H), 7.19 (dd, *J* = 7.6, 13.2 Hz, 1H), 4.68-4.58 (m, 2H), 4.55-4.33 (m, 2H), 3.90- 3.72 (m, 2H), 3.56-3.39 (m, 3H), 3.28-3.19 (m, 1H), 3.16-3.04 (m, 2H), 2.26 (td, *J* = 6.4, 12.4 Hz, 2H), 2.17-1.89 (m, 10H); LCMS (ESI, M+1): m/z = 622.3.

Example 253

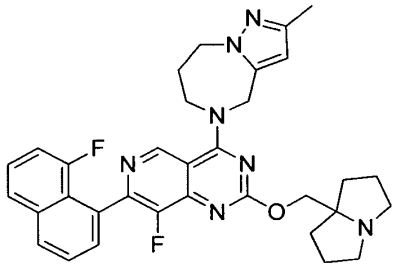


4-(3-(1*H*-1,2,4-triazol-1-yl)azetidin-1-yl)-8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidine

[0000844] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 8.96 (s, 1H), 8.28 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.84 (t, *J* = 4.0 Hz, 2H), 7.72 - 7.66 (m, 1H), 7.60 (dd, *J* = 0.8, 7.2 Hz, 1H), 7.52 (dt, *J* = 5.2, 8.0 Hz, 1H), 7.18 (dd, *J* = 7.6, 13.2 Hz, 1H), 5.90 - 5.78 (m, 1H), 5.55 - 4.94 (m, 4H), 4.43 (s, 2H), 3.37 - 3.32 (m, 2H), 2.97 - 2.86 (m, 2H), 2.20 - 2.11 (m, 2H), 2.09 - 1.90 (m, 4H), 1.90 - 1.81

(m, 2H); ^{19}F NMR (377 MHz, METHANOL-d_4) δ = -115.14, -140.68; LCMS (ESI, M+1): m/z = 555.3.

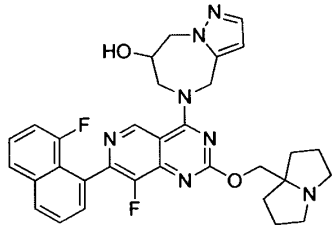
EXAMPLE 254



8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepin-5(6H)-yl)pyrido[4,3-d]pyrimidine

[0000845] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.25 (s, 1H), 8.13 (br d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.62 (dd, *J* = 0.8, 7.2 Hz, 1H), 7.58-7.50 (m, 1H), 7.20 (dd, *J* = 7.2, 13.2 Hz, 1H), 6.26 (s, 1H), 5.29-5.14 (m, 2H), 4.71-4.61 (m, 2H), 4.49-4.37 (m, 4H), 3.76-3.65 (m, 2H), 3.37-3.32 (m, 1H), 3.30-3.26 (m, 1H), 2.46-2.37 (m, 2H), 2.36-2.29 (m, 2H), 2.28-2.07 (m, 9H); LCMS (ESI, M+1): m/z = 582.3.

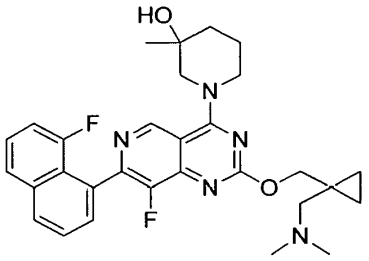
EXAMPLE 255



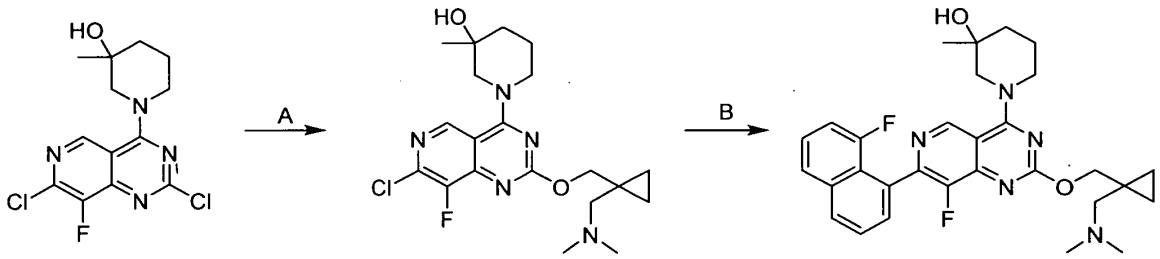
5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-7-ol

[0000846] The title compound was synthesized according to the procedure described for example 85. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.42 (d, *J* = 16.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.2 Hz,1H), 7.64-7.58 (m, 1H), 7.57-7.49 (m, 1H), 7.43 (d, *J* = 1.6 Hz, 1H), 7.22-7.15 (m, 1H), 6.60-6.50 (m, 1H), 5.60-5.45 (m, 1H), 5.14-5.00 (m, 1H), 4.67-4.55 (m, 2H), 4.54-4.44 (m, 1H), 4.43-4.27 (m, 4H), 3.20-3.09 (m, 2H), 2.82-2.73 (m, 2H), 2.15-2.04 (m, 2H), 2.02-1.85 (m, 4H), 1.84-1.74 (m, 2H); LCMS (ESI, M+1): m/z = 584.3.

EXAMPLE 256



1-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-7-(8-fluoronaphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

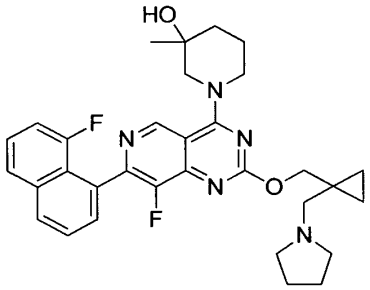


[0000847] Step A. 1-(7-chloro-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of 1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (200 mg, 1 *equiv.*), (1-((dimethylamino)methyl)cyclopropyl)methanol (78 mg, 1 *equiv.*), DIPEA (195 mg, 2.5 *equiv.*) and 4Å molecular sieves (40 mg) in dioxane (2.5 mL) was stirred at 90 °C for 14 hours under N_2 atmosphere. The reaction mixture was filtered. The filter cake was washed with DCM (20 mL). The combined organic phase was concentrated and purified by reversed phase flash

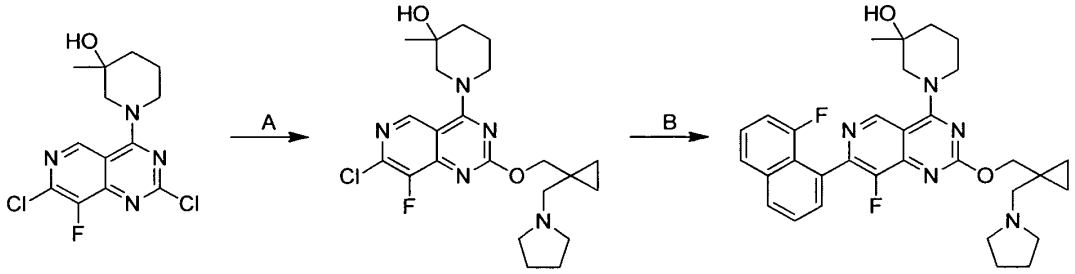
chromatography [water (0.1% formic acid)/acetonitrile 3:1] to afford the tittle compound (65 mg, 24% yield) as a light yellow solid; LCMS (ESI, M+1): m/z = 424.3.

[0000848] Step B. 1-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-7-(8-fluoronaphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of 1-(7-chloro-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (65 mg, 1 *equiv.*), 2-(8-fluoronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (50 mg, 184 μmol, 1.2 *equiv.*), cataCXium® A Pd G3 (12 mg, 0.1 *equiv.*) and K_3PO_4 (1.5 M in water, 307 μL, 3 *equiv.*) in methoxycyclopentane (1.5 mL) was degassed and stirred at 90 °C for 3 hours. The mixture was diluted with water (1 mL) and extracted with ethyl acetate (4 × 2 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile 13:7] and then prep-HPLC [column: waters Xbridge 150 × 25 mm × 5 μm; mobile phase: [water (10 mM NH_4HCO_3)/ACN]; B%: 43%-73%, 9 minutes] to afford the title compound (47.5 mg, 57% yield) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.20 (d, *J* = 5.2 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.62-7.52 (m, 1H), 7.53 (dt, *J* = 5.2, 8.0 Hz, 1H), 7.19 (dd, *J* = 8.0, 12.8 Hz, 1H), 4.51 (br dd, *J* = 4.4, 9.6 Hz, 1H), 4.39-4.36 (m, 2H), 4.26 (br d, *J* = 13.2 Hz, 1H), 3.63 (dd, *J* = 2.0, 13.2 Hz, 1H), 3.49-3.46 (m, 1H), 2.46-2.44 (m, 2H), 2.30 (s, 6H), 2.18-2.14 (m, 1H), 1.85-1.75 (m, 3H), 1.29 (d, *J* = 5.6 Hz, 3H), 0.75-0.72 (m, 2H), 0.54-0.52 (m, 2H); 19F NMR (400 MHz, methanol-d4) δ = -115, -141; LCMS (ESI, M+1): 534.4.

EXAMPLE 257



1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

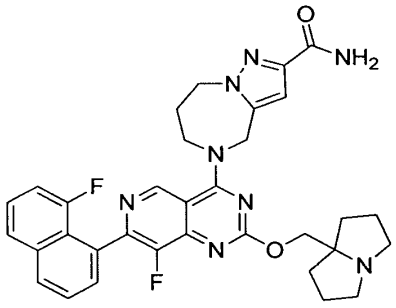


[0000849] Step A. 1-(7-chloro-8-fluoro-2-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of 1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (200 mg, 1.0 *equiv.*), (1-(pyrrolidin-1-ylmethyl)cyclopropyl)methanol (140 mg, 1.5 *equiv.*), 4Å molecular sieves (10.0 mg) in dioxane (1.5 mL) was added DIEA (234 mg, 315 µL, 3.0 *equiv.*). The reaction was stirred at 95 °C for 12 hours. After completion, the reaction mixture was diluted with water (1 mL) and extracted with Ethyl acetate (2 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by reversed-phase flash chromatography (water (0.1% formic acid)/ACN) to afford the title compound (93.0 mg, 33% yield) as a yellow oil; LCMS [ESI, M+1]: m/z = 450.1.

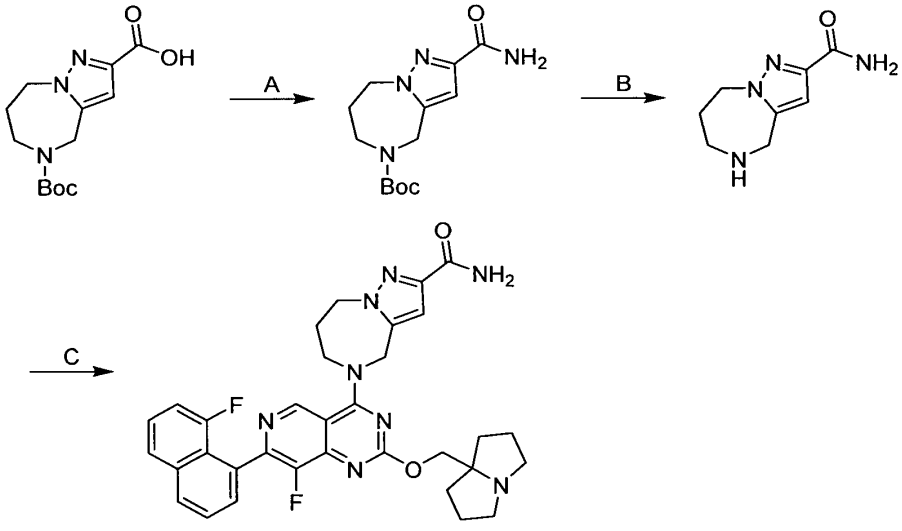
[0000850] Step B. 1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of 1-(7-chloro-8-fluoro-2-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (50.0 mg, 1.0 *equiv.*), 2-(8-fluoronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (36.3 mg, 1.2 *equiv.*), K_3PO_4 (1.5 M, 222 µL, 3.0 *equiv.*) in Methoxycyclopentane (1 mL) was added CataCXium A Pd G3 (8.09 mg, 11.1 µmol, 0.1 *equiv.*) under N_2. The reaction was stirred at 90 °C for 2 hours. After completion, the reaction mixture was diluted with water (1 mL) and extracted with Ethyl acetate (2 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase flash chromatography (water (0.1% formic acid)/ACN) and prep-HPLC (column: Phenomenex Synergi C18 150 × 25 mm × 10 µm; mobile phase: [water (0.225% formic acid)/ACN] B%: 12% - 42%, 10 min) and lyophilized to

afford the title compound (19.9 mg, 32% yield) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d4): δ 9.23 (d, J = 8.0 Hz, 1H), 8.54 (s, 1H), 8.12 (br d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.73 - 7.68 (m, 1H), 7.61 (dt, J = 1.2, 8.0 Hz, 1H), 7.56 - 7.51 (m, 1H), 7.20 (ddd, J = 1.6, 7.6, 13.2 Hz, 1H), 4.58 - 4.46 (m, 2H), 4.43 - 4.37 (m, 1H), 4.30 (br d, J = 13.2 Hz, 1H), 3.62 (dd, J = 2.0, 13.2 Hz, 1H), 3.43 (br t, J = 11.6 Hz, 1H), 3.30 - 3.05 (m, 6H), 2.22 - 2.10 (m, 1H), 2.00 (br s, 4H), 1.88 - 1.74 (m, 3H), 1.29 (d, J = 4.4 Hz, 3H), 0.90 - 0.75 (m, 4H); LCMS [ESI, M+1]: m/z = 560.2.

EXAMPLE 258



5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

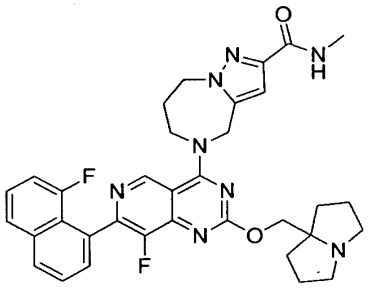


[0000851] Step A. tert-butyl-2-carbamoyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: To a solution of 5-tert-butoxycarbonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (1.00 g, 1.0 *equiv.*), TEA (2.16 g, 6.0 *equiv.*) and HATU (2.70 g, 2.0 *equiv.*) in THF (10 mL) was added NH_4Cl (570 mg, 3.0 *equiv.*). The mixture was stirred at 25 °C for 12 hours. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 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 (800 g, 80% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 281.2.

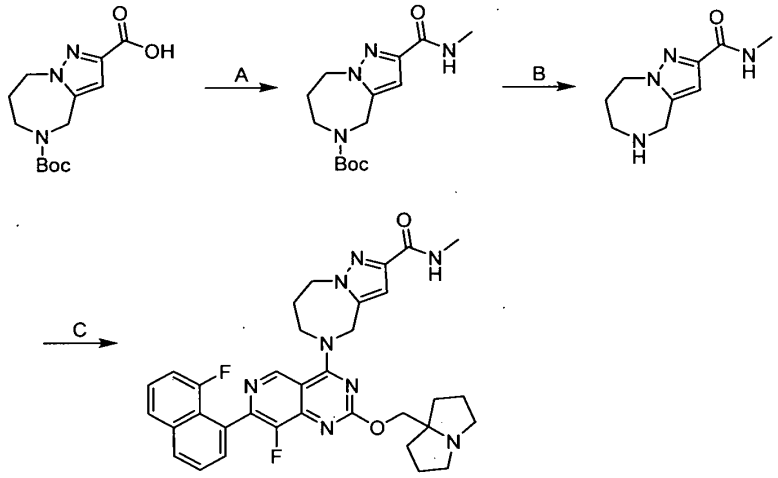
[0000852] Step B. 5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: To a solution of tert-butyl 2-carbamoyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (800 mg, 1.0 *equiv.*) in MeCN (8 mL) was added HCl•dioxane (4 M, 16 mL, 22 *equiv.*) at 0 °C. The reaction was stirred at 0 °C for 0.5 hour. The mixture was concentrated to afford the title compound (800 mg, crude, HCl) as a yellow solid; LCMS (ESI, M+1): m/z = 180.1.

[0000853] Step C. 5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: 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 (100 mg, 1.0 *equiv.*), 5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (408 mg, 10 *equiv.*, HCl) and 4Å molecular sieves (10 mg) in DMF (0.5 mL) was added DIEA (487 mg, 20 *equiv.*). The reaction was stirred at 40 °C for 24 hours. The residue was filtered and purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; mobile phase: water (0.225% formic acid)/ACN] B%: 15% - 45%, 7 minutes] to afford the title compound (15.2 mg, 13% yield) as a white solid; ^1H NMR (400 MHz, methanol-d_4) δ = 9.27-9.16 (m, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.74-7.67 (m, 1H), 7.61 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.53 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.24-7.14 (m, 1H), 6.88 (s, 1H), 5.35-5.16 (m, 2H), 4.58-4.45 (m, 6H), 3.56-3.43 (m, 2H), 3.17-3.04 (m, 2H), 2.57-2.35 (m, 2H), 2.28-2.19 (m, 2H), 2.18-2.03 (m, 4H), 2.02-1.92 (m, 2H); LCMS (ESI, M+1): m/z = 611.2.

EXAMPLE 259



5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

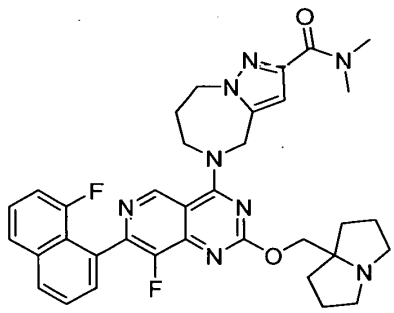


[0000854] Step A. tert-butyl-2-(methylcarbamoyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: To a solution of 5-tert-butoxycarbonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (1.00 g, 1.0 *equiv.*), TEA (2.16 g, 6.0 *equiv.*) and HATU (2.70 g, 2.0 *equiv.*) in THF (10 mL) was added methylamine (720 mg, 3.0 *equiv.*, HCl). The reaction was stirred at 25 °C for 3 hours. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 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 (900 g, 83% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 295.0.

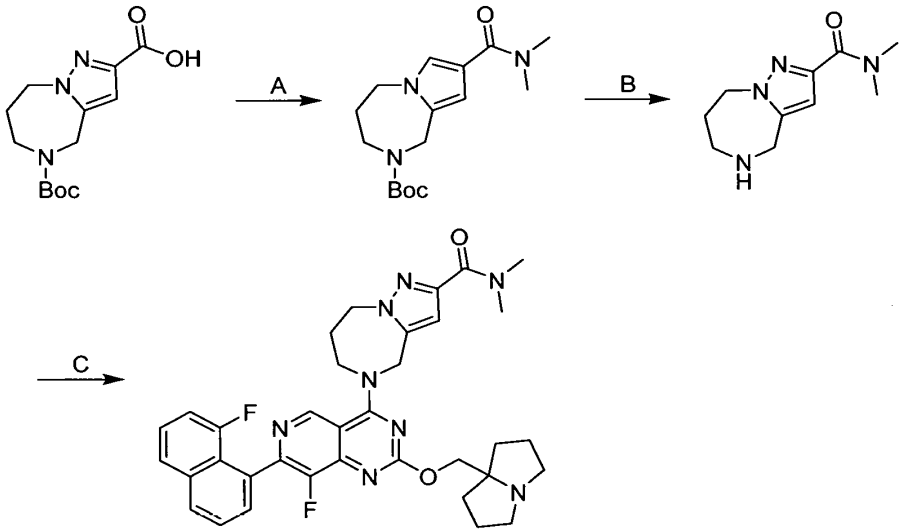
[0000855] Step B. N-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: To a solution of tert-butyl-2-(methylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (900 mg, 1.0 *equiv.*) in MeCN (9 mL) was added HCl•dioxane (4 M, 18 mL, 23 *equiv.*) at 0 °C. The reaction was stirred at 0 °C for 0.5 hour. The mixture was concentrated to afford the title compound (900 mg, crude) as a yellow solid; LCMS (ESI, M+): m/z = 194.2.

[0000856] Step C. 5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: 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, 1.0 *equiv.*), N-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (435 mg, 10 *equiv.*, HCl) and 4Å molecular sieves (10 mg) in DMF (0.5 mL) was added DIEA (487 mg, 20 *equiv.*). The reaction was stirred at 40 °C for 12 hours. The residue was filtered and purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; mobile phase: water (0.225% formic acid)/ACN] B%: 15%-45%, 7minutes] to afford the title compound (60.1 mg, 50% yield) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.22 (s, 1H), 8.12 (br d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.53 (dt, *J* = 5.2, 8.0 Hz, 1H), 7.19 (dd, *J* = 7.6, 13.2 Hz, 1H), 6.84 (s, 1H), 5.37-5.13 (m, 2H), 4.56 (s, 2H), 4.54-4.42 (m, 4H), 3.65-3.54 (m, 2H), 3.20 (td, *J* = 6.0, 11.6 Hz, 2H), 2.88 (s, 3H), 2.45 (br s, 2H), 2.33-2.23 (m, 2H), 2.23-2.09 (m, 4H), 2.09-2.00 (m, 2H); LCMS (ESI, M+1): m/z = 625.1.

EXAMPLE 260



5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

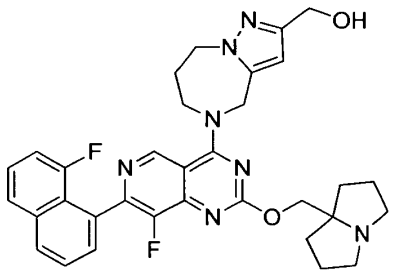


[0000857] Step A. tert-butyl-2-(dimethylcarbamoyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: To a solution of 5-tert-butoxycarbonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (1.00 g, 1.0 *equiv.*), TEA (1.08 g, 3.0 *equiv.*) and HATU (2.70 g, 7.11 mmol, 2.0 *equiv.*) in THF (10 mL) was added dimethylamine (2 M in THF, 2.0 *equiv.*). The mixture was stirred at 25 °C for 12 hours. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by reversed phase chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (1.00 g, 89% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 309.0.

[0000858] Step B. N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: To a solution of tert-butyl-2-(dimethylcarbamoyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (1.00 g, 1.0 *equiv.*) in MeCN (10 mL) was added HCl•dioxane (4 M, 20 mL, 25 *equiv.*) at 0 °C. The reaction was stirred at 0 °C for 0.5 hour. The mixture was concentrated to afford the title compound (1.00 g, crude, HCl) as a yellow liquid; LCMS (ESI, M+): m/z = 208.3.

[0000859] Step C. 5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: 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, 1.0 *equiv.*), N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (461 mg, 10 *equiv.*, HCl) and 4Å molecular sieves (10 mg) in DMF (0.5 mL) was added DIEA (487 mg, 20 *equiv.*). The reaction was stirred at 40 °C for 24 hours. The mixture was filtered and purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; A: water (0.225% formic acid)/ACN] B%: 15% - 45%, 7minutes] to afford the title compound (7.28 mg, 6.02% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.19 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.74-7.66 (m, 1H), 7.61 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.53 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.23-7.13 (m, 1H), 6.79 (s, 1H), 5.38-5.15 (m, 2H), 4.58-4.52 (m, 2H), 4.46 (br t, *J* = 4.8 Hz, 2H), 4.36 (s, 2H), 3.33 (s, 3H), 3.29-3.20 (m, 2H), 3.08 (s, 3H), 2.94-2.80 (m, 2H), 2.50-2.38 (m, 2H), 2.18-2.08 (m, 2H), 2.06-1.91 (m, 4H), 1.90-1.79 (m, 2H); LCMS (ESI, M+1): m/z = 639.1.

EXAMPLE 261

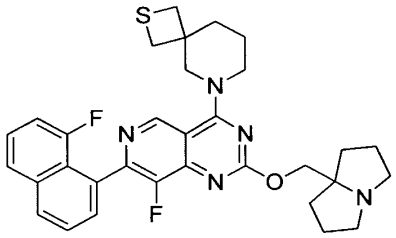


(5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanol

[0000860] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.24 (s, 1H), 8.13 (br d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.75-7.66 (m, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.54 (dt, *J* = 5.2, 8.0 Hz, 1H), 7.19 (dd, *J* = 7.6, 13.2 Hz, 1H), 6.46 (s, 1H), 5.3-5.17 (m, 2H), 4.56 (d, *J* = 17.6 Hz, 4H), 4.44 (br

d, J = 6.0 Hz, 4H), 3.64-3.56 (m, 2H), 3.20 (td, J = 6.0, 11.6 Hz, 2H), 2.42 (br s, 2H), 2.33-2.25 (m, 2H), 2.25-2.18 (m, 1H), 2.18-2.09 (m, 3H), 2.09-2.01 (m, 2H); LCMS (ESI, M+1): m/z = 598.3.

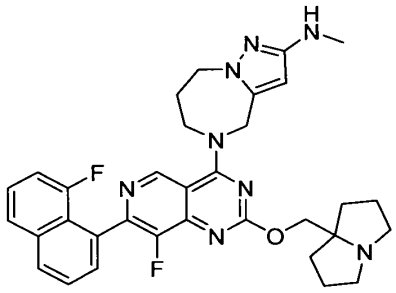
EXAMPLE 262



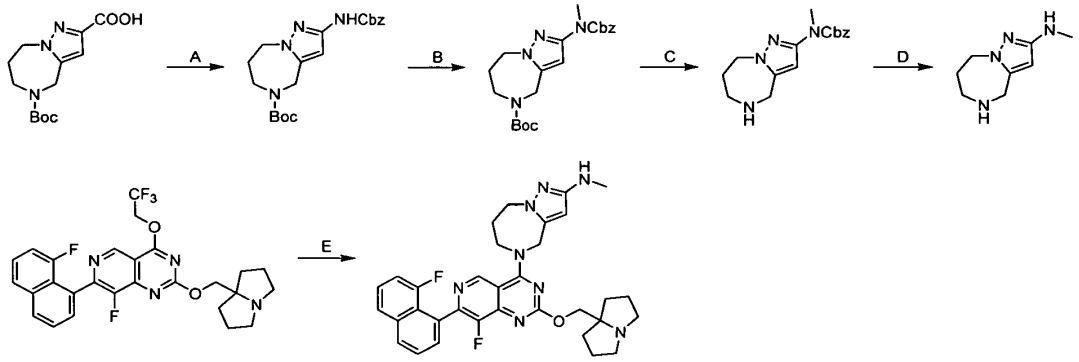
6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-thia-6-azaspiro[3.5]nonane

[0000861] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.14 (s, 1H), 8.12 (br d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.72-7.69 (m, 1H), 7.62 (dd, J = 0.8, 7.2 Hz, 1H), 7.53 (dt, J = 5.2, 8.0 Hz, 1H), 7.19 (dd, J = 7.2, 13.2 Hz, 1H), 4.57 (s, 2H), 4.43-4.36 (m, 2H), 4.02 (br dd, J = 4.4, 6.0 Hz, 2H), 3.46-3.43 (m, 2H), 3.16 (d, J = 9.2 Hz, 2H), 3.06-3.03 (m, 2H), 2.90 (t, J = 9.2 Hz, 2H), 2.22-2.17 (m, 2H), 2.15-2.05 (m, 4H), 1.97-1.93 (m, 4H), 1.83-1.77 (m, 2H); LCMS (ESI, M+1): m/z = 574.3.

EXAMPLE 263



5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine



[0000862] Step A. tert-butyl 2-(benzyloxycarbonylamino)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate: A mixture of 5-tert-butoxycarbonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (500 mg, 1.0 *equiv.*), 4Å MS (300 mg) and TEA (539 mg, 3.0 *equiv.*) in toluene (5 mL) and BnOH (1.15 g, 6.0 *equiv.*) was stirred at 110 °C for 0.5 hour under nitrogen. And then the mixture was cooled to 15 °C and DPPA (734 mg, 1.5 *equiv.*) was added at 15 °C. The mixture was stirred at 110 °C for 5 hours. The reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL), and dried over sodium sulfate, 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 the title compound (400 mg, 42% yield) as a gray solid; LCMS (ESI, M+1): m/z = 387.2.

[0000863] Step B. tert-butyl 2-[benzyloxycarbonyl(methyl)amino]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate: A mixture of tert-butyl 2-(benzyloxycarbonylamino)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (100 mg, 1.0 *equiv.*) in DMF (3 mL) was added K_2CO_3 (179 mg, 5.0 *equiv.*) and MeI (220 mg, 6.0 *equiv.*). The mixture was stirred at 50 °C for 3 hours. The reaction mixture was quenched with saturated NH_4Cl solution (20 mL). The mixture was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with brine (10 ml), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (Silica

gel, Petroleum ether/Ethyl acetate 20:1 to 1:1) to afford the title compound (85.0 mg, 82% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 401.3.

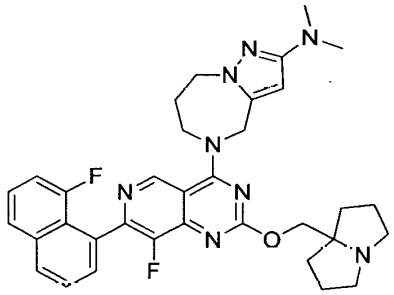
[0000864] Step C. benzyl N-methyl-N-(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2- yl)carbamate: To a solution of tert-butyl 2-[benzyloxycarbonyl(methyl)amino]-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (85.0 mg, 1.0 *equiv.*) in MeCN (1 mL) was added HCl•dioxane (4 M, 0.5 mL, 9.42 *equiv.*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The pH of the mixture was adjusted to 8 with saturated $NaHCO_3$ solution and the resulting was extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford the title compound (60.0 mg, 94% yield) as a yellow solid.

[0000865] Step D. N-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine: To a mixture of benzyl N-methyl-N-(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)carbamate (60.0 mg, 1.0 *equiv.*) in MeOH (3 mL) was added Pd/C (15.0 mg, 10% purity). The mixture was stirred at 25 °C for 2 hours under H_2 atmosphere (15 psi) before being filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (Silica gel, DCM / MeOH 5:1) to afford the title compound (32.0 mg, 88% yield) as a yellow solid; ^{1}H NMR (400 MHz, chloroform-d) δ = 5.41 (s, 1H), 4.24-4.11 (m, 2H), 3.78 (s, 2H), 3.21-3.09 (m, 2H), 2.80 (s, 3H), 1.82-1.74 (m, 2H); LCMS [ESI, M+1]: m/z = 167.3.

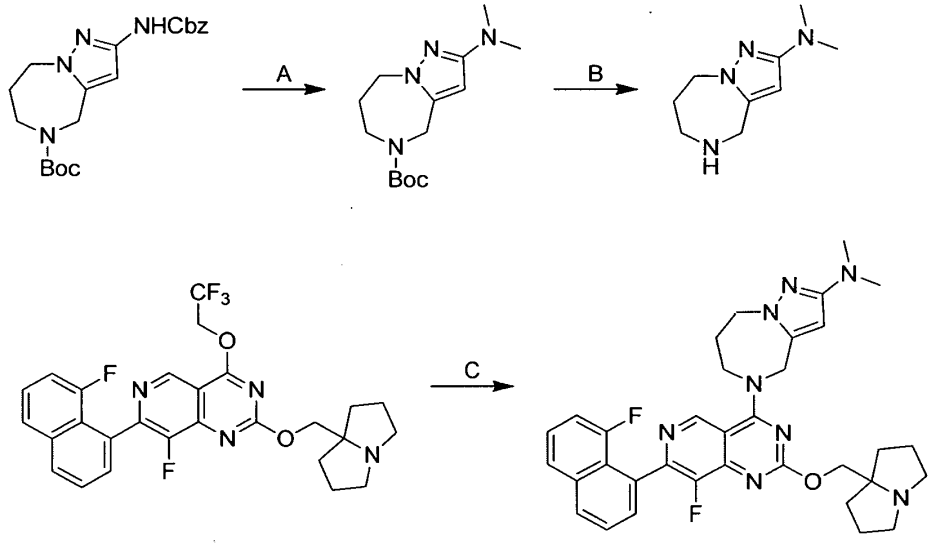
[0000866] Step E. 5-[8-fluoro-7-(8-fluoro-1-naphthyl)-2-(1,2,3,5,6,7-hexahydropyrrolizin-8-ylmethoxy)pyrido[4,3-d]pyrimidin-4-yl]-N-methyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepin-2-amine: To a solution of N-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (31.3 mg, 10 *equiv.*), 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 (10.0 mg, 1.0 *equiv.*), DIEA (7.31 mg, 3.0 *equiv.*) in DMF (0.05 mL) was degassed and stirred at 50 °C for 12 hours under N_2 atmosphere. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC [column: Phenomenex C 18 75 × 30 mm × 3 μm; mobile phase: water (0.1% formic acid)/ACN], B%: 12% - 42%, 7 min] to afford the title compound (3.84 mg, 33% yield) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d4): δ = 9.23 (s, 1H), 8.12 (br d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H),

7.71 (t, J = 7.2 Hz, 1H), 7.63-7.59 (m, 1H), 7.53 (dt, J = 4.8, 8.0 Hz, 1H), 7.19 (dd, J = 8.0, 13.2 Hz, 1H), 5.77 (s, 1H), 5.18-5.06 (m, 2H), 4.45 (s, 2H), 4.37 (br s, 2H), 4.30-4.21 (m, 2H), 3.41-3.34 (m, 2H), 3.03-2.93 (m, 2H), 2.77 (s, 3H), 2.39 (br s, 2H), 2.17 (br dd, J = 6.0, 12.0 Hz, 2H), 2.04 (dt, J = 6.4, 13.2 Hz, 4H), 1.91 (br dd, J = 6.8, 12.8 Hz, 2H); LCMS [ESI, M+1]: m/z = 597.4.

EXAMPLE 264



5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine



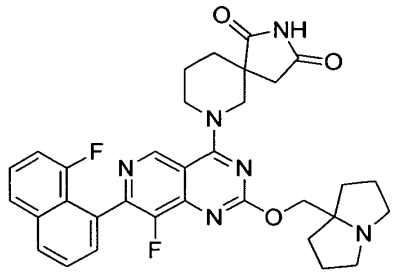
[0000867] Step A. tert-butyl 2-(dimethylamino)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: To a solution of tert-butyl-2-(((benzyloxy)carbonyl)amino)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (589 mg, 1.0 *equiv.*) and HCHO (371 mg, 37% purity, 3.0 *equiv.*) in MeOH (20.0 mL) was added Pd/C (500 mg, 10% purity) under N_2. The mixture was degassed and purged with H_2 for 3 times, and then stirred at 25 °C for 1 hour under H_2 (15 psi). The mixture was filtered, the filtrate was concentrated in vacuum. The crude product was purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the tittle compound (202 mg, 43% yield) as a yellow oil. LCMS (ESI, M+1): m/z = 281.2.

[0000868] Step B. N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine: To a solution of tert-butyl 2-(dimethylamino)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (170 mg, 1.0 *equiv.*) in MeCN (3.00 mL) was added HCl•dioxane (4 M, 6.00 mL, 39.6 *equiv.*). The mixture was stirred at 25 °C for 0.5 hour. The mixture was concentrated in vacuum to afford the tittle compound (131 mg, crude, HCl) as a white solid.

[0000869] Step C. 5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine: To a mixture of N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (129 mg, 4.5 *equiv.*, HCl) and DIEA (170 mg, 10.0 *equiv.*) 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 (70.0 mg, 1.0 *equiv.*) and DMF (0.5 mL). The mixture was stirred at 50 °C for 14 hours. The mixture was diluted with DMF (1.5 mL) and purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] and further purified by prep-HPLC (column: Phenomenex luna C18 150 × 25mm × 10 μm; mobile phase: water (0.1 % formic acid)/ACN] B%: 15%-45%, 10 mins) to afford the tittle compound (10.2 mg, 2.7% yield over two steps) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.23 (s, 1H), 8.12 (br d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.74-7.67 (m, 1H), 7.61 (dd, *J* = 0.8, 6.8 Hz, 1H), 7.53 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.19 (ddd, *J* = 0.8, 7.6, 13.2 Hz, 1H), 5.90 (s, 1H), 5.21-5.06 (m, 2H), 4.43-4.33 (m, 4H), 4.32-4.24 (m, 2H), 3.29-3.23 (m, 2H), 2.96-2.86 (m, 2H), 2.81 (s, 6H), 2.45-2.32

(m, 2H), 2.20-2.08 (m, 2H), 2.07-1.92 (m, 4H), 1.91-1.80 (m, 2H); LCMS (ESI, M+1): m/z = 611.4.

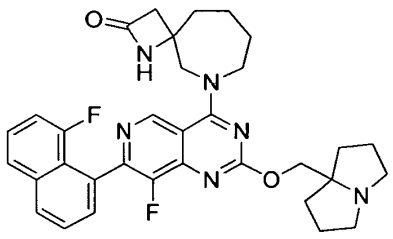
EXAMPLE 265



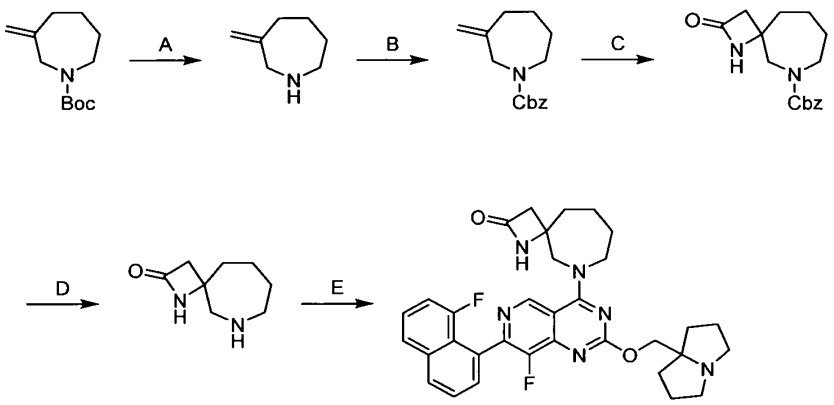
7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[1,3 d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decane-1,3-dione

[0000870] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.12 (d, *J* = 2.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.74 - 7.68 (m, 1H), 7.62 (ddd, *J* = 0.8, 7.2, 10.8 Hz, 1H), 7.54 (dt, *J* = 5.2, 8.0 Hz, 1H), 7.19 (ddd, *J* = 1.6, 7.6, 13.2 Hz, 1H), 4.66 (br dd, *J* = 6.0, 13.2 Hz, 1H), 4.52 (s, 2H), 4.42 (br dd, *J* = 5.2, 12.8 Hz, 1H), 3.95 (dt, *J* = 3.2, 10.4 Hz, 1H), 3.82 (d, *J* = 13.2 Hz, 1H), 3.59 - 3.47 (m, 2H), 3.18 - 3.08 (m, 2H), 2.97 (dd, *J* = 12.0, 18.0 Hz, 1H), 2.68 (d, *J* = 18.0 Hz, 1H), 2.30 - 2.19 (m, 3H), 2.17 - 2.04 (m, 5H), 2.04 - 1.83 (m, 4H); LCMS [ESI, M+1]: m/z = 599.4.

EXAMPLE 266



6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.6]decan-2-one



[0000871] Step A. 3-methyleneazepane: To a solution of tert-butyl 3-methyleneazepane-1-carboxylate (1.50 g, 1.0 *equiv.*) in MeCN (5 mL) was added HCl•dioxane (4 M, 10.0 mL, 5.63 *equiv.*). The mixture was stirred at 20 °C for 1 hour. After completion, the residue was concentrated to afford the title compound (1.50 g, crude, HCl) as a white solid.

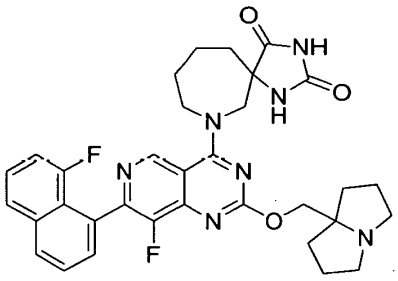
[0000872] Step B. benzyl 3-methyleneazepane-1-carboxylate: To a solution of 3-methyleneazepane (1.50 g, 1.0 *equiv.*, HCl) and DIEA (6.57 g, , 5.0 *equiv.*) in dichloromethane (20.0 mL) was added CbzCl (2.60 g, 1.50 *equiv.*). The mixture was stirred at 20 °C for 3 hours. The residue was concentrated to afford the title compound (2.70 g, crude) as a yellow solid.

[0000873] Step C. benzyl 2-oxo-1,6-diazaspiro[3.6]decane-6-carboxylate: To a solution of benzyl 3-methyleneazepane-1-carboxylate (2.70 g, 1.0 *equiv.*) in toluene (60.0 mL) was added a solution of sulfurisocyanatidic chloride (1.71 g, 1.10 *equiv.*) in toluene (20.0 mL) dropwise at 0 °C. After addition the mixture was stirred at 20 °C for 20 hours. After reaction completion, the mixture was slowly added to a vigorously stirred solution of Na_2SO_3 (3.0g) and K_2CO_3 (20 g) in water (60.0 mL). The mixture was stirred at 20 °C for 4 hours. Then the mixture was extracted with ethyl acetate (3 × 15 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (Al_2O_3, petroleum ether/ethyl acetate 10:1 then ethyl acetate/methanol 10:1) to afford the title compound (1.20 g, three steps 36% yield) as a yellow oil; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.46-7.29 (m, 5H), 5.26-5.02 (m, 2H), 3.87-3.52 (m, 3H), 3.36-3.15 (m, 1H), 2.98-2.59 (m, 2H), 1.96-1.70 (m, 4H), 1.65-1.43 (m, 2H); LCMS (ESI, M-41, 2M+1): m/z = 247.1, 577.4.

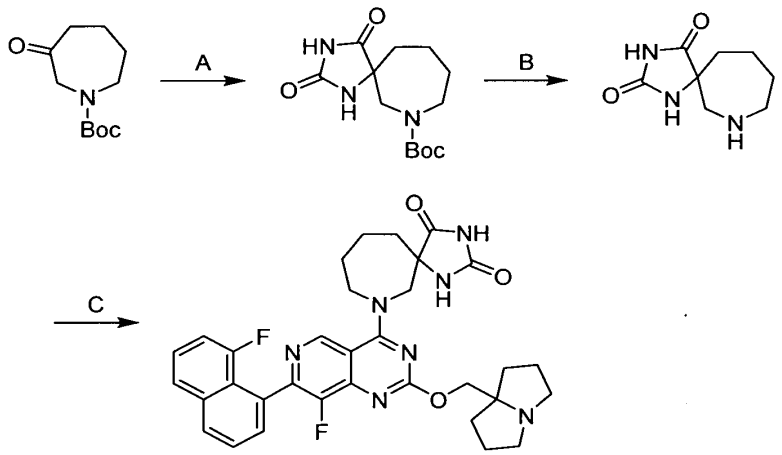
[0000874] Step D. 1,6-diazaspiro[3.6]decan-2-one: To a solution of benzyl 2-oxo-1,6-diazaspiro[3.6]decane-6-carboxylate (200 mg, 1.0 *equiv.*) in MeOH (5.0 mL) was added Pd/C (50 mg, 10% purity) under N_2. The suspension was degassed in vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 Psi) at 20°C for 12 hours. The mixture was filtered and concentrated to afford the title compound (120 mg, crude) as a yellow oil.

[0000875] Step E. 6-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.6]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 (65.0 mg, 1.0 *equiv.*) and DIEA (110 mg, 149 µL, 7.0 *equiv.*) in DMF (2 mL) was added 1,6-diazaspiro[3.6]decan-2-one (94.5 mg, 5.0 equiv.). The mixture was stirred at 40 °C for 12 hours. After reaction completion, the mixture was filtered and purified by prep-HPLC (column: Phenomenex luna C18 150 × 25 mm × 10 µm; mobile phase: [water (0.1 % formic acid)/ACN], B%: 20%-50%, 7 min) to afford the title compound (32.1 mg, 43% yield over two steps) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.22 (d, *J* = 4.0 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.70 (dd, *J* = 7.2, 8.0 Hz, 1H), 7.63-7.58 (m, 1H), 7.56-7.50 (m, 1H), 7.19 (dd, *J* = 7.6, 12.8 Hz, 1H), 4.85-4.78 (m, 2H), 4.46-4.35 (m, 2H), 4.32-4.22 (m, 1H), 4.21-4.05 (m, 2H), 3.38-3.33 (m, 1H), 3.10 (dd, *J* = 3.6, 14.8 Hz, 1H), 2.98-2.89 (m, 2H), 2.82 (dd, *J* = 3.6, 14.8 Hz, 1H), 2.25- 2.09 (m, 4H), 2.08-1.94 (m, 6H), 1.94-1.84 (m, 3H), 1.83-1.72 (m, 1H); LCMS (ESI, M+1): m/z = 585.4.

EXAMPLE 267



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[4.6]undecane-2,4-dione



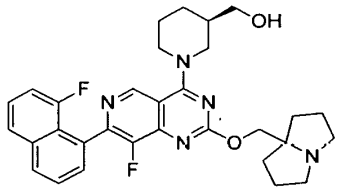
[0000876] Step A. tert-butyl 2,4-dioxo-1,3,7-triazaspiro[4.6]undecane-7-carboxylate: To a solution of tert-butyl 3-oxoazepane-1-carboxylate (2.00 g, 1.0 *equiv.*), $(NH_4)_2CO_3$ (2.70 g, 3.0 *equiv.*) in EtOH (10 mL) and water (10 mL) was added KCN (1.12 g, 1.8 *equiv.*). The reaction was stirred at 85 °C for 16 hours. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to afford the title compound (2.20 g, 83% yield) as a white solid; ^{1}H NMR (400 MHz, dimethylsulfoxide-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+1): m/z = 284.0.

[0000877] Step B. 1,3,7-triazaspiro[4.6]undecane-2,4-dione: To a solution of tert-butyl 2,4-dioxo-1,3,7-triazaspiro[4.6]undecane-7-carboxylate (500 mg, 1.0 *equiv.*) in MeCN (5 mL) was added HCl•dioxane (4 M, 2.5 mL, 5.6 *equiv.*) at 0 °C. The reaction was stirred at 0 °C for 0.5 hour. The mixture was concentrated to afford the title compound (500 mg, crude, HCl salt) as a yellow liquid; LCMS (ESI, M+): m/z = 183.1.

[0000878] Step C. 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[4.6]undecane-2,4-dione: 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 (100 mg, 1.0 *equiv.*), 1,3,7-triazaspiro[4.6]undecane-2,4-dione (345 mg, 10 *equiv.*), DIEA (487 mg, 20 *equiv.*) and 4Å molecular sieves (10 mg) in DMF (0.5 mL) was stirred at 40 °C for 24 hours. The residue was filtered and purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; mobile phase: [water (0.225% formic

acid)/ACN] B%: 15% - 45%, 7minutes] to afford the title compound (32.7 mg, 52.9 μmol, 28% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.30 (d, J = 5.6 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.75-7.68 (m, 1H), 7.65-7.59 (m, 1H), 7.54 (dt, J = 5.2, 8.0 Hz, 1H), 7.20 (dd, J = 7.2, 13.2 Hz, 1H), 4.98 (dd, J = 11.6, 14.2 Hz, 1H), 4.60-4.47 (m, 2H), 4.43-4.28 (m, 1H), 4.20-4.00 (m, 2H), 3.61 (qd, J = 6.0, 11.6 Hz, 2H), 3.24-3.10 (m, 2H), 2.32-2.19 (m, 4H), 2.19-2.08 (m, 6H), 2.07-1.98 (m, 2H), 1.95-1.70 (m, 2H); LCMS (ESI, M+1): m/z = 614.1.

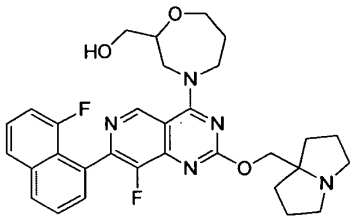
EXAMPLE 268



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

[0000879] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.10 (s, 1H), 8.11 (br d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.52 (dt, J = 5.2, 8.0 Hz, 1H), 7.18 (dd, J = 7.6, 13.2 Hz, 1H), 4.76 - 4.58 (m, 2H), 4.47 (s, 2H), 3.60 (dd, J = 4.8, 11.2 Hz, 1H), 3.53 - 3.44 (m, 2H), 3.42 - 3.32 (m, 3H), 3.03 - 2.94 (m, 2H), 2.24 - 2.14 (m, 2H), 2.12 - 1.98 (m, 5H), 1.98 - 1.88 (m, 4H), 1.84 - 1.73 (m, 1H), 1.53 - 1.41 (m, 1H); LCMS [ESI, M+H]: m/z = 546.3.

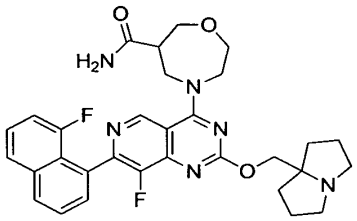
EXAMPLE 269



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

[0000880] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.22 (s, 1H), 8.12 (br d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.71 (dt, *J* = 2.8, 7.2 Hz, 1H), 7.65-7.57 (m, 1H), 7.54 (dt, *J* = 5.2, 8.0 Hz, 1H), 7.24-7.14 (m, 1H), 4.70-4.64 (m, 1H), 4.63-4.55 (m, 2H), 4.39-4.29 (m, 1H), 4.28-4.20 (m, 1H), 4.16 (td, *J* = 4.0, 12.8 Hz, 1H), 4.00-3.91 (m, 1H), 3.84-3.73 (m, 1H), 3.73-3.64 (m, 2H), 3.64-3.53 (m, 3H), 3.23-3.13 (m, 2H), 2.36-2.22 (m, 3H), 2.20-2.08 (m, 5H), 2.06-1.99 (m, 2H); LCMS (ESI, M+1): m/z = 562.3.

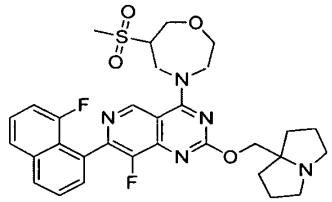
EXAMPLE 270



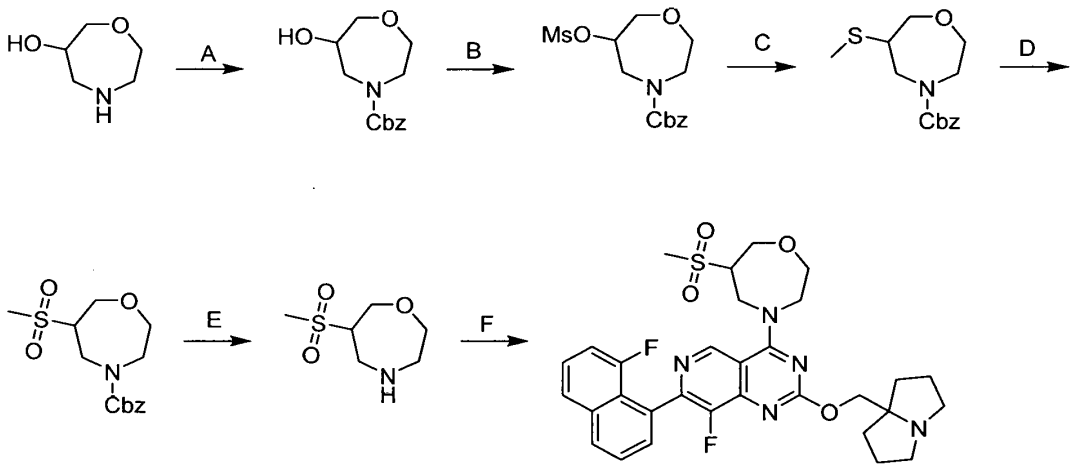
4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane-6-carboxamide

[0000881] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.22 (s, 1H), 8.13 (br d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.71 (dt, *J* = 2.8, 7.6 Hz, 1H), 7.66-7.58 (m, 1H), 7.54 (dt, *J* = 5.2, 7.6 Hz, 1H), 7.19 (td, *J* = 6.8, 13.2 Hz, 1H), 4.73-4.66 (m, 1H), 4.60 (br s, 2H), 4.44-4.33 (m, 1H), 4.26-4.05 (m, 5H), 3.93-3.79 (m, 1H), 3.72-3.59 (m, 2H), 3.28-3.18 (m, 3H), 2.37-2.25 (m, 2H), 2.25-2.12 (m, 4H), 2.12-2.02 (m, 2H); LCMS (ESI, M+1): m/z = 575.2.

EXAMPLE 271



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



[0000882] Step A. benzyl 6-hydroxy-1,4-oxazepane-4-carboxylate: To a solution of 1,4-oxazepan-6-ol (539 mg, 1.0 *equiv.*) and DIEA (1.78 g, 3.0 *equiv.*) in DCM (10 mL) at 0 °C was added CbzCl (1.18 g, 1.5 *equiv.*). The mixture was stirred at 0 °C for 1 hour and then warmed to 25 °C for 12 hours. The reaction mixture was diluted with ethyl acetate (10 mL) and water (20 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 in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, neutralized with solid $NaHCO_3$, and concentrated in vacuum to remove acetonitrile. The aqueous layer was extracted with ethyl acetate (2 × 8 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuum to afford the title compound (660 mg, 56.40% yield) as a yellow oil; ^1H NMR (400 MHz, DMSO) δ = 7.43 - 7.27 (m, 5H), 5.09 (s, 2H), 5.03 - 4.96 (m, 1H), 3.89 - 3.43 (m, 7H), 3.32 - 3.19 (m, 1H), 3.09 (dt, J = 8.0, 13.9 Hz, 1H); LCMS (ESI, M+1): m/z =252.2.

[0000883] Step B. benzyl 6-((methylsulfonyl)oxy)-1,4-oxazepane-4-carboxylate: To a solution mixture of benzyl 6-hydroxy-1,4-oxazepane-4-carboxylate (400 mg, 1.0 *equiv.*) and TEA (483 mg, 3.0 *equiv.*) in DCM (8 mL) at 0 °C was added MsCl (645 mg, 3.5 *equiv.*). The mixture was stirred at 0 °C for 1 hour. The mixture was quenched with water (20 mL) and extracted with dichloromethane (2 × 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to afford the title compound (524 mg, crude) as a yellow solid which was used to next step without further purification.

[0000884] Step C. benzyl 6-(methylthio)-1,4-oxazepane-4-carboxylate: To a solution of benzyl 6-((methylsulfonyl)oxy)-1,4-oxazepane-4-carboxylate (524 mg, 1.0 *equiv.*) in DMF (10 mL) at 0 °C was added MeSNa (335mg, 3.0 *equiv.*). The reaction mixture was heated to 60 °C for 2 hours. The mixture was diluted with ethyl acetate (8 mL) and water (15 mL), and the aqueous layer was extracted with ethyl acetate (8 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, neutralized with solid $NaHCO_3$ and concentrated in vacuum to remove acetonitrile. The aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to afford the title compound (175 mg, 39.0% yield) as a yellow oil; ^{1}H NMR (400 MHz, DMSO) δ = 7.42 - 7.28 (m, 5H), 5.14 - 5.04 (m, 2H), 3.98 - 3.82 (m, 2H), 3.75 - 3.62 (m, 3H), 3.53 (m, 1H), 3.43 - 3.32 (m, 1H), 3.30 - 3.22 (m, 1H), 2.99 - 2.83 (m, 1H), 2.10 (s, 1H), 2.08 - 1.97 (m, 2H) LCMS (ESI, M+1): m/z = 282.1.

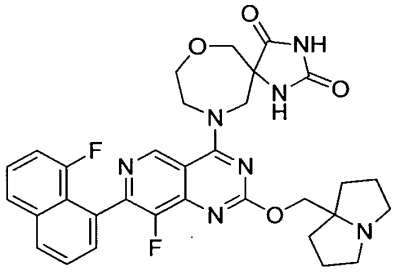
[0000885] Step D. benzyl 6-(methylsulfonyl)-1,4-oxazepane-4-carboxylate: To a solution of benzyl 6-methylsulfanyl-1,4-oxazepane-4-carboxylate (170 mg, 1.0 *equiv.*) in DCM (3 mL) was added *m*-CPBA (368 mg, 3.0 *equiv.*) at 0 °C. The reaction mixture was stirred at 25 °C for 2 hours. The mixture was quenched with saturated Na_2SO_3 solution (10 mL). The organic phase was separated, and then washed with $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuum 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 neutralized with solid $NaHCO_3$, and concentrated in vacuum to remove acetonitrile. The aqueous layer was extracted with ethyl acetate

(2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuum to afford the title compound (144 mg, 76.0% yield) as a colorless oil; ^{1}H NMR (400 MHz, DMSO) δ = 7.45 - 7.29 (m, 5H), 5.17 - 5.08 (m, 2H), 4.20 - 4.09 (m, 2H), 3.85 - 3.75 (m, 2H), 3.67 - 3.48 (m, 3H), 3.42 - 3.34 (m, 1H), 3.30 - 3.21 (m, 1H), 2.98 (br d, *J* = 16.0 Hz, 3H); LCMS (ESI, M+1): m/z = 314.0.

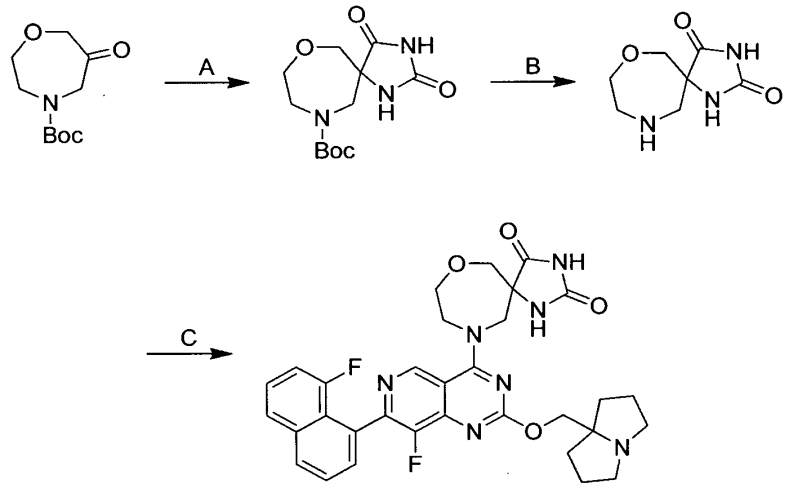
[0000886] Step E. 6-(methylsulfonyl)-1,4-oxazepane: To a mixture of benzyl 6-(methylsulfonyl)-1,4-oxazepane-4-carboxylate (130 mg, 1.0 *equiv.*) in MeOH (3 mL) was added Pd/C (20 mg, 10% purity) under N_2. The suspension was degassed in vacuum and purged with H_2 for three times. The mixture was stirred at 25 °C under H_2 (15 Psi) for 3 hours. The mixture was filtered and the filtrate was concentrated in vacuum to afford the title compound (74 mg, crude) as a colorless oil; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 4.33 - 4.25 (m, 1H), 4.13 (dd, *J* = 5.6, 13.6 Hz, 1H), 3.87 - 3.80 (m, 1H), 3.66 - 3.58 (m, 1H), 3.48 - 3.38 (m, 2H), 3.28 - 3.19 (m, 1H), 2.99 - 2.95 (m, 3H), 2.95 - 2.86 (m, 2H).

[0000887] Step F. 4-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-(methylsulfonyl)-1,4-oxazepane: To a solution of 6-(methylsulfonyl)-1,4-oxazepane (54.1 mg, 2.9 *equiv.*) in DMF (0.3 mL) were added DIEA (40.4 mg, 3.0 *equiv.*), 4Å molecular sieves (10 mg) and 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (60 mg, 1.0 *equiv.*, formic acid salt). The reaction mixture was stirred at 40 °C for 12 hours. The mixture was filtered. The filtrate was purified by prep-HPLC [column: Phenomenex Luna C18 150 × 25 mm × 10 um; mobile phase: [water (0.1% formic acid)/acetonitrile] B%: 12%-42%, 10min] to afford the title compound (25.4 mg, 39.3% yield) as a white solid; ^{1} 1H NMR (400 MHz, methanol-d_4) δ = 9.22 (s, 1H), 8.54 (br s, 1H), 8.12 (br d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.71 (dt, *J* = 3.8, 7.6 Hz, 1H), 7.62 (dd, *J* = 7.2, 19.8 Hz, 1H), 7.57 - 7.49 (m, 1H), 7.23 - 7.14 (m, 1H), 5.18 - 5.05 (m, 1H), 4.72 - 4.65 (m, 2H), 4.53 - 4.41 (m, 1H), 4.32 (td, *J* = 4.8, 12.4 Hz, 1H), 4.24 - 4.10 (m, 5H), 4.05 (br d, *J* = 3.2 Hz, 1H), 3.63 - 3.52 (m, 2H), 3.23 - 3.14 (m, 2H), 3.11 (s, 3H), 2.37 - 2.23 (m, 2H), 2.21 - 2.08 (m, 4H), 2.07 - 1.98 (m, 2H); LCMS (ESI, M+1): m/z = 610.3.

EXAMPLE 272



10-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-oxa-1,3,10-triazaspiro[4.6]undecane-2,4-dione

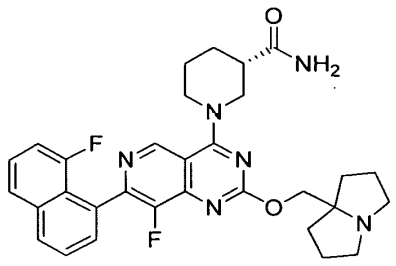


[0000888] Step A. tert-butyl 2,4-dioxo-10-oxa-1,3,7-triazaspiro[4.6]undecane-7-carboxylate: To a solution of tert-butyl 6-oxo-1,4-oxazepane-4-carboxylate (2.00 g, 1.0 *equiv.*) and $(NH_4)_2CO_3$ (2.68 g, 3.0 *equiv.*) in EtOH (10 mL) and water (10 mL) was added KCN (907 mg, 1.5 *equiv.*). The reaction was stirred at 85 °C for 16 hours. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to afford the title compound (2.40 g, 90% yield) as a white solid; ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ = 11.55-9.81 (m, 1H), 8.23-8.09 (m, 1H), 3.82-3.62 (m, 5H), 3.61-3.47 (m, 2H), 3.46-3.41 (m, 1H), 1.44-1.34 (m, 9H); LCMS (ESI, M-100): m/z = 186.2.

[0000889] Step B. 7-oxa-1,3,10-triazaspiro[4.6]undecane-2,4-dione: To a solution of tert-butyl 2,4-dioxo-10-oxa-1,3,7-triazaspiro[4.6]undecane-7-carboxylate (500 mg, 1.0 *equiv.*) in MeCN (2.5 mL) was added HCl•dioxane (4 M, 5 mL, 11.4 *equiv.*) at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. The mixture was concentrated to afford the title compound (450 mg, crude, HCl) as a white liquid; LCMS (ESI, M+1): m/z = 186.2.

[0000890] Step C. 10-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-7-oxa-1,3,10-triazaspiro[4.6]undecane-2,4-dione: 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 (100 mg, 1.0 *equiv.*), 10-oxa-1,3,7-triazaspiro[4.6]undecane-2,4-dione (349 mg, 10 *equiv.*), DIEA (487 mg, 20 *equiv.*) and 4Å molecular sieves (10 mg) in DMF (0.5 mL) was stirred at 40 °C for 96 hours. The residue was filtered and purified by prep-HPLC [column: Phenomenex C18 75 × 30 mm × 3 μm; mobile phase: [water (0.1% formic acid)/acetonitrile]; B%: 12% - 42%, 7minutes] to afford the title compound (68.0 mg, 58% yield) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.28 (d, *J* = 2.9 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.75-7.67 (m, 1H), 7.66-7.58 (m, 1H), 7.54 (dt, *J* = 5.2, 8.0 Hz, 1H), 7.19 (dd, *J* = 7.6, 13.2 Hz, 1H), 5.04 (dd, *J* = 14.4, 17.6 Hz, 1H), 4.59-4.54 (m, 1H), 4.53-4.47 (m, 1H), 4.46-4.37 (m, 1H), 4.36-4.31 (m, 1H), 4.31-4.24 (m, 2H), 4.24-4.16 (m, 1H), 4.11-3.99 (m, 1H), 3.89 (d, *J* = 12.6 Hz, 1H), 3.66-3.52 (m, 2H), 3.24-3.10 (m, 2H), 2.32-2.21 (m, 2H), 2.15 (quind, *J* = 7.2, 13.6 Hz, 4H), 2.09-1.97 (m, 2H); LCMS (ESI, M+1): m/z = 616.4.

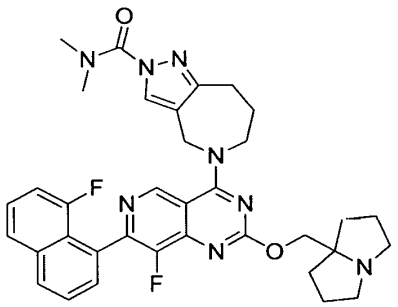
EXAMPLE 273



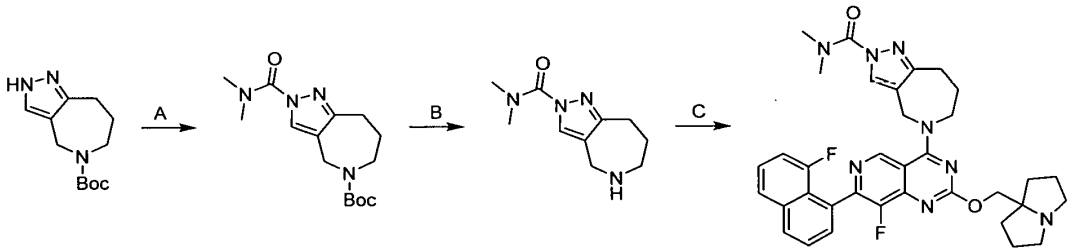
(S)-1-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3-carboxamide

[0000891] The title compound was synthesized according to the procedure described for example 84. ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.10 (s, 1H), 8.53 (s, 1H), 8.12 (br d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.74 - 7.67 (m, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.54 (dt, J = 5.2, 8.0 Hz, 1H), 7.19 (dd, J = 7.6, 13.2 Hz, 1H), 4.73 - 4.62 (m, 1H), 4.60 - 4.56 (m, 2H), 4.56 - 4.46 (m, 1H), 3.74 - 3.50 (m, 4H), 3.21 - 3.10 (m, 2H), 2.82 - 2.72 (m, 1H), 2.33 - 2.22 (m, 2H), 2.21 - 2.07 (m, 5H), 2.07 - 1.92 (m, 4H), 1.92 - 1.77 (m, 1H); HPLC: >99% ee, Chiralcel IC-3 50 × 4.6 mm I.D., 3 μm Mobile phase:A = Heptane; B=40% EtOH (0.05%DEA), Flow rate:1mL/min, 254 nm, t_R =6.421 min; LCMS [ESI, M-55]: m/z = 559.3.

EXAMPLE 274



5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydropyrazolo[4,3-c]azepine-2(4H)-carboxamide



[0000892] Step A. tert-butyl 2-(dimethylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[4,3-c]azepine-5(2H)-carboxylate: A solution of tert-butyl 4,6,7,8-tetrahydropyrazolo[4,3-c]azepine-5(2H)-carboxylate (890 mg, 1.0 *equiv.*) in THF (18 mL) was added NaH (300 mg, 2.0 *equiv.*) at 0 °C and the mixture was stirred at 0 °C for 0.5 hour. Then N,N-dimethylcarbamoyl chloride (605

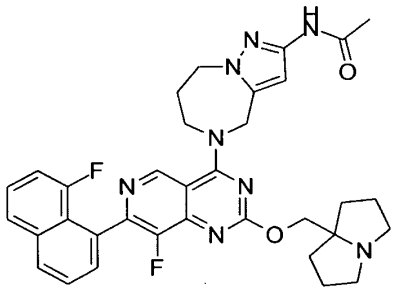
mg, 1.5 *equiv.*) was added into the mixture and the resulting was stirred at 25 °C for 2 hours. The mixture was quenched with water (50 ml) at 0 °C and extracted with ethyl acetate (20 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 10:1 to 3:1) to afford the title compound (860 mg, 74.4% yield) as a yellow solid; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 7.88 (br s, 1H), 4.42 - 4.24 (m, 2H), 3.75 - 3.60 (m, 2H), 3.33 - 3.13 (m, 6H), 2.94 - 2.84 (m, 2H), 1.91 - 1.77 (m, 2H), 1.50 - 1.33 (m, 9H).

[0000893] Step B. N,N-dimethyl-5,6,7,8-tetrahydropyrazolo[4,3-c]azepine-2(4H)-carboxamide: To a solution of tert-butyl 2-(dimethylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[4,3-c]azepine-5(2H)-carboxylate (860 mg, 1.0 *equiv.*) in ACN (5 mL) at 0 °C was added HCl•dioxane (4 M, 14.3 *equiv.*). The reaction mixture was stirred at 0 °C for 0.5 hour. The mixture was concentrated in vacuum to afford the title compound (682 mg, crude, HCl) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 8.15 (s, 1H), 4.29 (s, 2H), 3.57 - 3.52 (m, 2H), 3.19 (br s, 6H), 3.05 - 2.95 (m, 2H), 2.09 - 2.02 (m, 2H).

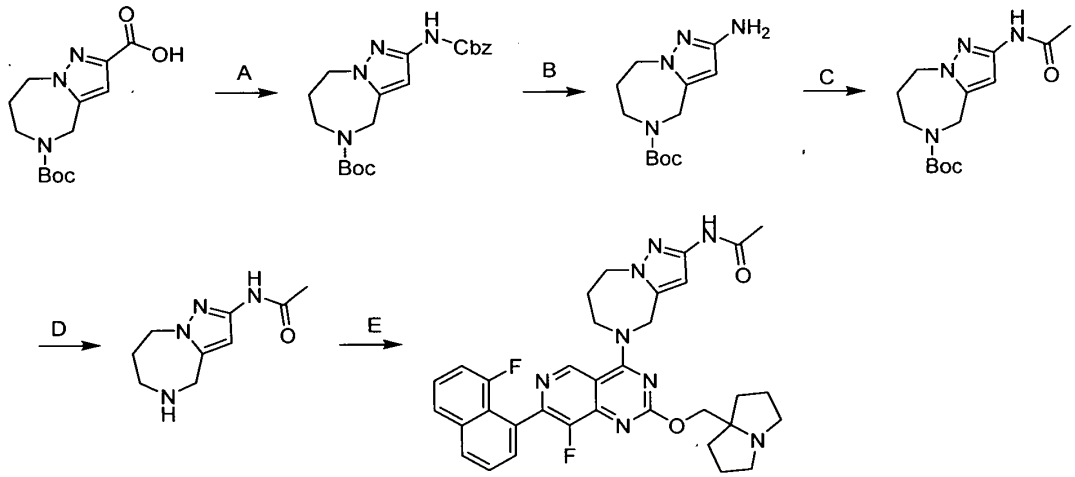
[0000894] Step C. 5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydropyrazolo[4,3-c]azepine-2(4H)-carboxamide: To a solution of N,N-dimethyl-5,6,7,8-tetrahydropyrazolo[4,3-c]azepine-2(4H)-carboxamide (46.1 mg, 2.4 *equiv.*) in DMF (0.5 mL) were added DIEA (60.9 mg, 5.0 *equiv.*), 4 Å molecular sieves (5 mg) and 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, 1.0 *equiv.*). The reaction mixture was stirred at 40 °C for 12 hours. The mixture was filtered and the filtrate was purified by prep-HPLC [column: Phenomenex Synergi Polar-RP 100 × 25 mm × 4 um; mobile phase: [water (0.01% TFA)/acetonitrile];, B%: 35%-55% over 7 min]. The desired fractions were collected and concentrated in vacuum to remove acetonitrile. The mixture was lyophilized to give a residue. The residue was re- purified by prep-HPLC [column: Phenomenex C18 75 × 30mm × 3 um; mobile phase: [water (0.1% formic acid)/acetonitrile]; B%: 18%-48%, 7min]. The desired fractions were collected and lyophilized to afford the title compound (10.2 mg, 16.8% yield) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.15 (s, 1H), 8.54 (s, 1H), 8.23 (s, 1H), 8.11 (br d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.74 - 7.66 (m, 1H), 7.60 (dd, J

= 0.8, 7.2 Hz, 1H), 7.52 (dt, *J* = 5.2, 8.0 Hz, 1H), 7.18 (dd, *J* = 7.2, 13.2 Hz, 1H), 5.20 - 5.03 (m, 2H), 4.46 - 4.39 (m, 2H), 4.36 (s, 2H), 3.29 - 3.23 (m, 2H), 3.18 (br s, 5H), 3.05 - 2.98 (m, 2H), 2.87 (td, *J* = 6.4, 10.8 Hz, 2H), 2.31 - 2.23 (m, 2H), 2.19 - 2.08 (m, 2H), 1.98 (tq, *J* = 6.4, 12.6 Hz, 4H), 1.89 - 1.79 (m, 2H); LCMS (ESI, M+1): m/z = 639.4.

EXAMPLE 275



N-(5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-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-yl)acetamide



[0000895] Step A. tert-butyl 2-(((benzyloxy)carbonyl)amino)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: A mixture of 5-tert-butoxycarbonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (3 g, 1.0 *equiv.*), 4Å molecular sieves

(1.00 g), TEA (3.24 g, 3.0 *equiv.*) and BnOH (6.92 g, 6.0 *equiv.*) in toluene (50 mL) was stirred at 110 °C for 0.5 hour under nitrogen. Then the mixture was cooled to 15 °C and DPPA (4.40 g, 1.5 *equiv.*) was added at 15 °C. The mixture was stirred at 110 °C for 5 hours. The reaction mixture was diluted with ethyl acetate (70 mL) and water (200 mL), and extracted with ethyl acetate (50 mL). The combined organic phase was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum 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 (2.1 g, 50.0% yield) as a yellow solid; LCMS [ESI, M-55]: m/z = 387.3.

[0000896] Step B. tert-butyl 2-amino-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: tert-butyl2-(benzyloxycarbonylamino)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (470 mg, 1.0 *equiv.*) was dissolved in MeOH (10 mL) and charged with N_2. To the solution was added Pd/C (50 mg, 10% purity) under nitrogen. The mixture was stirred at 25 °C for 12 hours under H_2 (15 psi). The mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, neutralized with solid $NaHCO_3$ and concentrated in vacuum to remove acetonitrile. The aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to afford the title compound (270 mg, 84.9% yield) as a yellow oil; ^{1}H NMR (400 MHz, CHLOROFORM-d) δ = 5.66 - 5.45 (m, 1H), 4.41 - 4.26 (m, 2H), 4.21 - 4.16 (m, 2H), 3.76 - 3.40 (m, 4H), 1.90 - 1.83 (m, 2H), 1.42 (s, 9H); LCMS [ESI, M+1]: 253.1.

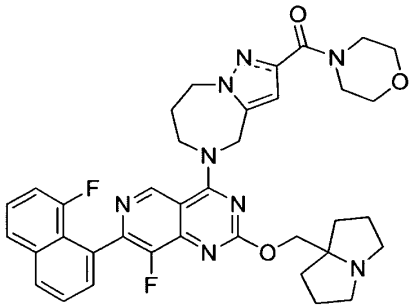
[0000897] Step C. tert-butyl 2-acetamido-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: To a solution of tert-butyl 2-amino-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (270 mg, 1.0 *equiv.*) in DCM (2 mL) were added TEA (325 mg, 3.0 *equiv.*) and acetylchloride (126 mg, 1.5 *equiv.*) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 hour. The reaction mixture was diluted with ethyl acetate (15 mL) and water (30 mL), and 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 reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and neutralized with solid $NaHCO_3$ and concentrated in vacuum to remove acetonitrile. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The

combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to afford the title compound (273 mg, 85.8% yield) as a white solid; LCMS [ESI, M+1]: 295.2.

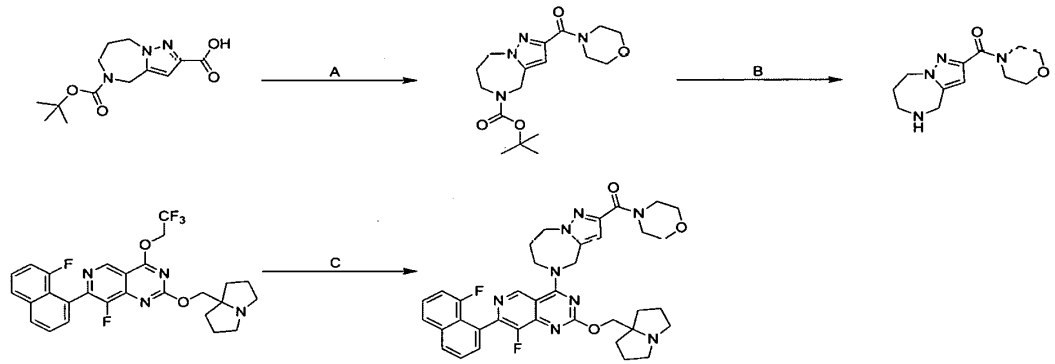
[0000898] Step D. N-(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)acetamide: To a solution of tert-butyl 2-acetamido-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (310 mg, 1.0 *equiv.*) in dioxane (1.5 mL) at 0 °C was added HCl•dioxane (4 M, 11 *equiv.*). The reaction mixture was stirred at 0 °C for 0.5 hour. The mixture was concentrated in vacuum to afford the title compound (200 mg, crude) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 6.45 (s, 1H), 4.45 (s, 2H), 4.34 - 4.26 (m, 2H), 3.70 (br d, J = 4.4 Hz, 2H), 2.09 (s, 3H), 1.83 (br s, 2H).

[0000899] Step E. N-(5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-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-yl)acetamide: A mixture of N-(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)acetamide (110 mg, 2.0 *equiv.*), DIEA (183 mg, 5.0 *equiv.*) and 4Å molecular sieves (20 mg) in DMF (1 mL) were stirred at 25 °C for 0.5 hour. Then 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (150 mg, 1.0 *equiv.*) was added into the reaction mixture and the resulting was stirred at 40 °C for 12 hours. The mixture was filtered and the filtrate was purified by prep-HPLC [column: Unisil 3-100 C18 Ultra 150 × 50mm × 3 um; mobile phase: [water (0.1% formic acid)/acetonitrile], B%: 5%-35%, 10 min]. The desired fraction was collected and lyophilized to afford the title compound (26.8 mg, 15.1% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.22 (s, 1H), 8.54 (s, 1H), 8.12 (br d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.73 - 7.67 (m, 1H), 7.61 (dd, J = 1.2, 7.2 Hz, 1H), 7.53 (dt, J = 5.2, 8.0 Hz, 1H), 7.19 (ddd, J = 0.8, 7.6, 13.2 Hz, 1H), 6.71 (s, 1H), 5.27 - 5.12 (m, 2H), 4.52 (s, 2H), 4.46 (br t, J = 5.2 Hz, 2H), 4.37 - 4.29 (m, 2H), 3.56 - 3.45 (m, 2H), 3.15 - 3.05 (m, 2H), 2.48 - 2.38 (m, 2H), 2.30 - 2.20 (m, 2H), 2.19 - 2.03 (m, 7H), 2.03 - 1.92 (m, 2H); LCMS (ESI, M+1): m/z = 625.4.

EXAMPLE 276



(5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-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-yl)(morpholino)methanone



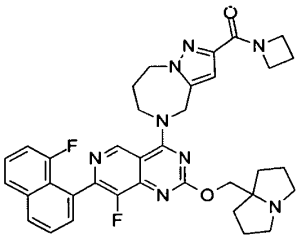
[0000900] Step A. tert-butyl 2-(morpholine-4-carbonyl)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: To a solution of 5-tert-butoxycarbonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (300 mg, 1.0 *equiv.*), morpholine (278 mg, 3.0 *equiv.*) and DIEA (1.65 g, 12 *equiv.*) in ethyl acetate (3 mL) was added T_3P (2.04 g, 6.0 *equiv.*) at 0 °C. The mixture was stirred at 0~25 °C for 2 hours. The mixture was concentrated under reduced pressure to give a residue and the residue was purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (320 mg, 85% yield) as a white oil; LCMS (ESI, M+1): m/z = 351.3.

[0000901] Step B. morpholino(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanone: To a solution of tert-butyl 2-(morpholine-4-carbonyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (310 mg, 1.0 *equiv.*) in MeCN (3 mL) was

added HCl•dioxane (4 M, 6.8 *equiv.*) at 0 °C. The mixture was stirred at 0~25 °C for 0.5 hour. The mixture was concentrated under reduced pressure to afford the title compound (215 mg, crude) as a white solid;

[0000902] Step C. (5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-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-yl)(morpholino)methanone: To a solution of morpholino(5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanone (212 mg, 3.0 *equiv.*) in DMF (3 mL) was added DIEA (219 mg, 6.0 *equiv.*) and 4Å molecular sieves (40 mg). 8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (150 mg, 1.0 *equiv.*). The mixture was stirred at 40 °C for 16 hours. DIEA (365 mg, 10 *equiv.*) was added, the mixture was stirred at 40 °C for 20 hours. The reaction mixture was filtered and purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] and re-purified by prep-HPLC [column: Phenomenex luna C18 150 × 25 mm × 10 μm, mobile phase: [water (0.1% formic acid)/acetonitrile], B%: 22%-52%, 7min] and lyophilized to afford the title compound (8.66 mg, 4.3% yield) as a yellow solid; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.20 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.72-7.67 (m, 1H), 7.61 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.53 (dt, *J* = 4.8, 8.0 Hz, 1H), 7.19 (ddd, *J* = 0.8, 7.6, 13.2 Hz, 1H), 6.80 (s, 1H), 5.33-5.21 (m, 2H), 4.56-4.51 (m, 2H), 4.50-4.45 (m, 2H), 4.44 (s, 2H), 4.04 (br s, 2H), 3.75-3.65 (m, 6H), 3.42-3.34 (m, 2H), 3.03-2.95 (m, 2H), 2.48-2.39 (m, 2H), 2.23-2.15 (m, 2H), 2.10-1.97 (m, 4H), 1.96-1.88 (m, 2H), 1.37-1.31 (m, 2H); LCMS [ESI, M+1]:681.4.

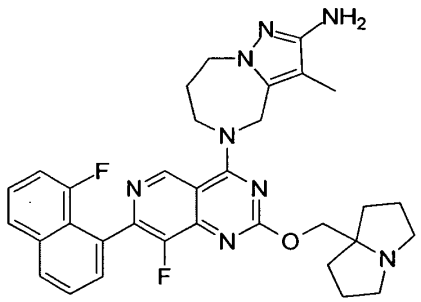
EXAMPLE 277



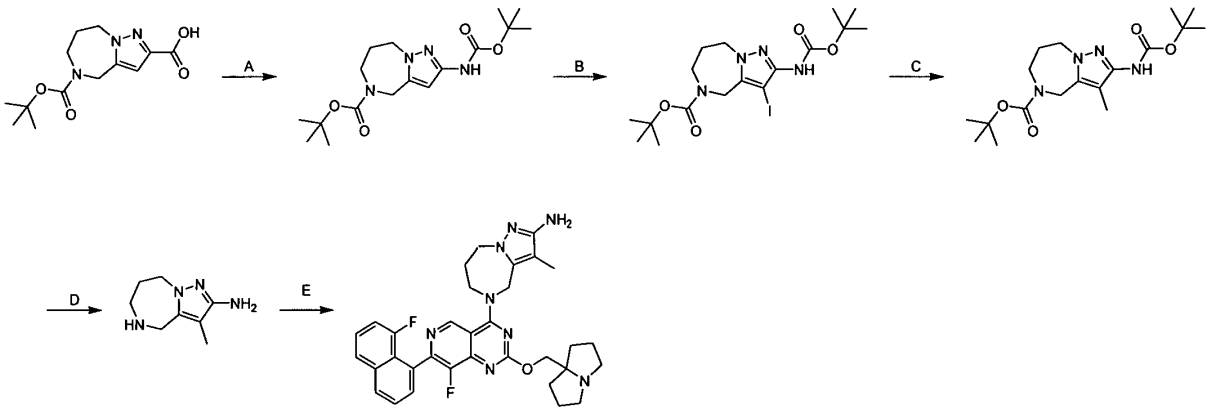
azetidin-1-yl(5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl)methanone

[0000903] The title compound was synthesized according to the procedure described for example 276. ^{1}H NMR (400 MHz, methanol-d4): δ = 9.21 (s, 1H), 8.53 (s, 1H), 8.12 (br d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.53 (dt, *J* = 5.2, 8.0 Hz, 1H), 7.19 (dd, *J* = 7.6, 13.2 Hz, 1H), 6.84 (s, 1H), 5.32 - 5.19 (m, 2H), 4.60 (br t, *J* = 7.6 Hz, 2H), 4.55 - 4.44 (m, 6H), 4.16 (br t, *J* = 7.6 Hz, 2H), 3.60 - 3.50 (m, 2H), 3.20 - 3.11 (m, 2H), 2.47 - 2.33 (m, 4H), 2.30 - 2.22 (m, 2H), 2.20 - 2.08 (m, 4H), 2.06 - 1.97 (m, 2H); LCMS [ESI, M+1]: m/z = 651.5.

EXAMPLE 278



5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine



[0000904] Step A. tert-butyl 2-((tert-butoxycarbonyl)amino)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: A mixture of 5-(tert-butoxycarbonyl)-5,6,7,8-tetrahydro-4H-

pyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (2.00 g, 1.0 *equiv.*), 4Å molecular sieves (2.00 g) and TEA (2.16 g, 3.0 *equiv.*) in toluene (20 mL) and 2-methylpropan-2-ol (15.5 g, 29.4 *equiv.*) was stirred at 110 °C for 0.5 hour under nitrogen. The mixture was cooled to 25 °C and DPPA (2.93 g, 1.5 *equiv.*) was added at 25 °C. The mixture was stirred at 110 °C for 5 hours before being quenched by addition of water (30 mL) and extracted with ethyl acetate (80 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated, and purified by reversed-phase HPLC [water (0.1 % formic acid)/ACN] to afford the title compound (1.50 g, 60% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 353.1.

[0000905] Step B. tert-butyl 2-((tert-butoxycarbonyl)amino)-3-iodo-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: To a solution of tert-butyl 2-((tert-butoxycarbonyl)amino)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (1.50 g, 1.0 *equiv.*) in MeCN (50 mL) was added NIS (1.92 g, 2.0 *equiv.*) at 25 °C, The mixture was stirred at 25 °C for 1 hour. The mixture was 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, 93% yield) as a yellow solid; LCMS (ESI, M+1): 479.2.

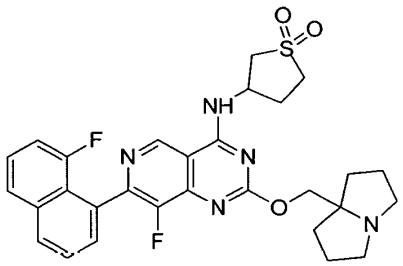
[0000906] Step C. tert-butyl 2-((tert-butoxycarbonyl)amino)-3-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate: A mixture of tert-butyl 2-((tert-butoxycarbonyl)amino)-3-iodo-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (1.90 g, 1.0 *equiv.*) , 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (3.5 M, 2.27 mL, 2.0 *equiv.*) , CataCXium A Pd G3 (578 mg, 0.2 *equiv.*) and K_3PO_4 (1.5 M, 7.94 mL, 3.0 *equiv.*) in THF (80 mL) was degassed and stirred at 60 °C for 24 hours under N_2 atmosphere. The mixture was quenched by addition of water (100 mL) and extracted with ethyl acetate (2 × 60 mL). The combined organic layers were dried over Na_2SO_4, and concentrated. The crude product was purified by reversed phase flash chromatography [water (0.1 % formic acid)/ACN] to afford the title compound (900 mg, 46% yield) as a yellow solid; LCMS (ESI, M+1): 367.2.

[0000907] Step D. 3-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine: To a solution of tert-butyl 2-((tert-butoxycarbonyl)amino)-3-methyl-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (300 mg, 1.0 *equiv.*) in MeCN (1 mL) was added HCl•dioxane (4 M, 2 mL, 9.77 *equiv.*) at 25 °C. The mixture was stirred at 25 °C for 0.5 hour. The mixture was concentrated in vacuum. The residue was diluted with MeOH (5 mL), treated with solid $NaHCO_3$

(1 g), filtered and the filtrate was concentrated in vacuum to afford the title compound (210 mg, crude, 2HCl) as a yellow solid; LCMS (ESI, M+1): m/z = 167.2.

[0000908] Step E. 5-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine: To a mixture of 3-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-2-amine (75.2 mg, 4.0 *equiv.*) and DIEA (73.1 mg, 5.0 *equiv.*) 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 (60.0 mg, 1.0 *equiv.*) and DMF (0.5 mL). The mixture was stirred at 40 °C for 14 hours. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography [water (0.1 % formic acid)/ACN], and further re-purified by prep-HPLC (column: Phenomenex Luna C18 150 × 25 mm × 10 μm; mobile phase: [water (0.1 % formic acid)/ACN], B%: 11%-41%, 10 min) to afford the title compound (2.05 mg, 2.9% yield) as an off-white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.15 (s, 1H), 8.53 (br s, 1H), 8.13 (br d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 6.4 Hz, 1H), 7.54 (dt, *J* = 5.2, 8.0 Hz, 1H), 7.19 (dd, *J* = 8.0, 13.2 Hz, 1H), 5.17-5.12 (m, 2H), 4.59 (br s, 2H), 4.40-4.35 (m, 2H), 4.23-4.19 (m, 2H), 3.65-3.55 (m, 2H), 3.25-3.18 (m, 2H), 2.41-2.04 (m, 10H), 2.04 (s, 3H); LCMS (ESI, M+1): m/z = 597.4.

EXAMPLE 279

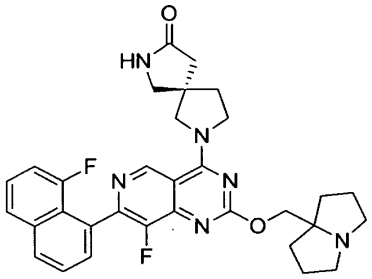


3-((8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)tetrahydrothiophene 1,1-dioxide

[0000909] The title compound was synthesized according to the procedure described for example 85. ^{1}H NMR (400 MHz, methanol-d4) δ ppm 9.26 - 9.24 (m, 1H), 9.25 (s, 1H), 8.12 (br d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.73-7.67 (m, 1H), 7.59 (d, *J* = 6.8 Hz, 1H), 7.53 (m,

7.9 Hz, 1H), 7.19 (dd, J = 7.2, 13.2 Hz, 1H), 5.23-5.14 (m, 1H), 4.32 (s, 2H), 3.81-3.72 (m, 1H), 3.49-3.40 (m, 1H), 3.30-3.22 (m, 2H), 3.16-3.07 (m, 2H), 2.81-2.70 (m, 3H), 2.56-2.44 (m, 1H), 2.15-2.03 (m, 2H), 1.96-1.92 (m, 4H), 1.82-1.72 (m, 2H). HPLC: >99%. SFC: Chiralcel OD-3 50×4.6mm I.D., 3 μm column A: 40% (MeOH: ACN = 4:1) (w/ 0.05% DEA), B: CO2, 3mL/min, 220 nm. LCMS [ESI, M+1]: m/z = 566.2.

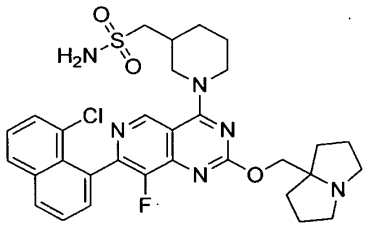
EXAMPLE 280



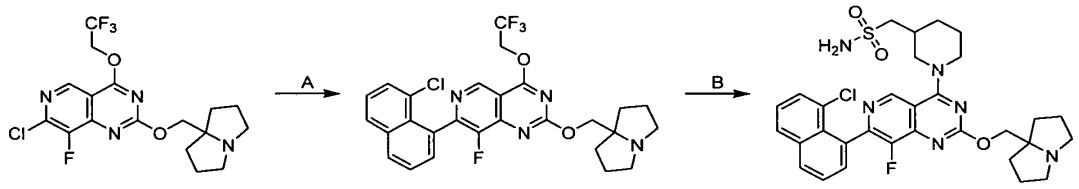
(S)-7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.4]nonan-3-one

[0000910] The title compound was synthesized according to the procedure described for example 85. LCMS (ESI, M+1): m/z = 571.3.

EXAMPLE 281



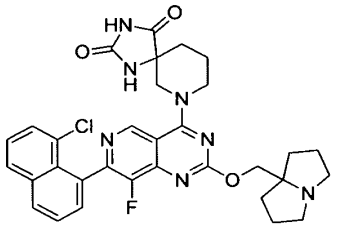
1-(1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide



[0000911] Step A. 7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1*H*-pyrrolizin-7a-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 (200 mg, 1.0 *equiv.*), (8-chloronaphthalen-1-yl)trimethylstannane (464 mg, 1.43 mmol, 3.0 *equiv.*), CuI (27.2 mg, 0.3 *equiv.*) and BINAP (59.2 mg, 0.2 *equiv.*) in toluene (8 mL) was added $Pd(dppf)Cl_2$ (34.8 mg, 0.1 *equiv.*) under N_2. The reaction was de-gassed and stirred at 90 °C for 2 hours under N_2. The mixture was filtered and purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (156 mg, 25% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 547.1.

[0000912] Step B. 1-(1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide: To a solution of 7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-*d*]pyrimidine (40.0 mg, 1.0 *equiv.*), piperidin-3-ylmethanesulfonamide (26.1 mg, 2.0 *equiv.*) and DIEA (28.4 mg, 3.0 *equiv.*) in DMF (0.5 mL) was added 4 Å molecular sieves (10 mg). The reaction was stirred at 40 °C for 2 hours. The mixture was filtered and purified by prep-HPLC [column: Waters Xbridge 150 × 25mm × 5μm; mobile phase: [water (10mM NH_4HCO_3)/ACN] B%: 42% - 72%, 8 min] and lyophilized to afford the title compound (13.8 mg, 29% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.08 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.69 (dt, *J* = 2.0, 7.6 Hz, 1H), 7.63 - 7.58 (m, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 4.99 (br d, *J* = 11.2 Hz, 1H), 4.56 (br d, *J* = 13.6 Hz, 1H), 4.47-4.36 (m, 2H), 3.70-3.58 (m, 1H), 3.39-3.33 (m, 1H), 3.29-3.21 (m, 2H), 3.21-3.09 (m, 2H), 2.90-2.81 (m, 2H), 2.58-2.46 (m, 1H), 2.22-2.08 (m, 3H), 2.04-1.90 (m, 5H), 1.87-1.74 (m, 3H), 1.68-1.56 (m, 1H); ^{19}F NMR (400 MHz, methanol-d4) δ = -139.695; LCMS (ESI, M+1): m/z = 625.2.

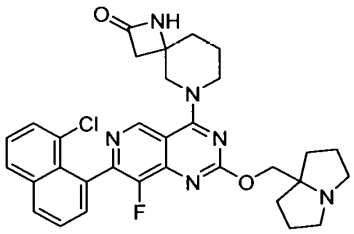
EXAMPLE 282



7-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione

[0000913] The title compound was synthesized according to the procedure described for example 281. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.09 (d, *J* = 3.6 Hz, 1H), 8.14 (d, *J* = 7.9 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.68(t, *J* = 5.6 Hz, 1H), 7.63-7.57 (m, 2H), 7.50 (t, *J* = 5.2 Hz, 13.6 Hz, 1H), 4.63 (dd, *J* = 5.2, 13.2 Hz, 1H), 4.48-4.45 (m, 1H), 4.37-4.30 (m, 2H), 3.85-3.68 (m, 2H), 3.25-3.14 (m, 2H), 2.89-2.74 (m, 2H), 2.31-2.19 (m, 1H), 2.18-2.00 (m, 4H), 1.99-1.87 (m, 5H), 1.85-1.76 (m, 2H); LCMS (ESI, M+1): m/z = 616.2.

EXAMPLE 283

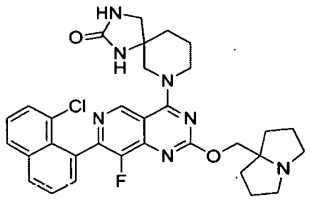


6-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one

[0000914] The title compound was synthesized according to the procedure described for example 281. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.07 (s, 1H), 8.14 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.04-7.98 (m, 1H), 7.72-7.65 (m, 1H), 7.63-7.57 (m, 2H), 7.54-7.48 (m, 1H), 4.38 (d, *J* = 13.6 Hz, 1H), 4.34-4.22 (m, 3H), 3.99 (d, *J* = 13.2 Hz, 1H), 3.88-3.70 (m, 1H), 3.16-3.04 (m, 2H), 2.92-

2.86 (m, 1H), 2.80-2.65 (m, 3H), 2.18-2.01 (m, 4H), 2.01-1.84 (m, 6H), 1.80-1.69 (m, 2H); LCMS (ESI, M+1): m/z = 587.2.

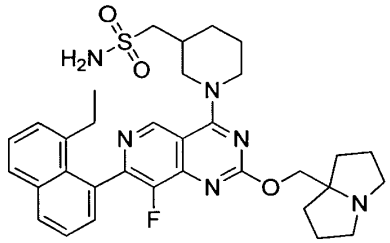
EXAMPLE 284



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

[0000915] The title compound was synthesized according to the procedure described for example 281. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.14 (s, 1H), 8.16-8.14 (d, J = 8.0 Hz, 1H), 8.2 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.66-7.57 (m, 2H), 7.54-7.50 (t, J = 8.0 Hz, 1H), 4.81 (s, 1H), 4.65–4.50 (m, 3H), 4.38–4.21 (m, 1H), 4.04–3.81 (m, 2H), 3.61-3.55 (m, 2H), 3.45-3.41 (m, 1H), 3.22-3.08 (m, 2H), 2.32-2.23 (m, 2H), 2.18-2.14 (m, 4H), 2.08-1.94 (m, 5H), 1.94-1.80 (m, 1H); LCMS (ESI, M+1): m/z = 602.3.

EXAMPLE 285

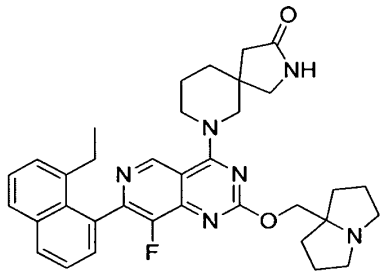


1-(1-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide

[0000916] The title compound was synthesized according to the procedure described for example 204. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.08 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.59-7.52 (m, 1H), 7.51-7.38 (m, 3H), 4.99-4.88 (m, 1H), 4.60-4.50 (m,

1H), 4.37-4.27 (m, 2H), 3.66-3.51 (m, 1H), 3.48-3.33 (m, 1H), 3.22-3.08 (m, 4H), 2.76-2.67 (m, 2H), 2.55-2.29 (m, 3H), 2.10 (dd, J = 6.4, 5.2 Hz, 3H), 1.98-1.86 (m, 5H), 1.82-1.70 (m, 3H), 1.67-1.58 (m, 1H), 0.93 (dd, J = 7.6, 2.0 Hz, 3H); ^{19}F NMR (377 MHz, METHANOL-d4) δ = -134.15, -147.26. LCMS (ESI, M+1): m/z = 619.2.

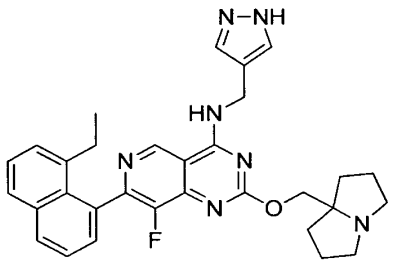
EXAMPLE 286



7-(7-(8-ethylnaphthalen-1-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

[0000917] The title compound was synthesized according to the procedure described for example 204. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.10 (s, 1H), 8.05 (dd, J = 1.2, 8.0 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.59 - 7.54 (m, 1H), 7.52 - 7.47 (m, 1H), 7.46 - 7.39 (m, 2H), 4.54 - 4.38 (m, 2H), 4.54 - 3.98 (m, 2H), 3.95 - 3.79 (m, 1H), 3.46 - 3.35 (m, 2H), 3.34 (br s, 1H), 3.30 - 3.24 (m, 2H), 3.01 (br d, J = 9.2 Hz, 2H), 2.49 - 2.17 (m, 6H), 2.07 (td, J = 6.3, 12.4 Hz, 4H), 1.91 (br s, 6H), 0.93 (q, J = 7.6 Hz, 3H). LCMS [ESI, M+1]: m/z = 595.4.

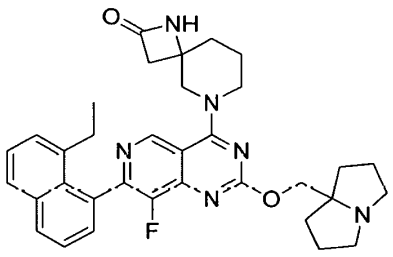
EXAMPLE 287



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

[0000918] The title compound was synthesized according to the procedure described for example 204. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ = 9.36 (br t, J = 5.2 Hz, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.67 (s, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 4.66 (br d, J = 5.2 Hz, 2H), 4.16 (s, 2H), 3.05-2.97 (m, 2H), 2.69-2.58 (m, 2H), 2.41-2.17 (m, 3H), 2.00-1.90 (m, 2H), 1.88-1.75 (m, 4H), 1.68-1.58 (m, 2H), 0.83 (t, J = 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 538.3.

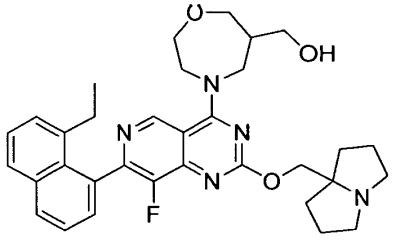
EXAMPLE 288



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

[0000919] The title compound was synthesized according to the procedure described for example 204. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ = 8.58 (br d, J = 7.6 Hz, 1H), 8.08 (d, J = 7.6 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.63-7.55 (m, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.45 (br d, J = 7.2 Hz, 1H), 7.39 (d, J = 7.2 Hz, 1H), 4.28-4.12 (m, 4H), 3.94-3.79 (m, 2H), 3.09-3.00 (m, 2H), 2.88-2.76 (m, 1H), 2.71-2.60 (m, 3H), 2.45-2.20 (m, 3H), 2.02-1.92 (m, 3H), 1.91-1.74 (m, 7H), 1.70-1.60 (m, 2H), 0.85 (t, J = 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 581.1.

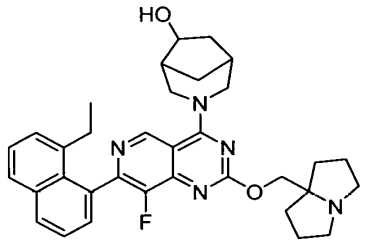
EXAMPLE 289



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

[0000920] The title compound was synthesized according to the procedure described for example 204. ^{1}H NMR (400 MHz, METHANOL-d4): δ = 9.26 - 9.21 (m, 1H), 8.53 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.61 - 7.53 (m, 1H), 7.52 - 7.36 (m, 3H), 4.71 - 4.53 (m, 3H), 4.47 - 4.37 (m, 1H), 4.18 - 3.93 (m, 4H), 3.89 - 3.77 (m, 1H), 3.71 - 3.49 (m, 5H), 3.19 - 3.08 (m, 2H), 2.56 - 2.22 (m, 5H), 2.19 - 1.96 (m, 6H), 0.98 (br s, 3H); LCMS [ESI, M+H]: m/z= 572.2.

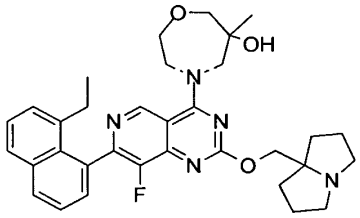
EXAMPLE 290



3-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol

[0000921] The title compound was synthesized according to the procedure described for example 204. ^{1}H NMR (400 MHz, methanol-d$_4$) δ 9.23 - 9.06 (m, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.59 - 7.53 (m, 1H), 7.51 - 7.37 (m, 3H), 5.01 - 4.92 (m, 1H), 4.84 - 4.76 (m, 1H), 4.36 - 4.26 (m, 3H), 3.78 (br dd, *J* = 7.6, 11.6 Hz, 1H), 3.53 - 3.45 (m, 1H), 3.20 - 3.08 (m, 2H), 2.81 - 2.72 (m, 2H), 2.47 - 2.17 (m, 5H), 2.15 - 2.06 (m, 2H), 2.02 - 1.85 (m, 5H), 1.85 - 1.74 (m, 3H), 1.45 - 1.27 (m, 1H), 0.95 - 0.89 (m, 3H); LCMS [ESI, M+1]: m/z=568.4.

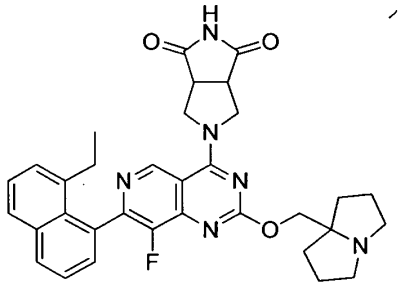
EXAMPLE 291



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

[0000922] The title compound was synthesized according to the procedure described for example 204 except for water (10 mM NH_4HCO_3)/ACN was used as a mobile phase for prep-HPLC. ^{1}H NMR (400 MHz, methanol-*d*4) δ = 9.53 (d, *J* = 5.2 Hz, 1H), 8.07-8.03 (m, 1H), 7.88-7.84 (m, 1H), 7.59-7.53 (m, 1H), 7.51-7.38 (m, 3H), 4.61-4.49 (m, 2H), 4.35-4.26 (m, 2H), 4.23-4.14 (m, 1H), 4.07-3.86 (m, 3H), 3.74-3.63 (m, 2H), 3.16-3.07 (m, 2H), 2.79-2.70 (m, 2H), 2.49-2.30 (m, 2H), 2.14-2.03 (m, 2H), 2.00-1.83 (m, 4H), 1.82 - 1.73 (m, 2H), 1.28 (d, *J* = 3.2 Hz, 3H), 0.97-0.89 (m, 3H); LCMS [ESI, M+1]: m/z=572.2

EXAMPLE 292

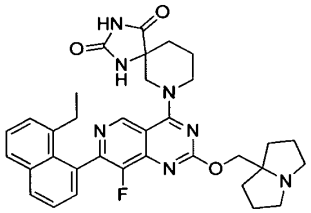


5-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione

[0000923] The title compound was synthesized according to the procedure described for example 204. ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.32 - 9.23 (m, 1H), 8.05 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.51-7.46 (m, 1H), 7.44 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 1H), 4.65 (br d, *J* = 12.4 Hz, 2H), 4.48-4.42 (m, 2H), 4.40-4.29 (m, 2H), 3.80-3.58 (m, 2H), 3.36-3.32 (m, 1H), 3.29 (br s, 1H), 3.01-2.85 (m, 2H), 2.48-2.26 (m, 2H),

2.17 (dtd, J = 2.4, 6.4, 12.4 Hz, 2H), 2.11-2.04 (m, 1H), 2.04-2.00 (m, 2H), 1.99-1.93 (m, 1H), 1.93-1.83 (m, 2H), 0.96-0.87 (m, 3H); LCMS (ESI, M+1): m/z = 581.1.

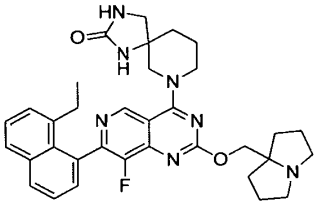
EXAMPLE 293



7-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione

[0000924] The title compound was synthesized according to the procedure described for example 291. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.11-9.10 (m, 1H), 8.05-8.03 (d, J = 7.2 Hz, 1H), 7.87-7.85 (d, J = 8.0 Hz, 1H), 7.58-7.54 (m, 1H), 7.50-7.38 (m, 3H), 4.65-4.60 (m, 1H), 4.54-4.39 (m, 1H), 4.37-4.27 (m, 2H), 3.89-3.80 (m, 1H), 3.77-3.68 (m, 1H), 3.24-3.08 (m, 2H), 2.79-2.73 (m, 2H), 2.50-2.29 (m, 2H), 2.28-2.19 (m, 1H), 2.16-2.00 (m, 4H), 1.99-1.88 (m, 5H), 1.83-1.72 (m, 2H), 0.94-0.88 (m, 3H); LCMS [ESI, M+1]: m/z = 610.3.

EXAMPLE 294

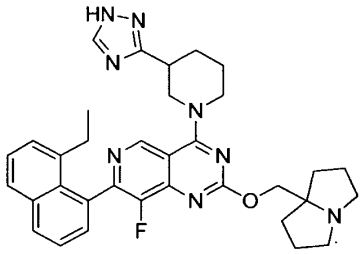


7-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one

[0000925] The title compound was synthesized according to the procedure described for example 204. ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.14 (d, J = 1.6 Hz, 1H), 8.05 (dd, J = 0.8, 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.59–7.55 (m, 1H), 7.51–7.47 (m, 1H), 7.46–7.38 (m, 2H), 4.68–4.36 (m, 3H), 4.41–4.33 (m, 1H), 4.30–4.17 (m, 1H), 4.07–3.80 (m, 2H), 3.66–3.51 (m, 2H),

3.42 (dd, J = 4.2, 9.6 Hz, 1H), 3.22–3.10 (m, 2H), 2.47–2.32 (m, 2H), 2.32–2.25 (m, 2H), 2.19–2.11 (m, 4H), 2.07–1.94 (m, 5H), 1.90–1.86 (m, 1H), 0.95–0.90 (m, 3H); LCMS [ESI, M+1]: m/z = 596.3.

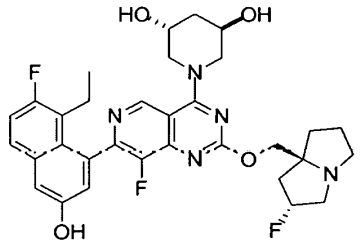
EXAMPLE 295



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

[0000926] The title compound was synthesized according to the procedure described for example 291. ^{1}H NMR (400 MHz, CD3OD, 298 K) δ (ppm) = 9.09 (d, J = 2.4 Hz, 1H), 8.25 (d, J = 4.4 Hz, 1H), 8.07 - 8.00 (m, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.52-7.37 (m, 3H), 4.55 (br t, J = 12.0 Hz, 1H), 4.35-4.24 (m, 2H), 3.87-3.65 (m, 2H), 3.41-3.33 (m, 1H), 3.14-3.06 (m, 2H), 2.73 (m, 2H), 2.47-2.26 (m, 3H), 2.14-2.01 (m, 4H), 2.01-1.70 (m, 8H), 0.92 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 593.3.

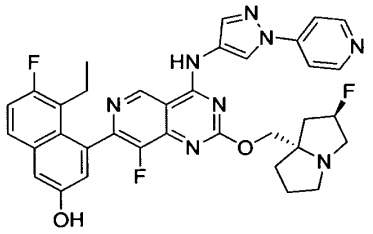
EXAMPLE 296



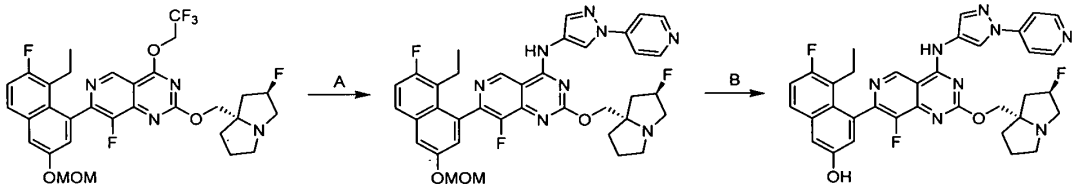
(3R,5R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidine-3,5-diol

[0000927] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.24 (dd, *J* = 2.8, 7.2 Hz, 1H), 7.67 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.24 (t, *J* = 9.2 Hz, 1H), 7.05 (dd, *J* = 2.4, 8.8 Hz, 1H), 5.39-5.22 (m, 1H), 4.37-4.31 (m, 1H), 4.30-4.19 (m, 5H), 3.84-3.75 (m, 2H), 3.21 (br d, *J* = 19.6 Hz, 3H), 3.01 (m, 1H), 2.54-2.42 (m, 1H), 2.39-2.12 (m, 4H), 2.04-1.88 (m, 5H), 0.84-0.76 (m, 3H). ^{19}F NMR (376 MHz, METHANOL-d4) δ = -121.237, -139.064, -173.716. HPLC: >99%. LCMS (ESI, M+1): m/z = 610.2.

EXAMPLE 297



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

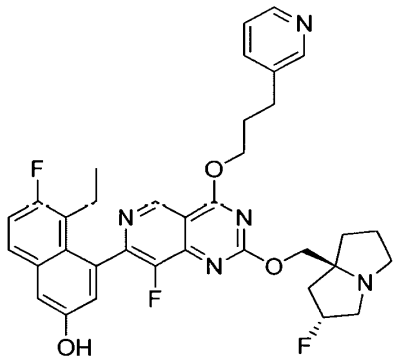


[0000928] Step A. 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-(1-(pyridin-4-yl)-1H-pyrazol-4-yl)pyrido[4,3-d]pyrimidin-4-amine: To the mixture of 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (143 mg, 1.0 *equiv.*), 1-(pyridin-4-yl)-1H-pyrazol-4-amine (110 mg, 2.5 *equiv.*, HCl), 4Å molecular sieves (50.0 mg) in DMAC (1.5 mL) was added CsF (340 mg, 10.0 *equiv.*), and the mixture was stirred at 40 °C for 14 hours. After reaction completion, the mixture was filtered and diluted with water (10 mL), extracted with ethyl acetate (2 × 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by reversed-phase flash chromatography [water (0.1% formic acid)/acetonitrile] to

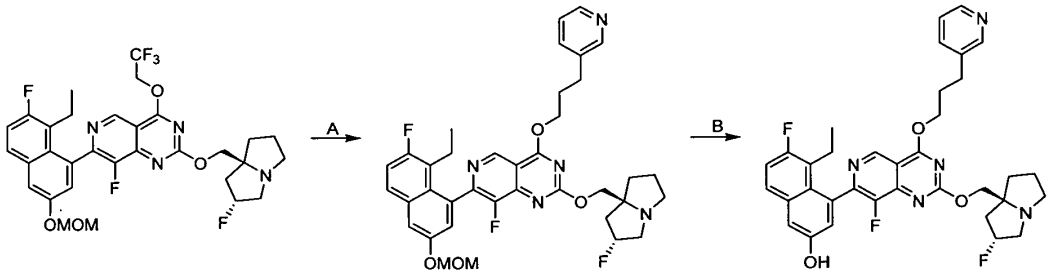
afford the title compound (106 mg, 62% yield over two steps) as a yellow solid; LCMS [ESI, M+1]: m/z = 697.2.

[0000929] Step B. 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-((1-(pyridin-4-yl)-1H-pyrazol-4-yl)amino)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol: To a solution of 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-N-(1-(pyridin-4-yl)-1H-pyrazol-4-yl)pyrido[4,3-d]pyrimidin-4-amine (50.0 mg, 1.0 *equiv.*) in ACN (1 mL) was added HCl•dioxane (4 M, 2 mL, 111.5 *equiv.*) at 0 °C. The reaction was stirred at 0 °C for 0.5 hour. After reaction completion, the mixture was concentrated under reduced pressure to give a residue. pH was adjusted with sat. aq. $NaHCO_3$ to 9 and the mixture was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by prep-HPLC (column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: [water (10mM NH_4HCO_3)/ACN,] B%: 45% - 75%, 10 min) and lyophilized to afford the title compound (14.9 mg, 31% yield) as an off-white solid; ^{1}H NMR (400 MHz, methanol-d4): δ = 9.39 (s, 1H), 9.06 (s, 1H), 8.67 - 8.61 (m, 2H), 8.23 (s, 1H), 7.93 - 7.88 (m, 2H), 7.69 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.32 (d, *J* = 2.8 Hz, 1H), 7.26 (t, *J* = 9.6 Hz, 1H), 7.08 (d, *J* = 2.8 Hz, 1H), 5.43 - 5.24 (m, 1H), 4.50 - 4.36 (m, 2H), 3.29 - 3.20 (m, 3H), 3.12 - 2.97 (m, 1H), 2.54 - 2.23 (m, 3H), 2.22 - 1.93 (m, 5H), 0.81 (t, *J* = 7.6 Hz, 3H); LCMS [ESI, M+1]: m/z = 653.3.

EXAMPLE 298



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

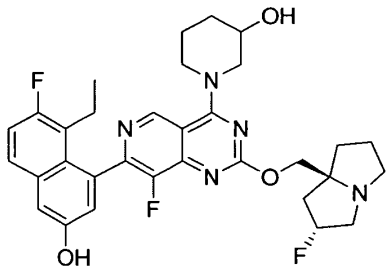


[0000930] Step A. 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(pyridin-3-yl)propoxy)pyrido[4,3-d]pyrimidine: To a mixture of 3-(pyridin-3-yl)propan-1-ol (15.1 mg, 110 μmol, 14.2 μL, 1.5 *equiv.*) and 4Å molecular sieves (5 mg) in THF (1 mL) was added LiHMDS (1.0 M in THF, 220 μL, 3.0 *equiv.*) at -40 °C and the mixture was stirred at -40 °C for 0.5 hour. Then 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 (50.0 mg, 73.3 μmol, 1.0 *equiv.*, formic acid salt) in THF (0.5 mL) was added into the above mixture and the mixture was stirred at 25 °C for 1 hour. The mixture was quenched by water (3 mL) at 0 °C. The mixture was diluted with ethyl acetate (4 mL), the layers were separated and the aqueous phase was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to afford the title compound (35.0 mg, 64% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 674.3.

[0000931] Step B. 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(pyridin-3-yl)propoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol: To a mixture of 7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(pyridin-3-yl)propoxy)pyrido[4,3-d]pyrimidine (60.0 mg, 89.1 μmol, 1.0 *equiv.*) in dichloromethane (0.60 mL) was added TFA (924 mg, 91 *equiv.*) at 0 °C and the mixture was stirred at 0 - 25 °C for 1.5 hours. The mixture was concentrated in vacuum and the pH value was adjusted to 8 with saturated $NaHCO_3$ solution. The mixture was diluted with ethyl acetate (4 mL) then separated. The aqueous layer was extracted with ethyl acetate (2 × 4 mL) and the combined organic layers were washed with brine (4 mL) and dried over Na_2SO_4. The mixture was filtered and concentrated in vacuum.

The mixture was purified by prep-HPLC [column: Waters Xbridge 150 × 25mm × 5um; mobile phase: water (10 mM NH_4HCO_3)/ACN], B%: 43%-73%, 9 min] to afford the title compound (13.3 mg, 23% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-*d*4) δ = 9.05 (s, 1H), 8.37 (dd, *J* = 1.6, 4.8 Hz, 1H), 7.82 (br d, *J* = 7.6 Hz, 1H), 7.68 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.38 (dd, *J* = 4.8, 7.6 Hz, 1H), 7.31 (d, *J* = 3.0 Hz, 1H), 7.26 (t, *J* = 9.2 Hz, 1H), 7.05 (s, 1H), 5.38-5.22 (m, 1H), 4.75 (t, *J* = 6.0 Hz, 2H), 4.35 (q, *J* = 10.4 Hz, 2H), 3.29-3.17 (m, 3H), 3.05-2.95 (m, 3H), 2.49-2.39 (m, 1H), 2.38-2.26 (m, 3H), 2.24-2.19 (m, 1H), 2.17-2.09 (m, 2H), 2.04-1.96 (m, 2H), 1.94-1.86 (m, 1H), 0.77 (t, *J* = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, methanol-*d*4) δ = -121.108, -138.808, -173.817; SFC condition: Column: Chiralcel OJ-3 50 × 4.6mm I.D., 3um; Mobile phase: Phase A for CO_2, and Phase B for MeOH (0.05% DEA); Gradient elution: MeOH (0.05% DEA) in CO_2 from 5% to 40%; Flow rate: 3mL/min; Detector: PDA; Column Temp: 35C; Back Pressure: 100 Bar; LCMS (ESI, M+1): m/z = 630.3.

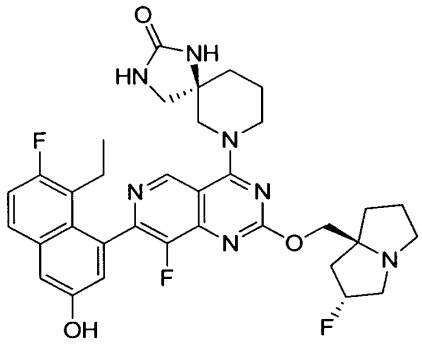
EXAMPLE 299



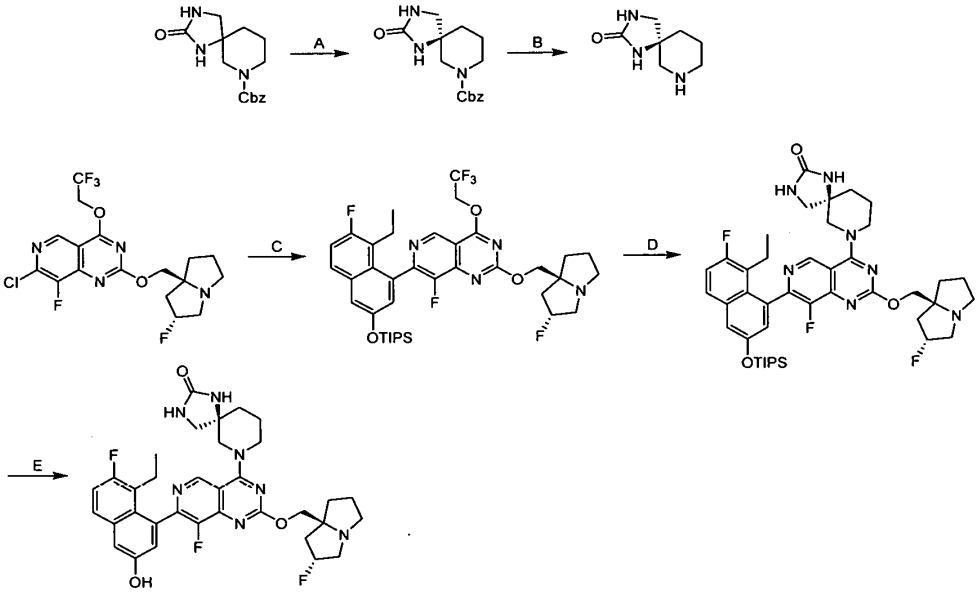
1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol

[0000932] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.21-9.13 (m, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.6 Hz, 1H), 7.09-7.02 (m, 1H), 5.51-5.32 (m, 1H), 4.52-4.37 (m, 2H), 4.27-4.19 (m, 1H), 4.13-3.94 (m, 3H), 3.93-3.83 (m, 1H), 3.64-3.41 (m, 3H), 3.24-3.14 (m, 1H), 2.56-2.30 (m, 3H), 2.28-2.05 (m, 6H), 2.03-1.95 (m, 1H), 1.84-1.69 (m, 2H), 0.84-0.75 (m, 3H); LCMS (ESI, M+1): m/z = 594.3.

EXAMPLE 300



(R)-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)-1,3,7triazaspiro[4.5]decan-2-one



[0000933] Step A. (R)-benzyl 2-oxo-1,3,7-triazaspiro[4.5]decane-7-carboxylate: SFC separation of benzyl 2-oxo-1,3,7-triazaspiro[4.5]decane-7-carboxylate (650mg) [column: DAICEL CHIRALPAK AY-H(250mm * 30 mm, 10 um); mobile phase: water (0.1% NH_4OH)-EtOH]; B%: 50%-50%, 4.8 min; 110 min]. The crude product was purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (200 mg,

54% yield) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.43-7.27 (m, 5H), 6.65 (s, 1H), 6.21 (s, 1H), 5.07 (br s, 2H), 3.59-3.43 (m, 2H), 3.18-2.91 (m, 4H), 1.71-1.52 (m, 3H), 1.47-1.30 (m, 1H).

[0000934] Step B. (S)-1,3,7-triazaspiro[4.5]decan-2-one: To a solution of benzyl (R)-benzyl 2-oxo-1,3,7-triazaspiro[4.5]decane-7-carboxylate (200 mg, 1.0 *equiv.*) in MeOH (30 mL) was added Pd/C (50.0 mg, 10% purity) under N_2. The mixture was stirred at 10 °C for 2 hours under H_2 (15 psi). The reaction mixture was filtered and concentrated to afford the title compound (120 mg, crude) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.36 (s, 1H), 6.08 (br s, 1H), 3.18-3.13 (m, 4H), 2.96 (d, J = 8.8 Hz, 1H), 2.20-2.10 (m, 1H), 1.64-1.41 (m, 4H).

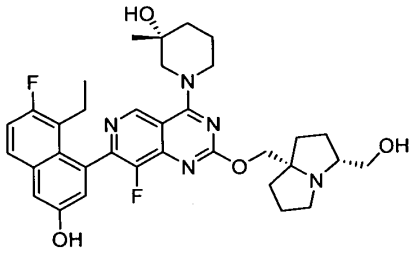
[0000935] Step C. 7-(8-ethyl-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a solution of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (1.0 g, 1.0 *equiv.*), CataCXium A Pd G3 (166 mg, 0.1 *equiv.*) and ((5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)triisopropylsilane (1.29 g, 1.20 *equiv.*) in THF (17 mL) was added K_3PO_4 (1.5 M, 3.0 *equiv.*) under N_2. The mixture was stirred at 60 °C for 1 hour. The reaction mixture was diluted with saturated NH_4Cl (20 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 Na_2SO_4, concentrated and purified by column chromatography [Silica gel, Petroleum ether/Ethyl acetate 1:0 to 3:1] to afford the title compound (crude) as a yellow solid; LCMS (ESI, M+1): m/z = 749.4.

[0000936] Step D. (R)-7-(7-(8-ethyl-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-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 7-(8-ethyl-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 (380 mg, 1.0 *equiv.*), 4Å molecular sieves (200 mg) and (S)-1,3,7-triazaspiro[4.5]decan-2-one (78.7 mg, 1.0 *equiv.*) in DMF (4.0 mL) was added DIEA (197 mg, 3.0 *equiv.*) .The mixture was stirred at 40 °C for 12 hours. The reaction mixture was filtered. The crude product was purified by reversed phase flash

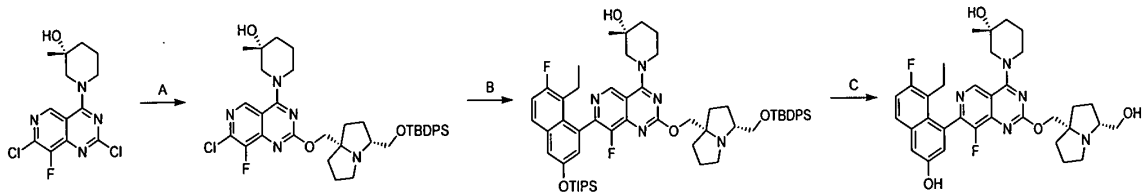
chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (180 mg, 44% yield) as a brown solid; LCMS (ESI, M+1): m/z = 804.3.

[0000937] Step E. (R)-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)-1,3,7-triazaspiro[4.5]decan-2-one: To a solution of (R)-7-(7-(8-ethyl-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one (180 mg, 1.0 *equiv.*) in DMF (1.0 mL) was added CsF (340 mg, 10 *equiv.*). The mixture was stirred at 10 °C for 0.5 hour. The reaction mixture was filtered and purified by prep-HPLC [Waters Xbridge 150 × 25mm × 5um; mobile phase: water (10 mM NH_4HCO_3)-ACN; B%: 34%-64%, 9min] to afford the title compound (125 mg, 86% yield) as a white solid; ^{1}H NMR (400 MHz, CD_3OD) δ = 9.11 (d, *J* = 4.0 Hz, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.6 Hz, 1H), 7.05 (d, *J* = 2.8 Hz, 1H), 5.40-5.21 (m, 1H), 4.33-4.24 (m, 2H), 4.18-3.84 (m, 4H), 3.47-3.38 (m, 1H), 3.28-3.14 (m, 3H), 3.05-2.96 (m, 1H), 2.55-2.08 (m, 5H), 2.06-1.81 (m, 7H), 0.87-0.72 (m, 3H); LCMS (ESI, M+1): m/z = 648.2.

EXAMPLE 301



(R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((3R,7aS)-3-(hydroxymethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



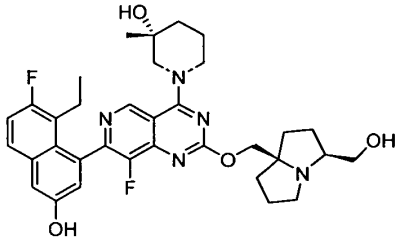
[0000938] Step A. (R)-1-(2-(((3R,7aS)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of ((3R,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol (408 mg, 1.1 *equiv.*) and 4Å molecular sieves (30 mg) in toluene (3 mL) was added *t*-BuONa (261 mg, 3.0 *equiv.*) at 0 °C. The reaction was stirred at 0 °C for 10 mins. Then (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (300 mg, 906 μmol, 1.0 *equiv.*) was added. The reaction was stirred at 0 °C for 1 hour. The mixture was quenched with water (4 mL) at 0 °C and extracted with ethyl acetate (3 × 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated, and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, neutralized with solid $NaHCO_3$, concentrated in vacuum to remove acetonitrile, and extracted with dichloromethane (2 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum to afford the title compound (580 mg, 89% yield) as a brown solid; ^{1}H NMR (400 MHz, methanol-d_4) δ 8.97 (s, 1H), 7.74 - 7.67 (m, 4H), 7.45 - 7.35 (m, 6H), 4.44 (br d, J = 13.2 Hz, 1H), 4.23 - 4.14 (m, 3H), 3.70 - 3.57 (m, 2H), 3.52 (d, J = 13.2 Hz, 1H), 3.30 - 3.25 (m, 1H), 3.04 - 2.88 (m, 2H), 2.83 - 2.73 (m, 1H), 2.19 - 2.12 (m, 1H), 2.10 - 2.02 (m, 2H), 1.93 - 1.83 (m, 3H), 1.81 - 1.73 (m, 3H), 1.72 - 1.60 (m, 3H), 1.22 (s, 3H), 1.04 (s, 9H); LCMS [ESI, M+1]: m/z = 704.2.

[0000939] Step B. (R)-1-(2-(((3R,7aS)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-ethyl-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(2-(((3R,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (530 mg, 1.0 *equiv.*), ((5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)triisopropylsilane (462 mg, 1.3 *equiv.*) and K_3PO_4 (1.5 M in water , 1.50 mL, 3.0 *equiv.*) in methoxycyclopentane (4.6 mL) was added CataCXium A Pd G3 (54.8 mg, 0.1 *equiv.*) under N_2. The reaction was stirred at 90 °C for 2.5 hours. The layers of the mixture were separated and the aqueous phase was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were concentrated and purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, neutralized with solid $NaHCO_3$, concentrated in vacuum to remove acetonitrile, and extracted with dichloromethane (2 × 15 mL). The combined organic

layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum to afford the title compound (193 mg, 23% yield) as a brown solid; LCMS [ESI, M+1, M/2+1]: m/z = 1014.7, 508.1.

[0000940] Step C. (R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((3R,7aS)-3-(hydroxymethyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of (R)-1-(2-(((3R,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H- pyrrolizin-7a-yl)methoxy)-7-(8-ethyl-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (163 mg, 1.0 *equiv.*) in DMF (0.8 mL) was added CsF (366 mg, 15 *equiv.*). The reaction was stirred at 20 °C for 15 hours. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, neutralized with solid $NaHCO_3$, concentrated in vacuum to remove acetonitrile, and extracted with dichloromethane (2 × 15 mL). The combined organic layer was washed with brine (15 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum. The residue was purified by prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: [water (10mM NH_4HCO_3)-AC,] B%: 35%-65%, 8 min] and lyophilized to afford the title compound (46.7 mg, 47% yield) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d_4) δ 9.20 (d, *J* = 1.2 Hz, 1H), 7.67 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.06 (t, *J* = 2.0 Hz, 1H), 4.54 (br d, *J* = 12.4 Hz, 1H), 4.34 - 4.24 (m, 3H), 3.68 - 3.59 (m, 1H), 3.59 - 3.52 (m, 2H), 3.50 - 3.42 (m, 1H), 3.13 - 3.01 (m, 1H), 2.98 - 2.84 (m, 2H), 2.54 - 2.41 (m, 1H), 2.26 - 2.11 (m, 3H), 2.06 - 1.99 (m, 1H), 1.98 - 1.92 (m, 2H), 1.92 - 1.84 (m, 2H), 1.83 - 1.66 (m, 5H), 1.29 (d, *J* = 10.0 Hz, 3H), 0.82 (q, *J* = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, methanol-d4) δ -121.198, -139.196; SFC: >99% ee, (S,S)Whelk-O1 100 × 4.6 mm I.D., 3.5 μm column, A: CO_2, B: 40% [IPA + ACN (w/ 0.05% DEA)], 3mL/min, 220 nm, t_R: 1.705 min; LCMS [ESI, M+1, M/2+1]: m/z = 620.2, 310.7.

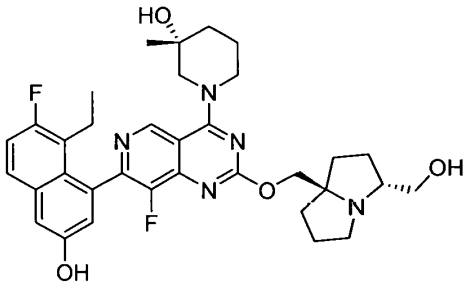
EXAMPLE 302



(R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((3S,7aR)-3-(hydroxymethyl)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

[0000941] The title compound was synthesized according to the procedure described for example 301. ^{1}H NMR (400 MHz, methanol-*d*4) δ ppm = 9.21 (s, 1H), 7.68 (dd, *J*=9.2, 6.0 Hz, 1 H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.28 - 7.21 (m, 1H), 7.08 - 7.04 (m, 1H), 4.55 (br d, *J* = 13.2 Hz, 1H), 4.40 - 4.20 (m, 3H), 3.68 - 3.59 (m, 1H), 3.59 - 3.50 (m, 2H), 3.50 - 3.40 (m, 1H), 3.16 - 3.06 (m, 1H), 3.02 - 2.87 (m, 2H), 2.48 (qd, *J* = 7.2, 14.4 Hz, 1H), 2.28 - 2.10 (m, 3H), 2.09 - 2.02 (m, 1H), 2.01 - 1.94 (m, 2H), 1.93 - 1.88 (m, 1H), 1.88 - 1.67 (m, 6H), 1.34 - 1.24 (m, 3H), 0.82 (q, *J* = 7. Hz, 3H); HPLC: >99% ee, Chiralcel IC-3 50 × 4.6 mm I.D., 3 μm column A: 50% (MeOH: ACN = 4:1) (w/ 0.05% DEA), B: CO_2, 3mL/min, 220 nm, t_R: 0.519 min; LCMS (ESI, M+1): m/z = 620.2.

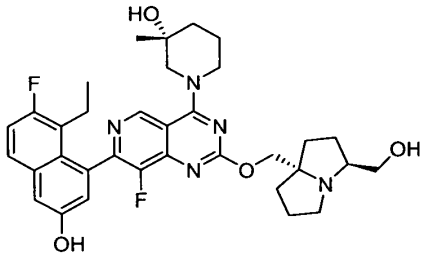
EXAMPLE 303



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

[0000942] The title compound was synthesized according to the procedure described for example 301. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.21 (s, 1H), 7.67 (dd, *J* = 6.0, 8.8 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.25 (t, *J* = 9.6 Hz, 1H), 7.06 (t, *J* = 2.4 Hz, 1H), 4.56 (br d, *J* = 12.8 Hz, 1H), 4.42-4.36 (m, 1H), 4.35-4.26 (m, 2H), 3.85 (dd, *J* = 6.8, 11.2 Hz, 1H), 3.73 (dd, *J* = 6.0, 11.2 Hz, 1H), 3.68-3.55 (m, 1H), 3.51-3.36 (m, 2H), 3.06-2.96 (m, 1H), 2.93-2.81 (m, 1H), 2.55-2.40 (m, 1H), 2.29-2.11 (m, 3H), 2.09-1.97 (m, 1H), 1.95-1.83 (m, 5H), 1.82-1.65 (m, 4H), 1.29 (d, *J* = 10.4 Hz, 3H), 0.87-0.75 (m, 3H); LCMS (ESI, M+1): m/z = 620.4.

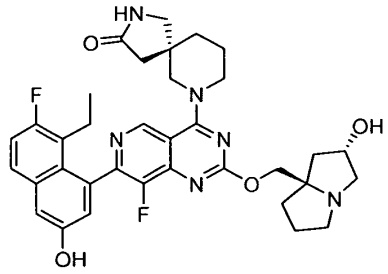
EXAMPLE 304



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

[0000943] The title compound was synthesized according to the procedure described for example 301. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.22 (s, 1H), 7.67 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.37-7.18 (m, 2H), 7.06 (s, 1H), 4.61-4.51 (m, 1H), 4.49-4.39 (m, 1H), 4.39-4.24 (m, 2H), 3.88-3.79 (m, 1H), 3.79-3.70 (m, 1H), 3.69-3.56 (m, 1H), 3.52-3.42 (m, 2H), 3.15-3.03 (m, 1H), 3.02-2.86 (m, 1H), 2.57-2.38 (m, 1H), 2.29-2.12 (m, 3H), 2.11-2.02 (m, 1H), 1.99-1.84 (m, 5H), 1.84-1.69 (m, 4H), 1.35-1.25 (m, 3H), 0.90-0.72 (m, *J* = 7.2, 3H); LCMS (ESI, M+1): m/z = 620.2.

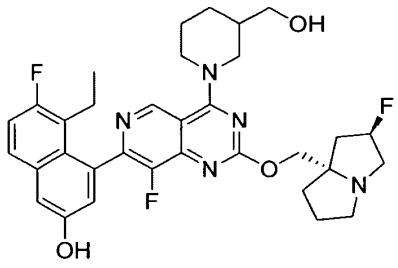
EXAMPLE 305



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

[0000944] The title compound was synthesized according to the procedure described for example 206 except for second eluted peak ((R)-7-(2-(((2S,7aR)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2,7-diazaspiro[4.5]decan-3-one) was collected during chiral prep HPLC in step C and carried through steps D, E and F. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.15 (s, 1H), 7.69 (dd, J = 9.2, 6.0 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.26 (t, J = 9.2 Hz, 1H), 7.05 (dd, J = 2.8, 4.4 Hz, 1H), 4.74 - 4.68 (m, 1H), 4.65 - 4.52 (m, 3H), 4.45 - 4.29 (m, 1H), 4.10 - 3.94 (m, 1H), 3.88 - 3.79 (m, 2H), 3.75 - 3.60 (m, 2H), 3.41 (d, J = 12 Hz, 1H), 3.29 (s, 2H), 2.58 - 2.19 (m, 10H), 1.97 - 1.82 (m, 4H), 0.86 - 0.76 (m, 3H); ^{19}F NMR (377 MHz, MeOD) δ =121.08, 139.33; LCMS (ESI, M+1): m/z = 645.1

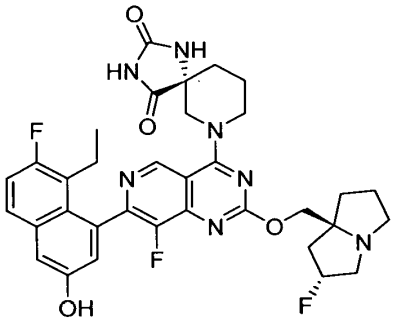
EXAMPLE 306



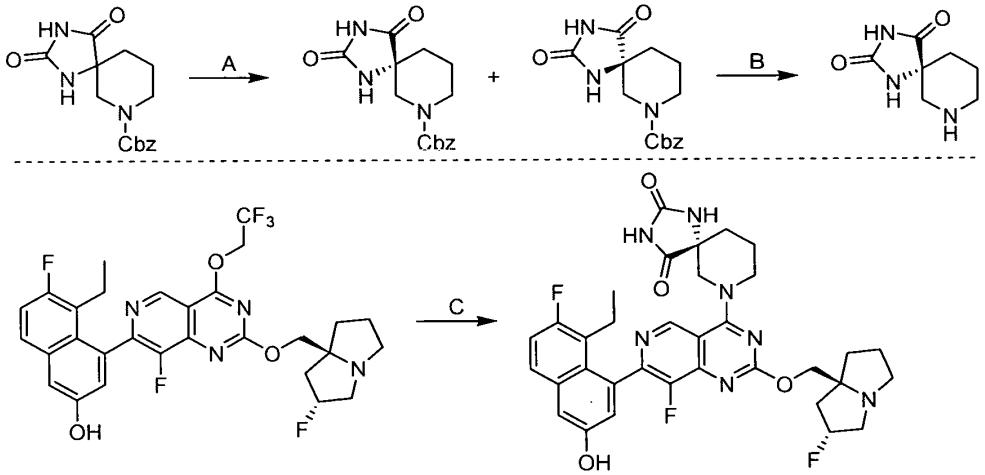
5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(hydroxymethyl)piperidin-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol

[0000945] The title compound was synthesized according to the procedure described for example 134. ^{1}H NMR (400 MHz, METHANOL-d4): δ = 9.08 (s, 1H), 7.67 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.28 - 7.22 (m, 1H), 7.06 (s, 1H), 5.41 - 5.20 (m, 1H), 4.76 - 4.64 (m, 1H), 4.63 - 4.50 (m, 1H), 4.37 - 4.20 (m, 2H), 3.63 - 3.56 (m, 1H), 3.54 - 3.44 (m, 2H), 3.38 - 3.33 (m, 1H), 3.29 - 3.12 (m, 3H), 3.01 (dt, *J* = 5.6, 9.6 Hz, 1H), 2.51 - 2.09 (m, 5H), 2.05 - 1.78 (m, 7H), 1.55 - 1.41 (m, 1H), 0.81 (t, *J* = 7.6 Hz, 3H); LCMS [ESI, M+H]: m/z = 608.3.

EXAMPLE 307



(R)-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)-1,3,7-triazaspiro[4.5]decane-2,4-dione

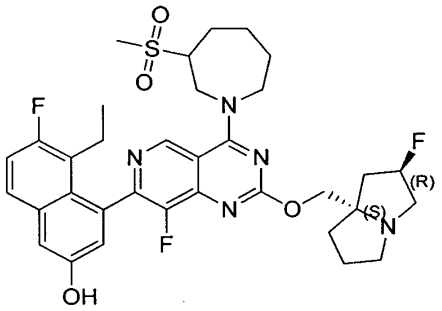


[0000946] Step A. (R)-benzyl 2,4-dioxo-1,3,7-triazaspiro[4.5]decane-7-carboxylate: Enantiomers of benzyl 2,4-dioxo-1,3,7-triazaspiro[4.5]decane-7-carboxylate were separated by chiral SFC [DAICEL CHIRALPAK IG (250mm*30mm,10um);A: 0.1%NH_3xH_2O B: MeOH, B%: 45%-45% over 4.3 min; 150 min] to afford the title compound (200 mg, 50% yield) as a yellow liquid; LCMS (ESI, M+1): m/z = 304.3.

[0000947] Step B. (R)-1,3,7-triazaspiro[4.5]decane-2,4-dione: To a solution of benzyl 2-oxo-1,3,9-triazaspiro[4.5]decane-9-carboxylate (200 mg, 1.0 *equiv.*) in MeOH (10 mL) was added Pd/C (200 mg, 10% purity) under N_2. The suspension was degassed in vacuum and purged with H_2 several times. The reaction was stirred under H_2 (15 psi) at 20 °C for 2 hours. The reaction mixture was filtered and the filtrate was concentrated to afford the title compound (150 mg, 71% yield) as a colorless liquid; LCMS (ESI, M+1): m/z = 170.2.

[0000948] Step C. (R)-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)-1,3,7-triazaspiro[4.5]decane-2,4-dione: To a solution of 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 (80.0 mg, 1.0 *equiv.*), (R)-1,3,7-triazaspiro[4.5]decane-2,4-dione (45.7 mg, 2.0 *equiv.*) and 4Å molecular sieves (10 mg) in DMF (1 mL) was added DIEA (52.3 mg, 3.0 *equiv.*). The mixture was stirred at 40 °C for 12 hours and then concentrated. The residue was purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; mobile phase: water (0.225% formic acid)/ACN] B%: 15%-45%, 7min] and lyophilized to afford the title compound (49.0 mg, 54.6% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.14 (d, *J* = 6.4 Hz, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 1H), 7.26 (t, *J* = 9.6 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 5.56-5.31 (m, 1H), 4.64 (br t, *J* = 12.8 Hz, 1H), 4.53-4.36 (m, 3H), 3.90-3.71 (m, 2H), 3.70-3.58 (m, 1H), 3.58-3.45 (m, 2H), 3.28-3.18 (m, 1H), 2.57-2.46 (m, 1H), 2.45-2.33 (m, 2H), 2.33-2.21 (m, 2H), 2.07 (br s, 4H), 2.06-1.90 (m, 3H), 0.90-0.70 (m, 3H); LCMS (ESI, M+1): m/z = 662.3.

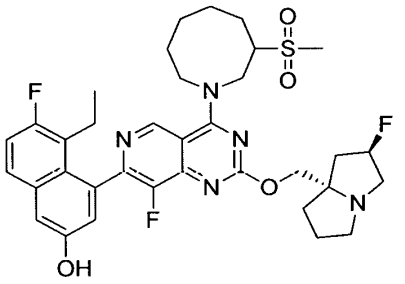
EXAMPLE 308



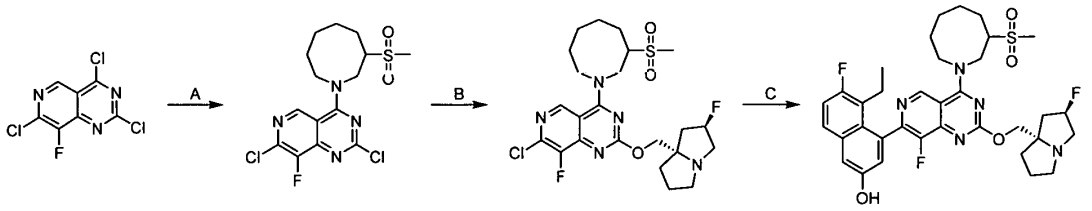
5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(methylsulfonyl)azepan-1-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol

[0000949] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.24 (dd, *J* = 2.0, 3.2 Hz, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.33-7.21 (m, 2H), 7.04 (dd, *J* = 2.4, 14.4 Hz, 1H), 5.55-5.28 (m, 1H), 5.05-4.92 (m, 1H), 4.64-4.46 (m, 2H), 4.36-4.23 (m, 1H), 4.21-4.04 (m, 1H), 3.97-3.73 (m, 2H), 3.65-3.39 (m, 3H), 3.25-3.15 (m, 1H), 3.14-3.08 (m, 3H), 2.61-2.41 (m, 2H), 2.40-2.23 (m, 4H), 2.21-1.99 (m, 6H), 1.93-1.80 (m, 1H), 1.56-1.36 (m, 1H), 0.94-0.66 (m, 3H); LCMS (ESI, M+1): m/z = 670.3.

EXAMPLE 309



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



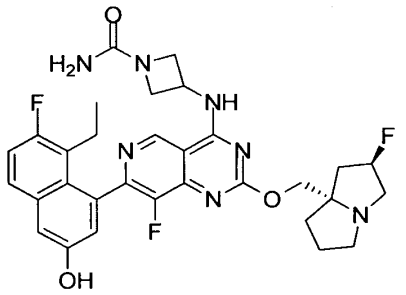
[0000950] Step A. 2,7-dichloro-8-fluoro-4-(3-(methylsulfonyl)azocan-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 2,4,7-trichloro-8-fluoro-pyrido[4,3-d]pyrimidine (130 mg, 1 *equiv.*), 3-methylsulfonylazocane (129.00 mg, 1.1 *equiv.*, HCl) in THF (1.5 mL) was added DIEA (333 mg, 5.0 *equiv.*). The mixture was stirred at -40 °C for 2 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated to afford the title compound (220 mg, crude) as a yellow solid; LCMS (ESI, M+1): m/z = 407.0.

[0000951] Step B. 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(methylsulfonyl)azocan-1-yl)pyrido[4,3-d]pyrimidine: To a solution of 2,7-dichloro-8-fluoro-4-(3-methylsulfonylazocan-1-yl)pyrido[4,3-d]pyrimidine (210 mg, 1.0 *equiv.*), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (164 mg, 2.0 *equiv.*) and 4Å MOLECULAR SIEVES (100 mg) in dioxane (1.5 mL) was added DIEA (200 mg, 3.0 *equiv.*). The reaction was stirred at 95 °C for 12 hours. The mixture was diluted with water (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 (90.0 mg, 32.5% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 530.1.

[0000952] Step C. 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3-(methylsulfonyl)azocan-1-yl)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-(3-(methylsulfonyl)azocan-1-yl)pyrido[4,3-d]pyrimidine (80.0 mg, 1.0 *equiv.*), Cs_2CO_3 (1.5 M, 302 µL, 3.0 *equiv.*) and CataCXium A Pd G3 (11.0 mg, 0.1 *equiv.*) in methoxycyclopentane (1 mL) was added 5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (62.0 mg, 1.3 *equiv.*). The reaction was stirred at 95 °C for 3 hours. The mixture was diluted with water (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 give a crude product. The crude product was purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30 mm × 3 μm; mobile phase: water (0.225% formic acid)/ACN] B%: 18%-48%, 7min] and lyophilized to afford the title compound (28.4 mg, 26.8% yield,) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d4) δ = 9.23 (d, *J* = 4.3 Hz, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.34-7.18 (m, 2H), 7.05 (d, *J* = 2.0 Hz, 1H), 5.47-5.25 (m, 1H), 5.19-5.07 (m, 1H), 4.59 (dt, *J* = 4.8, 9.6 Hz, 1H), 4.48-4.32 (m, 2H), 3.96-3.74 (m, 3H), 3.48-3.33 (m, 2H), 3.26 (br s, 1H), 3.15-3.03 (m, 4H), 2.53-2.32 (m, 3H), 2.30-2.21 (m, 1H), 2.20-2.13 (m, 2H), 2.11-1.91 (m, 7H), 1.89-1.68 (m, 2H), 1.57-1.41 (m, 1H), 0.86-0.70 (m, 3H); LCMS (ESI, M+1): m/z = 684.3.

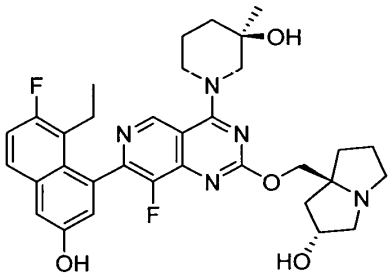
EXAMPLE 310



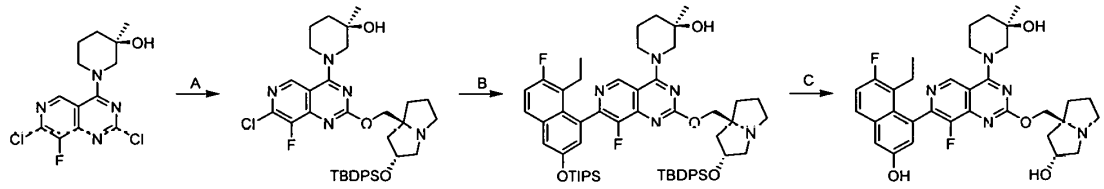
3-((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)azetidine-1-carboxamide

[0000953] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-*d4*) δ = 9.29 (s, 1H), 8.43 (s, 1H), 7.82-7.63 (m, 1H), 7.44-7.19 (m, 2H), 7.15-6.98 (m, 1H), 5.63-5.38 (m, 1H), 5.02-4.97 (m, 1H), 4.64-4.48 (m, 2H), 4.41 (br t, *J* = 8.0 Hz, 2H), 4.30 - 4.13 (m, 2H), 3.93-3.60 (m, 3H), 2.74-2.00 (m, 9H), 0.91-0.70 (m, 3H); LCMS (ESI, M+1): m/z = 608.2.

EXAMPLE 311



(2R,7aS)-7a-(((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)hexahydro-1H-pyrrolizin-2-ol



[0000954] Step A. (R)-1-(2-(((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (146 mg, 1.0 *equiv.*) in dioxane (2 mL) were added ((2S,7aR)-2-((tert-butyldiphenylsilyl)oxy)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (209 mg, 1.2 *equiv.*), DIEA (171 mg, 3.0 *equiv.*) and 4 Å molecular sieves (15 mg). The reaction was stirred at 90 °C for 16 hours. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, neutralized with solid $NaHCO_3$ and concentrated in vacuum to remove acetonitrile. Then the mixture was extracted with ethyl acetate (30 mL). The organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound (171 mg, 48% yield) as a yellow oil; ^1H NMR (400 MHz, methanol-d_4) δ = 8.98 (s, 1H), 7.65 - 7.65 (m, 1H), 7.65 - 7.64 (m, 1H), 7.70 - 7.61 (m, 2H), 7.47 - 7.30 (m, 6H), 4.64 - 4.51 (m, 3H), 4.21 - 4.13 (m, 2H), 3.54 - 3.47 (m, 1H), 3.27 - 3.18 (m, 2H), 3.16 - 3.03 (m, 3H), 2.16 - 2.04 (m, 4H), 1.92 - 1.59 (m, 6H), 1.24 (s, 3H), 1.08 - 1.03 (m, 9H).

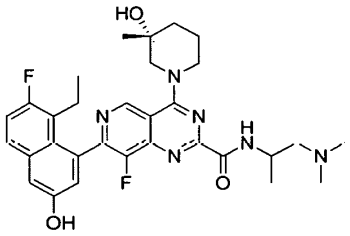
[0000955] Step B. (R)-1-(2-(((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-ethyl-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-

fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (R)-1-(2-(((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (205 mg, 1.0 *equiv.*), ((5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-yl)oxy)triisopropylsilane (168 mg, 1.2 *equiv.*), K_3PO_4 (1.5 M in water , 3.0 *equiv.*) and CataCXium A Pd G3 (21.6 mg, 0.1 *equiv.*) in methoxycyclopentane (2 mL) was de-gassed and stirred at 90 °C for 2 hours under N_2. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and neutralized with solid $NaHCO_3$, concentrated in vacuum to remove acetonitrile. Then the mixture was diluted with ethyl acetate (20 mL) and water (30 mL), extracted with ethyl acetate (10 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound (160 mg, 54% yield) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.21 (d, *J* = 3.4 Hz, 1H), 7.78 - 7.72 (m, 1H), 7.69 - 7.62 (m, 4H), 7.45 - 7.26 (m, 8H), 7.09 (dd, *J* = 2.4, 5.6 Hz, 1H), 4.61 - 4.54 (m, 1H), 4.44 (br d, *J* = 13.2 Hz, 1H), 4.28 - 4.13 (m, 3H), 3.64 - 3.49 (m, 1H), 3.21 - 3.12 (m, 3H), 2.87 - 2.79 (m, 1H), 2.55 - 2.42 (m, 1H), 2.13 (br d, *J* = 7.6 Hz, 4H), 1.99 - 1.66 (m, 6H), 1.39 - 1.30 (m, 3H), 1.29 - 1.21 (m, 5H), 1.14 (dd, *J* = 2.0, 7.2 Hz, 18H), 1.08 - 1.04 (m, 9H), 0.81 (t, *J* = 7.2 Hz, 3H); LCMS [ESI, M/2+1]: m/z = 501.0.

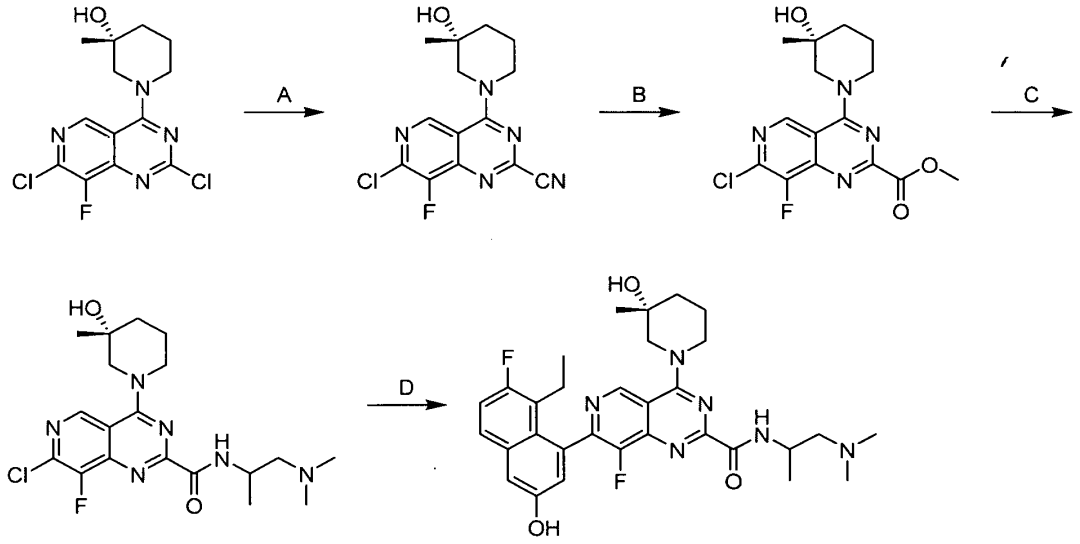
[0000956] Step C. (2R,7aS)-7a-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-2-ol: A solution of (R)-1-(2-(((2R,7aS)-2-((tert-butyldiphenylsilyl)oxy)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-ethyl-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (120 mg, 1.0 *equiv.*) and CsF (273 mg, 15 *equiv.*) in DMF (0.6 mL) was stirred at 18 °C for 7 hrs. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and lyophilized to afford the title compound (39 mg, 53% yield) as a white solid; ^{1}H NMR (400 MHz, CD3OD, 298 K) δ = 9.24 (s, 1H), 8.54 (br s, 1H), 7.68 (br dd, *J* = 5.6, 8.4 Hz, 1H), 7.31 (br d, *J* = 2.4 Hz, 1H), 7.25 (br t, *J* = 9.2 Hz, 1H), 7.05 (br s, 1H), 4.67 - 4.56 (m, 2H), 4.54 - 4.41 (m, 2H), 4.38 - 4.27 (m, 1H), 3.68 - 3.41 (m, 5H), 3.17 - 3.03 (m, 1H), 2.51 - 2.41 (m, 2H), 2.32 - 2.16 (m, 5H), 2.11 - 1.98 (m, 2H), 1.93 - 1.74 (m, 3H), 1.30 (br d, *J* = 9.2 Hz, 3H), 0.90 - 0.75 (m, 3H); SFC analysis: Column: Chiralpak AS-3 50×4.6mm I.D.,

3um; Mobile phase: Phase A for CO_2, and Phase B for MEOH(0.05%DEA); Gradient elution: B in A from 5% to 40%; Flow rate: 3mL/min; Detector: DAD; Column Temp: 35C; Back Pressure: 100Bar; LCMS [ESI, M+1]: m/z = 606.3.

EXAMPLE 312



N-(1-(dimethylamino)propan-2-yl)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine-2-carboxamide



[0000957] Step A. (R)-7-chloro-8-fluoro-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine-2-carbonitrile: To a mixture of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (800 mg, 1.0 *equiv.*), NaCN (280 mg, 2.4 *equiv.*) and DABCO (27.1 mg, 0.1 *equiv.*) in DMSO (10 mL) was stirred at 60 °C for 12 hours. After reaction completion, the mixture was diluted with ethyl acetate (20 mL) and extracted with water (3 × 10 mL). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and

concentrated under reduced pressure to give a residue. Te residue was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) to afford the title compound (170 mg, 19% yield) as a black brown oil. LCMS [ESI, M+1]: m/z = 322.2.

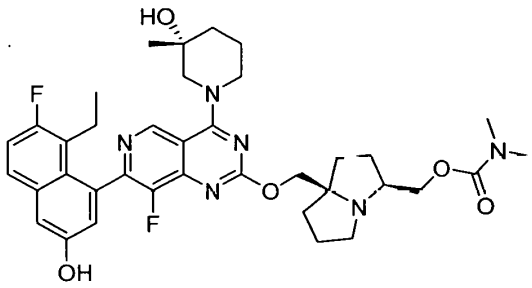
[0000958] Step B. (R)-methyl 7-chloro-8-fluoro-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine-2-carboxylate: To a solution of (R)-7-chloro-8-fluoro-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine-2-carbonitrile (170 mg, 1.0 *equiv.*) in MeOH (0.5 mL) was added HCl•MeOH (4 M, 5 mL, 37.8 *equiv.*). The mixture was stirred at 50 °C for 1 hour. After completion, the reaction mixture was concentrated under reduced pressure to give a residue, diluted sat. aq. $NaHCO_3$ to adjust the pH to 9, extracted with ethyl acetate (3 × 5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford the title compound (143 mg, crude) as a black brown oil; LCMS [ESI, M+1]: m/z = 355.2.

[0000959] Step C. 7-chloro-N-(1-(dimethylamino)propan-2-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine-2-carboxamide: To a solution of (R)-methyl 7-chloro-8-fluoro-4-(3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine-2-carboxylate (135 mg, 1.0 *equiv.*) in MeOH (0.5 mL) was added N1,N1-dimethylpropane-1,2-diamine (777 mg, 20.0 *equiv.*). The reaction was stirred at 25 °C for 1 hour. After completion, the reaction mixture was filtered. The filtrate was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) to afford the title compound (33 mg, 20% yield over two steps) as a yellow oil; LCMS [ESI, M+1]: m/z = 425.2.

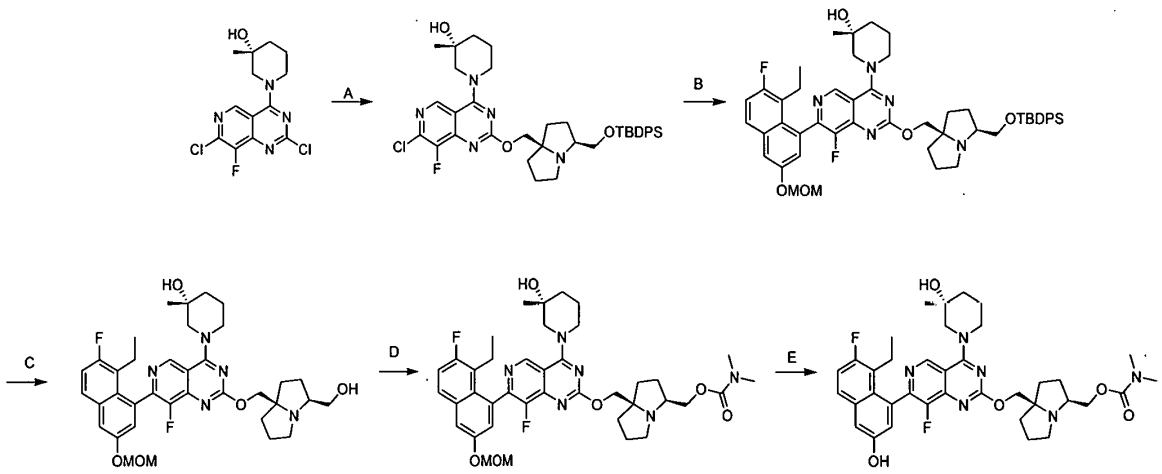
[0000960] Step D. N-(1-(dimethylamino)propan-2-yl)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine-2-carboxamide: To a mixture of 7-chloro-N-(1-(dimethylamino)propan-2-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidine-2-carboxamide (15.0 mg, 1.0 *equiv.*), 5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (14.5 mg, 1.3 *equiv.*), K_3PO_4 (1.5 M, 70.6 μL, 3.0 *equiv.*) in methoxycyclopentane (1 mL) was added CataCXium A Pd G3 (2.57 mg, 0.1 *equiv.*). The reaction was stirred at 90 °C for 2 hours. After reaction completion, the mixture was quenched by water (2 mL) and extracted with ethyl acetate (5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150 × 25 mm × 10 μm; mobile phase: water (0.1% formic

acid)/ACN, B%: 9% - 39%, 10 min) and lyophilized to afford the title compound (6.75 mg, 33% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d4): δ = 9.41 (dd, *J* = 3.2, 4.8 Hz, 1H), 8.53 (s, 1H), 7.70 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.27 (t, *J* = 9.2 Hz, 1H), 7.11 - 7.08 (m, 1H), 4.78 (br d, *J* = 13.6 Hz, 1H), 4.44 (br s, 2H), 3.63 - 3.45 (m, 2H), 3.04 - 2.92 (m, 1H), 2.76 - 2.68 (m, 1H), 2.56 (s, 6H), 2.49 - 2.37 (m, 1H), 2.28 - 2.11 (m, 2H), 1.93 - 1.75 (m, 3H), 1.36 - 1.29 (m, 6H), 0.84 - 0.76 (m, 3H); LCMS [ESI, M+1]: m/z = 579.4.

EXAMPLE 313



((3S,7aR)-7a-(((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)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate



[0000961] Step A. (R)-1-(2-(((3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-

3-ol: A mixture of ((3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol (408 mg, 1.1 *equiv.*uiv), 4 Å molecular sieves (20 mg) and *t*-BuONa (261 mg, 3.0 *equiv.*) in toluene (3 mL) was stirred at 0 °C for 10 mins. Then (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (300 mg, 1.0 *equiv.*) was added and the mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched by water (40 mL) at 0 °C and extracted with ethyl acetate (3 × 20 mL). Then the combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, neutralized with solid $NaHCO_3$ and concentrated in vacuum to remove acetonitrile. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated in vacuum to afford the title compound (484 mg, 66.4% yield) as a black solid; LCMS (ESI, M+1): m/z = 704.2.

[0000962] Step B. (R)-1-(2-(((3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(2-(((3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (495 mg, 1.0 *equiv.*) in methoxycyclopentane (8 mL) was added 2-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (329 mg, 1.3 *equiv.*), K_3PO_4 (1.5 M in water , 3.0 *equiv.*) and CataCXium A Pd G3 (51.2 mg, 0.1 *equiv.*) at 18 °C under N_2. The mixture was de-gassed and then heated to 90 °C for 3 hours. The reaction mixture was diluted with ethyl acetate (30 mL) and water (50 mL), the aqueous phase was extracted with ethyl acetate (20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated in vacuum to give a residue. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, neutralized with solid $NaHCO_3$ and concentrated in vacuum to remove ACN. Then the mixture was extracted with ethyl acetate (20 mL× 2). The combined organic phase was dried over anhydrous sodium sulfate and concentrated to afford the title compound (327 mg, 48.8% yield,) as a yellow solid; LCMS (ESI, M+1): m/z = 902.3.

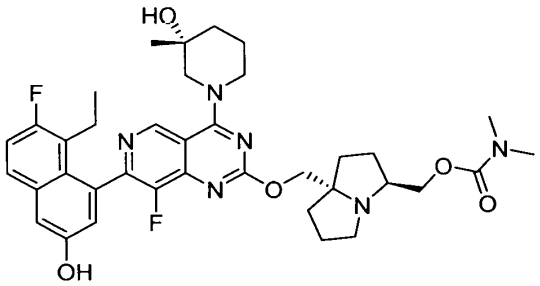
[0000963] Step C. (R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((3S,7aR)-3-(hydroxymethyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(2-(((3S,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (200 mg, 1.0 *equiv.*) in DMF (2 mL) was added CsF (505 mg, 15 *equiv.*). The reaction mixture was stirred at 40 °C for 12 hrs. The reaction mixture was diluted with ethyl acetate (15 mL) and water (30 mL), the aqueous phase 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 in vacuum 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 neutralized with solid $NaHCO_3$ and concentrated in vacuum to remove acetonitrile. Then the mixture was diluted with ethyl acetate (20 mL × 2), dried over anhydrous sodium sulfate and concentrated to afford the title compound (107 mg, 72.6% yield) as a yellow solid.

[0000964] Step D. ((3S,7aR)-7a-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate: To a solution of (R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((3S,7aR)-3-(hydroxymethyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (107 mg, 1.0 *equiv.*) in THF (1 mL) was added NaH (12.9 mg, 2.0 *equiv.*) at 0 °C. After stirring at 0 °C for 0.5 hour, N,N-dimethylcarbamoyl chloride (34.7 mg, 2.0 *equiv.*) in THF (1 mL) was added to the above mixture and the reaction was stirred at 0 °C for 2 hours. The mixture was quenched with water (10 mL) and extracted with ethyl acetate (8 mL× 2). The combined organic layers were were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to give a residue. The residue was purified by prep-HPLC [column: Water s Xbridge 150 × 25 mm × 5 μm; mobile phase:: water (10mM NH4HCO3)/ACN; B%: 56%-86%, 8 min]. The desired fraction was collected and lyophilized to afford the title compound (64 mg, 53.5% yield) as white solid; LCMS (ESI, M+1): m/z = 735.5.

[0000965] Step E. ((3S,7aR)-7a-(((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)hexahydro-

1H-pyrrolizin-3-yl)methyl dimethylcarbamate: To a solution of ((3S,7aR)-7a-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate (59 mg, 1.0 *equiv.*) in ACN (0.2 mL) was added HCl•dioxane (4 M, 20 *equiv.*) at 0 °C. The mixture was stirred at 0 °C for 0.5 hour. The mixture was concentrated in vacuum 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 neutralized with solid $NaHCO_3$, and concentrated in vacuum to remove acetonitrile. Then the mixture was diluted with ethyl acetate (20 mL× 2), dried over anhydrous sodium sulfate and concentrated in vacuum. Then the residue was purified by SFC (REGIS(S,S)WHELK-O1(250 mm × 25 mm, 10 μm); A: [0.1%NH_3H_2O ErOH]; B%: 50%-50%,4.0 min; 30 min). The desired fraction was collected and concentrated in vacuum to afford the title compound (19.9 mg, 16% yield) as a yellow solid; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.18 (s, 1H), 8.55 (s, 1H), 7.62 (dd, *J* = 6.0, 9.0 Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.22 (s, 1H), 7.04 (t, *J* = 2.6 Hz, 1H), 4.59 - 4.44 (m, 1H), 4.32 - 4.20 (m, 3H), 4.11 - 4.02 (m, 1H), 4.00 - 3.92 (m, 1H), 3.70 - 3.56 (m, 1H), 3.51 - 3.43 (m, 1H), 3.10 - 2.99 (m, 2H), 2.98 - 2.86 (m, 6H), 2.85 - 2.77 (m, 1H), 2.55 - 2.39 (m, 1H), 2.23 - 2.13 (m, 3H), 2.07 - 1.99 (m, 1H), 1.98 - 1.84 (m, 4H), 1.83 - 1.72 (m, 4H), 1.71 - 1.62 (m, 1H), 1.29 (d, *J* = 10.8 Hz, 3H), 0.81 (q, *J* = 7.2 Hz, 3H); ^{19}F NMR (400 MHz, DMSO, 273 K) δ = -122.415, -139.163; HPLC: >99% ee, Chiralcel ID-3 100 × 4.6 mm I.D., 3 μm column A: 20% (IPA/ACN = 4/1) (w/ 0.05% DEA), B: Heptane (0.05% DEA), 254 nm, t_R: 0.817 min; LCMS [ESI, M+1]: m/z =691.5.

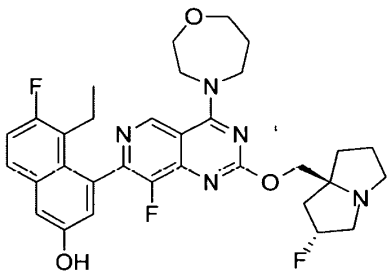
EXAMPLE 314



((3S,7aS)-7a-(((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)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate

[0000966] The title compound was synthesized according to the procedure described for example 313. ^{1}H NMR (400 MHz, METHANOL-d4) δ =9.24-9.19 (m, 1H), 7.71-7.65 (m, 1H), 7.32-7.29 (m, 1H), 7.28-7.22 (m, 1H), 7.07 (t, *J* = 2.4 Hz, 1H), 4.58-4.51 (m, 1H), 4.42-4.38 (m, 1H), 4.35-4.25 (m, 4H), 3.69-3.59 (m, 1H), 3.52-3.48 (m, 3H), 2.98-2.91 (m, 6H), 2.90-2.82 (m, 1H), 2.55-2.42 (m, 1H), 2.28-2.12 (m, 3H), 2.07-1.98 (m, 1H), 1.94-1.84 (m, 5H), 1.83-1.75 (m, 3H), 1.74-1.65 (m, 1H), 1.29 (d, *J* = 10.0 Hz, 3H), 0.86-0.77 (m, 3H); LCMS (ESI, M+1): m/z = 691.5.

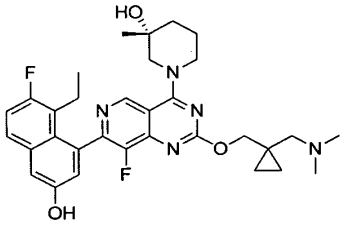
EXAMPLE 315



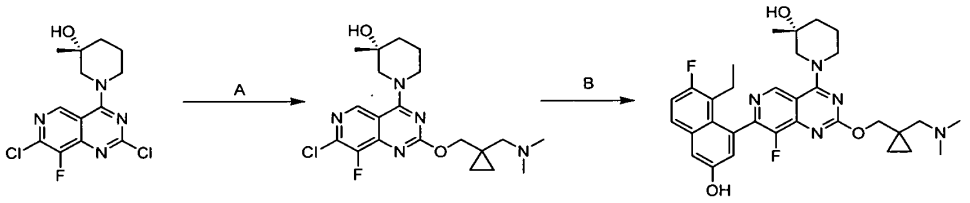
5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol

[0000967] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.19 (s, 1H), 7.69 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.32 (d, *J* = 2.8 Hz, 1H), 7.26 (t, *J* = 9.6 Hz, 1H), 7.06 (d, *J* = 2.8 Hz, 1H), 5.64-5.42 (m, 1H), 4.67-4.55 (m, 2H), 4.36-4.20 (m, 4H), 4.05 (t, *J* = 4.8 Hz, 2H), 3.98-3.71 (m, 5H), 3.44-3.34 (m, 1H), 2.72-2.50 (m, 2H), 2.50-2.33 (m, 2H), 2.32-2.24 (m, 2H), 2.23-2.05 (m, 4H), 0.80 (dt, *J* = 1.6, 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 594.3.

EXAMPLE 316



(R)-1-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

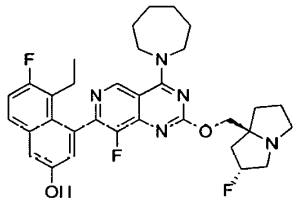


[0000968] Step A. (R)-1-(7-chloro-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (350 mg, 1.0 *equiv.*) and (1-((dimethylamino)methyl)cyclopropyl)methanol (205 mg, 1.5 *equiv.*) in DMF (4 mL) was added DIEA (410 mg, 3.0 *equiv.*) and 4Å molecular sieves (110 mg). The mixture was stirred at 40 °C for 12 hours. The mixture was filtered and purified by reversed phase flash chromatography [C18, water (0.1% formic acid) - ACN] to afford the title compound (360 mg, 80% yield) as a yellow solid; LCMS [ESI, M+1]: m/z = 424.2.

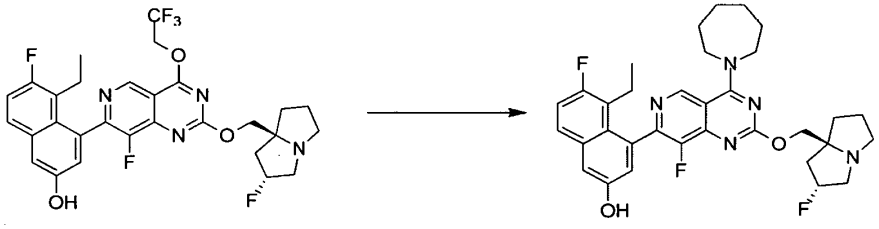
[0000969] Step B. (R)-1-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (R)-1-(7-chloro-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (50 mg, 1.0 *equiv.*), 5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (44.7 mg, 1.2 *equiv.*), K_3PO_4 (1.5 M, 236 μL, 3.0 *equiv.*) and CataCXium A Pd G3 (8.59 mg, 0.1 *equiv.*) in methoxycyclopentane (1 mL) was degassed and stirred at 90 °C for 2 hours under N_2 atmosphere. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (4 ×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by prep-HPLC [column: Water s Xbridge 150 × 25mm × 5 μm; mobile phase: water (10mM NH4HCO3)/ACN; B%: 44%-74%,

10min] to afford the title compound (24.6 mg, 36% yield) as a yellow solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.21 (s, 1H), 7.69-7.66 (m, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.27-7.22 (m, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 4.54-4.50 (m, 1H), 4.44-4.34 (m, 2H), 4.27 (t, *J* = 12.8 Hz, 1H), 3.70-3.55 (m, 1H), 3.52-3.40 (m, 1H), 2.62-2.41 (m, 3H), 2.36 (s, 6H), 2.25-2.10 (m, 2H), 1.93-1.71 (m, 3H), 1.29 (d, *J* = 10.4 Hz, 3H), 0.84-0.78 (m, 3H), 0.77-0.72 (m, 2H), 0.63-0.50 (m, 2H); LCMS [ESI, M+1]: m/z = 578.4.

EXAMPLE 317



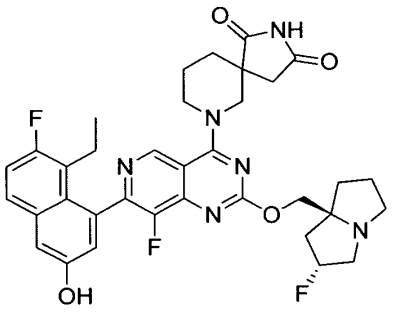
4-(4-(azepan-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol



[0000970] 4-(4-(azepan-1-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: To a solution of 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 (100 mg, 1.0 *equiv.*) and azepane (25.1 mg, 1.5 *equiv.*) in DMF (1 mL) were added DIEA (65.4 mg, 3 *equiv.*) and 4Å molecular sieves (30 mg). The mixture was stirred at 40 °C for 12 hours. The mixture was filtered and the filtrated was purified by prep-HPLC [column: Water s Xbridge 150 × 25 mm × 5 μm; mobile phase: [water (10mM NH_4HCO_3)/ACN] B%: 60%-90%, 10 min) to afford the tittle compound (49.1 mg, 47% yield) as a yellow solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.13 (s, 1H), 7.69-7.65 (m, 1H), 7.30 (d, *J* = 2.6 Hz, 1H), 7.24 (t, *J* = 9.6 Hz, 1H), 7.06 (d, *J* = 2.4 Hz,

1H), 5.40-5.20 (m, 1H), 4.35-4.21 (m, 2H), 4.17-4.03 (m, 4H), 3.30-3.20 (m, 2H), 3.20-3.13 (m, 1H), 3.05-2.95 (m, 1H), 2.52-2.46 (m, 1H), 2.38-2.10 (m, 4H), 2.08-1.95 (m, 6H), 1.93-1.82 (m, 1H), 1.73-1.71 (s, 4H), 0.82-0.78 (m, 3H); LCMS [ESI, M+1]: m/z = 592.3.

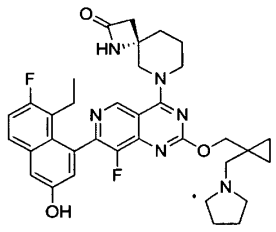
EXAMPLE 318



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]decane-1,3-dione

[0000971] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.10 (d, *J* = 1.6 Hz, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.06 (dd, *J* = 2.4, 4.8 Hz, 1H), 5.51 - 5.30 (m, 1H), 4.67 - 4.59 (m, 1H), 4.52 - 4.32 (m, 3H), 4.01 - 3.89 (m, 1H), 3.89 - 3.77 (m, 1H), 3.64 - 3.39 (m, 3H), 3.23 - 3.12 (m, 1H), 2.95 (dd, *J* = 14.4, 18.0 Hz, 1H), 2.67 (d, *J* = 18.0 Hz, 1H), 2.53 - 2.29 (m, 3H), 2.27 - 1.79 (m, 9H), 0.87 - 0.72 (m, 3H); LCMS [ESI, M+1]: m/z = 661.4.

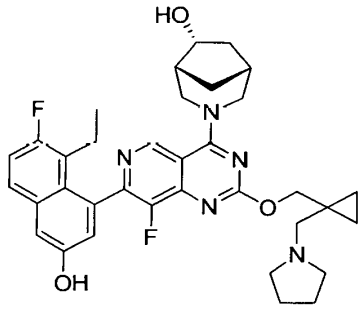
EXAMPLE 319



(S)-6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one

[0000972] The title compound was synthesized according to the procedure described for example 309 except for K_3PO_4 was used in step C instead of Cs_2CO_3. ^1H NMR (400 MHz, METHANOL-d_4) δ = 9.07 (s, 1H), 7.69-7.65 (m, 1H), 7.30 (d, J = 2.8 Hz, 1H), 7.25 (t, J = 12.4 Hz, 1H), 7.06-7.04 (m, 1H), 4.45-4.39 (m, 2H), 4.38-4.21 (m, 2H), 4.02-3.96 (m, 1H), 3.85-3.70 (m, 1H), 2.92-2.86 (m, 1H), 2.76-2.73 (m, 1H), 2.69-2.55 (m, 6H), 2.53-2.38 (m, 1H), 2.23-2.14 (m, 1H), 2.13-2.08 (m, 1H), 2.06-1.99 (m, 1H), 1.98-1.91 (m, 2H), 1.83-1.81 (m, 4H), 0.82-0.77 (m, 3H), 0.74-0.68 (m, 2H), 0.59-0.52 (m, 2H); LCMS [ESI, M+1]: m/z = 629.3.

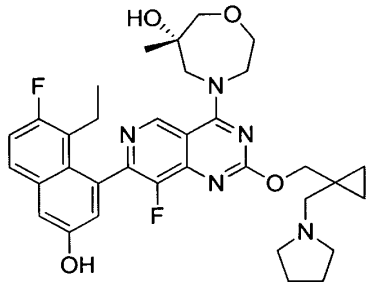
EXAMPLE 320



(1R,5R,6R)-3-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol

[0000973] The title compound was synthesized according to the procedure described for example 309. ^1H NMR (400 MHz, METHANOL-d_4) δ = 9.29 - 9.19 (m, 1H), 8.54 (s, 1H), 7.68 (dd, J = 6.0, 8.8 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.28 - 7.21 (m, 1H), 7.06 (dd, J = 2.4, 15.2 Hz, 1H), 4.98 (br d, J = 13.2 Hz, 1H), 4.82 - 4.68 (m, 1H), 4.51 - 4.37 (m, 2H), 4.36 - 4.27 (m, 1H), 3.85 - 3.71 (m, 1H), 3.55 - 3.38 (m, 1H), 3.23 - 2.95 (m, 6H), 2.56 - 2.35 (m, 2H), 2.31 - 2.11 (m, 3H), 2.04 - 1.88 (m, 5H), 1.82 (br s, 1H), 1.37 - 1.36 (m, 1H), 0.89 - 0.68 (m, 7H); LCMS [ESI, M+1]: 616.4.

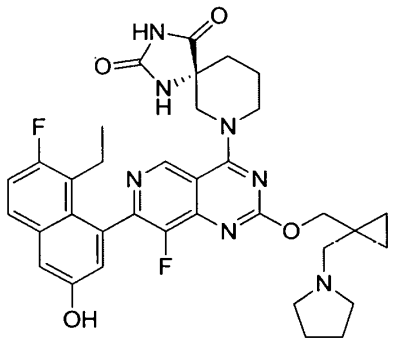
EXAMPLE 321



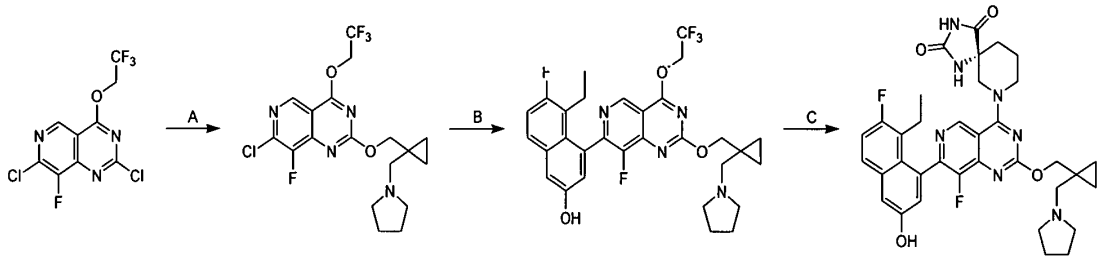
(S)-4-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol

[0000974] The title compound was synthesized according to the procedure described for example 309. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.59 (d, *J* = 5.6 Hz, 1H), 7.69 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.26 (t, *J* = 9.6 Hz, 1H), 7.06 (dd, *J* = 2.4, 14.2 Hz, 1H), 4.63-4.52 (m, 2H), 4.51-4.42 (m, 2H), 4.25-4.15 (m, 1H), 4.07-3.84 (m, 3H), 3.74-3.64 (m, 2H), 3.60-3.42 (m, 3H), 3.35 (s, 3H), 2.55-2.40 (m, 1H), 2.29-2.15 (m, 1H), 2.14-2.04 (m, 4H), 1.28 (d, *J* = 2.0 Hz, 3H), 0.98-0.85 (m, 4H), 0.84-0.76 (m, 3H); LCMS (ESI, M+1): m/z = 620.3.

EXAMPLE 322



(R)-7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione



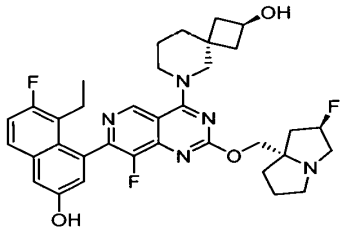
[0000975] Step A. 7-chloro-8-fluoro-2-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a suspension of 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (3.00 g, 1.0 *equiv.*) and 4Å molecular sieves (3.0 g) in THF (600 mL) was added a solution of [1-(pyrrolidin-1-ylmethyl)cyclopropyl]methanol (1.47 g, 1.0 *equiv.*) and DIEA (3.68 g, 3.0 *equiv.*) in THF (120 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour, then 20°C for 2 hours. The mixture was quenched by addition of brine (200 mL) and extracted with ethyl acetate (3 × 100 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 (260 mg, 12% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 435.0.

[0000976] Step B. 5-ethyl-6-fluoro-4-(8-fluoro-2-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)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-[[1-(pyrrolidin-1-ylmethyl)cyclopropyl]methoxy]-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (200 mg, 1.0 *equiv.*), 5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (218 mg, 1.5 *equiv.*) and Cs_2CO_3 (1.5 M, 920 µL, 3.0 *equiv.*) in methoxycyclopentane (3 mL) was added CataCXium A Pd G3 (33.5 mg, 0.10 *equiv.*). The reaction mixture was stirred at 90 °C for 3 hours. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 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 (160 mg, 57% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 589.2.

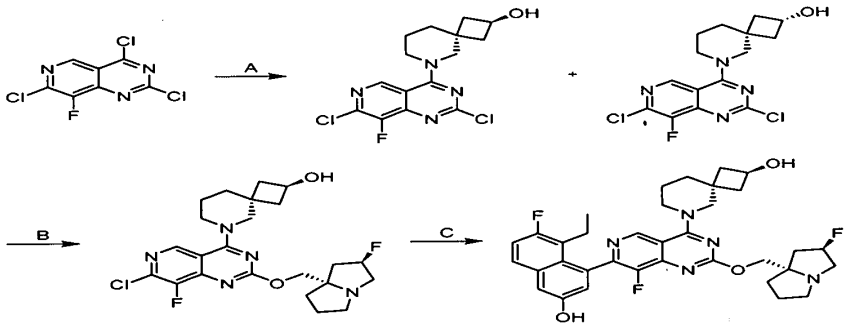
[0000977] Step C. (R)-7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((1-(pyrrolidin-1-ylmethyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione: To a solution of 5-ethyl-6-fluoro-4-[8-fluoro-2-[[1-(pyrrolidin-

1-ylmethyl)cyclopropyl]methoxy]-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl]naphthalen-2-ol (100 mg, 1.0 *equiv.*), (5R)-1,3,9-triazaspiro[4.5]decane-2,4-dione (57.5 mg, 2.0 *equiv.*) and 4Å molecular sieves (10 mg) in DMF (1 mL) was added DIEA (110 mg, 5.0 *equiv.*). The reaction was stirred at 40 °C for 12 hours. The residue was filtered and washed with DMF (1 mL), and purified by prep-HPLC [column: Phenomenex C18 75 × 30 mm × 3 μm; mobile phase: water (0.1% formic acid)/ACN; B%: 15% - 45% , 7min] and lyophilized to afford the title compound (47.9 mg, 43% yield) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d4) δ = 9.14 (d, *J* = 10.0 Hz, 1H), 7.69 (dd, *J* = 6.0, 8.4 Hz, 1H), 7.32 (t, *J* = 2.0 Hz, 1H), 7.26 (t, *J* = 9.6 Hz, 1H), 7.06 (dd, *J* = 2.8, 7.2 Hz, 1H), 4.60 (br t, *J* = 14.2 Hz, 3H), 4.50-4.29 (m, 3H), 3.91-3.80 (m, 1H), 3.80-3.56 (m, 1H), 3.30-3.25 (m, 2H), 3.20 (s, 2H), 2.57-2.29 (m, 1H), 2.29-2.10 (m, 2H), 2.10-1.98 (m, 5H), 1.97 (br d, *J* = 3.6 Hz, 2H), 0.95-0.84 (m, 2H), 0.83-0.69 (m, 5H); LCMS (ESI, M+1): m/z = 658.3.

EXAMPLE 323



trans-(2R,4r)-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-azaspiro[3.5]nonan-2-ol



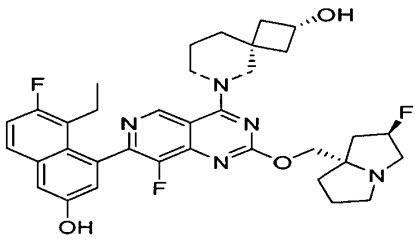
[0000978] Step A. 6-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol: To a solution of 2,4,7-trichloro-8-fluoro-pyrido[4,3-d]pyrimidine (2.0 g, 1.0 *equiv.*) in DCM (50 mL) was added DIEA (5.12 g, 6.90 mL, 5.0 *equiv.*) and 6-azaspiro[3.5]nonan-2-ol (1.13 g, 0.8 *equiv.*, HCl). The reaction was stirred at -40 °C for 0.5 hour. The mixture was diluted with water (20 mL) and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 × 10 mL). Combined the organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 50:1 to 1:1). The product was further purified by chiral SFC separation (DAICEL CHIRALPAK AY-H (250 mm × 30 mm, 10 μm); mobile phase: [0.1% NH3•H2O EtOH]; B%: 60%-60%, 8.5; 80 min) to afford (2s,4r)-6-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (trans product) as the first eluting peak (650 mg) as a yellow solid; ^{1}H NMR (400 MHz, dimethylsulfoxide-d6) δ 8.98 (s, 1H), 5.07 - 4.99 (d, J = 6.2 Hz, 1H), 4.16 - 4.05 (m, 1H), 3.87 - 3.94 (m, 4H), 2.20 - 2.10 (m, 2H), 1.74 - 1.62 (m, 4H), 1.58 - 1.50 (m, 2H); LCMS [ESI, M+1]: 357.0. The product was purified by SFC separation (DAICEL CHIRALPAK AY-H (250 mm × 30 mm, 10 μm); mobile phase: [0.1% NH3•H2O EtOH]; B%: 60%-60%, 8.5; 80 min) to afford the (2r,4s)-6-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol, (cis product) as the second eluting peak (650 mg) as a yellow solid; ^{1}H NMR (400 MHz, dimethylsulfoxide-d6) δ 9.03 (s, 1H), 4.97 (d, J = 6.4 Hz, 1H), 4.12 - 4.02 (m, 1H), 3.94 (s, 2H), 3.90 - 3.85 (m, 2H), 2.08 - 1.99 (m, 2H), 1.74 - 1.67 (br s, 4H), 1.65 - 1.59 (m, 2H); LCMS [ESI, M+1]: m/z = 357.1.

[0000979] Step B. (2R,4r)-6-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol: To a solution of (2s,4r)-6-(2,7-dichloro-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl)-6- azaspiro[3.5]nonan-2-ol (100 mg, 1.0 *equiv.*) in dioxane (2.0 mL) was added DIEA (108 mg, 146 μL, 3.0 *equiv.*) and ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (66.8 mg, 1.5 *equiv.*). The reaction was stirred at 90 °C for 16 hours. The mixture was concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and neutralized with solid $NaHCO_3$, concentrated in vacuum to remove ACN. The aqueous phase was extracted with ethyl acetate (2 × 6.0 mL). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford the title compound (100 mg, 71% yield) as a yellow solid; ^{1}H NMR (400 MHz, chloroform-d) δ 8.73

(s, 1H), 5.44 - 5.21 (m, 1H), 4.43 (quin, J = 7.2 Hz, 1H), 4.38 - 4.27 (m, 2H), 3.86 - 3.80 (m, 4H), 3.48 - 3.21 (m, 3H), 3.08 - 2.97 (m, 1H), 2.38 - 2.27 (m, 4H), 2.26 - 2.19 (m, 2H), 2.03 - 1.94 (m, 3H), 1.81 - 1.72 (m, 5H); LCMS [ESI, M+1]: m/z = 480.3.

[0000980] Step C. trans-(2R,4r)-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-azaspiro[3.5]nonan-2-ol: A mixture of (2R,4r)-6-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol (60 mg, 1.0 *equiv.*), 5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (47.4 mg, 1.2 *equiv.*), K_3PO_4 (1.5 M, 250 µL, 3.0 *equiv.*) and cataCXium-A-Pd-G3 (9.10 mg, 0.1 *equiv.*) in THF (1.5 mL) was degassed and purged with N_2 for 3 times, and then the reaction was stirred at 60 °C for 2 hours under N_2 atmosphere. The mixture was diluted with water (2.0 mL) and extracted with ethyl acetate (3 × 2.0 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and concentrated in vacuum to remove ACN. The aqueous layers was lyophilized. The residue was purified by prep-HPLC [Unisil 3-100 C18 Ultra 150 × 50 mm × 3 µm; mobile phase: water (0.1% formic acid)/ACN, B%: 14%-44% over 15 min]. The desired fractions were collected and lyophilized to afford the title compound (9.89 mg, 11% yield, 0.62FORMIC ACID) as a white solid; ^{1}H NMR (400 MHz, methanol-d4) δ 9.07 (s, 1H), 7.72 - 7.72 (m, 1H), 7.31 (d, J = 2.8 Hz, 1H), 7.29 - 7.22 (m, 1H), 7.07 (d, J = 2.4 Hz, 1H), 5.49 - 5.30 (m, 1H), 4.49 - 4.43 (m, 1H), 4.42 - 4.37 (m, 1H), 4.32 - 4.24 (m, 1H), 4.18 - 4.08 (m, 2H), 4.03 - 3.86 (m, 2H), 3.59 - 3.38 (m, 3H), 3.21 - 3.10 (m, 1H), 2.53 - 2.46 (m, 1H), 2.44 - 2.29 (m, 3H), 2.28 - 2.19 (m, 2H), 2.18 - 2.07 (m, 3H), 2.05 - 1.95 (m, 1H), 1.86 - 1.78 (m, 4H), 1.74 - 1.65 (m, 2H), 0.84 - 0.77 (m, 3H); LCMS [ESI, M+1]: m/z = 634.4.

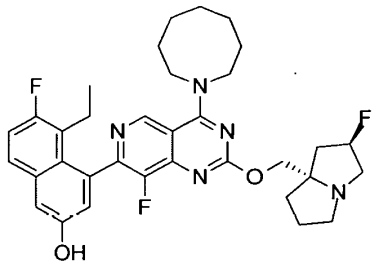
EXAMPLE 324



cis-(2S,4s)-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-azaspiro[3.5]nonan-2-ol

[0000981] The title compound was synthesized according to the procedure described for example 323 except using second eluting peak from chiral SFC separation (step A) in further steps B and C. ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.06 (s, 1H), 7.67 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 5.40-5.22 (m, 1H), 4.36-4.20 (m, 3H), 4.12-3.91 (m, 4H), 3.30-3.11 (m, 3H), 3.06-2.96 (m, 1H), 2.55-2.42 (m, 1H), 2.38-2.11 (m, 6H), 2.04-1.88 (m, 3H), 1.86-1.72 (m, 6H), 0.81 (br t, *J* = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, methanol-d4) δ = -121.085, -138.973, -173.678; SFC: >99% ee, Chiralpak IF-3 50 × 4.6 mm I.D., 3 μm column, A: CO_2, B: 30% MeOH (w/0.05% DEA), 3 mL/min, 220 nm, t_R: 3.449 min; LCMS (ESI, M+1): m/z = 634.3.

EXAMPLE 325

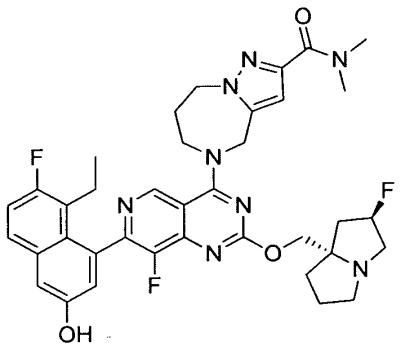


4-(4-(azocan-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol

[0000982] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ = 9.96 - 9.90 (m, 1H), 9.16 - 9.08 (m, 1H), 7.76

(dd, J = 6.0, 9.1 Hz, 1H), 7.39 - 7.29 (m, 2H), 7.03 (d, J = 2.4 Hz, 1H), 5.42 - 5.18 (m, 1H), 4.23 - 3.95 (m, 6H), 3.18 - 3.01 (m, 3H), 2.90 - 2.80 (m, 1H), 2.43 - 2.34 (m, 1H), 2.21 - 2.05 (m, 3H), 2.04 - 1.85 (m, 6H), 1.84 - 1.75 (m, 2H), 1.62 (br d, J = 5.2 Hz, 4H), 1.57 - 1.47 (m, 2H), 0.77 - 0.67 (m, 3H); LCMS (ESI, M+1): m/z = 606.4.

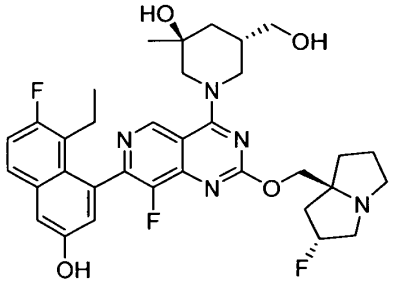
EXAMPLE 326



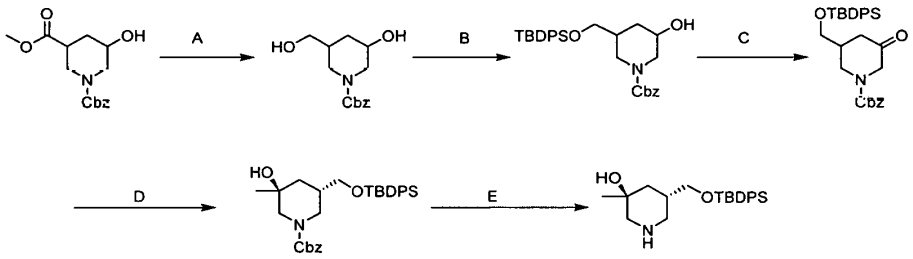
5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

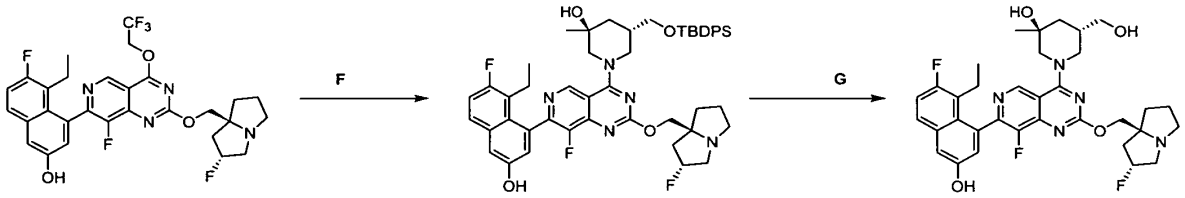
[0000983] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.21 (s, 1H), 7.68 (dd, J = 5.6, 9.2 Hz, 1H), 7.31 (d, J = 2.8 Hz, 1H), 7.25 (t, J = 9.6 Hz, 1H), 7.05 (d, J = 2.8 Hz, 1H), 6.76 (s, 1H), 5.50-5.19 (m, 3H), 4.66-4.52 (m, 4H), 4.52-4.33 (m, 4H), 3.52-3.43 (m, 2H), 3.34 (s, 3H), 3.23-3.13 (m, 1H), 3.08 (s, 3H), 2.52-2.42 (m, 3H), 2.36 (br dd, J = 9.2, 14.0 Hz, 1H), 2.31-2.21 (m, 1H), 2.20-2.07 (m, 3H), 2.06-1.93 (m, 1H), 0.90-0.67 (m, 3H); LCMS (ESI, M+1): m/z = 701.3.

EXAMPLE 327



(3RS,5RS)-1-(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)-5-(hydroxymethyl)-3-methylpiperidin-3-ol





[0000984] Step A. benzyl 3-hydroxy-5-(hydroxymethyl)piperidine-1-carboxylate: To a solution of 1-benzyl 3-methyl 5-hydroxypiperidine-1,3-dicarboxylate (5.00 g, 1.0 *equiv.*) in THF (100 mL) was added $LiAlH_4$ (970 mg, 1.5 *equiv.*) under N_2 at - 40 °C. The reaction was stirred at - 40 °C for 0.5 hour. The reaction mixture was quenched with water (970.5 mg), 15 % NaOH aqueous (970.5 mg), and water (3 × 970.5 mg) at 0 °C sequentially, then filtered. The filter cake was washed with ethyl acetate (2 × 25 mL), the filtrate was concentrated to give title compound (4.41 g, crude) as a colorless oil; LCMS (ESI, M+1): m/z = 266.2.

[0000985] Step B. benzyl 3-(((tert-butyldiphenylsilyl)oxy)methyl)-5-hydroxypiperidine-1-carboxylate: To a solution of benzyl 3-hydroxy-5-(hydroxymethyl)piperidine-1-carboxylate (4.41

g, 1.0 *equiv.*) in DCM (45 mL) was added imidazole (2.26 g, 2.0 *equiv.*) and TBDPSCl (5.48 g, 1.2 *equiv.*) at 0 °C. The reaction mixture was stirred at 25 °C for 1 hour. The mixture was quenched by addition of water (50 mL), and extracted with DCM (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) to give title compound (4.50 g, 52% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 504.4.

[0000986] Step C. benzyl 3-(((tert-butyldiphenylsilyl)oxy)methyl)-5-oxopiperidine-1-carboxylate: To a solution of benzyl 3-(((tert-butyldiphenylsilyl)oxy)methyl)-5-hydroxypiperidine-1-carboxylate (4.50 g, 1.0 *equiv.*) in DCM (50 mL) was added Dess-Martin reagent (7.58 g, 2.0 *equiv.*). The reaction mixture was stirred at 25 °C for 12 hours. The reaction mixture was quenched by addition of saturated sodium sulfite solution (300 mL) and filtered, then extracted with DCM (150 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (Silica gel, Petroleum ether/Ethyl acetate 20:1 to 3:1) to give the title compound (2.90 g, 64% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 502.1.

[0000987] Step D. (3RS,5RS)-benzyl 5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-hydroxy-3-methylpiperidine-1-carboxylate: To a solution of benzyl 3-(((tert-butyldiphenylsilyl)oxy)methyl)-5-oxopiperidine-1-carboxylate (2.90 g, 1.0 *equiv.*) in THF (20 mL) was added MeMgBr (3 M, 1.2 *equiv.*) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 hour. The reaction mixture was quenched by addition of water (20 mL) at 0 °C, extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated and purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) and then column chromatography (Silica gel, Petroleum ether/Ethyl acetate 20:1 to 1:1) to produce a yellow oil, which was further separated by SFC (column: DAICEL CHIRALPAK IC (250 mm × 30 mm, 5 μm); mobile phase: [0.1% NH_3H_2O IPA]; B%: 35% - 35%, 4.2; 60 min) and (column: REGIS(S,S)WHELK-O1 (250 mm × 25 mm, 10 μm); mobile phase: [0.1% NH_3H_2O IPA]; B%: 30% - 30%, 7.4; 50 min) to give the title compound (30.0 mg, 1% yield) as a yellow oil; LCMS (ESI, M+23): m/z = 540.4.

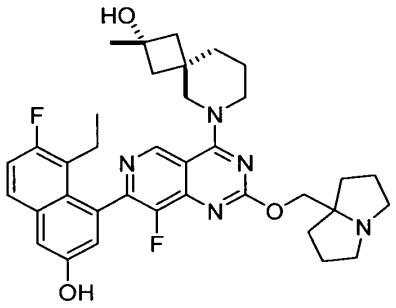
[0000988] Step E. (3S,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-methylpiperidin-3-ol: To a suspension of Pd/C (80 mg, 10% purity) in MeOH (1 mL) was added (3RS,5RS)-5-(((tert-

butyldiphenylsilyl)oxy)methyl)-3-methylpiperidin-3-ol (30 mg, 57.95 μmol, 1.0 *equiv.*) under N_2. The suspension was degassed in vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25 °C for 2 hours. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure to give the title compound (15 mg, crude) as a white solid.

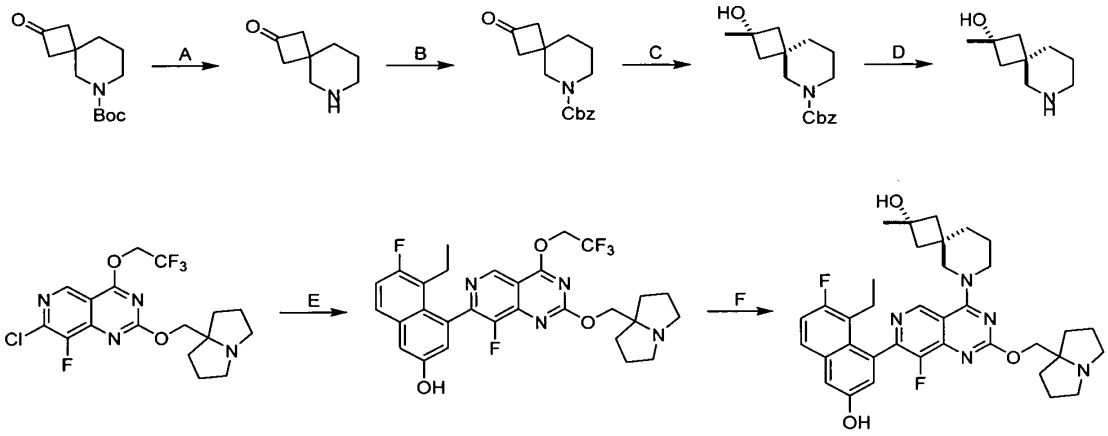
[0000989] Step F. (3S,5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol (20.0 mg, 1.0 *equiv.*), (3RS,5RS)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3-methylpiperidin-3-ol (12.9 mg, 1 *equiv.*), 4Å molecular sieves (10 mg) in DMF (0.5 mL) was added DIEA (4.36 mg, 1.0 *equiv.*). The mixture was stirred at 40 °C for 2 hours. The reaction mixture was filtered to give a solution which was purified by reversed-phase flash chromatography (C18, water (0.1 % formic acid)/ACN) to give the title compound (20.0 mg, 53% yield) as a yellow solid. LCMS (ESI, M+1): m/z = 876.2.

[0000990] Step G. (3RS,5RS)-1-(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)-5-(hydroxymethyl)-3-methylpiperidin-3-ol: To a solution of (3RS,5RS)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-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 (20 mg, 1.0 *equiv.*) in DMF (0.5 mL) was added CsF (34.7 mg, 10 *equiv.*). The reaction was stirred at 25 °C for 2 hours. The reaction mixture was filtered to give a solution which was purified by prep-HPLC (column: Phenomenex Luna C18 150 × 25 mm × 10 μm; mobile phase: water (0.1% formic acid)/ACN, B%: 10% - 40%, 10 min) and lyophilized to afford the title compound (6.56 mg, 43% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d4): δ = 9.27 (s, 1H), 8.51 (s, 1H), 7.68 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.06 (dd, *J* = 2.4, 8.0 Hz, 1H), 5.50 - 5.33 (m, 1H), 4.68 - 4.56 (m, 2H), 4.53 - 4.39 (m, 2H), 3.65 - 3.44 (m, 5H), 3.43 - 3.34 (m, 1H), 3.22 - 2.87 (m, 2H), 2.54 - 2.33 (m, 4H), 2.29 - 2.09 (m, 4H), 2.05 - 1.80 (m, 2H), 1.46 (dt, *J* = 5.2, 13.2 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 3H), 0.86 - 0.76 (m, 3H); LCMS (ESI, M+1): m/z = 638.4.

EXAMPLE 328



trans-6-(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)-2-methyl-6-azaspiro[3.5]nonan-2-ol



[0000991] Step A. 6-azaspiro[3.5]nonan-2-one: To a solution of tert-butyl 2-oxo-6-azaspiro[3.5]nonane-6-carboxylate (1.00 g, 1.0 *equiv.*) in MeCN (5 mL) was added HCl•dioxane (4 M, 9.57 *equiv.*). The mixture was stirred at 25 °C for 0.5 hour. The mixture was concentrated in vacuum to afford the title compound (734 mg, crude, HCl salt) as a yellow oil.

[0000992] Step B. benzyl 2-oxo-6-azaspiro[3.5]nonane-6-carboxylate: To a mixture of 6-azaspiro[3.5]nonan-2-one (3.67 g, 1.0 *equiv.*, HCl) in ethyl acetate (50 mL) was added TEA (10.6 g, 5.0 *equiv.*) and CbzCl (5.35 g, 1.5 *equiv.*) at 25 °C. The mixture was stirred at 25 °C for 12 hours. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 60 mL). The combined organic layers were dried over 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 (4.70 g, 81% yield over two steps) as a yellow oil; ^{1}H NMR (400 MHz, chloroform-*d*) δ = 7.40-7.29 (m, 5H), 5.14 (s, 2H), 3.60-3.45 (m, 4H), 2.97-2.75 (m, 2H), 2.74-2.65 (m, 2H), 1.82-1.74 (m, 2H), 1.61 (br s, 2H); LCMS (ESI, M+1): m/z = 274.1.

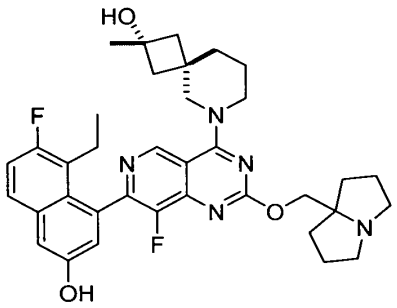
[0000993] Step C. trans-benzyl 2-hydroxy-2-methyl-6-azaspiro[3.5]nonane-6-carboxylate: To a solution of benzyl 2-oxo-6-azaspiro[3.5]nonane-6-carboxylate (500 mg, 1.0 *equiv.*) in acetonitrile (10 mL) was added MeMgBr (3 M, 1.22 mL, 2.0 *equiv.*) at 0 °C. The reaction was stirred at 0 °C for 0.5 hours. The mixture was quenched by addition of water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by reversed phase flash chromatography (water (0.1% formic acid)-ACN), and stereoisomers were further separated by SFC (column: daicel chiralpak IG 250 mm × 30 mm × 10 μm; mobile phase: 0.1% NH3•H2O in IPA – CO_2, 40%, 2.6 min over 40 min) to afford the title compound (100 mg, 19% yield) as a colorless oil; LCMS (ESI, M+1): m/z = 290.2.

[0000994] Step D. trans-2-methyl-6-azaspiro[3.5]nonan-2-ol: To a solution of trans-benzyl 2-hydroxy-2-methyl-6-azaspiro[3.5]nonane-6-carboxylate (100 mg, 1.0 *equiv.*) in MeOH (5 mL) was added $Pd(OH)_2$/C (20.0 mg, 20% purity) under N_2. The mixture was degassed and purged with H_2 for 3 times, and then stirred at 25 °C for 0.5 hours under H_2 (15 psi). The mixture was filtered and the filtrate was concentrated to afford the title compound (60.0 mg, crude) as a colorless oil.

[0000995] Step E. 5-ethyl-6-fluoro-4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-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 (420 mg, 1.0 *equiv.*), 5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (410 mg, 1.3 *equiv.*), CataCXium A Pd G3 (145 mg, 0.2 *equiv.*) and Cs_2CO_3 (1.5 M, 2.00 mL, 3.0 *equiv.*) in methoxycyclopentane (15 mL) were degassed and stirred at 100 °C for 3 hours under N_2 atmosphere. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over 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 (210 mg, 32% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 575.3.

[0000996] Step F. trans-6-(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)-2-methyl-6-azaspiro[3.5]nonan-2-ol: To a solution of 5-ethyl-6-fluoro-4-(8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol (100 mg, 1.0 *equiv.*) and trans-2-methyl-6-azaspiro[3.5]nonan-2-ol (54.0 mg, 2.0 *equiv.*) in DMF (2 mL) was added 4 Å molecular sieves (20 mg) and DIEA (67.5 mg, 3.0 *equiv.*). The mixture was stirred at 40 °C for 14 hours. The mixture was filtered and the filtrate was purified by prep-HPLC (column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: water (10mM NH4HCO3)-ACN, B%: 48%-78%, 10 min) to afford the title compound (35.7 mg, 31% yield) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.05 (s, 1H), 7.68 (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 (d, J = 2.4 Hz, 1H), 4.34-4.26 (m, 2H), 4.21-4.11 (m, 2H), 3.99 (d, J = 12.8 Hz, 1H), 3.90-3.78 (m, 1H), 3.17-3.06 (m, 2H), 2.57-2.43 (m, 1H), 2.20-2.02 (m, 4H), 1.98-1.86 (m, 9H), 1.86-1.73 (m, 4H), 1.36 (s, 3H), 0.81 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 630.5.

EXAMPLE 329

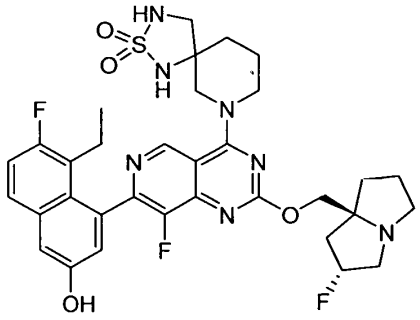


cis-6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-methyl-6-azaspiro[3.5]nonan-2-ol

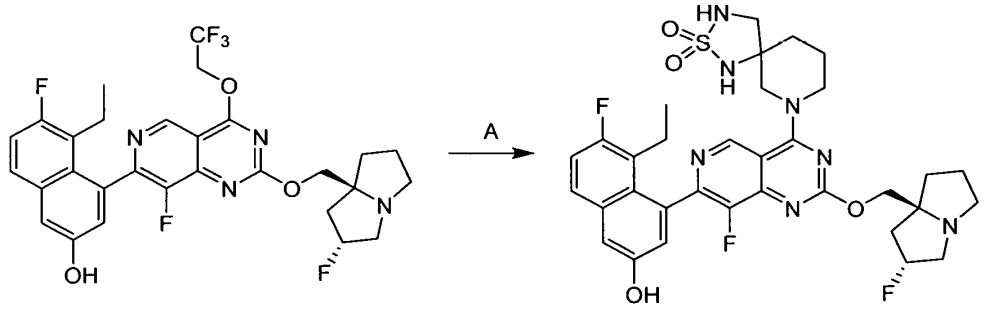
[0000997] The title compound was synthesized according to the procedure described for example 328 except for using the other eluting peak from SFC separation in step C in further steps D and F. ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.09 (s, 1H), 7.67 (dd, J = 6.0, 9.2 Hz, 1H), 7.30 (d, J = 2.8 Hz, 1H), 7.24 (t, J = 9.6 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 4.31 (s, 2H), 4.22-4.12 (m, 2H), 4.07-3.91 (m, 2H), 3.17-3.04 (m, 2H), 2.81-2.69 (m, 2H), 2.55-2.40 (m, 1H), 2.27-2.03 (m,

3H), 2.02-1.86 (m, 8H), 1.86-1.71 (m, 6H), 1.33 (s, 3H), 0.81 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 630.5.

EXAMPLE 330



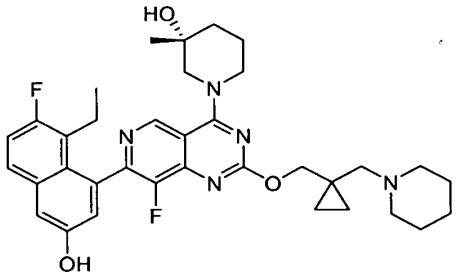
7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide



[0000998] Step A. 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-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide: To a mixture of 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 (50.0 mg, 1.0 *equiv.*), 2λ^6-thia-1,3,9-triazaspiro[4.5]decane 2,2-dioxide (32.3 mg, 2.0 *equiv.*) and 4Å molecular sieves (10 mg, 1.0 *equiv.*) in DMF (0.5 mL) was added DIEA (32.7 mg, 3.0 *equiv.*). The reaction was stirred at 40 °C for 12 hours. The residue was filtered and washed with DMF (1 mL). The filtrate was purified by prep-HPLC [column: Phenomenex C18 75 × 30 mm × 3 μm; mobile phase: water (0.1% formic acid)/ACN] B%: 15% -

45%, 7min] and lyophilized to afford the title compound (26.4 mg, 45% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d4) δ = 9.14 (s, 1H), 7.68 (ddd, *J* = 3.2, 5.6, 9.2 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 1H), 7.26 (dt, *J* = 1.6, 9.6 Hz, 1H), 7.04 (t, *J* = 3.2 Hz, 1H), 5.62-5.38 (m, 1H), 4.79-4.61 (m, 3H), 4.59-4.42 (m, 2H), 3.88-3.74 (m, 2H), 3.74-3.60 (m, 3H), 3.41 (td, *J* = 2.4, 12.0 Hz, 1H), 3.22 (dd, *J* = 1.6, 12.4 Hz, 1H), 2.71-2.49 (m, 2H), 2.48-2.30 (m, 2H), 2.28-2.15 (m, 3H), 2.15-2.00 (m, 3H), 2.00-1.81 (m, 2H), 0.80 (t, *J* = 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 684.4.

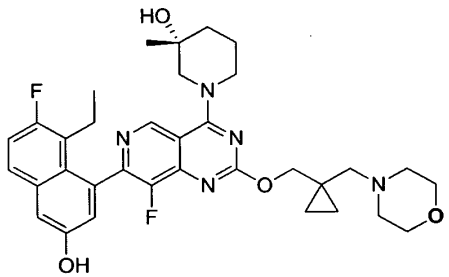
EXAMPLE 331



(R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((1-(piperidin-1-ylmethyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

[0000999] The title compound was synthesized according to the procedure described for example 309. ^{1}H NMR (400 MHz, chloroform-*d*) δ = 9.22 (s, 1H), 8.54 (s, 1H), 7.65 (s, 1H), 7.31 (s, 1H), 7.29 - 7.22 (m, 1H), 7.03 (br d, *J* = 1.2 Hz, 1H), 4.55 (br d, *J* = 13.2 Hz, 1H), 4.48-4.41 (m, 2H), 4.35-4.25 (m, 1H), 3.69-3.57 (m, 1H), 3.50-3.41 (m, 2H), 3.13-2.79 (m, 5H), 2.55-2.38 (m, 1H), 2.26-2.12 (m, 2H), 1.86-1.75 (m, 6H), 1.66-1.53 (m, 2H), 1.29 (d, *J* = 10.4 Hz, 3H), 0.89-0.78 (m, 5H), 0.75-0.66 (m, 2H); LCMS [ESI, M + 1] m/z = 618.4.

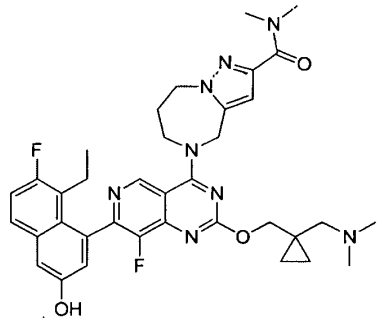
EXAMPLE 332



(R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((1-(morpholinomethyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

[00001000] The title compound was synthesized according to the procedure described for example 309. ^{1}H NMR (400 MHz, METHANOL-*d*4) δ =9.25 (s, 1H), 8.59-8.47 (m, 1H), 7.74-7.66 (m, 1H), 7.36-7.22 (m, 2H), 7.08 (br d, *J* = 19.1 Hz, 1H), 4.41 (s, 3H), 4.33-4.23 (m, 1H), 3.72-3.61 (m, 5H), 3.53-3.46 (m, 1H), 2.62-2.52 (m, 4H), 2.51-2.43 (m, 3H), 2.29-2.12 (m, 2H), 1.96-1.72 (m, 3H), 1.33-1.29 (m, 3H), 0.89-0.79 (m, 3H), 0.78-0.71 (m, 2H), 0.47 (s, 2H); LCMS [ESI, M + 1] : m/z = 620.1.

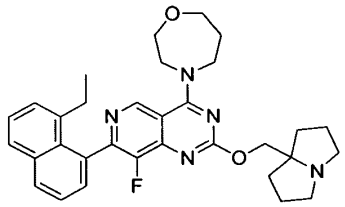
EXAMPLE 333



5-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

[00001001] The title compound was synthesized according to the procedure described for example 319. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.16 (s, 1H), 7.67 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.29 (d, *J* = 2.8 Hz, 1H), 7.24 (t, *J* = 9.2 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.72 (s, 1H), 5.37-5.17 (m, 2H), 4.58-4.54 (m, 2H), 4.48-4.32 (m, 4H), 3.33 (s, 3H), 3.13-3.02 (m, 3H), 2.50-2.37 (m, 5H), 2.31 (s, 6H), 2.21-2.11 (m, 1H), 0.78 (t, *J* = 7.2 Hz, 3H), 0.75-0.70 (m, 2H), 0.56-0.51 (m, 2H); LCMS (ESI, M+1): m/z = 671.1.

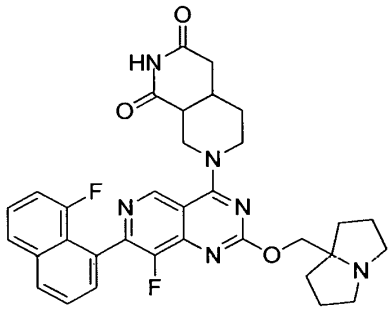
EXAMPLE 334



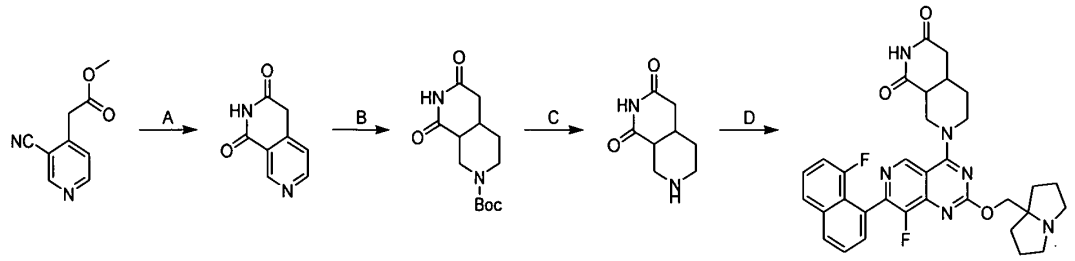
4-(7-(8-ethylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,4-oxazepane

[00001002] The title compound was synthesized according to the procedure described for example 204. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.19-9.15 (m, 1H), 8.09-8.04 (m, 1H), 7.91-7.85 (m, 1H), 7.62-7.55 (m, 1H), 7.53-7.39 (m, 3H), 4.40-4.34 (m, 2H), 4.33-4.23 (m, 4H), 4.11-4.04 (m, 2H), 3.92-3.84 (m, 2H), 3.27-3.17 (m, 2H), 2.89-2.80 (m, 2H), 2.51-2.31 (m, 2H), 2.27-2.19 (m, 2H), 2.18-2.09 (m, 2H), 2.05-1.90 (m, 4H), 1.88-1.79 (m, 2H), 1.00-0.91 (m, 3H); LCMS (ESI, M+1): m/z = 542.2.

EXAMPLE 335



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



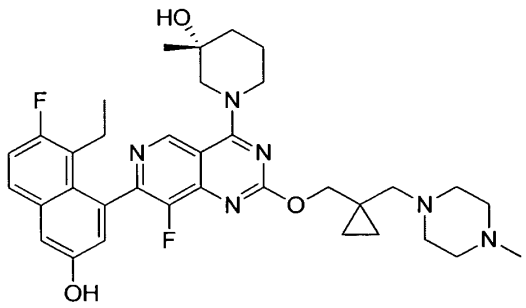
[00001003] Step A. 4H-2,7-naphthyridine-1,3-dione: A mixture of methyl 2-(3-cyano-4-pyridyl)acetate (500 mg, 1.0 equiv.), (1E)-acetaldehyde oxime (838 mg, 5.0 equiv.) and $RhCl(PPh_3)_3$ (263 mg, 0.1 equiv.) in toluene (15 mL) was degassed and stirred at 110 °C for 2 hours under N_2 atmosphere. The mixture was concentrated under reduced pressure and then diluted with water (20 mL). The mixture was refluxed at 100°C for 1 hour. After cooling to 20 °C, the mixture was filtered. The filter cake was triturated with EtOAc (10 mL) and MeOH (10 mL) to afford the title compound (300 mg, 52.2% yield) as a white solid; ^1H NMR (400 MHz, DMSO-d_6) δ = 12.41-11.59 (m, 1H), 10.52 (br s, 1H), 8.19 (s, 1H), 7.36 (br d, J = 7.2 Hz, 1H), 6.66 (br d, J = 7.2 Hz, 1H), 5.14 (s, 1H) LCMS (ESI, M+1): m/z = 163.0.

[00001004] Step B. tert-butyl 6,8-dioxooctahydro-2,7-naphthyridine-2(1H)-carboxylate: A mixture of 4H-2,7-naphthyridine-1,3-dione (400 mg, 1.0 equiv.), Boc_2O (1.62 g, 3.0 equiv.) and Pd/C (50 mg, 10% purity) in MeOH (10 mL) was degassed and purged with H_2 for 3 times before being stirred at 60 °C for 6 hours under H_2 atmosphere (1 atm). The mixture was filtered and concentrated under reduced pressure to afford the title compound (400 mg, crude) as a green oil; LCMS (ESI, M+1): m/z = 269.0.

[00001005] Step C. hexahydro-2,7-naphthyridine-1,3(2H,4H)-dione: A mixture of tert-butyl 6,8-dioxo-1,3,4,4a,5,8a-hexahydro-2,7-naphthyridine-2-carboxylate (400 mg, 1.0 equiv.) in DCM (3 mL) and TFA (1 mL) was stirred at 25 °C for 2 hours under N_2 atmosphere. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [column: Waters Atlantis T3 150 × 30 mm × 5 μm; mobile phase: mobile phase: water (0.1% formic acid)/ACN; B%: 1%-20%, 10 min] to afford the title compound (100 mg, 25% yield) as a green oil; ^1H NMR (400 MHz, METHANOL-d4) δ = 4.06-3.93 (m, 1H), 3.51-3.33 (m, 1H), 3.23-3.16 (m, 1H), 3.12-2.90 (m, 2H), 2.80-2.64 (m, 1H), 2.62-2.35 (m, 2H), 2.11-1.83 (m, 1H), 1.70-1.48 (m, 1H); LCMS (ESI, M+1): m/z = 169.2.

[00001006] Step D. 7-(8-fluoro-7-(8-fluoronaphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)hexahydro-2,7-naphthyridine-1,3(2H,4H)-dione: A mixture of 4a,5,6,7,8,8a-hexahydro-4H-2,7-naphthyridine-1,3-dione (63.0 mg, 2.0 equiv.), 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, 1.0 equiv.), DIEA (243 mg, 10.0 equiv.) and 4Å molecular sieves (10 mg) in DMF (0.01 mL) was stirred at 40 °C for 48 hours under N_2 atmosphere. The mixture was filtered. The residue was purified by *prep*-HPLC (neutral condition) to afford the title compound (6.2 mg, 5.3% yield) as an off-white solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.13 (s, 1H), 8.54 (s, 1H), 8.13 (br d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.76-7.67 (m, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.54 (dt, *J* = 5.2, 7.8 Hz, 1H), 7.20 (dd, *J* = 8.2, 13.2 Hz, 1H), 5.24 (br d, *J* = 14.0 Hz, 1H), 4.84-4.79 (m, 1H), 4.59 (s, 2H), 3.61-3.42 (m, 3H), 3.40-3.33 (m, 1H), 3.22-3.10 (m, 2H), 2.84-2.66 (m, 2H), 2.55-2.44 (m, 1H), 2.41-2.23 (m, 3H), 2.22-2.11 (m, 3H), 2.10-1.98 (m, 4H), 1.76-1.53 (m, 1H); LCMS (ESI, M+1): m/z = 599.4.

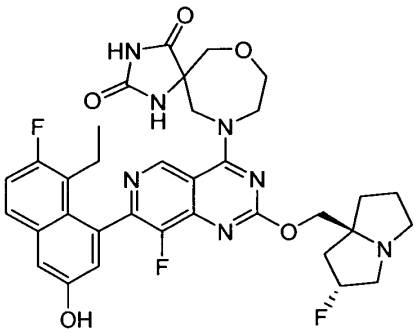
EXAMPLE 336



(R)-1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-((1-((4-methylpiperazin-1-yl)methyl)cyclopropyl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

[00001007] The title compound was synthesized according to the procedure described for example 309. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.20 (d, *J* = 4.0 Hz, 1H), 7.68 (dd, *J* = 8.8, 6.0 Hz, 1H), 7.32-7.30 (m, 1H), 7.25 (t, *J* = 9.6 Hz, 1H), 7.09-7.01 (m, 1H), 4.56-4.38 (m, 3H), 4.29-4.26 (m, 1H), 3.68-3.60 (m, 1H), 3.51-3.40 (m, 1H), 3.10-2.38 (m, 14H), 2.27-2.08 (m, 2H), 1.91-1.71 (m, 3H), 1.31-1.26 (m, 3H), 0.85-0.81 (m, 3H), 0.79-0.76 (m, 2H), 0.55-0.53 (m, 2H); LCMS (ESI, M+1): m/z = 633.5;

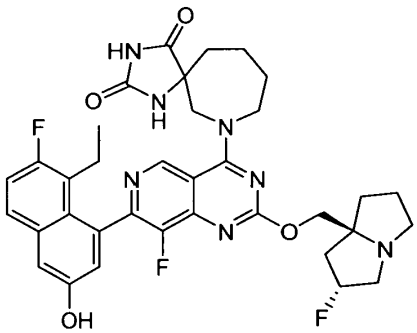
EXAMPLE 337



10-(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)-7-oxa-1,3,10-triazaspiro[4.6]undecane-2,4-dione

[00001008] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.35 (d, J = 1.6 Hz, 1H), 7.76 (dd, J = 6.0, 8.8 Hz, 1H), 7.39 (d, J = 2.8 Hz, 1H), 7.34 (t, J = 9.6 Hz, 1H), 7.13 (dd, J = 2.4, 7.2 Hz, 1H), 5.63-5.42 (m, 1H), 5.20-5.00 (m, 1H), 4.62-4.25 (m, 7H), 4.18-4.09 (m, 1H), 4.02-3.96 (m, 1H), 3.81-3.50 (m, 3H), 3.36-3.25 (m, 1H), 2.69-2.39 (m, 3H), 2.38- 2.06(m, 5H), 0.96-0.82 (m, 3H); LCMS (ESI, M+1): m/z = 678.1.

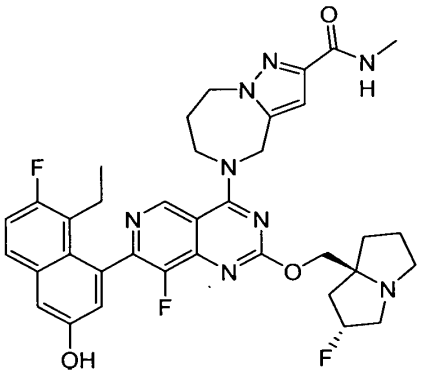
EXAMPLE 338



7-(7-(8-ethyl-7-fluoro-3-hydroxycnaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.6]undecane-2,4-dione

[00001009] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.28 (t, *J* = 3.2 Hz, 1H), 7.68 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.32-7.24 (m, 2H), 7.05 (d, *J* = 2.4 Hz, 1H), 5.54-5.33 (m, 1H), 5.00-4.95 (m, 1H), 4.52-4.40 (m, 3H), 4.21-4.05 (m, 2H), 3.63-3.61 (m, 3H), 3.26 (br d, *J* = 5.2 Hz, 1H), 2.50-2.45 (m, 3H), 2.20-2.11 (m, 9H), 1.88-1.84 (m, 2H), 0.84-0.77 (m, 3H); LCMS (ESI, M+1): m/z = 676.3.

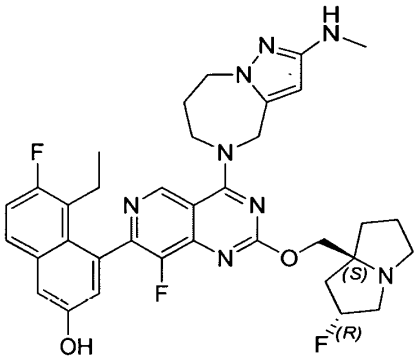
EXAMPLE 339



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

[00001010] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.19 (s, 1H), 7.67 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.33-7.20 (m, 2H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.82 (s, 1H), 5.52-5.12 (m, 3H), 4.60-4.30 (m, 6H), 3.65-3.38 (m, 3H), 3.18 (dt, *J* = 5.6, 9.2 Hz, 1H), 2.88 (s, 3H), 2.57-2.21 (m, 6H), 2.20-1.92 (m, 4H), 0.78 (t, *J* = 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 687.1.

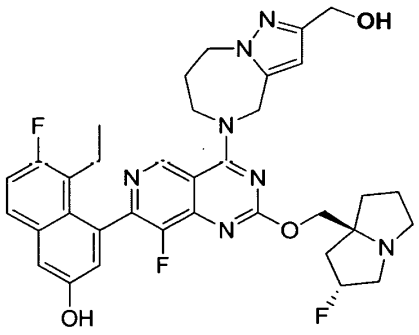
EXAMPLE 340



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

[00001011] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.21 (s, 1H), 7.67 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.25 (t, *J* = 9.6 Hz, 1H), 7.06 (d, *J* = 2.8 Hz, 1H), 5.75 (s, 1H), 5.32 (d, *J* = 54.4, 1H), 5.17-5.03 (m, 2H), 4.39-4.25 (m, 6H), 3.36 (br d, *J* = 2.8 Hz, 1H), 3.26-3.25 (m, 2H), 3.06 (dt, *J* = 6.0, 9.6 Hz, 1H), 2.76 (s, 3H), 2.49-2.46 (m, 1H), 2.38-2.03 (m, 6H), 2.02-1.87 (m, 3H), 0.79 (t, *J* = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 659.4.

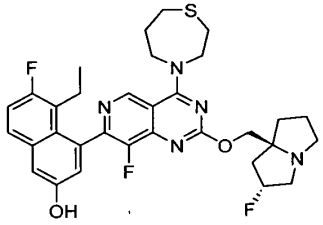
EXAMPLE 341



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

[00001012] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.24-9.16 (m, 1H), 7.68 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.34-7.19 (m, 2H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.44 (s, 1H), 5.51-5.33 (m, 1H), 5.32-5.06 (m, 2H), 4.73-4.24 (m, 8H), 3.72-3.40 (m, 3H), 3.26-3.15 (m, 1H), 2.58-2.21 (m, 6H), 2.19-1.96 (m, 4H), 0.78 (br t, *J* = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 660.1.

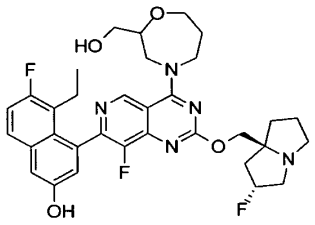
EXAMPLE 342



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

[00001013] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, Methanol-d$_4$) δ ppm 0.81 (td, *J*=7.2, 1.6 Hz, 3 H) 1.86 - 2.00 (m, 1 H) 2.01 - 2.11 (m, 2 H) 2.13 - 2.25 (m, 2 H) 2.27 - 2.56 (m, 5 H) 2.79 (t, *J*=6.0 Hz, 2 H) 3.10 (dt, *J*=9.2, 4.8 Hz, 1 H) 3.16 (br t, *J*=5.6 Hz, 2 H) 3.35 - 3.51 (m, 2 H) 4.23 - 4.43 (m, 6 H) 4.61 (br s, 1 H) 5.27 - 5.46 (m, 1 H) 7.07 (d, *J*=2.4 Hz, 1 H) 7.21 - 7.29 (m, 1 H) 7.31 (d, *J*=2.4 Hz, 1 H) 7.68 (dd, *J*=9.2, 6.0 Hz, 1 H) 8.53 (s, 1 H) 9.16 (s, 1 H); LCMS (ESI, M+1): m/z = 610.3

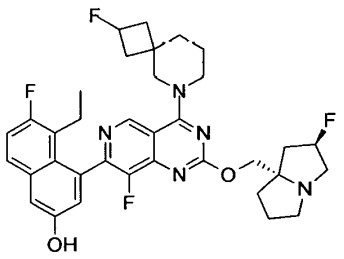
EXAMPLE 343



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

[00001014] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.20 (d, J = 2.8 Hz, 1H), 8.55 (s, 1H), 7.70 (dd, J = 6.0, 9.2 Hz, 1H), 7.33 (d, J = 2.8 Hz, 1H), 7.27 (t, J = 9.6 Hz, 1H), 7.08 (dd, J = 2.4, 8.8 Hz, 1H), 5.48-5.29 (m, 1H), 4.74-4.56 (m, 4H), 4.48-4.29 (m, 3H), 4.28-4.12 (m, 2H), 4.04-3.89 (m, 1H), 3.74-3.58 (m, 3H), 3.19-3.07 (m, 1H), 3.13-2.64 (m, 1H), 2.60-1.93 (m, 10H), 2.55-1.90 (m, 1H), 0.87-0.77 (m, 3H); LCMS (ESI, M+1):m/z = 624.4

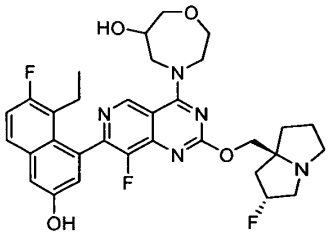
EXAMPLE 344



5-ethyl-6-fluoro-4-(8-fluoro-4-(2-fluoro-6-azaspiro[3.5]nonan-6-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol

[00001015] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, chloroform-d) δ = 9.06-8.97 (m, 1H), 7.58-7.51 (m, 1H), 7.23-6.87 (m, 3H), 5.96-5.73 (m, 1H), 5.45-5.09 (m, 3H), 4.66-4.48 (m, 2H), 4.43-4.19 (m, 2H), 3.44-2.93 (m, 6H), 2.57-2.35 (m, 3H), 2.25-2.16 (m, 2H), 2.03-1.85 (m, 4H), 1.82-1.62 (m, 5H), 0.89-0.74 (m, 3H); LCMS (ESI, M+1): m/z = 636.3.

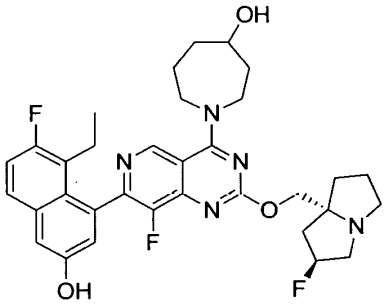
EXAMPLE 345



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)-1,4-oxazepan-6-ol

[00001016] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.33 (d, J = 11.6 Hz, 1H), 8.55 (s, 1H), 7.67 (dd, J =6.0, 9.2 Hz, 1H), 7.30 (d, J = 2.8 Hz, 1H), 7.25 (t, J = 9.6 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 5.37 (br s, 1H), 4.46-4.39 (m, 1H), 4.37-4.21 (m, 5H), 4.17-4.00 (m, 3H), 4.00-3.89 (m, 1H), 3.79-3.67 (m, 1H), 3.24 (br s, 1H), 3.18 (s, 1H), 3.01 (dt, J = 6.0, 9.6 Hz, 1H), 2.56-2.45 (m, 1H), 2.36-2.11 (m, 4H), 2.08-1.81 (m, 4H), 0.87-0.73 (m, 3H); LCMS (ESI,M+1):m/z=610.4.

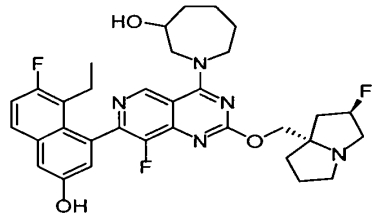
EXAMPLE 346



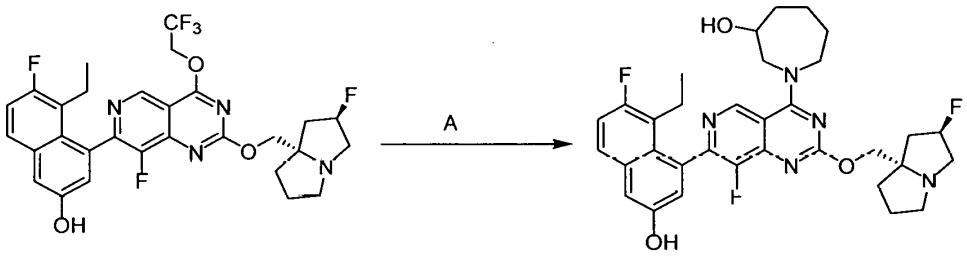
1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)azepan-4-ol

[00001017] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, MeOH-d_4) δ = 9.17 (s, 1H), 8.49 (br s, 1H), 7.68 (dd, J = 6.0, 9.2 Hz, 1H), 7.31 (d, J = 2.8 Hz, 1H), 7.25 (t, J = 9.6 Hz, 1H), 7.05 (d, J = 2.8 Hz, 1H), 5.51-5.33 (m, 1H), 4.52-4.46 (m, 1H), 4.44-4.37 (m, 1H), 4.25-4.17 (m, 1H), 4.25-4.15 (m, 1H), 4.13 (br t, J = 5.6 Hz, 1H), 4.06-3.95 (m, 2H), 3.67-3.45 (m, 3H), 3.25 - 3.17 (m, 1H),2.55-2.35 (m, 3 H), 2.34-2.18 (m, 4H), 2.17-2.05 (m, 3H), 2.02-1.84 (m, 3H), 1.83-1.70 (m, 1H), 0.80 (t, J = 7.2 Hz, 3H). LCMS (ESI, M+1): m/z =608.1

EXAMPLE 347

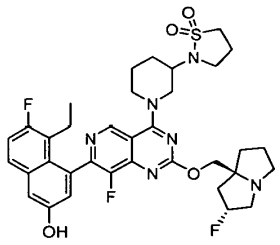


1-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)azepan-3-ol



[00001018] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.35-9.18 (m, 1H), 8.56-8.41 (m, 1H), 7.68 (dd, J = 6.0, 8.8 Hz, 1H), 7.36-7.19 (m, 2H), 7.05 (dd, J = 2.8, 4.4 Hz, 1H), 5.53-5.31 (m, 1H), 4.59 (s, 1H), 4.54-4.37 (m, 3H), 4.19 (td, J = 4.0, 8.4 Hz, 1H), 4.14 (t, J = 6.4 Hz, 1H), 3.88-3.76 (m, 1H), 3.46 (s, 3H), 3.26-3.18 (m, 1H), 2.54-1.92 (m, 12H), 1.68 (d, J = 10.8 Hz, 1H), 1.55-1.40 (m, 1H), 0.88-0.72 (m, 3H); LCMS [ELSD, M+1] : m/z = 608.1

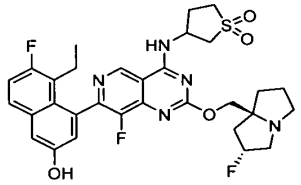
EXAMPLE 348



2-(1-(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)piperidin-3-yl)isothiazolidine 1,1-dioxide

[00001019] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.09 (s, 1H), 7.76 (br dd, J = 6.0, 8.8 Hz, 1H), 7.44-7.25 (m, 2H), 7.02 (br s, 1H), 5.47-5.11 (m, 1H), 4.60 (br t, J = 13.6 Hz, 1H), 4.50-4.35 (m, 1H), 4.21-4.03 (m, 2H), 3.71-3.59 (m, 2H), 3.22 (br d, J = 3.6 Hz, 3H), 3.14-2.94 (m, 4H), 2.86-2.65 (m, 2H), 2.37-2.30 (m, 1H), 2.29-2.19 (m, 2H), 2.18-2.08 (m, 2H), 2.03 (br d, J = 16.4 Hz, 3H), 1.94-1.71 (m, 6H), 0.72 (q, J = 7.2 Hz, 3H);LCMS (ESI, M+1): m/z = 697.4.

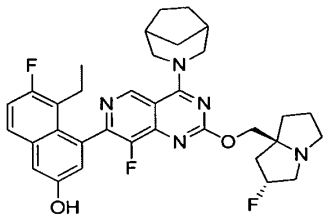
EXAMPLE 349



3-((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)amino)tetrahydrothiophene 1,1-dioxide

[00001020] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.36 (d, J = 2.0 Hz, 1H), 9.10 (br d, J = 6.8 Hz, 1H), 8.35 (s, 1H), 7.77 (dd, J = 6.0, 9.2 Hz, 1H), 7.41 - 7.28 (m, 2H), 6.99 (d, J = 2.4 Hz, 1H), 5.41 - 5.17 (m, 1H), 5.14 - 5.02 (m, 1H), 4.23 - 4.03 (m, 2H), 3.76 - 3.59 (m, 2H), 3.06 - 2.98 (m, 2H), 2.86 - 2.78 (m, 1H), 2.72 - 2.65 (m, 2H), 2.35 - 2.29 (m, 3H), 2.13 - 1.97 (m, 4H), 1.95 - 1.68 (m, 4H), 0.71 (t, J = 7.6 Hz, 3H), LCMS (ESI, M+1): m/z = 628.2.

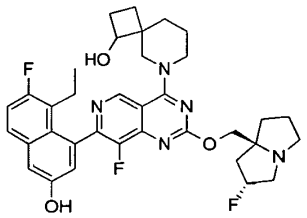
EXAMPLE 350



4-(4-(3-azabicyclo[3.2.1]octan-3-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

[00001021] The title compound was synthesized according to the procedure described for example 330. LCMS (ESI, M+1): m/z = 604.0.

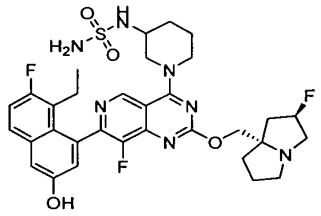
EXAMPLE 351



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-azaspiro[3.5]nonan-1-ol

[00001022] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.14 (d, J = 6.0 Hz, 1H), 8.61-8.44 (m, 1H), 7.75-7.62 (m, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.25 (t, J = 9.6 Hz, 1H), 7.07 (t, J = 3.2 Hz, 1H), 5.49-5.27 (m, 1H), 4.52-4.27 (m, 3H), 4.25-4.11 (m, 1H), 4.10-3.81 (m, 3H), 3.57-3.37 (m, 3H), 3.20-3.08 (m, 1H), 2.55-2.16 (m, 6H), 2.14-2.05 (m, 2H), 2.00-1.84 (m, 4H), 1.83-1.72 (m, 2H), 1.72-1.55 (m, 1H), 1.38-1.30 (m, 1H), 0.86-0.74 (m, 3H). LCMS (ESI, M+1): m/z = 634.5.

EXAMPLE 352

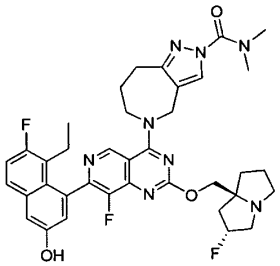


7-(8-ethyl-7-fluoro-3-hydroxy-1-naphthyl)-8-fluoro-2-(((2R,7aS)- 2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-[3-(sulfamoylamino)-1-piperidyl]pyrido[4,3-d]pyrimidine

[00001023] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.12 (s, 1H), 7.69-7.60 (m, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.23 (t, J = 9.2 Hz, 1H), 7.05 (t, J = 3.2 Hz, 1H), 5.41-5.20 (m, 1H), 4.79-4.67

(m, 1H), 4.46-4.23 (m, 3H), 3.75-3.60 (m, 2H), 3.58-3.45 (m, 1H), 3.28-3.11 (m, 3H), 3.04-2.95 (m, 1H), 2.57-2.43 (m, 1H), 2.41-2.12 (m, 5H), 2.05-1.87 (m, 4H), 1.85-1.67 (m, 2H), 0.87-0.73 (m, 3H); LCMS [ESI, M+1]: m/z = 672.2.

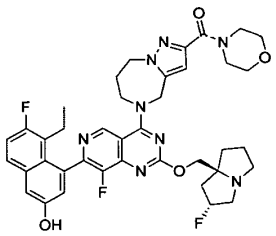
EXAMPLE 353



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

[00001024] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.97 (s, 1H), 9.16 (s, 1H), 8.20 (s,1H), 7.76 (dd, J = 6.0, 9.2 Hz, 1H), 7.38-7.31 (m, 2H), 7.01 (d, J = 2.4 Hz, 1H), 5.46-5.26 (m, 1H), 5.12-5.00 (m, 2H), 4.32 (br s, 5H), 3.10 (br s, 6H), 2.99-2.82 (m, 3H), 2.43-1.74 (m, 1H), 1.23 (s, 1H), 0.70 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 701.4.

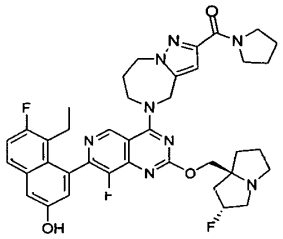
EXAMPLE 354



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

[00001025] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, CD_3OD) δ = 9.25 (s, 1H), 7.75-7.65 (m, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.26 (t, *J* = 9.2 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.79 (s, 1H), 5.68-5.51 (m, 1H), 5.38-5.30 (m, 1H), 5.28- 5.20 (m, 1H), 4.83-4.75 (m, 2H), 4.73-4.59 (m, 2H), 4.53 (br d, *J* = 5.6 Hz, 2H), 4.12-4.03 (m, 2H), 3.95-3.87 (m, 2H), 3.77-3.64 (m, 6H), 3.52-3.42 (m, 1H), 2.83-2.05 (m, 11H), 0.78 (t, *J* = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z= 743.3.

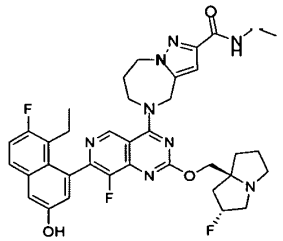
EXAMPLE 355



(5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-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-yl)(pyrrolidin-1-yl)methanone

[00001026] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, CD_3OD) δ = 9.24 (s, 1H), 7.73-7.65 (m, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.26 (t, *J* = 9.2 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.85 (s, 1H), 5.65-5.43 (m, 1H), 5.39-5.19 (m, 2H), 4.59-4.42 (m, 6H), 3.98-3.87 (m, 2H), 3.81-3.71 (m, 2H), 3.60 (t, *J* = 6.8 Hz, 2H), 2.71-2.06 (m, 11H), 2.03-1.81 (m, 5H), 0.78 (t, *J* = 7.2 Hz, 3H); LCMS [ESI, M+1]: m/z =727.4.

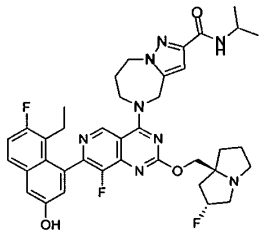
EXAMPLE 356



N-ethyl-5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-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]diazepine-2-carboxamide

[00001027] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.94 (s, 1H), 9.20 (s, 1H), 8.09 (br t, J = 6.0 Hz, 1H), 7.83-7.69 (m, 1H), 7.39-7.30 (m, 2H), 7.00 (d, J = 2.4 Hz, 1H), 6.65 (s, 1H), 5.53-5.00 (m, 3H), 4.56-4.47 (m, 2H), 4.42-4.25 (m, 2H), 4.22-3.96 (m, 2H), 3.27-3.15 (m, 3H), 3.13-2.74 (m, 3H), 2.33 (br s, 2H), 2.21-1.97 (m, 5H), 1.88-1.73 (m, 3H), 1.05 (t, J = 7.2 Hz, 3H), 0.70 (br t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z =701.1.

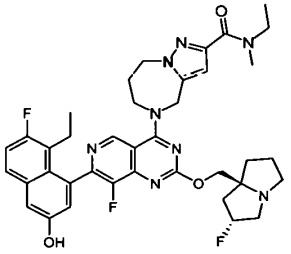
EXAMPLE 357



5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-*N*-isopropyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-*a*][1,4]diazepine-2-carboxamide

[00001028] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.09-10.83 (m, 1H), 9.27 (s, 1H), 7.81-7.73 (m, 2H), 7.40-7.32 (m, 2H), 7.02 (d, J = 2.4 Hz, 1H), 6.77 (s, 1H), 5.68-5.50 (m, 1H), 5.36-5.19 (m, 2H), 4.64-4.38 (m, 6H), 4.09-4.00 (m, 1H), 3.91-3.84 (m, 1H), 3.17-3.08 (m, 1H), 2.23-2.00 (m, 5H), 1.29-1.24 (m, 7H), 1.12 (d, J = 6.4 Hz, 6H), 0.70 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 715.5.

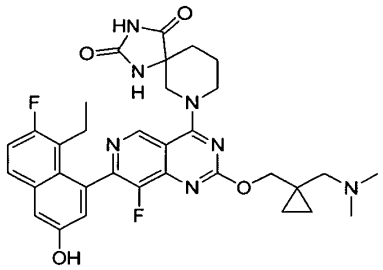
EXAMPLE 358



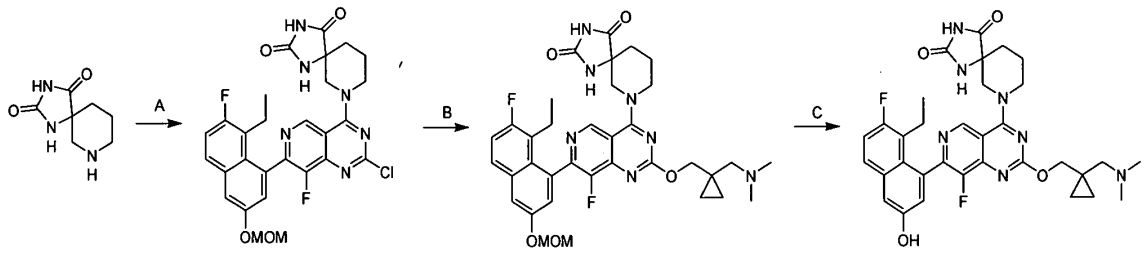
N-ethyl-5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N-methyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

[00001029] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.26 (s, 1H), 8.09 (s, 1H), 7.69 (dd, J = 6.0, 9.0 Hz, 1H), 7.32 (d, J = 2.8 Hz, 1H), 7.26 (t, J = 9.6 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 6.76 (br d, J = 4.0 Hz, 1H), 5.70-5.48 (m, 1H), 5.37-5.19 (m, 2H), 4.76-4.43 (m, 6H), 4.03-3.73 (m, 3H), 4.05-3.70 (m, 1H), 3.62-3.43 (m, 2H), 3.06 (s, 1H), 2.84-2.02 (m, 11H), 1.22 (td, J = 7.2, 11.8 Hz, 3H), 0.78 (br t, J = 7.2 Hz, 3H); LCMS (ESI,M+1):m/z=715.5

EXAMPLE 359



7-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione

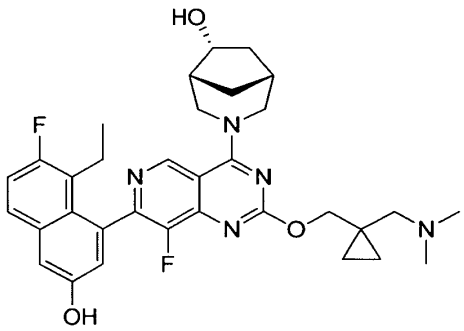


[00001030] Step A. 7-(2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione: To a solution of 2,4-dichloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidine (200 mg, 1.0 *equiv.*) in DCM (2 mL) was added DIEA (172 mg, 3.0 *equiv.*) and 1,3,7-triazaspiro[4.5]decane-2,4-dione (75.2 mg, 1.0 *equiv.*) at -40 °C. The reaction mixture was stirred at -40 °C for 1 hour. The mixture was poured dropwise into ice-cold saturated NH_4Cl solution (8 mL). Then the mixture was extracted with ethyl acetate (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum 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 neutralized with solid $NaHCO_3$, and concentrated in vacuum to remove acetonitrile. The aqueous layer was extracted with ethyl acetate (10 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to afford the title compound (170 mg, 64.7% yield) as a white solid; LCMS (ESI, M+1): m/z = 583.2.

[00001031] Step B. 7-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione: To a solution of 7-(2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione (170 mg, 1.0 *equiv.*) in THF (2 mL) were added (1-((dimethylamino)methyl)cyclopropyl)methanol (113 mg, 3.0 *equiv.*), DIEA (113 mg, 3.0 *equiv.*) and 4 Å molecular sieves (10 mg). The reaction mixture was stirred at 40 °C for 12 hours. The mixture was filtered. The filter cake was triturated with dichloromethane / methanol 10:1 (10 mL) at 25 °C for 15 mins to afford the title compound (140 mg, 68.5% yield) as a white solid; LCMS (ESI, M+1): m/z = 676.4.

[00001032] Step C. 7-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione: To a solution of 7-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione (130 mg, 1.0 *equiv.*) in MeCN (1 mL) was added HCl•dioxane (4 M, 6.0 *equiv.*) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The mixture was concentrated in vacuum 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 lyophilized to afford the title compound (92.7 mg, 69.1% yield, formic acid salt) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.14 (d, J = 4.0 Hz, 1H), 8.50 (br s, 1H), 7.69 (dd, J = 6.0, 9.2 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.26 (t, J = 9.2 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 4.70 - 4.53 (m, 2H), 4.45 - 4.38 (m, 2H), 3.95 - 3.74 (m, 2H), 3.23 - 3.09 (m, 2H), 2.87 (s, 6H), 2.55 - 2.35 (m, 1H), 2.32 - 2.03 (m, 3H), 2.03 - 1.89 (m, 2H), 1.00 - 0.90 (m, 2H), 0.87 - 0.71 (m, 5H); LCMS (ESI, M+1): m/z =632.4.

EXAMPLE 360

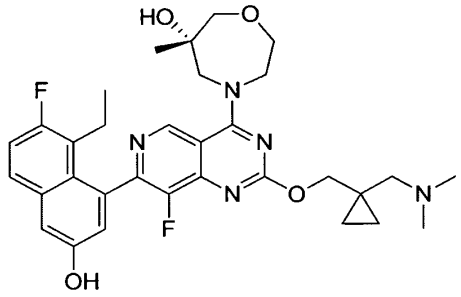


(1R,5R,6R)-3-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol

[00001033] The title compound was synthesized according to the procedure described for example 359 except for TsOH (10 *equiv.*) in DCM was used in step C. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.28-9.18 (m, 1H), 7.67 (dd, J = 5.6, 8.8 Hz, 1H), 7.34-7.28 (m, 1H), 7.27-7.20 (m, 1H), 7.06 (dd, J = 2.8, 13.2 Hz, 1H), 4.63-4.51 (m, 2H), 4.37 (s, 2H), 4.35-4.28 (m, 1H),

3.82-3.7 (m, 1H), 3.52-3.43 (m, 1H), 2.55-2.44 (m, 3H), 2.423-2.38 (m, 1H), 2.37-2.29 (m, 6H), 2.28-2.10 (m, 3H), 1.96-1.88 (m, 1H), 1.85-1.77 (m, 1H), 1.46-1.37 (m, 1H), 0.85-0.76 (m, 3H), 0.76-0.70 (m, 2H), 0.57-0.49 (m, 2H); LCMS (ESI, M+1): m/z = 590.2.

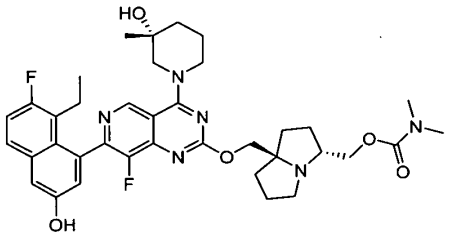
EXAMPLE 361



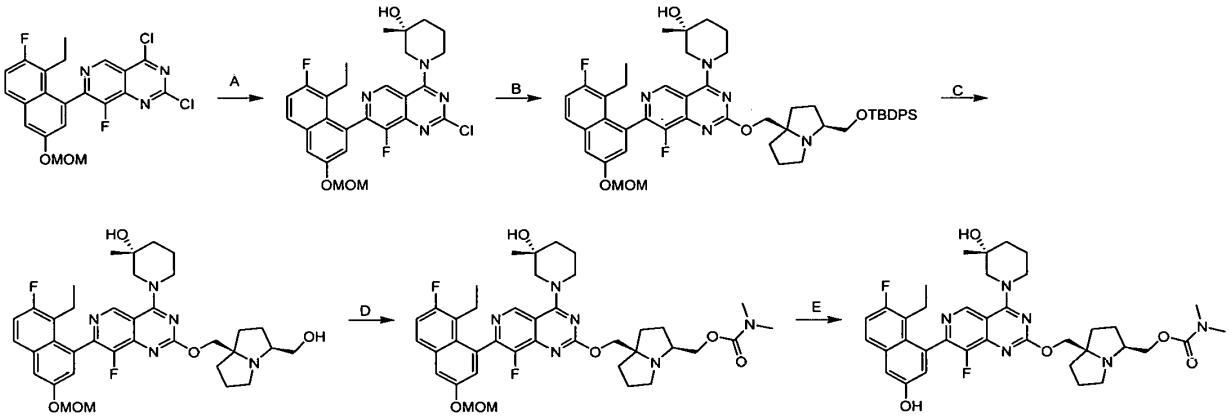
(S)-4-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol

[00001034] The title compound was synthesized according to the procedure described for example 360. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.53 (d, *J* = 4.4 Hz, 1H), 7.67 (dd, *J* = 6.0, 8.98 Hz, 1H), 7.33-7.19 (m, 2H), 7.10-7.00 (m, 1H), 4.57-4.44 (m, 2H), 4.39 (dd, *J* = 5.6, 10.4 Hz, 2H), 4.24-4.13 (m, 1H), 4.08-3.94 (m, 2H), 3.93-3.84 (m, 1H), 3.74-3.61 (m, 2H), 2.5-2.40 (m, 3H), 2.31 (s, 6H), 2.24-2.13 (m, 1H), 1.27 (d, *J* = 2.8 Hz, 3H), 0.84-0.76 (m, 3H), 0.76-0.69 (m, 2H), 0.57-0.51 (m, 2H); LCMS (ESI, M+1): m/z =594.1.

EXAMPLE 362



((3R,7aR)-7a-(((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)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate



[00001035] Step A. (R)-1-(2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of 2,4-dichloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine (5.00 g, 1.0 *equiv.*) in DCM (50 mL) were added 4 Å molecular sieves (30 mg, 1.0 *equiv.*), DIEA (7.18 g, 5.0 *equiv.*) and (3R)-3-methylpiperidin-3-ol (1.85 g, 1.1 *equiv.*, HCl) at -40 °C. The reaction mixture was stirred at -40 °C for 15 mins. The reaction mixture was diluted with DCM (30 mL) and water (40 mL), and extracted with DCM (20 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and neutralized with solid $NaHCO_3$, and concentrated in vacuum to remove acetonitrile. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to afford the title compound (4.9 g, 81.4% yield) as an off-yellow solid; LCMS (ESI, M+1): m/z = 529.2.

[00001036] Step B. (R)-1-(2-(((3R,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of ((3R,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methanol (465 mg, 1.2 *equiv.*) in toluene (5 mL) were added 4 Å molecular sieves (20 mg) and *t*-BuONa (273 mg, 3.0 *equiv.*) at 0 °C and the resulting mixture was stirred for 10 minutes. Then (R)-1-(2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-

3-ol (500 mg, 1.0 *equiv.*) was added and the mixture was stirred at 0 °C for 1 hour. The reaction mixture was diluted with ethyl acetate (15 mL) and water (20 mL), and extracted with ethyl acetate (10 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum 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 neutralized with solid $NaHCO_3$, and concentrated in vacuum to remove acetonitrile. The aqueous layer was extracted with ethyl acetate (10 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to afford the title compound (600 mg, 67.5% yield) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.22 (d, J = 2.2 Hz, 1H), 7.80 (dd, J = 5.6, 9.2 Hz, 1H), 7.69 (qd, J = 1.8, 6.0 Hz, 4H), 7.62 (d, J = 2.8 Hz, 1H), 7.47 - 7.38 (m, 6H), 7.31 (t, J = 9.2 Hz, 1H), 7.22 (t, J = 3.2 Hz, 1H), 5.33 (s, 2H), 4.65 - 4.48 (m, 2H), 4.42 - 4.23 (m, 3H), 3.97 (dd, J = 5.6, 10.8 Hz, 1H), 3.90 - 3.78 (m, 1H), 3.69 - 3.55 (m, 1H), 3.53 - 3.39 (m, 5H), 2.96 - 2.82 (m, 2H), 2.58 - 2.42 (m, 1H), 2.29 - 2.06 (m, 3H), 1.96 - 1.73 (m, 8H), 1.71 - 1.60 (m, 1H), 1.31 - 1.26 (m, 3H), 1.08 - 1.03 (m, 9H), 0.82 (dt, J = 4.8, 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 902.6.

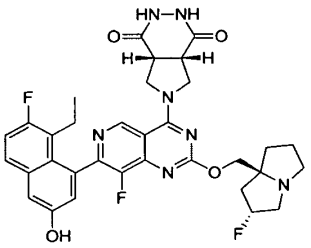
[00001037] Step C. (R)-1-(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((3R,7aR)-3-(hydroxymethyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(2-(((3R,7aR)-3-(((tert-butyldiphenylsilyl)oxy)methyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (300 mg, 1.0 *equiv.*) in DMF (3 mL) was added CsF (758 mg, 15 *equiv.*). The reaction mixture was stirred at 40 °C for 12 hours. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and neutralized with solid $NaHCO_3$, and concentrated in vacuum to remove acetonitrile. The aqueous layer was extracted with ethyl acetate (5 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate, and concentrated in vacuum to afford the title compound (190 mg, 85.5% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 664.4.

[00001038] Step D. ((3R,7aR)-7a-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate: To a solution of (R)-1-

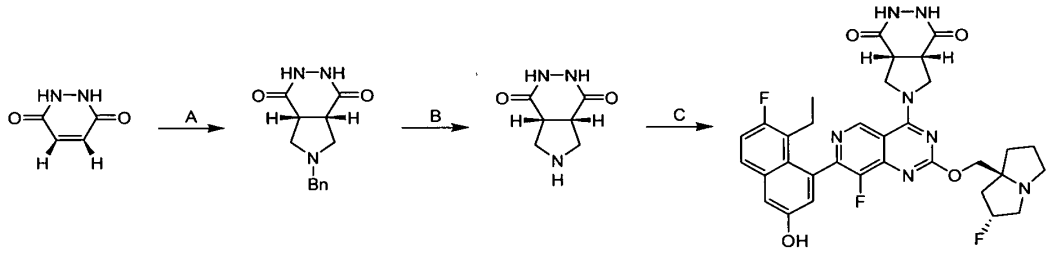
(7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((3R,7aR)-3-(hydroxymethyl)hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (190 mg, 1.0 *equiv.*) in THF (2 mL) was added NaH (22.9 mg, 60% purity, 2.0 *equiv.*) at 0 °C. After stirring at 0 °C for 0.5 hour, N,N-dimethylcarbamoyl chloride (46.17 mg, 1.5 *equiv.*) in THF (1 mL) was added and the resulting was stirred at 0 °C for 2 hours. The mixture was quenched with water (10 ml) and extracted with ethyl acetate (2 ×10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and neutralized with solid $NaHCO_3$, and concentrated in vacuum to remove acetonitrile. The aqueous layer was extracted with ethyl acetate (2 × 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, and concentrated in vacuum to give a residue. Then the residue was purified by prep-TLC (silica gel, DCM / MeOH 10:1) to afford the title compound (45 mg, 21.4% yield) as a yellow solid; LCMS (ESI, M+1): m/z =735.6.

[00001039] Step E. ((3R,7aR)-7a-(((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)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate: To a solution of ((3R,7aR)-7a-(((7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate (32 mg, 1.0 *equiv.*) in MeCN (0.3 mL) was added HCl•dioxane (4 M, 55 *equiv.*) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 hour. The mixture was concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and lyophilized to afford the title compound (15.6 mg, 45.4% yield, formic acid salt) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.26 - 9.21 (m, 1H), 8.55 (s, 1H), 7.68 (dd, J = 6.0, 9.2 Hz, 1H), 7.34 - 7.20 (m, 2H), 7.06 (s, 1H), 4.82 - 4.70 (m, 2H), 4.52 - 4.22 (m, 3H), 4.14 - 3.97 (m, 1H), 3.88 - 3.74 (m, 1H), 3.69 - 3.54 (m, 1H), 3.52 - 3.35 (m, 1H), 3.34 - 2.30 (m, 2H), 2.95 - 2.91 (m, 5H), 2.51 - 2.40 (m, 1H), 2.35 - 2.09 (m, 4H), 2.07 - 1.89 (d, J = 14. Hz, 5H), 1.86 - 1.67 (m, 4H), 1.29 (d, J = 9.2 Hz, 3H), 0.86 - 0.74 (m, 3H); LCMS (ESI, M+1): m/z =691.4.

EXAMPLE 363



(4aR,7aS)-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)hexahydro-1H-pyrrolo[3,4-d]pyridazine-1,4(4aH)-dione



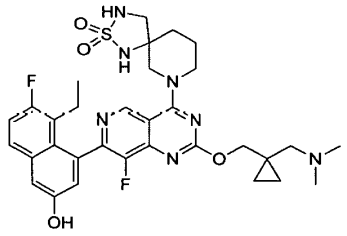
[00001040] Step A. (4aR,7aS)-6-benzylhexahydro-1H-pyrrolo[3,4-d]pyridazine-1,4(4aH)-dione: To a solution of 1,2-dihydropyridazine-3,6-dione (10.0 g, 1.0 *equiv.*) in dichloromethane (90.0 mL) was added N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (42.4 g, 2.0 *equiv.*) at 0 °C. The resulting mixture was stirred at 0 °C for 5 minutes, then TFA (1.02 g, 0.1 *equiv.*) in dichloromethane (10 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 2 hours. The mixture was quenched by addition of water (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (3 × 50 mL), dried over anhydrous sodium sulfate, concentrated and triturated with dichloromethane / methyl alcohol 10:1 (3 × 100 mL) at 25 °C for 30 minutes and filtered to afford the title compound (10 g, crude) as a yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36-7.26 (m, 5H), 4.59 (d, J = 13.2 Hz, 1H), 4.31 (d, J = 12.8 Hz, 1H), 3.21-3.10 (m, 2H), 3.01-2.91 (m, 2H), 2.75 (dt, J = 8.0, 9.6 Hz, 2H).

[00001041] Step B. (4aR,7aS)-hexahydro-1H-pyrrolo[3,4-d]pyridazine-1,4(4aH)-dione: To a suspension of Pd/C (0.20 g, 10% purity) in MeOH (40.0 mL) was added (4aR,7aS)-6-benzylhexahydro-1H-pyrrolo[3,4-d]pyridazine-1,4(4aH)-dione (1.00 g, 1.0 *equiv.*) under N_2

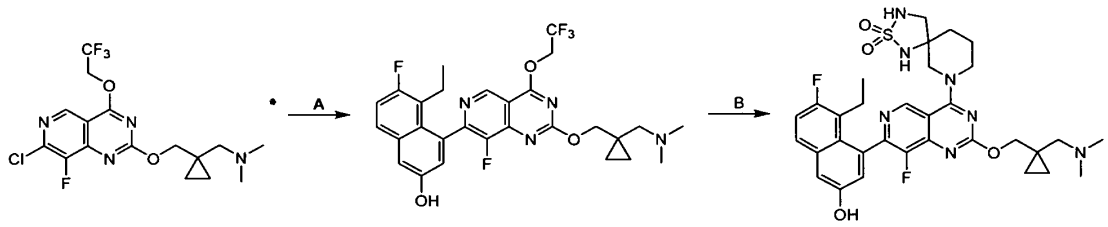
atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15 Psi) at 25 °C for 1 hour. The mixture was filtered and concentrated to afford the title compound (0.23 g, 36% yield over two steps) as a yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.15-3.10 (m, 2H), 2.92-2.88 (m, 1H), 2.88-2.85 (m, 1H), 2.83-2.75 (m, 2H).

[00001042] Step C. (4aR,7aS)-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)hexahydro-1H-pyrrolo[3,4-d]pyridazine-1,4(4aH)-dione: To a solution of 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 (150 mg, 1.0 *equiv.*) in DMF (2.0 mL) were added (4aR,7aS)-hexahydro-1H-pyrrolo[3,4-d]pyridazine-1,4(4aH)-dione (58.9 mg, 1.5 *equiv.*), DIEA (98.1 mg, 3.0 *equiv.*) and 4 Å molecular sieves (70 mg). The mixture was stirred at 40 °C for 16 hours. After reaction completion, the mixture was filtered and purified by prep-HPLC [column: Waters Xbridge 150 × 25mm × 5 μm; mobile phase: water (10 mM NH_4HCO_3) - ACN, B%: 30%-50%, 9min] and re-purified by prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: water (10mM ammonium hydroxide)-ACN, B%: 7%-37%, 9min] to afford the title compound (16.9 mg, 10% yield, 99.2% purity)as a white solid; ^{1}H NMR (400 MHz, Methanol-d4) δ 9.29 (s, 1H), 7.68 (dd, J = 5.6, 9.2 Hz, 1H), 7.31 (d, J = 2.8 Hz, 1H), 7.25 (t, J = 9.6 Hz, 1H), 7.07 (d, J = 2.8 Hz, 1H), 5.43-5.21 (m, 1H), 4.51-4.21 (m, 6H), 3.58-3.46 (m, 2H), 3.31-3.16 (m, 3H), 3.03 (dt, J = 5.6, 9.2 Hz, 1H), 2.55-2.42 (m, 1H), 2.42-2.11 (m, 4H), 2.07-1.85 (m, 3H), 0.81 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 648.4.

EXAMPLE 364



7-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide

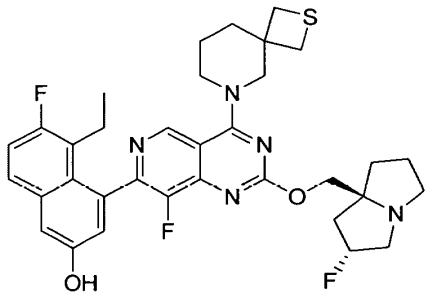


[00001043] Step A. 4-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol: To a mixture of 1-(1-(((7-chloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine (500 mg, 1.0 *equiv.*), 5-ethyl-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-2-ol (464 mg, 1.2 *equiv.*), K_3PO_4 (1.5 M, 2.45 mL, 3.0 *equiv.*) in methoxycyclopentane (5 mL) was added CataCXium A Pd G3 (89.0 mg, 0.1 *equiv.*). The reaction mixture was stirred at 90 °C for 2 hours under N_2 atmosphere. The reaction mixture was quenched by addition of water (5 mL), and extracted with ethyl acetate (15 mL). The combined organic layer was dried over anhydrous sodium sulfate, concentrated and purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) to give title compound (333 mg, 47% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 563.3.

[00001044] Step B. 7-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide: To a mixture of 4-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-ethyl-6-fluoronaphthalen-2-ol (170 mg, 1.0 *equiv.*), 2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide (69.3 mg, 1.2 *equiv.*), 4Å molecular sieves (20.0 mg) in DMF (2 mL) was added DIEA (195 mg, 5.0 *equiv.*). The reaction mixture was stirred at 40 °C for 12 hours. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex Synergi C18 150 × 25 mm × 10 μm; mobile phase: [water (0.1% formic acid) - ACN]; B%: 13% - 43%, 10 min) and lyophilized to afford title compound (141 mg, 69% yield) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d_4): δ = 9.12 (s, 1H), 8.52 (s, 1H), 7.68 (ddd, *J* = 3.2, 5.6, 9.2 Hz, 1H), 7.31 (d, *J* = 1.6 Hz, 1H), 7.28 - 7.22 (m, 1H), 7.03 (dd, *J* = 2.4, 10.0 Hz, 1H), 4.59 (br t, *J* = 12.0 Hz, 1H), 4.51 - 4.38 (m, 3H), 3.85 - 3.73 (m, 1H), 3.72 - 3.60 (m, 1H), 3.37 (dd, *J* = 12.0, 14.4 Hz, 1H), 3.20 (d, *J* = 12.0 Hz, 1H), 3.15 - 3.05 (m, 2H), 2.83 (s, 6H), 2.49 (ddd,

J = 6.4, 7.6, 14.4 Hz, 1H), 2.26 - 2.11 (m, 1H), 2.08 - 1.99 (m, 2H), 1.97 - 1.81 (m, 2H), 0.93 (s, 2H), 0.83 - 0.75 (m, 5H) LCMS(ESI, M+1): m/z = 654.0.

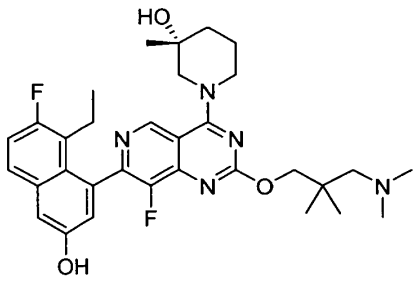
EXAMPLE 365



5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2-thia-6-azaspiro[3.5]nonan-6-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol

[00001045] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.15 (s, 1H), 7.68 (dd, J = 6.0, 9.2 Hz, 1H), 7.31 (d, J = 2.8 Hz, 1H), 7.25 (t, J = 9.6 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 5.52-5.32 (m, 1H), 4.63-4.41 (m, 3H), 4.30 (dd, J = 13.2, 19.2 Hz, 1H), 4.18-4.04 (m, 1H), 3.93 (qd, J = 6.4, 12.8 Hz, 1H), 3.64-3.40 (m, 3H), 3.24-3.11 (m, 3H), 2.95-2.78 (m, 2H), 2.55-2.30 (m, 3H), 2.28-2.09 (m, 4H), 2.06-1.87 (m, 3H), 1.77 (q, J = 5.6 Hz, 2H), 0.80 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 636.4.

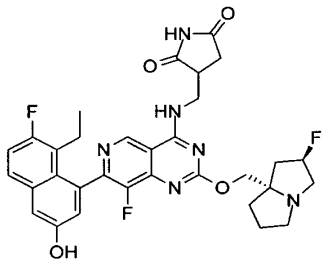
EXAMPLE 366



(R)-1-(2-(3-(dimethylamino)-2,2-dimethylpropoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

[00001046] The title compound was synthesized according to the procedure described for example 309. ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.24 (d, J = 2.0 Hz, 1H), 8.55-8.49 (m, 1H), 7.68 (dd, J = 5.8, 9.2 Hz, 1H), 7.31 (d, J = 2.8 Hz, 1H), 7.26 (t, J = 9.6 Hz, 1H), 7.06 (t, J = 2.0 Hz, 1H), 4.34 (s, 2H), 4.33-4.28 (m, 1H), 3.69-3.59 (m, 1H), 3.55-3.38 (m, 2H), 3.02 (br s, 2H), 2.76 (br s, 6H), 2.52-2.42 (m, 1H), 2.24-2.13 (m, 2H), 1.89-1.77 (m, 3H), 1.30 (d, J = 9.8 Hz, 3H), 1.18 (s, 6H), 0.81 (q, J = 7.6 Hz, 3H); LCMS [ESI, M+1]: m/z =580.3.

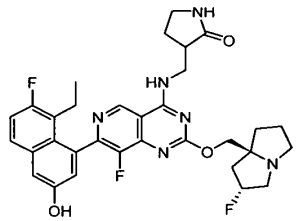
EXAMPLE 367



3-(((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)pyrrolidine-2,5-dione

[00001047] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.21-9.18 (m, 1H), 8.47 (s, 1H), 7.69 (dd, J = 6.0, 9.2 Hz, 1H), 7.31 (d, J = 2.8 Hz, 1H), 7.26 (t, J = 9.6 Hz, 1H), 7.06-7.02 (m, 1H), 5.58-5.37 (m, 1H), 4.60-4.46 (m, 3H), 4.19-4.08 (m, 1H), 4.03-3.93 (m, 1H), 3.80-3.54 (m, 3H), 3.51-3.41 (m, 1H), 3.01-2.88 (m, 1H), 2.74 (dd, J = 4.8, 18.2 Hz, 1H), 2.62-2.28 (m, 4H), 2.24-2.04 (m, 4H), 0.79 (t, J = 7.2 Hz, 3H) LCMS [ESI, M+1]: m/z = 621.3.

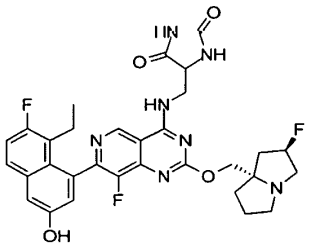
EXAMPLE 368



3-(((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)amino)methyl)pyrrolidin-2-one

[00001048] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, MeOD-d_4) δ =9.15 (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), 7.04 (d, J = 2.4 Hz, 1H), 5.42-5.22 (m, 1H), 4.33 (q, J = 10.8 Hz, 2H), 4.04 (dd, J = 6.0, 13.6 Hz, 1H), 3.83 (dd, J = 8.0, 13.2 Hz, 1H), 3.46-3.33 (m, 3H), 3.27-3.11 (m, 3H), 3.06-2.91 (m, 2H), 2.54-.28 (m, 3H), 2.27-1.82 (m, 8H), 0.79 (t, J = 7.2 Hz, 3H); ^{19}F NMR (400 MHz, MeOD-d_4) δ =-121.18 (br s, 1F), -139.08 (br s, 1F), -173.55 (br t, J = 14.2 Hz, 1F); LCMS (ESI, M+1): m/z = 607.3.

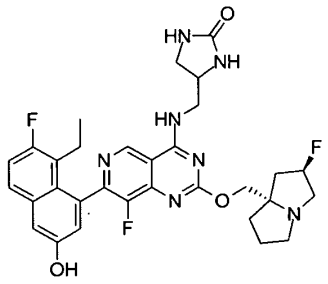
EXAMPLE 369



5-(((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)imidazolidine-2,4-dione

[00001049] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.19 (s, 1H), 8.49 (br s, 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), 7.04 (s, 1H), 5.58-5.34 (m, 1H), 4.66-4.51 (m, 4H), 4.14 (td, J = 4.4, 13.6 Hz, 1H), 4.05-3.94 (m, 1H), 3.75-3.50 (m, 3H), 2.61-2.27 (m, 4H), 2.24-1.98 (m, 4H), 0.78 (br t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 622.3.

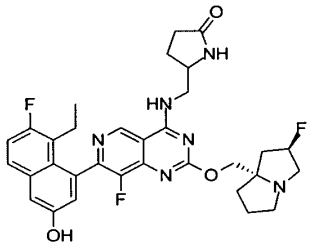
EXAMPLE 370



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)imidazolidin-2-one

[00001050] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.22-9.17 (m, 1H), 8.48 (br s, 1H), 7.68 (dd, J = 6.0, 9.2 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.26 (br t, J = 9.2 Hz, 1H), 7.04 (br s, 1H), 5.56-5.40 (m, 1H), 4.64-4.48 (m, 3H), 4.24-4.10 (m, 1H), 4.05-3.89 (m, 1H), 3.81-3.58 (m, 4H), 3.44-3.35 (m, 1H), 2.58-2.09 (m, 9H), 0.78 (br t, J = 6.0 Hz, 3H); LCMS (ESI, M+1): m/z = 608.3.

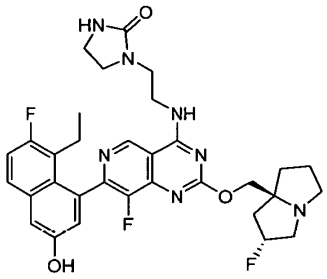
EXAMPLE 371



5-(((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

[00001051] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.22 (s, 1H), 8.45 (s, 1H), 7.71 (dd, J = 6.0, 9.2 Hz, 1H), 7.34 (d, J = 2.8 Hz, 1H), 7.28 (t, J = 9.6 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 5.74-5.32 (m, 1H), 4.66-4.50 (m, 3H), 4.13 (br s, 1H), 3.96 - 3.66 (m, 5H), 2.70-2.45 (m, 4H), 2.43-2.33 (m, 3H), 2.31-2.20 (m, 2H), 2.19-1.98 (m, 3H), 0.81 (br t, J = 7.2 Hz, 3H) LCMS [ESI, M+1]: m/z = 607.3.

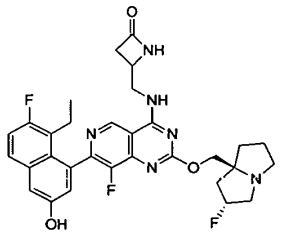
EXAMPLE 372



1-(2-((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)amino)ethyl)imidazolidin-2-one

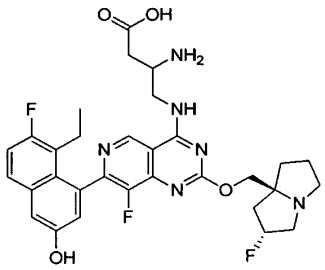
[00001052] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.13-9.76 (m, 1H), 9.24 (s, 1H), 9.12 (s, 1H), 7.76 (dd, J = 6.0, 8.8 Hz, 1H), 7.41-7.29 (m, 2H), 7.00 (s, 1H), 6.34 (s, 1H), 5.45-5.16 (m, 1H), 4.22-4.12 (m, 1H), 4.12-4.03 (m, 1H), 3.82-3.70 (m, 1H), 3.69-3.58 (m, 1H), 3.55-3.45 (m, 2H), 3.41 (s, 1H), 3.28-3.21 (m, 2H), 3.16-3.06 (m, 2H), 3.05-2.98 (m, 1H), 2.89-2.78 (m, 1H), 2.44-2.25 (m, 2H), 2.18-1.97 (m, 4H), 1.89-1.75 (m, 3H), 0.72-0.68 (m, 3H); LCMS (ESI, M+1): m/z = 622.1.

EXAMPLE 373

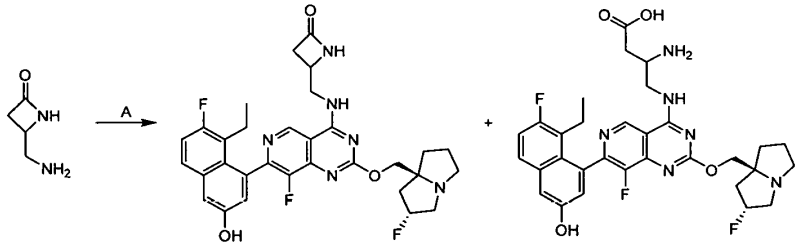


4-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)azetidin-2-one

EXAMPLE 374



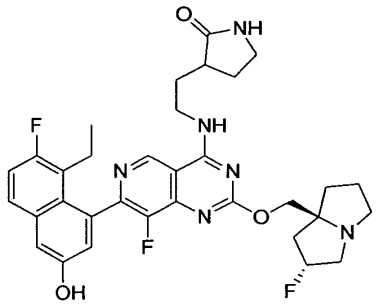
3-amino-4-((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)butanoic acid



[00001053] Step A. 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)azetidin-2-one and 3-amino-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)butanoic acid: To a solution of 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 (60.0 mg, 1.0 *equiv.*) in *N,N*-dimethylformamide (1.00 mL) was added 4Å molecular sieves (30.0 mg), diisopropylethylamine (39.3 mg, 3.0 *equiv.*) and 4-(aminomethyl)azetidin-2-one (20.3 mg, 2.0 *equiv.)*. The mixture was stirred at 40 °C for 16 hours. The mixture was filtered. The filtrate was purified by prep-HPLC [column: 3_Phenomenex Luna C18 75 × 30 mm × 3 μm; mobile phase: water (0.1% HCl)-acetonitrile; B%: 23%-43%, 7minutes] and prep-HPLC [column: water s Xbridge 150 × 25 mm × 5 μm; mobile phase: water (ammonium bicarbonate)-acetonitrile; B%: 34%-64%, 9min] 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)azetidin-2-one (7.14 mg, 11% yield) as a

white solid (second eluting peak); ^{1}H NMR (400 MHz, MeOD-d4) δ =9.15 (s, 1H), 7.68 (dd, J = 5.6, 8.8 Hz, 1H), 7.30 (d, J = 2.8 Hz, 1H), 7.25 (t, J = 9.2 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 5.40-5.20 (m, 2H), 4.70-4.51 (m, 2H), 4.39-4.24 (m, 2H), 4.07 (br d, J = 1.6 Hz, 1H), 4.02-3.85 (m, 2H), 3.27-3.17 (m, 3H), 3.17-3.09 (m, 1H), 3.07-2.97 (m, 1H), 2.87-2.79 (m, 1H), 2.55-2.29 (m, 2H), 2.29-2.08 (m, 4H), 2.04-1.84 (m, 4H), 0.79 (br t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 593.3; and 3-amino-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)butanoic acid (11.8 mg, 17.5% yield) as white solid (first eluting peak); ^{1}H NMR (400 MHz, MeOD-d4) δ =9.17 (s, 1H), 7.68 (dd, J = 6.0, 9.2 Hz, 1H), 7.31 (d, J = 2.8 Hz, 1H), 7.25 (t, J = 9.6 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 5.44-5.22 (m, 1H), 4.42-4.31 (m, 2H), 4.00-3.88 (m, 2H), 3.84-3.73 (m, 1H), 3.42-3.33 (m, 1H), 3.26 (br d, J = 7.6 Hz, 1H), 3.12-3.00 (m, 1H), 2.66-2.56 (m, 1H), 2.53-2.35 (m, 3H), 2.33-2.10 (m, 4H), 2.09-1.88 (m, 4H), 0.78 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 611.1.

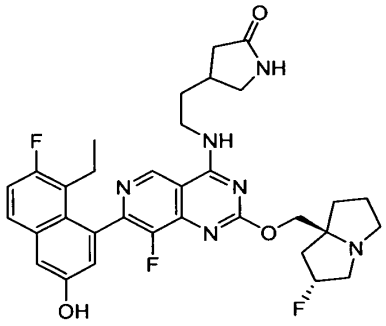
EXAMPLE 375



3-(2-((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)ethyl)pyrrolidin-2-one

[00001054] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, MeOD-d4) δ =9.18 (s, 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), 7.05 (d, J = 2.4 Hz, 1H), 5.51-5.30 (m, 1H), 4.55-4.39 (m, 2H), 3.93-3.69 (m, 2H), 3.67-3.43 (m, 3H), 3.42-3.34 (m, 2H), 3.26-3.13 (m, 1H), 2.64-2.51 (m, 1H), 2.51-2.38 (m, 3H), 2.38-2.19 (m, 3H), 2.19-2.08 (m, 3H), 2.07-1.78 (m, 3H), 1.40-1.35 (m, 1H), 0.78 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 621.1.

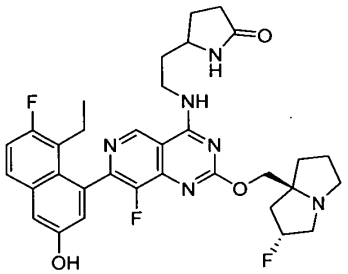
EXAMPLE 376



4-(2-((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)amino)ethyl)pyrrolidin-2-one

[00001055] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, MeOD) δ = 9.18 (s, 1H), 8.45 (s, 1H), 7.68 (dd, J = 5.6, 9.2 Hz, 1H), 7.34-7.30 (m, 1H), 7.25 (t,J = 9.2 Hz, 1H), 7.05 (s, 1H), 5.68-5.38 (m, 1H), 4.64-4.52 (m, 3H), 3.90-3.66 (m, 5H), 3.61 (dd, J = 8.0, 9.6 Hz, 1H), 3.15(dd, J = 6.8, 9.2 Hz, 1H), 2.73-2.31 (m, 6H), 2.30-2.03 (m, 5H), 2.02-1.87 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 621.3.

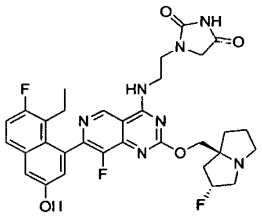
Example 377



5-(2-((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)amino)ethyl)pyrrolidin-2-one

[00001056] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, MeOD) δ = 9.12 (s, 1H), 7.68 (dd, J = 6.0, 9.2 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.25-7.22 (m, 1H), 7.03 (d, J = 2.4 Hz, 1H), 5.44-5.21 (m, 1H), 4.60 (s, 2H), 4.41-4.26 (m, 2H), 3.90-3.70 (m, 3H), 3.23 (s, 1H), 3.04-3.03 (m, 1H), 2.53-2.21 (m, 6H), 2.20-2.09 (m, 2H), 2.06-1.86 (m, 6H), 0.80-0.76 (m, 3H); LCMS (ESI, M+1): m/z = 621.3.

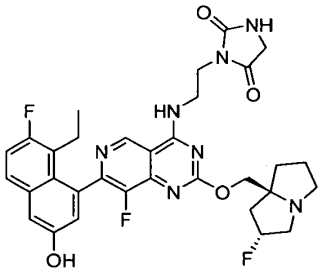
EXAMPLE 378



1-(2-((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)ethyl)imidazolidine-2,4-dione

[00001057] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.11 (s, 1H), 8.48 (s, 1H), 7.69 – 7.66 (m, 1H), 7.31 (d, J = 2.8 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.04 (d, J = 2.8 Hz, 1H), 5.54 – 5.40 (m, 1H), 4.57 – 4.55 (m, 1H), 4.50 – 4.49 (m, 1H), 4.18 (t, J = 5.6 Hz, 1H), 3.83 – 3.70 (m, 2H), 3.62 – 3.27 (m, 5H), 3.31 – 3.27 (m, 1H), 2.46 – 2.45 (m, 1H), 2.41 – 2.18 (m, 6H), 2.16 – 2.05 (m, 1H), 0.78 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 636.4.

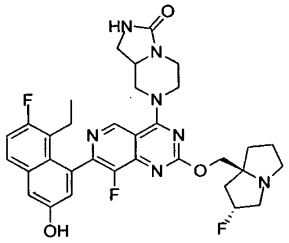
EXAMPLE 379



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

[00001058] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, MeOD) δ = 9.07 (s, 1H), 8.50 (s, 1H), 7.68 (dd, J = 9.2, 6.0 Hz, 1H), 7.31 (d, J = 2.4 Hz, 1H), 7.25 (t, J = 9.6 Hz, 1H), 7.04 (d, J = 2.0 Hz, 1H), 5.56-5.34 (m, 1H), 4.59-4.48 (m, 2H), 3.99-3.84 (m, 6H), 3.72 (s, 1H), 3.57-3.47 (m, 2H), 3.26-3.18 (m, 1H), 2.64-2.24 (m, 4H), 2.21-2.00 (m, 4H), 0.78 (t, J= 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 636.3.

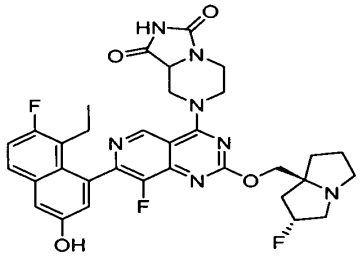
EXAMPLE 380



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

[00001059] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.13 (s, 1H), 7.70 (dd, J = 5.9, 9.0 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 7.27 (t, J = 9.2 Hz, 1H), 7.07 (t, J = 2.4 Hz, 1H), 5.49 - 5.24 (m, 1H), 4.77 - 4.58 (m, 3H), 4.46 - 4.29 (m, 2H), 4.17 - 4.05 (m, 1H), 3.95 (br d, J = 12.4 Hz, 1H), 3.73 - 3.61 (m, 1H), 3.52 - 3.39 (m, 3H), 3.31 - 3.19 (m, 3H), 3.16 - 3.04 (m, 1H), 2.57 - 2.46 (m, 1H), 2.45 - 2.26 (m, 2H), 2.24 - 2.13 (m, 2H), 2.11 - 2.01 (m, 2H), 2.00 - 1.89 (m, 1H), 0.81 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 634.3.

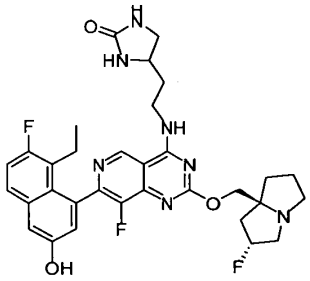
EXAMPLE 381



7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl) tetrahydroimidazo[1,5-a]pyrazinee-1,3(2*H*,5*H*)-dione

[00001060] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, MeOD-d_4) δ = 9.15 (s, 1H), 8.50 (s, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.26 (t, *J* = 9.2 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 5.53 - 5.24 (m, 1H), 4.63 (d, *J* = 12.4 Hz, 1H), 4.53 - 4.37 (m, 3H), 4.16 (d, *J* = 13.2 Hz, 1H), 3.68 - 3.52 (m, 2H), 3.52 - 3.46 (m, 1H), 3.43 - 3.35 (m, 4H), 3.19 - 3.08 (m, 1H), 2.57 - 2.28 (m, 3H), 2.27 - 2.15 (m, 2H), 2.13 - 2.03 (m, 2H), 2.03 - 1.94 (m, 1H), 0.80 (dt, *J* = 2.4, 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 648.2.

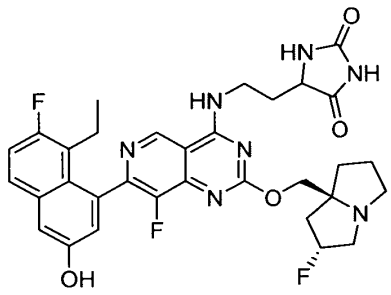
EXAMPLE 382



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

[00001061] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.15 (s, 1H), 8.47 (s, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.31 (d, *J* = 2.8 Hz, 1H), 7.25 (t, *J* = 10.0 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 5.59 - 5.35 (m, 1H), 4.64 - 4.47 (m, 2H), 3.98-3.88 (m, 1H), 3.86 - 3.77 (m, 2H), 3.76 - 3.53 (m, 4H), 3.26 - 3.20 (m, 1H), 2.66 - 2.52 (m, 1H), 2.50 - 2.40 (m, 2H), 2.38 - 2.28 (m, 1H), 2.26 - 2.13 (m, 3H), 2.12 - 2.05 (m, 1H), 2.04 - 1.94 (m, 2H), 0.78 (t, *J* = 7.2 Hz, 3H). LCMS (ESI, M+1): m/z = 622.1.

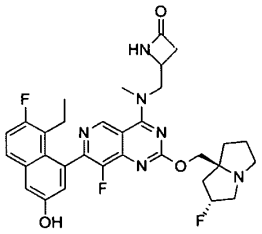
EXAMPLE 383



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

[00001062] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.13 (d, *J* = 4.0 Hz, 1H), 8.46 (s, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.03 (t, *J* = 3.2 Hz, 1H), 5.63 - 5.40 (m, 1H), 4.69 - 4.48 (m, 3H), 4.31 - 4.24 (m, 1H), 4.15 - 3.92 (m, 1H), 3.89 - 3.80 (m, 1H), 3.77 - 3.62 (m, 3H), 2.71 - 2.54 (m, 1H), 2.49 - 2.35 (m, 3H), 2.31 - 2.19 (m, 4H), 2.18 - 2.08 (m, 2H), 0.79 (q, *J* = 6.8 Hz, 3H); LCMS (ESI, M+1): m/z = 636.3

EXAMPLE 384

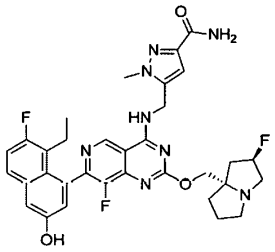


4-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7*aS*)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)(methyl)amino)methyl)azetidin-2-one

[00001063] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-*d*6) δ = 10.21-9.90 (m, 1H), 9.28 (s, 1H), 8.18 (br d, *J* = 4.8 Hz, 1H), 7.80-7.72 (m, 1H), 7.40-7.29 (m, 2H), 7.01 (d, *J* = 2.4 Hz, 1H), 5.38-5.17 (m, 1H),

4.17-4.01 (m, 5H), 3.62 (s, 3H), 3.14-2.97 (m, 4H), 2.84-2.74 (m, 2H), 2.30-1.92 (m, 4H), 1.93-1.90 (m, 1H), 1.89-1.74 (m, 3H), 0.73 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 607.4.

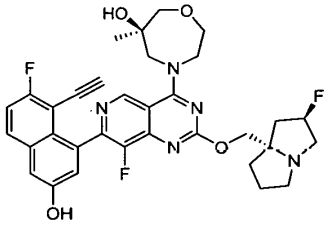
EXAMPLE 385



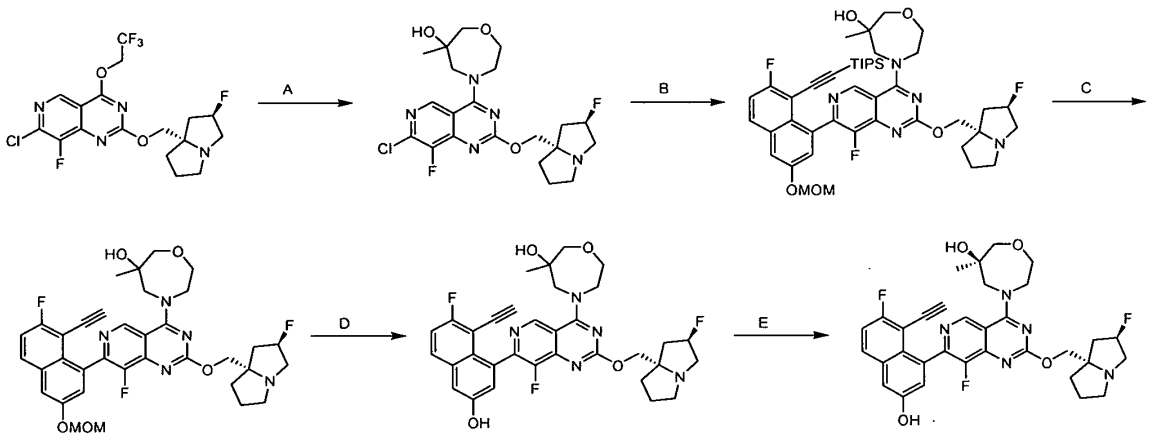
5-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)-1-methyl-1H-pyrazole-3-carboxamide

[00001064] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.92 (s, 1H), 9.50 (m, 1H), 9.34 (s, 1H), 8.13 (s, 1H), 7.76 (m, 1H), 7.41 (s, 1H), 7.38 - 7.29 (m, 2H), 7.20 - 7.12 (m, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.66 (s, 1H), 5.42 - 5.20 (m, 1H), 4.93 - 4.74 (m, 2H), 4.24 - 4.07 (m, 2H), 3.98 (s, 3H), 3.17 - 3.05 (m, 3H), 2.91 - 2.84 (m, 1H), 2.36 - 2.30 (m, 1H), 2.20 - 1.99 (m, 4H), 1.89 - 1.74 (m, 3H), 0.71 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 647.1

EXAMPLE 386



(R)-4-(7-(8-ethynyl-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



[00001065] Step A. 4-(7-chloro-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 6-methyl-1,4-oxazepan-6-ol (117 mg, 1.3 *equiv.*), 4Å molecular sieves (30 mg) and DIEA (353 mg, 4.0 *equiv.*) in DMF (3 mL) was stirred at 15 °C for 0.5 hour. Then 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (300 mg, 1.0 *equiv.*) was added into the above mixture and the mixture was stirred at 40 °C for 4 hours. After reaction completion, the mixture was filtered and the filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, neutralized with solid $NaHCO_3$ and concentrated in vacuum to remove acetonitrile. The aqueous phase was extracted with ethyl acetate (2 × 15 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to afford the title compound (210 mg, 62% yield) as a white solid; ^1H NMR (400 MHz, DMSO-d_6) δ = 9.31 (s, 1H), 5.27 (br d, J = 53.6 Hz, 1H), 5.15 (s, 1H), 4.37 - 4.26 (m, 1H), 4.20 - 4.11 (m, 2H), 4.08 - 3.96 (m, 3H), 3.95 - 3.89 (m, 1H), 3. 82 - 3.73 (m, 1H), 3.57 - 3.48 (m, 2H), 3.11 - 2.99 (m, 3H), 2.87 - 2.78 (m, 1H), 2.13 - 2.03 (m, 2H), 2.01 - 1.94 (m, 1H), 1.88 - 1.72 (m, 3H), 1.13 (s, 3H); LCMS [ESI, M+1]: 470.1.

[00001066] Step B. 4-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-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-chloro-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 (190 mg, 1.0 *equiv.*), ((2-

fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (311 mg, 1.5 *equiv.*) and K_3PO_4 (1.5 M in water , 809 µL, 3.0 *equiv.*) in THF (2.4 mL) was added CataCXium A Pd G3 (29.5 mg, 0.1 *equiv.*) under N_2. The mixture was degassed and stirred at 60 °C for 2.5 hours under N_2. After completion, the mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 × 6 mL). The combined organic layers were concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and neutralized with solid $NaHCO_3$, concentrated in vacuum to remove acetonitrile. The aqueous phase was extracted with ethyl acetate (25 mL). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to afford the title compound (316 mg, 89% yield) as a yellow solid; LCMS [ESI, M+1, M/2+1]: 820.3, 410.9.

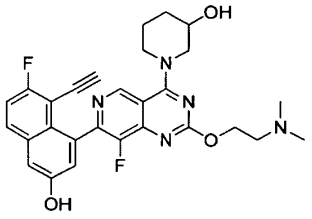
[00001067] Step C. 4-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol: A mixture of 4-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol (320 mg, 1.0 *equiv.*) and CsF (889 mg, 15 *equiv.*) in DMF (1.6 mL) was stirred at 25 °C for 2 hours. After reaction completion, the mixture was filtered and the filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected, neutralized with solid $NaHCO_3$ and concentrated in vacuum to remove acetonitrile. The mixture was extracted with ethyl acetate (20 mL). The organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated in vacuum to afford the title compound (242 mg, 92% yield) as a yellow solid; ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.39 (d, *J* = 47.2 Hz, 1H), 8.10 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.55 (t, *J* = 8.8 Hz, 1H), 7.39 (dd, *J* = 1.6, 9.2 Hz, 1H), 5.38 (s, 2H), 5.36 - 5.08 (m, 2H), 4.42 - 4.31 (m, 1H), 4.20 - 4.05 (m, 4H), 4.02 - 3.93 (m, 2H), 3.90 - 3.79 (m, 1H), 3.63 - 3.49 (m, 2H), 3.44 (s, 3H), 3.30 (br s, 1H), 3.15 - 3.00 (m, 3H), 2.87 - 2.79 (m, 1H), 2.15 - 2.03 (m, 2H), 1.99 (s, 1H), 1.88 - 1.73 (m, 3H), 1.19 - 1.16 (m, 3H); ^{19}F NMR (376 MHz, DMSO-d6) δ = -108.987, -140.166, -172.173; LCMS [ESI, M+1, M/2+1]: 664.3, 332.7.

[00001068] Step D. 4-(7-(8-ethynyl-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-

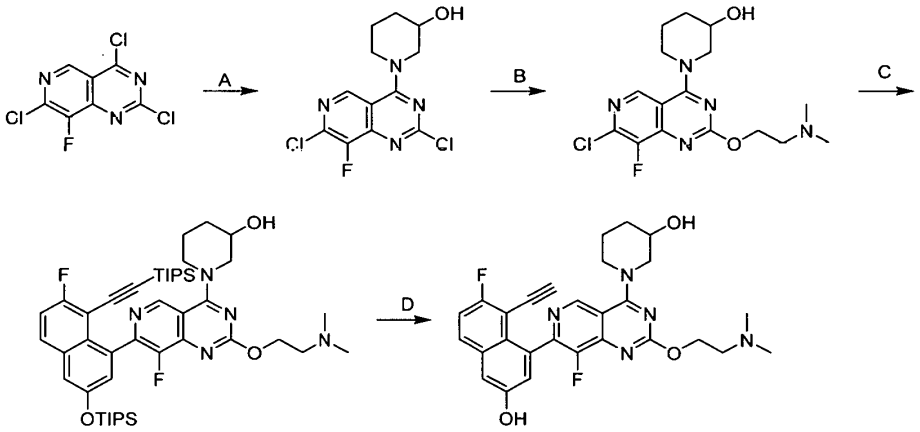
methyl-1,4-oxazepan-6-ol: To a mixture of 4-(7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol (260 mg, 1.0 *equiv.*) in dichloromethane (1 mL) was added TFA (1.54 g, 34 *equiv.*) at 0 °C and the mixture was stirred at 0 - 15 °C for 2 hours. After reaction completion, the mixture was concentrated in vacuum. The residue was neutralized with saturated $NaHCO_3$ solution and extracted with ethyl acetate (2 × 8 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and neutralized with $NaHCO_3$ solid, concentrated in vacuum to remove acetonitrile. The mixture was extracted with ethyl acetate (2 × 20 mL) and the combined organic phase was washed with brine (25 mL), dried over anhydrous Na_2SO_4. The mixture was concentrated in vacuum to afford the title compound (177 mg, 70% yield) as a yellow solid; LCMS [ESI, M+1]: 620.2.

[00001069] Step E. (R)-4-(7-(8-ethynyl-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: Stereoisomers of 4-(7-(8-ethynyl-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 (177 mg) were separated by SFC (column: DAICEL CHIRALPAK AD (250 mm × 30 mm, 10 um); mobile phase: A: [0.1% NH3•H2O - IPA], B: CO_2, B%: 35% - 35%, 6.8 min over 90 min). Both peaks were further re-purified by prep-HPLC [column: Water s Xbridge 150 × 25mm × 5μm; mobile phase: water (10mM NH_4HCO_3)-ACN; B%: 30% - 60%, 8 min] followed by another prep-HPLC [column: PhenomenexGemini-NX C18 75 × 30mm × 3μm; mobile phase: water (0.05% ammonia hydroxide v/v) - ACN, B%: 25% - 55%, 7 min] to afford the title compound (peak 2) (35.1 mg, 19% yield) as an orange solid; SFC: 97.4%: Chiralpak IE-3 50 × 4.6mm I.D., 3μm; A: Heptane (0.05% DEA); B: 25% EtOH (0.05% DEA); 1mL/min; 220 nm, t_R: 6.204 min; ^{1}H NMR (400 MHz, methanol-d4) δ = 9.42 (d, *J* = 43.2 Hz, 1H), 7.88 - 7.81 (m, 1H), 7.36 - 7.29 (m, 2H), 7.22 (dd, *J* = 2.4, 10.4 Hz, 1H), 5.30 (br d, *J* = 54.0 Hz, 1H), 4.64 - 4.43 (m, 2H), 4.35 - 4.15 (m, 3H), 4.07 - 3.83 (m, 3H), 3.75 - 3.56 (m, 2H), 3.48 - 3.41 (m, 1H), 3.29 - 3.13 (m, 3H), 3.05 - 2.97 (m, 1H), 2.38 - 2.18 (m, 2H), 2.16 - 2.08 (m, 1H), 2.04 - 1.95 (m, 2H), 1.94 - 1.83 (m, 1H), 1.27 (d, *J* = 13.6 Hz, 3H); LCMS (ESI, M+1): m/z = 620.3.

EXAMPLE 387



1-(2-(2-(dimethylamino)ethoxy)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol



[00001070] Step A. 1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol: A solution of 2,4,7-trichloro-8-fluoropyrido[4,3-*d*]pyrimidine (200 mg, 1.0 *equiv.*), DIEA (512 mg, 5.0 *equiv.*) and 4 Å molecular sieves (20 mg) in DCM (4 mL) at 18 °C under N_2 was de-gassed and piperidin-3-ol was added dropwise at -40 °C (218 mg, 2.0 *equiv.*, HCl) under N_2. The reaction was stirred at -40 °C for 15 minutes. The mixture was quenched with water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated in vacuum to give a residue and the residue was purified by reversed phase flash chromatography [C18, water (0.1% formic acid) - ACN] to afford the title compound (193 mg, 77% yield) as a yellow solid. LCMS (ESI, M+1): m/z = 316.9.

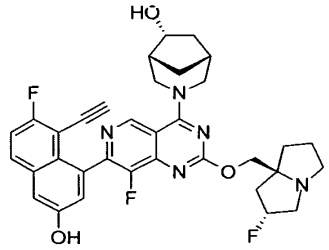
[00001071] Step B. 1-(7-chloro-2-(2-(dimethylamino)ethoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol: A stirred mixture of of 1-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol (129 mg, 1.0 *equiv.*), DIEA (157 mg, 3.0 *equiv.*) and 2-(dimethylamino) ethanol

(366 mg, 10 *equiv.*) was heated to 90 °C for 3 hours. The mixture was diluted with ethyl acetate (10 mL) and water (20 mL). The aqueous phase was extracted with ethyl acetate (20 mL), the combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, concentrated and the residue was purified by reversed phase flash chromatography [C18, water (0.1% formic acid) - ACN] to afford the title compound (126 mg, 84% yield) as a yellow solid. LCMS (ESI, M+1): m/z = 370.1.

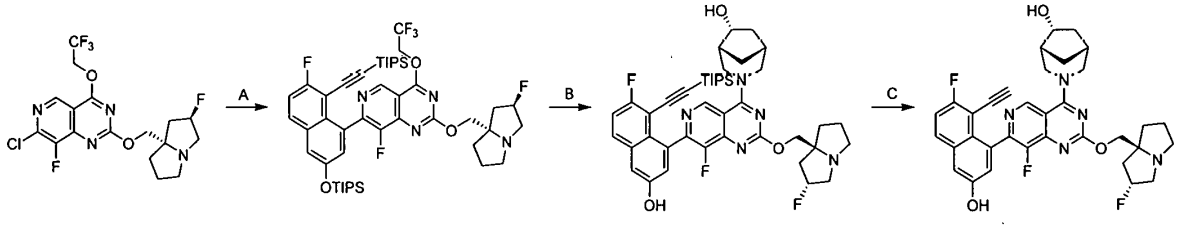
[00001072] Step C. 1-(2-(2-(dimethylamino)ethoxy)-8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol: A mixture of ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane (243 mg, 1.2 *equiv.*), 1-(7-chloro-2-(2-(dimethylamino)ethoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol (120 mg, 1.0 *equiv.*), Cs_2CO_3 (1.5 M in water , 3.0 *equiv.*) and CataCXium A Pd G3 (24 mg, 0.1 *equiv.*) in methoxycyclopentane (4 mL) was de-gassed and attired at 90 °C for 2.5 hours under N_2. The mixture was diluted with ethyl acetate (10 mL) and water (20 mL). The aqueous phase 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 to give a residue and the residue was purified by reversed phase flash chromatography [C18, water (0.1% formic acid) - ACN] to afford the title compound (115 mg, 42% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 832.4.

[00001073] Step D. 1-(2-(2-(dimethylamino)ethoxy)-7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol: A mixture of 1-(2-(2-(dimethylamino)ethoxy)-8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-ol (60 mg, 1.0 *equiv.*) and CsF (164 mg, 15 *equiv.*) in DMF (0.6 mL) was stirred at 18 °C for 12 hours. After reaction completion, the mixture was filtered and the filtrate was was purified by prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: water (10 mM NH_4HCO_3)-ACN, B%: 24% - 54%, 7 min) to afford the title compound (5.3 mg, 14% yield) as a white solid; ^{1}H NMR (400 MHz, CD3OD, 298 K) δ (ppm) = 9.12-9.02 (m, 1H), 7.85 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.36-7.28 (m, 2H), 7.22 (dd, *J* = 2.4, 10.4 Hz, 1H), 4.66-4.59 (m, 2H), 4.29-4.17 (m, 1H), 4.14-3.76 (m, 4H), 3.50-3.38 (m, 1H), 2.84 (t, *J* = 5.6 Hz, 2H), 2.37 (s, 6H), 2.18-2.01 (m, 2H), 1.84-1.68 (m, 2H) LCMS [ESI, M+1]: m/z = 520.2.

EXAMPLE 388



(1R,5R,6R)-3-(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-azabicyclo[3.2.1]octan-6-ol

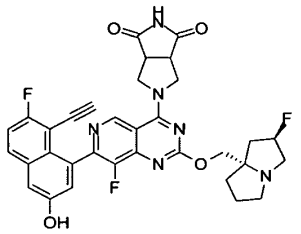


[00001074] Step A. 8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: A mixture of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (130 mg, 1.0 *equiv.*), ((6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-((triisopropylsilyl)ethynyl)naphthalen-2-yl)oxy)triisopropylsilane (204 mg, 1.1 *equiv.*), Cs_2CO_3 (1.5 M in water , 3.0 *equiv.*) and CataCXium A Pd G3 (21.6 mg, 0.1 *equiv.*) in methoxycyclopentane (2 mL) was de-gassed and stirred at 100 °C for 2.5 hours under N_2. The reaction mixture was diluted with ethyl acetate (15 mL) and water (30 mL). The aqueous phase 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 reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and neutralized with solid $NaHCO_3$, concentrated in vacuum to afford the title compound (260 mg, 97% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 901.3.

[00001075] Step B. 3-(8-fluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol: 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 (260 mg, 1.0 *equiv.*), (1R,5R,6R)-3-azabicyclo[3.2.1]octan-6-ol (47.7 mg, 1.3 *equiv.*), DIEA (112 mg, 3.0 *equiv.*) and 4Å molecular sieves (20 mg) in DMF (3 mL) was stirred at 40 °C for 12 hrs. Additional amounts of (1R,5R,6R)-3-azabicyclo[3.2.1]octan-6-ol (25.7 mg, 0.7 *equiv.*) and DIEA (37.3 mg, , 1.0 *equiv.*) were introduced into the reaction mixture and the resulting was stirred at 40 °C for 12 hrs. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and neutralized with solid $NaHCO_3$, concentrated in vacuum to remove ACN. The aqueous phase was extracted with ethyl acetate (10 mL × 2). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford the title compound (110 mg, 44% yield) as a white solid; LCMS (ESI, M+1): m/z = 772.3.

[00001076] Step C. (1R,5R,6R)-3-(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-azabicyclo[3.2.1]octan-6-ol: To a solution of 3-(8-fluoro-7-(7-fluoro-3-hydroxy-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol (100 mg, 1.0 *equiv.*) in DMF (1 mL) was added CsF (295 mg, 15 *equiv.*). The reaction was stirred at 20 °C for 12 hours. The mixture was filtered and the filtrate was purified by prep-HPLC [column: Water s Xbridge 150 × 25 mm × 5 μm; mobile pjase: water (10mM NH_4HCO_3)-ACN, B%: 38%-68%, 9 min] and lyophilized to afford the title compound (33.8 mg, 42% yield) as a yellow solid; ^{1}H NMR (400 MHz, CD3SOCD3, 298 K) δ (ppm) = 10.58 - 9.93 (m, 1H), 9.36 - 9.01 (m, 1H), 8.00 - 7.91 (m, 1H), 7.49 - 7.34 (m, 2H), 7.26 - 7.13 (m, 1H), 5.37 - 5.17 (m, 1H), 5.10 - 4.54 (m, 2H), 4.51 - 4.05 (m, 3H), 4.01 - 3.94 (m, 1H), 3.93 - 3.86 (m, 1H), 3.77 - 3.63 (m, 1H), 3.23 (br d, J = 12.8 Hz, 1H), 3.14 - 2.97 (m, 3H), 2.86 - 2.77 (m, 1H), 2.32 (s, 1H), 2.18 - 1.92 (m, 5H), 1.92 - 1.58 (m, 5H), 1.33 - 1.20 (m, 1H); LCMS (ESI, M+1): m/z = 616.2

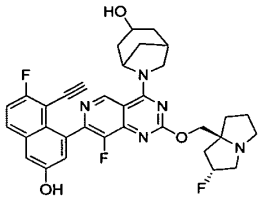
EXAMPLE 389



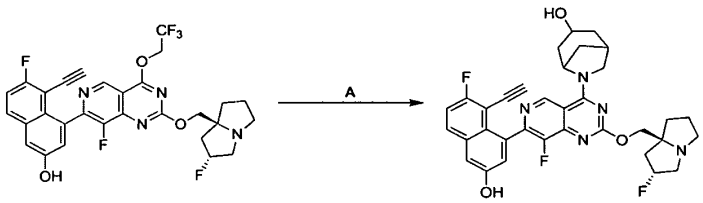
5-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione

[00001077] The title compound was synthesized according to the procedure described for example 388. ^{1}H NMR (400 MHz, methanol-d4) δ 9.23 (s, 1H), 7.90 - 7.83 (m, 1H), 7.38 - 7.28 (m, 2H), 7.23 (d, J = 2.4 Hz, 1H), 5.55 - 5.36 (m, 1H), 4.76 - 4.73 (m, 1H), 4.65 - 4.61 (m, 1H), 4.56 - 4.46 (m, 2H), 4.41 - 4.33 (m, 1H), 4.31 - 4.22 (m, 1H), 3.79 - 3.71 (m, 2H), 3.71 - 3.52 (m, 3H), 3.36 - 3.33 (m, 1H), 3.26 - 3.24 (m, 1H), 2.60 - 2.37 (m, 2H), 2.34 - 2.26 (m, 1H), 2.24 - 2.14 (m, 2H), 2.11 - 1.99 (m, 1H); LCMS (ESI, M+1): m/z = 629.3.

EXAMPLE 390

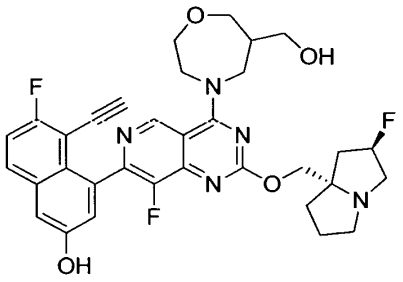


6-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azabicyclo[3.2.1]octan-3-ol



[00001078] Step A. 6-(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)-6-azabicyclo[3.2.1]octan-3-ol: To a solution of 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 (100 mg, 1.0 *equiv.*) and 4Å molecular sieves (20.0 mg) in DMF (1 mL) was added DIEA (371 mg, 0.50 mL, 16.9 *equiv.*) and 6-azabicyclo[3.2.1]octan-3-ol (123 mg, 3.0 *equiv.*, TFA). The mixture was stirred at 40 °C for 12 hours. The mixture was filtered and the filtrate was purified by prep-HPLC (column: Phenomenex luna C18 150 × 25mm × 10 μm; mobile phase: [water (0.1% formic acid)-ACN]; B%: 12%-42%, 10.5 min) to afford the title compound (15.6 mg, 14% yield) as a yellow solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.27 - 9.10 (m, 1H), 7.84 (dd, *J* = 5.6, 8.4 Hz, 1H), 7.36 - 7.27 (m, 2H), 7.27 - 7.17 (m, 1H), 5.40 - 5.21 (m, 1H), 4.97 (br s, 1H), 4.40 - 4.18 (m, 4H), 4.16 - 4.05 (m, 1H), 3.27 - 3.12 (m, 3H), 3.07 - 2.95 (m, 1H), 2.82 - 2.53 (m, 2H), 2.40 - 2.27 (m, 1H), 2.26 - 2.11 (m, 3H), 2.07 - 1.95 (m, 4H), 1.95 - 1.85 (m, 2H), 1.84 - 1.62 (m, 2H); LCMS (ESI, M+1): m/z = 616.5.

EXAMPLE 391

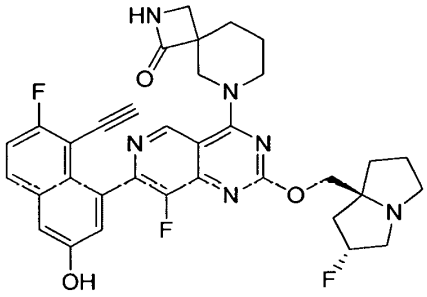


5-ethynyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(6-(hydroxymethyl)-1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol

[00001079] The title compound was synthesized according to the procedure described for example 390. 1H NMR (400 MHz, METHANOL-d4) δ = 9.19 (d, *J* = 14.4 Hz, 1H), 8.51 (br s, 1H), 7.89 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.35 (t, *J* = 9.2 Hz, 1H), 7.24 (dd, *J* = 2.4, 10.8 Hz, 1H), 5.55 - 5.34 (m, 1H), 4.74 - 4.54 (m, 2H), 4.53 - 4.48 (m, 1H), 4.48 - 4.30 (m, 2H), 4.20 - 4.10 (m, 2H), 4.09 (br s, 2H), 3.94 - 3.77 (m, 1H), 3.70 - 3.61 (m, 3H), 3.60 - 3.48 (m,

3H), 3.29 - 3.20 (m, 1H), 2.59 - 2.34 (m, 3H), 2.32 - 2.22 (m, 1H), 2.21 - 2.11 (m, 2H), 2.10 - 1.97 (m, 1H); LCMS (ESI, M+1): m/z = 620.3.

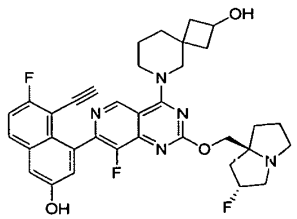
EXAMPLE 392



6-(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)-2,6-diazaspiro[3.5]nonan-1-one

[00001080] The title compound was synthesized according to the procedure described for example 390. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.01 (d, *J* = 8.0 Hz, 1H), 7.85 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.36 - 7.27 (m, 2H), 7.23 (dd, *J* = 2.4, 6.4 Hz, 1H), 5.40 - 5.20 (m, 1H), 4.43 - 4.27 (m, 3H), 4.26 - 4.19 (m, 1H), 4.13 - 3.98 (m, 1H), 3.85 - 3.60 (m, 1H), 3.42 - 3.33 (m, 1H), 3.29 - 3.12 (m, 5H), 3.00 (dt, *J* = 5.6, 9.2 Hz, 1H), 2.39 - 2.26 (m, 1H), 2.24 - 2.02 (m, 5H), 2.02 - 1.82 (m, 4H); LCMS (ESI, M+1): m/z = 629.5.

Example 393

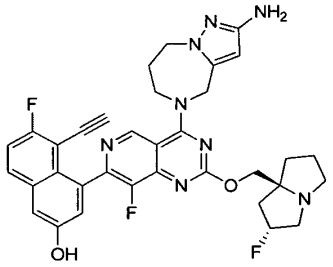


6-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol

[00001081] The title compound was synthesized according to the procedure described for example 390. 1H NMR (400 MHz, METHANOL-d4) δ = 9.05 - 8.96 (m, 1H), 7.86 (dd, J = 5.6,

9.2 Hz, 1H), 7.43 - 7.28 (m, 1H), 7.39 - 7.26 (m, 1H), 7.24 - 7.18 (m, 1H), 5.45 - 5.15 (m, 1H), 4.36 - 4.30 (m, 1H), 4.39 - 4.17 (m, 1H), 4.16 - 4.09 (m, 1H), 4.06 (br s, 1H), 4.02 - 3.95 (m, 1H), 3.95 - 3.84 (m, 1H), 3.47 - 3.35 (m, 1H), 3.28 - 3.12 (m, 3H), 3.06 - 2.98 (m, 1H), 2.39 - 2.32 (m, 1H), 2.32 - 2.26 (m, 1H), 2.25 - 2.11 (m, 3H), 2.05 - 1.96 (m, 2H), 1.96 - 1.67 (m, 5H); LCMS (ESI, M+1): m/z = 630.4.

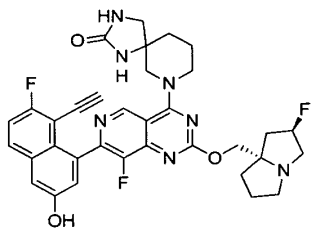
Example 394



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-ethynyl-6-fluoronaphthalen-2-ol

[00001082] The title compound was synthesized according to the procedure described for example 390. 1H NMR (400 MHz, METHANOL-d4) δ = 9.19 (s, 1H), 8.47 (s, 1H), 7.87 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.36 - 7.30 (m, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 5.79 (s, 1H), 5.53 - 5.34 (m, 1H), 5.18 - 5.03 (m, 2H), 4.54 - 4.41 (m, 2H), 4.38 (br d, *J* = 4.8 Hz, 2H), 4.25 (br dd, *J* = 4.0, 5.6 Hz, 2H), 3.70 - 3.47 (m, 3H), 3.40 (d, *J* = 2.4 Hz, 1H), 3.24 (dt, J = 6.0, 9.6 Hz, 1H), 2.55 - 2.43 (m, 1H), 2.39 (br d, *J* = 4.0 Hz, 3H), 2.32 - 2.23 (m, 1H), 2.23 - 2.12 (m, 2H), 2.09 - 1.98 (m, 1H); LCMS (ESI, M+1): m/z = 641.2

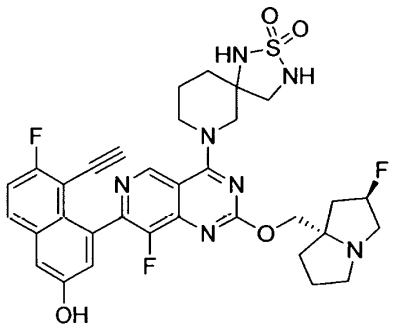
EXAMPLE 395



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)-1,3,7-triazaspiro[4.5]decan-2-onc

[00001083] The title compound was synthesized according to the procedure described for example 390. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.06 (s, 1H), 8.51 (br s, 1H), 7.86 (ddd, *J* = 1.6, 5.6, 9.2 Hz, 1H), 7.39 - 7.26 (m, 2H), 7.22 (dd, *J* = 2.4, 4.4 Hz, 1H), 5.52 - 5.29 (m, 1H), 4.52 - 4.36 (m, 2H), 4.36 - 4.28 (m, 1H), 4.25 - 3.98 (m, 2H), 3.97 - 3.78 (m, 1H), 3.63 - 3.49 (m, 1H), 3.49 - 3.40 (m, 3H), 3.40 - 3.36 (m, 1H), 3.28 (br d, *J* = 2.0 Hz, 1H), 3.21 - 3.11 (m, 1H), 2.53 - 2.30 (m, 2H), 2.30 - 2.18 (m, 1H), 2.16 - 1.94 (m, 6H), 1.92 - 1.82 (m, 1H). LCMS (ESI, M+1): m/z = 644.2.

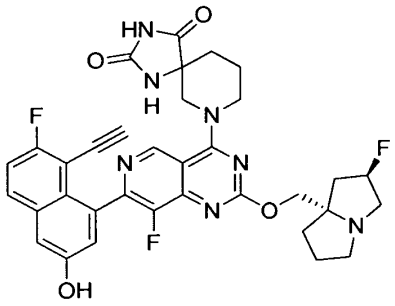
EXAMPLE 396



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-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide

[00001084] The title compound was synthesized according to the procedure described for example 390. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.19 (d, *J* = 14.4 Hz, 1H), 8.51 (br s, 1H), 7.89 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.35 (t, *J* = 9.2 Hz, 1H), 7.24 (dd, *J* = 2.4, 10.8 Hz, 1H), 5.55 - 5.34 (m, 1H), 4.74 - 4.54 (m, 2H), 4.53 - 4.48 (m, 1H), 4.48 - 4.30 (m, 2H), 4.20 - 4.10 (m, 2H), 4.09 (br s, 2H), 3.94 - 3.77 (m, 1H), 3.70 - 3.61 (m, 3H), 3.60 - 3.48 (m, 3H), 3.29 - 3.20 (m, 1H), 2.59 - 2.34 (m, 3H), 2.32 - 2.22 (m, 1H), 2.21 - 2.11 (m, 2H), 2.10 - 1.97 (m, 1H); LCMS (ESI, M+1): m/z = 680.2.

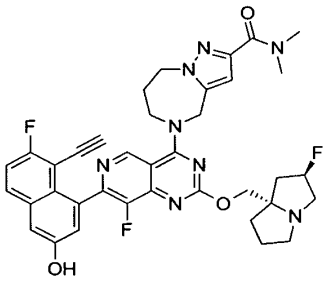
EXAMPLE 397



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)-1,3,7-triazaspiro[4.5]decane-2,4-dione

[00001085] The title compound was synthesized according to the procedure described for example 390. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.05 (d, *J* = 6.4 Hz, 1H), 7.86 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.23 (dd, *J* = 2.4, 4.8 Hz, 1H), 5.38 - 5.22 (m, 1H), 4.64 - 4.58 (m, 1H), 4.56 - 4.49 (m, 1H), 4.45 - 4.13 (m, 3H), 3.97 - 3.56 (m, 3H), 3.23 - 3.12 (m, 2H), 3.05 - 2.96 (m, 1H), 2.37 - 2.23 (m, 2H), 2.23 - 2.13 (m, 2H), 2.12 - 2.03 (m, 2H), 2.03 - 1.91 (m, 4H). LCMS (ESI, M+1): m/z = 658.4.

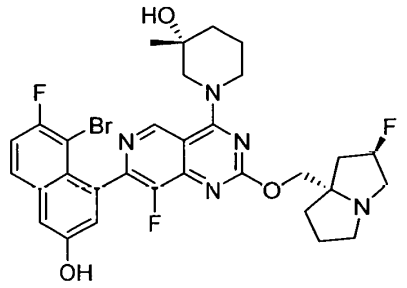
EXAMPLE 398



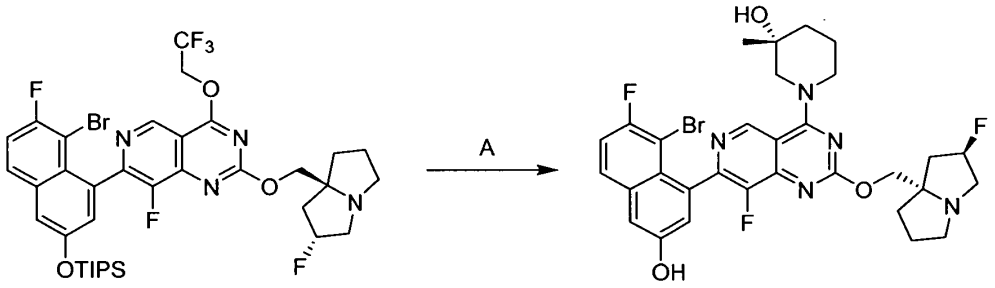
5-(7-(8-ethynyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-*a*][1,4]diazepine-2-carboxamide

[00001086] The title compound was synthesized according to the procedure described for example 390. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.14 (s, 1H), 7.88 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.38-7.31 (m, 2H), 7.23 (d, *J* = 2.4 Hz, 1H), 6.79 (s, 1H), 5.42-5.19 (m, 3H), 4.61-4.55 (m, 2H), 4.46 (br t, *J* = 5.6 Hz, 2H), 4.35-4.21 (m, 2H), 3.43 (d, *J* = 4.8 Hz, 1H), 3.36 (s, 2H), 3.28-3.14 (m, 3H), 3.10 (s, 3H), 3.06-2.98 (m, 1H), 2.46 (br s, 2H), 2.07-1.84 (m, 4H), 2.37-1.84 (m, 3H); LCMS (ESI, M+1): m/z = 697.3.

EXAMPLE 399



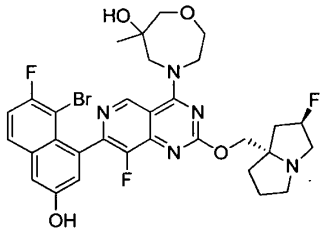
(R)-1-(7-(8-bromo-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



[00001087] Step A. (S)-1-(7-(8-bromo-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 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 (100 mg, 1.0 *equiv.*) in DMF (0.5 mL) were added DIEA (129 mg, 8.0 *equiv.*), 4Å molecular sieves (5 mg, 1.00 *equiv.*) and (3R)-3-methylpiperidin-3-ol

(28.4 mg, 1.97 *equiv.*). The mixture was stirred at 40 °C for 12 hours. The reaction mixture was filtered and the filtrate was purified by prep-HPLC (column: Phenomenex Luna C18 150 × 25mm × 10 μm; mobile phase: [water (0.1% formic acid)-ACN]; B%: 16%-46%, 8 min) and lyophilized to afford the title compound (13.2 mg, 16% yield) as a brown solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.23 (d, *J* = 11.2 Hz, 1H), 8.61 - 8.38 (m, 1H), 7.91 - 7.82 (m, 1H), 7.41 - 7.33 (m, 2H), 7.24 (dd, *J* = 2.8, 4.4 Hz, 1H), 5.52 - 5.35 (m, 1H), 4.59 (br d, *J* = 13.2 Hz, 1H), 4.54 - 4.40 (m, 2H), 4.33 (br dd, *J* = 5.6, 13.2 Hz, 1H), 3.73 - 3.59 (m, 2H), 3.59 - 3.51 (m, 2H), 3.49 - 3.41 (m, 1H), 3.28 - 3.19 (m, 1H), 2.60 - 2.33 (m, 2H), 2.32 - 2.24 (m, 1H), 2.23 - 2.09 (m, 3H), 2.07 - 1.98 (m, 1H), 1.90 - 1.73 (m, 3H), 1.30 (d, *J* = 6.4 Hz, 3H); LCMS (ESI, M+1): m/z = 658.2.

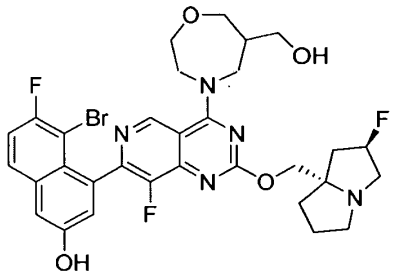
EXAMPLE 400



4-(7-(8-bromo-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-methyl-1,4-oxazepan-6-ol

[00001088] The title compound was synthesized according to the procedure described for example 399. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.54 (dd, *J* = 2.8, 12.0 Hz, 1H), 8.51 (s, 1H), 7.86 (ddd, *J* = 1.2, 5.6, 9.2 Hz, 1H), 7.43 - 7.32 (m, 2H), 7.24 (dd, *J* = 2.4, 14.4 Hz, 1H), 5.48 - 5.28 (m, 1H), 4.59 - 4.49 (m, 2H), 4.48 - 4.33 (m, 2H), 4.23 - 4.14 (m, 1H), 4.06 - 3.87 (m, 3H), 3.75 - 3.63 (m, 2H), 3.55 - 3.36 (m, 3H), 3.21 - 3.09 (m, 1H), 2.49 - 2.28 (m, 2H), 2.26 - 2.18 (m, 1H), 2.14 - 2.04 (m, 2H), 2.03 - 1.92 (m, 1H), 1.28 (s, 3H). LCMS (ESI, M+1): m/z = 674.2.

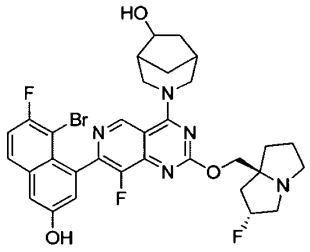
EXAMPLE 401



5-bromo-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

[00001089] The title compound was synthesized according to the procedure described for example 399. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.34 - 9.16 (m, 1H), 8.59 - 8.46 (m, 1H), 7.88 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.46 - 7.34 (m, 2H), 7.27 (dd, *J* = 2.4, 11.2 Hz, 1H), 5.54 - 5.35 (m, 1H), 4.67 (dt, *J* = 4.4, 9.2 Hz, 1H), 4.60 - 4.39 (m, 3H), 4.21 - 3.94 (m, 4H), 3.92 - 3.78 (m, 1H), 3.69 - 3.44 (m, 6H), 3.28 - 3.17 (m, 1H), 2.35 (br s, 3H), 2.31 - 1.98 (m, 4H); LCMS (ESI, M+1): m/z = 674.2.

EXAMPLE 402

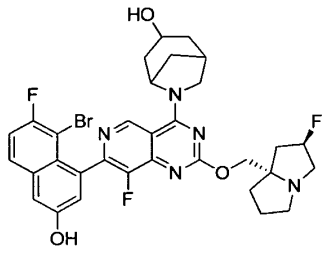


3-(7-(8-bromo-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-azabicyclo[3.2.1]octan-6-ol

[00001090] The title compound was synthesized according to the procedure described for example 399. ^{1}HNMR (400 MHz, METHANOL-d4) δ = 9.32 - 9.20 (m, 1H), 8.59 - 8.47 (m, 1H), 7.88 (ddd, *J* = 1.2, 5.6, 9.2 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.40 - 7.35 (m, 1H), 7.26 (dd, *J* = 2.4, 16.8 Hz, 1H), 5.53 - 5.35 (m, 1H), 5.03 (br d, *J* = 9.6 Hz, 1H), 4.80 (br s, 1H), 4.54 - 4.47 (m,

1H), 4.46 - 4.38 (m, 1H), 4.38 - 4.30 (m, 1H), 3.91 - 3.74 (m, 1H), 3.71 - 3.43 (m, 4H), 3.28 - 3.18 (m, 1H), 2.59 - 2.37 (m, 3H), 2.36 - 2.21 (m, 3H), 2.21 - 2.11 (m, 2H), 2.09 - 1.92 (m, 2H), 1.89 - 1.78 (m, 1H), 1.45 - 1.35 (m, 1H); LCMS (ESI, M+1): m/z = 670.1.

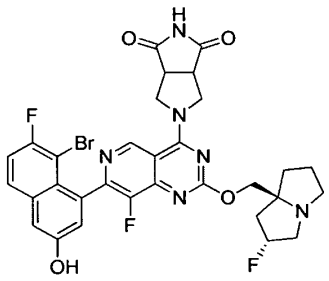
EXAMPLE 403



6-(7-(8-bromo-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

[00001091] The title compound was synthesized according to the procedure described for example 399. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.30 (br d, *J* = 7.2 Hz, 1H), 8.50 (s, 1H), 7.86 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.34 (s, 2H), 7.29 - 7.19 (m, 1H), 5.53 - 5.35 (m, 1H), 5.00 (br s, 1H), 4.55 - 4.34 (m, 3H), 4.31 - 4.24 (m, 1H), 4.14 (br s, 1H), 3.74 - 3.52 (m, 3H), 3.27 - 3.21 (m, 1H), 2.84 - 2.58 (m, 2H), 2.55 (br s, 1H), 2.45 - 2.26 (m, 2H), 2.17 (br dd, *J* = 5.2, 9.2 Hz, 3H), 2.10 - 1.98 (m, 3H), 1.94 - 1.76 (m, 2H). LCMS (ESI, M+1): m/z = 670.2.

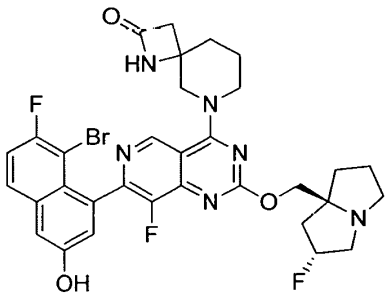
EXAMPLE 404



5-(7-(8-bromo-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)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione

[00001092] The title compound was synthesized according to the procedure described for example 399. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.26 (s, 1H), 8.51 (br s, 1H), 7.86 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.40 - 7.33 (m, 2H), 7.24 (d, *J* = 2.4 Hz, 1H), 5.47 - 5.29 (m, 1H), 4.64 (br t, *J* = 12.0 Hz, 2H), 4.47 - 4.42 (m, 1H), 4.41 - 4.30 (m, 3H), 3.81 - 3.72 (m, 2H), 3.57 - 3.45 (m, 1H), 3.45 - 3.35 (m, 2H), 3.20 - 3.10 (m, 1H), 2.51 - 2.30 (m, 2H), 2.29 - 2.17 (m, 1H), 2.15 - 2.05 (m, 2H), 2.04 - 1.93 (m, 1H); LCMS (ESI, M+1): m/z = 682.9.

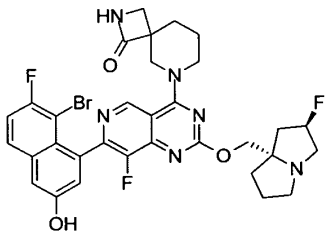
EXAMPLE 405



6-(7-(8-bromo-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)-1,6-diazaspiro[3.5]nonan-2-one

[00001093] The title compound was synthesized according to the procedure described for example 399. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.11 (s, 1H), 8.45 (br s, 1H), 7.87 (br dd, *J* = 5.8, 8.0 Hz, 1H), 7.43 - 7.33 (m, 2H), 7.25 (br s, 1H), 5.58 - 5.34 (m, 1H), 4.63 - 4.26 (m, 4H), 4.09 - 3.96 (m, 1H), 3.92 - 3.54 (m, 4H), 3.29 - 3.22 (m, 1H), 2.99 - 2.72 (m, 2H), 2.62 - 2.25 (m, 3H), 2.23 - 1.92 (m, 7H) LCMS (ESI, M+1): m/z = 683.2.

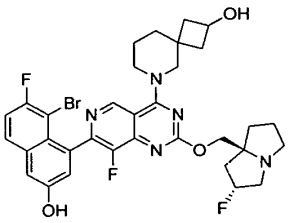
EXAMPLE 406



6-(7-(8-bromo-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2,6-diazaspiro[3.5]nonan-1-one

[00001094] The title compound was synthesized according to the procedure described for example 399. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.09 (d, *J* = 2.0 Hz, 1H), 8.49 (br d, *J* = 2.4 Hz, 1H), 7.86 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.42-7.33 (m, 2H), 7.25 (t, *J* = 3.2 Hz, 1H), 5.57-5.28 (m, 1H), 4.54-4.27 (m, 4H), 4.26-3.91 (m, 2H), 3.70-3.45 (m, 3H), 3.29-3.17 (m, 3H), 2.57-2.35 (m, 2H), 2.32-2.08 (m, 6H), 2.07-1.89 (m, 2H); LCMS (ESI, M+1): m/z = 683.2.

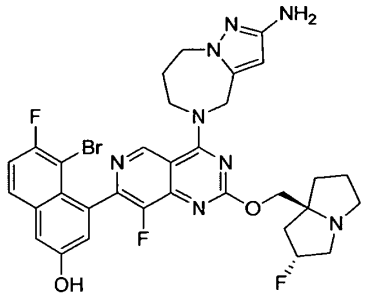
EXAMPLE 407



6-(7-(8-bromo-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-azaspiro[3.5]nonan-2-ol

[00001095] The title compound was synthesized according to the procedure described for example 399. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.11 - 9.05 (m, 1H), 8.54 - 8.43 (m, 1H), 7.91 - 7.82 (m, 1H), 7.43 - 7.31 (m, 2H), 7.30 - 7.22 (m, 1H), 5.52 - 5.36 (m, 1H), 4.56 - 4.44 (m, 2H), 4.32 - 4.24 (m, 1H), 4.15 - 3.95 (m, 4H), 3.69 - 3.50 (m, 3H), 3.27 - 3.19 (m, 1H), 2.53 - 2.15 (m, 7H), 2.09 - 2.00 (m, 1H), 1.88 - 1.72 (m, 6H); LCMS (ESI, M+1): m/z = 684.2.

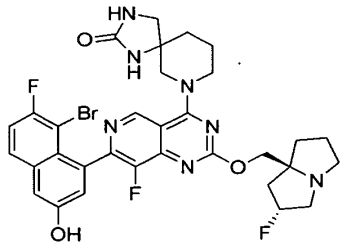
EXAMPLE 408



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-bromo-6-fluoronaphthalen-2-ol

[00001096] The title compound was synthesized according to the procedure described for example 399. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.20 (s, 1H), 7.87 - 7.83 (m, 1H), 7.42 - 7.33 (m, 2H), 7.25 (d, J = 2.0 Hz, 1H), 5.78 (s, 1H), 5.51 - 5.33 (m, 1H), 5.19 - 5.01 (m, 2H), 4.51 - 4.39 (m, 2H), 4.38 - 4.32 (m, 2H), 4.27 - 4.18 (m, 2H), 3.65 - 3.42 (m, 3H), 3.25 - 3.15 (m, 1H), 2.54 - 2.41 (m, 1H), 2.40 - 2.30 (m, 3H), 2.30 - 2.21 (m, 1H), 2.19 - 2.09 (m, 2H), 2.07 - 1.96 (m, 1H); LCMS (ESI, M+1): m/z = 695.2.

EXAMPLE 409

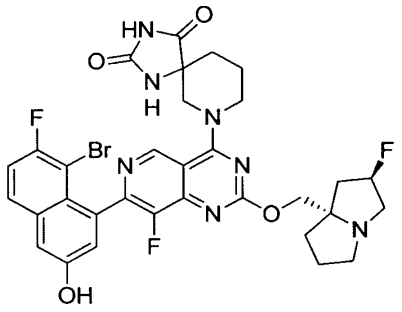


7-(7-(8-bromo-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one

[00001097] The title compound was synthesized according to the procedure described for example 399. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.09 (s, 1H), 7.91 - 7.79 (m, 1H), 7.46 - 7.31 (m, 2H), 7.24 (s, 1H), 5.44 - 5.19 (m, 1H), 4.37 - 4.23 (m, 2H), 4.19 - 4.06 (m, 2H), 4.05 -

3.89 (m, 2H), 3.52 - 3.34 (m, 2H), 3.27 - 3.18 (m, 3H), 3.05 - 2.96 (m, 1H), 2.39 - 2.12 (m, 3H), 2.05 - 1.84 (m, 7H); LCMS (ESI, M+1): m/z = 698.1.

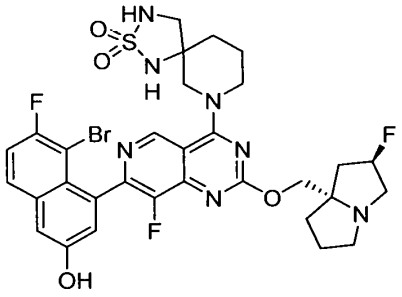
EXAMPLE 410



7-(7-(8-bromo-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)-1,3,7-triazaspiro[4.5]decane-2,4-dione

[00001098] The title compound was synthesized according to the procedure described for example 399. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.09 (s, 1H), 7.85 (dd, *J* = 6.0, 8.8 Hz, 1H), 7.40 - 7.20 (m, 3H), 5.45 - 5.15 (m, 1H), 4.54 - 4.40 (m, 2H), 4.31 - 4.18 (m, 2H), 3.86 - 3.70 (m, 2H), 3.23 - 3.16 (m, 2H), 3.13 - 2.93 (m, 2H), 2.39 - 2.17 (m, 4H), 2.16 - 2.08 (m, 2H), 2.03 - 1.98 (m, 2H), 1.95 - 1.88 (m, 2H). LCMS (ESI, M+1): m/z = 712.0.

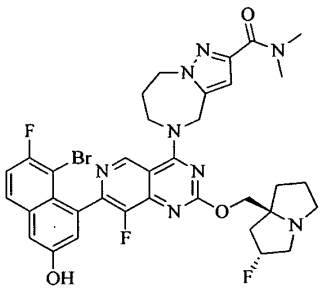
EXAMPLE 411



7-(7-(8-bromo-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-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide

[00001099] The title compound was synthesized according to the procedure described for example 399. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.11 (d, *J* = 7.2 Hz, 1H), 8.54 - 8.43 (m, 1H), 7.86 (td, *J* = 5.2, 9.2 Hz, 1H), 7.41 - 7.31 (m, 2H), 7.23 (t, *J* = 2.0 Hz, 1H), 5.57 - 5.34 (m, 1H), 4.65 (br dd, *J* = 4.0, 14.4 Hz, 1H), 4.62 - 4.53 (m, 1H), 4.52 - 4.41 (m, 2H), 3.85 - 3.76 (m, 1H), 3.74 - 3.50 (m, 4H), 3.45 - 3.38 (m, 1H), 3.28 - 3.18 (m, 2H), 2.62 - 2.38 (m, 2H), 2.38 - 2.27 (m, 1H), 2.22 - 2.13 (m, 2H), 2.12 - 2.00 (m, 3H), 1.99 - 1.83 (m, 2H); LCMS (ESI, M+1): m/z = 734.1.

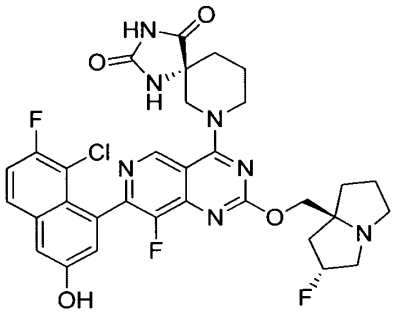
EXAMPLE 412



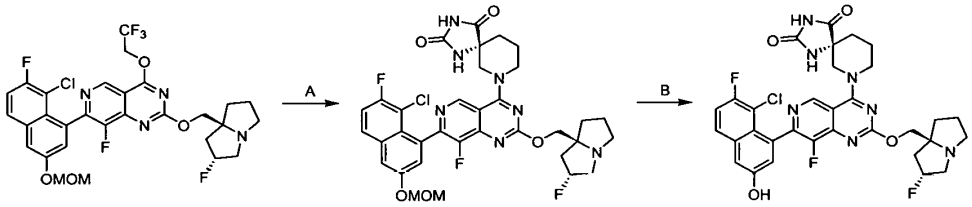
5-(7-(8-bromo-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

[00001100] The title compound was synthesized according to the procedure described for example 399. ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.19 (s, 1H), 8.52 (br s, 1H), 7.86 (dd, *J* = 5.4, 8.8 Hz, 1H), 7.43 - 7.33 (m, 2H), 7.24 (d, *J* = 2.4 Hz, 1H), 6.76 (s, 1H), 5.46 - 5.19 (m, 3H), 4.60 (br s, 4H), 4.42 - 4.30 (m, 2H), 3.54 - 3.45 (m, 1H), 3.42 - 3.36 (m, 2H), 3.34 (s, 3H), 3.21 - 3.11 (m, 1H), 3.11 - 3.06 (m, 3H), 2.51 - 2.50 (m, 1H), 2.18 - 2.16 (m, 1H), 2.50 - 2.16 (m, 5H), 2.13 - 1.92 (m, 3H); LCMS (ESI, M+1): m/z = 751.0.

EXAMPLE 413



(R)-7-(7-(8-chloro-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)-1,3,7-triazaspiro[4.5]decane-2,4-dione

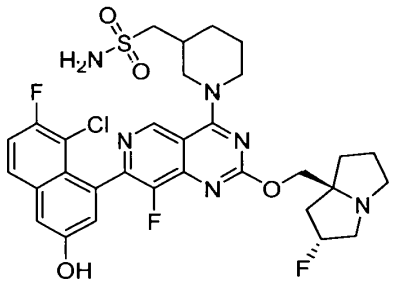


[00001101] Step A. (R)-7-(7-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione: To a mixture of 7-(8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (100 mg, 1.0 *equiv.*), (5R)-1,3,9-triazaspiro[4.5]decane-2,4-dione (78.9 mg, 3.0 *equiv.*) and 4Å molecular sieves (10 mg) in DMF (1 mL) was added DIEA (100 mg, 5.0 *equiv.*). The reaction was stirred at 40 °C for 12 hours. The residue was filtered and purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (110 mg, 92% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 712.3.

[00001102] Step B. (R)-7-(7-(8-chloro-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)-1,3,7-triazaspiro[4.5]decane-2,4-dione: To a solution of (R)-7-(7-(8-chloro-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)-1,3,7-triazaspiro[4.5]decane-2,4-dione (50 mg, 1.0

equiv.) in DCM (2 mL) and MeOH (2 mL) was added TsOH (121 mg, 10 *equiv.*). The reaction was stirred at 10 °C for 12 hours. The residue was filtered and purified by prep-HPLC [column: Phenomenex C18 75 × 30 mm × 3 μm; mobile phase: water (0.1% formic acid)/ACN] B%: 10% - 40%, 7min] and lyophilized to afford the title compound (20.0 mg, 41% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d4) δ = 9.15 (d, *J* = 14.8 Hz, 1H), 7.83 (ddd, *J* = 1.6, 5.6, 9.2 Hz, 1H), 7.52-7.29 (m, 2H), 7.27-7.17 (m, 1H), 5.64-5.43 (m, 1H), 4.77-4.28 (m, 6H), 3.95-3.67 (m, 4H), 3.44-3.32 (m, 1H), 2.72-2.52 (m, 1H), 2.51-2.29 (m, 2H), 2.29-2.05 (m, 4H), 2.05-1.87 (m, 2H); LCMS (ESI, M+1): m/z = 668.2.

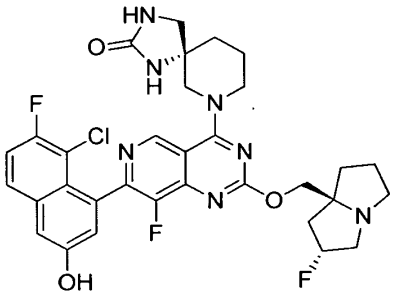
EXAMPLE 414



1-(1-(7-(8-chloro-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)piperidin-3-yl)methanesulfonamide

[00001103] The title compound was synthesized according to the procedure described for example 413 except for HCl•dioxane in MeCN was added in step B. ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.06 (d, *J* = 2.0 Hz, 1H), 7.92 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.55 (t, *J* = 8.8 Hz, 1H), 7.41 (d, *J* = 2.4 Hz, 1H), 7.19 (s, 1H), 7.03-6.70 (m, 2H), 5.38-5.17 (m, 1H), 4.70-4.53 (m, 1H), 4.45-4.31 (m, 1H), 4.19-4.00 (m, 2H), 3.16-3.03 (m, 4H), 3.03-2.96 (m, 2H), 2.86-2.78 (m, 1H), 2.42-2.34 (m, 1H), 2.33 (m, 1H), 2.20-2.09 (m, 1H), 2.09-1.98 (m, 3H), 1.92-1.69 (m, 5H), 1.60-1.45 (m, 1H); LCMS (ESI, M+1): m/z = 677.3.

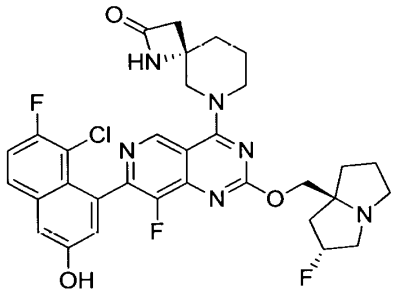
EXAMPLE 415



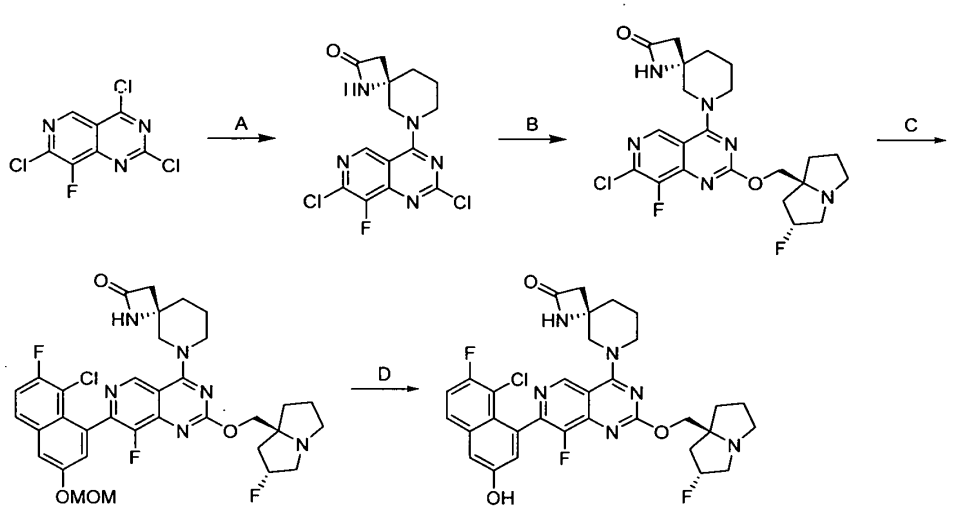
(S)-7-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decan-2-one

[00001104] The title compound was synthesized according to the procedure described for example 413. ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.14 (d, *J* = 7.2 Hz, 1H), 7.85-7.66 (m, 1H), 7.47-7.31 (m, 2H), 7.25-7.18 (m, 1H), 5.65-5.33 (m, 1H), 4.63-4.54 (m, 2H), 4.39 (br t, *J* = 13.2 Hz, 1H), 4.31-4.16 (m, 1H), 4.05-3.63 (m, 5H), 3.47-3.34 (m, 2H), 2.73-2.45 (m, 2H), 2.43 (br d, *J* = 4.4 Hz, 5H), 2.09-1.76 (m, 4H); LCMS (ESI, M+1): m/z = 654.2.

EXAMPLE 416



(S)-6-(7-(8-chloro-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)-1,6-diazaspiro[3.5]nonan-2-one



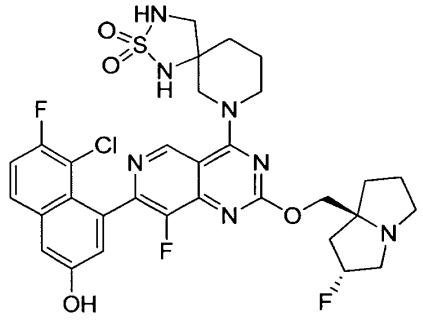
[00001105] Step A. (S)-6-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one: To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (500 mg, 1.0 *equiv.*), (S)-1,6-diazaspiro[3.5]nonan-2-one (138 mg, 0.5 *equiv.*) in DCM (5 mL) was added DIEA (767 mg, 1.03 mL, 3.0 *equiv.*). The mixture was stirred at - 40 °C for 0.5 hour. After reaction completion, the mixture was concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) to afford the title compound (330 mg, 46% yield) as a white solid; LCMS [ESI, M+1]: m/z = 356.1.

[00001106] Step B. (S)-6-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one: To a mixture of (S)-6-(2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one (300 mg, 1.0 *equiv.*), ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (268 mg, 2.0 *equiv.*), 4Å molecular sieves (10.0 mg, 1.0 *equiv.*) in dioxane (3 mL) was added DIEA (544 mg, 733 μL, 5.0 *equiv.*). The reaction was stirred at 90 °C for 12 hours. After completion, the reaction mixture was quenched by addition of water (3 mL), and extracted with Ethyl acetate (10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) to afford the title compound (210 mg, 52% yield) as a yellow solid; LCMS [ESI, M+1]: m/z = 479.1.

[00001107] Step C. (S)-6-(7-(8-chloro-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)-1,6-diazaspiro[3.5]nonan-2-one: To a solution of (S)-6-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one (130 mg, 1.0 *equiv.*), (8-chloro-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)trimethylstannane (328 mg, 3.0 *equiv.*) in toluene (3 mL) was added $Pd(dppf)Cl_2$ (19.8 mg, 0.1 *equiv.*), BINAP (33.8 mg, 0.2 *equiv.*), CuI (15.5 mg, 0.3 *equiv.*) under N_2. The reaction was stirred at 90 °C for 2 hours under N_2. After reaction completion, the mixture was quenched by addition of water (3 mL), and then extracted with Ethyl acetate (6 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) to afford the title compound (57.0 mg, 17% yield) as a green oil; LCMS [ESI, M+1]: m/z = 683.4.

[00001108] Step D. (S)-6-(7-(8-chloro-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)-1,6-diazaspiro[3.5]nonan-2-one: To a solution of (S)-6-(7-(8-chloro-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)-1,6-diazaspiro[3.5]nonan-2-one (52.0 mg, 1.0 *equiv.*) in DCM (0.5 mL) was added TFA (770 mg, 0.5 mL, 88 *equiv.*) at 0 °C. The reaction was stirred at 0 °C for 0.5 hour. After reaction completion, the mixture was concentrated under reduced pressure to give a residue. The pH of the residue was adjusted to 9 with sat. aq. $NaHCO_3$ and the resulting mixture was extracted with DCM (3 × 2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150 × 25 mm × 10 μm; mobile phase: [water (0.1% formic acid) - ACN]; B%: 8% - 38%, 10 min) and lyophilized to afford the title compound (26.3 mg, 49% yield, formic acid salt) as a white solid; ^1H NMR (400 MHz, methanol-d4): δ = 9.10 (d, *J* = 3.2 Hz, 1H), 8.49 (br s, 1H), 7.82 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.43 - 7.37 (m, 2H), 7.22 (d, *J* = 2.4 Hz, 1H), 5.49 - 5.32 (m, 1H), 4.47 - 4.37 (m, 3H), 4.36 - 4.26 (m, 1H), 3.99 (dd, *J* = 2.8, 13.2 Hz, 1H), 3.86 - 3.75 (m, 1H), 3.62 - 3.43 (m, 3H), 3.18 (dt, *J* = 5.6, 9.6 Hz, 1H), 2.91 (dd, *J* = 6.8, 14.8 Hz, 1H), 2.79 - 2.73 (m, 1H), 2.53 - 2.33 (m, 2H), 2.31 - 2.21 (m, 1H), 2.17 - 2.08 (m, 3H), 2.06 - 1.90 (m, 4H); LCMS [ESI, M+1]: m/z = 638.9.

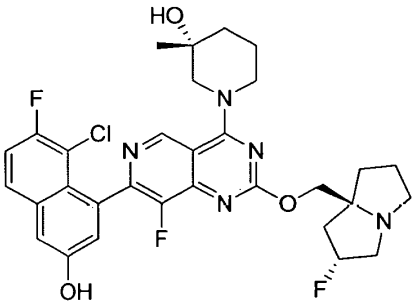
EXAMPLE 417



7-(7-(8-chloro-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-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide

[00001109] The title compound was synthesized according to the procedure described for example 414. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.19-9.05 (m, 1H), 7.81 (ddd, *J* = 3.6, 5.6, 9.2 Hz, 1H), 7.43-7.35 (m, 2H), 7.24-7.19 (m, 1H), 5.58-5.33 (m, 1H), 4.73-4.55 (m, 2H), 4.55-4.25 (m, 3H), 3.90-3.67 (m, 2H), 3.66-3.45 (m, 3H), 3.44-3.33 (m, 1H), 3.29-3.19 (m, 2H), 2.61-2.37 (m, 2H), 2.36-2.25 (m, 1H), 2.22-2.12 (m, 2H), 2.11-1.99 (m, 3H), 1.95-1.79 (m, 2H); LCMS (ESI, M+1): m/z = 690.2.

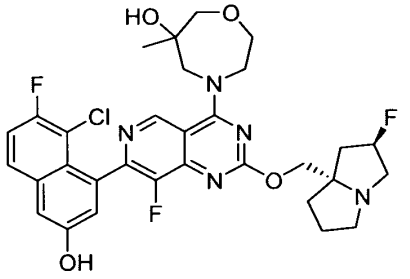
EXAMPLE 418



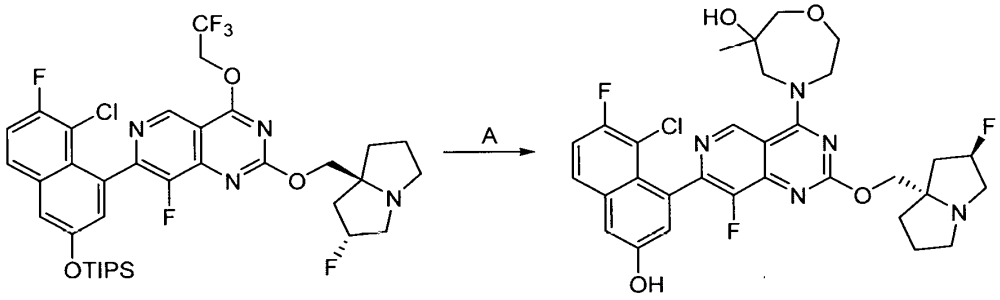
(R)-1-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

[00001110] The title compound was synthesized according to the procedure described for example 414. ^{1}H NMR (400 MHz, METHANOL-d_4) δ= 9.23 (s, 1H), 8.49 (br s, 1H), 7.85-7.79 (m, 1H), 7.44-7.35 (m, 2H), 7.22 (t, J = 2.8 Hz, 1H), 5.57-5.29 (m, 1H), 4.60 (br s, 2H), 4.54-4.50 (m, 1H), 4.47-4.41 (m, 1H), 4.37-4.28 (m, 1H), 3.73-3.63 (m, 1H), 3.62-3.55 (m, 2H), 3.50-3.41 (m, 1H), 3.28-3.19 (m, 1H), 2.60-2.38 (m, 2H), 2.36-2.25 (m, 1H), 2.21-2.12 (m, 3H), 2.08-1.98 (m, 1H), 1.90-1.75 (m, 3H), 1.30 (d, J = 8.4 Hz, 3H); LCMS (ESI, M+1): m/z = 614.3.

EXAMPLE 419



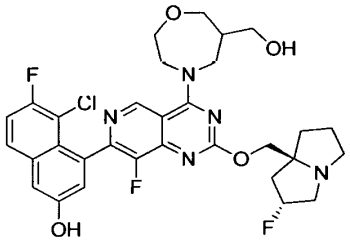
4-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-methyl-1,4-oxazepan-6-ol



[00001111] Step A. 4-(7-(8-chloro-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-methyl-1,4-oxazepan-6-ol: To a mixture of 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 (126 mg, 1 *equiv.*) and 4Å MS (15 mg) in DMF (0.5 mL) was added DIEA (172 mg, 8 *equiv.*) and 6-methyl-1,4-oxazepan-6-ol (83.9 mg, 3 *equiv.*, HCl).

The mixture was stirred at 40 °C for 12 hr .The reaction mixture was filtered and purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 × 30mm × 3um; mobile phase: [water (0.1% formic acid)-ACN]; B%: 8%-38%, 10min) to afford the title compound (28.7 mg, 25% yield) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.74 - 9.39 (m, 1H), 8.57 - 8.42 (m, 1H), 8.01 - 7.66 (m, 1H), 7.50 - 7.30 (m, 2H), 7.29 - 7.12 (m, 1H), 5.50 - 5.31 (m, 1H), 4.57 (br s, 2H), 4.49 - 4.37 (m, 2H), 4.25 - 4.14 (m, 1H), 4.08 - 3.86 (m, 3H), 3.77 - 3.63 (m, 2H), 3.51 - 3.43 (m, 2H), 3.23 - 3.10 (m, 2H), 2.57 - 2.41 (m, 1H), 2.38 - 2.21 (m, 2H), 2.17 - 1.95 (m, 3H), 1.29 (br s, 3H):LCMS [ESI, M+1]: m/z = 630.1.

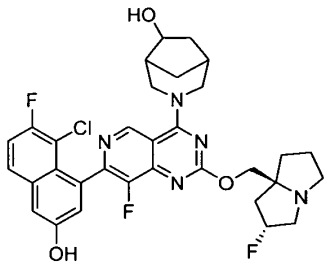
EXAMPLE 420



5-chloro-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

[00001112] The title compound was synthesized according to the procedure described for example 413. ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.22 (d, J = 6.8 Hz, 1H), 7.85-7.65 (m, 1H), 7.44-7.34 (m, 2H), 7.27-7.17 (m, 1H), 5.62-5.40 (m, 1H), 4.80-4.53 (m, 4H), 4.52-4.31 (m, 1H), 4.18-3.93 (m, 3H), 3.93-3.62 (m, 4H), 3.62-3.53 (m, 2H), 3.41-3.32 (m, 1H), 2.75-2.38 (m, 3H), 2.38-2.13 (m, 4H), 2.13-1.91 (m, 1H); LCMS (ESI, M+1): m/z = 630.5.

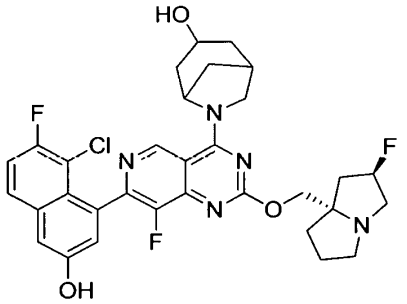
EXAMPLE 421



3-(7-(8-chloro-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)-3-azabicyclo[3.2.1]octan-6-ol

[00001113] The title compound was synthesized according to the procedure described for example 419. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.25 (dd, J = 1.6, 14.8 Hz, 1H), 7.83 (dd, J = 5.6, 9.2 Hz, 1H), 7.45 - 7.36 (m, 2H), 7.23 (dd, J = 2.4, 13.6 Hz, 1H), 5.51 - 5.30 (m, 1H), 4.98 (br s, 1H), 4.83 (br s, 1H), 4.49 - 4.40 (m, 1H), 4.39 - 4.29 (m, 2H), 3.85 - 3.74 (m, 1H), 3.59 - 3.50 (m, 1H), 3.37 (br s, 3H), 3.21 - 3.12 (m, 1H), 2.53 - 2.32 (m, 3H), 2.32 - 2.18 (m, 3H), 2.16 - 2.05 (m, 2H), 2.04 - 1.90 (m, 2H), 1.87 - 1.78 (m, 1H), 1.40 (br dd, J = 2.0, 13.6 Hz, 1H); LCMS [ESI, M+1]: m/z =626.1.

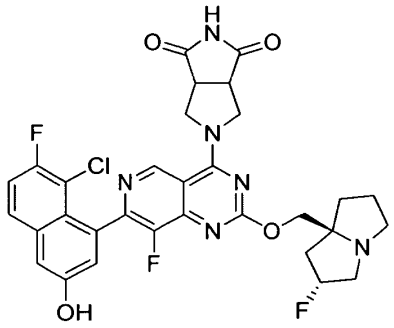
EXAMPLE 422



6-(7-(8-chloro-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

[00001114] The title compound was synthesized according to the procedure described for example 419. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.36 - 9.14 (m, 1H), 8.49 (br s, 1H), 7.82 (dd, J = 5.6, 9.2 Hz, 1H), 7.44 - 7.34 (m, 2H), 7.24 - 7.16 (m, 1H), 5.57 - 5.38 (m, 1H), 5.00 (br s, 1H), 4.61 - 4.46 (m, 2H), 4.42 - 4.32 (m, 1H), 4.32 - 4.19 (m, 1H), 4.14 (br s, 1H), 3.72 (br s, 1H), 3.70 - 3.57 (m, 2H), 3.27 (br s, 1H), 2.86 - 2.62 (m, 2H), 2.60 - 2.48 (m, 1H), 2.45 - 2.32 (m, 1H), 2.31 - 2.17 (m, 3H), 2.17 - 2.10 (m, 1H), 2.10 - 1.96 (m, 3H), 1.95 - 1.74 (m, 2H). LCMS [ESI, M+1]: m/z = 626.2.

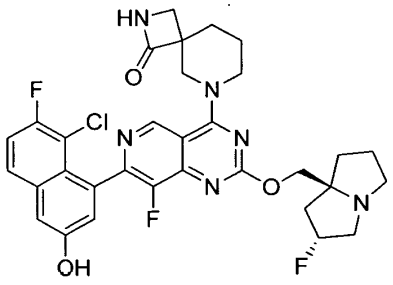
EXAMPLE 423



5-(7-(8-chloro-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)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione

[00001115] The title compound was synthesized according to the procedure described for example 419. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.28 (s, 1H), 8.46 (br s, 1H), 7.82 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.43 - 7.36 (m, 2H), 7.22 (d, *J* = 2.4 Hz, 1H), 5.54 - 5.36 (m, 1H), 4.64 (br d, *J* = 13.2 Hz, 2H), 4.60 - 4.46 (m, 2H), 4.43 - 4.30 (m, 2H), 3.81 - 3.55 (m, 3H), 3.69 - 3.53 (m, 3H), 3.30 - 3.23 (m, 1H), 2.63 - 2.37 (m, 2H), 2.36 - 2.27 (m, 1H), 2.25 - 2.15 (m, 2H), 2.13 - 2.00 (m, 1H). LCMS [ESI, M+1]: m/z = 639.1.

EXAMPLE 424

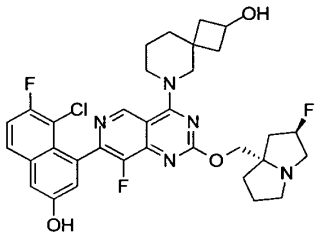


6-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2,6-diazaspiro[3.5]nonan-1-one

[00001116] The title compound was synthesized according to the procedure described for example 419. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.08 (s, 1H), 7.83 - 7.83 (m, 1H), 7.44 - 7.34 (m, 2H), 7.23 (s, 1H), 5.53 - 5.34 (m, 1H), 4.55 - 4.49 (m, 1H), 4.48 - 4.42 (m, 1H), 4.36 -

4.28 (m, 2H), 4.21 - 4.09 (m, 1H), 4.08 - 3.95 (m, 1H), 3.71 - 3.59 (m, 1H), 3.59 - 3.46 (m, 2H), 3.30 - 3.21 (m, 2H), 3.21 - 3.18 (m, 1H), 2.59 - 2.35 (m, 2H), 2.33 - 2.25 (m, 1H), 2.22 - 2.12 (m, 4H), 2.12 - 2.00 (m, 2H), 1.97 - 1.87 (m, 1H); LCMS [ESI, M+1]: 639.1.

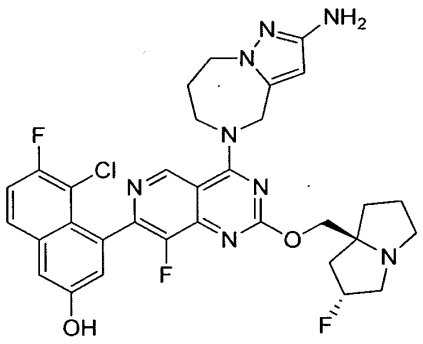
EXAMPLE 425



6-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol

[00001117] The title compound was synthesized according to the procedure described for example 419. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.05 (d, *J* = 7.6 Hz, 1H), 8.50 (br s, 1H), 7.80 (dd, *J* = 5.2, 9.2 Hz, 1H), 7.45-7.32 (m, 2H), 7.22 (t, *J* = 2.4 Hz, 1H), 5.55-5.27 (m, 1H), 4.50-4.35 (m, 2H), 4.32-4.22 (m, 1H), 4.12-3.90 (m, 4H), 3.65-3.36 (m, 3H), 3.18 (br d, *J* = 4.5 Hz, 1H), 2.52-2.16 (m, 6H), 2.15-1.96 (m, 3H), 1.84-1.66 (m, 6H); LCMS [ESI, M+1]: m/z = 640.2.

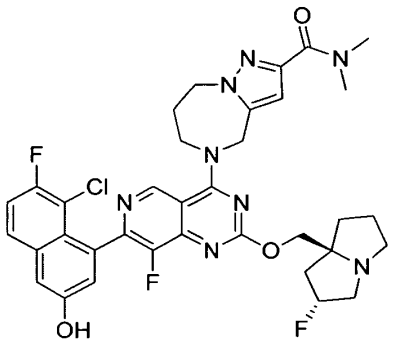
EXAMPLE 426



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-chloro-6-fluoronaphthalen-2-ol

[00001118] The title compound was synthesized according to the procedure described for example 419. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.19 (s, 1H), 7.83 - 7.79 (m, 1H), 7.43 - 7.34 (m, 2H), 7.22 (d, *J* = 2.4 Hz, 1H), 5.78 (s, 1H), 5.48 - 5.30 (m, 1H), 5.17 - 5.01 (m, 2H), 4.45 - 4.40 (m, 1H), 4.39 - 4.32 (m, 3H), 4.27 - 4.21 (m, 2H), 3.56 - 3.36 (m, 3H), 3.18 - 3.10 (m, 1H), 2.48 - 2.29 (m, 4H), 2.28 - 2.17 (m, 1H), 2.15 - 2.05 (m, 2H), 2.05 - 1.92 (m, 1H); LCMS [ESI, M+1]: m/z = 651.3.

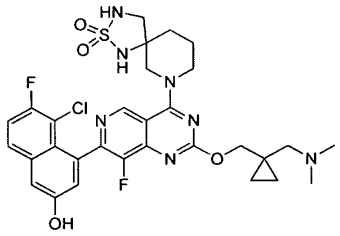
EXAMPLE 427



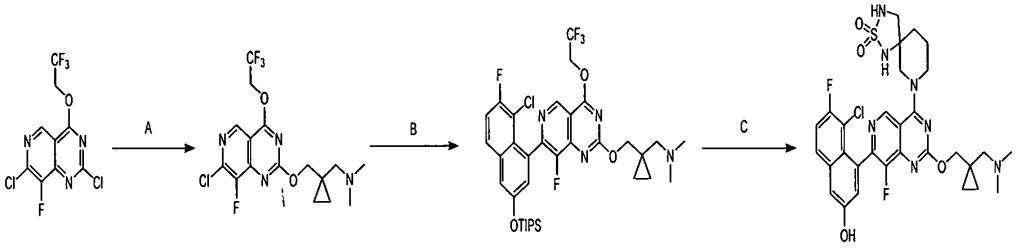
5-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide

[00001119] The title compound was synthesized according to the procedure described for example 419. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.21 (s, 1H), 8.61 - 8.44 (m, 1H), 7.83 (dd, *J* = 5.2, 9.2 Hz, 1H), 7.45 - 7.37 (m, 2H), 7.23 (d, *J* = 2.4 Hz, 1H), 6.78 (s, 1H), 5.52 - 5.20 (m, 3H), 4.56 (br d, *J* = 6.4 Hz, 2H), 4.51 - 4.38 (m, 4H), 3.66 - 3.43 (m, 3H), 3.35 (s, 3H), 3.25 - 3.17 (m, 1H), 3.10 (s, 3H), 2.55 - 2.26 (m, 5H), 2.22 - 1.98 (m, 3H); LCMS [ESI, M+1]: 707.2.

EXAMPLE 428



7-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide



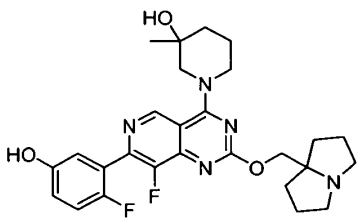
[00001120] Step A. 1-(1-(((7-chloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine: To a solution of 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (6 g, 1.0 *equiv.*) and (1-((dimethylamino)methyl)cyclopropyl)methanol (2.21 g, 0.9 *equiv.*) in THF (60 mL) was added DIEA (7.36 g, 3 *equiv.*) and 4Å molecular sieves (1 g) at -40 °C, The mixture was stirred at -40 °C for 0.5 hour. The mixture was filtered, diluted with water (60 mL) and extracted with ethyl acetate (3 × 60 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by reversed phase flash chromatography [C18, water (0.1% formic acid) - ACN] to afford the title compound (3.0 g, 35% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 409.1.

[00001121] Step B. 1-(1-(((7-(8-chloro-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine: A mixture of 1-(1-(((7-chloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine (500 mg, 1.0 *equiv.*), ((5-chloro-6-fluoro-4-(trimethylstannyl)naphthalen-

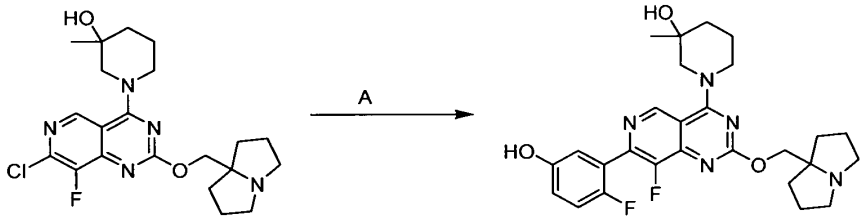
2-yl)oxy)triisopropylsilane (1.26 g, 2.0 *equiv.*), CuI (23.3 mg, 0.1 *equiv.*), BINAP (152 mg, 0.2 *equiv.*) and Pd(dppf)Cl_2 (89.5 mg, 0.1 *equiv.*) in toluene (8 mL) was degassed and stirred at 90 °C for 6 hours under N_2 atmosphere. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by reversed phase flash chromatography [C18, water (0.1% formic acid) - ACN] to afford the title compound (0.5 g, 48% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 725.3.

[00001122] Step C. 7-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide: To a solution of 1-(1-(((7-(8-chloro-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine (157 mg, 1.0 *equiv.*) and 2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide (58.0 mg, 1.1 *equiv.*) in DMF (1 mL) were added 4Å molecular sieves (40 mg) and DIEA (107 mg, 3 *equiv.*). The mixture was stirred at 60 °C for 12 hours. The mixture was filtered, diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by reversed phase flash chromatography [C18, water (0.1% formic acid) - ACN] and prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: water (NH_4HCO_3)-ACN; B%: 30%-60%, 10 min] to afford the title compound (16.3 mg, 9% yield) as an off-white solid; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.07 (d, *J* = 2.4 Hz, 1H), 7.82-7.76 (m, 1H), 7.42-7.33 (m, 2H), 7.24-7.16 (m, 1H), 4.50-4.27 (m, 4H), 3.92 (d, *J* = 13.3 Hz, 1H), 3.72 (d, *J* = 13.2 Hz, 1H), 3.41 (d, *J* = 11.6 Hz, 1H), 3.20 (dd, *J* = 3.2, 12.0 Hz, 1H), 2.60-2.54 (m, 1H), 2.42-2.35 (m, 1H), 2.33 (s, 6H), 2.12-1.76 (m, 4H), 0.79-0.70 (m, 2H), 0.58-0.49 (m, 2H). LCMS (ESI, M+1): m/z = 660.0.

EXAMPLE 429

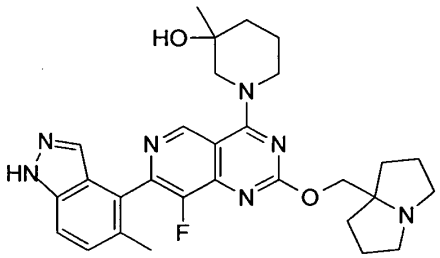


1-(8-fluoro-7-(2-fluoro-5-hydroxyphenyl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

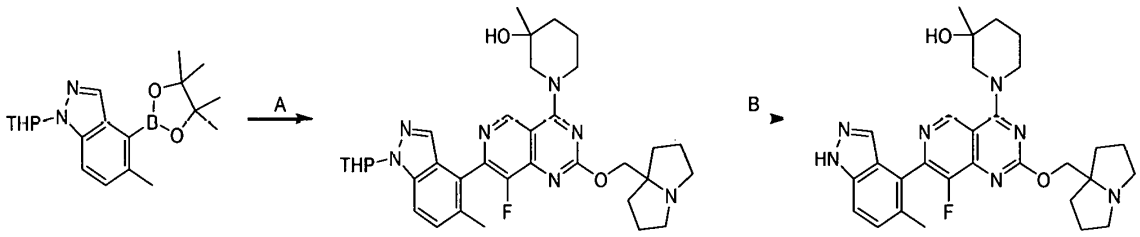


[00001123] Step A. 1-(8-fluoro-7-(2-fluoro-5-hydroxyphenyl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (50 mg, 1.0 *equiv.*), 4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (55 mg, 2 *equiv.*) and K_3PO_4 (1.5 M in water, 229 μL, 3 *equiv.*) in THF (0.5 mL) was added cataCXium-A-Pd-G3 (8.4 mg, 0.1 *equiv.*). The mixture was degassed and stirred at 60 °C for 2 hours. Upon reaction completion, the mixture was diluted with water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC [column: Phenomenex luna C18 150 × 25mm × 10um; mobile phase: water (0.225% formic acid)-ACN; B: 5%-35%, 11.5min)] to afford the title compound (37.1 mg, 66.5 μmol, 56.0% yield, formic acid salt) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.26 (s, 1H), 8.50 (br s, 1H), 7.12 - 7.06 (m, 1H), 7.04 (dd, *J* = 3.0, 5.6 Hz, 1H), 6.93 (td, *J* = 3.6, 8.8 Hz, 1H), 4.64 (s, 2H), 4.60 (br d, *J* = 13.1 Hz, 1H), 4.31 (br d, *J* = 13.3 Hz, 1H), 3.74 - 3.66 (m, 2H), 3.62 (d, *J* = 13.4 Hz, 1H), 3.44 - 3.36 (m, 1H), 3.30 - 3.24 (m, 2H), 2.32 (ddd, *J* = 3.1, 6.8, 12.3 Hz, 2H), 2.27 - 2.05 (m, 7H), 1.90 - 1.71 (m, 3H), 1.28 (s, 3H); LCMS(M+H): 512.3.

EXAMPLE 430



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

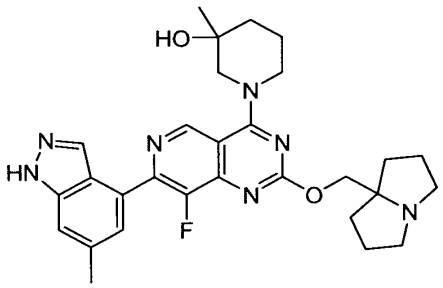


[00001124] Step A. 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of 1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (30 mg, 1 *equiv.*) in n-BuOH (0.6 mL) was added 5-methyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (35.3 mg, 1.5 *equiv.*), K_3PO_4 (1.5 M in water, 138 μL, 3 *equiv.*) and X-Phos-Pd-G4 (5.92 mg, 0.1 *equiv.*). The mixture was stirred at 60 °C for 2 hours under N_2 atmosphere. The mixture was poured into water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine 5mL, dried over Na_2SO_4, concentrated and purified by reverse phase flash chromatography (water (0.225% formic acid)) to afford the title compound (30 mg, 70.5% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 616.4.

[00001125] Step B. 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(5-methyl-1H-indazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of 1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(5-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (30 mg, 1 *equiv.*) in MeOH (1 mL) was added HCl•dioxane (4 M, 0.5 mL, 41 *equiv.*). The mixture was stirred at 25 °C for 2

hours under N_2 atmosphere. The mixture was dried with a stream of N_2 and purified by prep-HPLC [column: Phenomenex Synergi C18 150 × 25 mm × 10 μm; mobile phase: water (0.225% formic acid)-ACN; B%: 8%-38%, 10 minutes] to afford the title compound (6.31 mg, 22% yield) as an off-white solid; ^{1}HNMR (400 MHz, METHANOL-d_4) δ = 9.34 (s, 1H), 7.71 (s, 1H), 7.61 (d, J=8.4 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 4.64 (s, 3H), 4.36 (m, 1H), 3.71-3.58 (m, 3H), 3.44 (br s, 1H), 3.28-3.20 (m, 2H), 2.38-2.27 (m, 5H), 2.25-2.12 (m, 5H), 2.08 (m, 2H), 1.80 (br s, 3H), 1.30 (s, 3H); LCMS (ESI, M+1): m/z = 532.3.

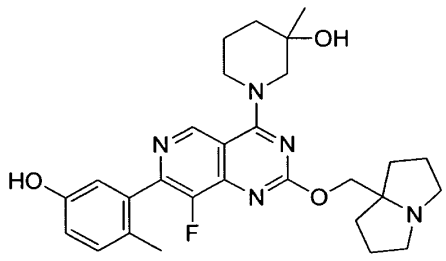
EXAMPLE 431



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

[00001126] The title compound was synthesized according to the procedure described for example 430. ^{1}HNMR (400 MHz, METHANOL-d_4) δ = 9.32 (s, 1H), 8.21 (s, 1H), 7.51 (d, J = 13.6 Hz, 2H), 4.58 (s, 3H), 4.36-4.28 (m, 1H), 3.66-3.53 (m, 3H), 3.48-3.37 (m, 1H), 3.22-3.11 (m, 2H), 2.58 (s, 3H), 2.35-2.24 (m, 2H), 2.23-2.08 (m, 5H), 2.04 (s, 2H), 1.91-1.72 (m, 3H), 1.29 (s, 3H); LCMS (ESI, M+1): m/z = 532.3.

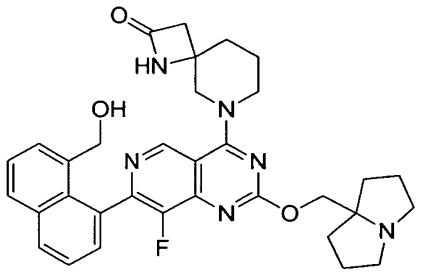
EXAMPLE 432



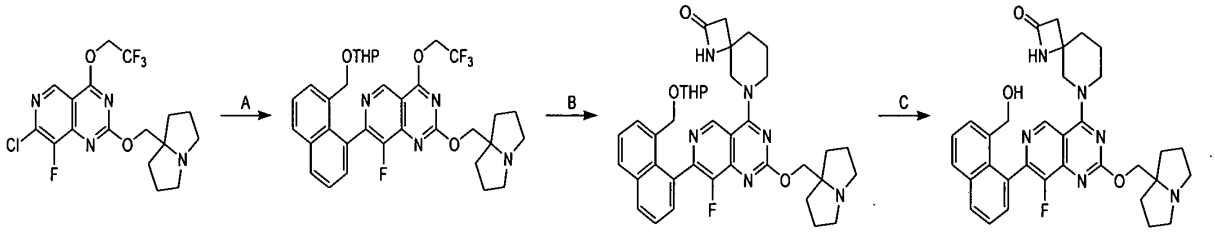
1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(5-hydroxy-2-methylphenyl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

[00001127] The title compound was synthesized according to the procedure described for example 429. ^{1}HNMR (400 MHz, METHANOL-d_4) δ = 9.24 (s, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.89-6.73 (m, 2H), 4.65 (s, 2H), 4.63-4.56 (m, 1H), 4.35-4.28 (m, 1H), 3.74-3.66 (m, 2H), 3.62 (d, J = 13.3 Hz, 1H), 3.45-3.36 (m, 1H), 3.30-3.24 (m, 2H), 2.38-2.28 (m, 2H), 2.26-2.16 (m, 4H), 2.14 (s, 3H), 2.13-2.06 (m, 3H), 1.88-1.74 (m, 3H), 1.29 (s, 3H); LCMS (ESI, M+1): m/z = 508.3.

EXAMPLE 433



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



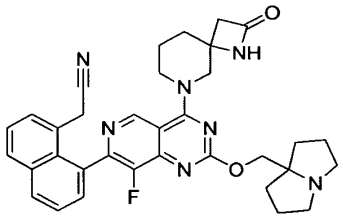
[00001128] Step A. 8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)naphthalen-1-yl)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a solution of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (150 mg, 1 *equiv.*), 4,4,5,5-tetramethyl-2-(8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)naphthalen-1-yl)-1,3,2-dioxaborolane (131 mg, 1 *equiv.*) and Cs_2CO_3 (1.5 M in water , 713 µL, 3 *equiv.*) in methoxycyclopentane (2.5 mL) was added cataCXium A Pd G3 (26.0 mg, 0.1 *equiv.*). The mixture was stirred at 90°C for 3 hours under N_2.

The mixture was poured into water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated and purified by reversed phase flash chromatography (water (0.225% formic acid)) to afford the title compound (80 mg, 35.8% yield) as a yellow oil; LCMS (ESI, M+1): m/z =627.3

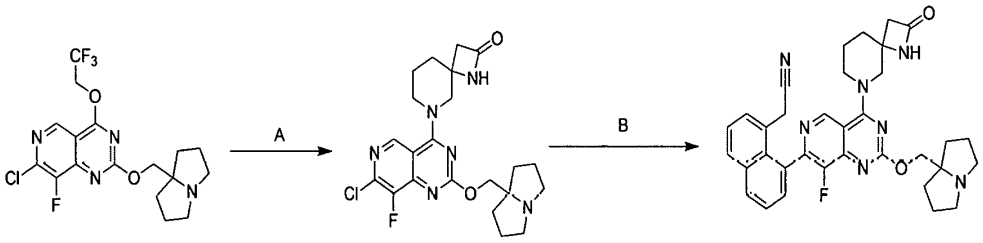
[00001129] Step B. 6-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one: A mixture of 8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)naphthalen-1-yl)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (80 mg, 1 *equiv.*) and 1,6-diazaspiro[3.5]nonan-2-one (21.5 mg, 1.2 *equiv.*) and DIEA (82.5 mg, 5 *equiv.*) in DMF (1 mL) was stirred at 40°C for 2 hours. The mixture was filtered and purified by reversed phase flash chromatography (water (0.225% formic acid)) to afford the title compound (60 mg, 70.5% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 667.5.

[00001130] Step C. 6-(8-fluoro-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)-7-(8-(hydroxymethyl)naphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one: To a solution of 6-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one (30 mg, 1 *equiv.*) in EtOH (0.5 mL) was added TsOH•H2O (9.41 mg, 1.1 *equiv.*). The mixture was stirred at 25 °C for 16 hours. The mixture was poured into water (5 mL). The pH of the mixture was adjusted to 8 with saturated aqueous $NaHCO_3$. The resulting solution was extracted with ethyl acetate (2 × 5 mL). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated and purified by prep-HPLC [column: Unisil 3-100 C18 Ultra 150 × 50 mm ×3 μm; mobile phase: water (0.225% formic acid)-ACN; B%: 10%-40%, 10 minutes] to afford the title compound (5.75 mg, 21% yield) as a white solid; ^{1}H NMR (400 MHz, MeOD-d4) δ = 9.20-9.07 (m, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 8.02-7.93 (m, 1H), 7.73 (d, *J* = 6.8 Hz, 1H), 7.65-7.54 (m, 2H), 7.48 (d, *J* = 6.8 Hz, 1H), 4.64-4.54 (m, 2H), 4.46-4.22 (m, 4H), 4.05 (m, 1H), 3.98-3.82 (m, 1H), 3.56-3.55 (m, 2H), 3.19-3.13 (m, 2H), 2.97-2.73 (m, 2H), 2.29-2.00 (m, 12H); LCMS (ESI, M+1): m/z = 583.5.

EXAMPLE 434



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

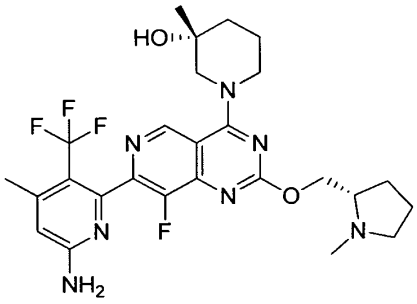


[00001131] Step A. 6-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one: To a solution of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (100 mg, 1.0 *equiv.*), 1,8-diazaspiro[3.5]nonan-2-one (43.3 mg, 1.3 *equiv.*) in DMF (1.0 mL) was added DIEA (92.1 mg, 3.0 *equiv.*) and 4 Å molecular sieves (40 mg). The mixture was stirred at 40 °C for 12 hours. The mixture was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile]. The desired fractions were collected and neutralized with solid $NaHCO_3$, concentrated in vacuum to remove ACN. The aqueous layer was lyophilized to afford title compound (73 mg, 65% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 461.1.

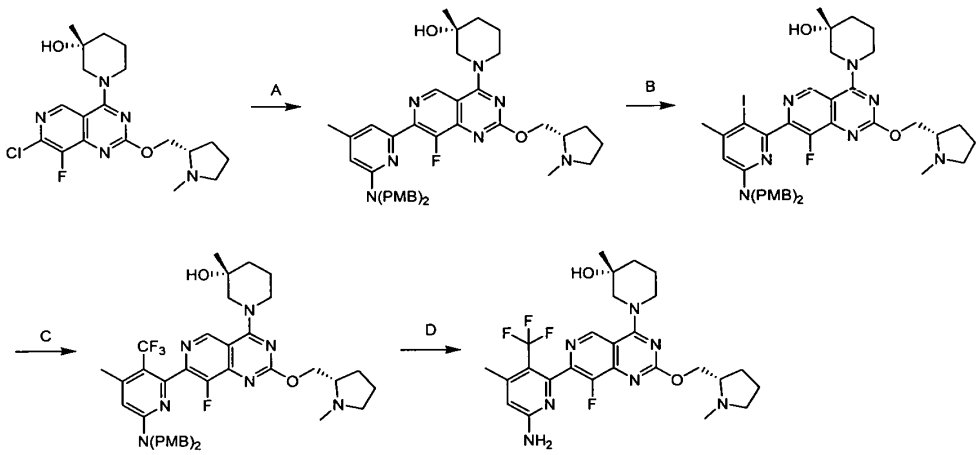
[00001132] Step B. 2-(8-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2-oxo-1,6-diazaspiro[3.5]nonan-6-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)acetonitrile: A mixture of 6-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one (50 mg, 1.0 *equiv.*), 2-(8-trimethylstannyl-1-naphthyl)acetonitrile (71.6 mg, 2.0 *equiv.*) and cataCXium A Pd G3 (7.90 mg, 0.1 *equiv.*) in DMAC (0.5 mL) was degassed stirred at 90 °C for 3 hours under N_2 atmosphere. The mixture was directly purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN]. The desired fractions

were re-purified by prep-HPLC [Waters Xbridge 150 × 25mm × 5μm; mobile phase: water (10mM NH_4HCO_3)-ACN, B%: 34%-64%, 10min] and lyophilized to afford title compound (16.6 mg, 25% yield) as a white solid; HPLC: >99% ee, Chiralcel OJ-3 50×4.6mm I.D., 3 μm column A: 60% MeOH + 40% ACN (w/ 0.05% DEA), B: CO_2, 3mL/min, 220 nm, t_R: 1.827 min; ^{1}H NMR (400 MHz, methanol-d4) δ = 9.07 (s, 1H), 8.56 (s, 1H), 8.18 (d, *J* = 7.2 Hz, 1H), 8.11 (d, *J* = 7.2 Hz, 1H), 7.71-7.65 (m, 2H), 7.65-7.58 (m, 2H), 4.27-4.15 (m, 2H), 4.12-4.04 (m, 2H), 3.96-3.70 (m, 2H), 3.68v3.57 (m, 2H), 2.98-2.89 (m, 2H), 2.86-2.79 (m, 1H), 2.67-2.62 (m, 1H), 2.58-2.53 (m, 2H), 2.03-1.95 (m, 1H), 1.94-1.85 (m, 5H), 1.84-1.79 (m, 4H), 1.62-1.53 (m, 2H); LCMS (ESI, M+1): m/z =592.2.

EXAMPLE 435



(R)-1-(7-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



[00001133] Step A. (R)-1-(7-(6-(bis(4-methoxybenzyl)amino)-4-methylpyridin-2-yl)-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(7-chloro-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (1.80 g, 1.0 *equiv.*) in DMAC (20 mL) was added cataCXium A Pd G3 (320 mg, 0.1 *equiv.*) and N,N-bis[(4-methoxyphenyl)methyl]-4-methyl-6-tributylstannyl-pyridin-2-amine (4.20 g, 1.50 *equiv.*). The mixture was stirred at 90 °C for 12 hours. The reaction mixture was filtered, concentrated and purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (2.20 g, 69% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 722.4.

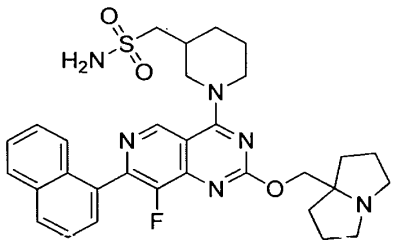
[00001134] Step B. (R)-1-(7-(6-(bis(4-methoxybenzyl)amino)-3-iodo-4-methylpyridin-2-yl)-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (R)-1-(7-(6-(bis(4-methoxybenzyl)amino)-4-methylpyridin-2-yl)-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (1.0 g, 1.0 *equiv.*) in AcOH (20 mL) was added dropwise solution of NIS (467 mg, 1.5 *equiv.*) in AcOH (5 mL). The mixture was stirred at 25 °C for 2 hours. The reaction 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 the title compound (800 mg, 64% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 848.3.

[00001135] Step C. (R)-1-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of CuI (225 mg, 5.0 *equiv.*) and KF (68.5 mg, 5.0 *equiv.*) were heated in vacuum with gentle shaking until a greenish color was obtained. To the mixture was added a solution of (R)-1-(7-(6-(bis(4-methoxybenzyl)amino)-3-iodo-4-methylpyridin-2-yl)-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (200 mg, 1.0 *equiv.*) and trimethyl(trifluoromethyl)silane (168 mg, 5.0 *equiv.*) in DMF (3 mL). The mixture was stirred at 20 °C for 3 hours. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (3 × 5 mL), dried over anhydrous sodium sulfate, concentrated and

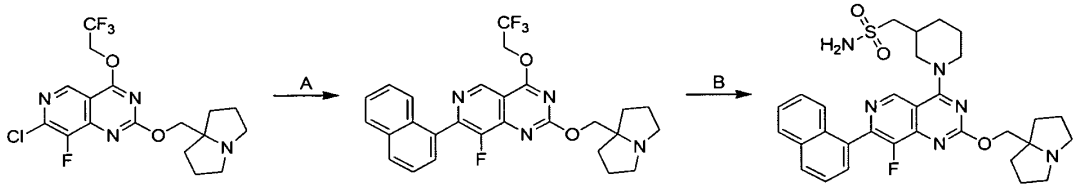
purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (60.0 mg, 32% yield) as a yellow solid. LCMS (ESI, M+1): m/z = 790.4.

[00001136] Step D. (R)-1-(7-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A solution of (R)-1-(7-(6-(bis(4-methoxybenzyl)amino)-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (60.0 mg, 1.0 *equiv.*) in TFA (1 mL) was stirred at 25 °C for 2 hours. The reaction mixture was concentrated. The residue was purified by reversed-phase HPLC [C18, water (0.1 % formic acid)/ACN] and further re-purified by prep-HPLC [column: Phenomenex Gemini-NX C18 75 × 30mm × 3um; mobile phase: water (0.225% formic acid)-ACN; B%: 12%-42%, 7min] and lyophilized to afford the title compound (19.3 mg, 46% yield, formic acid salt) as a light yellow solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.21 (s, 1H), 6.63 (s, 1H), 4.80-4.73 (m, 1H), 4.66-4.59 (m, 1H), 4.58-4.50 (m, 1H), 4.29 (br d, J = 13.2 Hz, 1H), 3.66-3.50 (m, 3H), 3.47-4.37 (m, 1H), 3.08-2.96 (m, 1H), 2.93 (s, 3H), 2.46 (d, J = 1.6 Hz, 3H), 2.38-2.27 (m, 1H), 2.18-1.94 (m, 4H), 1.89-1.72 (m, 3H), 1.28 (s, 3H) LCMS (ESI, M+1): m/z = 550.2.

EXAMPLE 436



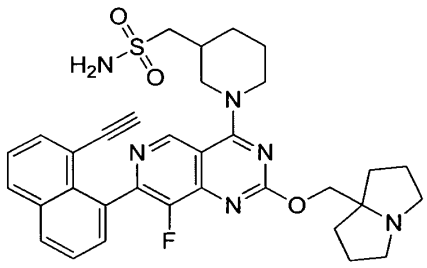
(1-(8-fluoro-7-(naphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide



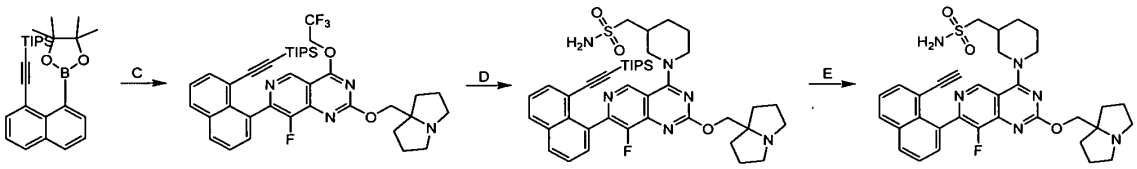
[00001137] Step A. 8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(naphthalen-1-yl)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a solution of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (300 mg, 1.0 *equiv.*), Cs_2CO_3 (1.5 M, 3.0 *equiv.*) and naphthalen-1-ylboronic acid (184 mg, 1.5 *equiv.*) in methoxycyclopentane (5 mL) was added CataCXium A Pd G3 (51.9 mg, 0.1 *equiv.*) under N_2. The reaction was stirred at 90 °C for 2 hours under N_2. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (15 mL), 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 (250 mg, 68% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 513.2.

[00001138] Step B. (1-(8-fluoro-7-(naphthalen-1-yl)-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide: To a solution of 8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(naphthalen-1-yl)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (0.10 g, 1.0 *equiv.*), piperidin-3-ylmethanesulfonamide (69.6 mg, 2.0 *equiv.*) and DIEA (75.7 mg, 3.0 *equiv.*) in DMF (0.5 mL) was added 4 Å molecular sieves (10 mg). The reaction was stirred at 40 °C for 12 hours. The mixture was filtered and purified by prep-HPLC [Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: water (10mM NH_4HCO_3)-ACN, B%: 33% - 63%, 2 min] and lyophilized to afford the title compound (66.9 mg, 58% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.15 (s, 1H), 8.08-8.02 (m, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.71-7.61 (m, 3H), 7.57-7.46 (m, 2H), 4.93 (br d, *J* = 13.6 Hz, 1H), 4.57 (br d, *J* = 12.8 Hz, 1H), 4.37-4.27 (m, 2H), 3.64-3.55 (m, 1H), 3.37 (dd, *J* = 10.4, 13.2 Hz, 1H), 3.23-3.16 (m, 1H), 3.15-3.07 (m, 3H), 2.75-2.67 (m, 2H), 2.57-2.46 (m, 1H), 2.18-2.06 (m, 3H), 1.97-1.85 (m, 5H), 1.84-1.70 (m, 3H), 1.68-1.56 (m, 1H); ^{19}F NMR (400 MHz, methanol-d_4) δ = -139.847; LCMS [ESI, M+1, M/2+1]: 591.3, 296.2.

EXAMPLE 437



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



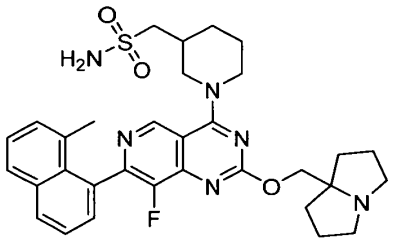
[00001139] Step A. 8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)-7-(8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidine: A mixture of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (250 mg, 1.0 equiv.), triisopropyl((8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane (310 mg, 1.2 equiv.), CataCXium A Pd G3 (43.3 mg, 0.1 equiv.) and Cs_2CO_3 (1.5 M in water, 1.19 mL, 3.0 equiv.) in methoxycyclopentane (3.5 mL) was degassed and then heated to 90 °C for 3 hours under N_2. The mixture was diluted with EtOAc (50 mL) and water (60 mL). The aqueous layer was extracted with EtOAc (2 × 40 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 (158 mg, 36% yield, 93% purity) as a yellow oil; LCMS (ESI, M+1): m/z = 693.3.

[00001140] Step B. 1-(1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide: A mixture of piperidin-3-ylmethanesulfonamide (84.9 mg, 2.0 equiv.), DIEA (154 mg, 5.0 equiv.), 8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)-7-(8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidine (165 mg, 1.0 equiv.) and 4Å molecular sieves (10 mg) in DMF (0.5 mL) was stirred at 40 °C for 36

hours. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography [C18, water (0.1% formic acid) - ACN] to afford the title compound (94 mg, 46% yield). Yellow solid; LCMS (ESI, M+1): m/z = 771.3.

[00001141] Step C. 1-(1-(7-(8-ethynylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide: A solution of 1-(1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide (95 mg, 123 μmol, 1.0 equiv.) and CsF (281 mg, 15 equiv.) in DMF (0.5 mL) was stirred at 18 °C for 2 hours. The mixture was filtered and the filtrate was purified by reversed phase flash chromatography [C18, water (0.1% formic acid) - ACN] and re-purified by prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: water (10 mM NH_4HCO_3)-ACN; B%: 30% - 60%, 8 min] to afford the title compound (12.3 mg, 16% yield, 98% purity) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.03 (s, 1H), 8.07 (dd, *J* = 8.0, 18.4 Hz, 2H), 7.77-7.72 (m, 1H), 7.67 (m, 1H), 7.59 (m, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 4.98-4.90 (m, 1H), 4.61-4.48 (m, 1H), 4.37-4.27 (m, 2H), 3.69-3.51 (m, 1H), 3.50-3.36 (m, 1H), 3.23-3.06 (m, 5H), 2.73 (m, 2H), 2.58-2.43 (m, 1H), 2.18-2.05 (m, 3H), 1.98-1.82 (m, 6H), 1.77-1.72 (m, 2H), 1.69-1.56 (m, 1H); LCMS (ESI, M+1): m/z = 615.2

EXAMPLE 438

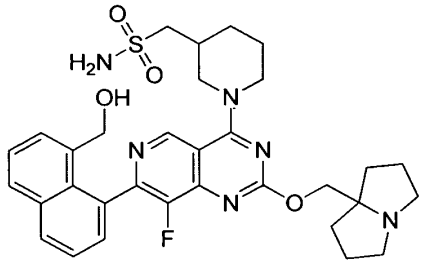


1-(1-(8-fluoro-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)-7-(8-methylnaphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide

[00001142] The title compound was synthesized according to the procedure described for example 436. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.08 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.60 - 7.53 (m, 1H), 7.48 - 7.39 (m, 2H), 7.31 (d, *J* = 6.8 Hz, 1H), 5.00 -

4.89 (m, 1H), 4.57 (dd, J = 11.2, 7.6 Hz, 1H), 4.38 - 4.26 (m, 2H), 3.63 - 3.53 (m, 1H), 3.43 - 3.33 (m, 1H), 3.22 - 3.09 (m, 4H), 2.77 - 2.69 (m, 2H), 2.56 - 2.46 (m, 1H), 2.11 (dt, J = 12.0, 5.6 Hz, 3H), 2.04 (d, J = 5.2 Hz, 3H), 1.92 (td, J =12.0, 6.0 Hz, 5H), 1.82 - 1.70 (m, 3H), 1.67 - 1.58 (m, 1H); LCMS (ESI, M+1): m/z 605.3.

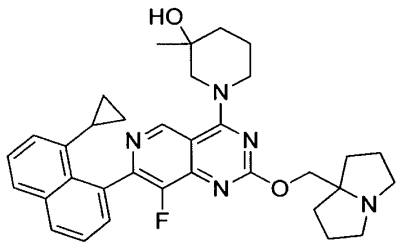
EXAMPLE 439



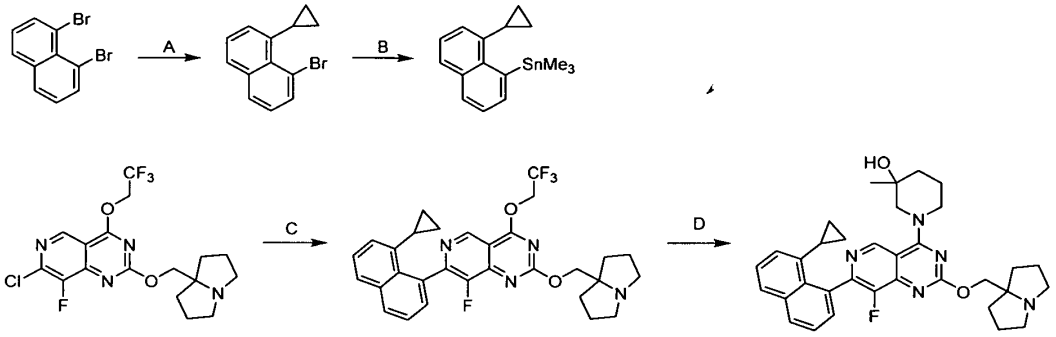
1-(1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-(hydroxymethyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide

[00001143] The title compound was synthesized according to the procedure described for example 433. ^{1}H NMR (400 MHz, methanol-d4) δ ppm = 9.08 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.62-7.53 (m, 2H), 7.44-7.51 (m, 1H), 4.98-4.96 (m, 1H), 4.64-4.52 (m, 1H), 4.42-4.28 (m, 4H), 3.69-3.53 (m, 1H), 3.42-3.34 (m, 1H), 3.25-3.08 (m, 4H), 2.85-2.68 (m, 2H), 2.61-2.44 (m, 1H), 2.15-2.11 (m, 3H), 1.99-1.88 (m, 5H), 1.83-1.73 (m, 3H), 1.68-1.58 (m, 1H); LCMS (ESI, M+1): m/z = 621.2.

EXAMPLE 440



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



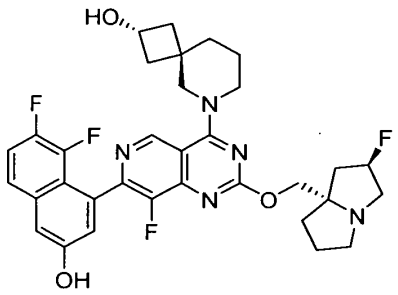
[00001144] Step A. 1-bromo-8-cyclopropylnaphthalene: To a solution of 1,8-dibromonaphthalene (5.00 g, 1.0 *equiv.*) in dioxane (45.0 mL) and water (15.0 mL) was added cyclopropylboronic acid (2.25 g, , 1.5 *equiv.*), K_3PO_4 (13.4 g, 3.6 *equiv.*) and $Pd(dppf)Cl_2$ (640 mg, 0.05 *equiv.*). The mixture was degassed and stirred at 100 °C for 6 hours. After reaction completion, the mixture was quenched by water (30 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were concentrated and purified by purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (2.20 g, 14% yield, 82% purity) as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.83 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.55-7.49 (m, 1H), 7.44-7.37 (m, 1H), 7.33-7.25 (m, 1H), 3.09-2.99 (m, 1H), 1.20-1.13 (m, 2H), 0.96-0.88 (m, 2H).

[00001145] Step B. (8-cyclopropylnaphthalen-1-yl)trimethylstannane: To a solution of 1-bromo-8-cyclopropylnaphthalene (4.40 g, 1.0 *equiv.*) in toluene (45.0 mL) were added trimethyl(trimethylstannyl)stannane (31.6 g, 96.6 mmol, 20.0 mL, 5.0 *equiv.*) and $Pd(PPh_3)_4$ (2.06 g, 0.1 *equiv.*) under N_2 atmosphere. The mixture was stirred at 110 °C for 18 h. After reaction completion, the mixture was concentrated under reduced pressure at 40 °C. The crude product was purified by column chromatography [Silica gel, petroleum ether] and reversed-phase flash chromatography C18, water (0.1% NH3•H2O)/ACN] to afford the title compound (2.46 g, 42% yield) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87-7.77 (m, 2H), 7.70 (br dd, *J* = 0.8, 8.0 Hz, 1H), 7.45-7.34 (m, 2H), 7.15 (d, *J* = 7.2 Hz, 1H), 2.67-2.43 (m, 1H), 1.16-1.09 (m, 2H), 0.95-0.86 (m, 2H), 0.47-0.32 (m, 9H).

[00001146] Step C. 7-(8-cyclopropylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a reaction mixture of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (500 mg, 1.19 mmol, 1.0 *equiv.*) in toluene (10.0 mL) was added (8-cyclopropylnaphthalen-1-yl)trimethylstannane (1.18 g, 3.56 mmol, 3.0 *equiv.*), CuI (67.9 mg, 356 μmol, 0.3 *equiv.*), BINAP (148 mg, 238 μmol, 0.2 *equiv.*) and $Pd(dppf)Cl_2$ (86.9 mg, 119 μmol, 0.1 *equiv.*). The reaction mixture was stirred at 110 °C for 10 hours under N_2 atmosphere. After reaction completion, the mixture was diluted with water (10 mL), then extracted with ethyl acetate (3 × 30 mL). The combined organic layers were concentrated under reduced pressure at 40 °C. The residue was purified by reversed-phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (160 mg, 23% yield) as a yellow solid; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.23 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.83 (t, *J* = 4.8 Hz, 1H), 7.60 - 7.53 (m, 1H), 7.52-7.48 (m, 1H), 7.44 (d, *J* = 4.8 Hz, 2H), 5.07 (q, *J* = 8.2 Hz, 2H), 4.43 (br s, 2H), 3.27 (br s, 2H), 2.72 (br d, *J* = 6.4 Hz, 2H), 2.12 (br dd, *J* = 5.6, 11.3 Hz, 2H), 1.94 (br s, 4H), 1.81-1.68 (m, 2H), 1.66-1.58 (m, 1H), 0.58 (qd, *J* = 4.9, 9.5 Hz, 1H), 0.51-0.40 (m, 1H), 0.37-0.27 (m, 1H), 0.04 - 0.09 (m, 1H);

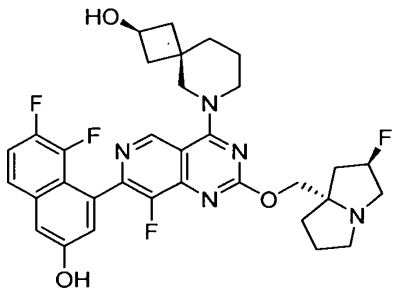
[00001147] Step D. 1-(7-(8-cyclopropylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of 7-(8-cyclopropylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (140 mg, 1.0 *equiv.*) in DMF (2.0 mL) were added DIEA (164 mg, 5.0 *equiv.*) and 3-methylpiperidin-3-ol (58.7 mg, 2.0 *equiv.*). The mixture was stirred at 40 °C for 16 hours. After reaction completion, the mixture was quenched with water (10 mL), and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated and purified by prep-HPLC [column: Waters Xbridge 150 × 25mm × 5μm; mobile phase: water (10mM NH_4HCO_3)-ACN, B%: 52%-82%, 2min] to afford the title compound (47.5 mg, 32% yield, 98.5% purity) as a white solid;; ^1H NMR (400 MHz, DMSO-d_6) δ = 9.18 (d, *J* = 9.6 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.65-7.57 (m, 1H), 7.54-7.43 (m, 2H), 7.38 (d, *J* = 7.2 Hz, 1H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.36-4.21 (m, 1H), 4.11-3.93 (m, 3H), 3.68-3.45 (m, 1H), 3.01-2.86 (m, 2H), 2.57-2.52 (m, 2H), 2.05-1.95 (m, 1H), 1.92-1.51 (m, 13H), 1.15 (d, *J* = 9.6 Hz, 3H), 0.56 (dt, *J* = 4.4, 8.8 Hz, 1H), 0.39-0.21 (m, 2H), 0.08-0.10 (m, 1H); LCMS (ESI, M+1): m/z = 568.3.

EXAMPLE 441

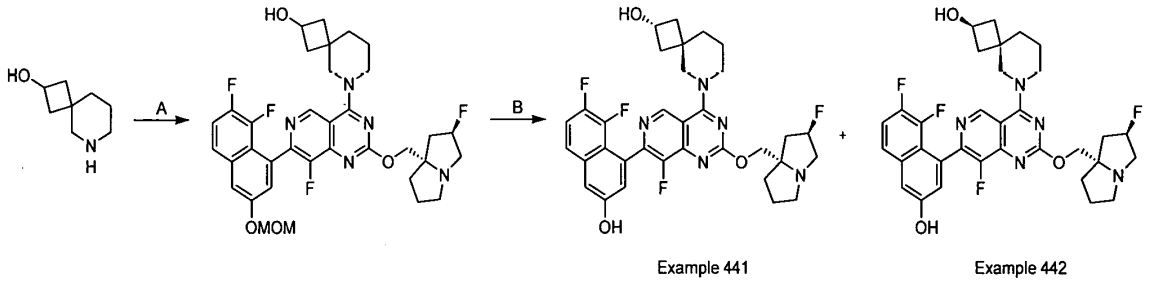


trans-6-(7-(7,8-difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol

EXAMPLE 442



cis-6-(7-(7,8-difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol



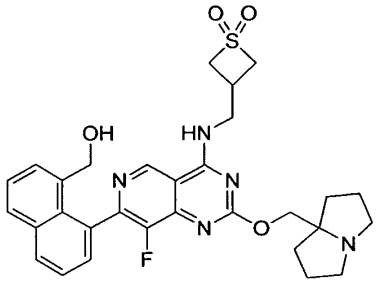
[00001148] Step A. 6-(7-(7,8-difluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol: To a solution of 6-azaspiro[3.5]nonan-2-ol (317 mg, 5.0 *equiv.*, HCl) in DMF (1.0 mL) was added 4Å molecular sieves (20 mg) and DIEA (461 mg, 10 *equiv.*). The mixture was stirred at 60 °C for 30 minutes before 7-(7,8-difluoro-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 (240 mg, 1.0 *equiv.*, formic acid salt) was added. The mixture was stirred at 60 °C for 12 hours. The reaction mixture was filtered and purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (100 mg, 40% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 668.4.

[00001149] Step B. 6-(7-(7,8-difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-6-azaspiro[3.5]nonan-2-ol: To a mixture of 6-(7-(7,8-difluoro-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-azaspiro[3.5]nonan-2-ol (90.0 mg, 1.0 *equiv.*) in DCM (0.5 mL) was added TFA (308 mg, 20 *equiv.*) in one portion at 0 °C under N_2. The mixture was stirred at 0 °C for 1 hour. The reaction mixture was diluted with water (3.0 mL), the aqueous phase was extracted with DCM (3 × 5 mL). The combined organic phase was washed with brine (10 mL), dried over anhydrous sodium sulfate, concentrated and purified by reversed phase flash chromatography (C18, water (0.1% formic acid) - ACN) and re-purified by prep-HPLC [column: Waters Xbridge 150 × 25mm × 5μm; mobile phase: water (10mM NH_4HCO_3)-ACN, B%: 40%-70%, 10min] and lyophilized to afford the first eluting peak – Example 441 (6.28 mg, 7.0% yield) as a white solid, ^{1}H NMR (400 MHz, methanol-d4) δ = 9.05 (s, 1H), 7.68-7.55 (m, 1H), 7.45-7.36 (m, 1H), 7.33 (t, *J* = 2.4 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 5.47-5.18 (m, 1H), 4.39-4.24 (m, 3H), 4.10-3.91 (m, 4H), 3.30-3.18 (m, 3H), 3.10-2.96 (m, 1H), 2.42-2.11 (m, 5H), 2.07-1.90 (m, 3H), 1.85-1.79 (m, 4H), 1.75-1.64 (m, 2H); LCMS (ESI, M+1): m/z = 624.2;

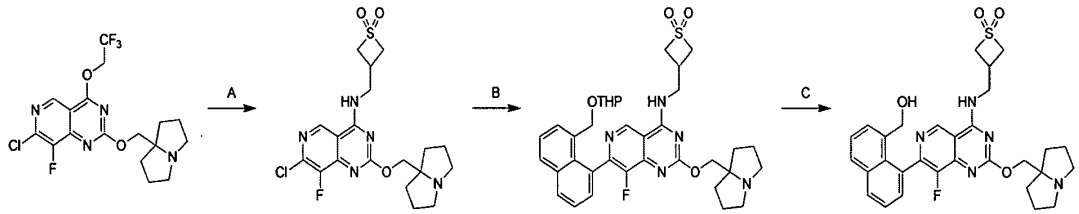
and the second eluting peak- Example 442 (8.91 mg, 10% yield) as a white solid. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.07 (s, 1H), 7.65-7.57 (m, 1H), 7.45-7.36 (m, 1H), 7.33 (t, *J* = 2.0 Hz, 1H), 7.26-7.22 (m, 1H), 5.48-5.19 (m, 1H), 4.45-4.19 (m, 3H), 4.11-3.93 (m, 4H), 3.45-3.34 (m,

1H), 3.30-3.21 (m, 2H), 3.14-2.97 (m, 1H), 2.46-2.12 (m, 5H), 2.10-1.92 (m, 3H), 1.89-1.72 (m, 6H); LCMS (ESI, M+1): m/z = 624.2; LCMS (ESI, M+1): m/z = 624.2.

EXAMPLE 443



3-(((8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-(hydroxymethyl)naphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)amino)methyl)thietane1,1-dioxide



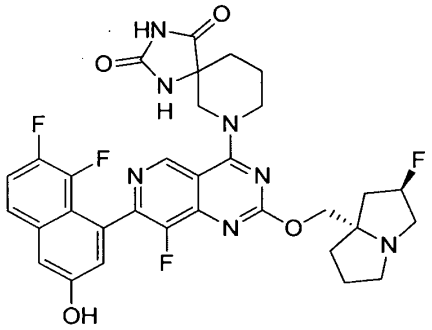
[00001150] Step A: 3-(((7-chloro-8-fluoro-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)amino)methyl)thietane 1,1-dioxide: To a solution of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (200 mg, 1.0 *equiv.*) in DMF (2 mL) was added 3-(aminomethyl)thietane 1,1-dioxide (77.1 mg, 1.2 *equiv.*) and DIEA (307 mg, 5.0 *equiv.*). The mixture was stirred at 40 °C for 2 hours. The pH of the mixture was adjusted to 7 with 1N HCl and the resulting mixture was filtered. The filter cake was dried in vacuum to give the title compound (140 mg, 65% yield) as a white solid. LCMS (ESI, M+1): 456.2.

[00001151] Step B: 3-(((8-fluoro-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)-7-(8-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)naphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)amino)methyl)thietane 1,1-dioxide: To a solution of 3-(((7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)thietane 1,1-dioxide (50

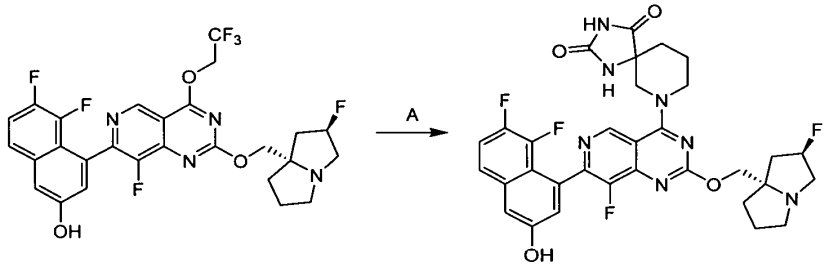
mg, 1.0 *equiv.*) and 4,4,5,5-tetramethyl-2-(8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)naphthalen-1-yl)-1,3,2-dioxaborolane (60.6 mg, 1.5 *equiv.*) in n-BuOH (1.5 mL) was added K_3PO_4 (1.5 M, 3.0 *equiv.*) and XPhos Pd G3 (9.44 mg, 0.1 *equiv.*). The mixture was stirred at 60 °C for 2 hours. The mixture was filtered through a pad of celite and concentrated in vacuum. The residue was purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] and Prep-HPLC [column: Unisil 3-100 C18 Ultra 150 × 50 mm × 3 μm; mobile phase: water (0.225% formic acid)-CAN, B%: 9%-39%, 10 min] to give the title compound (10 mg, 13.8% yield) as a yellow solid. LCMS [ESI, M+1]: 662.0.

[00001152] Step C: 3-(((8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-(hydroxymethyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)thietane 1,1-dioxide: To a solution of 3-(((8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)thietane 1,1-dioxide (10 mg, 1.0 *equiv.*) in MeOH (0.5 mL) was added HCl•dioxane (4 M, 20 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The mixture was concentrated in vacuum. The residue was purified by Prep-HPLC [column: Unisil 3-100 C18 Ultra 150 × 50 mm × 3 μm; mobile phase: water (0.225% formic acid)-CAN, B%: 9%-39%, 10 min] to give the title compound (2.39 mg, 27% yield) as an off-white solid. ^{1}H NMR(400 MHz, MeOD-d4) δ = 9.18 (s, 1H), 8.13-8.05 (m, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 6.4 Hz, 1H), 7.64-7.54 (m, 2H), 7.46 (dd, *J* = 1.2, 7.2 Hz, 1H), 4.72 (s, 2H), 4.36 (m, 2H), 4.29-4.20 (m, 2H), 4.17-4.03 (m, 4H), 3.72-3.63 (m, 2H), 3.28-3.26 (m, 2H), 3.11-2.99 (m, 1H), 2.38-2.07 (m, 8H). LCMS [ESI, M+1]: 578.3.

EXAMPLE 444

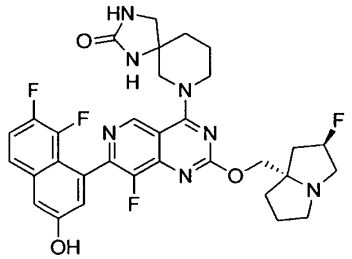


7-(7-(7,8-difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione



[00001153] Step A. 7-(7-(7,8-difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione: A mixture of 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 (60 mg, 1.0 *equiv.*), 1,3,9-triazaspiro[4.5]decane-2,4-dione (74 mg, 4.25 *equiv.*), DIEA (40.07 mg, 54 μL, 3.01 *equiv.*), 4Å molecular sieves (20 mg) in DMF (1 mL) was degassed and stirred at 40 °C for 18 hours. The mixture was filtered. The filtrate was purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to give a crude product. The crude product was re-purified by prep-HPLC (column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: [water (0.225% formic acid)-ACN]; B%: 11%-41%, 10 min) and lyophilized to give the title compound (34.1 mg, 50 % yield) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.20 (s, 1H), 8.50 (s, 1H), 7.62 (dd, *J* = 4.4, 9.2 Hz, 1H), 7.45 - 7.36 (m, 1H), 7.34 (t, *J* = 2.0 Hz, 1H), 5.50 - 5.33 (m, 1H), 4.66 (br d, *J* = 13.2 Hz, 1H), 4.56 - 4.35 (m, 3H), 3.83 - 3.49 (m, 5H), 3.25 - 3.14 (m, 1H), 2.56 - 1.87 (m, 10H); LCMS [ESI, M+1]: 652.3.

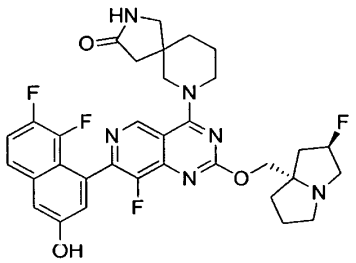
EXAMPLE 445



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

[00001154] The title compound was synthesized according to the procedure described for example 203. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.11 (s, 1H), 7.78-7.64 (m, 1H), 7.62-7.45 (m, 1H), 7.37 (s, 1H), 7.24 (s, 1H), 7.00 (br s, 1H), 6.30 (s, 1H), 5.41-5.15 (m, 1H), 4.20-3.91 (m, 4H), 3.78-3.63 (m, 2H), 3.24-2.94 (m, 6H), 2.88-2.75 (m, 1H), 2.20-1.97 (m, 4H), 1.88-1.70 (m, 6H); LCMS (ESI, M+1): m/z = 638.2.

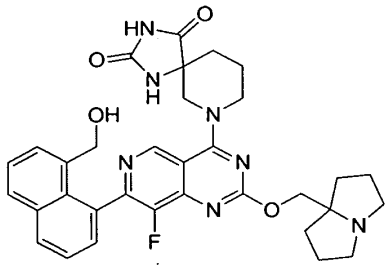
EXAMPLE 446



7-(7-(7,8-difluoro-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

[00001155] The title compound was synthesized according to the procedure described for example 203. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.07 (s, 1H), 7.67-7.57 (m, 1H), 7.44-7.35 (m, 1H), 7.35-7.31 (m, 1H), 7.26-7.21 (m, 1H), 5.43-5.18 (m, 1H), 4.36-4.19 (m, 2H), 4.17-3.95 (m, 4H), 3.39-3.33 (m, 2H), 3.28-3.16 (m, 3H), 3.06-2.95 (m, 1H), 2.43-2.10 (m, 5H), 2.05-1.82 (m, 7H); LCMS (ESI, M+1): m/z = 637.3;

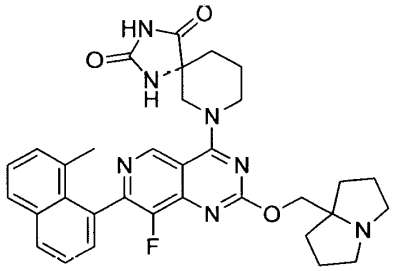
EXAMPLE 447



7-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-(hydroxymethyl)naphthalen-1-yl)pyrido[4,3-*d*]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decanc-2,4-dionc

[00001156] The title compound was synthesized according to the procedure described for example 433. ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.13 - 9.07 (m, 1H), 8.08 (dd, J = 1.2, 8.0 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.75 (br d, J = 7.2 Hz, 1H), 7.58 (m, 2H), 7.48 (d, J = 7.2 Hz, 1H), 4.63 (br d, J = 6.8 Hz, 1H), 4.54 - 4.40 (m, 1H), 4.36 - 4.22 (m, 4H), 3.85 - 3.67 (m, 2H), 3.17 - 3.06 (m, 2H), 2.73 (m, 2H), 2.30 - 2.19 (m, 1H), 2.14 - 1.99 (m, 4H), 1.98 - 1.83 (m, 5H), 1.80 - 1.71 (m, 2H); LCMS (ESI, M+1): m/z = 612.2.

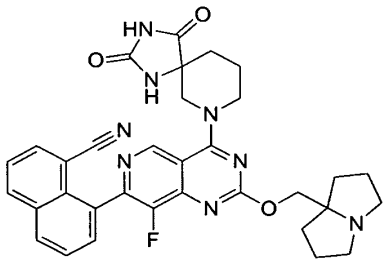
EXAMPLE 448



7-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-methylnaphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione

[00001157] The title compound was synthesized according to the procedure described for example 436. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.17 - 9.06 (m, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.48-7.40 (m, 2H), 7.35-7.25 (m, 1H), 4.63 (br dd, J = 5.6, 13.6 Hz, 1H), 4.52-4.37 (m, 1H), 4.35-4.23 (m, 2H), 3.86-3.64 (m, 2H), 3.17-3.06 (m, 2H), 2.73 (td, J = 6.4, 10.4 Hz, 2H), 2.30-2.17 (m, 1H), 2.14-2.02 (m, 5H), 2.02-1.94 (m, 3H), 1.94-1.84 (m, 4H), 1.81-1.72 (m, 2H); LCMS (ESI, M+1): m/z = 596.1.

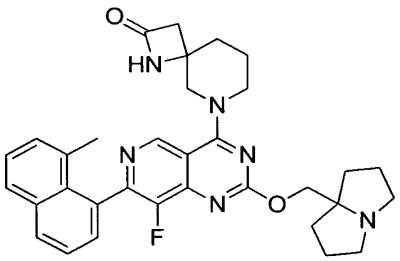
EXAMPLE 449



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

[00001158] The title compound was synthesized according to the procedure described for example 436. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.14 (s, 1H), 8.41-8.35 (m, 1H), 8.27 - 8.20 (m, 1H), 8.07 - 8.02 (m, 1H), 7.85 - 7.78 (m, 2H), 7.73 - 7.67 (m, 1H), 4.65 (br d, *J* = 13.2 Hz, 1H), 4.55-4.44 (m, 1H), 4.38-4.26 (m, 2H), 3.88-3.66 (m, 2H), 3.22-3.11 (m, 2H), 2.78 (td, *J* = 6.4, 10.4 Hz, 2H), 2.31-2.20 (m, 1H), 2.16-2.02 (m, 4H), 1.99-1.87 (m, 5H), 1.84-1.74 (m, 2H); LCMS (ESI, M+1): m/z = 607.2.

EXAMPLE 450

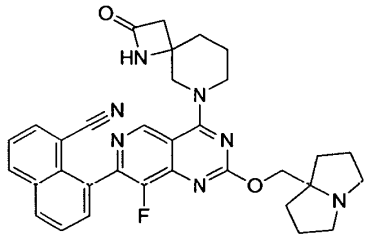


6-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-methylnaphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one

[00001159] The title compound was synthesized according to the procedure described for example 436. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.13 (d, *J* = 2.4 Hz, 1H), 8.05 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.63-7.53 (m, 1H), 7.48-7.41 (m, 2H), 7.32 (br d, *J* = 7.2 Hz, 1H), 4.67-4.58 (m, 2H), 4.42 (d, *J* = 13.2 Hz, 1H), 4.37-4.28 (m, 1H), 4.02 (dd, *J* = 4.4, 13.2 Hz, 1H), 3.91-3.82 (m, 1H), 3.70-3.60 (m, 2H), 3.28-3.18 (m, 2H), 2.96-2.87 (m, 1H), 2.82-2.74

(m, 1H), 2.35-2.27 (m, 2H), 2.26-2.14 (m, 4H), 2.13-2.08 (m, 2H), 2.07-2.01 (m, 5H), 1.97 (br dd, J = 4.0, 7.6 Hz, 2H); LCMS (ESI, M+1): m/z = 567.1.

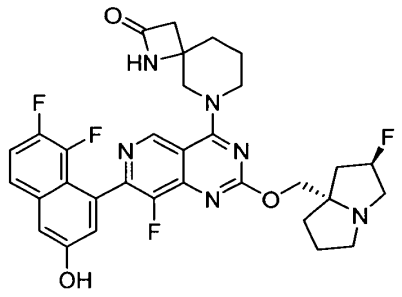
EXAMPLE 451



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

[00001160] The title compound was synthesized according to the procedure described for example 436. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.11 (s, 1H), 8.40-8.35 (m, 1H), 8.26-8.20 (m, 1H), 8.04 (dd, J = 1.2, 7.2 Hz, 1H), 7.85-7.78 (m, 2H), 7.73-7.66 (m, 1H), 4.41-4.18 (m, 4H), 4.09-4.00 (m, 1H), 3.97-3.73 (m, 1H), 3.19-3.09 (m, 2H), 2.81-2.92 (m, 1H), 2.80-2.70 (m, 3H), 2.16-2.03 (m, 4H), 2.01-1.87 (m, 6H), 1.83-1.73 (m, 2H); LCMS (ESI, M+1): m/z = 578.3.

EXAMPLE 452

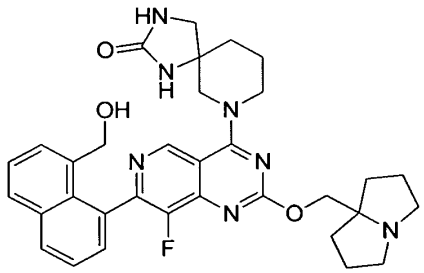


6-(7-(7,8-difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7aS)-2-fluorohexahydro-1*H*-pyrrolizin-7*a*-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one

[00001161] The title compound was synthesized according to the procedure described for example 444. ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.09 (s, 1H), 7.65-7.57 (m, 1H), 7.44-7.35

(m, 1H), 7.33 (t, J = 2.0 Hz, 1H), 7.26-7.22 (m, 1H), 5.45-5.17 (m, 1H), 4.49-4.20 (m, 4H), 4.03-3.90 (m, 1H), 3.83-3.68 (m, 1H), 3.30-3.14 (m, 3H), 3.06-2.96 (m, 1H), 2.95-2.86 (m, 1H), 2.80-2.71 (m, 1H), 2.40-2.07 (m, 4H), 2.06-1.83 (m, 6H); LCMS (ESI, M+1): m/z = 623.2.

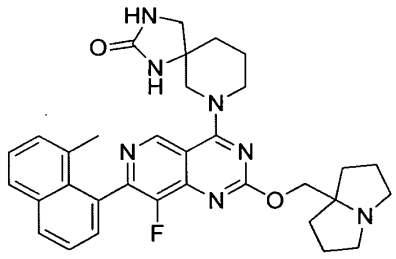
EXAMPLE 453



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

[00001162] The title compound was synthesized according to the procedure described for example 433. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.10 (br d, *J* = 6.4 Hz, 1H), 8.08 (br d, *J* = 6.8 Hz, 1H), 7.95 (br d, *J* = 7.6 Hz, 1H), 7.75 (br s, 1H), 7.63-7.53 (m, 2H), 7.49 (br s, 1H), 4.36-4.22 (m, 4H), 4.15-3.87 (m, 4H), 3.48-3.40 (m, 1H), 3.28 (br s, 1H), 3.16-3.05 (m, 2H), 2.78-2.67 (m, 2H), 2.13-2.02 (m, 2H), 2.01-1.82 (m, 8H), 1.81-1.71 (m, 2H); ^{19}F NMR (376 MHz, methanol-d4) δ = -139.118; LCMS (ESI, M+1): m/z = 598.3.

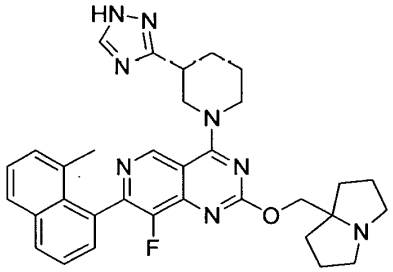
EXAMPLE 454



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

[00001163] The title compound was synthesized according to the procedure described for example 436. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.16 (d, *J* = 2.4 Hz, 1H), 8.06 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.50-7.40 (m, 2H), 7.32 (dd, *J* = 3.2, 6.8 Hz, 1H), 4.70-4.65 (m, 1H), 4.61-4.55 (m, 1H), 4.41 (dd, *J* = 8.8, 12.8 Hz, 1H), 4.25 (br dd, *J* = 4.0, 13.2 Hz, 1H), 4.06-3.93 (m, 1H), 3.88 (dd, *J* = 10.4, 12.8 Hz, 1H), 3.74-3.62 (m, 2H), 3.43 (dd, *J* = 1.6, 9.6 Hz, 1H), 3.30-3.21 (m, 3H), 2.37-2.27 (m, 2H), 2.26-2.14 (m, 4H), 2.09 (dd, *J* = 6.4, 12.8 Hz, 2H), 2.03 (d, *J* = 8.8 Hz, 3H), 1.98 (br s, 3H), 1.92-1.84 (m, 1H); LCMS (ESI, M+1): m/z = 582.1.

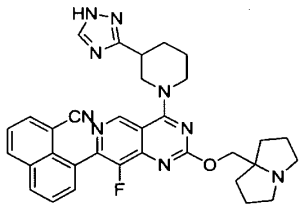
EXAMPLE 455



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

[00001164] The title compound was synthesized according to the procedure described for example 436. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.09 (d, *J* = 2.0 Hz, 1H), 8.22 (d, *J* = 4.4 Hz, 1H), 8.08-7.99 (m, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.48-7.39 (m, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 4.65-4.50 (m, 1H), 4.35-4.19 (m, 2H), 3.78 (ddd, *J* = 10.4, 13.2, 20.0 Hz, 1H), 3.73-3.64 (m, 1H), 3.42-3.32 (m, 2H), 3.11-3.02 (m, 2H), 2.70 (td, *J* = 6.8, 10.4 Hz, 2H), 2.36-2.27 (m, 1H), 2.15-2.05 (m, 3H), 2.04 (s, 4H), 2.00-1.91 (m, 2H), 1.91-1.86 (m, 2H), 1.86-1.79 (m, 1H), 1.78-1.68 (m, 2H); LCMS (ESI, M+1): m/z = 579.1.

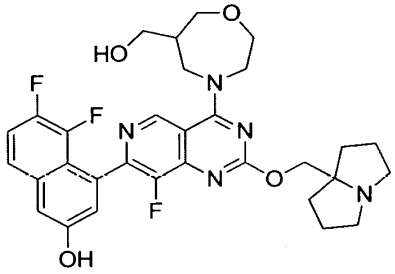
EXAMPLE 456



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

[00001165] The title compound was synthesized according to the procedure described for example 436. ^{1}H NMR (400 MHz, methanol-d$_4$) δ = 9.12 (s, 1H), 8.38-8.36 (m, 1H), 8.29-8.17 (m, 2H), 8.05-8.02 (m, 1H), 7.85-7.77 (m, 2H), 7.71-7.66 (m, 1H), 4.65-4.54 (m, 1H), 4.37-4.26 (m, 2H), 3.79-3.61 (m, 2H), 3.41-3.33 (m, 1H), 3.17-3.06 (m, 2H), 2.77-2.70 (m, 2H), 2.36-2.26 (m, 1H), 2.14-1.82 (m, 10H), 1.81-1.72 (m, 2H); LCMS (ESI, M+1): m/z = 590.3.

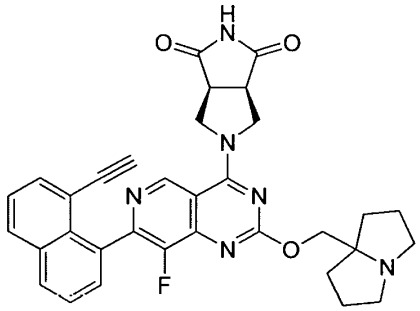
EXAMPLE 457



5,6-difluoro-4-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(6-(hydroxymethyl)-1,4-oxazepan-4-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol

[00001166] The title compound was synthesized according to the procedure described for example 203. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.32-9.20 (m, 1H), 7.63 (br dd, *J* = 4.8, 8.4 Hz, 1H), 7.46-7.39 (m, 1H), 7.38-7.33 (m, 1H), 7.32-7.22 (m, 1H), 4.81-4.64 (m, 3H), 4.52-4.35 (m, 1H), 4.18-4.03 (m, 2H), 4.02-3.94 (m, 1H), 3.88-3.79 (m, 1H), 3.75-3.67 (m, 2H), 3.61-3.53 (m, 2H), 3.35-3.31 (m, 1H), 3.30-3.20 (m, 2H), 3.12-2.97 (m, 1H), 2.40-2.28 (m, 2H), 2.27-2.16 (m, 4H), 2.15-1.99 (m, 3H); LCMS (ESI, M+1): m/z = 596.3.

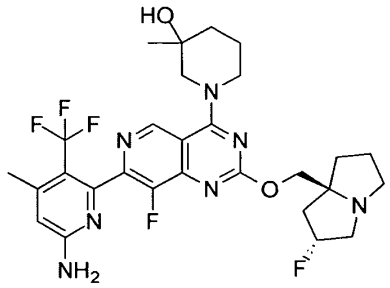
EXAMPLE 458



(3aR,6aS)-5-(7-(8-ethynylnaphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione

[00001167] The title compound was synthesized according to the procedure described for example 437. ^{1}H NMR (400 MHz, CD3OD) δ= 9.24 (s, 1H), 8.58-8.53 (m, 1H), 8.16-8.11 (m, 1H), 8.10-8.05 (m, 1H), 7.78-7.74 (m, 1H), 7.73-7.66 (m, 1H), 7.66 - 7.60 (m, 1H), 7.58 - 7.50 (m, 1H), 4.81-4.74 (m, 1H), 4.70-4.60 (m, 1H), 4.42-4.31 (m, 1H), 4.27 (br dd, *J* = 9.2, 12.4 Hz, 1H), 3.81-3.69 (m, 2H), 3.55-3.46 (m, 2H), 3.16-3.05 (m, 3H), 2.34-1.91 (m, 10H); LCMS (ESI, M+1): m/z = 577.2.

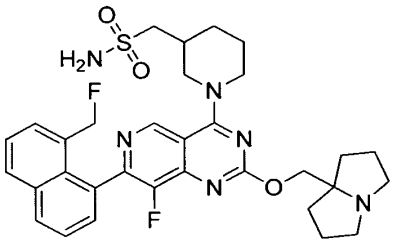
EXAMPLE 459



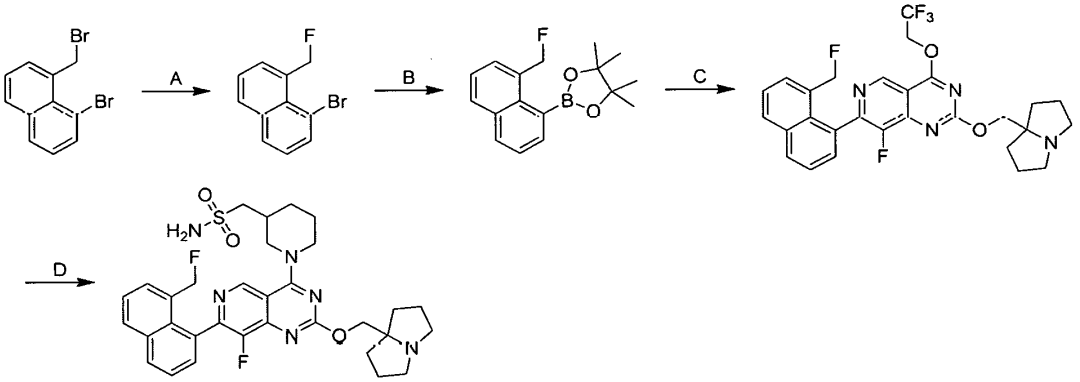
1-(7-(6-amino-4-methyl-3-(trifluoromethyl)pyridin-2-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

[00001168] The title compound was synthesized according to the procedure described for example 435 using intermediate 48 instead of intermediate 46 in step A. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.13 (s, 1H), 6.78 (s, 2H), 6.50 (s, 1H), 5.40-5.16 (m, 1H), 4.78-4.64 (m, 1H), 4.37-4.25 (m, 1H), 4.15 - 4.07 (m, 1H), 4.05 - 3.96 (m, 2H), 3.56 (br d, J = 13.2 Hz, 1H), 3.29-3.27 (m, 1H), 3.14-2.99 (m, 3H), 2.87-2.78 (m, 1H), 2.39-2.33 (m, 3H), 2.17-2.09 (m, 1H), 2.06-1.93 (m, 3H), 1.90-1.59 (m, 6H), 1.15 (s, 3H); LCMS (ESI, M+1): m/z = 594.2.

EXAMPLE 460



1-(1-(8-fluoro-7-(8-(fluoromethyl)naphthalen-1-yl)-2-((hexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide



[00001169] Step A. 1-bromo-8-(fluoromethyl)naphthalene: To a solution of 1-bromo-8-(bromomethyl)naphthalene (2.0 g, 1.0 *equiv.*) in DMSO (20 mL) was added tetrabutylammonium fluoride trihydrate (10.5 g, 5.0 *equiv.*). The reaction was stirred at 120 °C for 2 hours. The mixture was diluted with ethyl acetate (30 mL) and water (50 mL) then separated. The aqueous phase was extracted with ethyl acetate (30 mL). The organic layer was washed with brine (3 × 20 mL) and dried over Na_2SO_4, concentrated and purified by column chromatography [silica gel, petroleum

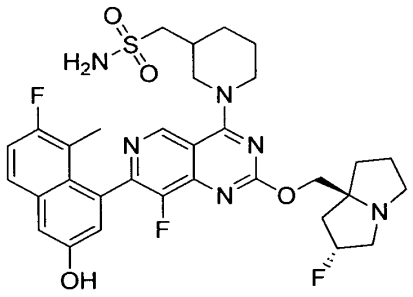
ether] to afford the title compound (1.30 g, 78% yield) as a yellow solid; ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ = 8.10-8.02 (m, 2H), 7.96 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.79 (br d, *J* = 7.2 Hz, 1H), 7.64-7.58 (m, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 6.32-6.19 (d, *J* = 47.6 Hz, 2H); ^{19}F NMR (376 MHz, dimethylsulfoxide-d6) δ = -195.731.

[00001170] Step B. 2-(8-(fluoromethyl)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: To a solution of 1-bromo-8-(fluoromethyl)naphthalene (1.20 g, 1.0 *equiv.*), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.91 g, 1.50 *equiv.*) and KOAc (1.48 g, 3.0 *equiv.*) in dioxane (20 mL) was added Pd(dppf)Cl_2 (367 mg, 0.1 *equiv.*) under N_2 atm. The reaction was stirred at 90 °C for 1.5 hours. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated and purified by prep-TLC [Silica gel, petroleum ether/ethyl acetate 100:1] to afford the title compound (1.08 g, 75% yield) as a yellow solid; ^{1}H NMR (400 MHz, chloroform-d) δ = 7.93 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.88-7.82 (m, 2H), 7.55-7.43 (m, 3H), 6.15-6.02 (d, *J* = 47.2 Hz, 2H), 1.46 (s, 12H); ^{19}F NMR (376 MHz, chloroform-d) δ = -204.598.

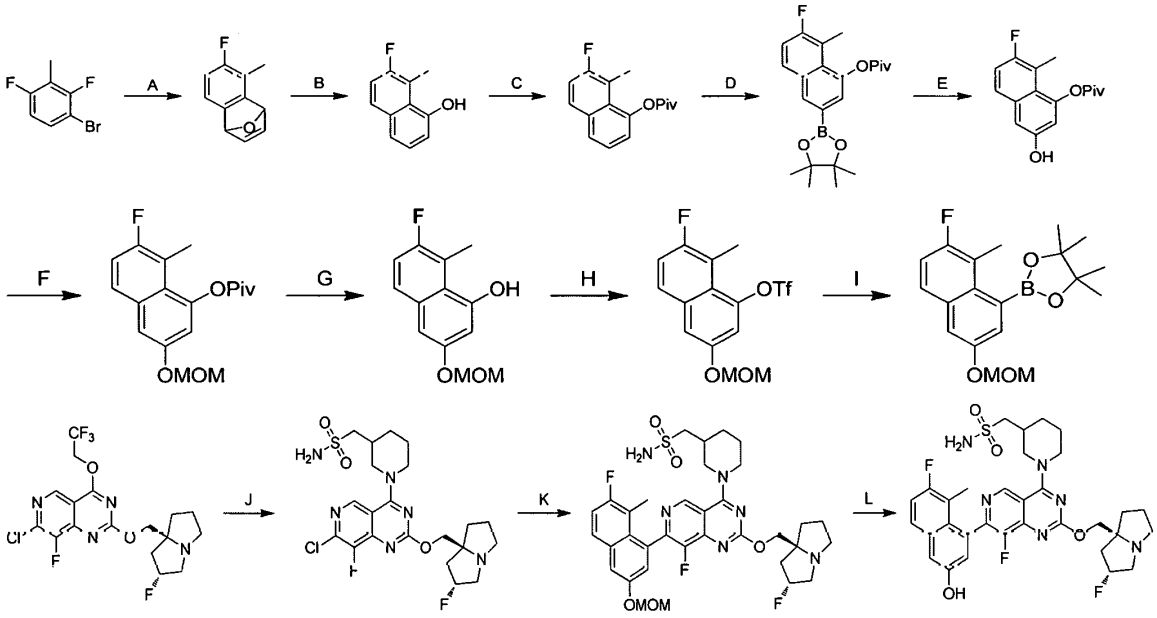
[00001171] Step C. 8-fluoro-7-(8-(fluoromethyl)naphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a solution of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (1.20 g, 1.0 *equiv.*), 2-(8-(fluoromethyl)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (979 mg, 1.20 *equiv.*) and Cs_2CO_3 (1.5 M, 3.0 *equiv.*) in methoxycyclopentane (15 mL) was added CataCXium A Pd G3 (208 mg, 0.1 *equiv.*) under N_2. The reaction was stirred at 90 °C for 2 hours under N_2. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 × 15 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 (0.3 g, 18% yield) as a yellow solid; ^{1}H NMR (400 MHz, chloroform-d) δ 9.26 (s, 1H), 8.05 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.65 - 7.59 (m, 2H), 7.59 - 7.50 (m, 2H), 5.15 - 5.06 (m, 3H), 5.02 (s, 1H), 4.45 (br s, 2H), 3.40 - 3.16 (m, 2H), 2.82 - 2.67 (m, 2H), 2.18 - 2.08 (m, 2H), 2.02 - 1.91 (m, 4H), 1.80 - 1.74 (m, 2H); ^{19}F NMR (376 MHz, chloroform-d) δ = -73.277, -136.576; LCMS (ESI, M+1): m/z = 545.3.

[00001172] Step D. 1-(1-(8-fluoro-7-(8-(fluoromethyl)naphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide: To a solution of 8-fluoro-7-(8-(fluoromethyl)naphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 1.0 *equiv.*), piperidin-3-ylmethanesulfonamide (24.6 mg, 1.5 *equiv.*) and DIEA (35.6 mg, 3.0 *equiv.*) in DMF (0.5 mL) was added 4Å molecular sieves (8 mg). The reaction was stirred at 40 °C for 12 hours. The mixture was filtered and purified by prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: water (10mM NH_4HCO_3)-ACN, B%: 31%-61%, 8 min]. The desired fraction was collected and concentrated lyophilized to afford the title compound (30.7 mg, 53% yield) as a yellow solid; ^{1}H NMR (400 MHz, methanol-d4) δ = 9.10 (s, 1H), 8.12 (dd, *J* = 0.8, 8.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.67-7.62 (m, 2H), 7.61-7.52 (m, 2H), 5.16-5.01 (m, 2H), 4.98 (br d, *J* = 13.6 Hz, 1H), 4.58 (br d, *J* = 12.4 Hz, 1H), 4.44-4.30 (m, 2H), 3.64-3.54 (m, 1H), 3.41-3.33 (m, 1H), 3.23-3.09 (m, 4H), 2.83-2.73 (m, 2H), 2.58-2.46 (m, 1H), 2.19-2.07 (m, 3H), 2.00-1.88 (m, 5H), 1.86-1.73 (m, 3H), 1.68-1.56 (m, 1H); ^{19}F NMR (376 MHz, methanol-d4) δ = -138.958, -204.127; LCMS (ESI, M+1): m/z = 623.3.

EXAMPLE 461



1-(1-(8-fluoro-7-(7-fluoro-3-hydroxy-8-methylnaphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide



[00001173] Step A. 6-fluoro-5-methyl-1,4-dihydro-1,4-epoxynaphthalene: To a solution of 1-bromo-2,4-difluoro-3-methylbenzene (80.0 g, 1.0 *equiv.*) and furan (52.6 g, 2.0 *equiv.*) in toluene (1000 mL) was added n-BuLi (2.5 M, 185 mL, 1.2 *equiv.*) at -40 °C. The mixture was stirred at 15 °C for 16 hours. The mixture was quenched with saturated aqueous NH_4Cl (800 mL) and extracted with ethyl acetate (800 mL). The organic phase was concentrated and purified by column chromatography [Silica gel, petroleum ether/ethyl acetate 1:0 to 10:1] to afford the title compound (30.0 g, crude) as a yellow oil.

[00001174] Step B. 7-fluoro-8-methylnaphthalen-1-ol: To a solution of 6-fluoro-5-methyl-1,4-dihydro-1,4-epoxynaphthalene (30.0 g, 1.0 *equiv.*) in EtOH (150 mL) was added HCl (150 mL, 36%, 8.9 *equiv.*). The reaction mixture was stirred at 80 °C for 3 hours. The mixture was concentrated and quenched with saturated aqueous $NaHCO_3$ (300 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic phase was washed with brine (150 mL), dried, concentrated and purified by column chromatography [Silica gel, petroleum ether/ethyl acetate 100:1 to 10:1] to afford the title compound (10.0 g, 15% yield over two steps) as a yellow oil; ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.59 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.24-7.16 (m, 2H), 6.76 (d, *J* = 7.6 Hz, 1H), 5.67 (s, 1H), 2.84 (d, *J* = 2.8 Hz, 3H); LCMS (ESI, M+1): m/z = 177.2.

[00001175] Step C. 7-fluoro-8-methylnaphthalen-1-yl pivalate: To a solution of 7-fluoro-8-methylnaphthalen-1-ol (10.0 g, 1.0 *equiv.*), DIEA (22.0 g, 3.0 *equiv.*) in DCM (100 mL) was added 2,2-dimethylpropanoyl chloride (9.58 g, 1.4 *equiv.*) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The mixture was quenched with water (50 mL) and extracted with ethyl acetate (100 mL). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography [Silica gel, petroleum ether/ethyl acetate 50:1 to 20:1] to afford the title compound (10.8 g, 73% yield) as a yellow oil; ^{1}H NMR (400 MHz, chloroform-d) δ = 7.74-7.65 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.27-7.21 (m, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 2.64 (d, *J* = 2.4 Hz, 3H), 1.46 (s, 9H).

[00001176] Step D. 7-fluoro-8-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl pivalate: To a mixture of 7-fluoro-8-methylnaphthalen-1-yl pivalate (7.00 g, 1.0 *equiv.*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (6.83 g, 1.0 *equiv.*), 4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine (433 mg, 0.06 *equiv.*) in hexane (240 mL) was added (1,5-Cyclooctadiene)(methoxy)iridium(I) dimer (891 mg, 1.34 mmol, 0.05 *equiv.*) under N_2. The mixture was stirred at 60 °C for 3 hours. The mixture was concentrated and purified by column chromatography [Silica gel, petroleum ether/ethyl acetate 100:1 to 15:1] to afford the title compound (6.00 g, crude) as a white solid.

[00001177] Step E. 7-fluoro-3-hydroxy-8-methylnaphthalen-1-yl pivalate: To a mixture of 7-fluoro-8-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl pivalate (6.00 g, 1.0 *equiv.*), THF (45 mL) and water (21 mL) were added H_2O_2 (13.4 g, 30% purity, 7.6 *equiv.*) and AcOH (46.6 g, 50 *equiv.*) at 10 °C. The mixture was stirred at 25 °C for 1 hour. The mixture was quenched with saturated aqueous Na_2SO_3 (400 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic phase was washed with brine (200 mL), dried over anhydrous sodium sulfate, concentrated and purified by column chromatography [Silica gel, petroleum ether/ethyl acetate 20:1 to 5:1] and reversed phase flash chromatography [C18, water (0.1 % NH3•H2O)-ACN] to afford the title compound (1.70 g, 23% yield over two steps) as an off-white solid; ^{1}H NMR (400 MHz, chloroform-d) δ = 7.41 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.16 (t, *J* = 9.2 Hz, 1H), 6.92 (d, *J* = 2.4 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 2.58 (d, *J* = 2.0 Hz, 3H), 1.45 (s, 9H).

[00001178] Step F. 7-fluoro-3-(methoxymethoxy)-8-methylnaphthalen-1-yl pivalate: To a solution of 7-fluoro-3-hydroxy-8-methylnaphthalen-1-yl pivalate (2.30 g, 1.0 *equiv.*), DIEA (3.23

g, 3.0 *equiv.*) in DCM (30 mL) was added chloro(methoxy)methane (889 mg, 1.3 *equiv.*) at 0 °C. The mixture was stirred at 20 °C for 1 hour. The mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layer was concentrated and purified by column chromatography [Silica gel, petroleum ether/ethyl acetate 20:1 to 5:1] to afford the title compound (2.60 g, 97% yield) as a white solid; ^{1}H NMR (400 MHz, chloroform-d) δ = 7.57 (dd, *J* = 5.2, 9.0 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.20 (t, *J* = 9.2 Hz, 1H), 6.79 (d, *J* = 2.4 Hz, 1H), 5.27 (s, 2H), 3.52 (s, 3H), 2.59 (d, *J* = 2.4 Hz, 3H), 1.45 (s, 9H); LCMS (ESI, M+1): m/z = 321.2.

[00001179] Step G. 7-fluoro-3-(methoxymethoxy)-8-methylnaphthalen-1-ol: To a solution of 7-fluoro-3-(methoxymethoxy)-8-methylnaphthalen-1-yl pivalate (2.60 g, 1.0 *equiv.*) in MeOH (26 mL) was added KOH (1.37 g, 3.0 *equiv.*). The reaction mixture was stirred at 20 °C for 0.5 hour. The pH of the mixture was to adjusted to 5 with 0.1 N HCl and extracted with ethyl acetate (2 × 80 mL). The organic phase was concentrated to afford the title compound (1.60 g, 83% yield) as a brown solid; ^{1}H NMR (400 MHz, chloroform-d) δ = 7.46 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.16 (t, *J* = 9.2 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.55 (d, *J* = 2.0 Hz, 1H), 5.25 (s, 2H), 3.52 (s, 3H), 2.78 (d, *J* = 2.6 Hz, 3H).

[00001180] Step H. 7-fluoro-3-(methoxymethoxy)-8-methylnaphthalen-1-yl trifluoromethanesulfonate: To a solution of 7-fluoro-3-(methoxymethoxy)-8-methylnaphthalen-1-ol (1.60 g, 1.0 *equiv.*), DIEA (2.63 g, 3.0 *equiv.*) in DCM (25 mL) was added Tf_2O (2.48 g, 1.3 *equiv.*) at -40 °C. The mixture was stirred at -40 °C for 0.5 hour. The reaction mixture was diluted with DCM (50 mL) and water (15 mL). The organic phase was washed with brine (20 mL), dried over anhydrous sodium sulfate, concentrated and purified by column chromatography [Silica gel, petroleum ether/ethyl acetate 20:1 to 6:1] to afford the title compound (2.30 g, 89% yield) as a yellow oil; ^{1}H NMR (400 MHz, chloroform-d) δ = 7.61 (dd, *J* = 5.2, 9.2 Hz, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.31-7.28 (m, 1H), 7.26 (s, 1H), 5.29 (s, 2H), 3.53 (s, 3H), 2.73 (d, *J* = 2.4 Hz, 3H).

[00001181] Step I. 2-(7-fluoro-3-(methoxymethoxy)-8-methylnaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: To a mixture of 7-fluoro-3-(methoxymethoxy)-8-methylnaphthalen-1-yl trifluoromethanesulfonate (1.00 g, 1.0 *equiv.*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.38 g, 2.0 equiv.), AcOK

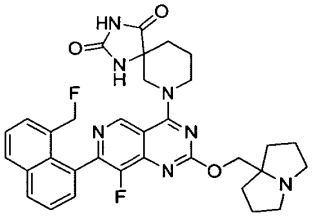
(933 mg, 3.5 equiv.) in dioxane (10 mL) was added Pd(dppf)Cl_2 (199 mg, 0.1 equiv.) under N_2. The reaction was stirred at 100 °C for 1.5 hours. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mL). The organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography [Silica gel, petroleum ether/ethyl acetate 50:1 to 15:1] to afford the title compound (500 mg, 53% yield) as a colorless oil; ^{1}H NMR (400 MHz, chloroform-d) δ = 7.57 (dd, J = 5.6, 8.8 Hz, 1H), 7.45-7.39 (m, 2H), 7.20 (t, J = 9.2 Hz, 1H), 5.32-5.23 (m, 2H), 3.51 (s, 3H), 2.63 (d, J = 2.4 Hz, 3H), 1.44 (s, 12H).

[00001182] Step J. 1-(1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide: 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 (60.0 mg, 1.0 *equiv.*), 3-piperidylmethanesulfonamide (26.8 mg, 1.1 *equiv.*), and DIEA (53.0 mg, 3.0 *equiv.*) in DMF (1 mL) was stirred at 20 °C for 1 hour. The mixture was filtered and purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (60.0 mg, 82% yield) as a white solid; LCMS (ESI, M+1): m/z = 517.3.

[00001183] Step K. 1-(1-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-methylnaphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide: To a mixture of 1-(1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide (60.0 mg, 1.0 *equiv.*), 2-(7-fluoro-3-(methoxymethoxy)-8-methylnaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (48.2 mg, 1.2 *equiv.*), K_3PO_4 (1.5 M in water , 232 µL, 3.0 *equiv.*) in methoxycyclopentane (1 mL) was added cataCXium A Pd G3 (8.45 mg, 0.1 *equiv.*) under N_2 atmosphere. The reaction mixture was stirred at 90 °C for 2 hours. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic phase was washed with brine (5 mL), dried over anhydrous Na_2SO_4, concentrated and purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (42.0 mg, 51% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 701.2.

[00001184] Step L. 1-(1-(8-fluoro-7-(7-fluoro-3-hydroxy-8-methylnaphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide: To a solution of (1-(8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-methylnaphthalen-1-yl)-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide (39.0 mg, 1.0 *equiv.*) in ACN (0.5 mL) was added HCl•dioxane (4 M, 1 mL, 72 *equiv.*) at 0°C. The mixture was stirred at 0 °C for 0.5 hour. The reaction mixture was concentrated at room temperature. The residue was dissolved in ethyl acetate (20 mL) and water (3 mL). The pH of the mixture was adjusted to 8 with solid $NaHCO_3$ while cooling the mixture with ice bath. The mixture was extracted with ethyl acetate (2× 15 mL), dried over anhydrous Na_2SO_4, concentrated and purified by prep-HPLC [column: Phenomenex Synergi C18 150 × 25 mm × 10 μm; mobile phase: water (0.1% formic acid) - ACN; B%: 10%-40%, 10 minutes] to afford the title compound (22.3 mg, 57% yield, 0.64 formic acid salt) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.13 (d, *J* = 1.2 Hz, 1H), 7.68 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.11 (dd, *J* = 2.8, 8.8 Hz, 1H), 5.57-5.34 (m, 1H), 5.20-5.03 (m, 1H), 4.60-4.44 (m, 3H), 3.76-3.46 (m, 4H), 3.29-3.11 (m, 3H), 2.65-2.30 (m, 4H), 2.23-2.00 (m, 4H), 1.97-1.88 (m, 1H), 1.85-1.71 (m, 4H), 1.70-1.56 (m, 1H); LCMS (ESI, M+1): m/z = 657.3.

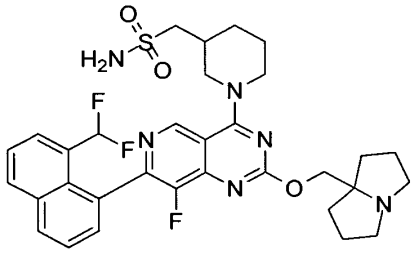
EXAMPLE 462



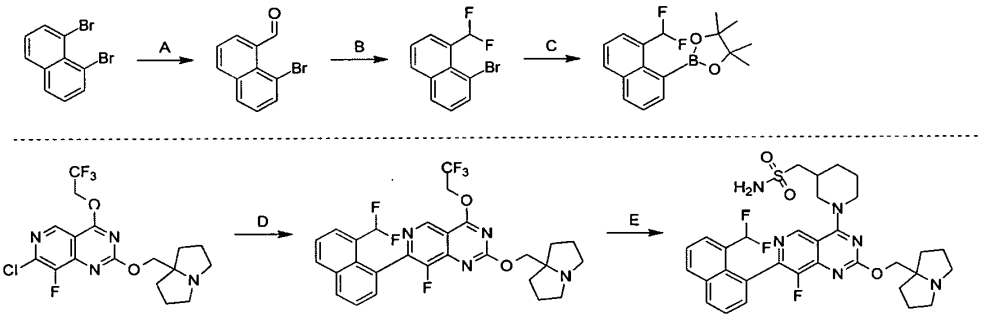
7-(8-fluoro-7-(8-(fluoromethyl)naphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione

[00001185] The title compound was synthesized according to the procedure described for example 460. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.17 (s, 1H), 8.19-8.05 (m, 2H), 7.74-7.50 (m, 4H), 5.12 (d, *J* = 47.6 Hz, 2H), 4.68-4.64 (m, 2H), 4.59-4.45 (m, 2H), 3.95-3.80 (m, 2H), 3.76-3.61 (m, 2H), 3.28-3.17 (m, 2H), 2.35-1.96 (m, 12H); LCMS (ESI, M+1): m/z = 614.4.

EXAMPLE 463



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



[00001186] Step A. 8-bromo-1-naphthaldehyde: To a solution of 1,8-dibromonaphthalene (10.0 g, 1.0 *equiv.*) in THF (200 mL) was added n-BuLi (2.5 M, 18.2 mL, 1.3 *equiv.*) at -60 °C dropwise under N_2 atm. After stirring for 5 minutes at -60 °C, DMF (25.6 g, 26.9 mL, 10 *equiv.*) was added dropwise to the mixture. The reaction was warmed up to 25 °C and stirred for another 25 minutes. The mixture was quenched with water (150 mL) and concentrated to remove THF. The residue was extracted with ethyl acetate (2 × 150 mL). The organic layer was dried over Na_2SO_4, concentrated in vacuum. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate 100:1 to 50:1) to afford the title compound (5.0 g, 61% yield) as a yellow solid; ^{1}H NMR (400 MHz, chloroform-d) δ = 11.44 (s, 1H), 8.03-7.98 (m, 1H), 7.93-7.87 (m, 3H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H).

[00001187] Step B. 1-bromo-8-(difluoromethyl)naphthalene: To a solution of 8-bromo-1-naphthaldehyde (2.50 g, 1.0 *equiv.*) in DCM (30 mL) was added a solution of DAST (6.86 g, 4.0 *equiv.*) in DCM (10 mL) slowly at -40 °C. The reaction was stirred at 25 °C for 12 hours. The

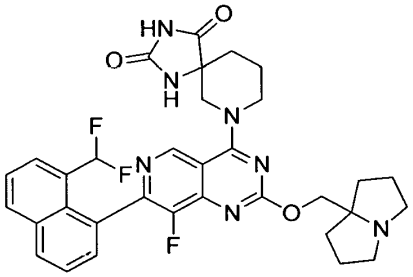
mixture was neutralized with saturated aqueous ice-cold $NaHCO_3$ solution (300 mL) and layers were separated. The aqueous phase was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by silica gel chromatography [petroleum ether/ethyl acetate 1:0 to 100:1] to afford the title compound (1.40 g, 51% yield) as a white solid; ^{1}H NMR (400 MHz, chloroform-d) δ = 8.56-8.56 (m, 1H), 8.12 (d, *J* = 7.2 Hz, 1H), 8.00-7.92 (m, 2H), 7.91-7.86 (m, 1H), 7.61-7.56 (m, 1H), 7.33 (t, *J* = 7.6 Hz, 1H).

[00001188] Step C. 2-(8-(difluoromethyl)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: A mixture of 1-bromo-8-(difluoromethyl)naphthalene (1.50 g, 1.0 *equiv.*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (2.22 g, 1.5 *equiv.*), KOAc (1.72 g, 3.0 *equiv.*) and $Pd(dppf)Cl_2$ (427 mg, 0.1 *equiv.*) in dioxane (30 mL) was degassed and stirred at 90 °C for 2 hours under N_2 atmosphere. The mixture was diluted with water (4.0 mL) and extracted with ethyl acetate (3 × 5.0 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by silica gel chromatography [petroleum ether/ethyl acetate 1:0 to 50:1] to afford the title compound (750 mg, 42% yield) as a white solid; ^{1}H NMR (400 MHz, chloroform-d) δ = 8.08-7.77 (m, 5H), 7.54-7.46 (m, 2H), 1.46 (s, 12H).

[00001189] Step D. 7-(8-(difluoromethyl)naphthalen-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, 1.0 *equiv.*), 2-(8-(difluoromethyl)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (159 mg, 1.1 *equiv.*), CataCXium A Pd G3 (34.6 mg, 0.1 *equiv.*) and K_3PO_4 (1.5 M in water , 951 µL, 3.0 *equiv.*) in methoxycyclopentane (4.0 mL) was degassed and stirred at 90 °C for 3 hours under N_2 atmosphere. The mixture was diluted with water (3.0 mL) and extracted with ethyl acetate (3 × 3.0 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 (70 mg, 26% yield) as a yellow solid; ^{1}H NMR (400 MHz, chloroform-d) δ = 9.26 (s, 1H), 8.13-8.05 (m, 2H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.66-7.54 (m, 2H), 7.58-7.54 (m, 1H), 6.58-6.25 (m, 1H), 5.13-5.05 (m, 2H), 4.36 (s, 2H), 3.19-3.09 (m, 2H), 2.68 (td, *J* = 6.8, 10.0 Hz, 2H), 2.11-2.06 (m, 1H), 2.05-2.00 (m, 1H), 1.90 (q, *J* = 6.4 Hz, 4H), 1.74-1.69 (m, 2H).

[00001190] Step E. 1-(1-(7-(8-(difluoromethyl)naphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide: To a solution of 7-(8-(difluoromethyl)naphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (30 mg, 1.0 *equiv.*) and piperidin-3-ylmethanesulfonamide (14.3 mg, 1.50 *equiv.*) in DMF (0.5 mL) were added DIEA (20.7 mg, 3.0 *equiv.*) and 4 Å molecular sieves (10 mg). The mixture was stirred at 40 °C for 12 hours. The mixture was filtered and purified by prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: water (10mM NH_4HCO_3)-ACN, B%: 40%-70%, 10 min] and re-purified by prep-HPLC [column: Unisil 3-100 C18 Ultra 150 × 50 mm × 3 μm; mobile phase: water (0.225% formic acid)-ACN, B%: 15%-45%, 10 min] and lyophilized to afford the title compound (11.7 mg, 34% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d_4) δ 9.17 (s, 1H), 8.24 - 8.15 (m, 2H), 7.94 (d, J = 7.2 Hz, 1H), 7.68 (q, J = 8.0 Hz, 2H), 7.63-7.57 (m, 1H), 6.59-6.27 (m, 1H), 5.14 (br d, J = 12.0 Hz, 1H), 4.71-4.65 (m, 1H), 4.64-4.54 (m, 2H), 3.76-3.67 (m, 1H), 3.61-3.50 (m, 2H), 3.25-3.10 (m, 4H), 2.61-2.47 (m, 1H), 2.33 (td, J = 6.4, 12.8 Hz, 2H), 2.21-2.11 (m, 4H), 2.11-1.88 (m, 5H), 1.85-1.71 (m, 1H), 1.68-1.56 (m, 1H); LCMS (ESI, M+1): m/z = 641.4.

EXAMPLE 464

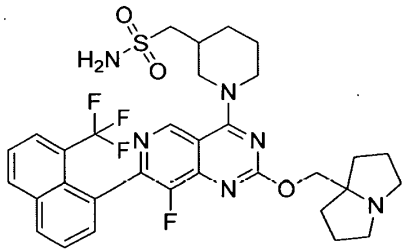


7-(7-(8-(difluoromethyl)naphthalen-1-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,3,7-triazaspiro[4.5]decane-2,4-dione

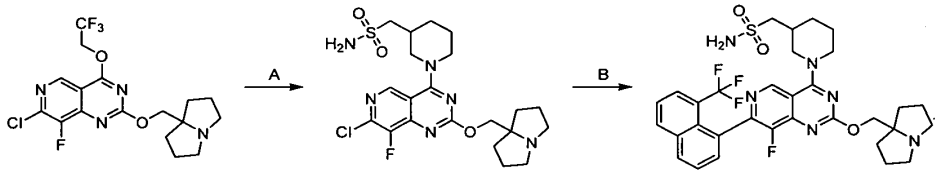
[00001191] The title compound was synthesized according to the procedure described for example 463. ^{1}H NMR (400 MHz, methanol-d_4) δ = 9.13 (s, 1H), 8.23-8.14 (m, 2H), 7.95 (d, J = 7.2 Hz, 1H), 7.73-7.65 (m, 2H), 7.63-7.58 (m, 1H), 6.60-6.26 (m, 1H), 4.69-4.65 (m, 1H), 4.54-4.45 (m, 1H), 4.38-4.26 (m, 2H), 3.84-3.70 (m, 2H), 3.21-3.11 (m, 2H), 2.81-2.72 (m, 2H), 2.30-

2.20 (m, 1H), 2.14-2.02 (m, 4H), 1.99-1.87 (m, 5H), 1.84-1.74 (m, 2H); LCMS (ESI, M+1): m/z = 632.4.

EXAMPLE 465



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

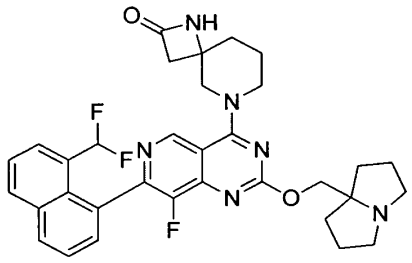


[00001192] Step A. 1-(1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide: To a mixture of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (200 mg, 1.0 *equiv.*), piperidin-3-ylmethanesulfonamide (102 mg, 1.2 *equiv.*), 4Å molecular sieves (10.0 mg) in DMF (2 mL) was added DIEA (184 mg, 248 µL, 3.0 *equiv.*). The reaction was stirred at 40 °C for 4 hours. After reaction completion, the mixture was filtered to give a solution. The crude product was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) to afford the title compound (135 mg, 57% yield) as a yellow solid; LCMS [ESI, M+1]: m/z = 499.2.

[00001193] Step B. 1-(1-(8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)-7-(8-(trifluoromethyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide: To a mixture of (1-(1-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)piperidin-3-yl)methanesulfonamide (135 mg, 1.0

equiv.), 4,4,5,5-tetramethyl-2-(8-(trifluoromethyl)naphthalen-1-yl)-1,3,2-dioxaborolane (113 mg, 1.3 *equiv.*), K_3PO_4 (1.5 M, 541 µL, 3.0 *equiv.*) in methoxycyclopentane (1 mL) was added CataCXium A Pd G3 (19.7 mg, 0.1 *equiv.*) under N_2. The reaction was stirred at 90 °C for 2 hours. After completion, the reaction mixture was quenched by addition of water (1 mL) and extracted with ethyl acetate (6 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase flash chromatography (water (0.1% formic acid) - ACN) and prep-HPLC (column: Waters Xbridge 150 × 25 mm × 5 µm; mobile phase: water (10mM NH_4HCO_3)-ACN, B%: 36% - 66%, 10 min) and lyophilized to afford the title compound (3.53 mg, 2% yield) as a white solid; ^1H NMR (400 MHz, methanol-d4): δ = 9.06 (d, *J* = 2.4 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 7.2 Hz, 1H), 7.78 - 7.72 (m, 1H), 7.71 - 7.63 (m, 2H), 4.98 (br s, 1H), 4.60 - 4.48 (m, 1H), 4.40 - 4.27 (m, 2H), 3.69 - 3.54 (m, 1H), 3.40 - 3.34 (m, 1H), 3.26 - 3.07 (m, 4H), 2.79 - 2.67 (m, 2H), 2.53 (br dd, *J* = 4.0, 7.2 Hz, 1H), 2.11 (qd, *J* = 5.6, 12.0 Hz, 3H), 1.98 - 1.88 (m, 5H), 1.98 - 1.71 (m, 3H), 1.68 - 1.57 (m, 1H); LCMS [ESI, M+1]: m/z = 659.5.

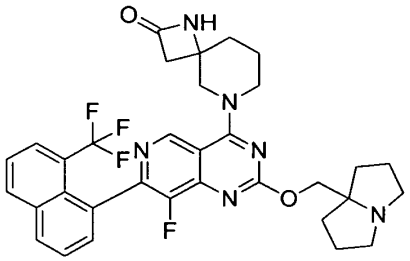
EXAMPLE 466



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

[00001194] The title compound was synthesized according to the procedure described for example 463. H NMR (400 MHz, methanol-d_4) δ = 9.14 (s, 1H), 8.25-8.13 (m, 2H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.72-7.65 (m, 2H), 7.62-7.62 (m, 1H), 6.59-6.26 (m, 1H), 4.53-4.39 (m, 3H), 4.37-4.27 (m, 1H), 4.07-3.98 (m, 1H), 3.91-3.78 (m, 1H), 3.42-3.34 (m, 2H), 3.05-2.95 (m, 2H), 2.94-2.74 (m, 2H), 2.24-2.15 (m, 2H), 2.15-2.07 (m, 2H), 2.06-1.96 (m, 6H), 1.96-1.87 (m, 2H); LCMS (ESI, M+1): m/z = 603.4.

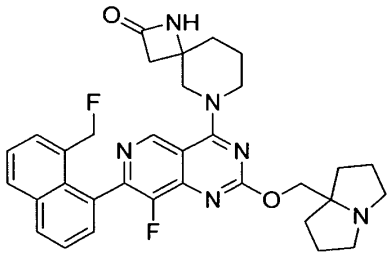
EXAMPLE 467



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

[00001195] The title compound was synthesized according to the procedure described for example 465. ^{1}H NMR (400 MHz, methanol-d4): δ = 9.06 (d, *J* = 3.6 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 8.21 (dd, *J* = 1.2, 8.4 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.80 - 7.60 (m, 3H), 4.43 - 4.20 (m, 4H), 4.00 (dd, *J* = 5.6, 13.2 Hz, 1H), 3.88 - 3.71 (m, 1H), 3.17 - 3.07 (m, 2H), 2.94 - 2.84 (m, 1H), 2.80 - 2.70 (m, 3H), 2.08 (ddd, *J* = 6.0, 13.2, 19.2 Hz, 4H), 2.01 - 1.87 (m, 6H), 1.82 - 1.73 (m, 3H); LCMS [ESI, M+1]: m/z = 621.4.

EXAMPLE 468

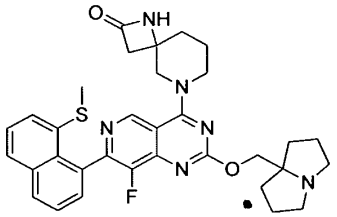


6-(8-fluoro-7-(8-(fluoromethyl)naphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one

[00001196] The title compound was synthesized according to the procedure described for example 460. ^{1}H NMR (400 MHz, methanol-d4): δ = 9.14 (s, 1H), 8.51 (s, 1H), 8.16 - 8.04 (m, 2H), 7.69 - 7.51 (m, 4H), 5.15 - 4.98 (m, 2H), 4.70 - 4.57 (m, 2H), 4.42 (br d, *J* = 13.2 Hz, 1H), 4.37 - 4.27 (m, 1H), 4.00 (d, *J* = 13.2 Hz, 1H), 3.90 - 3.80 (m, 1H), 3.69 - 3.58 (m, 2H), 3.26 - 3.17

(m, 2H), 2.95 - 2.88 (m, 1H), 2.81 - 2.73 (m, 1H), 2.35 - 2.25 (m, 2H), 2.24 - 2.01 (m, 8H), 2.00 - 1.92 (m, 2H); LCMS [ESI, M+1]: m/z = 585.3.

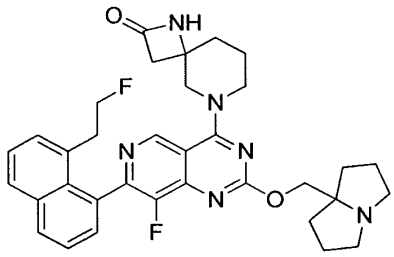
EXAMPLE 469



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

[00001197] The title compound was synthesized according to the procedure described for example 436. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.08 (d, *J* = 4.8 Hz, 1H), 8.06 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.86-7.784 (m, 1H), 7.68-7.58 (m, 1H), 7.55-7.49 (m, 3H), 4.58-4.48 (m, 2H), 4.45-4.18 (m, 2H), 4.07-4.01 (m, 1H), 3.96-3.73 (m, 1H), 3.54-3.41 (m, 2H), 3.13-3.01 (m, 2H), 2.93-2.71 (m, 2H), 2.25 (s, 3H), 2.24-2.19 (m, 1H), 2.17-2.02 (m, 6H), 2.00-1.96 (m, 4H) LCMS (ESI, M+1): m/z = 599.3.

EXAMPLE 470

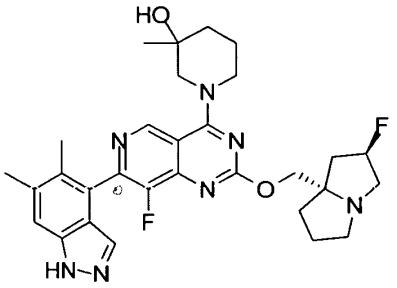


6-(8-fluoro-7-(8-(2-fluoroethyl)naphthalen-1-yl)-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one

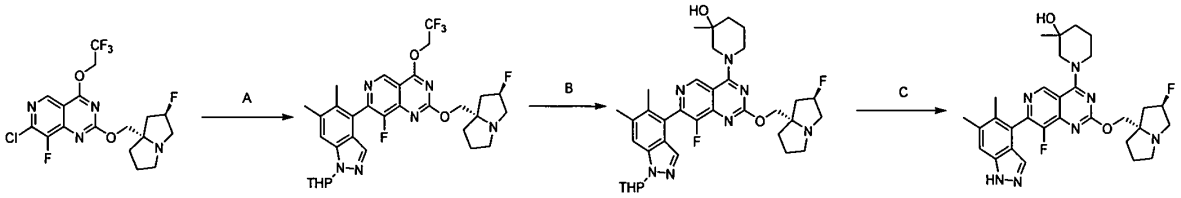
[00001198] The title compound was synthesized according to the procedure described for example 434; ^{1}H NMR (400 MHz, methanol-*d*4) δ = 9.15 (d, *J* = 2.0 Hz, 1H), 8.09 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.66-7.41 (m, 4H), 4.70-4.60 (m, 2H), 4.47-4.19 (m, 4H),

4.10-3.79 (m, 2H), 3.72-3.61 (m, 2H), 3.30-3.20 (m, 2H), 2.94-2.84 (m, 1H), 2.83-2.65 (m, 3H), 2.37-2.27 (m, 2H), 2.26-2.14 (m, 4H), 2.13-1.93 (m, 6H); LCMS (ESI, M+1): m/z = 599.3.

EXAMPLE 471



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



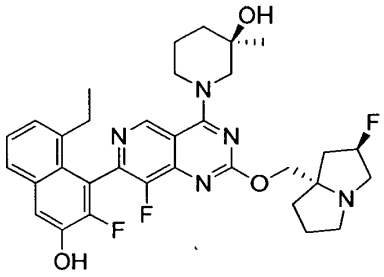
[00001199] Step A. 7-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: A mixture of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (200 mg, 1.0 *equiv.*), 5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (406 mg, 2.5 *equiv.*), cataCXium A Pd G3 (33.2 mg, 0.1 *equiv.*) and K_3PO_4 (1.5 M, 912 μL, 3.0 *equiv.*) in THF (4.0 mL) was degassed and stirred at 60 °C for 2 hours under N_2 atmosphere. The mixture was diluted with water (5.0 mL) and extracted with ethyl acetate (3 × 5.0 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 title compound (176 mg, 60% yield) as a yellow solid; ^{1}H NMR (400 MHz, chloroform-d) δ = 9.35 (d, *J* = 4.4 Hz, 1H), 7.63-7.57 (m, 1H), 7.54 (d, *J* = 16.9 Hz, 1H), 5.78-5.68 (m, 1H), 5.46-5.23 (m, 1H), 5.15-5.01 (m, 2H), 4.54-4.34 (m, 2H), 4.10-3.98

(m, 1H), 3.82-3.72 (m, 1H), 3.54-3.22 (m, 3H), 3.11-2.99 (m, 1H), 2.64-2.53 (m, 1H), 2.51 (s, 3H), 2.40-2.26 (m, 2H), 2.20 (s, 3H), 2.17-2.13 (m, 1H), 2.11-2.07 (m, 1H), 2.04-1.99 (m, 2H), 1.85-1.60 (m, 5H); LCMS (ESI, M+1): m/z = 633.4.

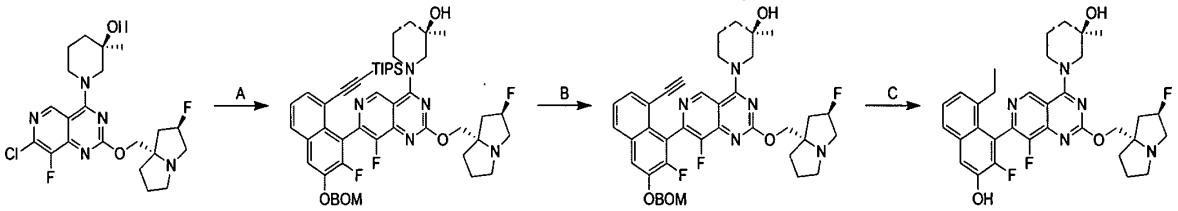
[00001200] Step B. 1-(7-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of 7-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (200 mg, 1.0 *equiv.*) in DMF (2.0 mL) was added 3-methylpiperidin-3-ol (95.9 mg, 2.0 *equiv.*, HCl), DIEA (204 mg, 5.0 *equiv.*) and 4 Å molecular sieves (50 mg). The reaction was stirred at 40 °C for 12 hours. The mixture was filtered and purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford title compound (173 mg, 84% yield) as a yellow solid; ^{1}H NMR (400 MHz, chloroform-d) δ = 9.28-9.19 (m, 1H), 7.69-7.62 (m, 1H), 7.51 (br d, *J* = 10.4 Hz, 1H), 5.77-5.68 (m, 1H), 5.39-5.15 (m, 1H), 4.52-4.37 (m, 2H), 4.35-4.18 (m, 2H), 4.09-3.96 (m, 1H), 3.83-3.69 (m, 1H), 3.54-3.37 (m, 1H), 3.36-3.22 (m, 3H), 3.20-3.10 (m, 1H), 3.02-2.92 (m, 1H), 2.63-2.52 (m, 1H), 2.50 (s, 3H), 2.30-2.24 (m, 1H), 2.22 (s, 3H), 2.20-2.10 (m, 3H), 2.08 (br s, 1H), 1.99-1.84 (m, 5H), 1.78-1.62 (m, 5H), 1.35 (s, 3H); LCMS (ESI, M+1): m/z = 648.6.

[00001201] Step C. 1-(7-(5,6-dimethyl-1H-indazol-4-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 1-(7-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-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 mg, 1.0 *equiv.*) in ACN (0.15 mL) was added HCl•dioxane (4 M, 289 μL, 15 *equiv.*). The reaction was stirred at 0 °C for 1 hour. The mixture was concentrated and purified by prep-HPLC [column: Waters Xbridge 150 × 25mm × 5 μm; mobile phase: water (10mM NH4HCO3), B: ACN, B%: 34%-64%, 9min] and lyophilized to afford the title compound (27.2 mg, 62% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d$_4$) δ 9.28 (dd, *J* = 1.0, 7.2 Hz, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 7.50 (s, 1H), 5.40-5.19 (m, 1H), 4.68-4.51 (m, 2H), 4.37-4.23 (m, 3H), 3.69-3.61 (m, 1H), 3.51-3.37 (m, 1H), 3.24 (br s, 1H), 3.19 (br s, 1H), 3.07-2.96 (m, 1H), 2.51 (s, 3H), 2.41-2.26 (m, 1H), 2.26-2.19 (m, 4H), 2.19-2.10 (m, 2H), 2.05-1.95 (m, 2H), 1.94-1.83 (m, 2H), 1.82-1.72 (m, 2H), 1.29 (d, *J* = 1.2 Hz, 3H); LCMS (ESI, M+1): m/z = 564.4.

EXAMPLE 472



(3R)-1-(7-(8-ethyl-2-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

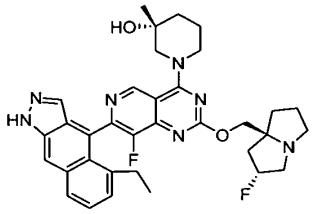


[00001202] Step A. (3R)-1-(7-(3-((benzyloxy)methoxy)-2-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a mixture of (R)-1-(7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (2.00 g, 1.0 *equiv.*), ((6-((benzyloxy)methoxy)-7-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (3.89 g, 1.5 *equiv.*), K_3PO_4 (1.5 M in water , 8.81 mL, 3.0 *equiv.*) in methoxycyclopentane (30 mL) was added CataCXium A Pd G3 (321 mg, 0.1 *equiv.*) under N_2. The mixture was stirred at 90 °C for 8 hours. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 × 15 mL). The combined organic phase was washed with brine (20 mL), 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 (1.20 g, 31% yield) as a brown oil; LCMS (ESI, M+1): m/z = 880.5.

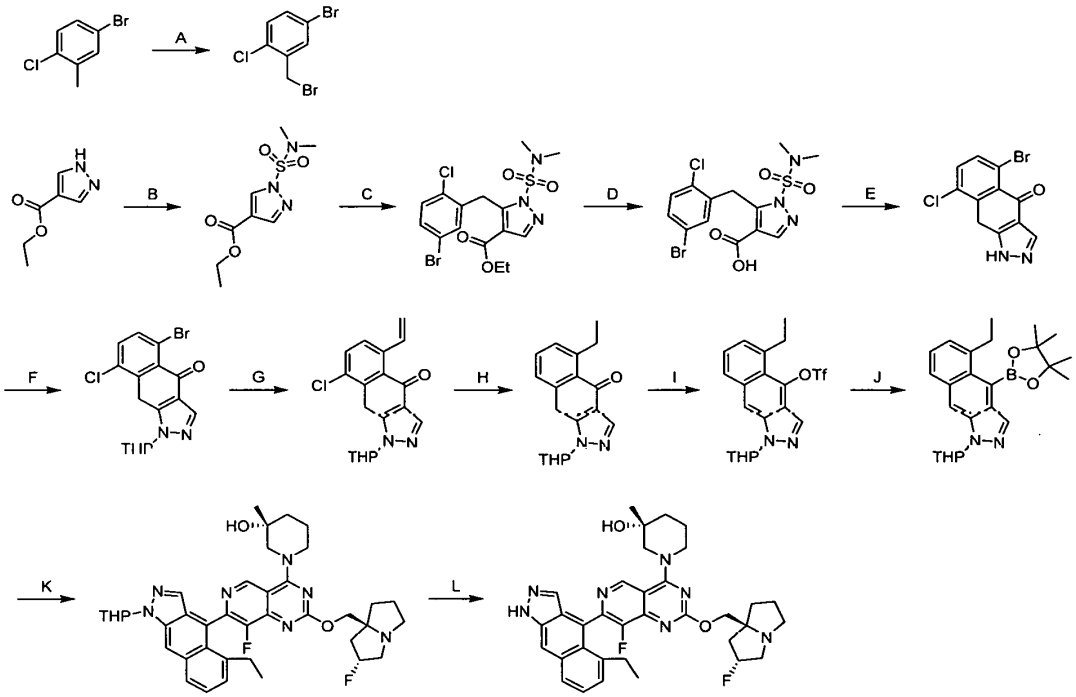
[00001203] Step B. (3R)-1-(7-(3-((benzyloxy)methoxy)-8-ethynyl-2-fluoronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To the solution of (3R)-1-(7-(3-((benzyloxy)methoxy)-2-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (1.10 g, 1.0 *equiv.*) in DMF (5 mL) was added CsF (1.90 g, 10 *equiv.*). The mixture was stirred at 25 °C for 1 hour. The mixture was filtered and purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)/ACN] to afford the title compound (820 mg, 89% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 724.4.

[00001204] Step C. (3R)-1-(7-(8-ethyl-2-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 (3R)-1-(7-(3-((benzyloxy)methoxy)-8-ethynyl-2-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 (200 mg, 1.0 *equiv.*) in MeOH (3 mL) was added Pd/C (40.0 mg, 10% purity) under N_2 atmosphere. The mixture was degassed, purged with H_2 and stirred at 25 °C for 12 hours under H_2 (15 psi) atmosphere. The mixture was filtered, concentrated and purified by prep-HPLC [column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: water (0.25% formic acid) - ACN; B%: 14%-44%, 10 minutes] to afford the title compound (37.8 mg, 21% yield, 0.5FORMIC ACID) as a yellow solid; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.28 (d, *J* = 3.2 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 9.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 5.56-5.33 (m, 1H), 4.64-4.40 (m, 3H), 4.37-4.26 (m, 1H), 3.75-3.38 (m, 5H), 3.28-3.18 (m, 1H), 2.61-2.33 (m, 2H), 2.33-2.23 (m, 2H), 2.23-2.10 (m, 4H), 2.09-1.97 (m, 1H), 1.91-1.71 (m, 3H), 1.29 (d, *J* = 9.2 Hz, 3H), 0.89 (td, *J* = 7.5, 9.7 Hz, 3H); LCMS (ESI, M+1): m/z = 608.4.

EXAMPLE 473



(3R)-1-(7-(5-ethyl-1H-benzo[f]indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



[00001205] Step A. 4-bromo-2-(bromomethyl)-1-chlorobenzene: A mixture of 4-bromo-1-chloro-2-methylbenzene (50 g, 1.0 equiv.), NBS (47.6 g, 1.1 equiv.), AIBN (799 mg, 0.02 equiv.) in MeCN (600 mL) was stirred at 90 °C for 12 hours. The mixture was concentrated in vacuum and the residue was purified by column chromatography (Silica gel, ethyl acetate/petroleum ether 10:1) to afford the title compound (60 g, 87% yield) as a white solid ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.61 (d, J = 2.4 Hz, 1H), 7.40 (dd, J = 2.4, 8.4 Hz, 1H), 7.30-7.26 (m, 1H), 4.54 (s, 2H).

[00001206] Step B. ethyl 1-(N,N-dimethylsulfamoyl)-1H-pyrazole-4-carboxylate: To a mixture of ethyl 1H-pyrazole-4-carboxylate (10 g, 1.0 equiv.) and DABCO (8.81 g, 1.1 equiv.) in MeCN (100 mL) was added N,N-dimethylsulfamoyl chloride (11.3 g, 8.41 mL, 1.1 equiv.). The mixture was stirred at 20 °C for 1 hour before being concentrated in vacuum and the residue was purified by column chromatography (Silica gel, petroleum ether/ethyl acetate 3:1) to afford the title compound (15 g, 85% yield) as a white solid. LCMS (ESI, M+1): m/z = 248.0.

[00001207] Step C. ethyl 5-(5-bromo-2-chlorobenzyl)-1-(N,N-dimethylsulfamoyl)-1H-pyrazole-4-carboxylate: To a solution of ethyl 1-(N,N-dimethylsulfamoyl)-1H-pyrazole-4-carboxylate (6 g, 1.0 equiv.) in THF (60 mL) was added LDA (2 M, 14.6 mL, 1.2 equiv.) and HMPA (5.22 g, 5.12 mL, 1.2 equiv.) at -78 °C. After stirring at -78 °C for 1 hour, 4-bromo-2-(bromomethyl)-1-chlorobenzene (8.28 g, 1.2 equiv.) was added into the mixture. The mixture was stirred at -78 °C for 2 hours and at 20 °C for 1 hour before being diluted with ethyl acetate (100 mL), washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography (Silica gel, petroleum ether/ethyl acetate 3:1). The desired fractions were collected and concentrated in vacuum to give a residue and the residue was triturated with methanol (30 mL), dried in vacuum to afford the title compound (3 g, 27% yield) as a white solid. LCMS (ESI, M+1): m/z = 452.1.

[00001208] Step D. 5-(5-bromo-2-chlorobenzyl)-1-(N,N-dimethylsulfamoyl)-1H-pyrazole-4-carboxylic acid: A mixture of ethyl 5-(5-bromo-2-chlorobenzyl)-1-(N,N-dimethylsulfamoyl)-1H-pyrazole-4-carboxylate (20 g, 1.0 equiv.) and NaOH (44.4 g, 25 equiv.) in dioxane (120 mL) and water (120 mL) was stirred at 90 °C for 2 hours. The mixture was extracted with ethyl acetate (300 mL), washed with brine (200 mL), dried over Na_2SO_4 and concentrated in vacuum to afford the title compound (20.5 g, crude) as a white solid and used into next step without further purification.

[00001209] Step E. 5-bromo-8-chloro-1H-benzo[f]indazol-4(9H)-one: A mixture of 5-(5-bromo-2-chlorobenzyl)-1-(N,N-dimethylsulfamoyl)-1H-pyrazole-4-carboxylic acid (22 g, 1.0 equiv.) in CF_3SO_3H (220 mL) was stirred at 90 °C for 3 hours. The mixture was poured into ice water (500 mL) and filtered. The filter cake was diluted with ethyl acetate (500 mL) and filtered, the filtrate was washed with saturated sodium bicarbonate (400 mL), brine (400 mL), dried over Na_2SO_4 and concentrated in vacuum to afford the title compound (7.5 g, 48% yield) that was used in the next step without further purification as a yellow solid. LCMS (ESI, M+1): m/z = 298.8.

[00001210] Step F. 5-bromo-8-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[f]indazol-4(9H)-one:To a mixture of 5-bromo-8-chloro-1H-benzo[f]indazol-4(9H)-one (6.5 g, 1.0 equiv.) and TsOH (376 mg, 0.1 equiv.) in THF (60 mL) was added DHP (5.51 g, 5.99 mL, 3.0 equiv.) at 15 °C. The mixture was stirred at 15 °C for 15 mins before being concentrated in vacuum. The residue was purified by reversed phase flash chromatography [water (0.1% formic

acid)/acetonitrile] to afford the title compound (3.7 g, 40% yield) as a yellow oil. LCMS (ESI, M-83): m/z = 298.8.

[00001211] Step G. 8-chloro-1-(tetrahydro-2H-pyran-2-yl)-5-vinyl-1H-benzo[f]indazol-4(9H)-one: A mixture of 5-bromo-8-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[f]indazol-4(9H)-one (550 mg, 1.0 equiv.), potassium trifluoro(vinyl)boranuide (579 mg, 3 equiv.), $Pd(dppf)Cl_2$ (105 mg, 0.1 equiv.) and Na_2CO_3 (458 mg, 3.0 equiv.) in dioxane (5 mL) and water (1.5 mL) was stirred at 90 °C for 3 hours. The mixture was concentrated in vacuum and the residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to afford the title compound (220 mg, 46% yield) as a yellow solid. LCMS (ESI, M+1): m/z = 328.9.

[00001212] Step H. 5-ethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[f]indazol-4(9H)-one: A mixture of 8-chloro-1-(tetrahydro-2H-pyran-2-yl)-5-vinyl-1H-benzo[f]indazol-4(9H)-one (300 mg, 1.0 equiv.), Pd/C (10 mg, 10%, 1 equiv.) and $NaHCO_3$ (76.6 mg, 1.0 equiv.) in MeOH (10 mL) was stirred at 20 °C for 1 hours under H_2 atmosphere (15 psi). The mixture was filtered and concentrated in vacuum and the residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to afford the title compound (110 mg, 41% yield) as a yellow solid. LCMS (ESI, M+1): m/z = 297.2.

[00001213] Step I. 5-ethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[f]indazol-4-yl trifluoromethanesulfonate: To a solution of 5-ethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[f]indazol-4(9H)-one (50 mg, 1.0 equiv.) and DIEA (87.2 mg, 4.0 equiv.) in DCM (1.0 mL) was added Tf_2O (95.2 mg, 2.0 equiv.) at -40 °C. The mixture was stirred at -40 °C for 15 mins. After completion, the residue was purified by column chromatography (Silica gel, petroleum ether/ethyl acetate 5:1) to afford the title compound (45 mg, 51% yield) as a yellow solid. LCMS (ESI, M+1): m/z = 429.1.

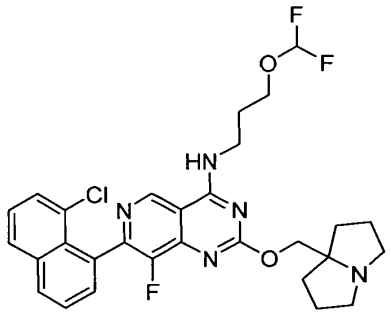
[00001214] Step J. 5-ethyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[f]indazole: A mixture of 5-ethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[f]indazol-4-yl trifluoromethanesulfonate (30 mg, 1.0 equiv.), 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (35.9 mg, 40.6 μL, 4.0 equiv.), TEA (28.3 mg, 4.0 equiv.) and $Pd(dppf)Cl_2$ (5.12 mg, 0.1 equiv.) in MeCN (1 mL) was stirred at 80 °C for 5 hours under N_2 atm. The mixture was concentrated in vacuum and the residue was purified by column chromatography (Silica gel,

petroleum ether/ethyl acetate 5:1) to afford the title compound (24 mg, 71% yield) as a yellow oil. LCMS (ESI, M+1): m/z = 407.2.

[00001215] Step K. (3R)-1-(7-(5-ethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[f]indazol-4-yl)-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 5-ethyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[f]indazole (15 mg, 1.0 equiv.), (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 (33.5 mg, 2.0 equiv.), CataCXium A Pd G3 (2.69 mg, 0.1 equiv.) and K_3PO_4 (1.5 M in water, 3.0 equiv.) in THF (1.0 mL) was stirred at 60 °C for 12 hours under N_2. The mixture was concentrated in vacuum to give a residue and the residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] to afford the title compound (18 mg, 50% yield) as a yellow oil. LCMS (ESI, M+1): m/z = 698.4.

[00001216] Step L. (3R)-1-(7-(5-ethyl-1H-benzo[f]indazol-4-yl)-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 (3R)-1-(7-(5-ethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[f]indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (16 mg, 1.0 equiv.) in TFA (1.23 g, 471 equiv.) and DCM (0.5 mL) was stirred at 15 °C for 0.5 hours. After completion, the mixture was concentrated in vacuum and the residue was purified by reversed phase flash chromatography [water (0.1% formic acid)/acetonitrile] followed by prep-HPLC (column: Phenomenex Synergi C18 150 × 25 mm × 10 μm; mobile phase: water (0.225% formic acid)-ACN, B%: 16%-36%, 10 min) to afford the title compound (2.51 mg, 17% yield) as a yellow solid. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.34 (d, *J* = 10.4 Hz, 1H), 8.22 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 18.4 Hz, 1H), 7.43 (dd, *J* = 6.8, 8.4 Hz, 1H), 5.49-5.31 (m, 1H), 4.61 (br s, 1H), 4.48- 4.33 (m, 3H), 3.75-3.60 (m, 1H), 3.55-3.37 (m, 4H), 3.19-3.09 (m, 1H), 2.63-2.30 (m, 4H), 2.29-1.95 (m, 5H), 1.94-1.76 (m, 3H), 1.33 (d, *J* = 10.0 Hz, 3H), 1.00 (q, *J* = 7.6 Hz, 3H). LCMS (ESI, M+1): m/z = 614.4

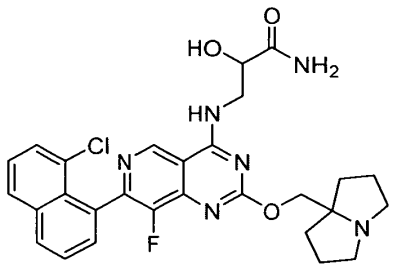
EXAMPLE 474



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

[00001217] The title compound was synthesized according to the procedure described for example 101. LCMS (ESI, M+1): m/z = 572.2

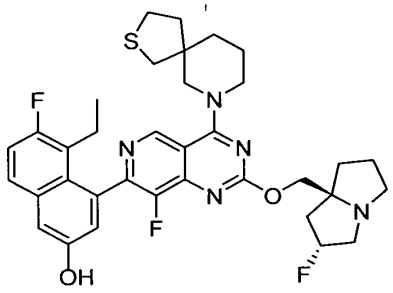
EXAMPLE 475



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

[00001218] The title compound was synthesized according to the procedure described for example 101. LCMS (ESI, M+1): m/z = 551.1

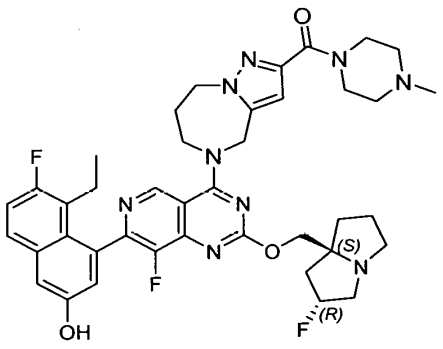
EXAMPLE 476



5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2-thia-7-azaspiro[4.5]decan-7-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol

[00001219] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, Acetic) δ = 9.50 (s, 1H), 8.16-8.09 (m, 1H), 7.71 (dd, J = 6.0, 8.8 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.29 (t, J = 9.6 Hz, 1H), 7.22 (t, J = 2.8 Hz, 1H), 5.69-5.49 (m, 1H), 5.02-4.73 (m, 2H), 4.72-4.52 (m, 1H), 4.51-4.26 (m, 1H), 4.21-4.09 (m, 2H), 4.07-3.63 (m, 3H), 3.49-3.36 (m, 1H), 3.07-2.74 (m, 4H), 2.72-2.46 (m, 4H), 2.39-2.25 (m, 4H), 2.08 (br s, 1H), 2.02-1.78 (m, 5H), 0.86 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 650.2.

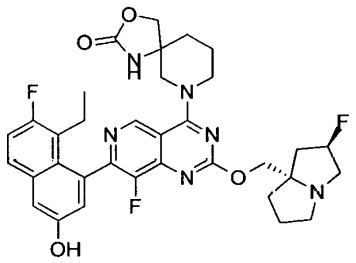
EXAMPLE 477



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

[00001220] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.23 (s, 1H), 7.69 (dd, J = 6.0, 9.0 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.26 (t, J = 9.6 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.87 (s, 1H), 5.67-5.51 (m, 1H), 5.41-5.20 (m, 3H), 5.01-4.90 (m, 2H), 4.82 (br s, 2H), 4.75-4.36 (m, 7H), 4.11-3.80 (m, 3H), 3.46 (td, J = 5.6, 10.7 Hz, 3H), 2.95 (s, 3H), 2.81 - 2.03 (m, 11H), 0.78 (br t, J = 7.2 Hz, 3H), LCMS (ESI, M+1): m/z = 756.5.

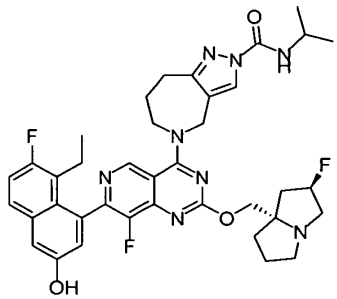
EXAMPLE 478



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)-3-oxa-1,7-diazaspiro[4.5]decan-2-one

[00001221] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.10 (s, 1H), 7.71-7.65 (m, 1H), 7.31 (d, J = 2.6 Hz, 1H), 7.25 (t, J = 9.4 Hz, 1H), 7.05 (d, J = 2.6 Hz, 1H), 5.45-5.26 (m, 1H), 4.44-4.28 (m, 4H), 4.16 (d, J = 9.0 Hz, 2H), 4.00-3.82 (m, 2H), 3.51-3.38 (m, 1H), 3.14-3.05 (m, 1H), 2.62-2.11 (m, 6H), 2.09-1.96 (m, 6H), 1.94-1.79 (m, 2H), 0.86-0.73 (m, 3H); LCMS (ESI, M+1): m/z = 649.2.

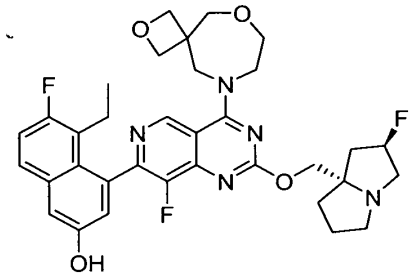
EXAMPLE 479



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

[00001222] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d6) δ = 10.16-9.72 (m, 1H), 9.15 (s, 1H), 8.25 (s, 1H), 8.22 (s, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.76 (dd, *J* = 6.0, 9.1 Hz, 1H), 7.40-7.29 (m, 2H), 7.01 (d, *J* = 2.4 Hz, 1H), 5.38-5.18 (m, 1H), 5.11-4.97 (m, 2H), 4.31 (br s, 2H), 4.17-4.05 (m, 2H), 4.00-3.89 (m, 1H), 3.12-3.05 (m, 2H), 3.01 (br s, 1H), 2.99-2.92 (m, 2H), 2.86-2.79 (m, 1H), 2.41-2.35 (m, 1H), 2.21-1.98 (m, 6H), 1.88-1.72 (m, 3H), 1.17 (d, *J* = 6.8 Hz, 6H), 0.70 (t, *J* = 7.2 Hz, 3H), LCMS (ESI, M+1): m/z = 715.5.

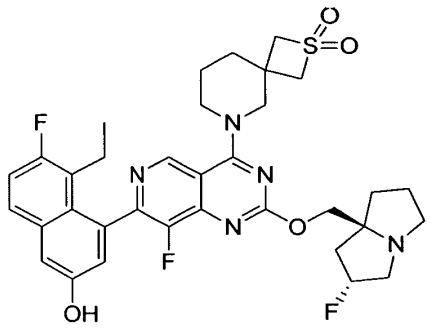
EXAMPLE 480



5-ethyl-6-fluoro-4-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)-4-(2,6-dioxa-9-azaspiro[3.6]decan-9-yl)pyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-2-ol

[00001223] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.93 (s, 1H), 9.22 (s, 1H), 7.83-7.70 (m, 1H), 7.42-7.28 (m, 2H), 7.01 (d, *J* = 2.4 Hz, 1H), 5.28 (d, *J* = 64.0 Hz 1H), 4.62-4.48 (m, 3H), 4.36 (t, *J* = 6.8 Hz 3H), 4.18-4.12 (m, 1H), 4.07 (d, *J* = 1.2 Hz 1H), 4.02-3.92 (m, 4H), 3.89 (d, *J* = 4.4 Hz 2H), 3.09 (d, *J* = 10.0 Hz, 2H), 3.01 (s, 1H), 2.86-2.79 (m, 1H), 2.41-2.34 (m, 1H), 2.21-2.08 (m, 2H), 2.02 (d, *J* = 10.4 Hz, 2H), 1.90-1.71 (m, 3H), 0.73 (t, *J* = 7.2 Hz, 3H); LCMS $[M+1]^+$: m/z = 636.2.

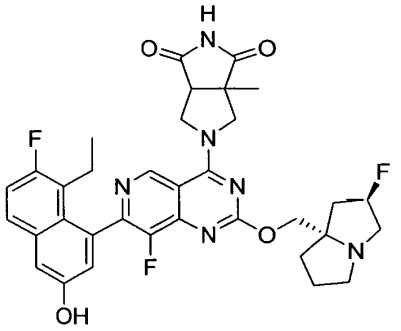
EXAMPLE 481



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)-2-thia-6-azaspiro[3.5]nonane 2,2-dioxide

[00001224] The title compound was synthesized according to the procedure described for example 135. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.12 (s, 1H), 7.68 (dd, *J* = 6.0, 9.2 Hz, 1H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.25 (t, *J* = 9.6 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 5.5-5.32 (m, 1H), 4.52 (s, 2H), 4.46-4.30 (m, 2H), 4.22-4.06 (m, 4H), 4.05-3.97 (m, 2H), 3.70-3.55 (m, 1H), 3.55-3.42 (m, 2H), 3.26-3.16 (m, 1H), 2.61-2.42 (m, 2H), 2.40-2.26 (m, 2H), 2.25-2.10 (m, 3H), 2.10-2.02 (m, 3H), 1.82 (br s, 2H), 0.80 (dt, *J* = 1.2, 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 668.4.

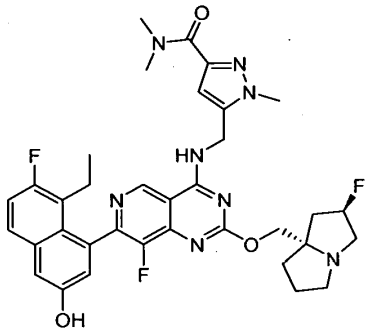
EXAMPLE 482



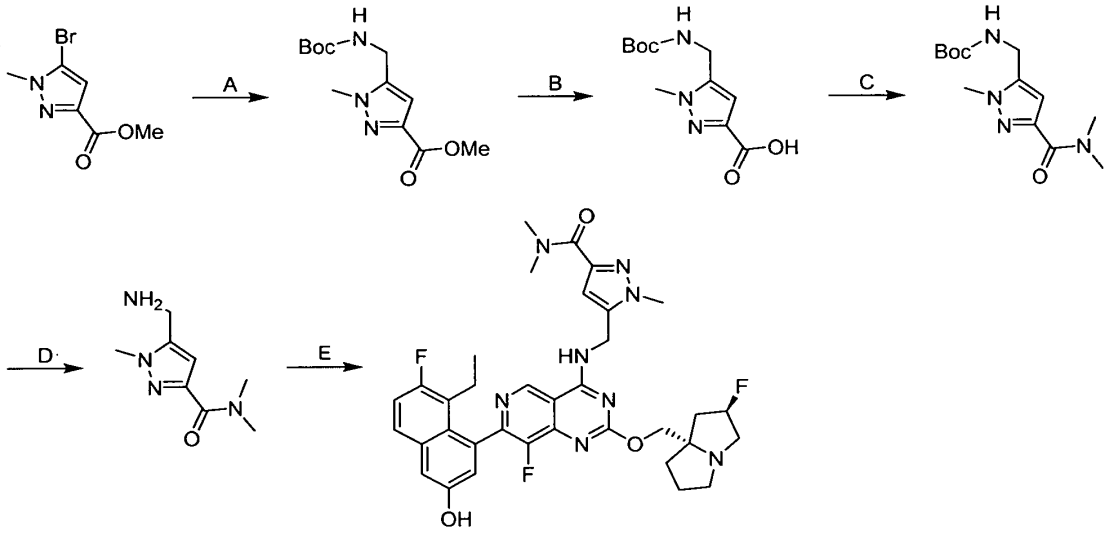
5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3a-methyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione

[00001225] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.85-10.93 (m, 1H), 9.26 (s, 1H), 8.18 (s, 1H), 7.77 (dd, J = 6.0, 9.2 Hz, 1H), 7.42-7.29 (m, 2H), 7.02 (d, J = 2.4 Hz, 1H), 5.41-5.17 (m, 1H), 4.55-4.41 (m, 2H), 4.40-4.30 (m, 1H), 4.20-4.12 (m, 1H), 4.10-4.04 (m, 1H), 3.95 (d, J = 12.0 Hz, 1H), 3.44 (s, 1H), 3.10 (d, J = 11.2 Hz, 2H), 3.02 (s, 1H), 2.87-2.81 (m, 1H), 2.36-2.31 (m, 1H), 2.17-1.97 (m, 4H), 1.89-1.74 (m, 3H), 1.50 (s, 3H), 0.80-0.66 (m, 3H); LCMS [M+1] $^+$: m/z = 647.2.

EXAMPLE 483



5-(((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)amino)methyl)-N,N,1-trimethyl-1H-pyrazole-3-carboxamide



[00001226] Step A. methyl 5-[(tert-butoxycarbonylamino)methyl]-1-methyl-pyrazole-3-carboxylate: A mixture of methyl 5-bromo-1-methyl-pyrazole-3-carboxylate (0.95 g, 1.0 equiv.), potassium (((tert-butoxycarbonyl)amino)methyl)trifluoroborate (1.2 g, 1.2 equiv.), $Pd(PPh_3)_2Cl_2$ (152 mg, 0.05 equiv.), RuPhos (405 mg, 0.2 equiv.) and Na_2CO_3 (1.4 g, 3.0 equiv.) in dioxane (20 mL) and H_2O (2 mL) was degassed and stirred at 120 °C for 12 hours. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried over Na_2SO_4, filtered and concentrated to give a residue, which was purified by flash silica gel chromatography (Ethyl acetate in Petroleum ether 42~46%) to afford the title compound (0.82 g, 70% yield) as a yellow gum; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.71 (s, 1H), 4.82 (s, 1H), 4.37 (d, J = 5.6 Hz, 2H), 3.92 (m, 6H), 1.46 (s, 9H).

[00001227] Step B. 5-[(tert-butoxycarbonylamino)methyl]-1-methyl-pyrazole-3-carboxylic acid: To a solution of methyl 5-[(tert-butoxycarbonylamino)methyl]-1-methyl-pyrazole-3-carboxylate (700 mg, 1.0 equiv.) in THF (10 mL) and H_2O (10 mL) was added $LiOH•H_2O$ (218mg, 2.0 equiv.). The reaction was stirred at 25 °C for 2 hours. The pH of the mixture was adjusted to 2~3 with 1 N HCl. The resulting mixture was diluted with H_2O (150 mL) and extracted with DCM (3 × 150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound (560 mg, 2.19 mmol, 84% yield) as a yellow gum. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.76 (s, 1H), 4.89 (br s, 1H), 4.39 (d, J = 4.4 Hz, 2H), 3.95 (s, 3H), 1.46 (s, 9H)

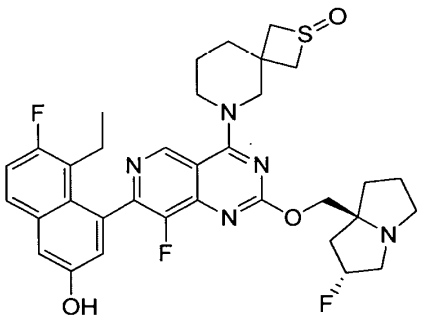
[00001228] Step C. tert-butyl N-[[5-(dimethylcarbamoyl)-2-methyl-pyrazol-3yl]methyl]carbamate: To a solution of 5-[(tert-butoxycarbonylamino)methyl]-1-methyl-pyrazole-3-carboxylic acid (550 mg, 1 equiv.) and dimethylamine (351 mg, 2.0 equiv, HCl) in DMF (10 mL) was added HATU (1.64 g, 2.0 equiv.) and DIEA (1.39 g, 5.0 equiv.). The reaction was stirred at 25 °C for 2 hours. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (Ethyl acetate in Petroleum ether 72~80%) to afford the title compound (600 mg, 96% yield, 97% purity) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.54 (s, 1H), 4.96 (s, 1H), 4.36 (d, J = 5.6 Hz, 2H), 3.87 (s, 3H), 3.32 (s, 3H), 3.09 (s, 3H), 1.45 (s, 9H)

[00001229] Step D. 5-(aminomethyl)-N,N,1-trimethyl-pyrazole-3-carboxamide: To a solution of tert-butyl N-[[5-(dimethylcarbamoyl)-2-methyl-pyrazol-3-yl]methyl]carbamate (300 mg, 1.0

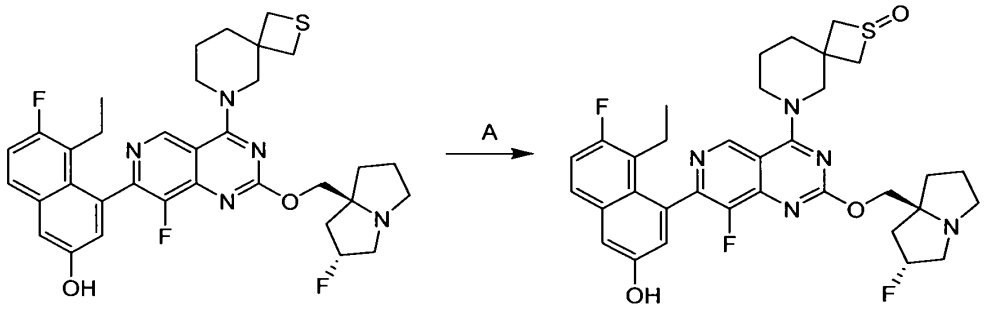
equiv.) in DCM (3 mL) was added HCl•dioxane (4 M, 0.1 equiv.). The reaction was stirred at 25 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to afford the title compound (228 mg, 98% yield, HCl) as a white solid.

[00001230] Step E. 5-(((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)amino)methyl)-N,N,1-trimethyl-1H-pyrazole-3-carboxamide: To a solution of 5-(aminomethyl)-N,N,1-trimethyl-pyrazole-3-carboxamide (129mg, 5.0 equiv, HCl) in DMSO (1.5 mL) were added K_2CO_3 (49.0 mg, 3.0 equiv.) and 4Å molecular sieves (10 mg). The reaction was stirred at 25 °C for 0.5 hour before 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 (70 mg, 1 equiv.) was added and the resulting mixture was stirred at 40 °C for 2 hours. The mixture was concentrated and the residue was purified by *prep*-HPLC (column: Phenomenex luna C18 150×25mm×10um; mobile phase: [water(0.1% formic acid)-ACN]; B%: 13%-43%, 9min) to afford the title compound (12.3 mg, 13% yield, 93.1% purity, formic acid salt) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.49 (br t, J = 5.2 Hz, 1H), 9.34 (s, 1H), 8.18 (s, 1H), 7.76 (dd, J = 6.0, 9.2 Hz, 1H), 7.40-7.28 (m, 2H), 7.00 (d, J = 2.4 Hz, 1H), 6.59 (s, 1H), 5.42-5.15 (m, 1H), 4.93-4.75 (m, 2H), 4.19-4.05 (m, 2H), 3.98 (s, 3H), 3.28 (s, 3H), 3.09 (d, J = 10.4 Hz, 2H), 3.01 (s, 1H), 2.95 (s, 3H), 2.87-2.78 (m, 1H), 2.38-2.28 (m, 1H), 2.18-1.95 (m, 4H), 1.88-1.72 (m, 3H), 0.71 (t, J = 7.2 Hz, 3H). LCMS [M+1] $^+$: m/z =675.3

EXAMPLE 484

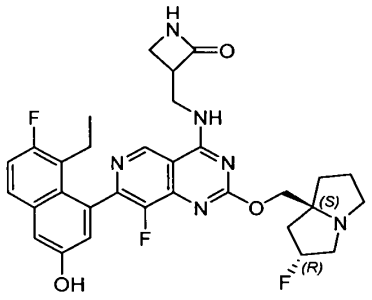


6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-thia-6-azaspiro[3.5]nonane 2-oxide

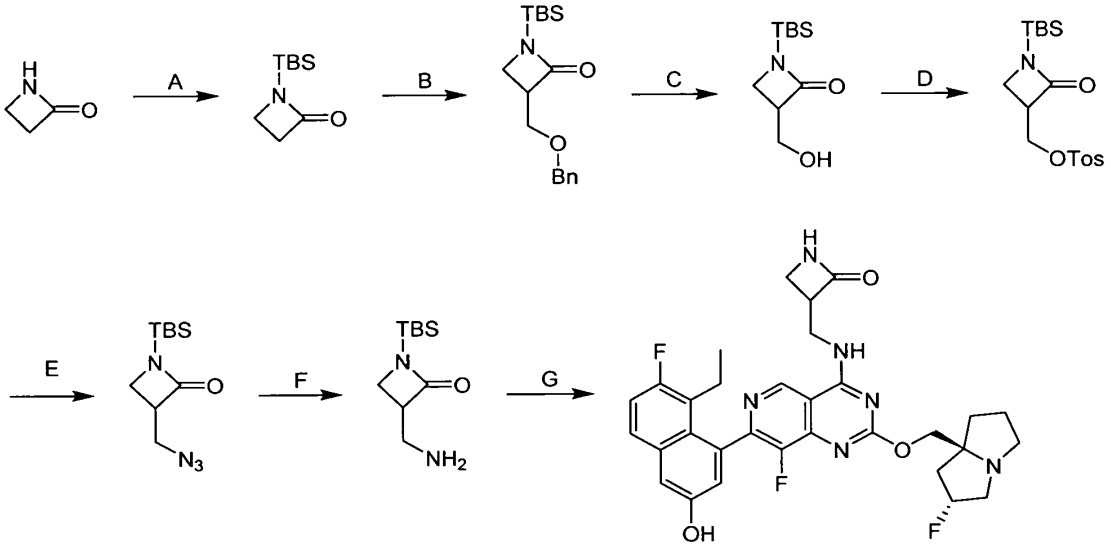


[00001231] Step A. 6-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-thia-6-azaspiro[3.5]nonane 2-oxide: To a solution of $NaIO_4$ (7.07 mg, 1.05 equiv.) in H_2O (0.5 mL) was added 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2-thia-6-azaspiro[3.5]nonan-6-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol (20.0 mg, 1.0 equiv.) at 0 °C. Then MeOH (0.4 mL) and dioxane (0.3 mL) was added to the mixture. The reaction mixture was stirred at 0 °C for 12 hours. The residue was filtered, washed with MeOH (1 mL), and the filtrate was purified by prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: water (10mM NH_4HCO_3)-ACN; B%: 32% - 62%, 8 min] and lyophilized to afford the title compound (4.36 mg, 21% yield) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.06 (s, 1H), 7.68 (dd, J = 6.0, 9.2 Hz, 1H), 7.30 (d, J = 2.4 Hz, 1H), 7.25 (t, J = 9.6 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 5.42-5.17 (m, 1H), 4.43-4.19 (m, 4H), 4.08-3.96 (m, 2H), 3.73-3.62 (m, 2H), 3.27-3.12 (m, 5H), 3.06-2.97 (m, 1H), 2.55-2.43 (m, 1H), 2.41-2.20 (m, 2H), 2.20-2.12 (m, 2H), 2.04-1.83 (m, 7H), 0.80 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 652.4.

EXAMPLE 485



3-(((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)amino)methyl)azetidin-2-one



[00001232] Step A. 1-[*tert*-butyl(dimethyl)silyl]azetidin-2-one: azetidin-2-one (2.00 g, 1.0 equiv.) and *tert*-butylchlorodimethylsilane (4.88 g, 1.1 equiv.) were dissolved in dichloromethane (25 mL) at 20°C under nitrogen atmosphere. A solution of diisopropylethylamine (5.46 g, 1.5 equiv.) in dichloromethane (15 mL) was added dropwise. The resulting mixture was stirred at 25 °C for 20 hours. The mixture was concentrated. The residue was diluted with petroleum ether/ethyl acetate (1:1, 100 mL) and the mixture was filtered. The filtrate was concentrated. The residue was purified by flash silica gel chromatography (ethyl acetate/petroleum ether 1:4) to afford the title compound (4.90 g, 94% yield) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.21 - 3.17 (m, 2H), 3.09-3.04 (m, 2H), 0.95 (d, J = 0.8 Hz, 9H), 0.23 (d, J = 1.2Hz, 6H); LCMS (ESI, M+1): m/z = 186.2.

[00001233] Step B. 3-(benzyloxymethyl)-1-[*tert*-butyl(dimethyl)silyl]azetidin-2-one: To a solution of ((chloromethoxy)methyl)benzene (1.86 g, 1.1 *equiv.)* in tetrahydrofuran (40 mL) was added lithium diisopropylamide (2.0 M in THF, 1.2 *equiv.)* at -70 °C under nitrogen atmosphere. After stirring at -70 °C for 0.5 hour, a solution of 1-[*tert*-butyl(dimethyl)silyl]azetidin-2-one (2.00 g, 1.0 *equiv.)* in tetrahydrofuran (8 mL) was added to above mixture at -70 °C. The resulting mixture was stirred at -70 °C for 1 hour and then warmed up to 25 °C and stirred at 25 °C for 16

hours. The mixture was quenched with saturated ammonium chloride solution (150 mL) at 0 °C under nitrogen atmosphere and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (petroleum ether/ethyl acetate 0 to 100%) to afford the title compound (1.8 g, 39% yield) as a colorless oil; LCMS (ESI, M+1): m/z = 306.2.

[00001234] Step C. 1-[*tert*-butyl(dimethyl)silyl]-3-(hydroxymethyl)azetidin-2-one: To a solution of 3-(benzyloxymethyl)-1-[*tert*-butyl(dimethyl)silyl]azetidin-2-one (2.06 g, 1.0 *equiv.)* in methanol (40 mL) was added palladium/carbon (2.00 g, 10% purity, wet) under nitrogen atmosphere. The suspension was degassed under vacuum and purged with hydrogen The mixture was stirred under hydrogen atmosphere (15.0 psi) at 40 °C for 16 hours. The reaction mixture was filtered. The filter cake was washed with methanol (2 × 20 mL). The combined filtrate was concentrated in vacuum to afford the title compound (1.20 g, 66% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 216.1.

[00001235] Step D. [1-[*tert*-butyl(dimethyl)silyl]-2-oxo-azetidin-3-yl]methyl 4-methylbenzenesulfonate: To a solution of 1-[*tert*-butyl(dimethyl)silyl]-3-(hydroxymethyl)azetidin-2-one (0.20 g, 1.0 *equiv.)* in dichloromethane (2 mL) was added 4-methylbenzenesulfonyl chloride (195 mg, 1.1 *equiv.)* and triethylamine (188 mg, 2.0 *equiv.)* at 0 °C. The mixture was stirred at 25 °C for 16 hours. The mixture was poured into water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic phase was washed with brine (2 × 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuum. Then the crude was purified by flash silica gel chromatography (petroleum ether/ethyl acetate 0 to 100%) to afford the title compound (130 mg, 37% yield) as a colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.78 (m, 2H), 7.50 (m, 2H), 4.23 (m, 2H), 3.67-3.59 (m, 1H), 3.26 (m, 1H), 2.93 (m, 1H),2.43 (s, 3H), 0.87 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H); LCMS (ESI, M+1): m/z = 370.2.

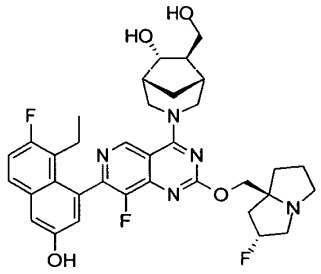
[00001236] Step E. 3-(azidomethyl)-1-(*tert*-butyldimethylsilyl)azetidin-2-one: To a solution of [1-[*tert*-butyl(dimethyl)silyl]-2-oxo-azetidin-3-yl]methyl 4-methylbenzenesulfonate (130 mg, 1.0 *equiv.)* in dimethylformamide (2 mL) was added sodium azide (68.6 mg, 3.0 *equiv*. The mixture was stirred at 60 °C for 16 hours. The mixture was poured into water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried

over anhydrous sodium sulfate, filtered and concentrated to afford the title compound (80 mg, crude) as a colorless liquid; LCMS (ESI, M+1): m/z = 240.1.

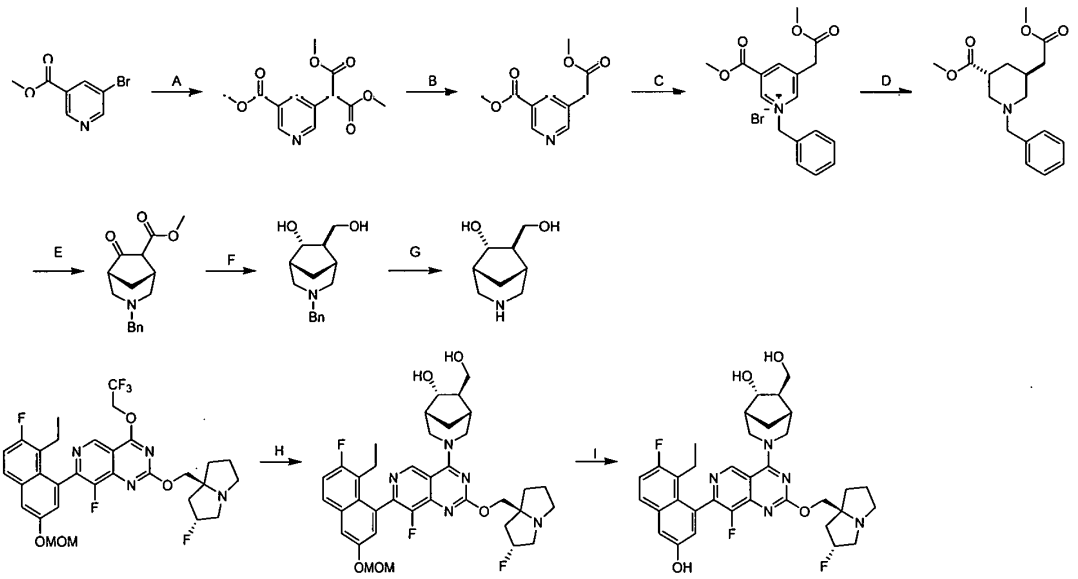
[00001237] Step F. 3-(aminomethyl)-1-[*tert*-butyl(dimethyl)silyl]azetidin-2-one: To a solution of 3-(azidomethyl)-1-[*tert*-butyl(dimethyl)silyl]azetidin-2-one (80.0 mg, 1.0 *equiv.)* in methanol (1 mL) was added palladium/carbon (40.0 mg, 10% purity, wet) under nitrogen atmosphere. The suspension was degassed under vacuum and purged with hydrogen. The mixture was stirred under hydrogen atmosphere (15.0 psi) at 25 °C for 16 hours. The reaction mixture was filtered. The filter cake was washed with methanol (2 × 5 mL). The filtrate was concentrated in vacuum to afford the title compound (60 mg, crude in 1 mL *N,N*-dimethylform amide) as a white liquid; LCMS (ESI, M+1): m/z = 215.1.

[00001238] Step G. 3-(((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)amino)methyl)azetidin-2-one: To a solution of 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 (30.0 mg, 1.0 *equiv.)* and 3-(aminomethyl)-1-[*tert*-butyl(dimethyl)silyl]azetidin-2-one (21.7 mg, 2.0 *equiv.)* in *N,N*-dimethylformamide (0.5 mL) was added diisopropylethylamine (19.6 mg, 3.0 *equiv.)* and 4Å molecular sieves (30 mg) at 25 °C. The mixture was stirred at 40 °C for 2 hours. The reaction mixture was filtered and the filtrate was purified by prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: water (10mM ammonium bicarbonate)/acetonitrile, B%: 34% - 64%, 8 min] to afford the title compound (2.33 mg, 7.7% yield) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ =9.95 (s, 1H), 9.32 (s, 1H), 9.20 (m, 1H), 7.92 (s, 1H), 7.77 (dd, J = 6.0, 9.2 Hz, 1H), 7.40-7.31 (m, 2H), 7.00 (d, J = 2.4 Hz, 1H), 5.46-5.24 (m, 1H), 4.25-4.10 (m, 2H), 4.03-3.94 (m, 1H), 3.78 (m, 1H), 3.60 (m, 1H), 3.14 (m, 2H), 2.94-2.75 (m, 2H), 2.44-2.23 (m, 2H), 2.22-2.04 (m, 4H), 1.91-1.77 (m, 3H), 1.24 (br s, 1H), 0.72 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 593.4.

EXAMPLE 486:



(1R,5R,6S,7R)-3-(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)-7-(hydroxymethyl)-3-azabicyclo[3.2.1]octan-6-ol



[00001239] Step A. dimethyl 2-(5-(methoxycarbonyl)pyridin-3-yl)malonate: A mixture of methyl 5-bromopyridine-3-carboxylate (25 g, 1.0 equiv.), dimethyl malonate (45.9 g, 3.0 equiv.), dicyclohexyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (11.0 g, 0.2 equiv.) and K_3PO_4 (73.7 g, 3.0 equiv.) in toluene (500 mL) was degassed and $Pd_2(dba)_3$ (10.6 g, 11.57 mmol, 0.1 equiv.) was added. The mixture was stirred at 100 °C for 12 hours under N_2 atmosphere. The mixture was diluted with water (100 mL), extracted with ethyl acetate (4 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by reversed phase flash

by reversed phase flash [C18, water0(0.1 % formic acid)-ACN] to afford the title compound (25 g, 79% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 268.1.

[00001240] Step B. methyl 5-(2-methoxy-2-oxoethyl)nicotinate: To a solution of dimethyl 2-(5-methoxycarbonyl-3-pyridyl)propanedioate (25 g, 1.0 equiv.) in DMSO (250 mL) was added LiCl (7.93 g, 2.0 equiv.) and H_2O (1.69 g, 1.0 equiv.). The mixture was stirred at 120 °C for 12 hours. The mixture was diluted with water (50 mL), extracted with ethyl acetate (4 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate 1:1) to afford the title compound (7 g, 34% yield) as a yellow solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 8.98 (d, J = 1.6 Hz, 1H), 8.65 (d, J = 2.0 Hz, 1H), 8.31-8.30 (m, 1H), 3.94 (s, 3H), 3.82 (s, 2H), 3.71 (s, 3H); LCMS (ESI, M+1): m/z = 210.1.

[00001241] Step C. 1-benzyl-3-(2-methoxy-2-oxoethyl)-5-(methoxycarbonyl)pyridin-1-ium: A mixture of methyl 5-(2-methoxy-2-oxoethyl)nicotinate (800 mg, 1.0 equiv.), TEA (1.06 g, 3.0 equiv.) in DCM (8 mL) was degassed and purged with N_2 for 3 times, BnCl (1.79 g, 3.0 equiv.) was added into the mixture at -40 °C. Then the mixture was stirred at -40 °C for 0.5 hour under N_2 atmosphere. The mixture was diluted with water (20 mL), extracted with DCM (4 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated to afford the title compound (1 g, crude) as a yellow oil.

[00001242] Step D. (3R, 5S)-methyl 1-benzyl-5-(2-methoxy-2-oxoethyl) piperidine-3-carboxylate: To a solution of methyl 1-benzyl-5-(2-methoxy-2-oxo-ethyl) pyridine-3-carboxylate (4 g, 1.0 equiv.) in MeOH (40 mL) was added PtO_2 (1.19 g, 0.4 equiv.) under N_2 atmosphere. The suspension was degassed and purged with H_2. The mixture was stirred under H_2 (50 Psi) at 40 °C for 12 hours. The reaction mixture was filtered and purified by prep-HPLC [column: Kromasil Eternity XT 250 × 80 mm × 10 μm; mobile phase: water (0.1% ammonia hydroxide)-ACN; B%: 45%-75%, 20min) and lyophilized to afford the title compound (1.2 g, 22% yield) as a yellow oil; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 7.33-7.23 (m, 5H), 3.65-3.60 (m, 6H), 3.60-3.49 (m, 2H), 3.12-3.04 (m, 1H), 2.93-2.91 (m, 1H), 2.69-2.59 (m, 1H), 2.08-2.07 (m, 2H), 2.05-2.04 (m, 2H), 1.95-1.63 (m, 1H), 1.68-1.63 (m, 1H), 1.14-1.01 (m, 1H); LCMS (ESI, M+1): m/z = 306.0.

[00001243] Step E. methyl 3-benzyl-7-oxo-3-azabicyclo [3.2.1] octane-6-carboxylate: To a solution of (3R, 5S)-methyl 1-benzyl-5-(2-methoxy-2-oxo-ethyl) piperidine-3-carboxylate (1.0 g, 1.0 equiv.) in THF (90 mL) was added t-BuOK (1.0 M, 9.82 mL, 3.0 equiv.). The mixture was stirred at 25°C for 12 hours. The mixture was diluted with water (50 mL), extracted with ethyl acetate (4 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate 15:1 to 10:1) to afford the title compound (350 mg, 24% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 274.0.

[00001244] Step F. (6S, 7R)-3-benzyl-7-(hydroxymethyl)-3-azabicyclo [3.2.1] octan-6-ol: To a solution of methyl 3-benzyl-7-oxo-3-azabicyclo [3.2.1] octane-6-carboxylate (350 mg, 1.0 equiv.) in THF (1 mL) was added $LiAlH_4$ (146 mg, 3.0 equiv.). The mixture was stirred at 0 °C for 2 hours. The mixture was diluted with water (20 mL), extracted with ethyl acetate (4 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated and purified by prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: water (0.1% ammonia hydroxide)-ACN; B%: 23%-53%, 9min] to afford the title compound (200 mg, 63% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 248.0.

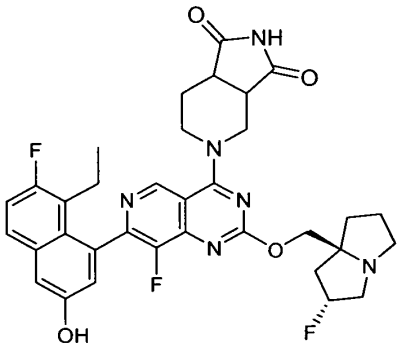
[00001245] Step G. (6S,7R)-7-(hydroxymethyl)-3-azabicyclo[3.2.1]octan-6-ol: To a solution of 3-benzyl-7-(hydroxymethyl)-3-azabicyclo[3.2.1]octan-6-ol (200 mg, 1.0 equiv.) in MeOH (3 mL) was added Pd/C (50 mg, 1.0 equiv.) under N_2 atmosphere. The suspension was degassed and purged with H_2 The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hours before being filtered and concentrated to afford the title compound (100 mg, 79% yield) as a white oil.

[00001246] Step H. (1R,5R,6S,7R)-3-(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)-7-(hydroxymethyl)-3-azabicyclo[3.2.1]octan-6-ol: To a solution of 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 (100 mg, 1.0 equiv.) and (1R,5R,6S,7R)-7-(hydroxymethyl)-3-azabicyclo[3.2.1]octan-6-ol (44.4 mg, 1.8 equiv.) in DMF (0.5 mL) was added DIEA (60.9 mg, 3.0 equiv.) and 4Å molecular sieves (20 mg). The mixture was stirred at 40 °C for 12 hours. The reaction mixture was filtered and purified by prep-HPLC [column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: water (0.1% formic

acid), / ACN; B%: 15%-45%, 2 min] to afford the title compound (50 mg, 46% yield) as white solid.

[00001247] Step I (1R,5R,6S,7R)-3-(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)-7-(hydroxymethyl)-3-azabicyclo[3.2.1]octan-6-ol: To a solution of (1R,5R,6S,7R)-3-(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)-7-(hydroxymethyl)-3-azabicyclo[3.2.1]octan-6-ol (50 mg, 1.0 equiv.) in MeOH (2 mL) was added HCl•MeOH (4 M, 2 mL, 111 equiv.). The mixture was stirred at 0 °C for 1 hour. The residue was filtered and the filtrate was purified by prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: water (0.1% ammonia hydroxide)/ACN; B%: 28%-58%, 9 min] and lyophilized to afford the title compound (37.8 mg, 80% yield) as a yellow solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.31-9.18 (m, 1H), 7.68-7.65 (m, 1H), 7.29-7.26 (m, 1H), 7.24-7.22 (m, 1H), 7.07-7.04 (m, 1H), 5.40-5.21 (m, 1H), 5.07-4.95 (m, 1H), 4.83-4.75 (m, 1H), 4.39-4.15 (m, 2H), 3.90-3.68 (m, 2H), 3.68-3.58 (m, 1H), 3.57-3.41 (m, 2H), 3.29-3.11 (m, 3H), 3.19-2.99 (m, 1H), 2.51-2.30 (m, 1H), 2.38-2.07 (m, 6H), 2.05-1.74 (m, 6H), 0.86-0.72 (m, 3H); LCMS (ESI, M+1): m/z = 650.4.

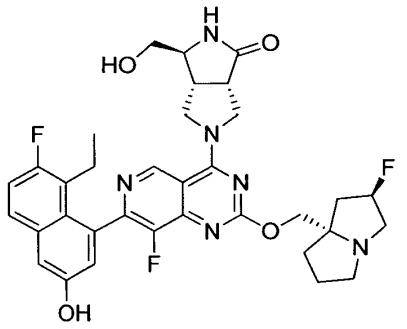
EXAMPLE 487



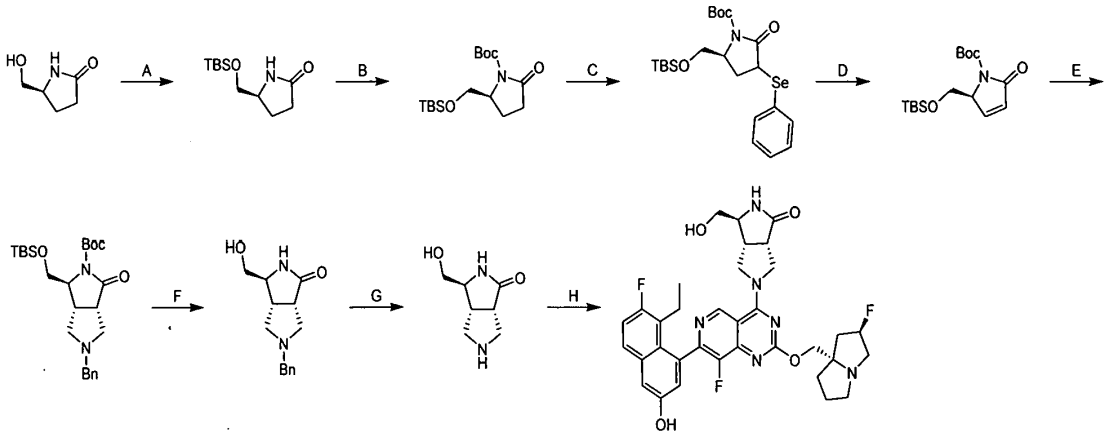
5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)hexahydro-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione

[00001248] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.22 (s, 1H), 8.57 (s, 1H), 7.69 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.32 (d, *J* = 2.8 Hz, 1H), 7.26 (t, *J* = 9.6 Hz, 1H), 7.08 (t, *J* = 2.8 Hz, 1H), 5.43-5.21 (m, 1H), 4.75 (br dd, *J* = 3.6, 13.6 Hz, 1H), 4.41-4.24 (m, 2H), 4.20-4.04 (m, 2H), 4.04 - 3.92 (m, 1H), 3.36 (br d, *J* = 3.6 Hz, 1H), 3.32-3.23 (m, 3H), 3.15 (br d, *J* = 1.6 Hz, 1H), 3.05-2.99 (m, 1H), 2.52-2.39 (m, 2H), 2.38-2.33 (m, 1H), 2.33 - 2.25 (m, 1H), 2.24-2.10 (m, 3H), 2.04-1.91 (m, 3H), 1.28-1.20 (m, 1H), 0.81 (q, *J* = 7.6 Hz, 3H); LCMS (ESI, M+1): m/z =647.

EXAMPLE 488



(3R,3aR,6aS)-5-(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)-3-(hydroxymethyl)hexahydropyrrolo[3,4-c]pyrrol-1(2H)-one



[00001249] Step A. (S)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)pyrrolidin-2-one: To a solution of (5S)-5-(hydroxymethyl)pyrrolidin-2-one (10.0 g, 1.0 *equiv.)* and imidazole (8.80 g, 1.5 *equiv.)* in dichloromethane (100 mL) was added tert-butyldimethylsilyl chloride (15.7 g, 1.2 *equiv.)* portion wise at 0-5 °C. The resulting mixture was allowed to warm up to 25-30 °C and stirred for 12 hours. The mixture was diluted with water (150 mL) and the layers were separated. The aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by flash silica gel chromatography [Ethyl acetate/Petroleum ether 50 to 100%] to afford the title compound (17.5 g, 83% yield) as a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$-d_4) δ = 5.98 (br s, 1H), 3.81-3.71 (m, 1H), 3.62 (dd, J = 4.0, 10.0 Hz, 1H), 3.44 (dd, J = 7.6, 10.0 Hz, 1H), 2.40-2.30 (m, 2H), 2.22-2.11 (m, 1H), 1.81-1.69 (m, 1H), 0.88 (s, 9H), 0.06 (s, 6H); LCMS (ESI, M+1): m/z = 230.2.

[00001250] Step B. *tert*-butyl (S)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-oxopyrrolidine-1-carboxylate: To a solution of (5S)-5-[[tert-butyl(dimethyl)silyl]oxymethyl]pyrrolidin-2-one (2.0 g, 1.0 *equiv.)* in dichloromethane (20 mL) was added *tert*-butyldicarbonate (2.8 g, 1.5 *equiv.)*, triethylamine (1.7 g, 2.0 *equiv.)* and 4-dimethylaminopyridine (106 mg, 0.1 *equiv.)*. The resulting mixture was stirred at 25 °C for 12 hours. The mixture was concentrated in vacuum. The residue was purified by flash silica gel chromatography [Ethyl acetate/Petroleum ether 1:4] to afford the title compound (2.25 g, 78 % yield) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$-d_4) δ = 4.22-4.13 (m, 1H), 3.92 (dd, J = 4.0, 10.4 Hz, 1H), 3.69 (dd, J = 2.0, 10.4 Hz, 1H), 2.78-2.64 (m, 1H), 2.38 (ddd, J = 2.0, 9.6, 17.6 Hz, 1H), 2.16-1.96 (m, 2H), 1.54 (s, 9H), 0.88 (s, 9H), 0.04 (d, J = 5.2 Hz, 6H); LCMS (ESI, M-99): m/z = 230.2.

[00001251] Step C. *tert*-butyl (5S)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2-oxo-3-(phenylselanyl)pyrrolidine-1-carboxylate: To a solution of *tert*-butyl (2S)-2-[[tert-butyl(dimethyl)silyl]oxymethyl]-5-oxo-pyrrolidine-1-carboxylate (1.0 g, 1.0 *equiv.)* in tetrahydrofuran (25 mL) was added lithium hexamethyldisilazide (1 M, 3.3 mL, 1.1 *equiv.)* dropwise at -60 °C under nitrogen atmosphere. The solution was stirred at -60 °C for 0.5 hour before a solution of phenyl selenohypochlorite (1.0 g, 1.75 *equiv.)* in tetrahydrofuran (5.0 mL) was added at -60 °C. The resulting mixture was stirred at -60 for additional 1 hour and then warmed to 25 °C and stirred at 25 °C for 12 hours. The mixture was quenched with saturated ammonium

chloride (40 mL) at 0-5 °C under nitrogen, and allowed to warm to 25 °C and stirred for 0.5 hour. The mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography [Ethyl acetate/Petroleum ether 10 to 15%] to afford the title compound (740 mg, 50% yield) as a yellow oil; LCMS (ESI, M-99): m/z = 386.2.

[00001252] Step D. tert-butyl (S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-5-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate: To a solution of tert-butyl (5S)-5-[[tert-butyl(dimethyl)silyl]oxymethyl]-2-oxo-3-phenylselanyl-pyrrolidine-1-carboxylate (740 mg, 1.0 *equiv.)* in dichloromethane (10.0 mL) was added pyridine (362 mg, 3.0 *equiv.)* at -70 °C, followed by slow addition of hydrogen peroxide (606 mg, 30% in water, 3.5 *equiv.)*. The resulting mixture was allowed to warm up to 25 °C and stirred at 25 °C for 12 hours. The mixture was diluted with water (20 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with saturated sodium sulfite and brine, dried over sodium sulfate, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography [Ethyl acetate/Petroleum ether 10 to 15%] to afford the title compound (230 mg, 34% yield) as a colorless oil; LCMS (ESI, M-99): m/z = 228.1.

[00001253] Step E. *tert*-butyl (1S,3aS,6aR)-5-benzyl-1-(((tert-butyldimethylsilyl)oxy)methyl)-3-oxohexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate: To a solution of *tert*-butyl (2S)-2-[[tert-butyl(dimethyl)silyl]oxymethyl]-5-oxo-2H-pyrrole-1-carboxylate (180 mg, 1.0 *equiv.)* and *N*-(methoxymethyl)-1-phenyl-*N*-(trimethylsilylmethyl)methanamine (391 mg, 3.0 *equiv.)* in dichloromethane (5.0 mL) was added TFA (25 mg, 0.4 *equiv.)* at 0 °C. After addition, the resulting mixture was stirred at 25 °C for 12 hours. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC [column: Phenomenex Luna C18 75 × 30 mm × 3 μm; mobile phase: water (0.1% HCl)-CH_3CN, B%: 39% -59%, 6 min] to afford the title compound (102 mg, 37 % yield) as a yellow solid; LCMS (ESI, M+1): m/z = 461.4.

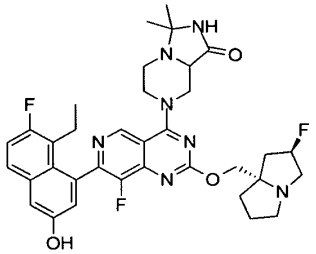
[00001254] Step F. (3S,3aR,6aS)-5-benzyl-3-(hydroxymethyl)hexahydropyrrolo[3,4-c]pyrrol-1(2H)-one: To a solution of *tert*-butyl (3aS,6S,6aR)-2-benzyl-6-[[tert-butyl(dimethyl)silyl]oxymethyl]-4-oxo-3,3a,6,6a-tetrahydro-1H-pyrrolo[3,4-c]pyrrole-5-carboxylate (102 mg, 1 equiv.) in methanol (1.0 mL) was added HCl•MeOH (1.0 mL, 4M). The

resulting mixture was stirred at 25 °C for 2 hours. The mixture was concentrated in vacuum to afford the title compound (65 mg, crude, HCl) as a white solid. LCMS (ESI, M+1): m/z = 247.1.

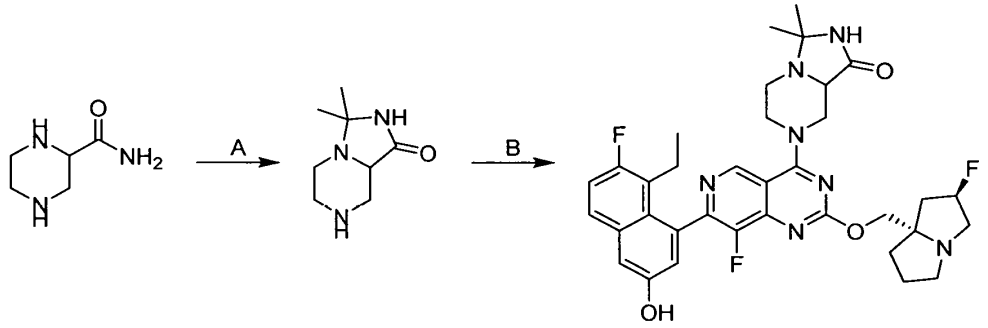
[00001255] Step G. (3S,3aR,6aS)-5-benzyl-3-(hydroxymethyl)hexahydropyrrolo[3,4-c]pyrrol-1(2H)-one: To a flask charged with Pd/C (20 mg, 10% purity) was added a solution of (1S,3aS,6aR)-5-benzyl-1-(hydroxymethyl)-1,2,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-3-one (65 mg, 1.0 equiv, hydrochloride) in methanol (2.0 mL). The mixture was degassed and stirred at 70 °C under H_2 (50 psi) for 24 hours. The mixture was filtered and the filtrate was concentrated. The residue was diluted with acetonitrile/water (v/v, 1/2) and lyophilized directly to give the title compound (45 mg, crude, hydrochloride) as a white gum; LCMS (ESI, M+1): m/z = 157.2.

[00001256] Step H. (3R,3aR,6aS)-5-(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)-3-(hydroxymethyl)hexahydropyrrolo[3,4-c]pyrrol-1(2H)-one: To a solution of (3aS,6S,6aR)-6-(hydroxymethyl)-2,3,3a,5,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrol-4-one (32.5 mg, 2.5 equiv, hydrochloride) and 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 (40 mg, 1.0 equiv.) in N,N-Dimethylformamide (3.0 mL) was added N,N-Diisopropylethylamine (34.9 mg, 4.0 equiv.) and 4 Å molecular sieves (80 mg). The resulting mixture was stirred at 40 °C for 12 hours. The filtrate was purified by prep-HPLC [column: Phenomenex Luna C18 75 × 30 mm × 3 μm; mobile phase: water (0.1% HCl)-CH_3CN; B%: 19%-39%, 6 min] to afford the title compound (13.8 mg, 29% yield, hydrochloride) as yellow solid; ^{1}H NMR (400 MHz, MeOD-d_4) δ = 9.48 (br s, 1H), 7.73 (br dd, J = 5.6, 8.8 Hz, 1H), 7.40 (s, 1H), 7.31 (br t, J = 9.2 Hz, 1H), 7.17 (br s, 1H), 5.73-5.47 (m, 1H), 4.55 (br s, 6H), 4.30-3.81 (m, 4H), 3.70 (br s, 3H), 3.48 (br s, 2H), 2.88-2.11 (m, 8H), 0.86 (br s, 3H); LCMS (ESI, M+1): m/z = 649.4.

EXAMPLE 489



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)-3,3-dimethylhexahydroimidazo[1,5-a]pyrazin-1(5H)-one

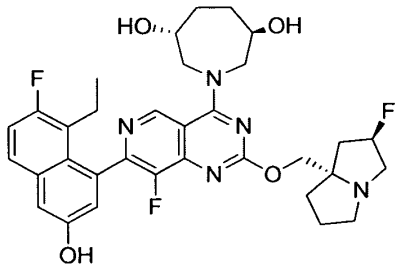


[00001257] Step A. 3,3-dimethylhexahydroimidazo[1,5-*a*]pyrazin-1(5H)-one: To a solution of piperazine-2-carboxamide (300 mg, 1.0 equiv.) in acetone (3.0 mL) was added 2-methoxyethanol (265 mg, 1.50 equiv.). The mixture was stirred at 40 °C for 2 hours. After completion, the reaction mixture was cooled to 25 °C, filtered and the filtrate was concentrated under reduced pressure to afford the title compound (170 mg, 43% yield) as a white solid; LCMS (ESI, M+1): m/z = 170.1.

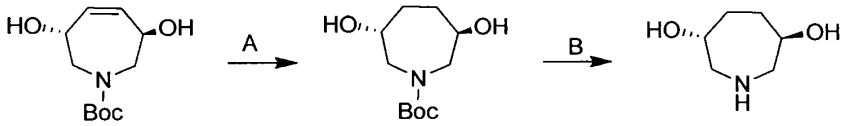
[00001258] Step B. 7-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-3,3-dimethylhexahydroimidazo[1,5-a]pyrazin-1(5H)-one: To a solution of 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol (60.0 mg, 1.0 equiv.) and 3,3-dimethyl-2,5,6,7,8,8a-hexahydroimidazo[1,5-*a*]pyrazin-1-one (85.7 mg, 5.0 equiv.) in DMF (0.50 mL) was added 4Å molecular sieves (10 mg) and diisopropylethylamine (39.3 mg, 3.0 equiv.). The mixture was stirred at 60 °C for 12 hours. The reaction mixture was cooled to 25 °C, filtered and the filtrate was partitioned between ethyl acetate (10 mL) and water (10 ml). The organic phase was separated, washed with saturated brine (2 × 5 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Phenomenex Luna C18 150 × 25 mm × 10 μm; mobile phase: A: water (0.1% formic acid)-ACN]; B%: 14%-44%, 10 min) to afford the title compound (2.88 mg, 4.23% yield) as an off-white solid; ^{1}H NMR (400 MHz, CD_3OD) δ = 9.16 (s, 1H), 7.72-7.65 (m, 1H), 7.32 (d, *J* = 2.8

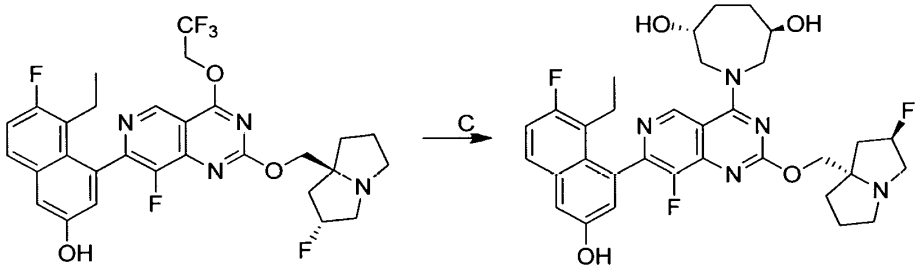
Hz, 1H), 7.26 (t, J = 9.6 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 5.53-5.36 (m, 1H), 4.58 (br s, 3H), 4.55-4.44 (m, 2H), 3.70 -3.64 (m, 1H), 3.58-3.50 (m, 2H), 3.46 (br s, 2H), 3.17 (br d, J = 11.2 Hz, 1H), 2.85-2.76 (m, 1H), 2.59-1.99 (m, 9H), 1.46 (s, 3H), 1.31 (s, 3H), 0.83-0.76 (m, 3H); LCMS (ESI, M+1): m/z = 662.4.

EXAMPLE 490



(3R,6R)-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)azepane-3,6-diol





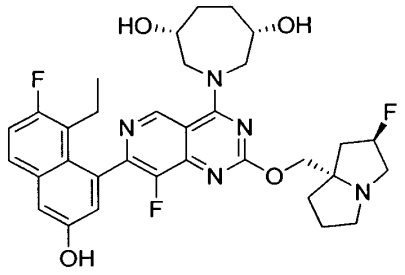
[00001259] Step A. (3R,6R)-tert-butyl 3,6-dihydroxyazepane-1-carboxylate: To a solution of tert-butyl 3,6-dihydroxy-2,3,6,7-tetrahydroazepine-1-carboxylate (500 mg, 2.18 mmol, 1.0 equiv.) in MeOH (8 mL) was added Pd/C (100 mg, 10% purity) under Ar. The suspension was degassed and purged with H_2. The mixture was stirred under H_2 (50 psi) at 30 °C for 16 hours. The mixture was filtered and the filtrate was concentrated under vacuum to afford the title compound (500 mg,

crude) as a yellow oil; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 3.84 (br s, 2H), 3.63 (br dd, *J* = 4.8, 14.4 Hz, 1H), 3.53 (br dd, *J* = 4.8, 14.2 Hz, 1H), 3.35 (s, 1H), 3.14 (br dd, *J* = 7.6, 14.0 Hz, 1H), 2.02 - 1.89 (m, 2H), 1.74 - 1.59 (m, 1H), 1.47 (s, 9H), 1.45 - 1.38 (m, 1H).

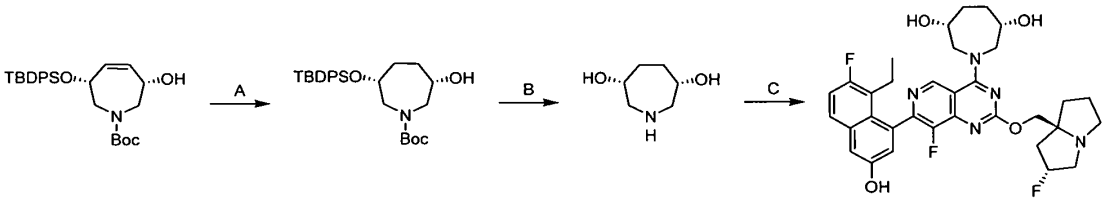
[00001260] Step B. (3R,6R)-azepane-3,6-diol: To a solution of tert-butyl 3,6-dihydroxyazepane-1-carboxylate (500 mg, 2.16 mmol, 1.0 equiv.) in MeCN (3 mL) was added HCl•dioxane (4 M, 6 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 hour. The mixture was concentrated in vacuum to afford the title compound (283 mg, crude, HCl) as a yellow oil.

[00001261] Step C. (3R,6R)-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)azepane-3,6-diol: A suspension of azepane-3,6-diol (111 mg, 660 µmol, 3.9 equiv, HCl), DIEA (109 mg, 844 µmol, 5.0 equiv.) and 4Å molecular sieves (10 mg) in DMF (0.5 mL) was stirred at 25 °C for 30 minutes. Then 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 (100 mg, 169 µmol, 1.0 equiv.) was added into the mixture and the mixture was stirred at 40 °C for 72 hours. The reaction mixture was diluted with ethyl acetate (5 mL) and water (10 mL). The mixture was extracted with ethyl acetate (5 mL) and the combined organic phase was washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate 3:1 then Dichloromethane: Methanol 5:1). Then the mixture was re-purified by prep-HPLC [column: Waters Xbridge 150 × 25 mm × 5 µm; mobile phase: water (10mM NH_4HCO_3)-ACN, B%: 34% - 54%, 8 min] to afford the title compound (5.8 mg, 5.47% yield) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.57-9.43 (m, 1H), 7.67 (dd, *J* = 5.6, 9.2 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.25 (t, *J* = 9.6 Hz, 1H), 7.05 (s, 1H), 5.41-5.20 (m, 1H), 4.38-4.19 (m, 6H), 3.94-3.83 (m, 2H), 3.29-3.16 (m, 3H), 3.07-2.97 (m, 1H), 2.56-2.42 (m, 1H), 2.40 - 2.06 (m, 6H), 2.05-1.86 (m, 3H), 1.70-1.58 (m, 2H), 0.84-0.76 (m, 3H); 1.53-1.31 (m, 1H); LCMS (ESI, M+1): m/z = 624.4.

EXAMPLE 491



(3R,6S)-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)azepane-3,6-diol



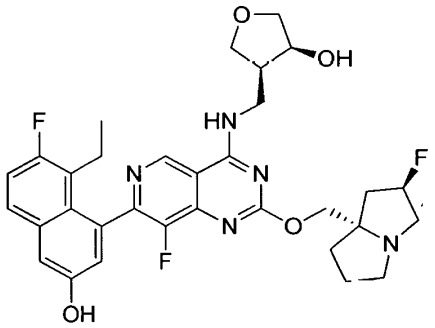
[00001262] Step A. (3R,6S)-tert-butyl 3-((tert-butyldiphenylsilyl)oxy)-6-hydroxyazepane-1-carboxylate: To a mixture of Pd/C (20 mg, 10% purity) in MeOH (5 mL) was added (3R,6S)-tert-butyl 3-((tert-butyldiphenylsilyl)oxy)-6-hydroxy-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (0.20 g, 1.0 equiv.). The mixture was degassed and purged with H_2 before being stirred at 25 °C for 16 hours (50 Psi). The mixture was filtered and concentrated to afford the tittle compound (165 mg, 82% yield) as a white solid. LCMS (ESI, M+1): m/z = 470.2.

[00001263] Step B. (3R,6S)-azepane-3,6-diol: To a solution of (3R,6S)-tert-butyl 3-((tert-butyldiphenylsilyl)oxy)-6-hydroxyazepane-1-carboxylate (160 mg, 1.0 *equiv.)* in ACN (2 mL) was added HCl•dioxane (4 M, 2.0 mL) at 0 °C. The solution was stirred at 0 °C for 0.5 hour. The mixture was filtered and triturated with ethyl acetate (2 mL) at 25 °C for 0.5 hour to afford the title compound (40 mg, 70% yield) as a white solid.

[00001264] Step C. (3R,6S)-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)azepane-3,6-diol: To a solution of 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 (150 mg, 1.0 equiv.) and (3R,6S)-azepane-3,6-diol (39.8 mg, 1.2 equiv.) in

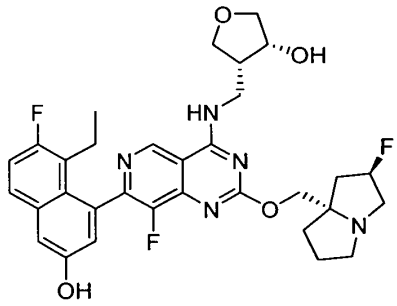
DMF (0.3 mL) were added DIEA (98.1 mg, 132 μL, 3.0 equiv.) and 4Å molecular sieves (20 mg). The mixture was stirred at 60 °C for 12 hours. The mixture was filtered and purified by reversed phase flash chromatography [C18, water (0.1 % formic acid)-ACN] to afford the title compound (15.8 mg, 10% yield) as a white solid. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.37 (s, 1H), 7.67 (dd, *J* = 5.6, 8.8 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.25 (t, *J* = 9.2 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 5.30 (d, *J* = 54.4 Hz, 1H), 4.56-4.40 (m, 2H), 4.37-4.13 (m, 4H), 3.92-3.83 (m, 2H), 3.29-3.16 (m, 3H), 3.05-2.88 (m, 1H), 2.56-2.42 (m, 1H), 2.39-2.10 (m, 4H), 2.07-1.88 (m, 5H), 1.86-1.74 (m, 2H), 0.80 (t, *J* = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 624.1.

EXAMPLE 492

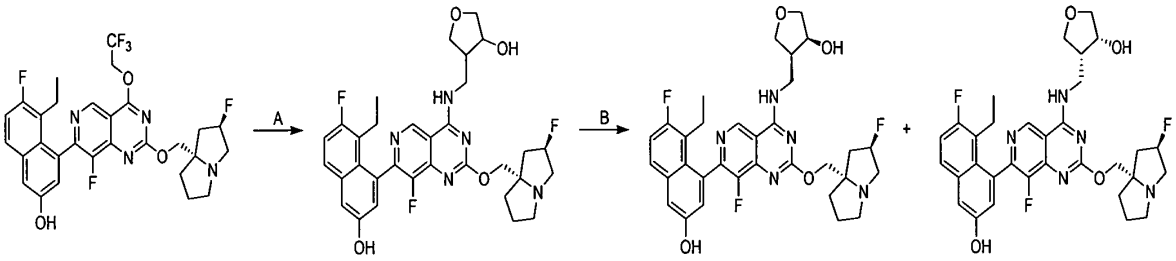


(3S,4S)-4-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)tetrahydrofuran-3-ol

EXAMPLE 493



(3R,4R)-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)tetrahydrofuran-3-ol

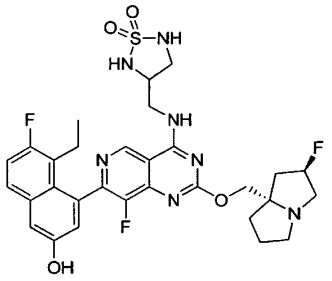


[00001265] Step A. 4-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)tetrahydrofuran-3-ol: To a solution of 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol (200 mg, 337 μmol, 1 *equiv.)* in DMF (4 mL) was added 4Å molecular sieves (50 mg), cis-4-(aminomethyl)tetrahydrofuran-3-ol (79.1 mg, 2.0 equiv.) and DIPEA (175 mg, 1.35 mmol, 4.0 equiv.). The mixture was stirred at 40 °C for 2 hours and concentrated. The residue was purified by *prep*-HPLC (column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: A: water (0.1% formic acid),-ACN; B%: 12%-42%, 9 min) to afford the title compound (120 mg, 51% yield) as a white solid; LCMS (ESI, M+1): m/z = 610.2.

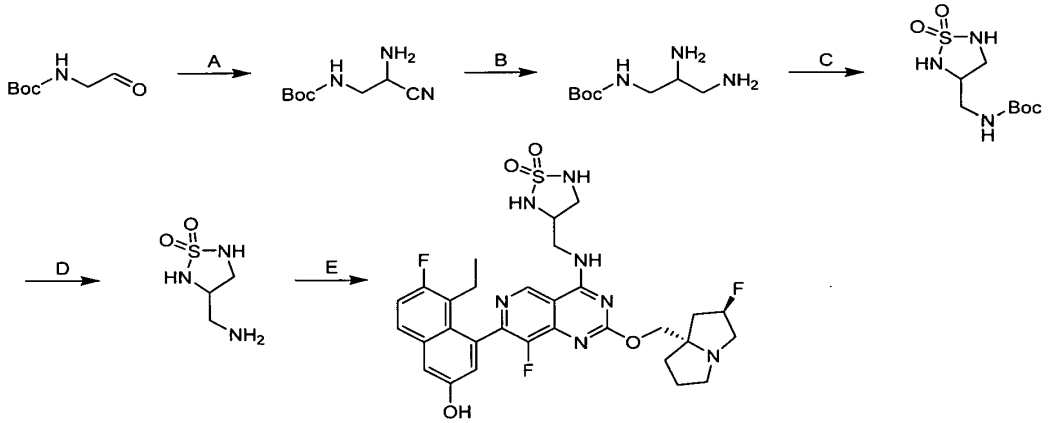
[00001266] Step B. (3S,4S)-4-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)tetrahydrofuran-3-ol: The mixture of 4-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)amino)methyl)tetrahydrofuran-3-ol (120 mg, 196.84 μmol, 1.0 equiv.) was separated by chiral SFC (column: DAICEL CHIRALCEL OJ (250 mm × 30 mm,10 μm); mobile phase: A: [0.1%$NH_3 \cdot H_2O$, B: IPA; B%: 25%-25%, 10.6; 159 min) to afford Example 492, second eluting peak (33.4 mg, 24% yield, HCOOH) as a yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.94 (s, 1H), 9.31 (s, 1H), 8.98-8.94 (m, 1H), 7.78-7.74 (m, 1H), 7.37-7.32

(m, 2H), 6.99 (s, 1H), 5.35-5.16 (m, 2H), 4.31 (s, 1H), 4.16 (d, J = 10.4 Hz, 1H), 4.07 (d, J = 10.4 Hz, 1H), 3.91-3.74 (m, 3H), 3.64-3.54 (m, 3H), 3.14-3.08 (m, 2H), 3.02 (s, 1H), 2.85-2.79 (m, 1H), 2.59-2.54 (m, 1H), 2.37-2.32 (m, 1H), 2.19-2.06 (m, 3H), 2.04-1.91 (m, 2H), 1.85-1.77 (m, 3H), 1.74 (s, 1H), 0.71 (t, J = 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 610.2, and Example 493, first eluting peak (35.7 mg, 26% yield, HCOOH) as a yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.96 (s, 1H), 9.31 (s, 1H), 8.96 (d, J = 4.4 Hz, 1H), 8.16 (s, 1H), 7.76 (t, J = 6.8 Hz, 1H), 7.36-7.32 (m, 2H), 6.99 (s, 1H), 5.34-5.16 (m, 2H), 4.31 (s, 1H), 4.15 (d, J = 10.4 Hz, 1H), 4.07 (d, J = 10.4 Hz, 1H), 3.91-3.83 (m, 2H), 3.80-3.74 (m, 1H), 3.64-3.55 (m, 4H), 3.14-3.02 (m, 1H), 2.83-2.82 (m, 2H), 2.33 (s, 1H), 2.19-1.94 (m, 4H), 1.90-1.77 (m, 3H), 0.71 (t, J = 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 610.2.

EXAMPLE 494



3-(((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)-1,2,5-thiadiazolidine 1,1-dioxide



[00001267] Step A. tert-butyl (2-amino-2-cyanoethyl)carbamatet: To a solution of tert-butyl (2-oxoethyl)carbamate (1.00 g, 1.0 *equiv.)* in methanol (10 mL) were added $Ti(i\text{-}PrO)_4$ (1.79 g, 1.0 *equiv.)* and NH_3 in methanol (7.00 M, 2.0 *equiv.)*. TMSCN (1.25 g, 2.0 *equiv.)* was added dropwise to the mixture at 0 °C. The mixture was stirred at 25 °C for 16 hours. The mixture was diluted with water (50 mL) and filtered. The filtrate was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford the title compound (1.14 g, 83% yield) as a yellow oil; ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ = 7.14 (br t, *J* = 5.6 Hz, 1H), 3.75 (br s, 1H), 3.21-3.06 (m, 2H), 2.36 (br s, 2H), 1.38 (s, 9H).

[00001268] Step B. tert-butyl (2,3-diaminopropyl)carbamate: A mixture of tert-butyl (2-amino-2-cyanoethyl)carbamatet (500 mg, 1.0 equiv.) and Raney Ni (694 mg, 3.0 equiv.) in MeOH (5 mL) and NH_3 in methanol (7.00 M, 1 mL) was degassed and purged with H_2 for 3 times. The mixture was stirred at 25 °C for 16 hours under H_2 atmosphere (15 psi). The reaction mixture was filtered and the filterate was concentrated to afford the title compound (500 mg, crude) as a yellow oil; ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ = 6.71 (br s, 1H), 2.94-2.84 (m, 1H), 2.82-2.73 (m, 1H), 2.57 (br s, 1H), 2.45 (br d, *J* = 6.2 Hz, 1H), 2.35-2.23 (m, 1H), 1.37 (s, 9H).

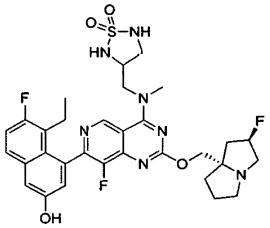
[00001269] Step C. tert-butyl ((1,1-dioxido-1,2,5-thiadiazolidin-3-yl)methyl)carbamate: To a solution of tert-butyl (2,3-diaminopropyl)carbamate (400 mg, 1.0 equiv.) in pyrdine (4 mL) was added dropwise sulfamide (203 mg, 1.0 equiv.) at 25 °C. The resulting mixture was stirred at 115 °C for 20 hours. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by *prep*-TLC (dichloromethane/methanol 10:1) to afford the title compound (100 mg, 16% yield over two steps) as a yellow oil; ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ = 6.96-6.85 (m, 3H), 3.65-3.55 (m, 1H), 3.33-3.30 (m, 1H), 3.09-2.97 (m, 3H), 1.38 (s, 9H).

[00001270] Step D. 3-(aminomethyl)-1,2,5-thiadiazolidine 1,1-dioxide: To a solution of tert-butyl ((1,1-dioxido-1,2,5-thiadiazolidin-3-yl)methyl)carbamate (41.0 mg, 1.0 equiv.) in DCM (0.50 mL) was added HCl•dioxane (4 M, 12.6 equiv.) at 0 °C. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated in vacuum to afford the title compound (30.0 mg, 98% yield, HCl) as a brown solid.

[00001271] Step E. 3-(((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)-

1,2,5-thiadiazolidine 1,1-dioxide: To a mixture of 3-(aminomethyl)-1,2,5-thiadiazolidine 1,1-dioxide (30.0 mg, 1.0 equiv, HCl), 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 (47.4 mg, 1.0 equiv.) in DMF (0.5 mL) were added DIEA (31.0 mg, 3.0 equiv.) and 4Å molecular sieves (10 mg). The mixture was stirred at 60 °C for 24 hours. The mixture was filtered and purified by *prep*-HPLC [column: Waters xbridge 150 × 25 mm × 10 μm; mobile phase: water (10 mM NH_4HCO_3), B: ACN, B%: 29%-59%, 8 min] to afford the title compound (10.4 mg, 19% yield) as a white solid; ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ = 9.94 (s, 1H), 9.33 (s, 1H), 9.13 (br d, *J* = 2.4 Hz, 1H), 7.77 (dd, *J* = 6.4, 9.2 Hz, 1H), 7.39-7.28 (m, 2H), 7.26-7.16 (m, 1H), 7.05 (br t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 5.48-5.18 (m, 1H), 4.31-3.97 (m, 3H), 3.76-3.59 (m, 2H), 3.57-3.45 (m, 1H), 3.22 (br dd, *J* = 5.2, 11.2 Hz, 5H), 2.97-2.84 (m, 1H), 2.27-2.17 (m, 1H), 2.16-2.00 (m, 3H), 1.97-1.72 (m, 3H), 0.71 (br t, *J* = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 644.0.

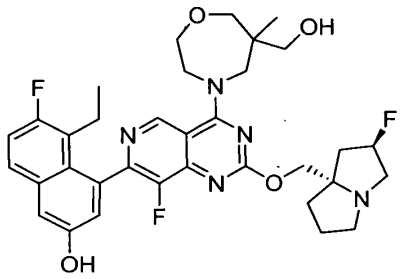
EXAMPLE 495



3-(((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)(methyl)amino)methyl)-1,2,5-thiadiazolidine 1,1-dioxide

[00001272] The title compound was synthesized according to the procedure described for example 494 using tert-butyl methyl(2-oxoethyl)carbamate instead of tert-butyl (2-oxoethyl)carbamate in step A. ^{1}H NMR (400 MHz, dimethylsulfoxide-d_6) δ = 9.95 - 9.87 (m, 1H), 9.35 - 9.24 (m, 1H), 7.81 - 7.70 (m, 1H), 7.40 - 7.27 (m, 2H), 7.25 - 7.15 (m, 1H), 7.08 - 7.02 (m, 1H), 7.02 - 6.98 (m, 1H), 5.42 - 5.17 (m, 1H), 4.30 - 3.99 (m, 4H), 3.98 - 3.82 (m, 1H), 3.67 - 3.58 (m, 3H), 3.57 - 3.45 (m, 1H), 3.23 - 2.96 (m, 5H), 2.94 - 2.77 (m, 1H), 2.19 - 2.02 (m, 4H), 1.91 - 1.75 (m, 3H), 0.78 - 0.70 (m, 3H); LCMS (ESI, M+1): m/z = 658.2.

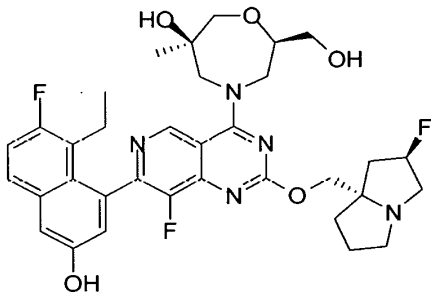
EXAMPLE 496



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

[00001273] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.19 (d, *J* = 5.3 Hz, 1H), 7.67 (dd, *J* = 6.0, 8.8 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.24 (t, *J* = 9.2 Hz, 1H), 7.06 (s, 1H), 5.43-5.25 (m, 1H), 4.49-4.23 (m, 4H), 4.22-3.98 (m, 4H), 3.77-3.65 (m, 1H), 3.59-3.45 (m, 2H), 3.44-3.34 (m, 2H), 3.29-3.19 (m, 1H), 3.11-3.02 (m, 1H), 2.58-2.34 (m, 2H), 2.34-2.09 (m, 4H), 2.08-1.98 (m, 2H), 1.97-1.87 (m, 1H), 0.98 (br d, *J* = 12.4 Hz, 3H), 0.84-0.74 (m, 3H); LCMS (ESI, M+1): m/z = 638.2

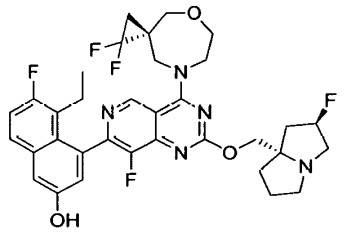
EXAMPLE 497



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

[00001274] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.67 (d, J = 5.6 Hz, 1H), 7.69-7.66 (m, 1H), 7.30 (t, J = 2.4 Hz, 1H), 7.25 (t, J = 9.6 Hz, 1H), 7.08-7.01 (m, 1H), 5.49-5.35 (m, 1H), 4.54 (d, J = 11.2 Hz, 1H), 4.44 (d, J = 11.2 Hz, 1H), 4.40-4.35 (m, 1H), 4.32 (d, J = 14.8 Hz, 1H), 4.18-4.02 (m, 3H), 3.86-3.82 (m, 1H), 3.74-3.64 (m, 3H), 3.55-3.49 (m, 2H), 3.25-3.18 (m, 1H), 2.56-2.11 (m, 8H), 2.06-2.00 (m, 1H), 1.25 (d, J = 4.0 Hz, 3H), 0.84-0.75 (m, 3H); LCMS (ESI, M+1): m/z = 654.4.

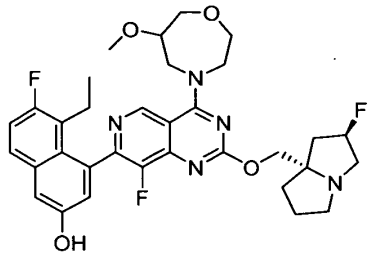
EXAMPLE 498



4-(4-((S)-1,1-difluoro-5-oxa-8-azaspiro[2.6]nonan-8-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

[00001275] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.95 (s, 1H), 9.15 (d, J = 6.4 Hz, 1H), 8.22 (s, 1H), 7.77 (m, 1H), 7.40-7.26 (m, 2H), 7.05-6.93 (m, 1H), 5.41-5.17 (m, 1H), 4.40-4.28 (m, 2H), 4.26-4.18 (m, 1H), 4.18-4.10 (m, 1H), 4.10-4.02 (m, 2H), 4.02-3.91 (m, 2H), 3.86-3.73 (m, 2H), 3.15-3.03 (m, 2H), 3.01 (s, 1H), 2.88-2.77 (m, 1H), 2.40-2.34 (m, 1H), 2.21-2.09 (m, 2H), 2.05 (m, 1H), 1.99 (m, 1H), 1.90-1.68 (m, 5H), 0.73 (m, 3H); LCMS (ESI, M+1): m/z = 656.1.

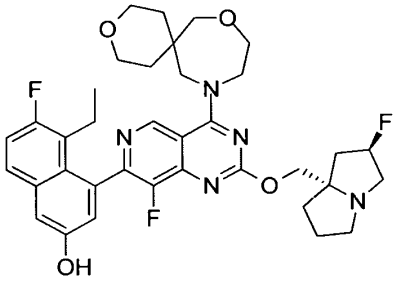
EXAMPLE 499



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

[00001276] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.04-9.84 (m, 1H), 9.23 (d, J = 2.4 Hz, 1H), 8.15 (s, 1H), 7.77 (dd, J = 6.0, 9.2 Hz, 1H), 7.42-7.25 (m, 2H), 7.02 (dd, J = 2.0, 5.6 Hz, 1H), 5.40-5.16 (m, 1H), 4.50-4.32 (m, 1H), 4.24-3.98 (m, 6H), 3.97-3.88 (m, 1H), 3.87-3.76 (m, 2H), 3.76-3.64 (m, 1H), 3.38 (d, J = 2.0 Hz, 3H), 3.14-3.05 (m, 2H), 3.02 (s, 1H), 2.87-2.78 (m, 1H), 2.21-1.93 (m, 5H), 1.90-1.75 (m, 3H), 0.73 (d, J = 3.2 Hz, 3H); LCMS (ESI, M+1): m/z = 624.2.

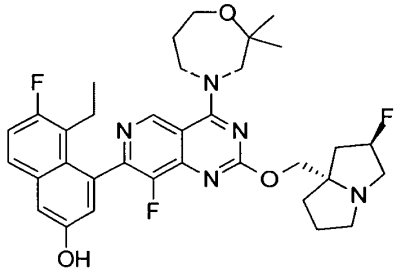
EXAMPLE 500



5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(3,8-dioxa-11-azaspiro[5.6]dodecan-11-yl)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol

[00001277] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.94 (s, 1H), 9.19 (s, 1H), 8.15 (s, 1H), 7.76 (m, 1H), 7.48-7.18 (m, 2 H), 7.03 (d, J = 2.4 Hz, 1 H), 5.29 (d, J = 54.0 1 H), 4.55 (d, J=14.0 Hz, 1 H), 4.26-4.12 (m, 2 H), 4.11-4.02 (m, 4 H), 3.68-3.47 (m, 6 H), 3.18-3.00 (m, 3 H), 2.86-2.80 (m, 1 H), 2.54 (s, 1 H), 2.41-2.34 (m, 1 H), 2.20-1.94 (m, 4 H), 1.89-1.89 (m, 3 H), 1.54-1.27 (m, 4 H), 0.72 (t, J = 7.38 Hz, 3 H); LCMS (ESI, M+1): m/z = 664.3.

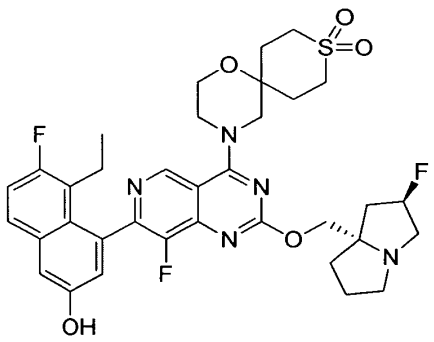
EXAMPLE 501



4-(4-(2,2-dimethyl-1,4-oxazepan-4-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

[00001278] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.05-9.87 (m, 1H), 9.10 (s, 1H), 8.24 (s, 1H), 7.76 (dd, J = 5.2, 8.4 Hz, 1H), 7.39-7.29 (m, 2H), 7.03 (d, J = 2.0 Hz, 1H), 5.21 (s, 1H), 4.45-4.31 (m, 1H), 4.19-4.00 (m, 4H), 4.00-3.92 (m, 1H), 3.88-3.77 (m, 2H), 3.08 (d, J = 6.8 Hz, 2H), 3.00 (s, 1H), 2.86-2.79 (m, 1H), 2.67 (s, 1H), 2.33 (s, 2H), 2.17-1.96 (m, 7H), 1.89-1.75 (m, 3H), 1.21-1.08 (m, 6H), 0.73 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 622.2.

EXAMPLE 502

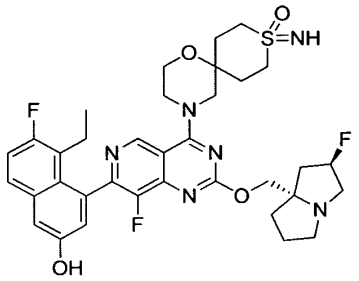


4-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1-oxa-9-thia-4-azaspiro[5.5]undecane 9,9-dioxide

[00001279] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.16 (s, 1H), 8.18 (s, 1H), 7.79-7.76 (m, 1H), 7.37 (d, J = 9.6 Hz, 1H), 7.34 (d, J = 2.4 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 5.36-5.22 (m, 1H),

4.18-4.15 (m, 1H), 4.10-4.07 (m, 1H), 4.02-4.00 (m, 2H), 3.96-3.90 (m, 4H), 3.17-3.14 (m, 2H), 3.11 (s, 1H), 3.07 (t, J = 3.2 Hz, 1H), 3.02 (s, 1H), 2.86-2.81 (m, 1H), 2.54 (s, 1H), 2.53-2.52 (m, 1H), 2.37-2.33 (m, 3H), 2.15-2.01 (m, 6H), 1.87-1.77 (m, 3H), 0.73 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 698.3.

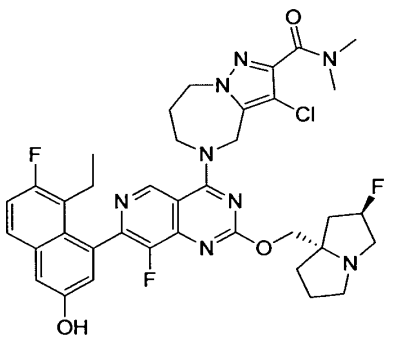
EXAMPLE 503



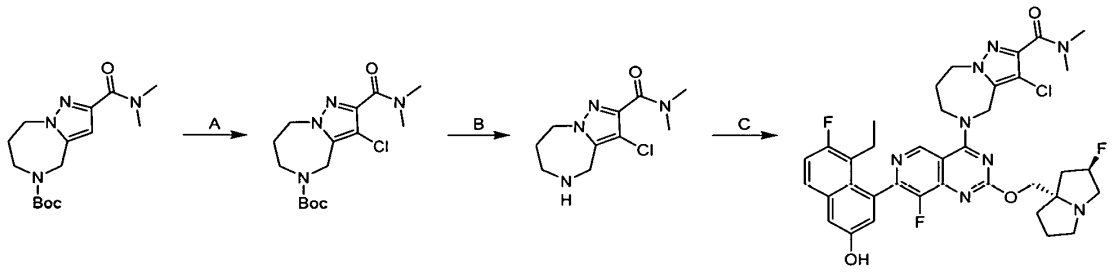
4-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorohexahydro-1*H*-pyrrolizin-7a-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-9-imino-1-oxa-9-thia-4-azaspiro[5.5]undecane 9-oxide

[00001280] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.08-9.84 (s, 1H), 9.22-9.06 (s, 1H), 7.79-7.75 (m, 1H), 7.40-7.30 (m, 2H), 7.01 (d, J = 2.4 Hz, 1H), 5.28 (d, J = 64.0 Hz, 1H), 4.21-4.12 (m, 1H), 4.10-4.05 (m, 1H), 4.04-3.95 (m, 2H), 3.95-3.84 (m, 4H), 3.53 (s, 1H), 3.11-3.00 (m, 5H), 2.95 (d, J = 12.8 Hz, 2H), 2.86-2.78 (m, 1H), 2.26 (d, J = 12.4 Hz, 2H), 2.18-2.10 (m, 2H), 2.10-1.94 (m, 5H), 1.87-1.74 (m, 3H), 0.72 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): m/z = 697.7.

EXAMPLE 504



3-chloro-5-(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)-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide



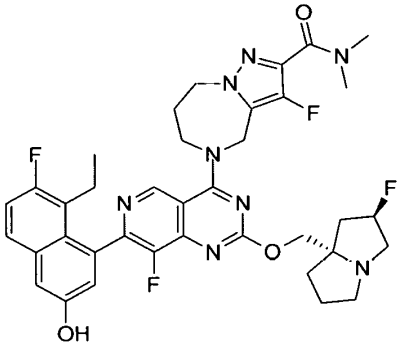
[00001281] Step A. tert-butyl3-chloro-2-(dimethylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate: To a solution of tert-butyl 2-(dimethylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (1.2 g, 1.0 equiv.) in DMF (12 mL) was added NCS (779 mg, 1.5 equiv.) at 0 °C. The mixture was stirred at 55 °C for 1 hour. The mixture was diluted with H_2O (30 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography [SiO_2, petroleum ether/ethyl acetate 10:1 to 1:1] to afford the title compound (740 mg, 51% yield) as a light yellow oil; ^1H NMR (400 MHz, CDCl3) δ = 4.50 (s, 2H), 4.45-4.35 (m, 2H), 3.75 (s, 2H), 3.10 (s, 6H), 1.97 (s, 2H), 1.44 (s, 9H); LCMS (ESI, M+1): m/z =343.4.

[00001282] Step B. 3-chloro-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: A mixture of tert-butyl 3-chloro-2-(dimethylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (100 mg, 292 μmol, 1.0 equiv.) in HCl•dioxane (1.0 mL) was stirred at 25 °C for 1 hour. The mixture concentrated to afford the title compound (45 mg, 50% yield, HCl) as a white solid, LCMS (ESI, M+1): m/z =243.0.

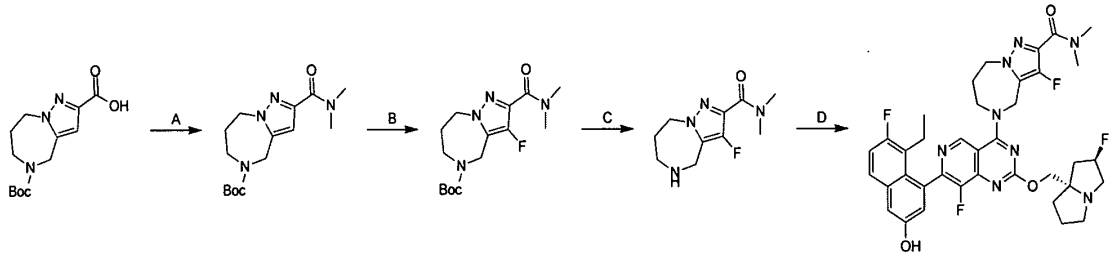
[00001283] Step C: 3-chloro-5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: A mixture of 3-chloro-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (45 mg, 3.5 equiv, HCl), 4Å molecular sieve (100 mg) and DIEA (16.4 mg, 3.0 equiv.) in DMF (0.05

mL) was stirred at 25 °C for 30 minutes. 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 (25 mg, 1.0 equiv.) was added and the mixture was stirred at 40 °C for 36 hours. The mixture was filtered and the filtrate was purified by prep-HPLC [column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: A: water (0.1% formic acid)-ACN; B%: 15%-45%, 9 minutes] to afford the title compound (8.52 mg, 24% yield, formic acid salt) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.93 (s, 1H), 9.16 (s, 1H), 8.13 (s, 1H), 7.77 (dd, J = 9.2 Hz, 6.0 Hz, 1H), 7.39-7.30 (m, 2H), 7.00 (d, J = 2.4 Hz, 1H), 5.45-5.35 (m, 1H), 5.31-5.09 (m, 3H), 4.47 (d, J = 6.8 Hz, 2H), 4.40-4.30 (m, 2H), 4.25-4.06 (m, 2H), 3.21-3.04 (m, 3H), 2.99 (d, J = 15.2 Hz, 6H), 2.96-2.72 (m, 2H), 2.42-2.37 (m, 2H), 2.17-1.77 (m, 8H), 0.72 (t, J = 7.6 Hz, 3H); LCMS (ESI, M+1): m/z = 735.2.

EXAMPLE 505



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



[00001284] Step A. tert-butyl 2-(dimethylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate: To a solution of 5-tert-butoxycarbonyl-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxylic acid (1.0 g, 1.0 equiv.) in Me_2NH (2 M in THF, 8.89 mL, 5.0 equiv.) was added DIEA (689 mg, 1.5 equiv.) and HATU (2.03 g, 1.5 equiv.). The mixture was stirred at 25 °C for 12 hours. The mixture was diluted with H_2O (4 mL) and filtered. The filtrate was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, concentrated and purified by reversed phase flash [water (0.1% formic acid)/acetonitrile] to afford the title compound (981 mg, 89% yield) as a yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.67-6.39 (m, 1H), 4.61-4.31 (m, 4H), 3.80-3.60 (m, 2H), 3.45-3.20 (m, 3H), 3.18-2.93 (m, 3H), 1.99-1.88 (m, 2H), 1.41 (s, 9H); LCMS (ESI, M+1): m/z = 308.9.

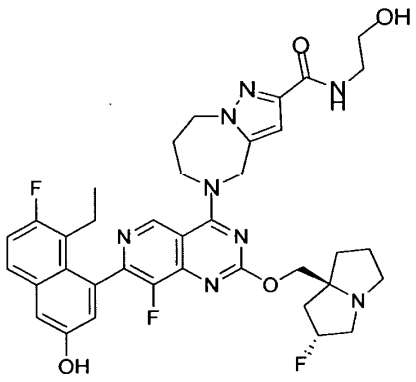
[00001285] Step B. tert-butyl 2-(dimethylcarbamoyl)-3-fluoro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate: To a solution of tert-butyl 2-(dimethylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (760 mg, 1.0 equiv.) in ACN (10 mL) was added 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (4.37 g, 5.0 equiv.). The mixture was stirred at 25 °C for 16 hours. The mixture was concentrated and purified by prep-HPLC [column: Phenomenex luna C18 200 × 40 mm × 10 μm; mobile phase: A: water (0.1% formic acid)-MeCN; B%: 25%-55%, 10 minutes] to afford the title compound (107 mg, 13% yield) as a yellow oil; LCMS (ESI, M+1): m/z = 326.9.

[00001286] Step C. 3-fluoro-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: To a solution of tert-butyl 2-(dimethylcarbamoyl)-3-fluoro-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (56 mg, 1.0 equiv.) in DCM (0.25 mL) and TFA (0.25 mL) was stirred at 25 °C for 1 hour. The mixture was concentrated to afford the title compound (91 mg, crude, TFA) as a yellow oil; LCMS (ESI, M+1): 226.9.

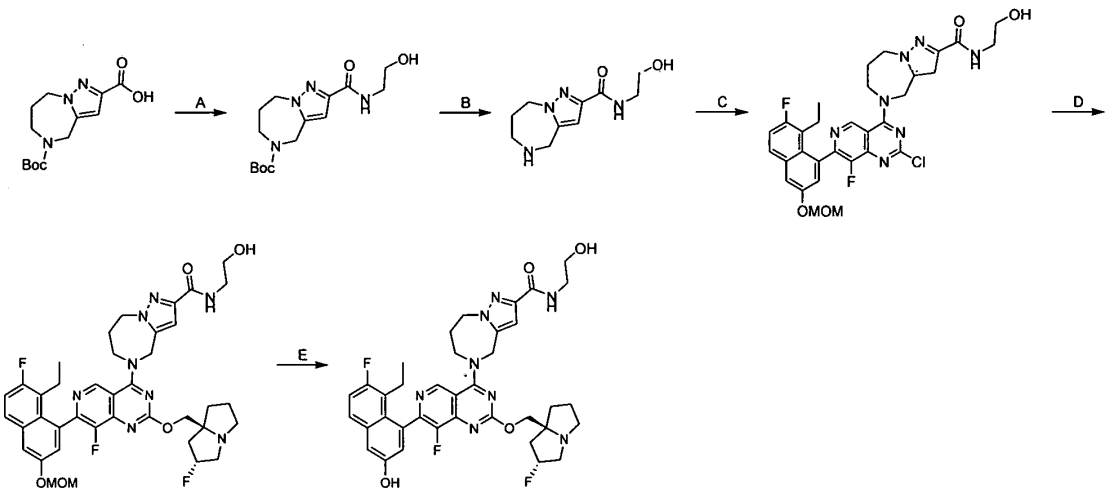
[00001287] Step D: 5-(7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-fluoro-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: A mixture of 5-ethyl-6-fluoro-4-(8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-2-ol (31.7 mg, 1.0 equiv.), 3-fluoro-N,N-dimethyl-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (91

mg, crude) , 4Å molecular sieve (10 mg) and K_2CO_3 (37.0 mg, 5.0 equiv.) in DMSO (0.5 mL) was stirred at 40 °C for 2 hours under N_2 atmosphere. The mixture was filtered and the filtrate was purified by prep-HPLC [column: Phenomenex luna C18 100 × 30 mm × 5 μm; mobile phase: A: water (0.1% formic acid)-MeCN; B%: 10%-40%, 10 minutes] to afford the title compound (8.89 mg, 20% yield, formic acid salt) as a white solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.94 (s, 1H), 9.18 (s, 1H), 8.15-8.12 (m, 1H), 7.77 (m, 1H), 7.40-7.29 (m, 2H), 7.00 (d, J = 2.4 Hz, 1H), 5.47-5.26 (m, 1H), 5.26-5.19 (m, 1H), 5.18-5.09 (m, 1H), 4.46 (d, J = 6.0 Hz, 4H), 4.29-3.95 (m, 2H), 3.14-3.09 (m, 3H), 2.98-2.91 (m, 3H), 2.42-2.28 (m, 4H), 2.27-1.53 (m, 9H), 0.71 (t, J = 7.2 Hz, 3H); LCMS (ESI, M+1): 719.1.

EXAMPLE 506



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



[00001288] Step A. tert-butyl 2-((2-hydroxyethyl)carbamoyl)-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 (200 mg, 1.0 *equiv.)* and TEA (108 mg, 1.5 *equiv.)* in DMF (2 mL) was added HATU (405 mg, 1.5 *equiv.)* and 2-aminoethanol (174 mg, 4.0 *equiv.)*. The reaction was stirred at 20 °C for 0.5 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-TLC (SiO_2, Petroleum ether / Ethyl acetate **1:1**) to afford the title compound (160 mg, 69% yield) as a colorless oil; LCMS (ESI, M+1): m/z=325.1

[00001289] Step B. N-(2-hydroxyethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: A solution of tert-butyl 2-(2-hydroxyethylcarbamoyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-5-carboxylate (160 mg, 1.0 *equiv.)* in HCl•dioxane (2 M, 2 mL, 8.1 *equiv.)* was stirred at 20 °C for 0.5 hour. The reaction mixture filtered, concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: A: water (10 mM NH_4HCO_3)-ACN]; B%: 1%-10%, 8 minutes) to afford the title compound (70.0 mg, 63% yield) as a white solid; LCMS (ESI, M+1): m/z = 225.2.

[00001290] Step C. 5-(2-chloro-7-(8-ethyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-N-(2-hydroxyethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: To a solution of N-(2-hydroxyethyl)-5,6,7,8-tetrahydro-4H-

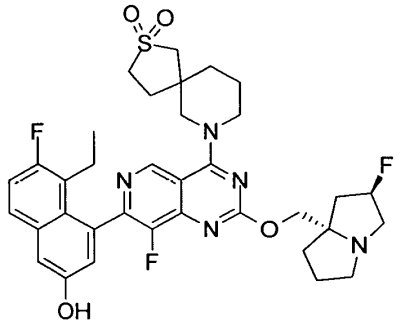
pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (70.0 mg, 1.0 *equiv.)* in DMF (1 mL) were added 2,4-dichloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidine (141 mg, 1.0 *equiv.)* and DIEA (121 mg, 3.0 *equiv.)*, and then the mixture was stirred at -40 °C for 10 minutes. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed phase flash chromatography (C18, water (0.1% formic acid)-ACN) to afford the title compound (60.0 mg, 30% yield) as a white solid; LCMS (ESI,M+1):m/z = 638.3.

[00001291] Step D. 5-(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)-N-(2-hydroxyethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: To a solution of 5-[2-chloro-7-[8-ethyl-7-fluoro-3-(methoxymethoxy)-1-naphthyl]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-N-(2-hydroxyethyl)-4,6,7,8-tetrahydropyrazolo[1,5-a][1,4]diazepine-2-carboxamide (30.0 mg, 1.0 *equiv.)* in THF (1.0 mL) were added ((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methanol (11.0 mg, 1.5 *equiv.)*, DIEA (18.0 mg, 3.0 *equiv.)* and 4 Å molecular sieves (10 mg). The mixture was stirred at 50 °C for 3 hours. The reaction mixture was concentrated under reduced pressure to afford the title compound as a colorless oil. LCMS (ESI, M+1): m/z =761.5.

[00001292] Step E. 5-(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)-N-(2-hydroxyethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide: To a solution of 5-(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)-N-(2-hydroxyethyl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine-2-carboxamide (25.0 mg, 1.0 *equiv.)* in MeOH (1 mL) was added HCl•MeOH (4 mol/L, 1.0 mL, 122 *equiv.)*. The mixture was stirred at 0 °C for 0.5 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (column: Waters Xbridge 150 × 25 mm × 5 μm; mobile phase: water (10 mM NH_4HCO_3)-ACN]; B%: 35%-55%, 8 minutes) to afford the title compound (16.0 mg, 68% yield) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.19 (d, *J* = 2.8 Hz, 1H), 7.81-7.57 (m, 1H), 7.36-7.21 (m, 2H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.84 (s, 1H), 5.43-5.15 (m, 3H), 4.68-4.16 (m, 9H), 3.67 (t, *J* = 5.6 Hz, 2H), 3.49-

3.44 (m, 2H), 3.14-3.04 (m, 1H), 2.53-2.32 (m, 4H), 2.33-2.15 (m, 3H), 2.12-1.91 (m, 3H), 0.78 (br t, J = 6.8 Hz, 3H); LCMS (ESI,M+1): m/z =717.5.

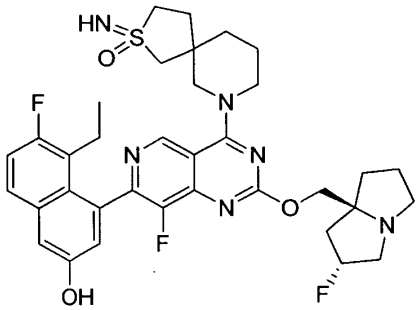
EXAMPLE 507



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-thia-7-azaspiro[4.5]decane 2,2-dioxide

[00001293] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, Methanol-d4) δ 9.08 (s, 1H), 7.66 (dd, J = 5.6, 9.0 Hz, 1H), 7.28 (d, J = 2.8 Hz, 1H), 7.23 (t, J = 9.6 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 5.42 - 5.18 (m, 1H), 4.49 - 4.31 (m, 2H), 4.30 - 4.14 (m, 2H), 4.06 - 3.83 (m, 2H), 3.44 - 3.33 (m, 1H), 3.29 - 3.12 (m, 5H), 3.08 - 2.96 (m, 2H), 2.58 - 2.42 (m, 1H), 0.85 - 0.73 (m, 3H); LCMS [ESI, M+1]: m/z = 682.4.

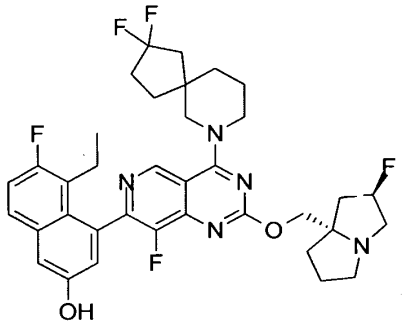
EXAMPLE 508



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-imino-2-thia-7-azaspiro[4.5]decane 2-oxide

[00001294] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR(400 MHz, METHANOL-*d*4) δ = 9.16 - 9.04 (m, 1H), 7.74 - 7.63 (m, 1H), 7.37 - 7.20 (m, 2H), 7.12 - 6.99 (m, 1H), 5.40 - 5.38 (m, 1H), 5.28 - 5.25 (m, 1H), 4.52 - 4.14 (m, 4H), 4.09 - 3.88 (m, 2H), 3.34 (br s, 4H), 3.26 - 2.98 (m, 4H), 2.49 (br s, 6H), 2.12 - 1.84 (m, 8H), 0.85 - 0.74 (m, 3H); LCMS[ESI, M+1]: m/z = 681.3.

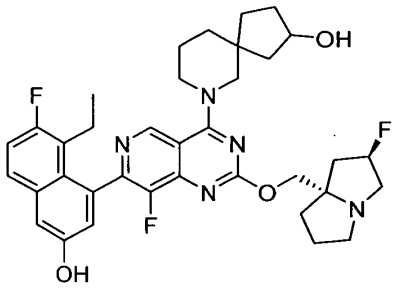
EXAMPLE 509



4-(4-(2,2-difluoro-7-azaspiro[4.5]decan-7-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

[00001295] The title compound was synthesized according to the procedure described for example 330.^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.10 (s, 1H), 8.58-8.46 (m, 1H), 7.70 (dd, *J* = 6.0, 8.8 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.27 (t, *J* = 9.6 Hz, 1H), 7.08 (s, 1H), 5.53-5.31 (m, 1H), 4.53-4.36 (m, 2H), 4.33-4.17 (m, 1H), 4.16-3.95 (m, 2H), 3.95-3.79 (m, 1H), 3.63-3.39 (m, 3H), 3.27-3.12 (m, 1H), 2.57-2.34 (m, 3H), 2.28-2.09 (m, 7H), 2.05-1.94 (m, 2H), 1.93-1.66 (m, 6H), 0.87-0.77 (m, 3H); ^{19}F NMR (377 MHz, METHANOL-d4) δ = -76.89 (br s, 1F), -88.50--94.55 (m, 1F), -121.07 (br d, *J* = 5.7 Hz, 1F), -137.84--141.32 (m, 1F), -173.71 (br s, 1F); LCMS (ESI, M+1): m/z = 668.5.

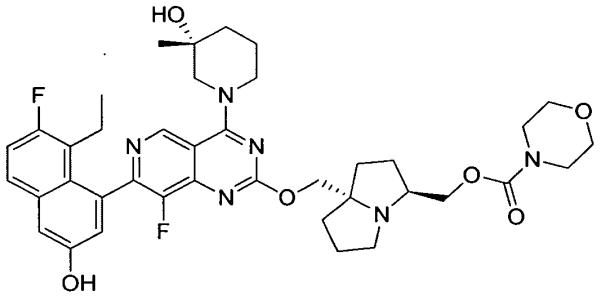
EXAMPLE 510



7-(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)-7-azaspiro[4.5]decan-2-ol

[00001296] The title compound was synthesized according to the procedure described for example 330. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 0.69-0.47 (m, 3 H) 1.15 (s, 1 H) 1.30-1.64 (m, 7 H) 1.71-1.86 (m, 6 H) 2.00-2.15 (m, 4 H) 2.78-2.86 (m, 1 H) 3.01 (s, 1 H) 3.08 (d, J =11.6 Hz, 2 H) 3.76 (m, 2 H) 3.93 (s, 1 H) 4.03-4.19 (m, 4 H) 4.42-4.56 (m, 1 H) 5.17-5.38 (m, 1 H) 7.03 (s, 1 H) 7.28-7.40 (m, 2 H) 7.76 (s, 1 H) 8.23 (s, 1 H) 9.12 (s, 1 H) 9.93 (s, 1 H); LCMS [M+1] $^+$: m/z = 648.3.

EXAMPLE 511

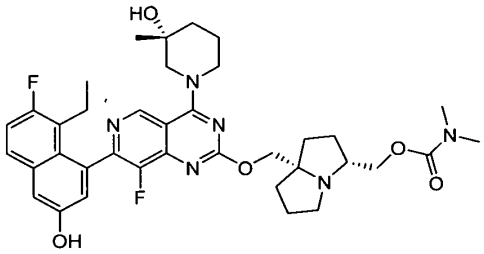


((3S,7aS)-7a-(((7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-4-((R)-3-hydroxy-3-methylpiperidin-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)hexahydro-1H-pyrrolizin-3-yl)methyl morpholine-4-carboxylate

[00001297] The title compound was synthesized according to the procedure described for example 313. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.21 (d, J = 3.6 Hz, 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), 7.07 (t, J = 3.2 Hz, 1H), 4.71-

4.41 (m, 2H), 4.34-4.19 (m, 3H), 4.16-4.06 (m, 1H), 4.06-3.92 (m, 1H), 3.68-3.57 (m, 5H), 3.49-3.42 (m, 4H), 3.10-2.97 (m, 2H), 2.91-2.70 (m, 1H), 2.55-2.40 (m, 1H), 2.25-2.09 (m, 3H), 2.07-1.99 (m, 1H), 1.98-1.88 (m, 3H), 1.87-1.72 (m, 5H), 1.72-1.62 (m, 1H), 1.29 (d, J = 10.4 Hz, 3H), 0.88-0.74 (m, 3H); LCMS (ESI, M+1): m/z = 733.4.

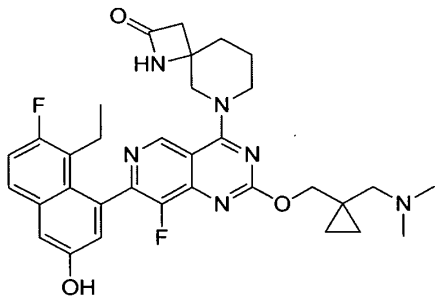
EXAMPLE 512



((3R,7aS)-7a-(((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)hexahydro-1H-pyrrolizin-3-yl)methyl dimethylcarbamate

[00001298] The title compound was synthesized according to the procedure described for example 362. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.21 (d, J = 4.0 Hz, 1H), 7.70-7.66 (m, 1H), 7.31-7.23 (m, 2H), 7.07-7.06 (m, 1H), 4.59-4.49 (m, 2H), 4.39-4.19 (m, 3H), 4.18-3.92 (m, 2H), 3.71-3.55 (m, 1H), 3.52-3.40 (m, 1H), 3.22-3.02 (m, 2H), 2.93-2.88 (m, 6H), 2.53-2.39 (m, 1H), 2.30-2.10 (m, 3H), 2.09-2.02 (m, 1H), 2.00-1.89 (m, 3H), 1.88-1.63 (m, 6H), 1.30-1.28 (m, 3H), 0.84-0.78 (m, 3H); LCMS (ESI, M+1): m/z = 691.4.

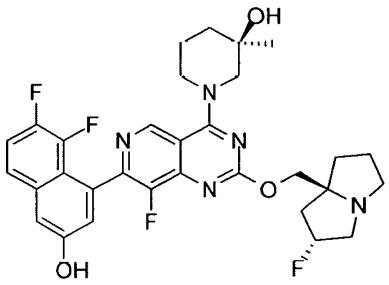
Example 513



6-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-7-(8-ethyl-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one

[00001299] The title compound was synthesized according to the procedure described for example 364. ^{1}H NMR (400 MHz, Methanol-d4) δ 9.07 (s, 1H), 7.67 (dd, J = 5.6, 9.2 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.24 (t, J = 9.6 Hz, 1H), 7.04 (t, J = 2.8 Hz, 1H), 4.42 - 4.21 (m, 4H), 3.96 (dd, J = 13.2, 18.4 Hz, 1H), 3.84 - 3.64 (m, 1H), 2.88 (dd, J = 6.0, 14.8 Hz, 1H), 2.78 - 2.68 (m, 1H), 2.50 - 2.36 (m, 3H), 2.29 (s, 6H), 2.21 - 2.04 (m, 2H), 2.04 - 1.86 (m, 3H), 0.79 (dt, J = 2.8, 7.2 Hz, 3H), 0.75 - 0.71 (m, 2H), 0.56 - 0.50 (m, 2H); LCMS [ESI, M+1]: m/z = 603.4.

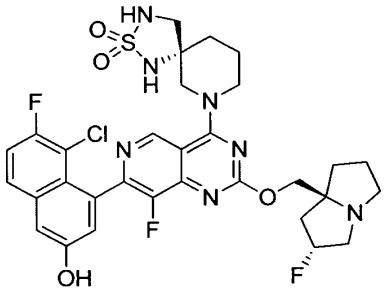
EXAMPLE 514



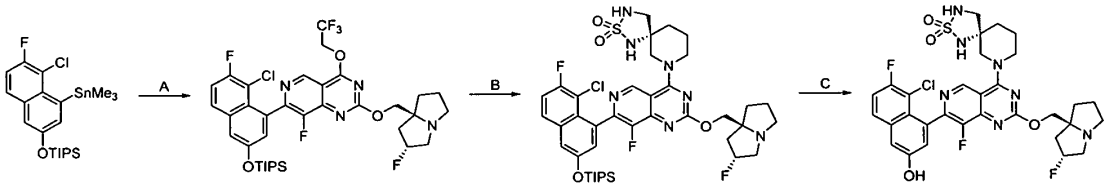
(R)-1-(7-(7,8-difluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

[00001300] The title compound was synthesized according to the procedure described for example 133. ^{1}H NMR (400 MHz, METHANOL-d$_4$) δ = 9.20 (d, *J* = 7.2 Hz, 1H), 7.64-7.56 (m, 1H), 7.44-7.35 (m, 1H), 7.32 (t, *J* = 2.0 Hz, 1H), 7.24 (dd, *J* = 2.0, 7.6 Hz, 1H), 5.30 (d, *J* = 54.4 Hz, 1H), 4.53 (br d, *J* = 12.4 Hz, 1H), 4.37-4.21 (m, 3H), 3.63 (dd, *J* = 2.4, 13.2 Hz, 1H), 3.45 (br t, *J* = 12.0 Hz, 1H), 3.30-3.12 (m, 3H), 3.04-2.96 (m, 1H), 2.40-2.09 (m, 4H), 2.05-1.71 (m, 6H), 1.29 (d, *J* = 5.2 Hz, 3H); LCMS (ESI, M+1): m/z = 598.2.

EXAMPLE 515



(*R*)-7-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro[4.5]decane2,2-dioxide



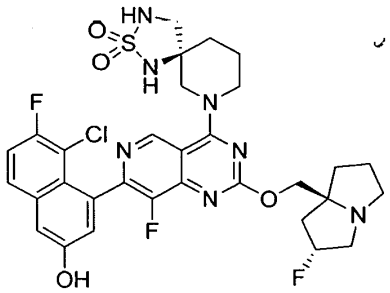
[00001301] Step A. 7-(8-chloro-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: A mixture of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorohexahydro-1H-pyrrolizin-7a-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (800 mg, 1.0 equiv.), ((5-chloro-6-fluoro-4-(trimethylstannyl)naphthalen-2-yl)oxy)triisopropylsilane (1.40 g, 1.49 equiv.), $Pd(dppf)Cl_2$ (133 mg, 0.1 equiv.), BINAP (227 mg, 0.2 equiv.) and CuI (104 mg, 0.3 equiv.) in toluene (30 mL) was degassed and stirred at 90 °C for 6 hours under N_2 atmosphere. The mixture was filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate 1:1) to give the title compound (230 mg, 14% yield) as a yellow oil. LCMS (ESI, M+1): m/z = 754.9.

[00001302] Step B. (*R*)-7-(7-(8-chloro-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide: To a solution of 7-(8-chloro-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-

pyrrolizin-7a(5*H*)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (230 mg, 1.0 equiv.) , (*R*)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide (87.3 mg, 1.5 equiv.) in DMF (2 mL) was added DIEA (196 mg, 5.0 equiv.) and 4Å molecular seives (300 mg). The mixture was stirred at 60 °C for 12 hours. The mixture was poured into water (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and the filtrate was concentrated to afford the title compound (262 mg, crude) as a yellow oil.

[00001303] Step C. (*R*)-7-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide: To a solution of (*R*)-7-(7-(8-chloro-7-fluoro-3-((triisopropylsilyl)oxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide (260 mg, 1.0 equiv.) in DMF (2.0 mL) was added CsF (46.6 mg, 1.0 equiv.). The mixture was stirred at 25 °C for 0.5 hour. The mixture was poured into water (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, then the mixture was filtered and the filtrate was concentrated. The residue was purified by prep-HPLC (column: Phenomenex C18 75 × 30 mm × 3 μm; mobile phase: water (0.1% formic acid)-ACN; B%: 20%-30%, 7 min) to afford the title compound (108 mg, 50.4% yield) as a white solid; ^{1}H NMR (400 MHz, methanol-d4) δ = 9.11 (d, J = 1.8 Hz, 1H), 8.48 (s, 1H), 7.81 (ddd, *J* = 3.4, 5.5, 9.0 Hz, 1H), 7.46 - 7.34 (m, 2H), 7.21 (t, J = 2.8 Hz, 1H), 5.59 - 5.34 (m, 1H), 4.76 - 4.37 (m, 5H), 3.86 - 3.54 (m, 5H), 3.42 (dd, *J* = 2.4, 11.9 Hz, 1H), 3.22 (dd, *J* = 3.2, 11.9 Hz, 1H), 2.65 - 2.37 (m, 2H), 2.37 - 2.29 (m, 1H), 2.27 - 2.15 (m, 2H), 2.13 - 1.99 (m, 3H), 1.98 - 1.93 (m, 1H), 1.92 - 1.83 (m, 1H); LCMS (ESI, M+1): m/z = 690.2.

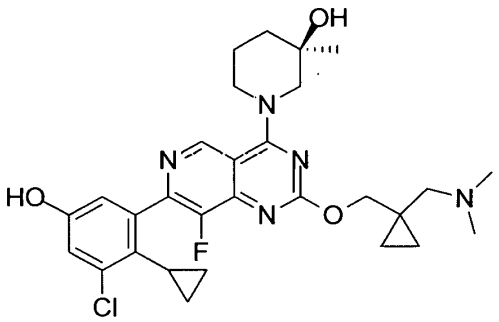
EXAMPLE 516



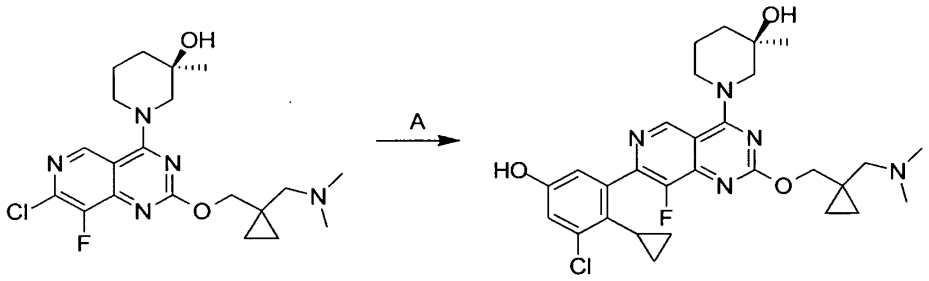
(S)-7-(7-(8-chloro-7-fluoro-3-hydroxynaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro [4.5]decane2,2-dioxide

[00001304] The title compound was synthesized according to the procedure described for example 515. ^{1}H NMR (400 MHz, methanol-d4) δ = 9.12 (d, *J* = 3.3 Hz, 1H), 8.47 (s, 1H), 7.81 (ddd, J = 3.5, 5.5, 9.1 Hz, 1H), 7.47-7.34 (m, 2H), 7.21 (dd, *J* = 2.5, 4.2 Hz, 1H), 5.60-5.37 (m, 1H), 4.77-4.32 (m, 5H), 3.89-3.53 (m, 5H), 3.41 (dd, *J* = 3.1, 12.0 Hz, 1H), 3.22 (dd, J = 3.4, 11.9 Hz, 1H), 2.65-2.40 (m, 2H), 2.38-2.29 (m, 1H), 2.27-2.16 (m, 2H), 2.13-2.00 (m, 3H), 1.96 (br d, *J* = 11.0 Hz, 1H), 1.92-1.83 (m, 1H); LCMS (ESI, M+1): m/z = 690.2.

EXAMPLE 517

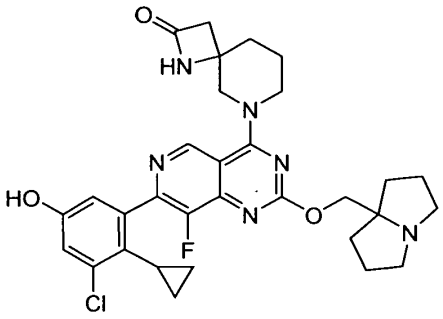


(R)-1-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol

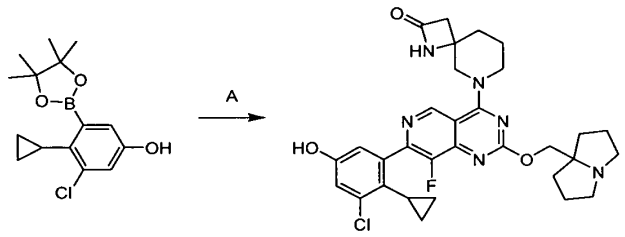


[00001305] Step A. (R)-1-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (R)-1-(7-chloro-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol (100 mg, 1.0 equiv.), 3-chloro-4-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (104 mg, 1.5 equiv.), cataCXium® A Pd G3 (34.4 mg, 0.2 equiv.), Cs_2CO_3 (1.0 M, 3.0 equiv.) in methoxycyclopentane (1.0 mL) was degassed and stirred at 80 °C for 3 hours under N_2 atmosphere. The mixture was diluted with water (5 mL), extracted with ethyl acetate (3 × 5 mL), the combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by prep-HPLC [column: Phenomenex luna C18 150 × 25 mm × 10 μm; mobile phase: water (0.1% formic acid)-ACN; B%: 13%-43%, 10 min] and lyophilized to afford the title compound (53.4 mg, 39% yield) as a yellow solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.24 (s, 1H), 6.97 (d, J = 2.8 Hz, 1H), 6.79 (d, J = 2.8 Hz, 1H), 4.61-4.52 (m, 1H), 4.42 (s, 2H), 4.31-4.26 (m, 1H), 3.60 (d, J = 13.2 Hz, 1H), 3.49-3.37 (m, 1H), 3.14-2.99 (m, 2H), 2.79 (s, 6H), 2.22-2.08 (m, 1H), 1.91-1.72 (m, 4H), 1.29 (s, 3H), 0.94-0.88 (m, 2H), 0.79-0.76 (m, 2H), 0.67-0.61 (m, 2H), 0.10-0.07 (m, 2H); LCMS (ESI, M+1): m/z = 556.2.

EXAMPLE 518

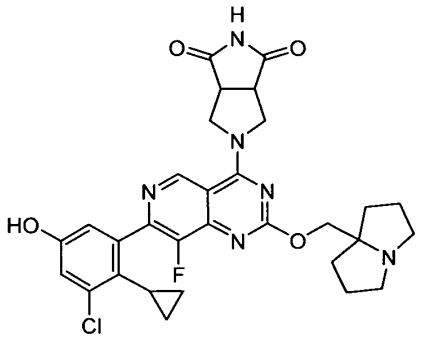


6-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one

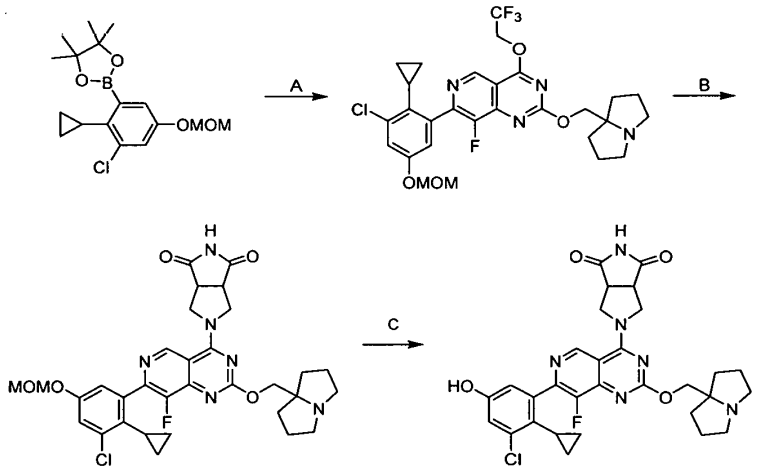


[00001306] Step A. 6-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one: To a solution of 6-(7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one (50.0 mg, 1.0 equiv.) in CPME (1 mL) was added CataCXium A Pd G3 (15.8 mg, 0.2 equiv.), 3-chloro-4-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (47.9 mg, 1.5 equiv.) and Cs_2CO_3 (1.5 M, 3.0 equiv.). The mixture was stirred at 100 °C for 2 hours under nitrogen atmosphere. The reaction mixture was poured into saturated aqueous NH_4Cl (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 diluted with MeOH (1 mL). The residue was purified by prep-HPLC [column: Phenomenex Luna C18 150 × 25 mm × 10 μm; mobile phase: water (0.1% formic acid)-ACN, B%: 12%-42%, 10 min] to afford the title compound (11.8 mg, 17% yield, formic acid salt) as a yellow solid; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.13 (s, 1H), 8.51 (br s, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.82-6.79 (m, 1H), 4.69-4.58 (m, 2H), 4.44-4.28 (m, 2H), 4.01 (br dd, J = 2.9, 13.0 Hz, 1H), 3.88-3.81 (m, 1H), 3.73-3.60 (m, 2H), 3.26 (td, J = 6.0, 11.6 Hz, 2H), 2.94-2.87 (m, 1H), 2.81-2.74 (m, 1H), 2.36-2.28 (m, 2H), 2.25-2.15 (m, 4H), 2.08 (td, J = 6.5, 12.6 Hz, 4H), 1.97 (br s, 2H), 1.89-1.81 (m, 1H), 0.67-0.47 (m, 2H), 0.13-0.02 (m, 2H); LCMS (ESI, M+1): m/z = 593.3.

EXAMPLE 519



5-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione



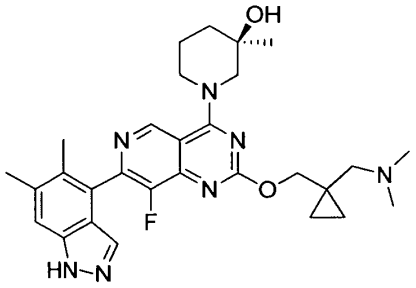
[00001307] Step A. 7-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine: To a solution of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (600 mg, 1.0 equiv.) in THF (12 mL) was added 2-[3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (579 mg, 1.2 equiv.), K_3PO_4 (1.5 M, 3.0 equiv.) and CataCXium A Pd G3 (104 mg, 0.1 equiv.). The mixture was stirred at 60 °C for 3 hours under nitrogen atmosphere. The mixture was diluted with water (200 mL) and extracted with EtOAc (2 × 50 mL). The combined

organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography [SiO_2, petroleum ether / ethyl acetate 10:1 to 0:1] to afford the title compound (400 mg, 41% yield) as a light yellow solid; LCMS (ESI, M+1): m/z = 597.3.

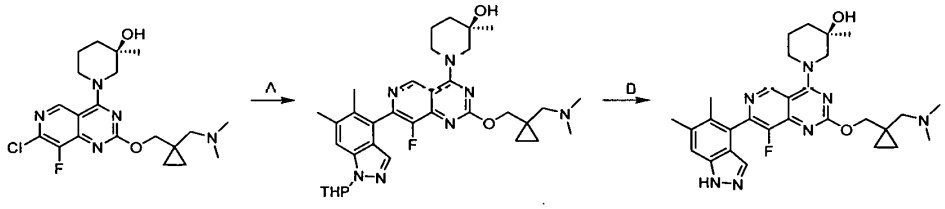
[00001308] Step B. 5-(7-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione: To a solution of 7-(3-chloro-2-cyclopropyl-5-(methoxymethoxy)phenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (50.0 mg, 1.0 equiv.) and 2,3,3a,6a-tetrahydro-1H-pyrrolo[3,4-c]pyrrole-4,6-dione (14.1 mg, 1.2 equiv.) in DMF (0.25 mL) and ACN (0.25 mL) was added K_3PO_4 (53.3 mg, 3.0 equiv.). The mixture was stirred at 40 °C for 16 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound (50.0 mg, crude) as a light yellow oil; LCMS (ESI, M+1): m/z = 637.4.

[00001309] Step C. 5-(7-(3-chloro-2-cyclopropyl-5-hydroxyphenyl)-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione: To a solution of 5-(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)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (50.0 mg, 1.0 equiv.) in ACN (1.0 mL) was added HCl•dioxane (4 M, 102 equiv.). The mixture was stirred at 20 °C for 1 hour. The mixture was concentrated. The residue was purified by prep-HPLC [column: Phenomenex Synergi C18 150 × 25 mm × 10 μm; mobile phase: water (0.1% formic acid)-ACN, B%: 8%-38%, 10 min] to afford the title compound (19.5 mg, 36% yield, FORMIC ACID) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 9.29 (s, 1H), 8.53 (s, 1H), 6.98 (d, J = 2.5 Hz, 1H), 6.81 (d, J = 2.5 Hz, 1H), 4.64 (br d, J = 13.9 Hz, 2H), 4.60 (s, 2H), 4.41-4.29 (m, 2H), 3.82-3.73 (m, 2H), 3.65-3.55 (m, 2H), 3.26-3.14 (m, 2H), 2.35-2.24 (m, 2H), 2.15 (tt, J = 6.6, 13.3 Hz, 4H), 2.09-1.99 (m, 2H), 1.90-1.79 (m, 1H), 0.69-0.53 (m, 2H), 0.06 (br s, 2H); LCMS (ESI, M+1): m/z = 593.2.

EXAMPLE 520



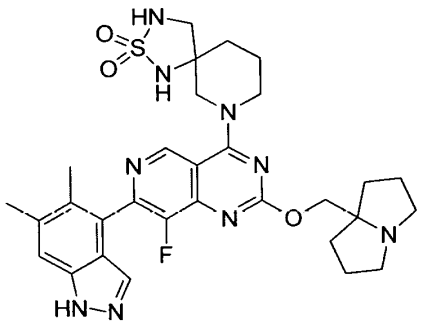
(3R)-1-(7-(5,6-dimethyl-1H-indazol-4-yl)-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol



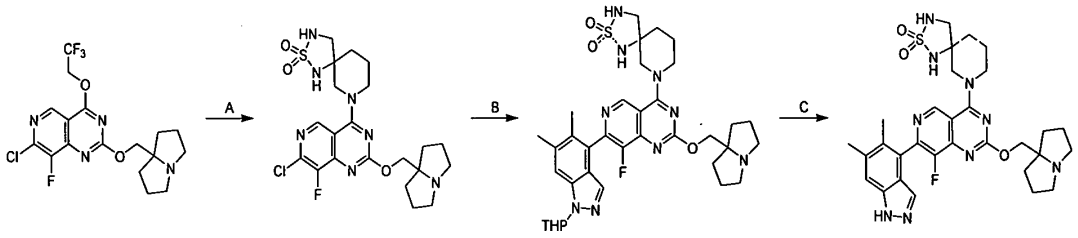
[00001310] Step A. (3R)-1-(7-(5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-4-yl)-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: A mixture of (3R)-1-[7-chloro-2-[[1-[(dimethylamino)methyl]cyclopropyl]methoxy]-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (120 mg, 1.0 equiv.), 5,6-dimethyl-1-tetrahydropyran-2-yl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indazole (111 mg, 1.10 equiv.), K_3PO_4 (1.5 M in water, 0.5 mL, 2.70 equiv.), and CataCXium A Pd G3 (20.6 mg, 0.1 equiv.) in methoxycyclopentane (2 mL) was degassed and stirred at 90 °C for 4 hours under N_2 atmosphere. The reaction mixture was diluted with ethyl acetate (5 mL) and water (10 mL) and the aqueous phase was extracted with ethyl acetate (5 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 [water (0.1% formic acid)-ACN] to afford the title compound (135 mg, 74% yield) as a white solid; LCMS (ESI, M+1): m/z = 618.5.

[00001311] Step B. (3R)-1-(7-(5,6-dimethyl-1H-indazol-4-yl)-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-ol: To a solution of (3R)-1-[2-[[1-[(dimethylamino)methyl]cyclopropyl]methoxy]-7-(5,6-dimethyl-1-tetrahydropyran-2-yl-indazol-4-yl)-8-fluoro-pyrido[4,3-d]pyrimidin-4-yl]-3-methyl-piperidin-3-ol (120 mg, 194 μmol, 1.0 equiv.) in DCM (2.0 mL) was added TFA (3.08 g, 139 equiv.). The reaction mixture was stirred at 20 °C for 1 hour. The mixture was poured into saturated $NaHCO_3$ solution (60 mL) and the pH was adjusted to 8. The mixture was extracted with ethyl acetate (2 × 20 mL), the organic layer was washed with saturated brine (20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum to give a residue. The residue was purified by prep-HPLC [column: Unisil 3-100 C18 Ultra 150 × 50 mm × 3 μm; mobile phase: water (0.1% formic acid)-ACN, B%: 3%-33% over 10 min] to afford the title compound (45.8 mg, 44% yield) as a white solid. ^1H NMR (400 MHz, METHANOL-d4) δ = 9.30 (d, J = 10.4 Hz, 1H), 8.53 (s, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.51 (s, 1H), 4.67-4.53 (m, 1H), 4.49-4.39 (m, 2H), 4.32 (br d, J = 1.2 Hz, 1H), 3.62 (dd, J = 4.4, 13.2 Hz, 1H), 3.49-3.34 (m, 1H), 3.17-3.02 (m, 2H), 2.82 (s, 6H), 2.51 (s, 3H), 2.23 (d, J = 3.2 Hz, 3H), 2.20-2.08 (m, 1H), 1.91-1.72 (m, 3H), 1.29 (d, J = 2.4 Hz, 3H), 0.96-0.88 (m, 2H), 0.83-0.75 (m, 2H); LCMS (ESI, M+1): m/z = 534.4.

EXAMPLE 521



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-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide



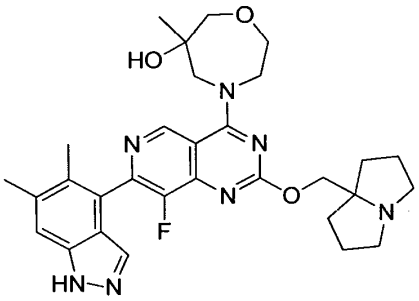
[00001312] Step A. 7-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide: A mixture of 7-chloro-8-fluoro-2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (0.4 g, 1 equiv.), 2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide (200 mg, 1.1 equiv.), DIPEA (246 mg, 2 equiv.) and 4Å molecular sieves (50 mg) in DMF (2.5 mL) was stirred at 40 °C for 13 hours under N_2 atmosphere. The mixture was filtered and purified by reversed phase flash chromatography [C18, water (0.1% formic acid)-ACN] to afford the title compound (0.3 g, 59% yield) as a yellow solid; LCMS (ESI, M+1): m/z = 512.2.

[00001313] 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-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide: To a mixture of 7-(7-chloro-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-2-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide (140 mg, 1.0 equiv.), 5,6-dimethyl-1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (100 mg, 1.0 equiv.) and K_3PO_4 (1.5 M, 547 µL, 3.0 equiv.) in methoxycyclopentane (2.5 mL) was added CataCXium A Pd G3 (20 mg, 0.1 equiv.) and the mixture was degassed and stirred at 90 °C for 2 hours under N_2 atmosphere. The mixture was diluted with H_2O (1 mL) and extracted with ethyl acetate (4 × 2 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by reversed phase flash [C18, water (0.1% formic acid)-ACN] to afford the title compound (74 mg, 36% yield) as a light yellow solid; LCMS (ESI, M+1): m/z = 706.4.

[00001314] 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-thia-1,3,7-triazaspiro[4.5]decane 2,2-dioxide: 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-thia-1,3,7-

triazaspiro[4.5]decane 2,2-dioxide (85 mg, 1.0 equiv.) in DCM (1.0 mL) was added TFA (1.2 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 0.75 hour. The mixture was poured into DCM (10 mL) and saturated $NaHCO_3$ aqueous (20 mL) at 0 °C. The pH of the mixture was adjusted to 9 with solid Na_2CO_3 while maintaining the temperature below 10 °C. The mixture was extracted with DCM (4 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by prep-HPLC [column: Phenomenex Luna C18 150 × 25 mm × 10 μm; mobile phase: water (0.1% formic acid)-ACN; B%: 7%-37%, 10 minutes] to afford the tittle compound (66.6 mg, 83% yield, 0.6 formic acid salt) as a white solid; ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.21 (s, 1H), 7.63 (br d, J = 17.2 Hz, 1H), 7.52 (br s, 1H), 4.75 (br d, J = 12.0 Hz, 2H), 4.64-4.54 (m, 2H), 3.82-3.67 (m, 4H), 3.45-3.36 (m, 1H), 3.27-3.22 (m, 3H), 2.51 (s, 3H), 2.33 (dt, J = 7.2, 12.0 Hz, 2H), 2.27-2.13 (m, 7H), 2.10-1.87 (m, 6H); LCMS (ESI, M+1): m/z = 622.4.

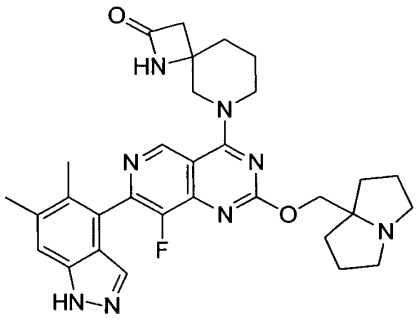
EXAMPLE 522



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

26. The title compound was synthesized according to the procedure described for example 521. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.67 (br d, J = 6.8 Hz, 1H), 7.60 (d, J = 7.2 Hz, 1H), 7.52 (s, 1H), 4.67-4.51 (m, 4H), 4.27-4.15 (m, 1H), 4.09-3.85 (m, 3H), 3.78-3.66 (m, 4H), 3.30-3.26 (m, 2H), 2.51 (s, 3H), 2.38-2.27 (m, 2H), 2.26-2.09 (m, 9H), 1.29 (s, 3H); LCMS (ESI, M+1): m/z = 562.4.

EXAMPLE 523



6-(7-(5,6-dimethyl-1H-indazol-4-yl)-8-fluoro-2-((hexahydro-1H-pyrrolizin-7a-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-1,6-diazaspiro[3.5]nonan-2-one

[00001315] The title compound was synthesized according to the procedure described for example 521. ^{1}H NMR (400 MHz, METHANOL-d4) δ = 9.21 (s, 1H), 7.60 (s, 1H), 7.52 (s, 1H), 4.69-4.58 (m, 2H), 4.41-4.39 (m, 1H), 4.38-4.29 (m, 1H), 4.03-3.93 (m, 1H), 3.92-3.79 (m, 1H), 3.72-3.61 (m, 2H), 3.27-3.21 (m, 2H), 2.95-2.90 (m, 1H), 2.81-2.73 (m, 1H), 2.51 (s, 3H), 2.35-2.27 (m, 2H), 2.25-2.20 (m, 4H), 2.20-2.11 (m, 4H), 2.11-2.02 (m, 3H), 2.07-1.95 (m, 2H); LCMS (ESI, M+1): m/z = 571.4.

EXAMPLE A: KRas Binding Assay

[00001316] This Example illustrates that exemplary compounds of the present invention bind to KRas and are capable of displacing a labeled tracer ligand occupying the KRas binding site. $KRas^{WT}$, $KRas^{G12A}$, $KRas^{G12C}$, $KRas^{G12D}$, $KRas^{G12R}$, $KRas^{G12S}$, $KRas^{G12V}$, $KRas^{G13D}$, or $KRas^{Q61H}$ was used in the assay.

[00001317] The ability of a compound to bind to KRas was measured using a TR-FRET displacement assay. Biotinylated KRas (corresponding to amino acids 1-169, produced at Accelegan Inc.) was incubated with custom made Cy5 labelled tracer, terbium streptavidin (Cisbio Inc.) and compound (1% DMSO final) in buffer (50 mM HEPES, pH 7.5, 5 mM $MgCl_2$, 0.005% Tween-20 and 1 mM DTT). After a 60-minute incubation at room temperature, the reaction was measured using a BMG LABTECH CLARIO star Plus via TR-FRET. 100 percent of control (POC) is determined by using a DMSO control and 0 POC is determined using a concentration of

control compound that completely inhibits binding of the tracer to KRas. The POC values were fit to a 4-parameter IC_{50} equation and the IC_{50} value reported.

Table 2

Binding to KRas (IC_{50} nM) by Exemplary Compounds of Formula (I)

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
1	330	565	866						
2	632	1006	2179						
3	8181	11740	20400						
4	43	21	31				23		
5	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
6	29	19	14	16	20	18	22	21	23
7	≤2	≤2	≤2	≤2	≤2	≤2	3	3	3
8	2242	2626	5406						
9	456	333	354						
10	≤2	≤2	3						
11	15510	20810	40130						
12	3	3	4						
13	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
14	29	52	109	58	58	51	51	61	80
15	24	42	81	38	42	37	41	42	52
16	26	39	60	29	31	29	32	33	40
17	746	1488	2227	961	921	1188	956	925	1861
18	23950	4446	6776	7540	4981	8795	6809	9372	13160
19	≥100000	64510	84320						
20	2395	3398	7389	2779	2982	3178	2967		
21	14850	9727	10720	12570	18800	12710	11430	12570	19430
22	9970	12130	14880			62060			
23	5275	4301	6176			4737			
24	≤2	≤2	≤2	≤2	≤2	≤2	≤2		
25	433	633	1312			679			
26	845	1261	2317						
27	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
28	3	≤2	3	≤2	≤2	≤2	3	3	3
29	20540	1965	4382	6198	3114	4319	5842	8190	13860
30	209	800	1271	1758	1452	1287	1743	1999	2900
31	14040	13200	12810						
32	98600	≥100000	86270						

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
33	6373	6612	10050						
34	11090	14960	≥100000	48730	53460	34950	28140		
35	12110	2522	1611					1659	4013
36	9	20	24						
37	41	57	93	52	63	56	68	88	88
38	≤2	≤2	≤2						
39	12520	25480	19750						
40	54950	66350	76920						
41	6477	3407	6391						
42	1861	1614	3088						
43	3782	1301	2270						
44	3229	2987	6238						
45	89	189	362						
46	14070	24030	22490					8793	18460
47	63390	70100	≥100000						
48	18360	20350	24070					16010	19890
49	69970	27940	18940						
50	39000	22590	22670						
51	21	35	69	36	38	35	32	36	50
52	235	25	39						
53	66380	49380	90250						
54	162	321	528						
55	139	212	410			295			
56	2614	3757	8341						
57	≤2	≤2	≤2					3	≤2
58	6	≤2	≤2						
59	≤2	≤2	≤2						
60	≤2	≤2	≤2						
61	≤2	≤2	≤2						
62	3	≤2	≤2					3	≤2
63	3	≤2	4					5	3
64	568	1356	2551	1303	1149	1059	997	1359	1547
65	14090	14990	45130			21030			
66	26920	44540	67780						
67	10370	11520	16100			14240			
68	11610	16950	27560						
69	2089	2733	4168						
70	14070	397	215	403	418	224	2857	11660	10840
71	3	≤2	6						

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
72	14050	10770	14020						
73	5	≤2	≤2						
74	≤2	≤2	3						
75	63100	2393	977			1835			
76	15490	3148	8872						
77	12820	1350	2205	1065	1172	1640	1410	1208	1907
78	677	1532	1759	2198	1242	1263	2676	3797	3297
79	15460	539	650						
80	29790	1595	1475	1576	2566	1253	6843	6313	10670
81	3564	802	1039	759	531	891	864	860	1168
82	≤2	≤2	≤2						
83	392	498	992	735	703	509	1195	1885	1992
84	12740	1864	2499	1647	2073	863	4288	5071	5864
85	44020	3704	2118	2845	4641	2153	4518	4656	10870
86	6901	3098	8490	2245	2391	3078	2408	3001	4775
87	3363	3657	11910	7119	10850	5938	6086	5257	9503
88	30710	2177	4367	1821	4239	2509	7175	9308	14660
89	2283	1021	2600	1252	1548	1061	1399	1811	3272
90	40220	3466	4190	5138	6483	4182	7236	8214	19550
91	≥100000	12660	2197	12700	17910	11350	14140	36630	31360
92	20760	1718	1976	6549	6867	3411	8804	8557	17330
93	83570	2935	3386	7842	10190	4053	14880	20410	21820
94	4510	146	115	240	368	183	1395	1246	1846
95	54980	4991	3061	4996	4122	3619	3994	7183	10350
96	62940	1944	3191	2497	3229	1947	5709	10730	22110
97	175	189	348	227	272	192	333	297	412
98	1889	3009	6415	2908	4014	2841	3356	3207	4765
99	≥100000	3967	16650	13590	21750	8334	32380	59770	98550
100	11810	17290	≥100000	50370	28810	39930	40320	49290	42010
101	15310	966	615	994	1343	679	3032	4233	2578
102	2289	365	479	634	191	399	1168	769	1178
103	15520	1834	1503	2086	2452	1891	3946	4212	4944
104	7613	2868	2819	1742	2018	2300	2333	3638	3208
105	9051	2806	5925	6703	5754	3511	8005	13840	13810
106	3631	612	1507	722	369	1125	2098	2335	2340
107	10750	3414	4619	6518	6848	3519	8525	8792	8776
108	19720	8102	4192						
109	10160	7426	4113	4275	7389	4250	3991	4340	4944

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
110	26900	3974	2482	9285	4365	5222	8814	9330	10080
111	2716	2012	3717	2416	2696	1742	2324	3624	3445
112	37540	25940	28120	25320	30990	27470	36620	13260	20740
113	14250	12000	16010	9476	10570	7110	8467	12060	12230
114	4380	2856	3747	2645	2806	2475	2705	29890	43270
115	30890	5804	4636	10530	10860	6558	11600	21170	22290
116	3309	4089	6267	2743	3593	4411	3449	2698	5199
117	31970	11110	10080	9152	11010	6570	9856	5679	8239
118	16100	7531	11350	8142	6237	7451	8554	8813	13960
119	31940	18040	15560	14400	14580	11600	15680	17210	27610
120	≥100000	≥100000	≥100000	33300	85290	19770	34070	≥100000	≥100000
121	42820	6637	12320	15460	18580	9100	12990	17330	25370
122	≥100000	6909	12450	14410	21750	3471	25970	86370	88200
123	4436	3192	7503	3181	2760	2341	3499	3484	4979
124	12620	1507	2190	2068	3869	1483	7022	7821	7135
125	60420	3923	4394	5517	7425	4250	13310	29060	39020
126	67250	≥100000	18430	13800	3967	9288	5967	7293	7502
127	25080	1698	2578	2681	1715	2192	4220	8699	11080
128	48980	8793	4142	11460	7803	9569	12810	13400	18430
129	2255	2795	4434	2687	2795	2531	3113	2496	4359
130	8361	10850	18260	10510	14240	9076	11430	25770	21930
131	14640	8300	2793	4463	9294	3453	8212	6561	7694
132	9	5	6						
133	≤2	≤2	≤2						
134	17	≤2	≤2						
135	31	3	3						
136	3	≤2	≤2						
137	≤2	≤2	3						
138	12	5	5						
139	8	≤2	≤2						
140	≤2	≤2	≤2						
141	≤2	≤2	≤2						
142	14	≤2	≤2						
143	4	≤2	≤2						
144	43	48	96	71	65	77	74	60	82
145	9	6	3						
146	≤2	≤2	3						
147	4	3	3						

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
148	3	≤2	≤2						
149	4	≤2	3						
150	≤2	≤2	≤2						
151	12	8	9						
152	175	8	10						
153	6	5	10	7	7	7	6	8	7
154	33	28	66	42	43	43	54	34	53
155	118	4	3						
156	≤2	≤2	≤2						
157	12	≤2	≤2						
158	152	78	81	85	69	41	103	83	102
159	39	3	5						
160	15	≤2	≤2						
161	68	7	9	12	15	7	20	16	17
162	31	≤2	3						
163	95	14	17						
164	28	3	3						
165	51	7	13	17	17	12	13	13	14
166	7	≤2	≤2						
167	16	≤2	≤2						
168	5	≤2	≤2						
169	4	≤2	≤2						
170	≤2	≤2	≤2						
171	89	3	9						
172	9	≤2	≤2						
173	6	4	6						
174	89	4	13						
175	38	≤2	≤2						
176	108	20	30						
177	3	≤2	≤2						
178	18	7	14						
179	12	4	3						
180	4	≤2	4						
181	29	17	10						
182	9	≤2	≤2						
183	4	4	5						
184	≤2	≤2	3						
185	11	9	9						
186	21	9	10						
187	12	5	6						

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
188	48	19	23						
189	32	18	18						
190	3	≤2	≤2						
191	9	4	4						
192	≤2	≤2	≤2						
193	≤2	≤2	≤2						
194	≤2	≤2	≤2						
195	16600	4909	1714						
196	≤2	≤2	≤2						
197	≤2	≤2	≤2						
198	86	9	8						
199	3	≤2	≤2						
200	≤2	≤2	≤2						
201	≤2	≤2	≤2						
202	≤2	≤2	≤2			≤2			
203	≤2	≤2	≤2						
204	1287	43	21	38	51	20	233	317	283
205	307	8	7	13	16	10	80	69	95
206	≤2	≤2	≤2						
207	17270	6166	13080	18100	46210	11750	26720	30390	46370
208	17450	824	494	1297	2263	677	4011	6246	7154
209	63350	2345	1615	3699	10080	2517	4957	13260	12720
210	≥100000	2940	37770	66550	≥100000	43260	≥100000	≥100000	≥100000
211	≥100000	14680	8034	12240	18720	10400	16940	20220	29830
212	15590	1349	880	2831	6449	3124	8356	10070	17370
213	≥100000	5573	4252	6194	7252	4198	16840	20540	17690
214	≥100000	12550	16350	28800	34560	9588	60030	95150	81100
215	≥100000	17000	8948	26070	23480	17750	33970	47090	57470
216	≥100000	17890	2571	13750	41050	6302	30890	59030	83190
217	64450	5159	7568	8986	11330	9878	13980	11610	19530
218	65930	2844	6534	14830	23180	6879	28910	≥100000	84810
219	65290	8833	4777	16210	13130	5652	15020	18130	20180
220	10820	6067	8672	6749	6309	8246	5570	6699	7473
221	586	556	191	271	313	498	284	308	231
222	≥100000	18230	31250	17790	26890	8984	35880	70090	52900

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
223	21110	930	665	1357	1801	1189	5601	6870	8654
224	64760	8476	4018	8455	7111	11710	6285	4834	9675
225	21660	6241	9389	14900	9898	8121	16590	23510	26140
226	6070	14070	51930						
227	1242	2430	3056			2718	3386		
228	147	148	224	1212	202	1019	2698	465	822
229	85340	3121	2117			4724	36850		
230	38750	7987	9849	11260	19660	10640	28440	35510	23350
231	97900	24560	8681	52100	31620	29610	49370	61490	62320
232	11920	7781	9993	17340	19370	13600	19190	17970	25900
233	6699	4635	5563	2647	7451	6154	4303	7383	5348
234	2022	1603	1846	2302	1764	1622	2640	1979	2587
235	2660	1700	2870	2152	2011	1650	2653	2714	3356
236	2331	623	3352	3395	897	2043	3497	2462	4439
237	9560	7612	9743	5337	8916	7594	4362	8292	6382
238	≥100000	19350	9182						
239	8653	4934	4812	1978	2212	1608	1830	1640	2673
240	1138	1550	777	586	492	597	478	350	498
241	17150	13610	8624						
242	8032	7632	12950	8192	6226	6956	11010	7859	13620
243	25360	2187	1056	1049	1808	1146	3320	2963	3585
244	18210	3574	3095	1848	3061	2823	5138	4856	5077
245	2991	11710	9831						
246	6414	22140	11260						
247	429	1827	2555	2108	2152	2682	1585	1182	2058
248	6807	9778	10530						
249	7856	1287	424	981	742	979	1061	1280	808
250	7315	3408	3992	3927	3799	6839	3579	3513	5313
251	6831	3870	14580	6125	5753	6401	3841	3784	6246
252	11	17	27	5	8	17	7	6	9
253	67330	4353	4082	3032	3589	2408	6002	14090	7718
254	2839	10830	7908						
255	6227	11010	15130						
256	2416	4536	8144	4627	5308	4048	4031	3796	6017
257	2432	3793	6914	5493	5219	4004	4026	3957	6028
258	320	858	1183	2066	1014	1381	3249	4383	4614
259	158	380	769	1521	649	825	2208	3299	3181
260	61	204	455	294	419	591	864	1173	1062
261	1606	3984	2606	5743	2317	2392	7099	9609	10650
262	960	1790	1663				1534		

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
263	1981	4033	3038	4936	3554	4408	9086	10960	12120
264	8160	13570	9856						
265	5309	2735	1923	3019	2505	3311	2458	2384	3188
266	6061	5255	13860						
267	4369	1712	1719	2496	2074	2253	1565	1367	2430
268	11350	6442	8884						
269	1909	1000	1056	1052	725	608	1063	1494	1826
270	2627	2095	7593			2834	4194		
271	2429	2444	7693				3001		
272	194	130	120	138	132	141	116	134	144
273	5150	2309	5202				3068		
274	375	867	2762				14700		
275	1656	9053	7165				24340		
276	212	303	1215				3219		
277	765	1801	4911				5287		
278	801	1985	1860				3673		
279	34330	3388	3624						
280	≥100000	≥100000	≥100000	≥100000	≥100000	9859	≥100000	≥100000	≥100000
281	213	170	81	59	67	75	61	125	51
282	30	15	18	16	15	16	15	18	17
283	97	90	129	97	91	77	113	157	142
284	38	41	58	46	45	44	46	54	50
285	976	864	350	367	359	426	323	447	293
286	313	521	674	370	407	410	608	498	555
287	8169	225	225	648	590	321	838	423	1158
288	53	67	78	95	82	68	89	71	113
289	5610	807	754	607	520	407	818	960	1071
290	582	171	176	183	147	207	276	236	290
291	140	277	439	229	192	161	269	209	218
292	21	61	180	97	26	88	68	55	77
293	10	4	5	5	6	6	6	7	5
294	9	9	15	13	12	13	14	16	14
295	2454	948	593	1801	2385	1896	2851	2873	3259
296	4	≤2	≤2						
297	54	≤2	9						
298	1516	133	99						
299	3	≤2	≤2						
300	≤2	≤2	≤2						
301	≤2	≤2	≤2						
302	≤2	≤2	≤2						

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
303	≤2	≤2	≤2						
304	≤2	≤2	≤2						
305	25	6	14						
306	7	4	4						
307	≤2	≤2	≤2						
308	6	4	10						
309	4	≤2	3						
310	8	≤2	≤2						
311	≤2	≤2	≤2						
312	388	254	203	156	172	212	202	242	280
313	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
314	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
315	≤2	≤2	≤2	≤2	≤2	≤2	≤2	3	≤2
316	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
317	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
318	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
319	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
320	3	≤2	3	≤2	≤2	≤2	≤2	≤2	≤2
321	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
322	≤2	≤2	≤2			≤2	≤2		
323	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
324	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
325	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
326	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
327	≤2	≤2	≤2						
328	9	6	18			9	9		
329	6602	1784	3379			2618	1029		
330	≤2	≤2	≤2			≤2	≤2		
331	≤2	≤2	≤2						
332	≤2	≤2	3						
333	≤2	≤2	5						
334	1480	699	738						
335	7827	≥100000	84490						
336	≤2	≤2	≤2						
337	3	3	5						
338	≤2	3	4						
339	≤2	≤2	≤2						
340	≤2	≤2	≤2						
341	≤2	3	≤2						
342	3	≤2	≤2						

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
343	≤2	≤2	≤2						
344	138	83	94						
345	5	3	4						
346	≤2	≤2	≤2						
347	3	3	3						
348	6	3	≤2						
349	20	4	7						
350	30	8	8						
351	13	15	11						
352	≤2	≤2	≤2						
353	≤2	≤2	≤2						
354	≤2	≤2	≤2						
355	≤2	≤2	≤2						
356	≤2	≤2	≤2						
357	≤2	≤2	≤2						
358	≤2	≤2	≤2						
359	≤2	≤2	≤2						
360	5	≤2	≤2						
361	≤2	≤2	≤2						
362	3	3	4						
363	201	57	10						
364	≤2	≤2	≤2						
365	≤2	≤2	≤2						
366	3	3	9						
367	≤2	≤2	≤2						
368	4	24	11						
369	5	3	4						
370	11	≤2	5						
371	7	≤2	5						
372	56	5	13						
373	5	≤2	≤2						
374	≤2	9	15						
375	44	8	9						
376	16	3	4						
377	≤2	3	12						
378	104	14	25						
379	111	14	34			21	26		
380	275	51	71			54	18		
381	23	11	21			16	5		
382	9	≤2	3						

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
383	13	3	8						
384	38	12	32						
385	≤2	≤2	≤2						
386	7	5	6						
387	124	130	125	128	113	96	106	130	153
388	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2	≤2
389	≤2	≤2	3	≤2	≤2	≤2	≤2	≤2	≤2
390	≤2	≤2	≤2						
391	≤2	≤2	≤2						
392	≤2	3	3						
393	≤2	≤2	≤2						
394	≤2	≤2	≤2						
395	≤2	≤2	≤2						
396	≤2	3	3						
397	≤2	≤2	≤2						
398	≤2	≤2	≤2						
399	≤2	≤2	≤2						
400	≤2	≤2	≤2						
401	≤2	≤2	≤2						
402	≤2	≤2	≤2						
403	6	≤2	≤2						
404	≤2	≤2	≤2						
405	≤2	≤2	≤2						
406	4	5	11						
407	≤2	≤2	≤2						
408	≤2	≤2	≤2						
409	≤2	≤2	≤2						
410	≤2	≤2	≤2						
411	≤2	≤2	≤2						
412	≤2	≤2	≤2						
413	≤2	≤2	3						
414	≤2	≤2	4						
415	≤2	40	3						
416	≤2	≤2	≤2						
417	≤2	≤2	≤2			≤2	≤2		
418	≤2	≤2	3						
419	3	3	8						
420	3	≤2	4						
421	3	≤2	≤2						
422	7	≤2	5						

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
423	≤2	≤2	≤2						
424	3	4	8						
425	≤2	≤2	≤2						
426	≤2	≤2	≤2						
427	≤2	≤2	≤2						
428	≤2	≤2	≤2						
429	2456	4438	8253						
430	6452	4764	8774	6824	7717	7825	8049	5493	8858
431	9624	15880	34430	19620	19670	17850	19720	13300	22220
432	1139	1930	3036	2267	2405	2413	2476	1675	2808
433	8780	10030	15370						
434	2203	3209	4510	5619	3523	3480	5130	6601	9266
435	3886	5440	6857	4911	5636	4839	4452	2062	6096
436	798	652	331	204	217	271	193	212	173
437	1432	2681	2764	1359	904	1401	715	754	897
438	238	239	99	109	106	130	95	117	87
439	7966	5785	2833	2145	2258	2528	2035	2435	1905
440	510	844	1722	758	690	550	714	767	940
441	3	≤2	≤2						
442	≤2	≤2	≤2						
443	53010	4206	6379	8474	6309	8200	18790	22220	32610
444	5	≤2	≤2						
445	4	≤2	≤2						
446	4	≤2	4						
447	1100	744	964	665	587	608	557	578	752
448	87	54	61	59	49	53	53	62	60
449	8394	3659	4382	5620	4163	3604	4072	5528	6403
450	250	238	344	356	276	235	335	481	388
451	2577	2856	4173	3123	2061	1902	2271	1994	3814
452	4	≤2	≤2						
453	274	569	1119	559	459	484	467	503	679
454	105	191	421	176	167	157	163	200	213
455	6352	5153	4506	5987	8171	8469	11720	13070	11620
456	48800	10680	6371						
457	31	6	10						
458	15	39	172	97	28	75	53	46	67
459	537	766	1006	815	821	822	688	586	793
460	2322	1469	548	760	759	916	693	763	664
461	≤2	≤2	≤2						
462	880	350	418	321	311	430	493	393	567

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
463	6494	3064	1362	1549	1401	2145	2402	1908	1685
464	986	469	513	507	355	459	661	506	717
465	15640	6097	10060						
466	2323	1656	2255	3312	2135	2313	2684	3579	3508
467	915	651	1015	968	1136	1110	1477	1800	1648
468	2876	2311	2902	2807	2482	2406	3018	4191	5109
469	127	105	149	180	146	135	196	256	231
470	406	355	503	347	341	348	475	565	663
471	309	427	1072	332	391	459	362	319	451
472	6	16	18						
473	11	8	14	8	9	9	10	11	11
474	8598	1751	3628	2953	3452	2386	6166	5974	6350
475	8546	1455	2621	3676	2748	2749	4600	7516	8141
476	≤2	≤2	4						
477	≤2	≤2	≤2						
478	≤2	≤2	5						
479	5	4	12						
480	38	7	6						
481	4	4	7						
482	≤2	≤2	3						
483	≤2	≤2	≤2						
484	23	28	48						
485	9	≤2	3						
486	336	170	186						
487	14	5	6						
488	22	27	51						
489	221	151	310						
490	≤2	≤2	3						
491	4	4	6						
492	84	15	14						
493	130	12	9						
494	3	≤2	≤2						
495	8	≤2	7						
496	24	11	6						
497	13	3	≤2						
498	5	3	3						
499	27	8	6						
500	235	104	103						
501	606	169	176						
502	638	457	607						

Ex. No.	G12D	G12V	G12R	G12A	G12S	G12C	WT	G13D	Q61H
503	305	82	124						
504	≤2	≤2	≤2						
505	≤2	≤2	≤2						
506	≤2	≤2	≤2						
507	≤2	≤2	4						
508	5	12	14						
509	6	6	12						
510	10	8	9						
511	≤2	≤2	≤2						
512	5	5	8						
513	≤2	≤2	3						
514	≤2	≤2	≤2						
515	≤2	≤2	≤2						
516									
517	≤2	3	6						
518	≤2	≤2	≤2						
519	≤2	≤2	≤2						
520	692	614	1749						
521	4	≤2	3						
522	292	390	759						
523	166	129	217						

EXAMPLE B: Inhibition of KRas Phosphorylation of ERK

by Exemplary Compounds of Formula (I)

[00001318] This Example illustrates that exemplary compounds of the present invention inhibit the phosphorylation of ERK downstream of KRas WT, G12C, G12D, G12R, G12S, G12V, G13D, Q61H.

[00001319] AsPC-1 (G12D, ATCC CRL-1682), A549 (G12S, ATCC CCL-185), HCT116 (G13D, ATCC CCL-247) cells were grown in DMEM medium supplemented with 10% fetal bovine serum and Penicillin/Streptomycin. NCI-H358 (G12C, ATCC CRL-5807), NCI-H460 (Q61H, ATCC HTB-117), NCI-H727 (G12V, ATCC CRL-5815), MKN1 (WTdep, JCRB JCRB0252), PSN-1 (G12R, ATCC CRM-CRL-3211) cells were grown in RPMI medium supplemented with 10% fetal bovine serum, 10mM HEPES, 10mM Sodium Pyruvate, and

Penicillin/Streptomycin. Cells were plated in black well clear bottom tissue culture treated 96 well plates (Corning, 3904) at a density of 20,000 cells/well and allowed to attach for 12-14 hours. Diluted compounds were then added in a final concentration of 0.5% DMSO. After 3 hours, 50 µL of 4.0% formaldehyde was added and the plates incubated at room temperature for 20 minutes. The plates were then dumped and permeabilized with 150 µL of ice cold 100% methanol for 10 minutes. Non-specific antibody binding to the plates was blocked using 100 µL Odyssey blocking buffer (LI-COR Biosciences, 927-60010) for 1 hour at room temperature.

[00001320] The amount of phospho-ERK was determined using an antibody specific for the phosphorylated form of ERK and compared to the amount of GAPDH. Primary antibodies used for the detection were added as follows: Phospho-ERK(Cell Signaling CS-9101) diluted 1:500 and GAPDH (Millipore MAB374) diluted 1:5000 in Odyssey blocking buffer + 0.05%Tween 20. The plates were incubated overnight at 4 C. The plates were washed 3X with 150uL PBS + 0.1% Tween 20.

[00001321] Secondary antibodies used to visualize primary antibodies were added as follows: Goat Anti-Rabbit-800 (LI-COR, 926-32211) and Goat Anti-Mouse-680 (LI-COR, 926-68070) diluted 1:800 both in Odyssey blocking buffer +0.05% TweenN_20, and were incubated for 1 hour at room temperature. The plates were washed 3X with 150uL PBS +0.1% Tween 20. Plates were imaged dry on a Li-COR Odyssey CLX plate reader.

[00001322] The phospho-ERK (Thr202/Tyr204) signal was normalized to the GAPDH signal for each well and percent of DMSO control values were calculated. IC50 values were generated using a 4-parameter fit of the dose response curve.

Table 3

Inhibition (IC_{50}, nM) of KRas-mediated Phosphorylation of ERK, Exemplary Compounds of Formula (I)

Ex. No.	AsPC-1	H727	MKN1	PSN1	A549	H460	HCT116	H358
4	519							
5	9	29	3	681	11	12	23	6
7	802	530	32	3592	1094	416	627	199
10	297							

Ex. No.	AsPC-1	H727	MKN1	PSN1	A549	H460	HCT116	H358
12	497							
13	18	44	10	773	140	13	42	11
14	847	4585	1383	≥10000	≥10000	≥10000	1594	725
15	731	≥10000	1255	≥10000	3635	≥10000	5157	495
16	654	≥10000	802	≥10000	1758	113	2176	1179
24	1684	4725	406	3687	≥10000	2825	1368	454
27	45	232	20	2924	300	33	88	22
28	78	308	24	≥10000	523	54	153	60
36	1544	3387	1181	≥10000	2151	557	1610	1127
37	2213	≥10000	1674	≥10000	8947	≥10000	4358	1719
38	966	1187	143	7617	3274	573	814	324
51	586	7226	873	≥10000	2638	≥10000	3719	715
57	82	115	22	4143	668	119	1075	50
58	24	242	23	1312	455	111	1457	24
59	577	769	107	≥10000	3562	296	1272	176
60	3892	1265	230	≥10000	5533	1031	3600	389
61	306	1109	46	≥10000	699	550	518	162
62	591	178	7	≥10000	87	154	410	24
63	15	56	5	1043	139	38	44	27
71	4734	2237	140	≥10000	≥10000	2170	1947	361
73	3494	756	23	≥10000	191	176	128	98
74	72	355	8	≥10000	63	55	662	10
82	18	65	10	1741	25	180	216	3
132	104	≥10000	27	≥10000	≥10000	206	≥10000	131
133	156	612	171	≥10000	55	49	650	41
134	≥10000	≥10000	178	≥10000	1489	666	≥10000	48
135	2061	≥10000	53	≥10000	2458	647	3272	37
136	351	181	7	≥10000	19	75	631	4
137	≥10000	≥10000	≥10000	≥10000	≥10000	≥10000	≥10000	2035
138	≥10000	≥10000	≥10000	≥10000	≥10000	≥10000	≥10000	≥10000
139	≥10000	≥10000	307	≥10000	≥10000	7514	≥10000	115
140	27	28	2		1	9	17	11
141	210	≥10000	282	≥10000	875	1108	≥10000	88
142	2866	≥10000	45	≥10000	≥10000	212	6959	78
143	≥10000	≥10000	300	≥10000	≥10000	≥10000	≥10000	527
145	≥10000	≥10000	258	≥10000	≥10000	847	≥10000	379
146	22	≥10000	22	2526	1057	204	1003	15
147	≥10000	≥10000	65	≥10000	1951	383	≥10000	79
148	105	260	76	3785	550	68	≥10000	15
149	9	206	16	1758	83	71	292	10

Ex. No.	AsPC-1	H727	MKN1	PSN1	A549	H460	HCT116	H358
150	435	626	13	≥10000	45	362	996	4
152	≥10000	≥10000	6290	≥10000	≥10000	≥10000	≥10000	≥10000
153	233	500				306		
154		≥10000		≥10000	8447		1455	840
155	1724	2666	196	≥10000	≥10000	399	≥10000	329
156	335	189	14	≥10000	33	141	323	10
157	751	4725	31	≥10000	448	585	893	31
159	≥10000	1997	133	≥10000	4070	1508	2112	139
160	5520	727	146	≥10000	974	471	1597	149
162	4526	4166				6769		
164	≥10000	≥10000	207	≥10000	≥10000	6825	≥10000	602
165	≥10000	≥10000	412	≥10000	≥10000	2923	≥10000	701
166		≥10000		≥10000	≥10000		≥10000	328
167	6763	1252				623		
168		1805		≥10000	≥10000		821	156
169	2892	1807				931		
170		3395		≥10000	≥10000		2353	470
171		≥10000		≥10000	≥10000		≥10000	≥10000
172	481	192				79		
173	180	304				145		
174		≥10000		≥10000	4952		≥10000	1288
175	1725	756				675		
176	≥10000	3954	701	≥10000	≥10000	3511	≥10000	1254
177		≥10000		≥10000	764		1699	54
178	606	2110				728		
179	785	675				274		
180	205	623				113		
181	1543	1613				584		
182	547	355				157		
183	399	720				137		
184	66	201				30		
185	306	481				424		
186	1593	1062				592		
187	470	550				133		
188	2067	2136				478		
189	1241	1426				377		
190	189	272				62		
191	665	714				230		
192	90	191				51		
193	94	133	4		12	44	63	41

Ex. No.	AsPC-1	H727	MKN1	PSN1	A549	H460	HCT116	H358
194	92	89	7			65		
196	361	452				48		
197	144	841	11			293		
198	2686	1754				803		
199	1318	798				314		
200	47	67	3		3	22	21	13
201	91	110	2			100		
202	60	159	3			74		
203	8014	1266				758		
206	6961	3330				3384		
296	2195	2085				619		
297	3430	450				660		
298	≥10000	≥10000	2712	≥10000	≥10000	≥10000	≥10000	5008
299		126		≥10000	108		333	29
300	251	372	37			71		
301	216	520	15			416		
302	152	360	5			193		
303	3288	3687				4115		
304	1369	2576				804		
305	≥10000	≥10000				≥10000		
306	405	461				306		
307	117	215				11		
308	489	627				372		
309	176	272				59		
310	≥10000	3372				3793		
311	738	2603				501		
386	1185	1024				299		
388		16				16		
441	119	139				70		
442	134	234				124		
444	2438	1736				656		
445	1615	2934				1189		
446	3669	2500				2194		
452	182	793				154		
457		3954				9409		
459	9936	≥10000				≥10000		
473		320				325		

EXAMPLE C

Inhibition of KRas Phosphorylation of ERK (HTRF) by Exemplary Compounds of Formula (I)

Cisbio HTRF Advanced pERK Assay Catalog #64AERPEH

- Cells: MKN1, PSN1

  Procedure:

  • Day 1: Seed 6,000 cells/well -25 µl/well in 384-well white solid bottom plate; RPM1_10% FBS. Incubate overnight at 37°C/5% CO2.

  • Day 2: Echo transfer 25 nl of 10 mM compound 10 point dilution at 1:3 (Cf=10 uM) and incubate for 3 hour at 37°C/5% CO2.

  • Add 8.5 µl/well of 4X Lysis Buffer/25X Blocking reagent (do not dump media) and incubate for 30 min at room temperature on shaker.

  • Add conjugate mixture of 4.25 ul/well 1X-pERK-D2 and 1X-pERK-K diluted in Detection Buffer for a total of 8.5 µl/well.

  • Incubate for 4 hours at room temperature covered.

  • Read HTRF using ClarioStar

- Cells: ASPC1, H727, A549, H460, HCT116, H358

  Culture/Assay media: RPMI-1640 + 10% FBS

  Procedure:

  Cell seeding

  1. To harvest cells from flask using 0.05% Trypsin/EDTA solution. Add 10 mL of media to stop trypsinizing. Pipette the cells into a conical bottom 50 mL centrifuge tube and centrifuge 5 min x 1000 rpm.

  2. Re-suspend the cell pellet in media, take a cell count, and then adjust the cell density using fresh media.

  3. Seed 6,000 cells into cell culture plate with 50 µL media. The

  4. Incubate cell plate overnight in a 37 °C, 5% CO2 incubator.

  Compound titrations

  1. Use Tecan to complete the compound addition. Compounds start from 10 uM top, 3-fold dilution, and 10 doses. The final DMSO concentration is 0.8%. Dispensed 0.2 uM Trametinib as Min control.

  2. Incubate cell plate for 3 hrs in the incubator.

  Detection with cisbio pERK HTRF kit

1. Dilute 1 volume of 4x lysis buffer with 3 volumes of deionized water. Then, add 100X the blocking reagent. Keep lysis buffer on the ice.
2. At the end of the compound treatment, flick-off the media.
3. Add 35 µL of lysis buffer per well using a Multidrop Combi. Then place on a plate agitator shaking at 300 rpm at 4 °C for 40 mins.
4. Make up the HTRF antibody buffer. For each assay plate, mix 50 µL of d2-conjugate antibody with 950 µL of detection buffer. Similarly, mix 50 µL of Cryptate antibody with 950 µL of detection buffer. Then mix the two diluted antibodies together.
5. Dispense 3.4 µL the antibody buffer to wells of an empty assay plate. Seal the plate and centrifuge plate 30 sec x 1000 rpm.
6. At the end of the 4 °C lysis, centrifuge the lysate plates 3 mins x 1500 rpm.
7. Use the Bravo to transfer 13.6 µL of lysate from cell culture plate to assay plate. Then incubate assay plate for 2 hrs at room temperature.
8. At the end of incubation, read plate on the Envision after centrifuging plate 30 sec x 1000 rpm.

Table 4

Inhibition (HTRF IC_{50} nM) of KRas -mediated Phosphorylation of ERK by Exemplary Compounds of Formula (I)

Ex. No.	AsPC-1	H727	MKN1	PSN1	A549	H460	HCT116	H358
4		943	113	≥10000				
5	2	6	1	364	2	5	10	2
10			13	3341				
12			26	≥10000				
13	4	13	5	1090	43	27	33	
16			275	≥10000				
25	≥10000	≥10000						
26	≥10000	≥10000						
28	20	159	21	7246	156	101	155	
57	32	55			175	119	2011	
58	75	45				69	179	
61	126	250				336	1644	
63	4	28			19	21	63	
71	2103	1924						

Ex. No.	AsPC-1	H727	MKN1	PSN1	A549	H460	HCT116	H358
74	65	84				151	336	
82	15	16	6	2325	15	22	106	10
132	623	912						
133	144	246					360	
136	318	52				83	243	
140	7	4	1	922	2	4	7	
141	641	2134						
146	92	400				327	607	
148	59	110				132	2209	
149	25	111			290	180	276	
150	66	12				167	115	
156	125	72				143	349	
162			187	≥10000				
167			3	≥10000				
169			100	≥10000				
172	96	26	41	≥10000		32	170	6
173	56	263	42	5542		176	454	95
175			39	≥10000				
178			49	≥10000				
179			10	6955				
180			10	6905				
181			139	6701				
182			5	6896				
183			2	4234				
184	7	90	7	1228	44	39	91	15
185			17	4837				
186			108	≥10000				
187			38	≥10000				
188			77	≥10000				
189			29	5543				
190			11	4990				
191			15	5847				
192			4	7340				
193	8	36	7	3789	44	42	82	
194	20	34	3	1346	63	55	686	4
196	97	167	39	314		33	114	31
197	57	348	23	≥10000		183	620	112
198			183	≥10000				
199			7	≥10000				
200	3	6	2	1010	5	5	11	

Ex. No.	AsPC-1	H727	MKN1	PSN1	A549	H460	HCT116	H358
201	23	42	15	2388	223	118	187	12
202	7	33	5	2493	9	28	47	4
203			35	3711				
206			34	≥10000				
296			53	≥10000				
297			154	≥10000				
300	38	89	7	1378				14
301	54	199	14	3928		216	456	46
302	31	82	3	2533	65	120	179	26
303			358	≥10000				
304			29	≥10000				
306			57	6803				
307	58	85	5	106		12	33	15
308	155	278	40	≥10000			284	
309	54	37	2	8328	113	57	26	26
311			15	≥10000				
313	13	28	7	2120	38	38	42	4
314	9	21	3	407	19	14	21	2
315	20	20	5	1959	28	34	24	5
316	8	32	1	2040	51	69	30	9
317	40	46	20	3931	197	287	98	985
318	133	69	13	877		65	60	
319	433	808	120	≥10000			6358	
320	115	82	10	5182		100	65	
321	16	30	3	7757	99	71	39	7
322	484	255	32	9090			300	
323	8	8	2	600	19	11	22	2
324	35	22	3	1442	95	99	61	14
325	49	45	17	5152		61	56	164
326	10	26	8	≥10000	138	253	274	18
327	23	98	14	6687	238	206	381	10
328	1719		271	≥10000			1278	
329	≥20000		≥10000	≥10000			≥20000	
330	29	61	8	305	84	52	57	11
331	4	35	1		6	16	27	3
332	6	31	2	710	13	22	48	3
333	603	2108	425	≥10000			9189	
336	32	129	4	4120	75	162	208	59
337	514	395	49	1843			438	
338	695	377	24	2878			487	

Ex. No.	AsPC-1	H727	MKN1	PSN1	A549	H460	HCT116	H358
339	48	72	12	≥10000	557	991	826	95
340	39	149	26	≥10000	353	373	999	55
341	472	1036	86	≥10000			1320	
342	23	46	4	2245	167	203	470	62
343	60	24	4	5928	91	128	128	7
344	3407	4815	796	≥10000				
345	83	138	13	8785		82	296	20
346	99	113	11	7392		166	133	57
347	118	73	98	4458		127	195	
348	275	273	7	≥10000			245	
349	475	1856	149	≥10000			2251	
350	241	334	209	≥10000			797	
351	228	551	48	7176	185	182	346	
352	948	1267	46	≥10000				
353	7	34	24	4807	80	149	396	19
354	14	48	14	≥10000	65	304	623	17
355	8	30	17	6773	140	270	471	16
356	16	63	40	9301	232	458	767	20
357	13	63	71	7478	576	805	1354	27
358	12	15	4	9767	44	131	167	3
359	345	782	60	4095			576	
360	49	62	2	9186		54	140	19
361	8	49	3	6817	122	85	231	17
362	73	313	37	5130	629	404	763	113
363	≥10000	≥10000	≥10000	≥10000				
364	121	578	26	≥10000	219	117	645	
365	17	24	10	2856	11	17	77	6
366	60	185	11	5531		108	321	61
367	505	244	58	≥10000			375	
368	4683	617	191	≥10000				
369	1341	471	294	≥10000				
370	2985	516	330	≥10000				
371	≥20000		387	≥10000			9341	
372			660	≥10000				
373	4066		103	≥10000			3841	
374	9382						≥10000	
376	≥10000						6491	
377	≥10000	7783	2298	≥10000				
378	≥10000						≥10000	
379	≥20000		≥10000	≥10000			≥20000	

Ex. No.	AsPC-1	H727	MKN1	PSN1	A549	H460	HCT116	H358
380	≥20000		1103	≥10000			3215	
381	≥20000		282	≥10000			741	
382	≥10000	5899	781	≥10000				
383	≥10000						≥10000	
384	≥10000	≥10000						
385	≥10000	4648	421	≥10000				
386			44	2877				
388	14	5	8	409	18	21	9	1
389	268	970	95	≥10000			1090	
390	195	16	8	748	114	175	190	
391	61	74	12	3987		143	563	22
392	1184	1371	336	6019			2250	
393	68	24	8	449	133	110	68	20
394	158	368	46	≥10000	567	1072	1715	
395	477	1377	299	≥10000				
396	3075	7481	525	≥10000				
397	903	1000					1460	
398	25	26	7	6694	102	387	348	10
399	3	16	1	357	14	18	23	4
400	27	87	7	3538	62	41	113	9
401	162	253	82	9961			1146	
402	12	14	3	514	34	51	46	4
403	426	79	20	3815	96	182	487	
404	136	822	55	≥10000			1375	
405	238	114	45	6734	247	155	2214	
406	880	748	306	≥10000				
407	27	15	15	1333	27	26	41	3
408	721	570	351	≥10000				
409	398	593	94	≥10000			1176	
410	365	603	157	3146			602	
411	63	83	40	146		48	92	9
412	19	51	34	5981	242	413	586	11
413	479	408	33	2530			484	
414	1334	269	32	3475			514	
415	548	903	46	≥10000			2557	
416	141	83	3	1305		283	2194	
417	182	57	20	110		63	79	
418	25	32	3	596	74	52	60	11
419	71	154	14	3481		182	319	58
420	859	366	56	≥10000			1313	

Ex. No.	AsPC-1	H727	MKN1	PSN1	A549	H460	HCT116	H358
421	61	26	4	1498	39	73	70	16
422	430	112	26	1813		303	539	
423	556	2218	110	≥10000				
424	817	1300	95	2815				
425	42	37	5	921	54	99	73	12
426	652	1220	264	≥10000				
427	32	59	84	7684	379	878	916	52
428	339	425	28	3280	183		896	
441			6	2884				
442			9	2847				
444	1690	1161	37	≥10000	734	1559	1761	
445			8199	≥10000				
446			786	≥10000				
452	204	165	41	4084	224	639	1512	
461	1148	239	18	3759			172	
472	89	406	80	9295		414	1072	231
476	36	148	14	3592		99	275	35
477	61	456	67	≥10000	865	1571	2835	180
478	192	871	80	≥10000	1247	713	5434	
479	203	115	328	≥10000		987		
480	240	100	6	≥10000	215	47	111	
481	387	643	49	5411		827	3150	
482	546	128	26	≥10000	390	124		
483	890	339	83	≥10000		1589		
484	4859	3034	1059	≥10000				
485	6623	1221						
486	≥10000	≥10000						
487	≥10000	4993						
488	≥10000		≥10000	≥10000				
490	395	205	41	≥10000	298	305	368	
491	1705	1532	182	≥10000				
492	3519		254	≥10000				
493	≥10000		622	≥10000				
494	354	795	135	≥10000		982	2169	
495	1350	1821						
496	95	407	68	8288	261	245	525	117
497	987	503	43	≥10000				
498	47	64	13	≥10000	48	66	168	21
499	109	100	13	≥10000	145	162	474	
500	1103	1898	239	≥10000				

Ex. No.	AsPC-1	H727	MKN1	PSN1	A549	H460	HCT116	H358
501	2064	3234	225	≥10000				
502	2102	6458	1938	≥10000				
503	≥10000	≥10000	≥10000	≥10000				
504	4	6	8	4834	11	53	81	2
505	14	50	31	≥10000		327		16
506	302	2221	703	≥10000		8909	≥10000	
507	25	262	7	1952	345	179	341	40
508	1552	2191						
509	144	338	89	6139	211	206	314	
510	186	388	73	5103	515	397	954	
511	8	25	2	1041	23	27	45	6
512	55	80	14	2827	68	130	291	53
513	1313	869	221	≥10000				
514	15	19	5	859	20	60	30	11
515	35	19			36	19	24	7
516	9316	5686						
517	203	321	42	≥10000				
518	≥10000	9212						
519	≥10000	≥10000						
520	≥10000	≥10000						
521	≥10000	≥10000						
522	≥10000	≥10000						
523	≥10000	≥10000						

EXAMPLE D: Anti-Proliferative Activity of Pan-KRas Inhibitors Against Mutations That Confer Resistance To Adagrasib

[00001323] To test the anti-proliferative activity of a prototype pan KRas inhibitor against mutations that confer resistance to adagrasib, mouse 3T3 fibroblasts were transduced with retroviruses that expressed various engineered human KRas mutant constructs. Cells were selected with puromycin to select for cells that were successfully transduced by the retrovirus and plated in ultra-low attachment plates where cells grew as 3 dimensional cultures. Cells were treated with a serial dilution of MRTX849 or Example 5 and 50% inhibitory concentration (IC50) values were calculated (Table 5). Example 5 demonstrated activity against numerous codon 12 mutations

including the G12W mutation predicted to result from a single nucleotide substitution from the cysteine 12 codon.

Table 5

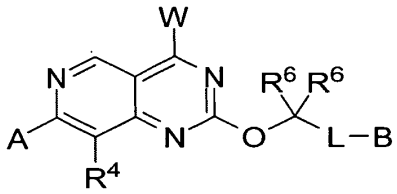
IC50 Values of the KRas G12C Inhibitor MRTX849 and the Pan KRas Inhibitor Example 5 in a 5-day Viability Assay in 3T3 Cells Engineered to Express MRTX849 Resistance Mutations

	MRTX849 (nM)	Example 5 (nM)
G12A	>3000	32
G12C	16.62	28.1
G12D	>3000	20.25
G12R	>3000	1742
G12V	>3000	94
G12W	>3000	50
G13D	>3000	610
Q61H	>3000	58

[00001324] While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

WHAT IS CLAIMED IS:

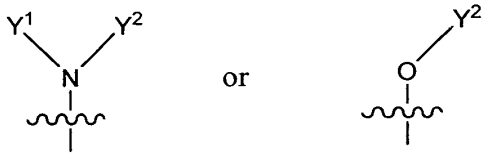
1. A compound of Formula (I):



Formula (I)

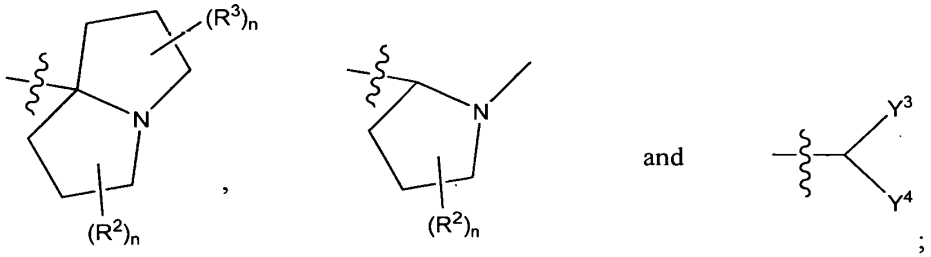
or a pharmaceutically acceptable salt thereof, wherein:

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:

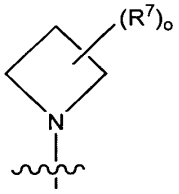


;

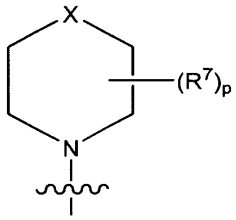
Y^1 is hydrogen, L-hydroxy optionally substituted with 1-4 R^8, L-alkoxy optionally substituted with 1-4 R^8, halogen, L-C3-C6 cycloalkyl optionally substituted with 1-4 R^9, L-heteroaryl optionally substituted with 1-4 R^8, L-aryl optionally substituted with 1-4 R^8, L-C(O)-NH_2, and L-heterocycle substituted 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:



or

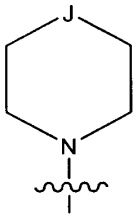


where X is selected from: a bond, -S-, -O-, -N< bound to a fused ring, -CH_2-, -CH_2-N-, -CH_2-N-CH_2-, -CH_2-CH_2-CH_2-, -CH_2-CH_2-, -O-CH_2- and -S-CH_2-;

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-, -CH_2-, -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, -$CH_2C(=O)N(R^5)_2$, -C3-C4 alkynyl$(NR^5)_2$, -$N(R^5)_2$, deuteroC2-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, HC(=O)-, -L-$OC(O)N(R^5)_2$, -CO_2R^5, or -$CO_2N(R^5)_2$;

each R^3 is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-$OC(O)N(R^5)_2$, -CO_2R^5, or -$CO_2N(R^5)_2$;

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 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), -$C(O)N(R^{10})_2$, -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 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(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;

each R^9 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)NH$_2$, -C(O)NH(C1-C3 alkyl), -C(O)N(C1-C3 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;

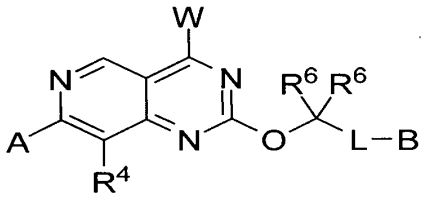
each L is independently a bond, -C1-C4 alkyl-, -C1-C4 alkyl-NH-, -NH-, -N(C1-C3 alkyl)- or cyclopropyl-CH$_2$-;

each n is 0-3;

o is 1-6; and

p is 1-8.

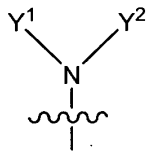
2. A compound of Formula (I):



Formula (IA)

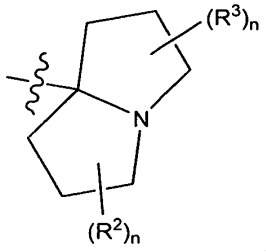
or a pharmaceutically acceptable salt thereof, wherein:

W is:



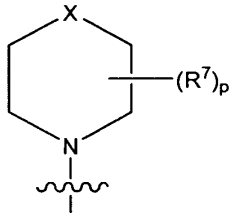
A is naphthyl optionally substituted with 1-4 R^1;

B is from :



;

Y^1 and Y^2 join to form:



where X is selected from: $-CH_2-$, $-CH_2-CH_2-$ and $-O-CH_2-$;

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, $-CH_2C(=O)N(R^5)_2$, -C3-C4 alkynyl$(NR^5)_2$, $-N(R^5)_2$, deuteroC2-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, HC(=O)-, -L-$OC(O)N(R^5)_2$, $-CO_2R^5$, or $-CO_2N(R^5)_2$;

each R^3 is independently hydrogen, hydroxy, halogen, cyano, C1-C3 alkyl, C1-C3 cyanoalkyl, C1-C3 hydroxyalkyl, HC(=O)-, -L-$OC(O)N(R^5)_2$, $-CO_2R^5$, or $-CO_2N(R^5)_2$;

each R^4 is independently hydrogen, halogen or C1 – C3 alkyl;

each R^5 is independently hydrogen or C1-C3 alkyl, or two R5 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 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(R^{10})$_2$, -NHC(O)H , -CN, aryl, -(CH_2)$_{1-2}$S(O)$_2$N(R^{10})$_2$, -NH-S(O)$_2$N(R^{10})$_2$, -O-S(O)$_2$N(R^{10})$_2$, S(O)$_2$$R^{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 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(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;

each R^9 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)NH_2, -C(O)NH(C1-C3 alkyl), -C(O)N(C1-C3 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-CH_2-;

each n is 0-3;

o is 1-6; and

p is 1-8.

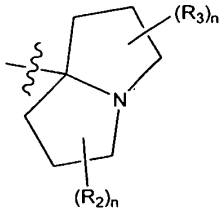
3. The compound or salt of claim 2, wherein each R1 is independently selected from halogen, hydroxy, C1-C3 alkoxy and C1-C4 alkyl.

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.

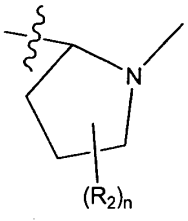
5. The compound or salt of claim 2, wherein each R7 is independently selected from hydrogen, C1-C4 alkyl, hydroxy, C1-C3 alkoxy, and wherein two R7 on non-adjacent atoms optionally join to form a 1-2 carbon bridge.

6. The compound or salt of claim 2, wherein each R6 is independently hydrogen or hydroxy.

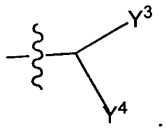
7. The compound or salt of claim 1, wherein B is:



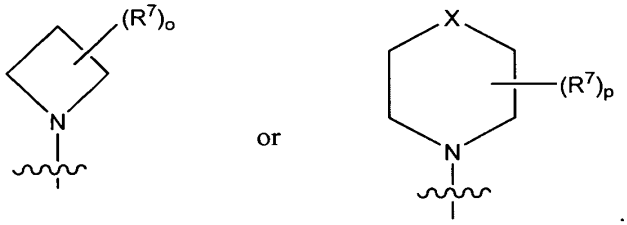
8. The compound or salt of claim 1, wherein B is:



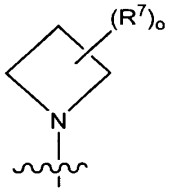
9. The compound or salt of claim 1, wherein B is:



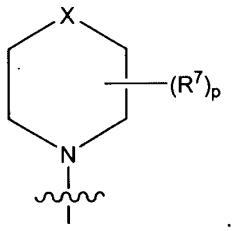
10. The compound or salt of any of claims 1-3, wherein Y^1 and Y^2 join to form:



11. The compound or salt of claim 4, wherein Y^1 and Y^2 join to form:



12. The compound or salt of claim 4, wherein Y^1 and Y^2 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 R^1 is C1-C4 alkyl.

18. The compound or salt of any of claims 1-6, wherein at least one R^1 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 R^1 is hydroxy.

21. The compound or salt of any of claims 1-6, wherein one R^2 is C1-C4 alkyl.

22. The compound or salt of any of claims 1-6, wherein at least one R^2 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 R^2 is hydroxy.

25. The compound or salt of any of claims 1-6, wherein at least one R^3 is C1-C4 alkyl.

26. The compound or salt of any of claims 1-6, wherein at least one R^3 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 R^3 is hydroxy.

29. The compound or salt of any of claims 1-6, wherein R^4 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 R^5 is C1-C4 alkyl.

32. The compound or salt of any of claims 1-6, wherein at least one R^5 is hydrogen.

33. The compound or salt of any of claims 1-6, wherein one or both R^6 are C1-C4 alkyl.

34. The compound or salt of any of claims 1-6, wherein one or both R^6 are hydrogen.

35. The compound or salt of any of claims 1-6, wherein two R^6 join to form C3-C6 cycloalkyl or heterocycle.

36. The compound or salt of any. of claims 1-6, wherein Y^1 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 Y^1 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 Y^1 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 Y^1 is L-heterocycle.

41. The compound or salt of claim 32, wherein the heterocycle is pyrrolidinone.

42. In certain embodiments of the invention Y^2 is hydrogen.

43. The compound or salt of any of claims 1-6, wherein Y^2 is C1-C4 alkyl;

44. The compound or salt of any of claims 1-6, wherein at least one R^8 is C1-C4 alkyl.

45. The compound or salt of any of claims 1-6, wherein at least one R^8 is hydroxy or C1-C3 alkyl-hydroxy.

46. The compound or salt of any of claims 1-6, wherein one or two R^8 are oxo (=O).

47. The compound or salt of any of claims 1-6, wherein at least one R^8 is aryl or heteroaryl.

48. The compound or salt of any of claims 1-6, wherein at least one R^8 is C(O)OH.

49. The compound or salt of any of claims 1-6, wherein at least one R^8 is $-C(O)NH_2$, -C(O)NH(C1-C3 alkyl) or $-C(O)N(C1\text{-}C3\ alkyl)_2$.

50. The compound or salt of any of claims 1-6, wherein at least one R^8 is $-NH_2$, -NH(C1-C3 alkyl); $-N(C1\text{-}C3\ alkyl)_2$.

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 $-C(O)NH_2$, -C(O)NH(C1-C3 alkyl) or $-C(O)N(C1\text{-}C3\ alkyl)_2$.

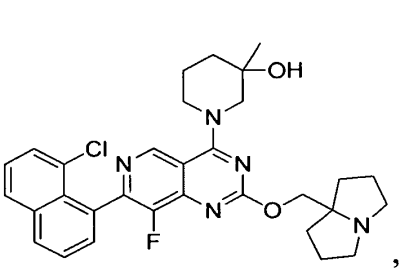
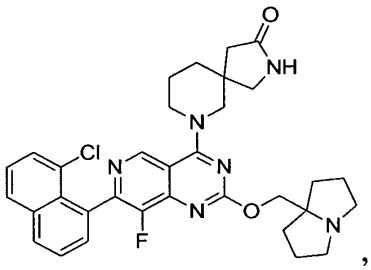
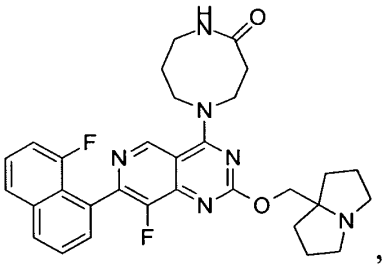
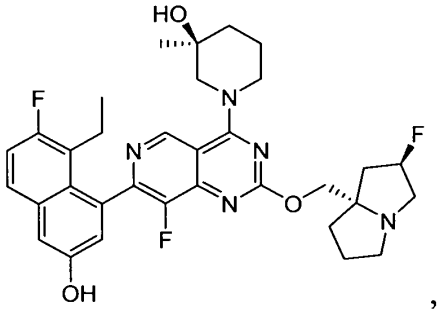
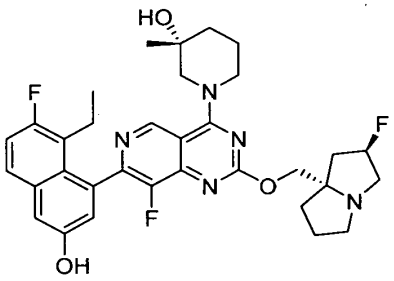
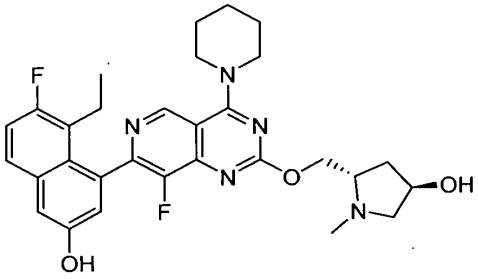
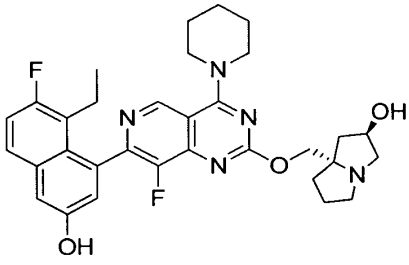
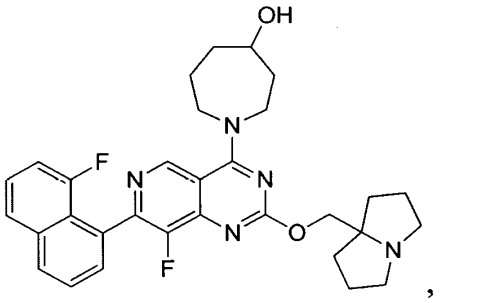
57. The compound or salt of any of claims 1-6, wherein Y^1 and Y^2 join to form piperidine, azepane, azocane, thiazepine, diazepane, oxazepane, azetidine, pyrrolidine, piperazine bound to a fused ring via nitrogen or thiomorpholine.

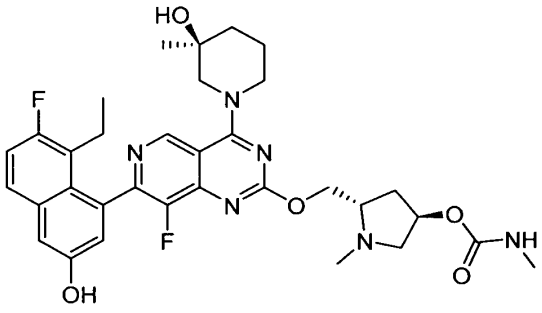
58. The compound or salt of any of claims 1-6, wherein two R^7 on the same atom join to form a spirocyclic ring selected from C3-C6 cycloalkyl and heterocycle, where said spirocyclic ring is optionally substituted with one or more substituents selected from oxo (=O), halogen, hydroxy, C1-C3 alkyl and -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: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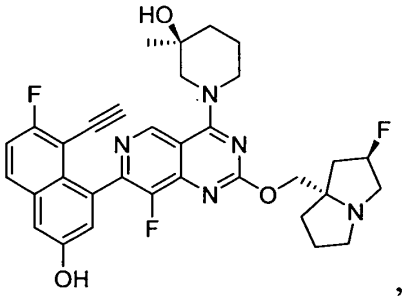
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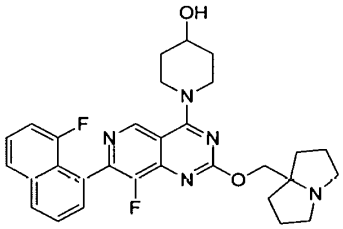
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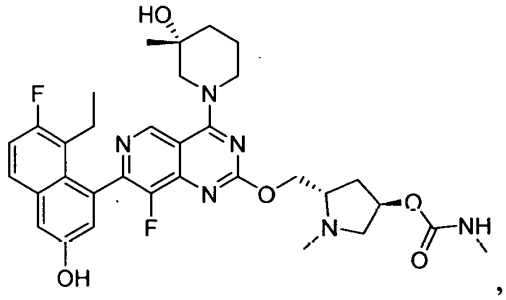
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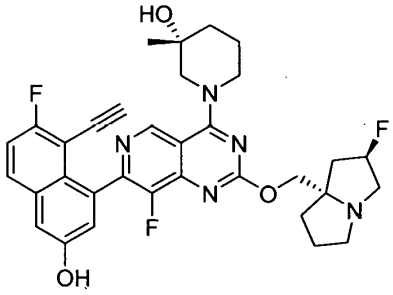
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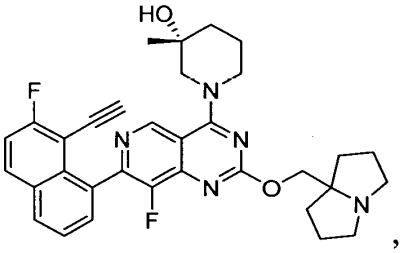
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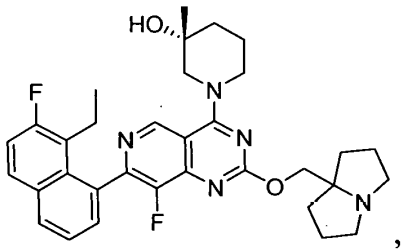
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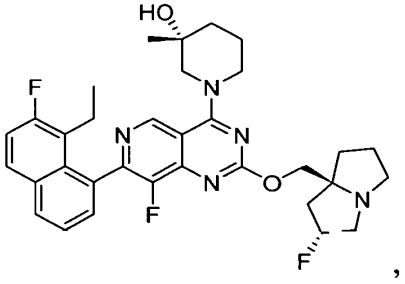
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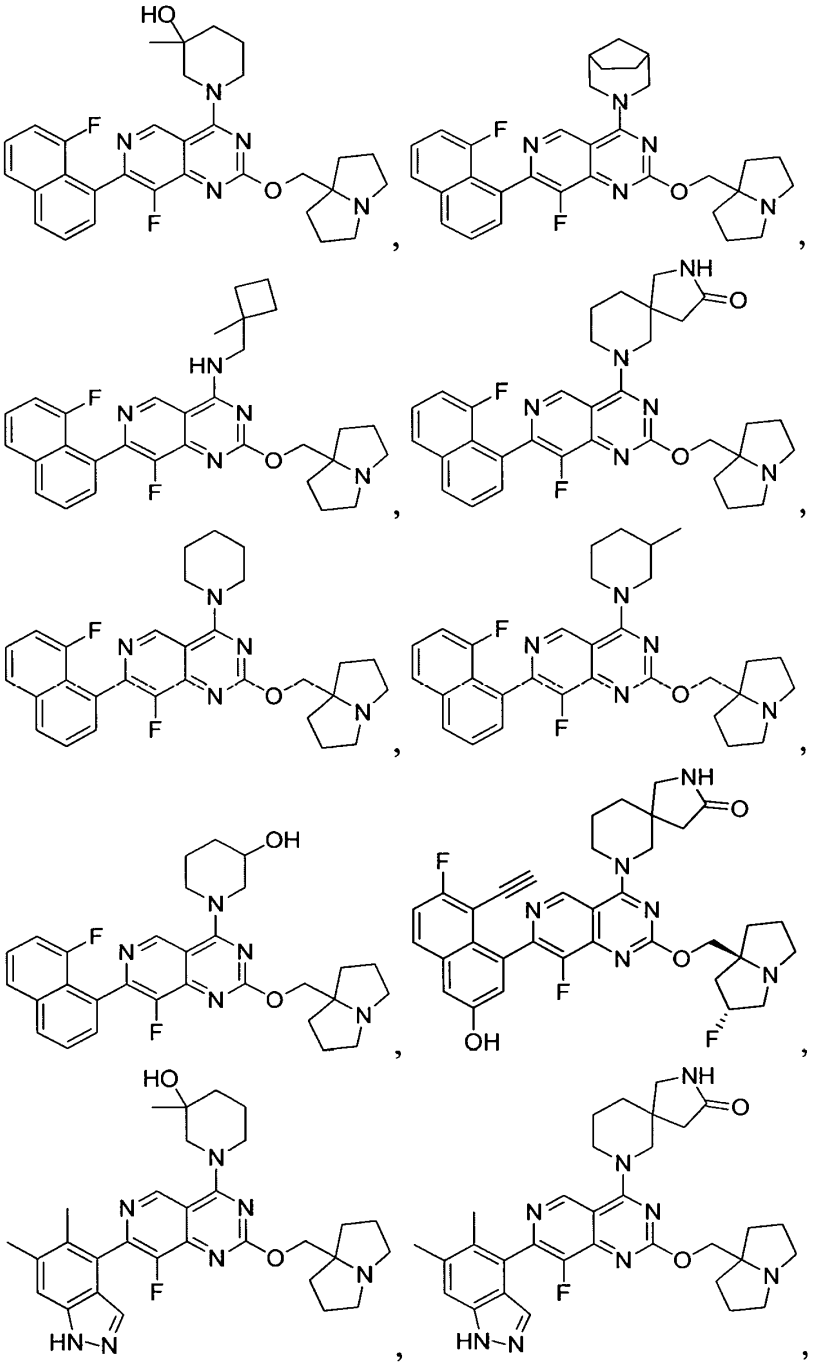

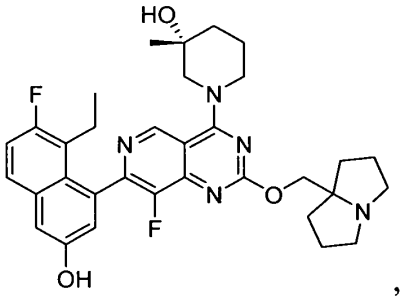
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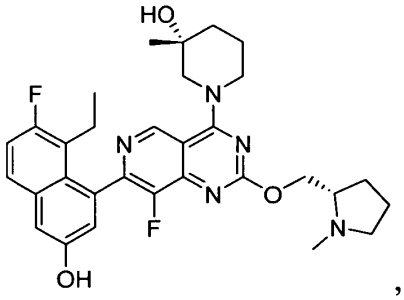
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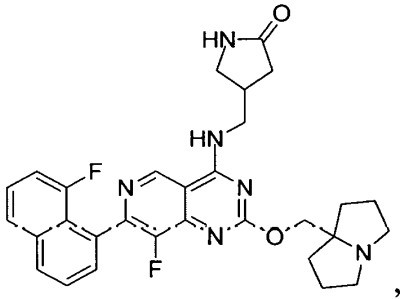
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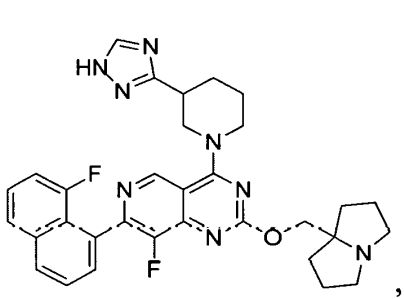
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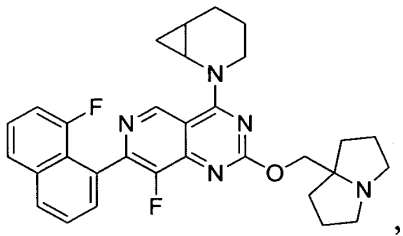
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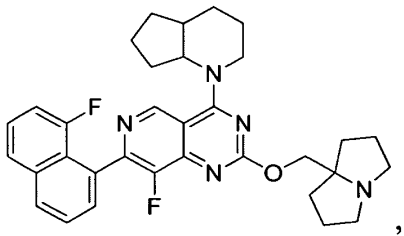
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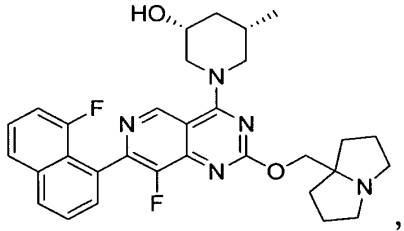
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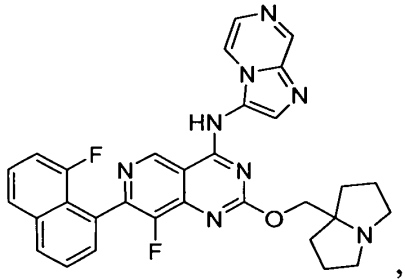
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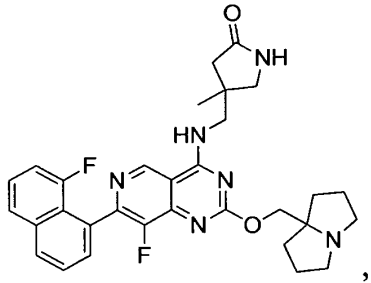
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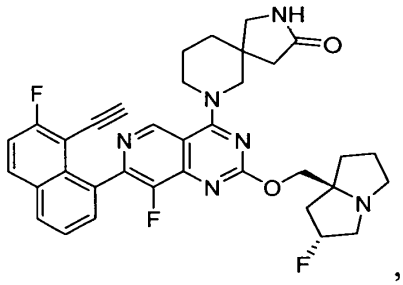
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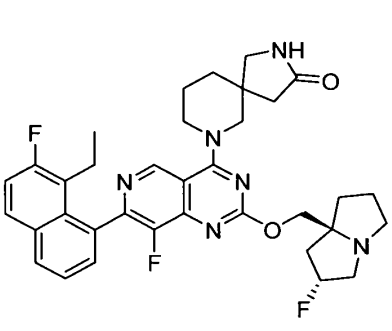
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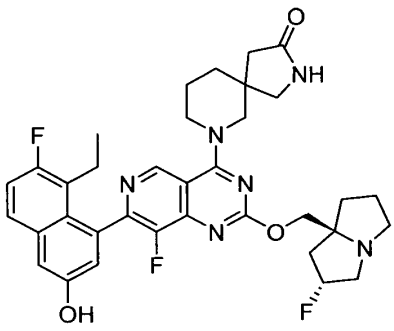
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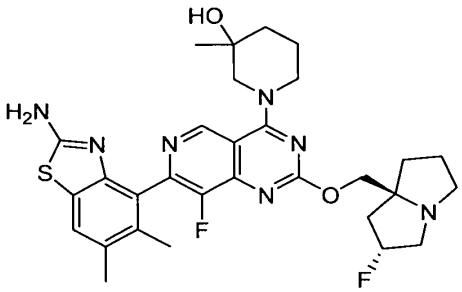
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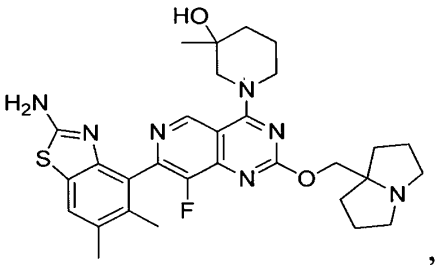
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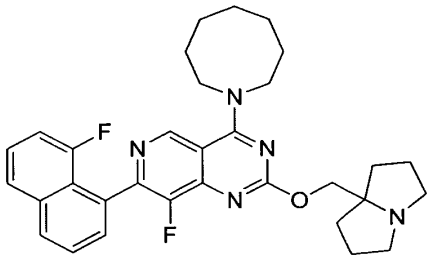
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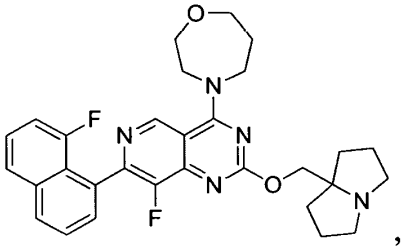
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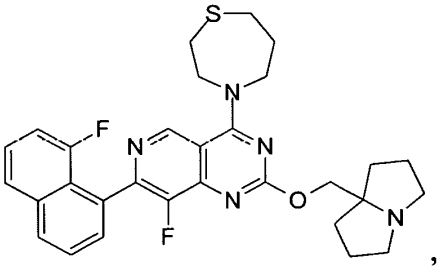
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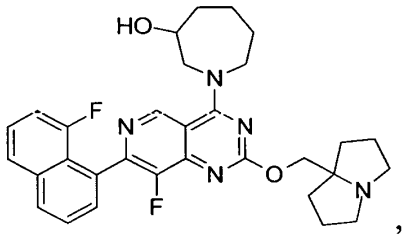
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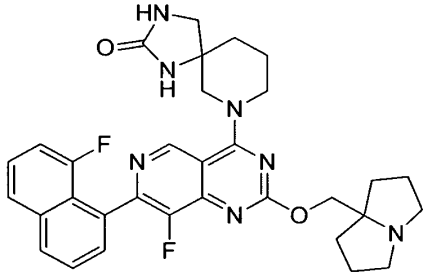
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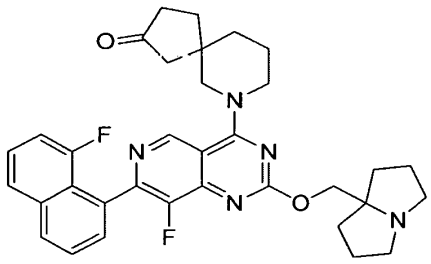
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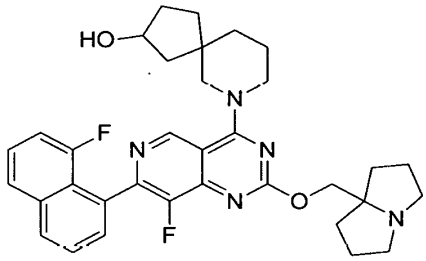
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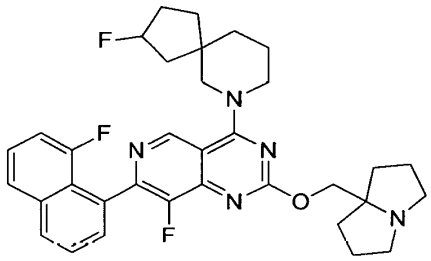
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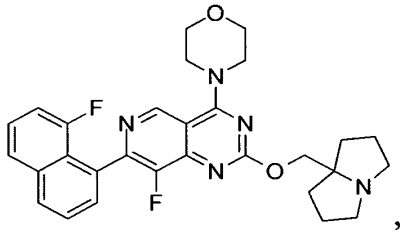
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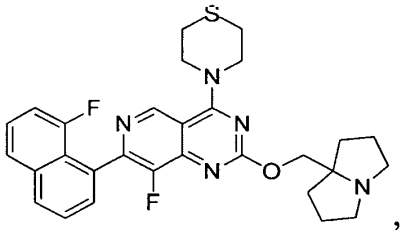
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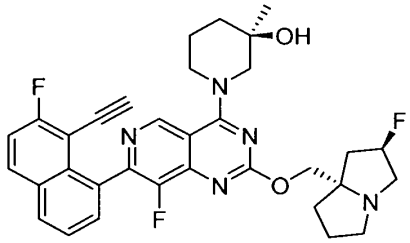
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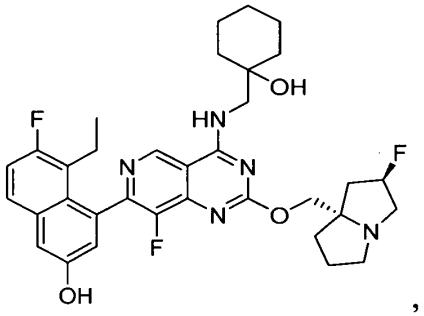
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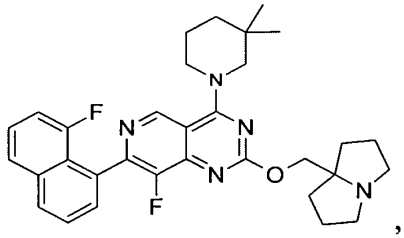
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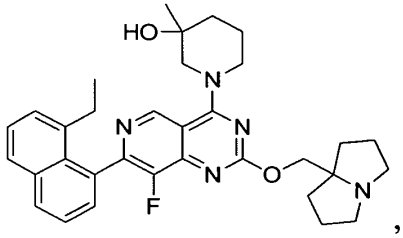
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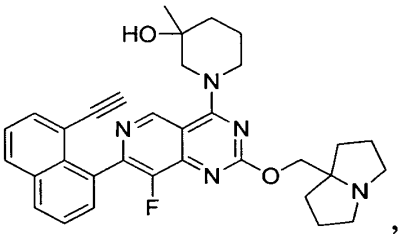
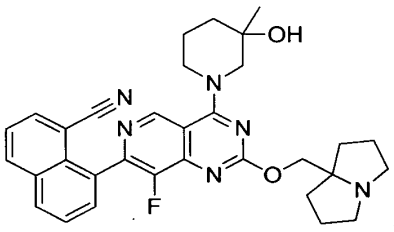
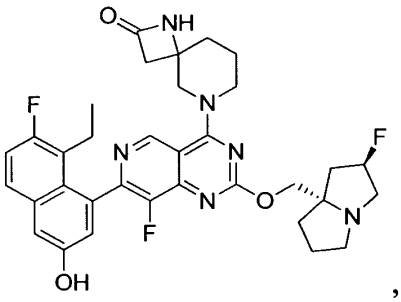
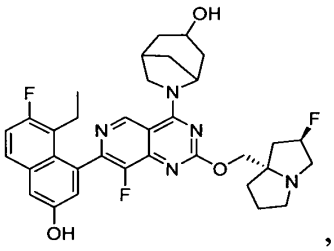
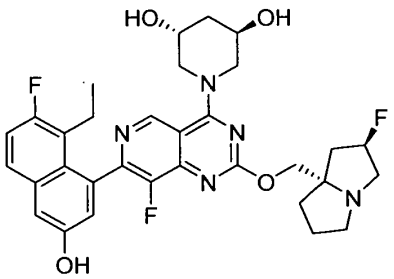
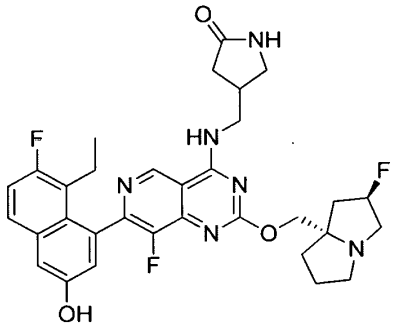
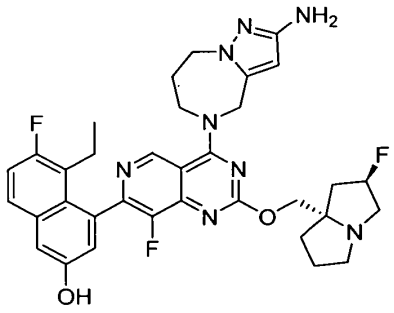
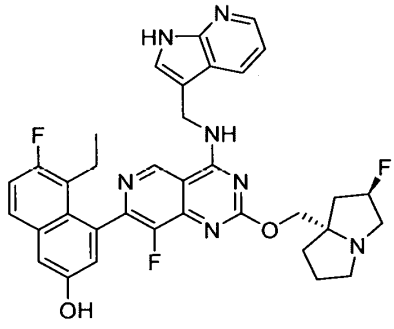

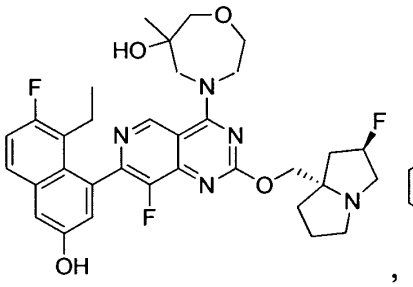
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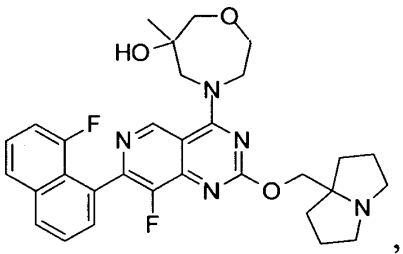
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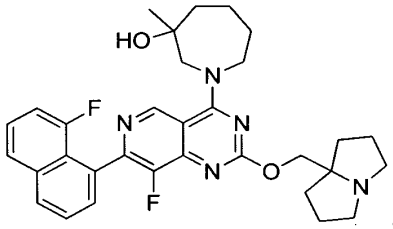
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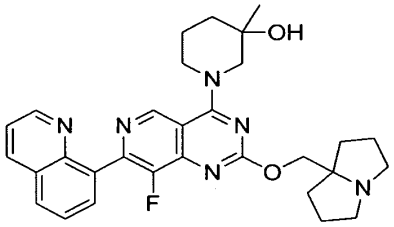
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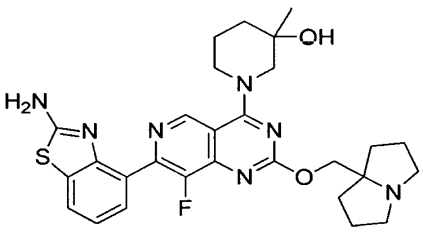
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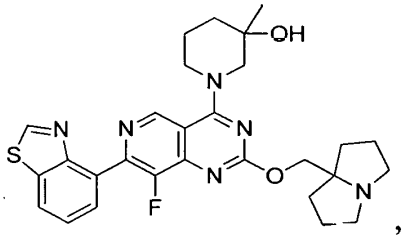
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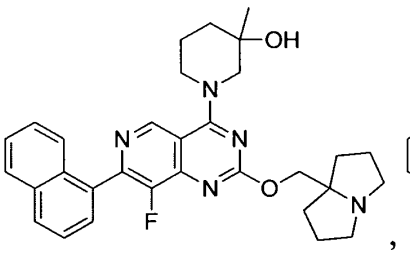
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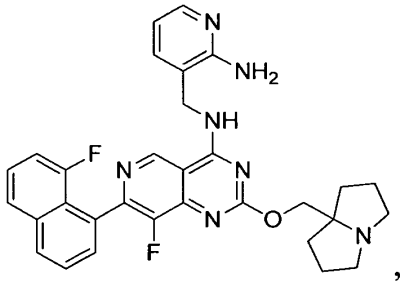
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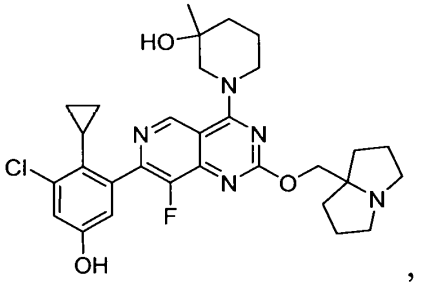
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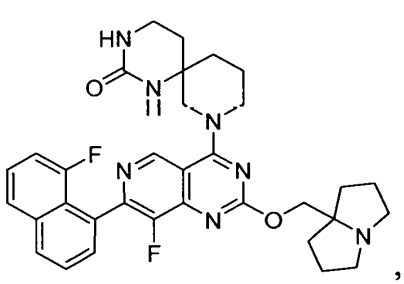

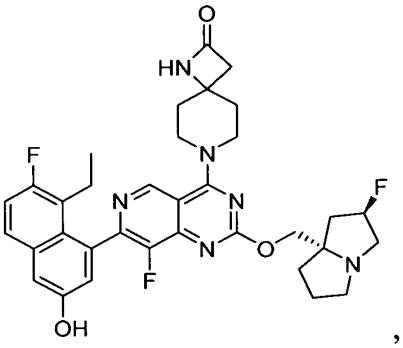
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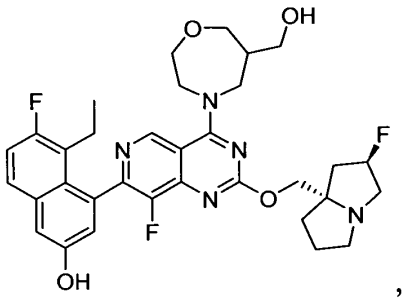
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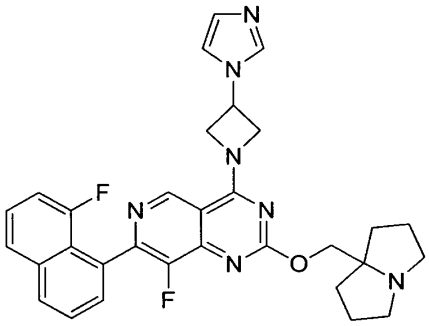
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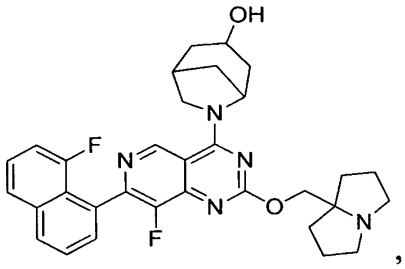
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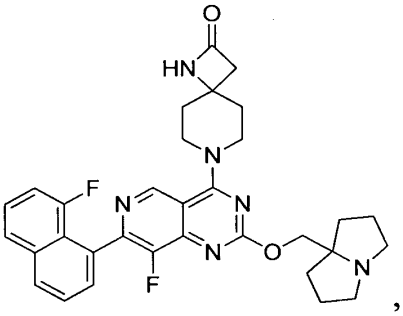
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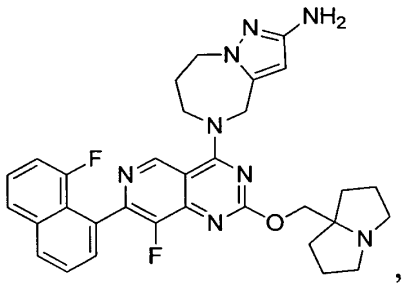
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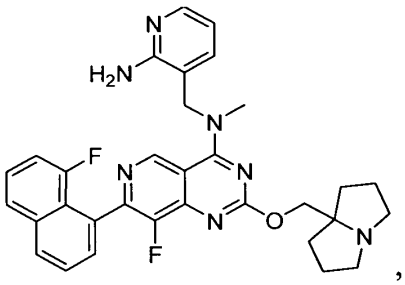
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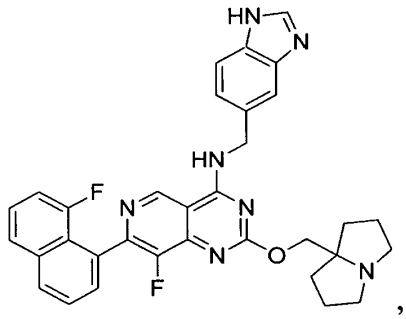
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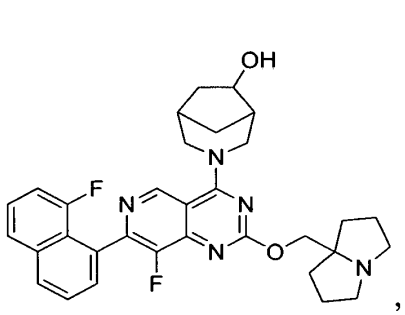
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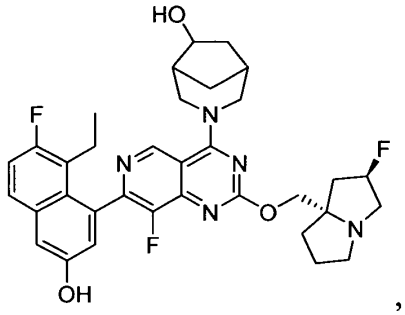
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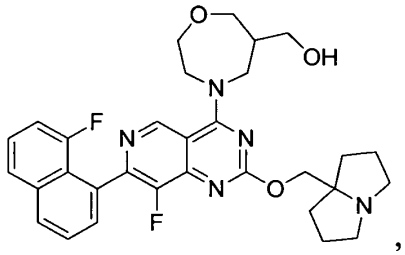
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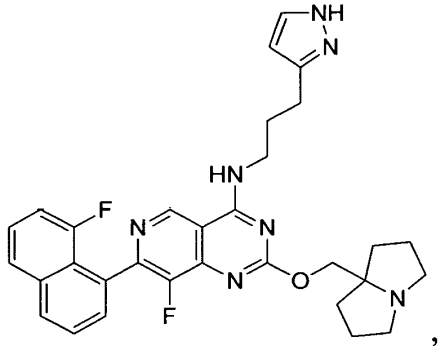
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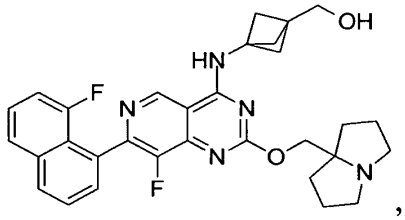
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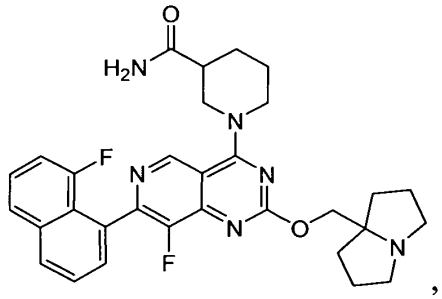
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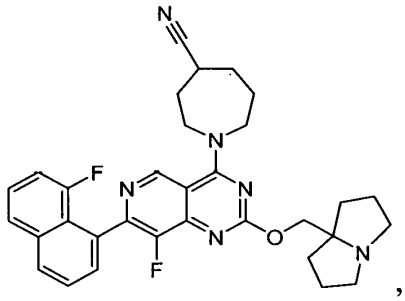
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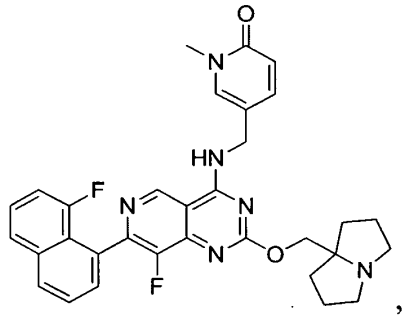
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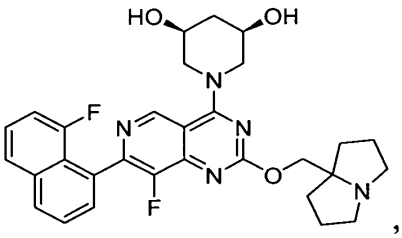
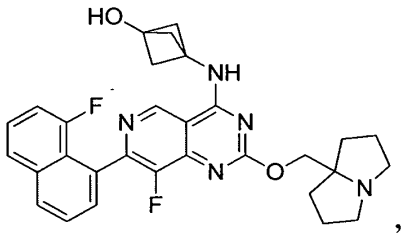
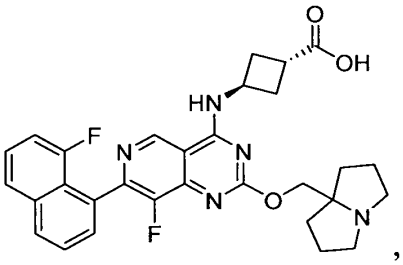
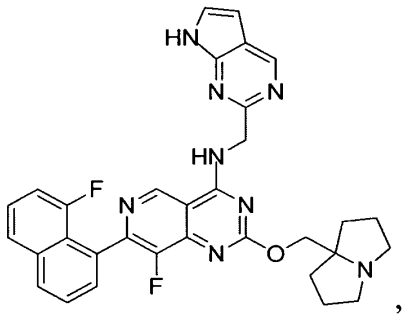
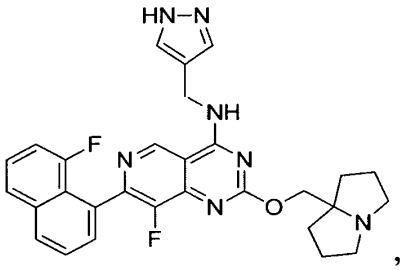
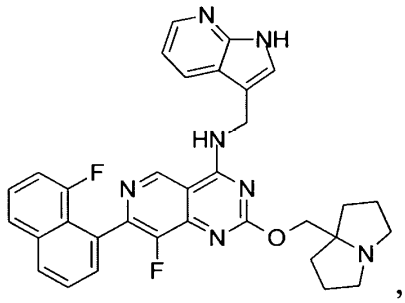
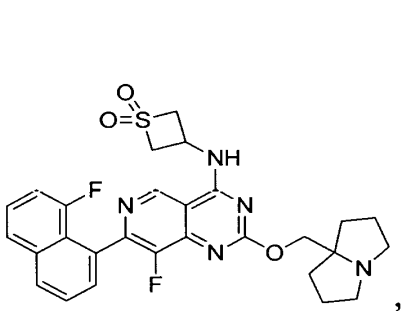
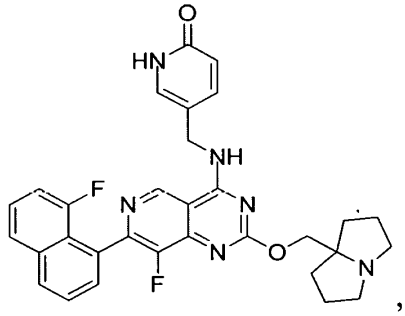
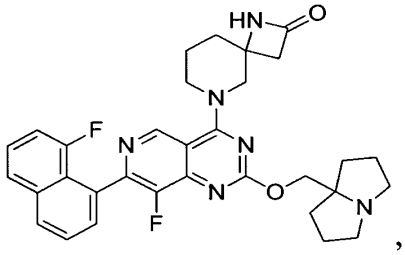
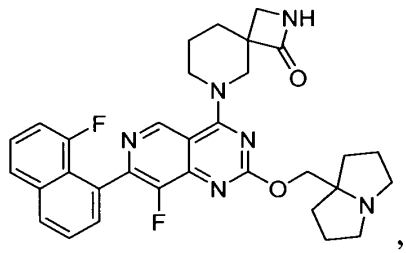

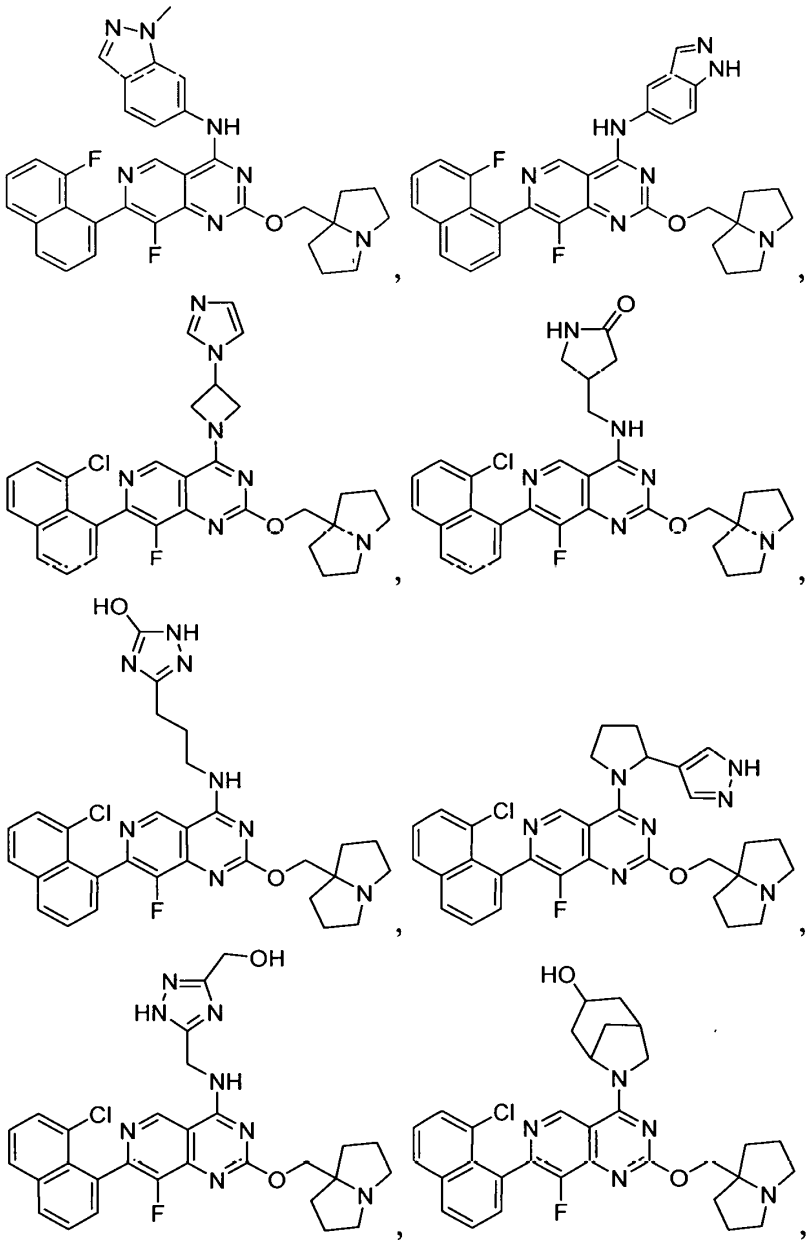

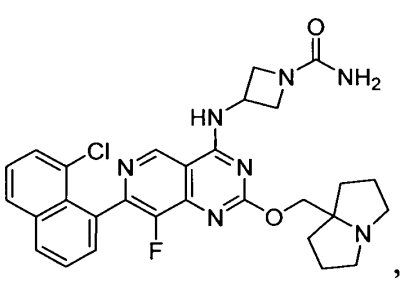
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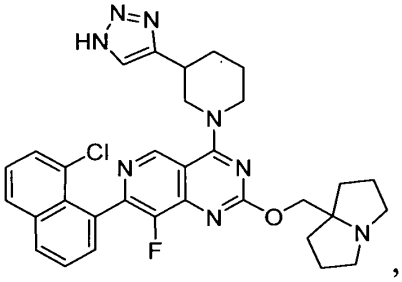
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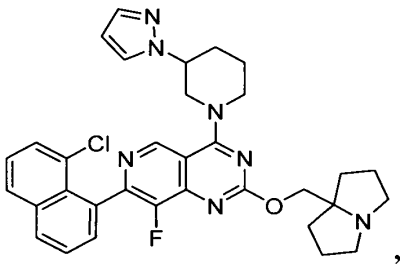
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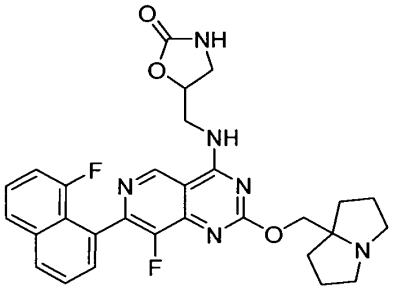
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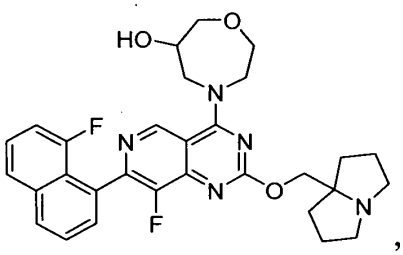
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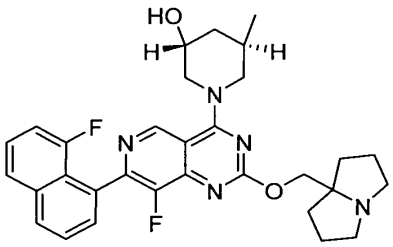
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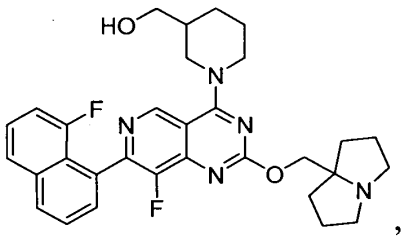
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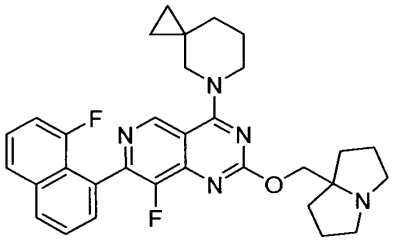
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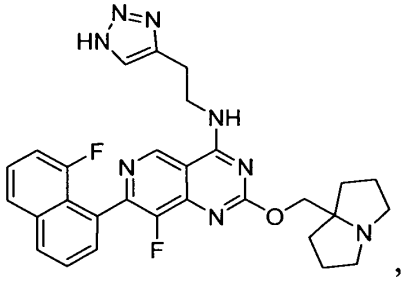
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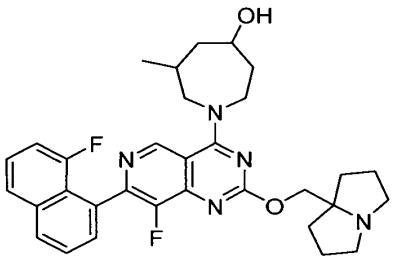
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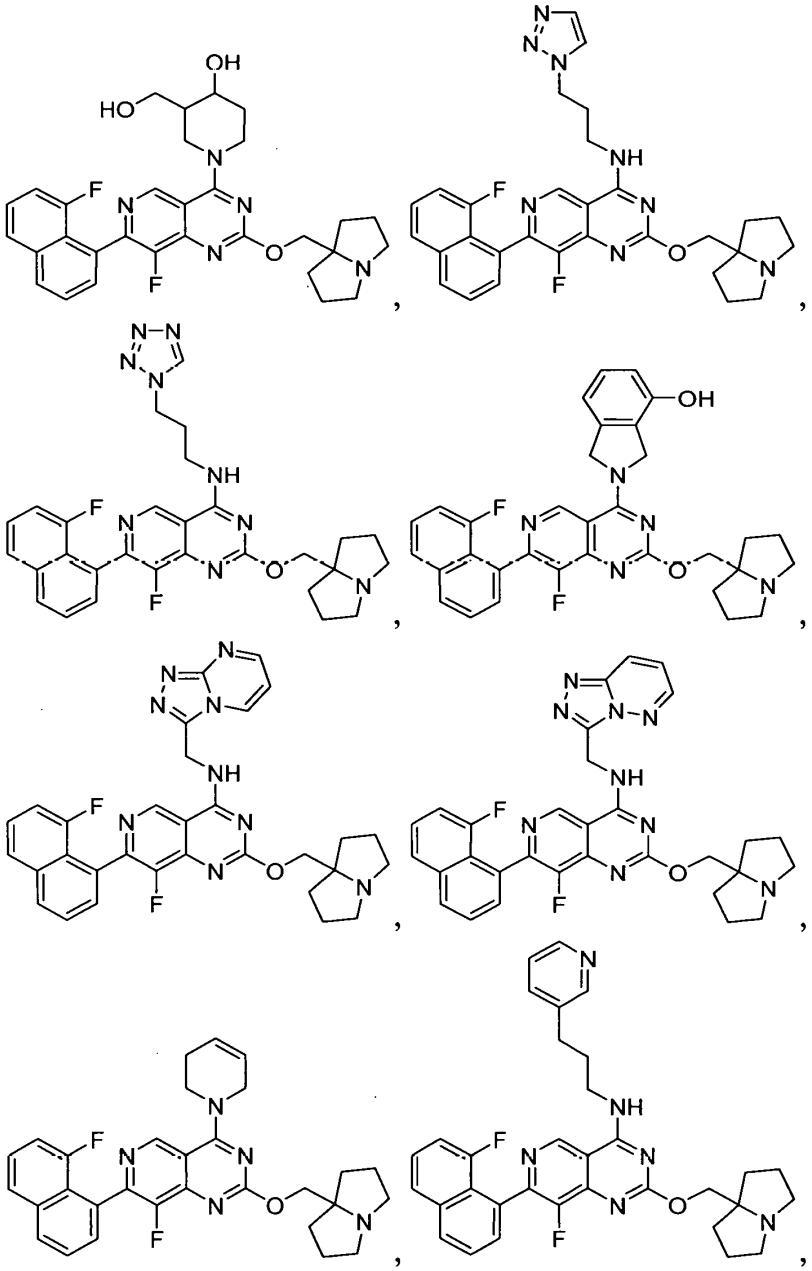

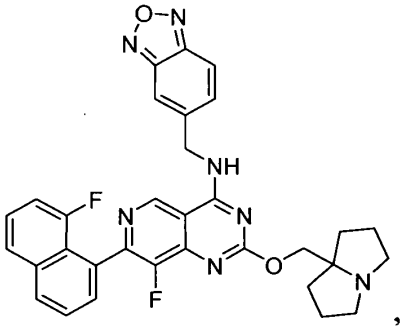
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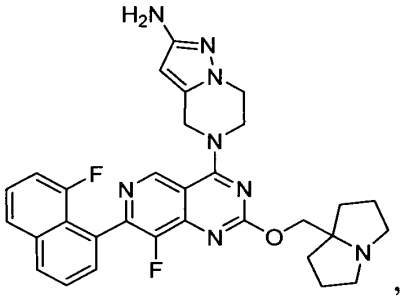
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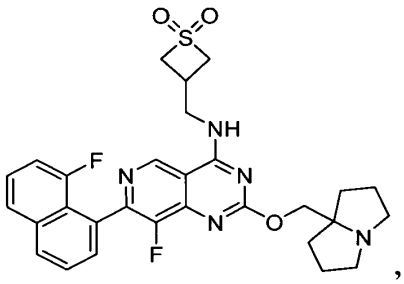
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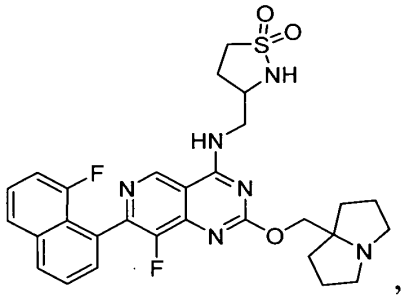
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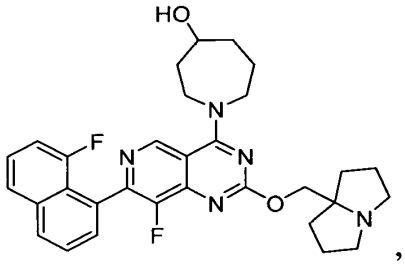
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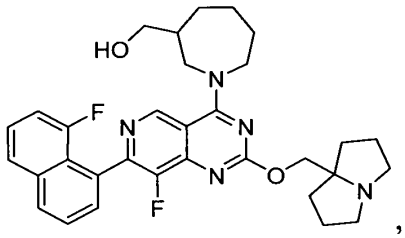
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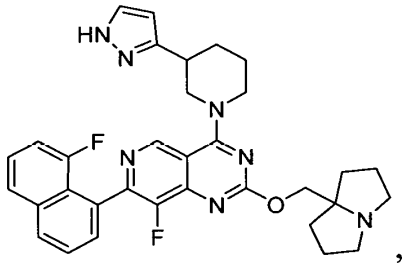
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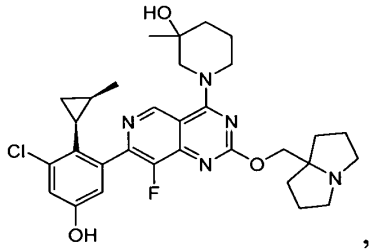
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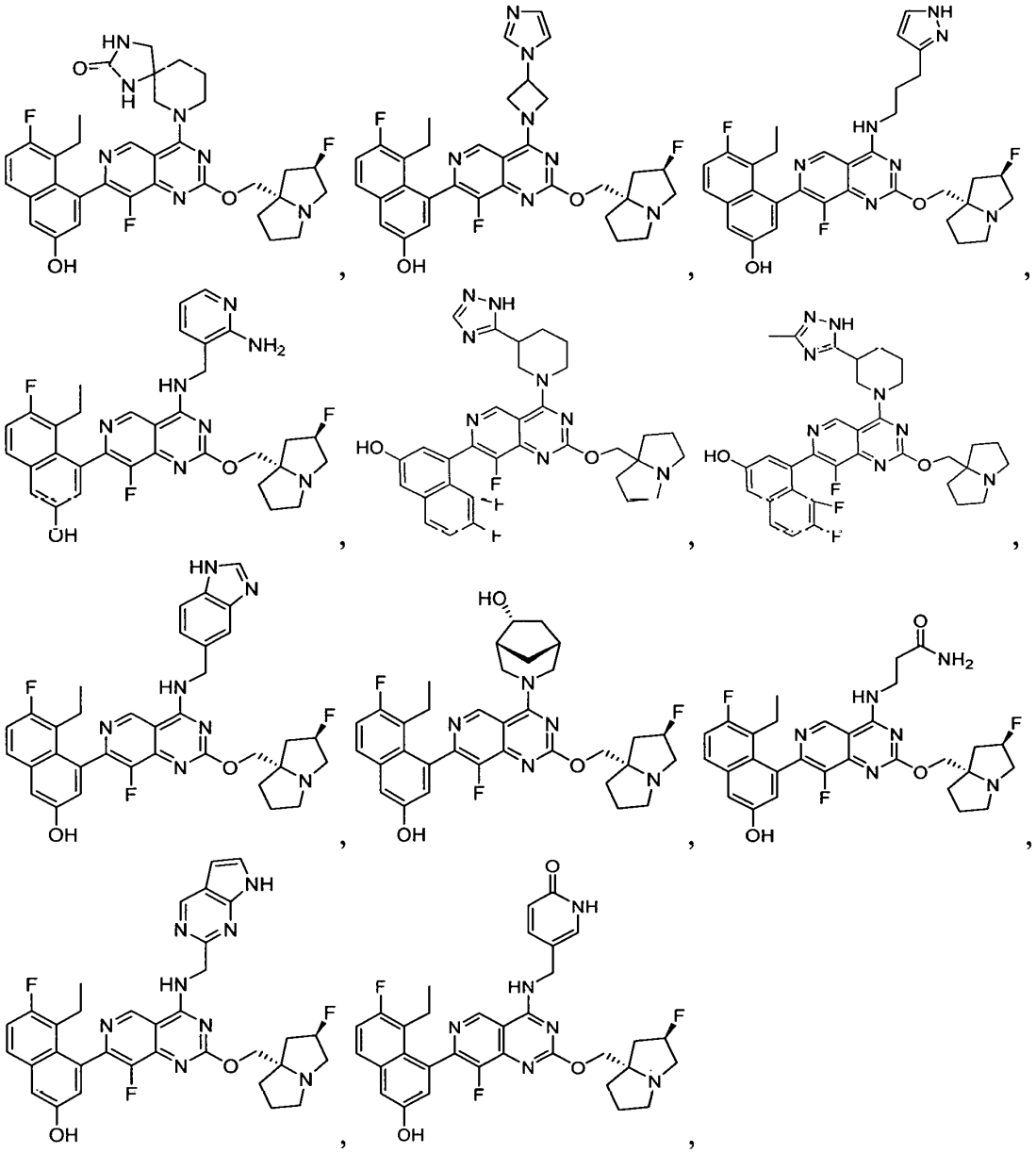

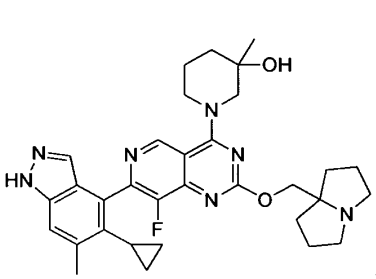
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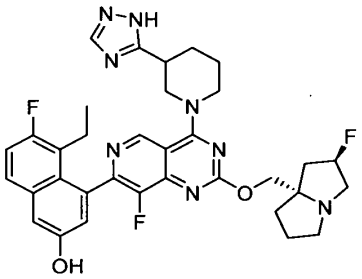
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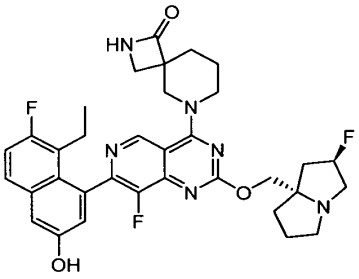
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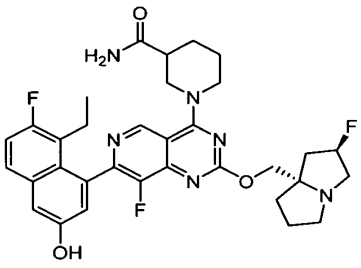
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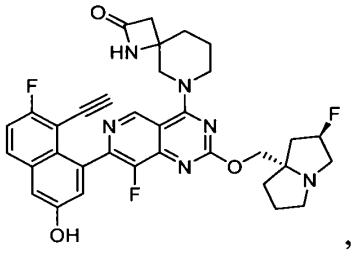
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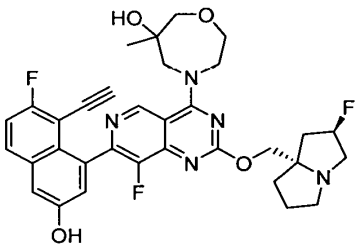
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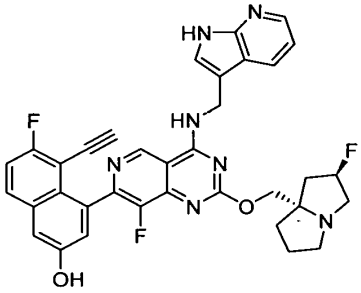
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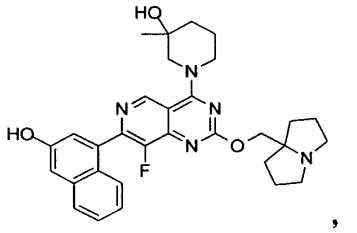
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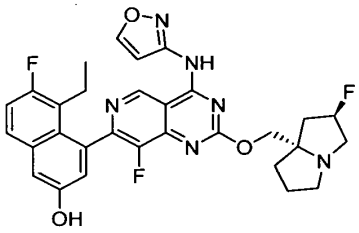
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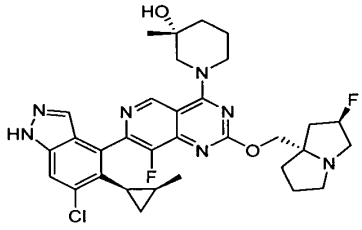
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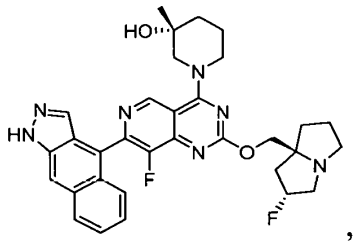
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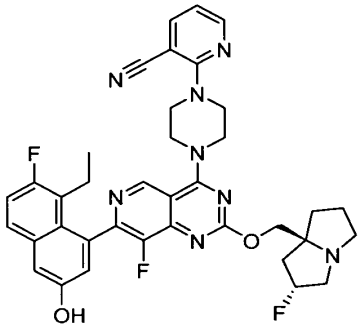
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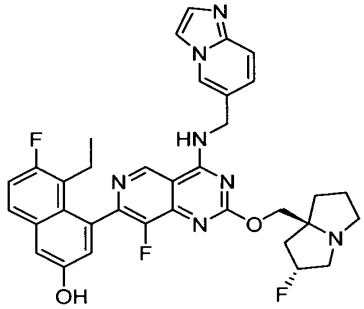
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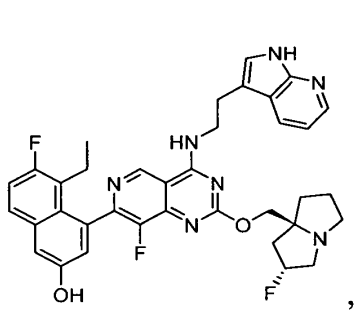
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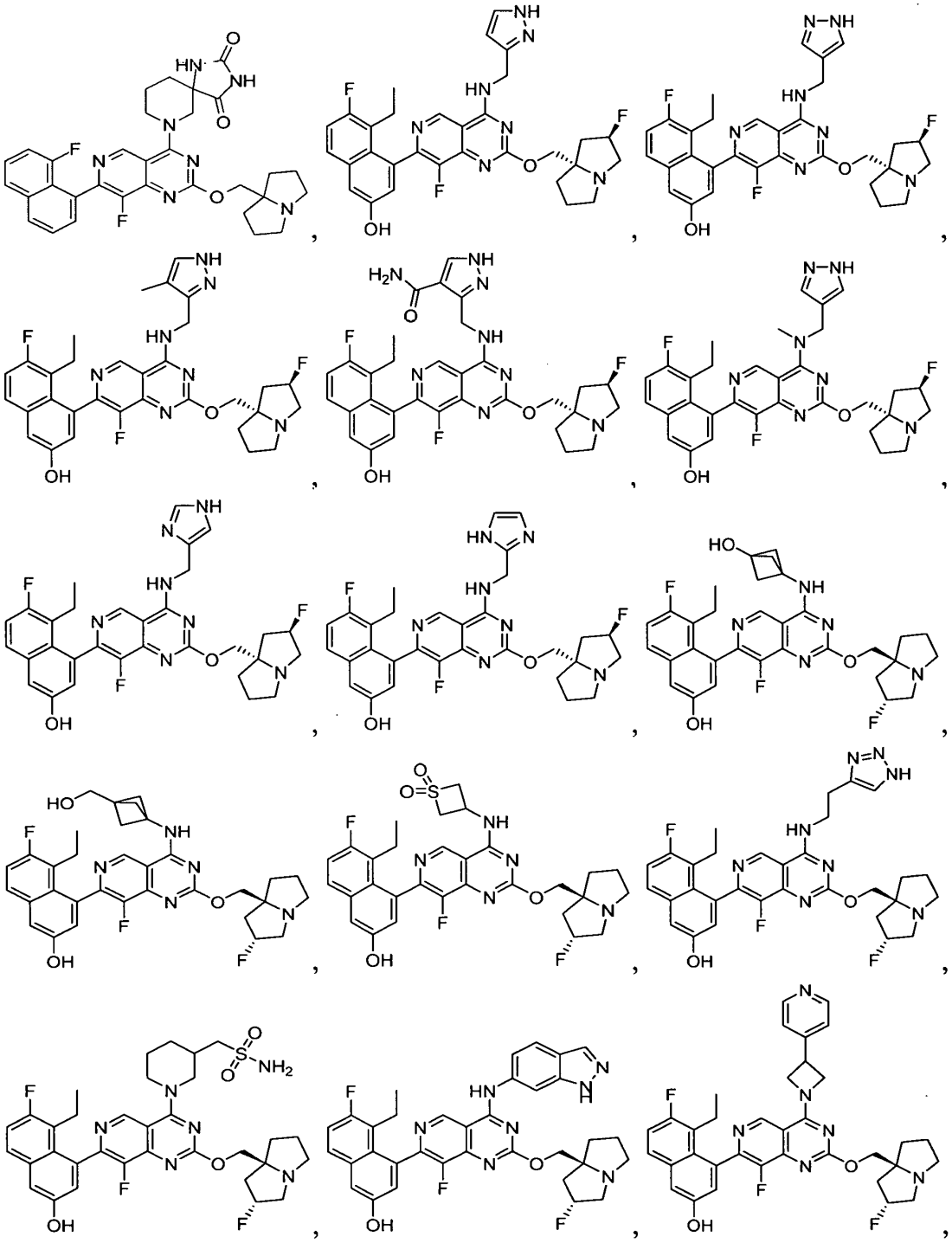

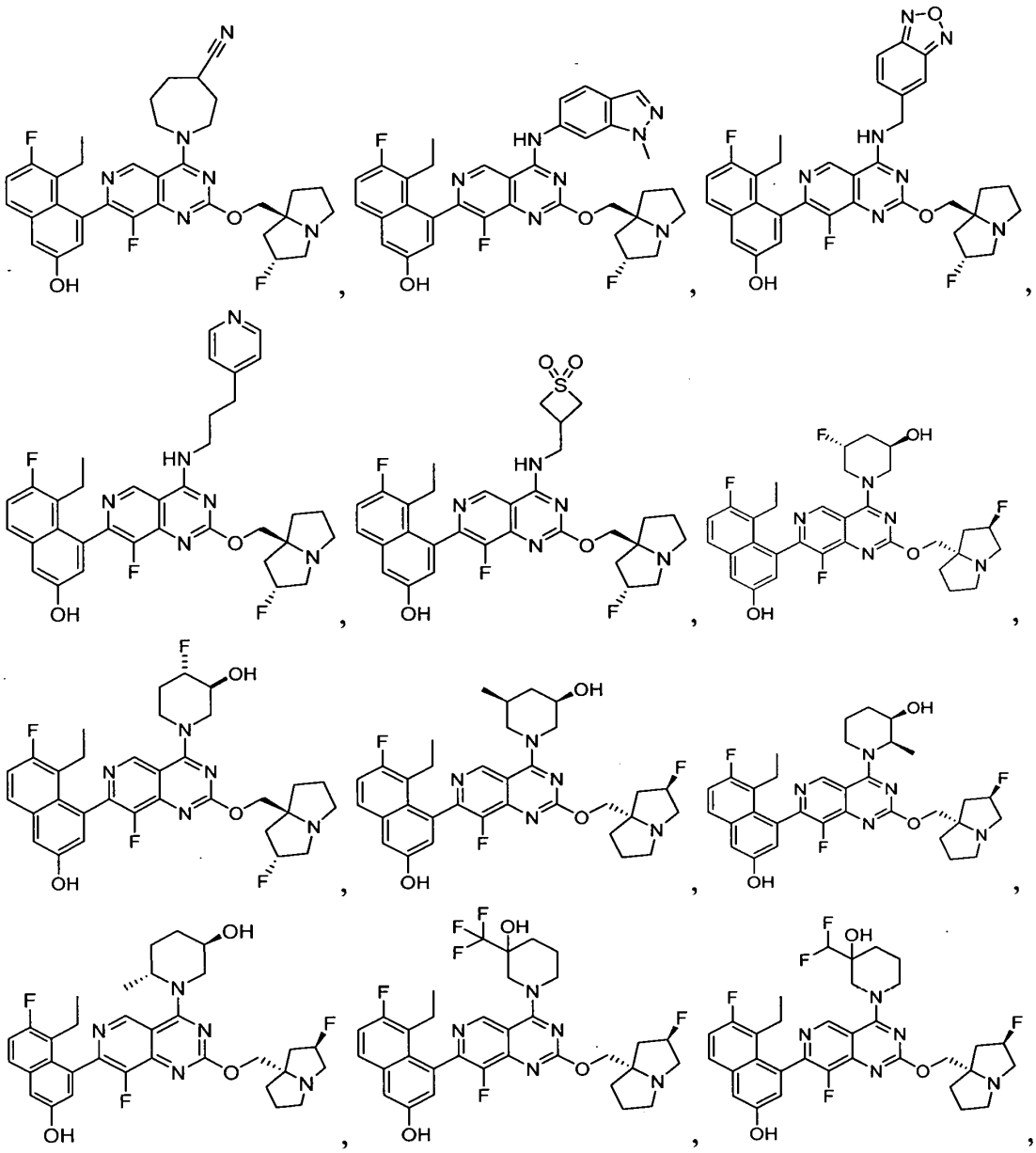

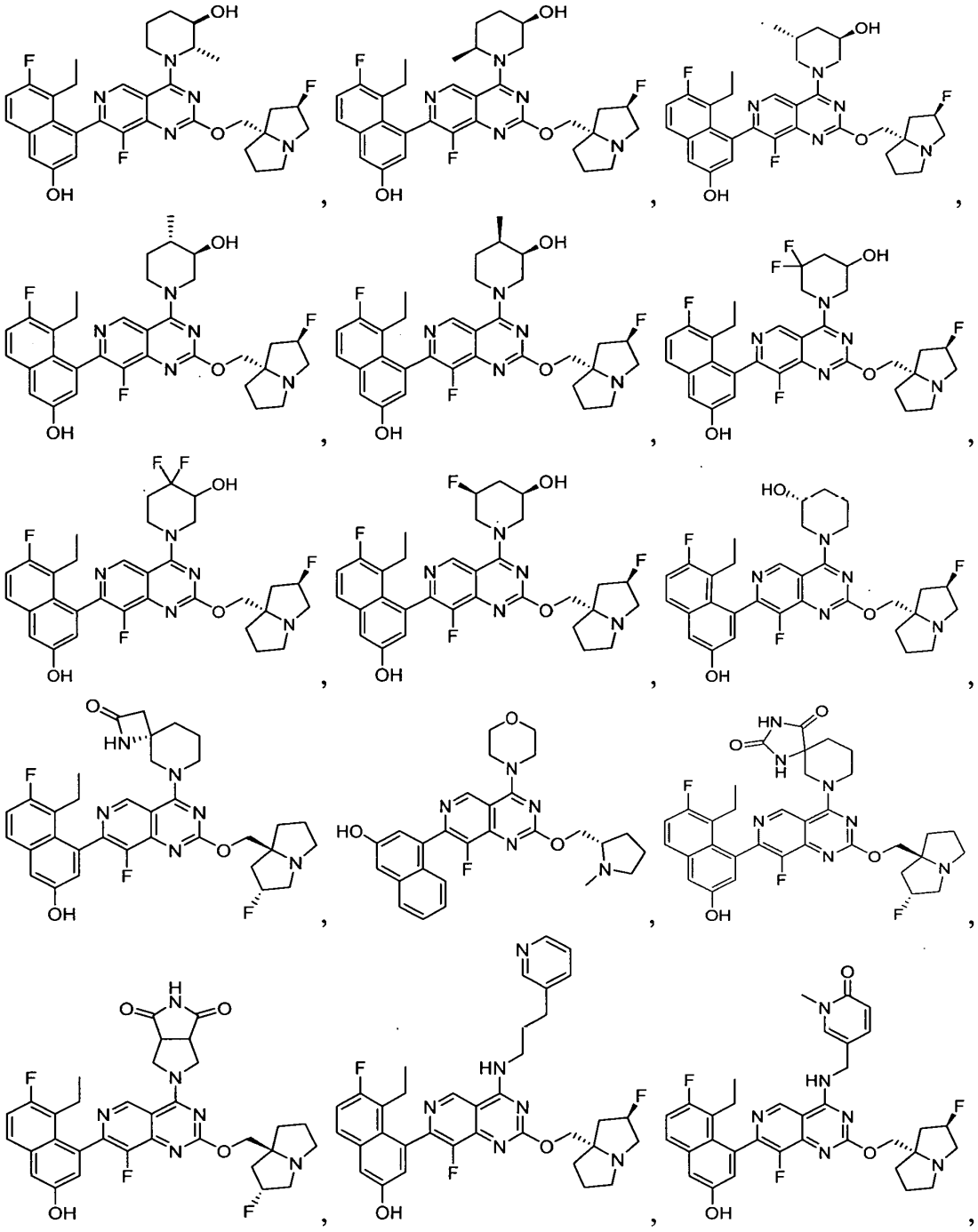

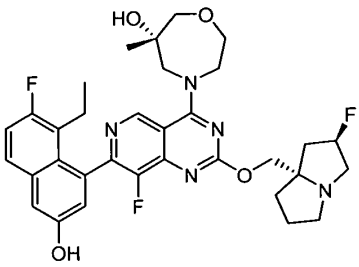
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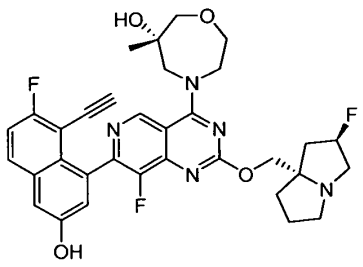
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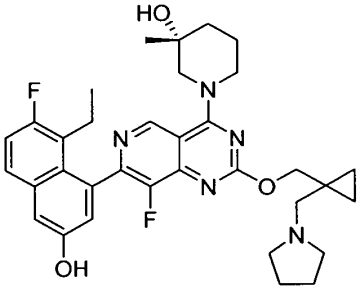
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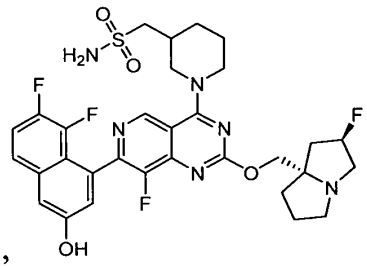
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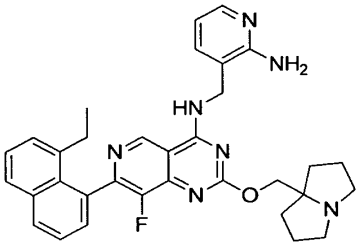
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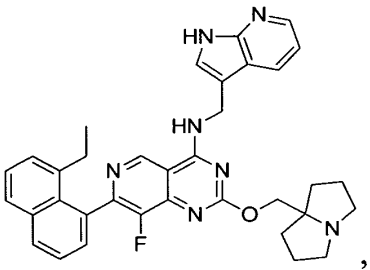
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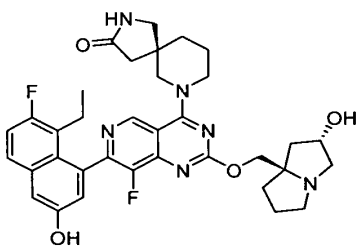
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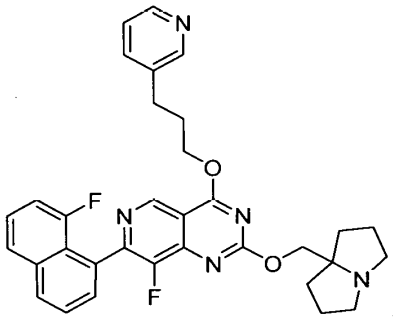
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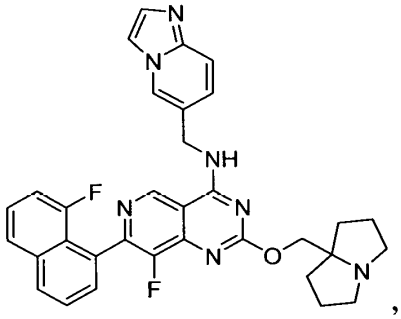
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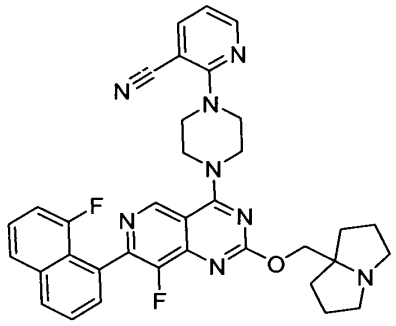
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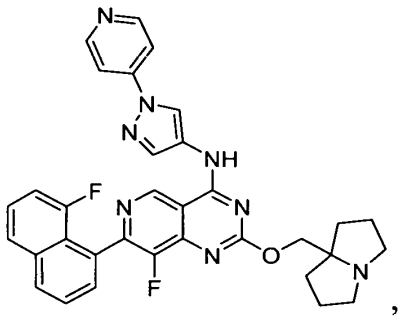
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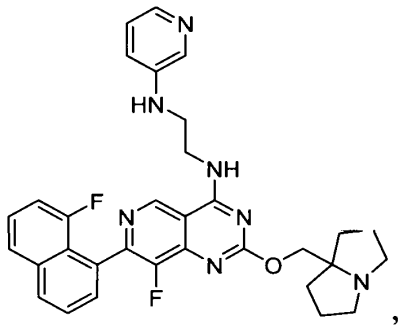
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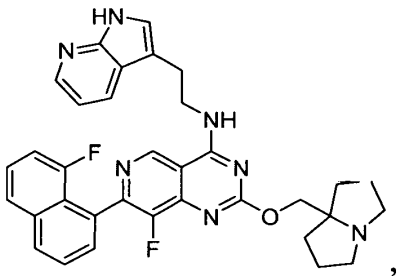
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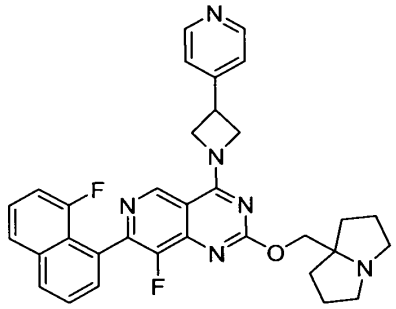
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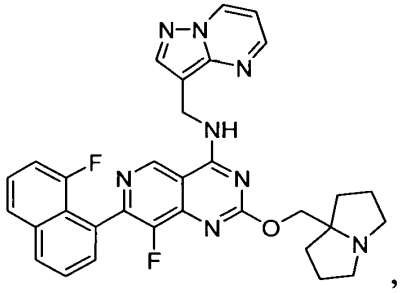
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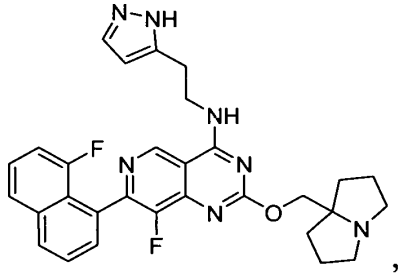
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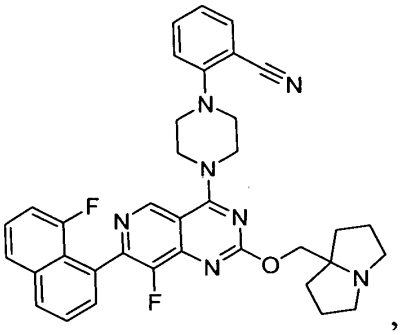
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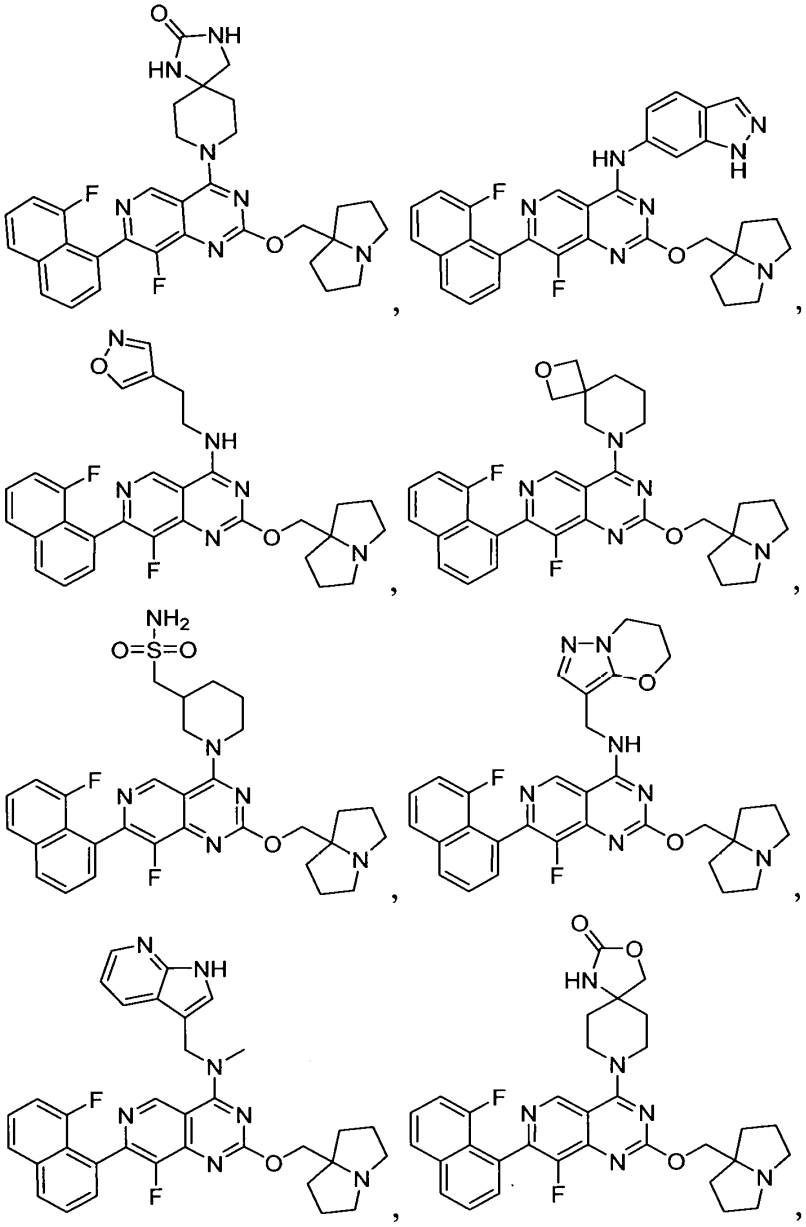

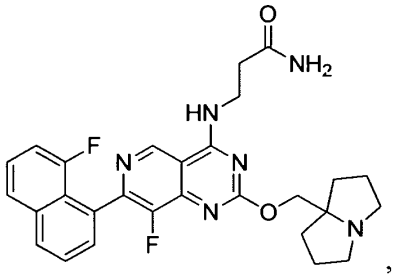
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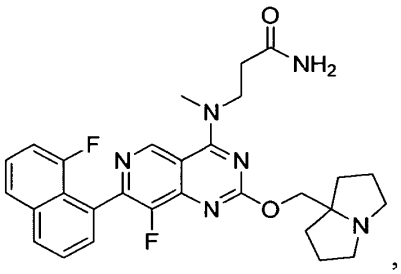
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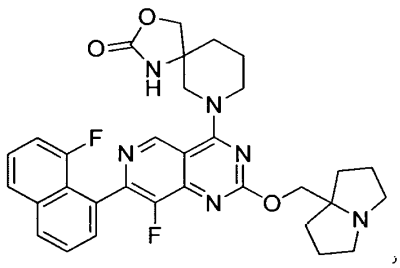
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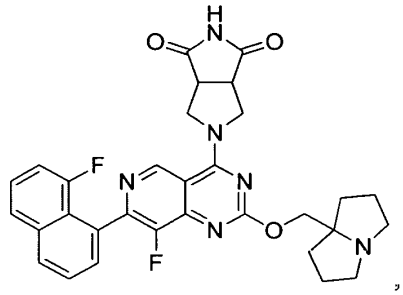
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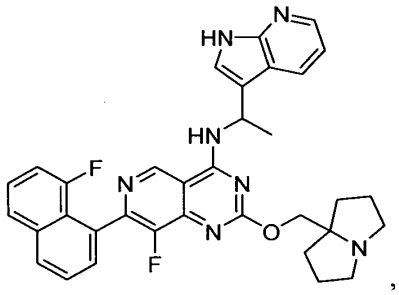
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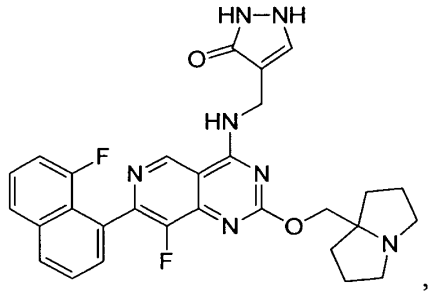
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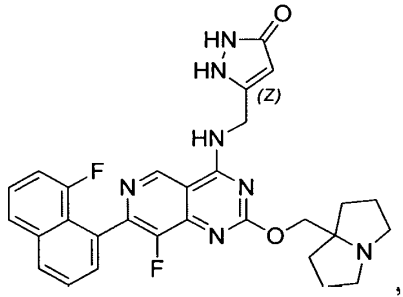
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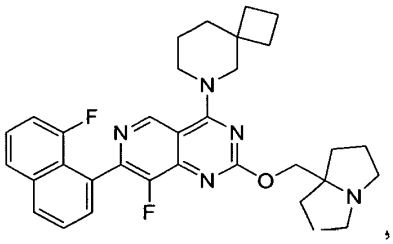
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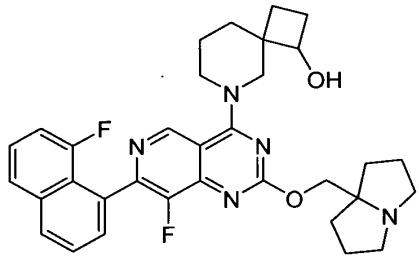
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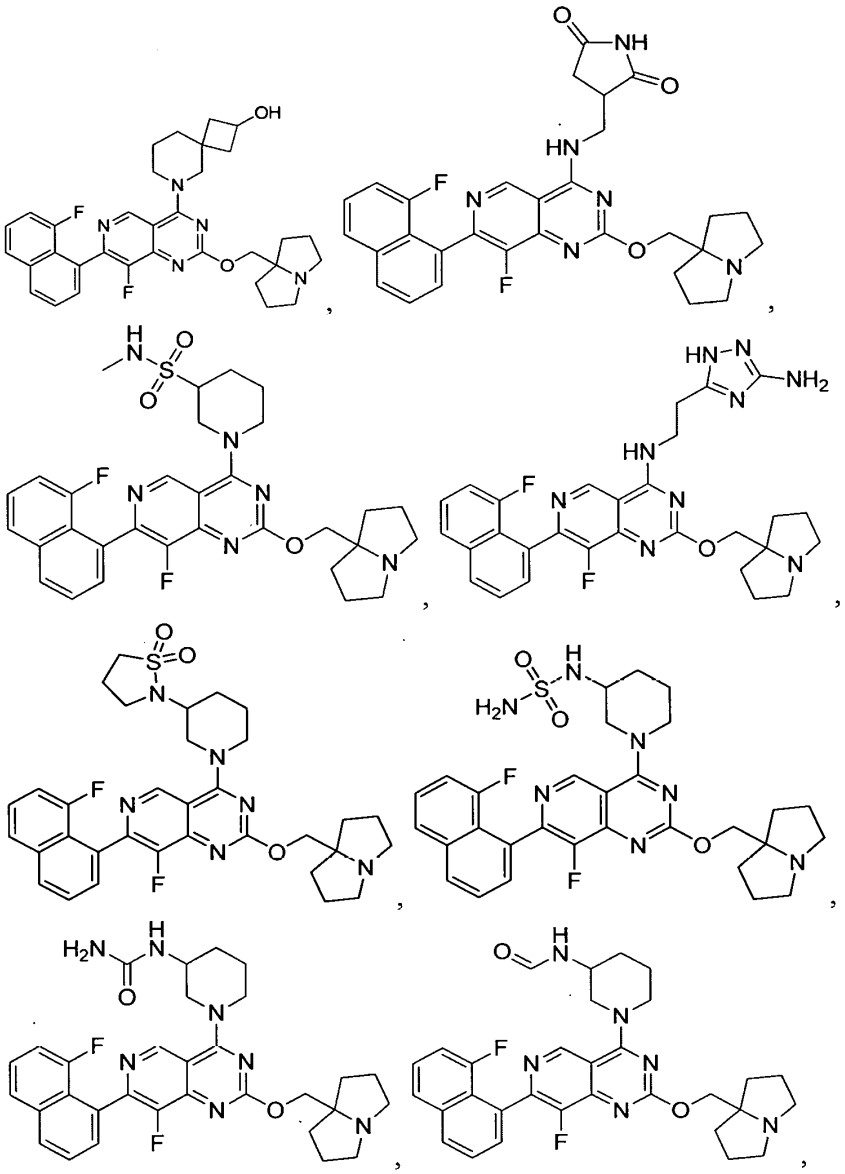

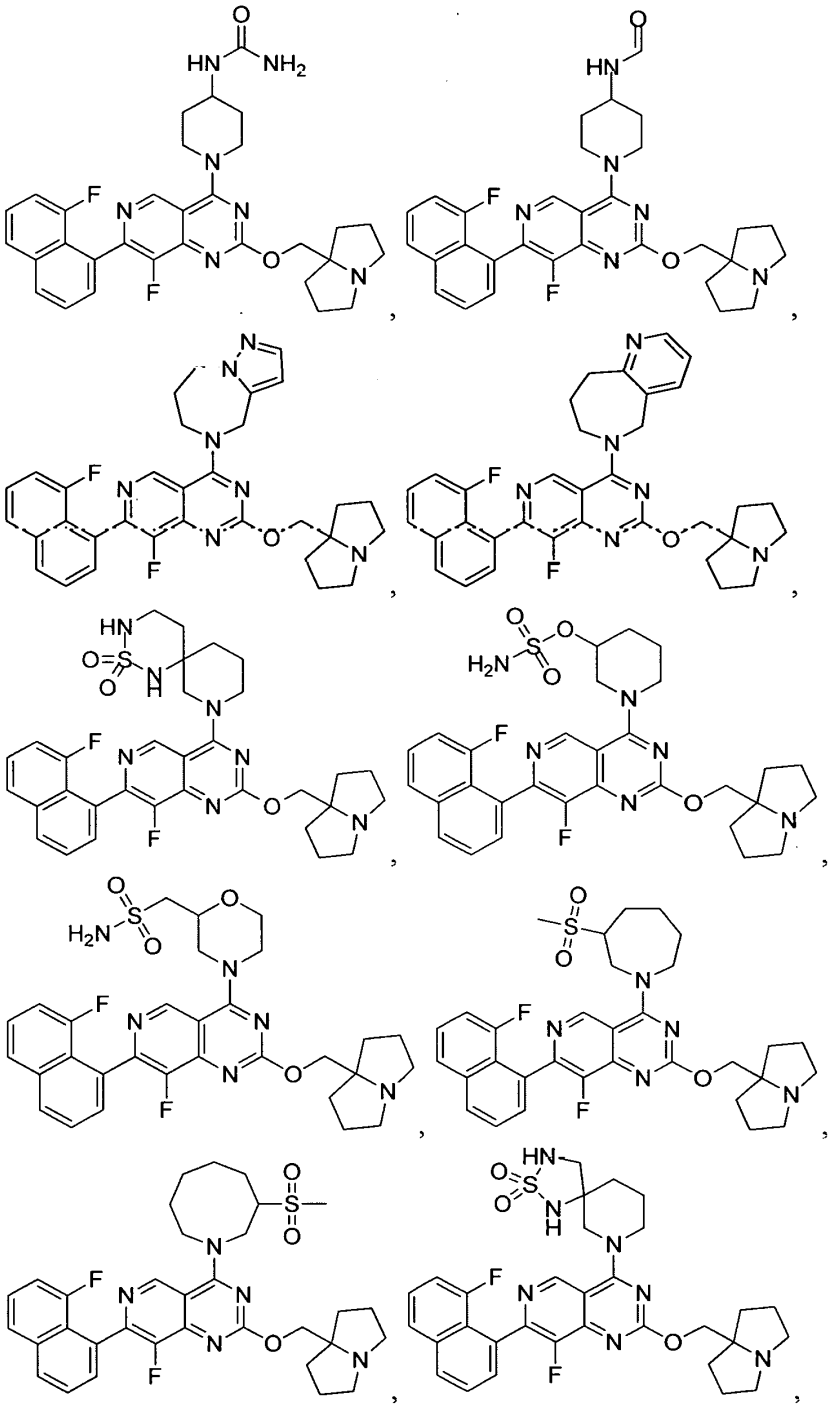

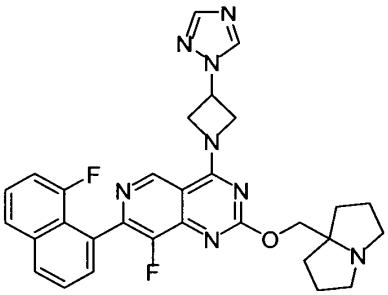
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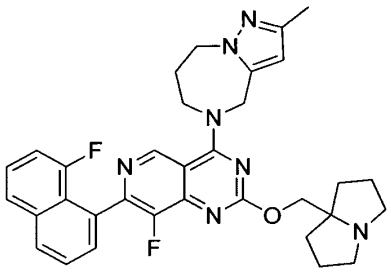
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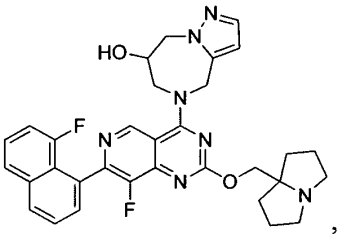
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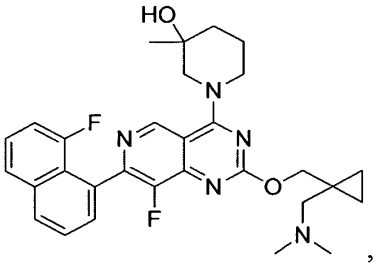
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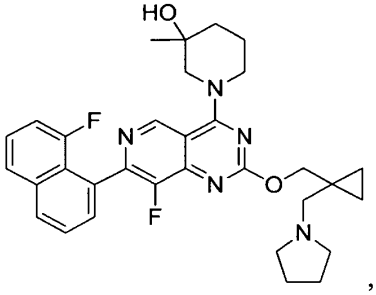
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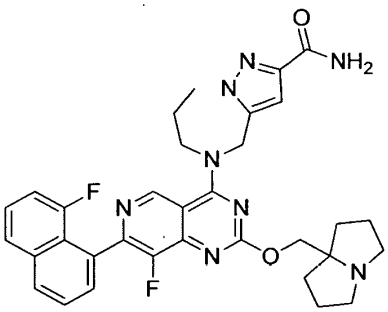
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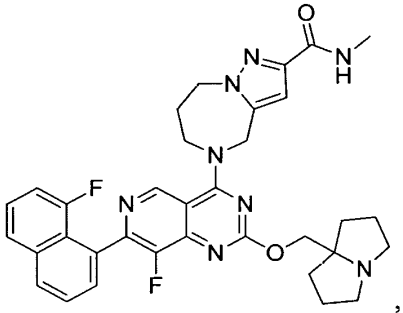
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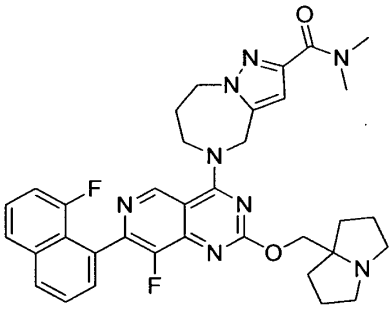
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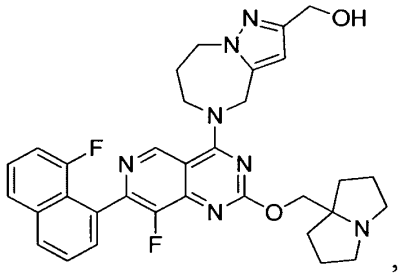
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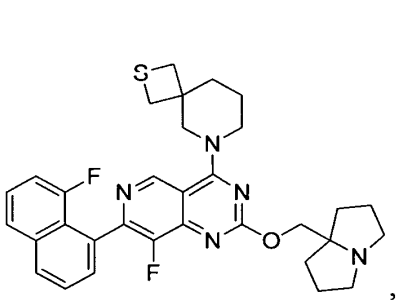
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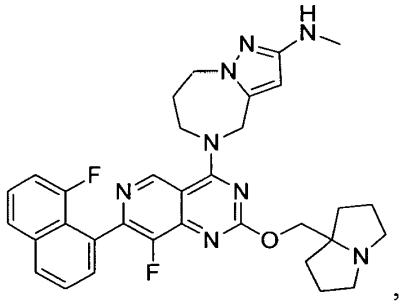
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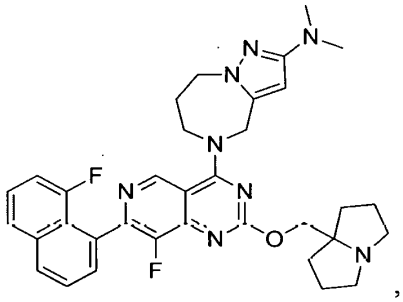
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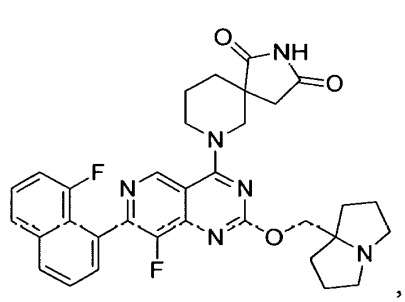
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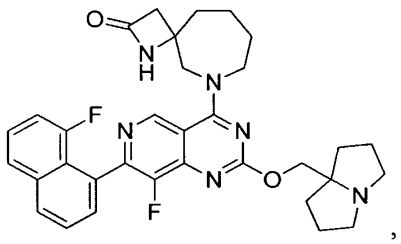
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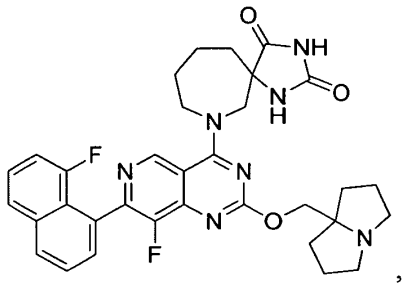
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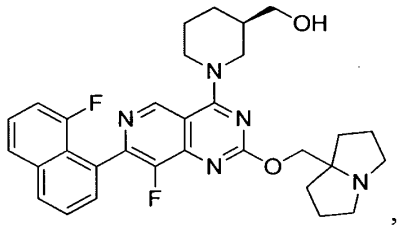
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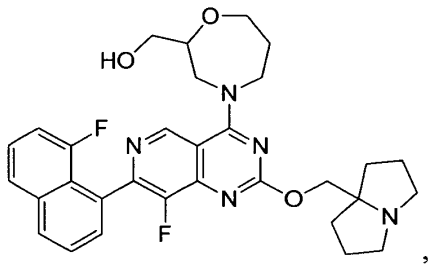
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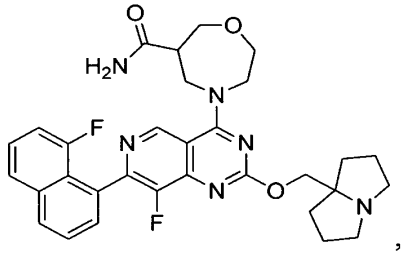
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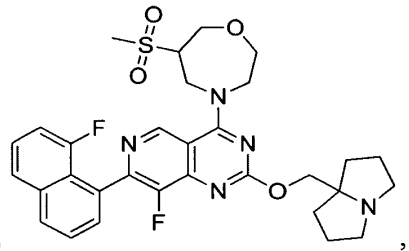
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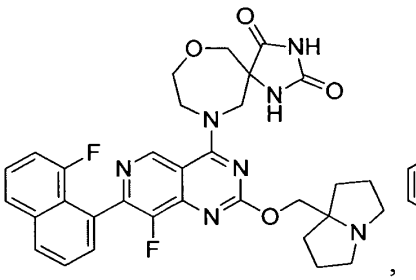
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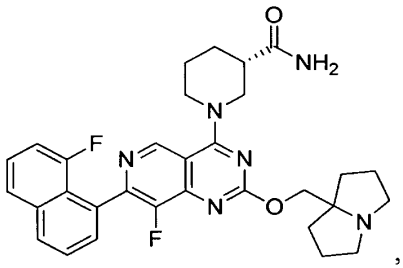
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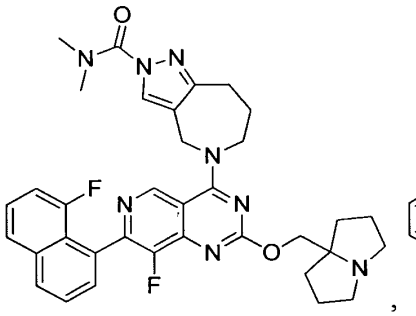
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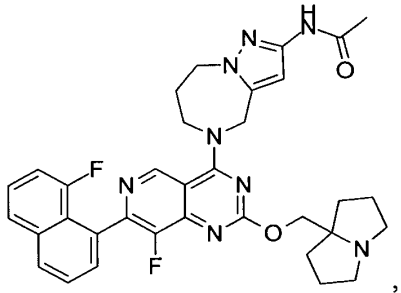
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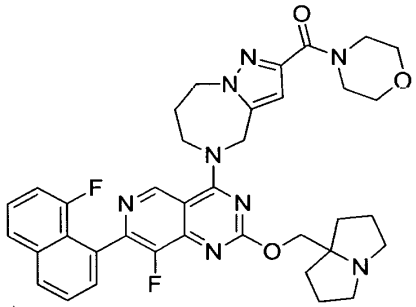
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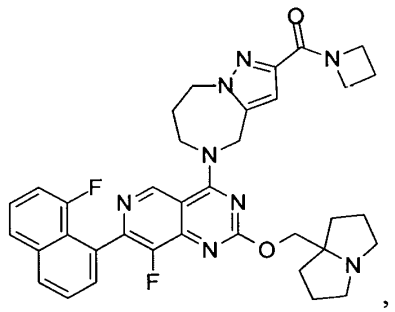
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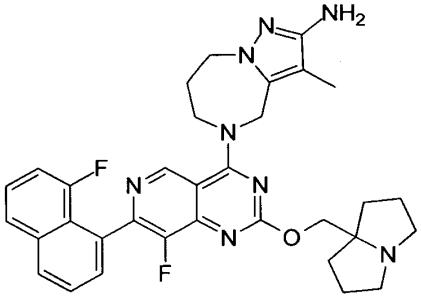
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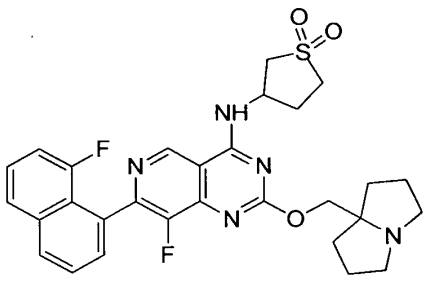
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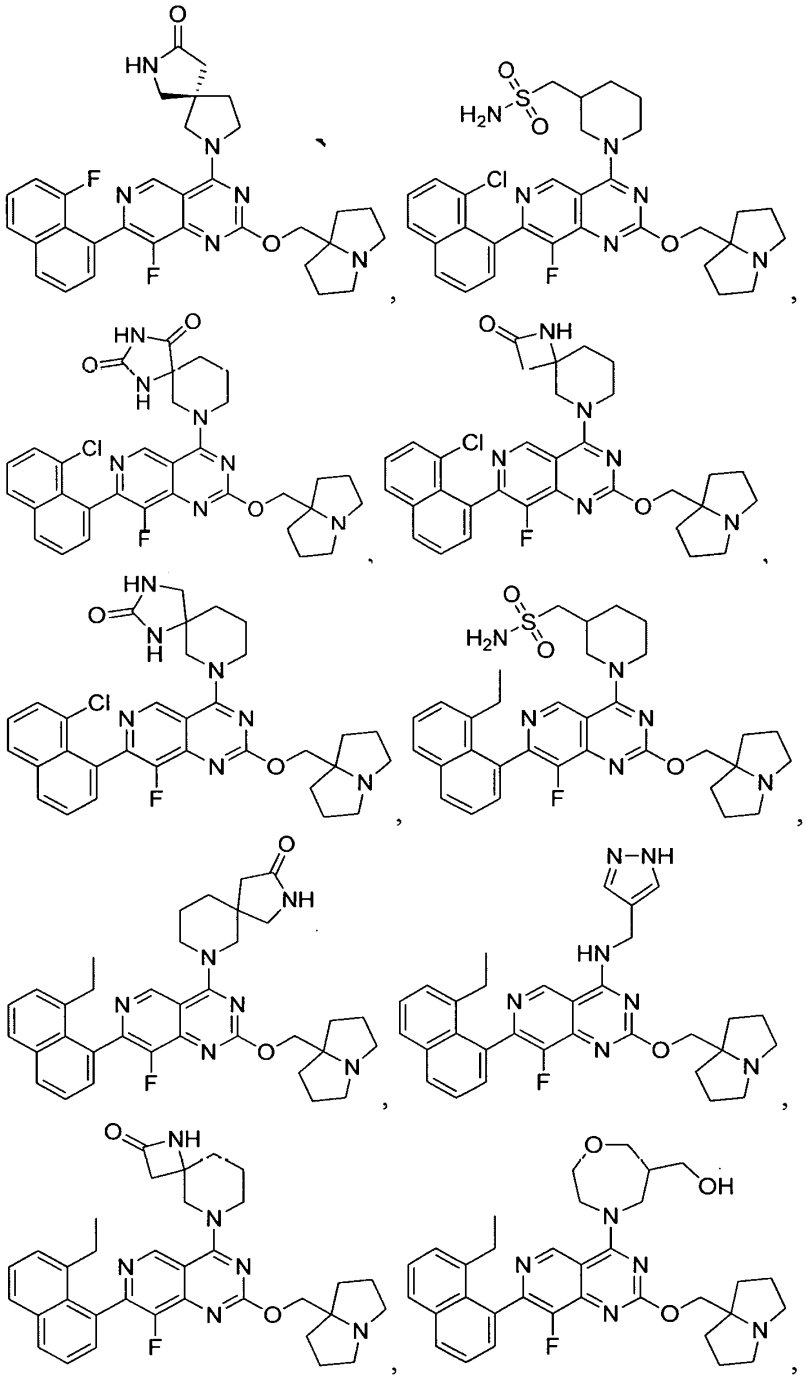

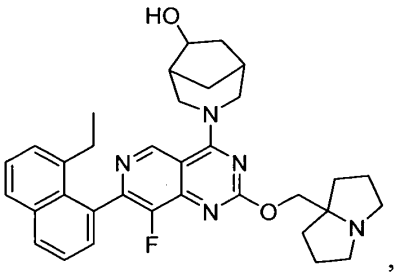
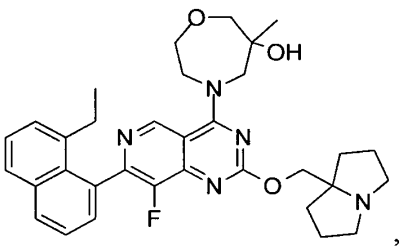
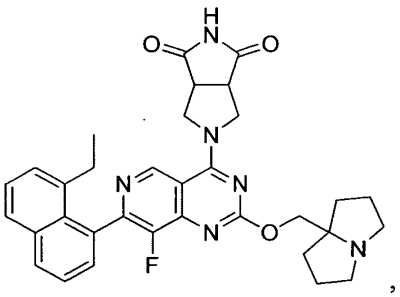
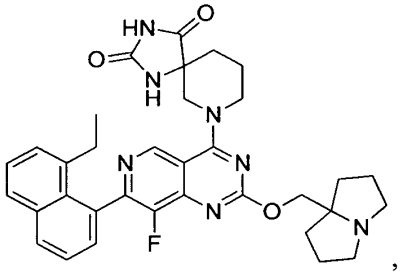
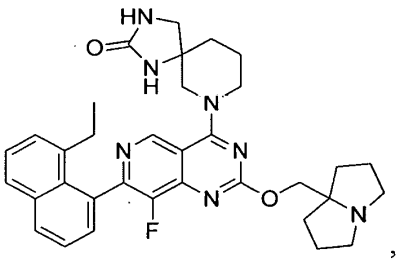
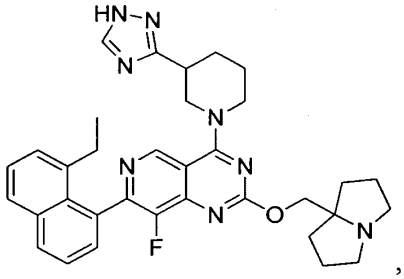
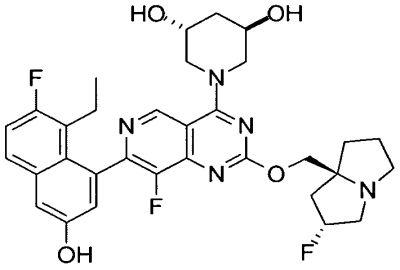
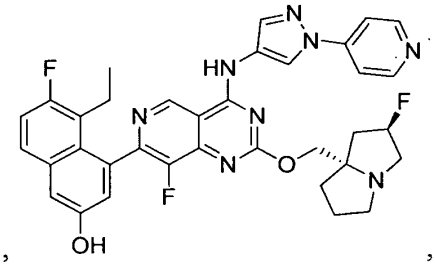

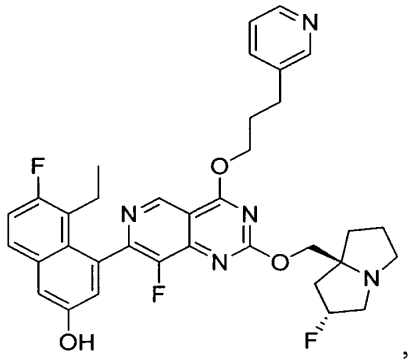
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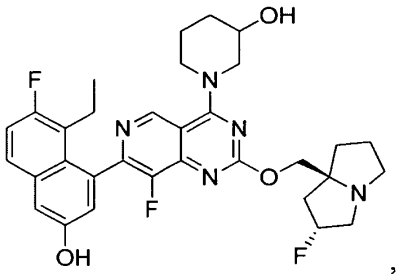
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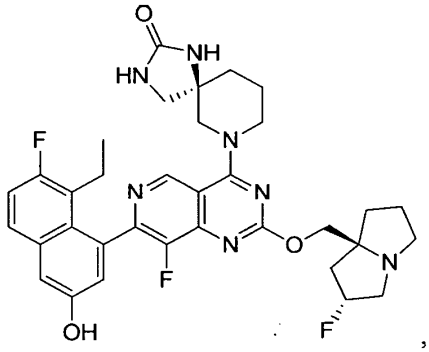
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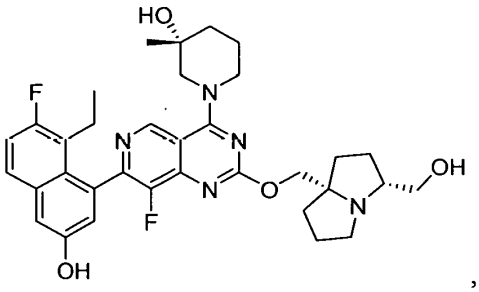
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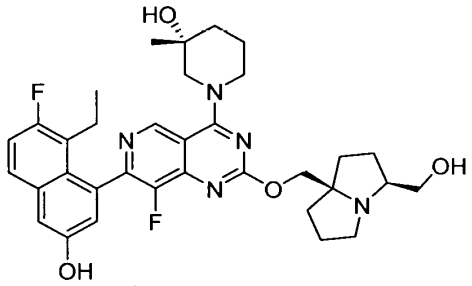
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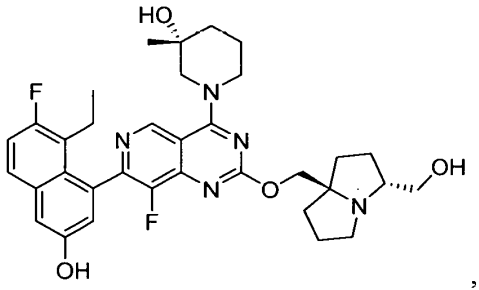
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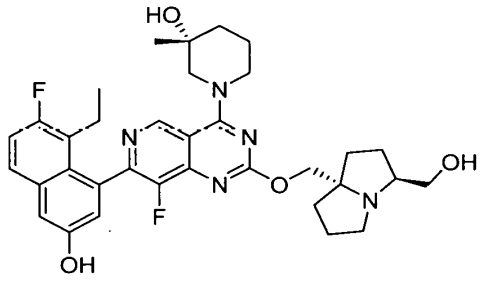
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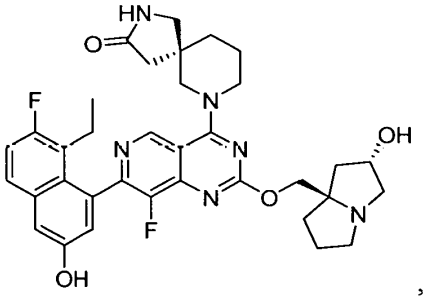
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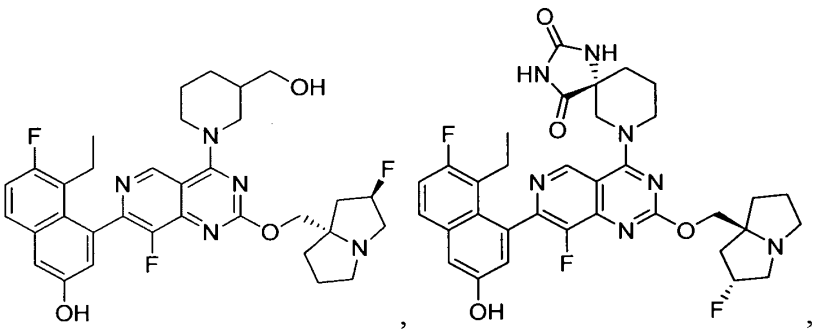

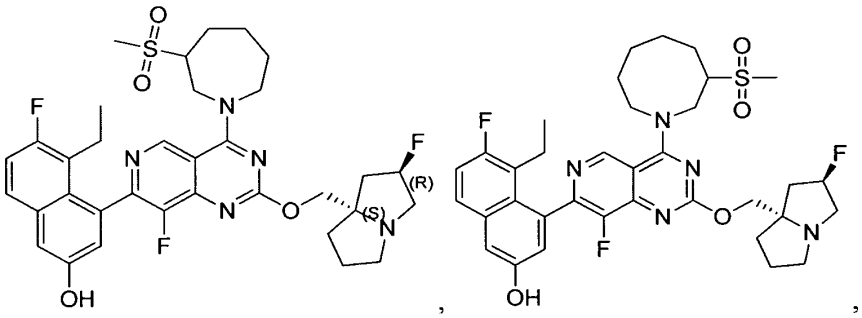

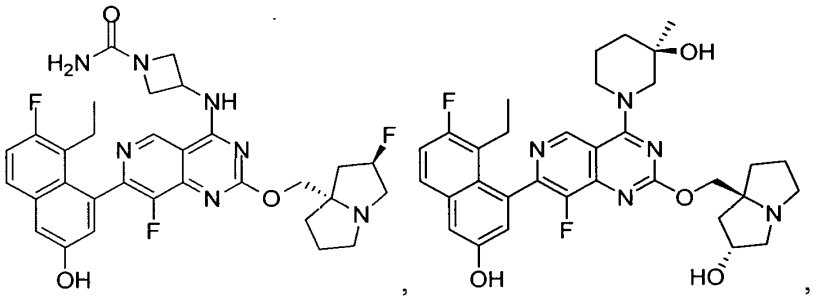

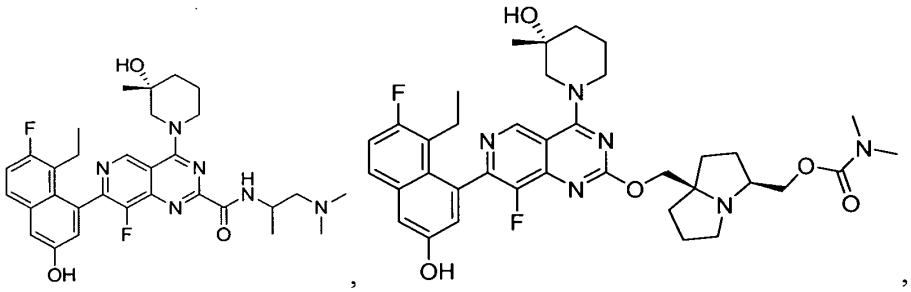

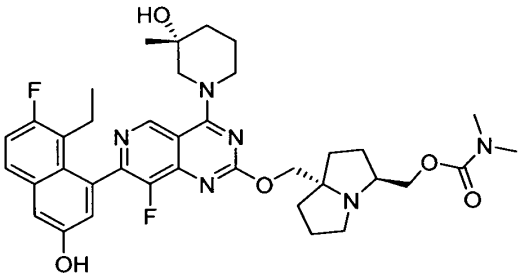
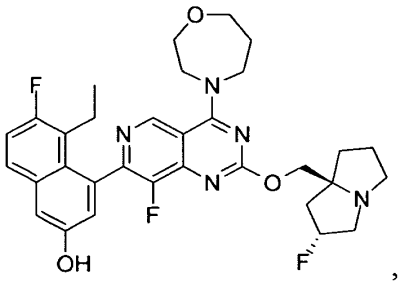
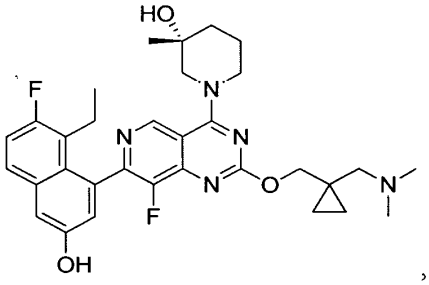
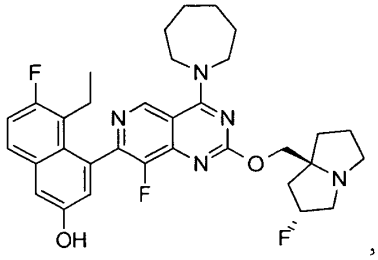
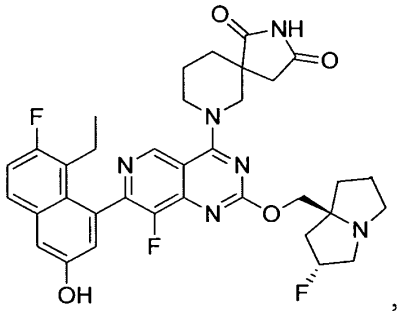
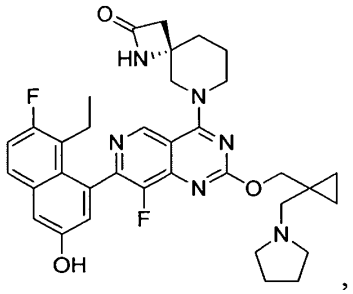
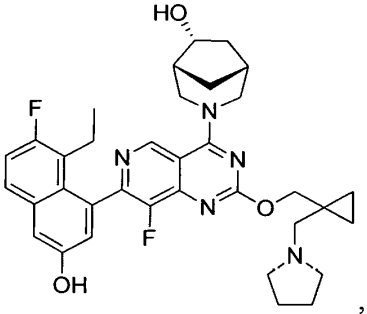
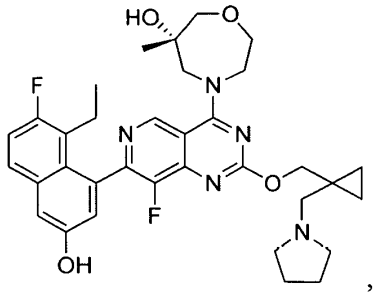

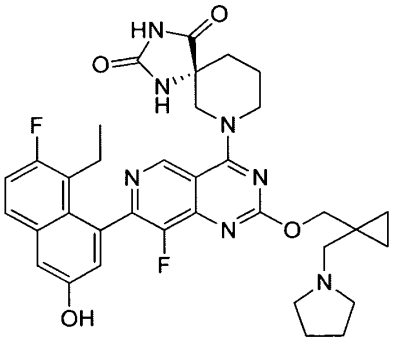
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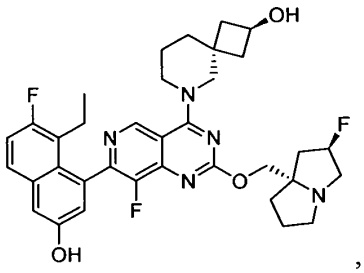
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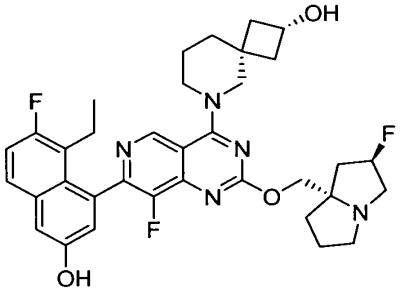
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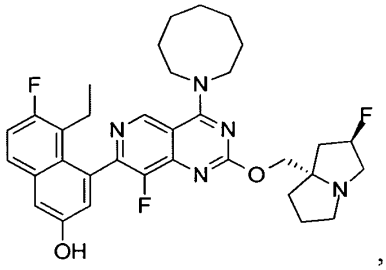
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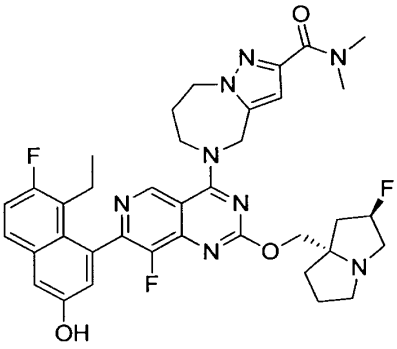
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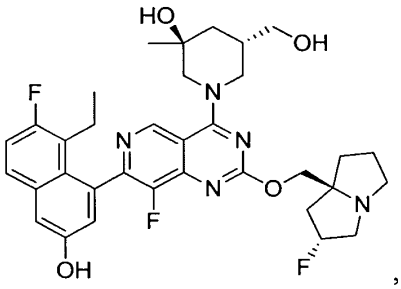
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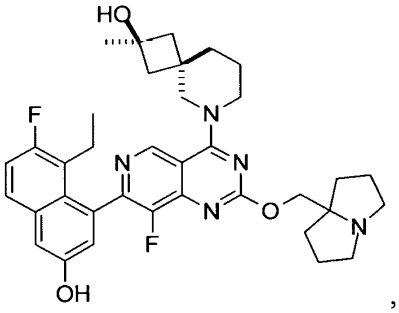
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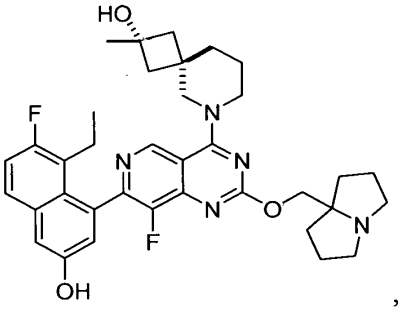
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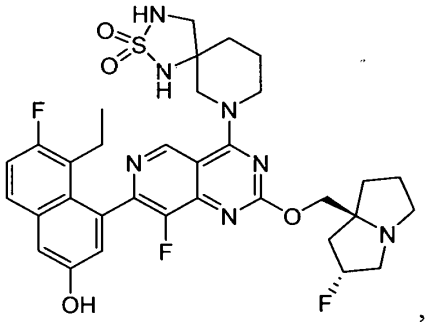
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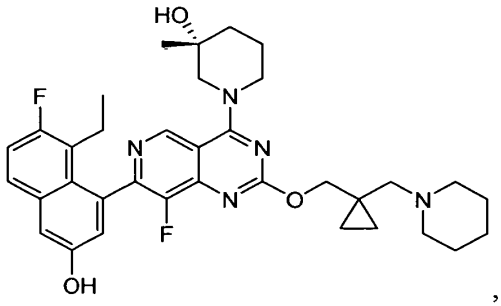
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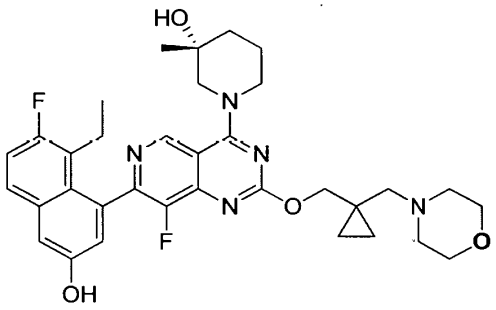
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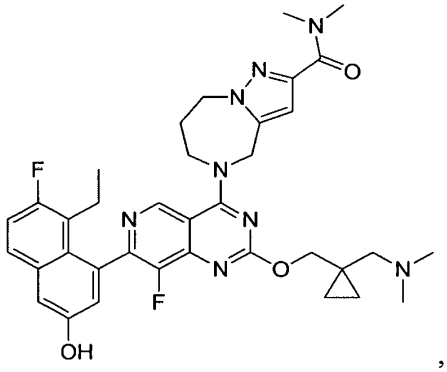
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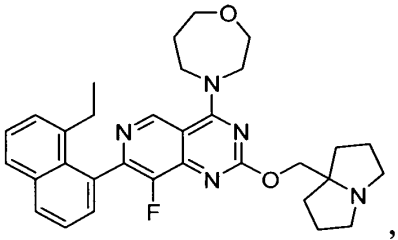
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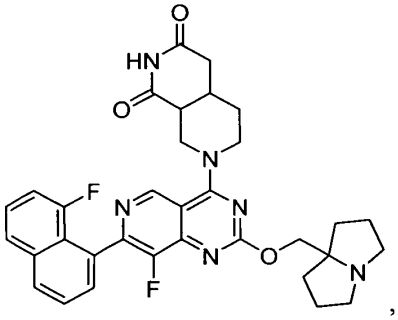
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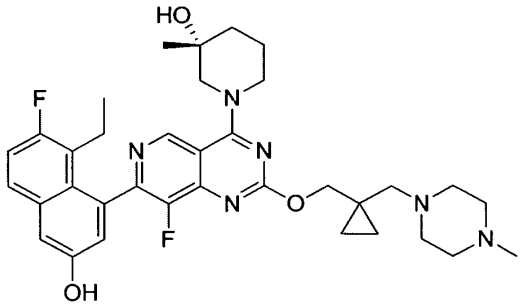
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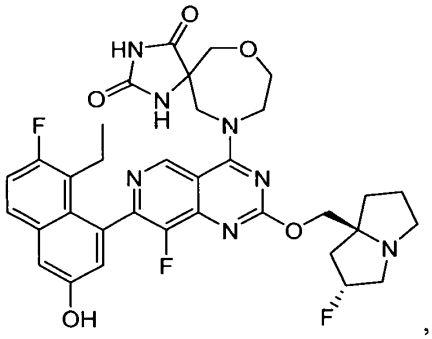
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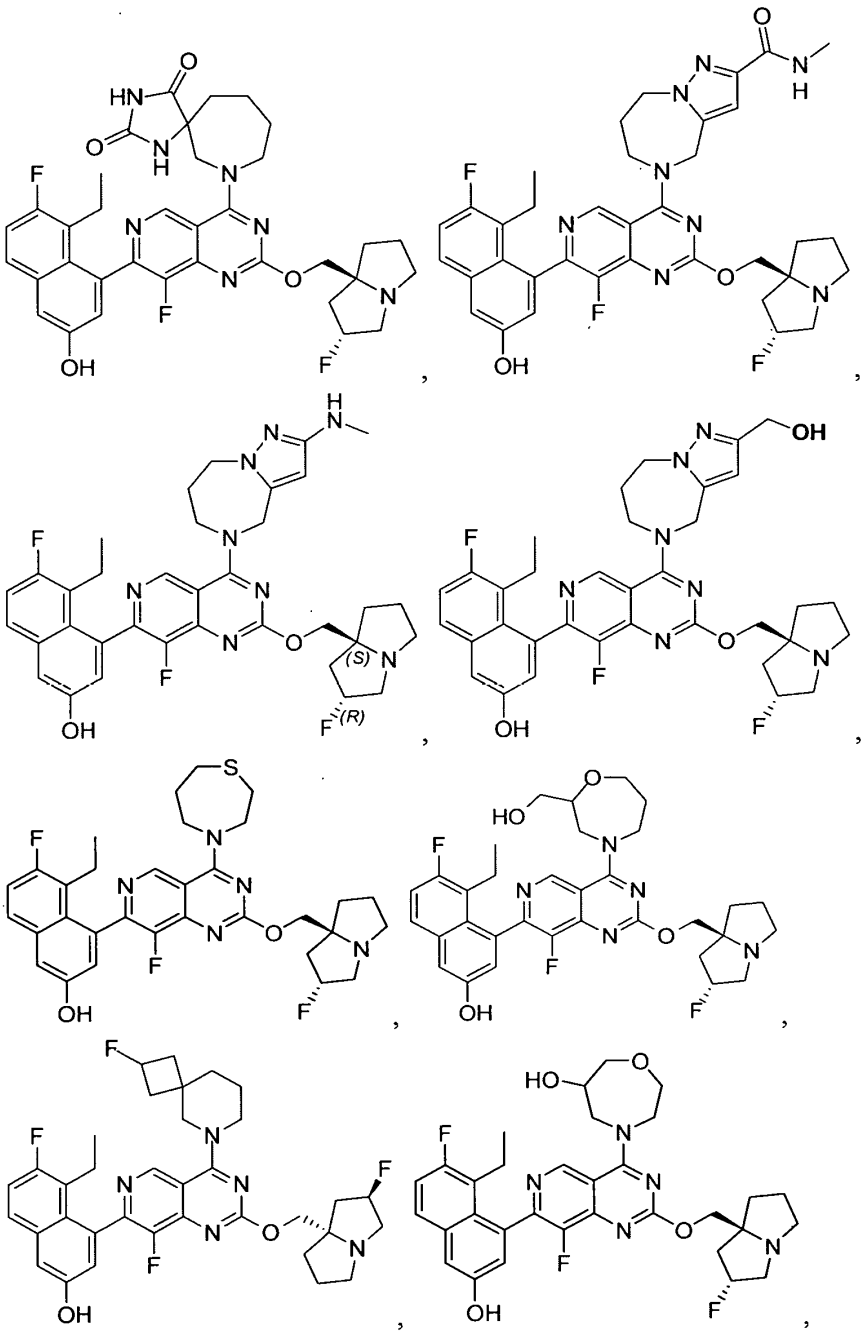

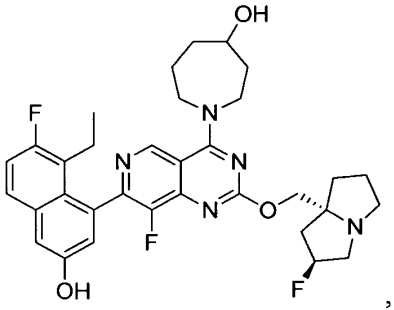
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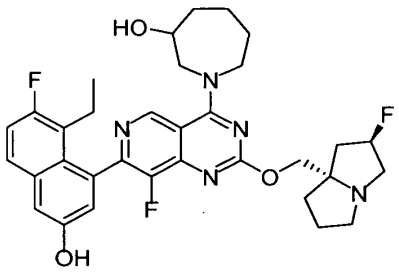
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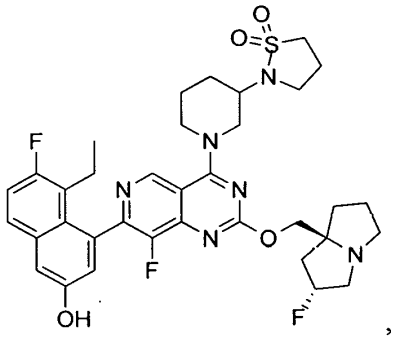
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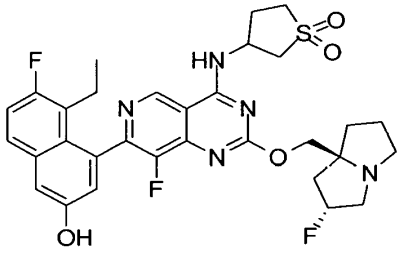
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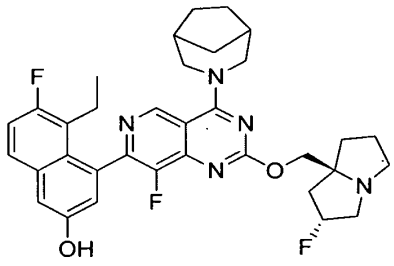
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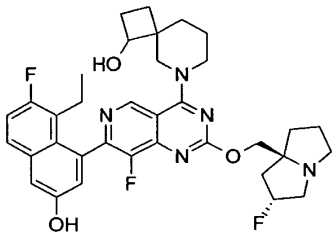
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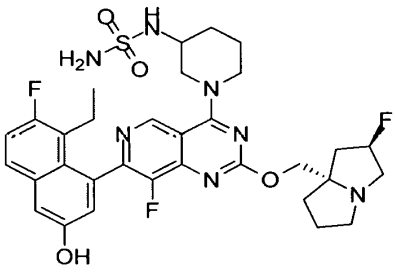
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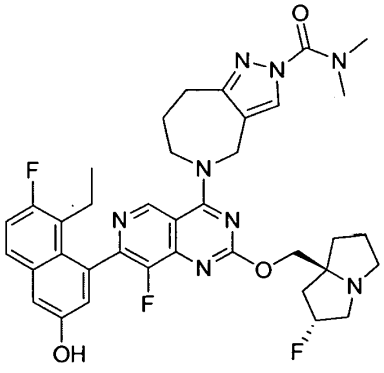
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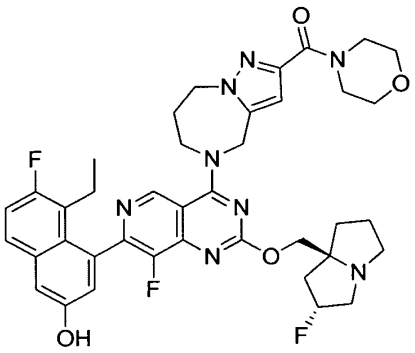
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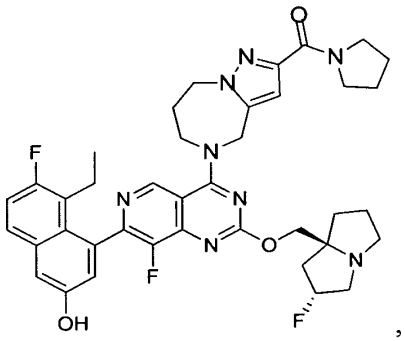
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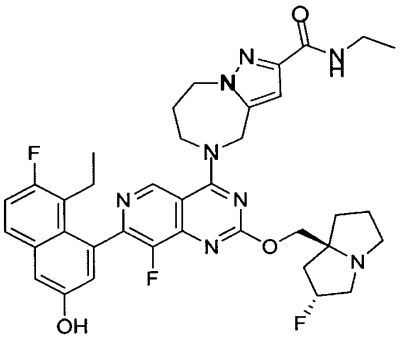
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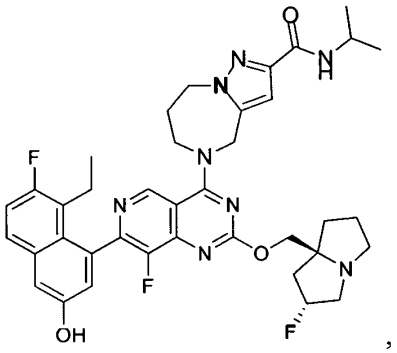
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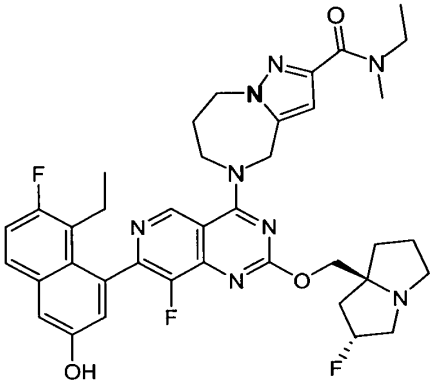
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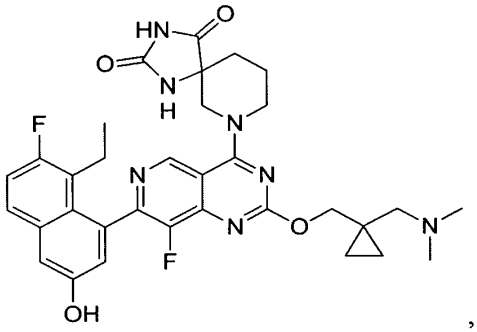
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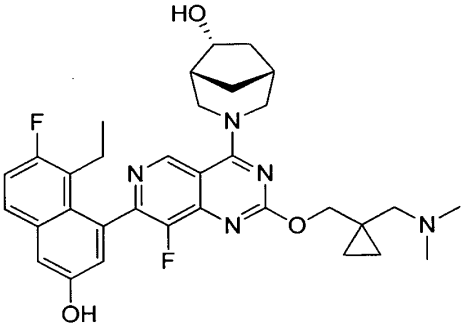
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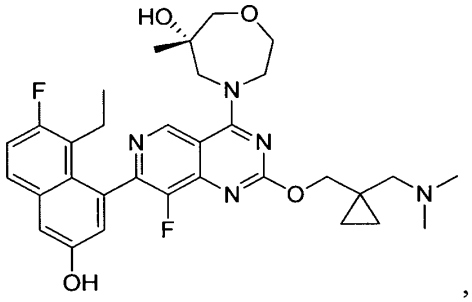
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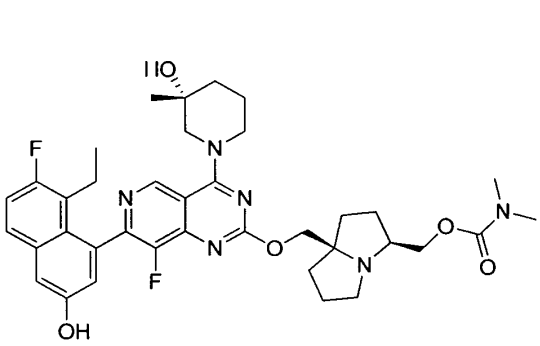
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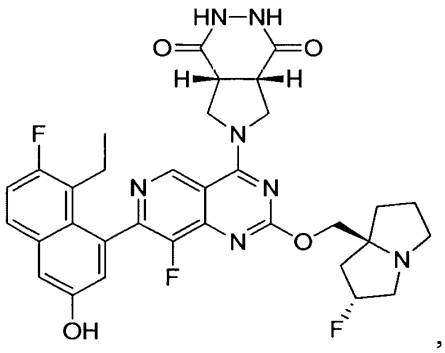
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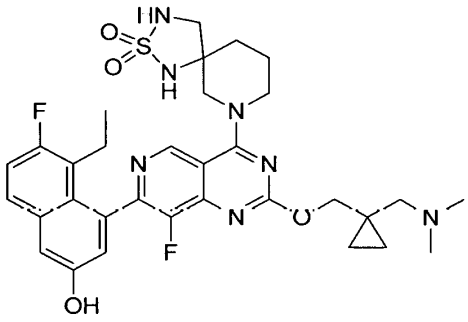
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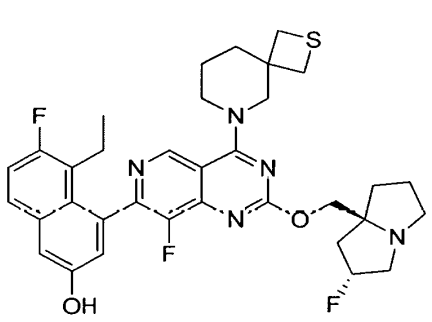
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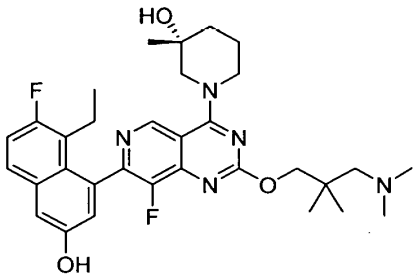
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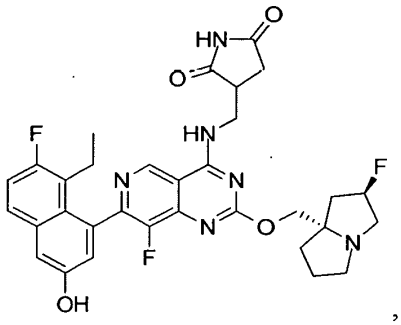
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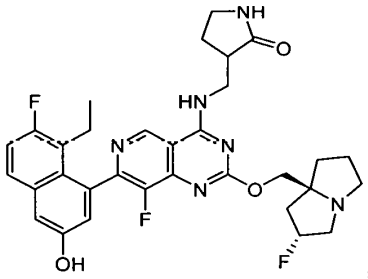
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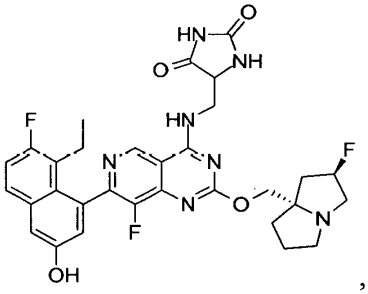
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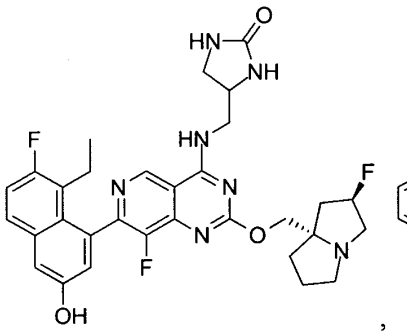
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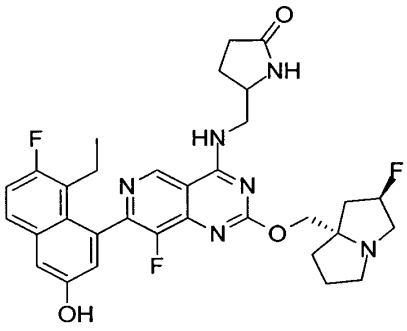
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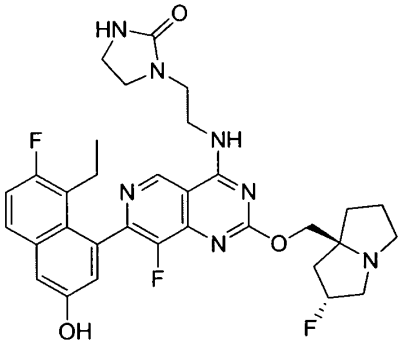
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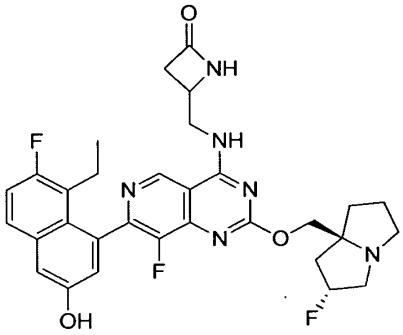
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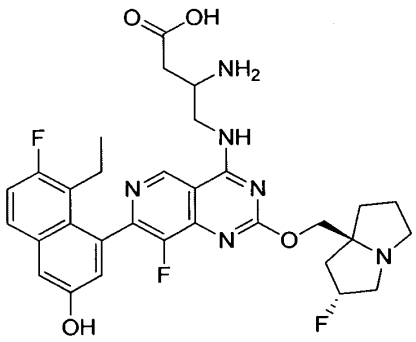
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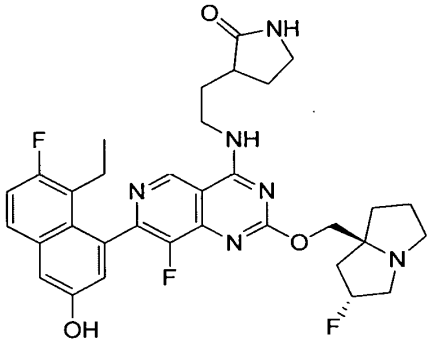
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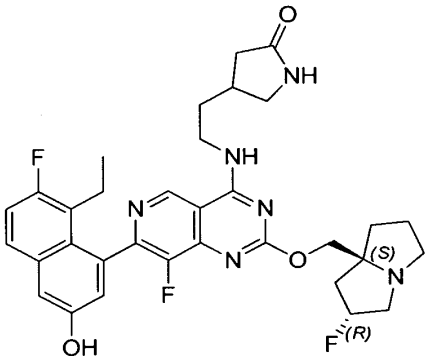
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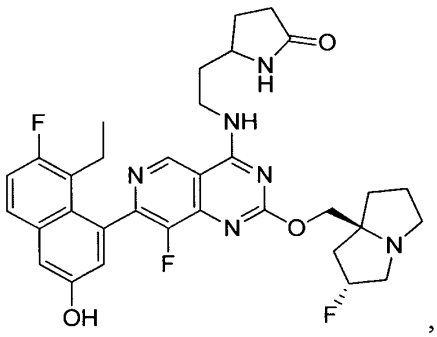
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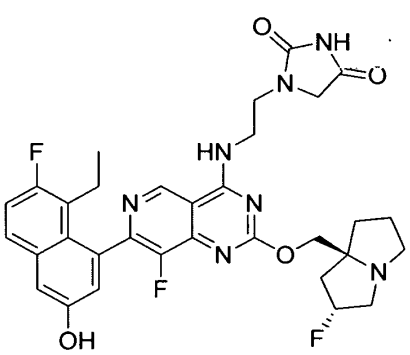
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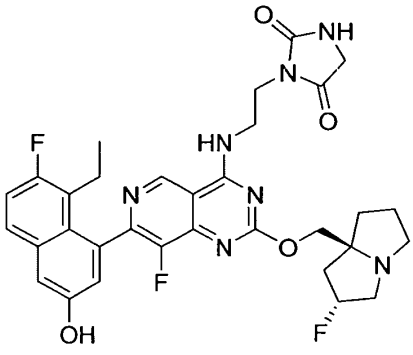
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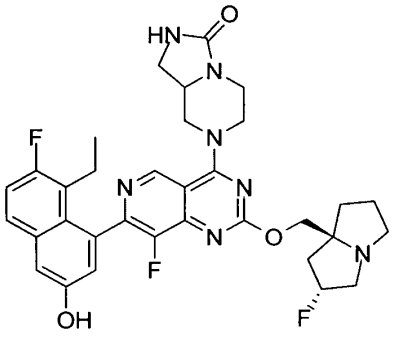
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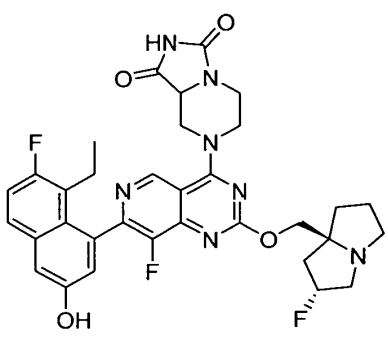
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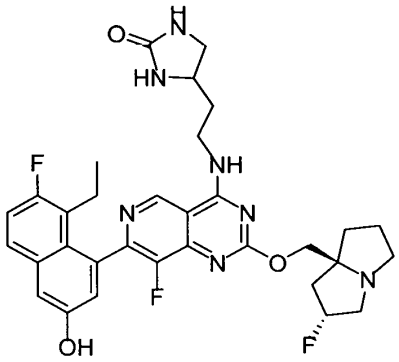
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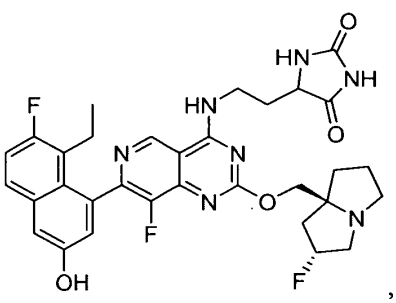
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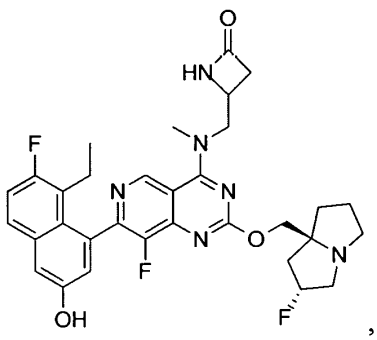
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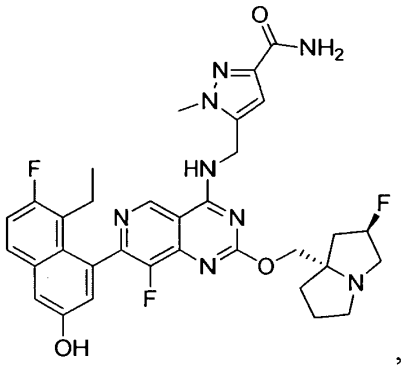
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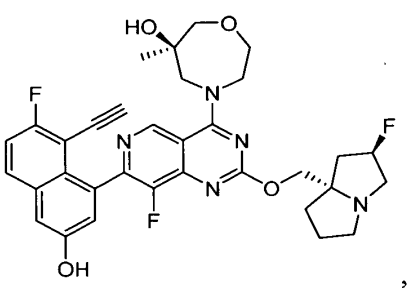
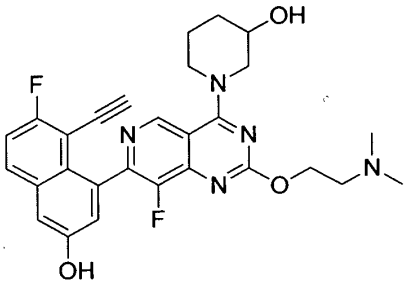
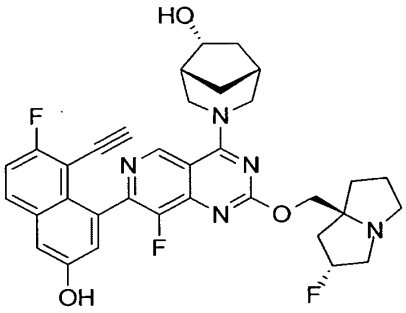
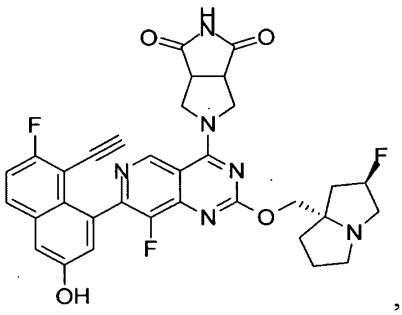
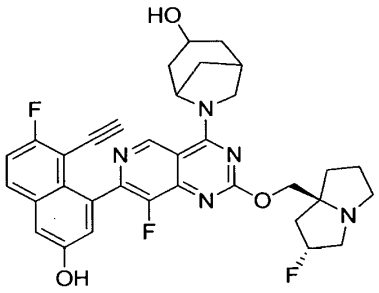
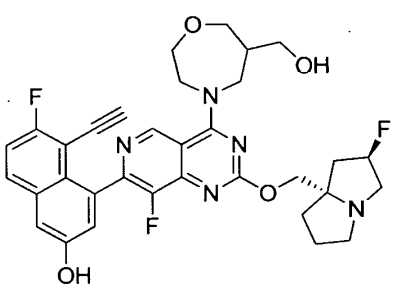
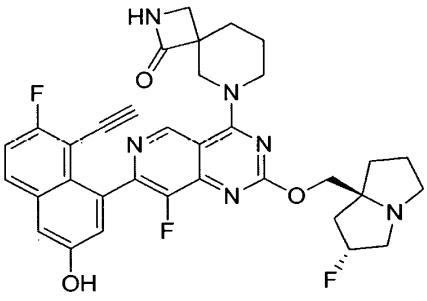
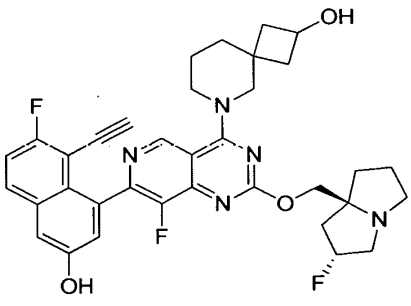

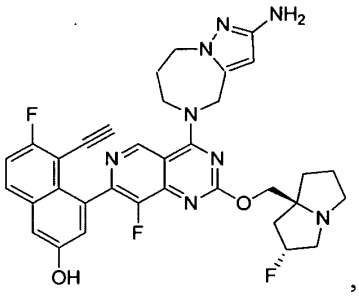
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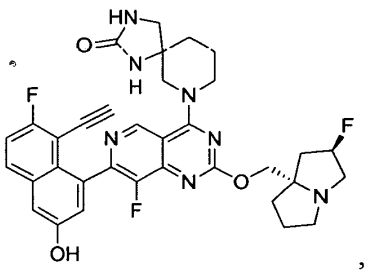
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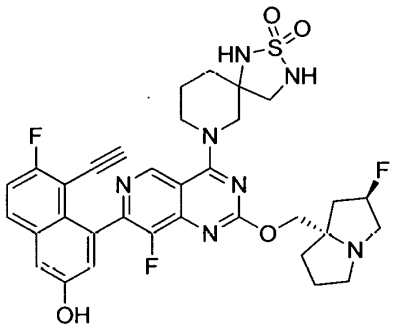
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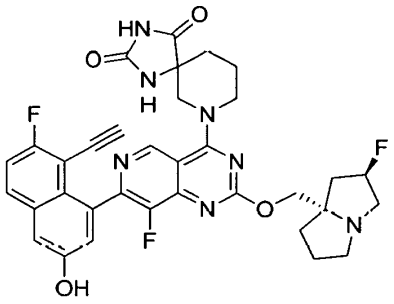
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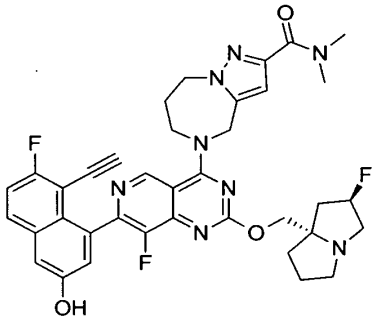
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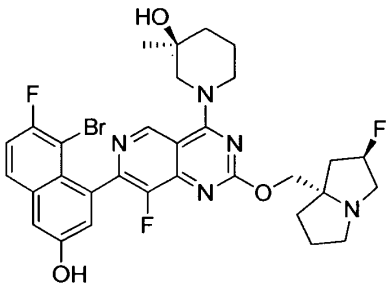
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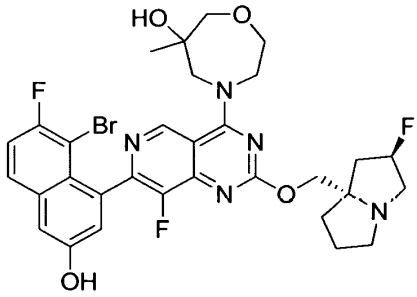
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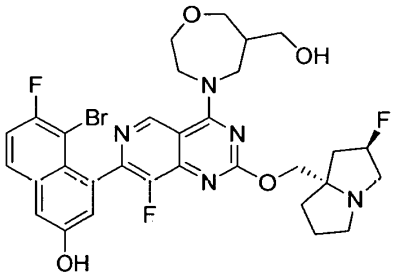
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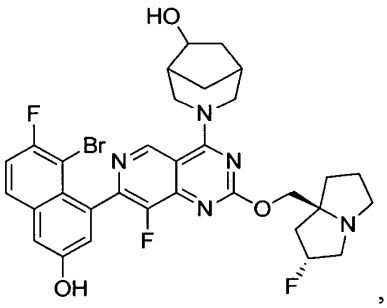
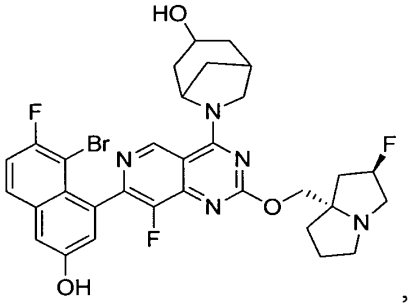
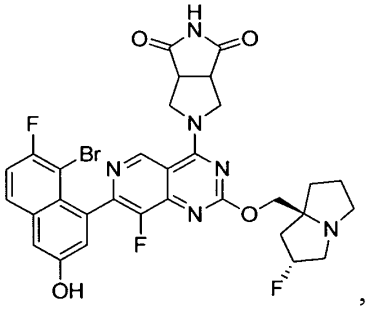
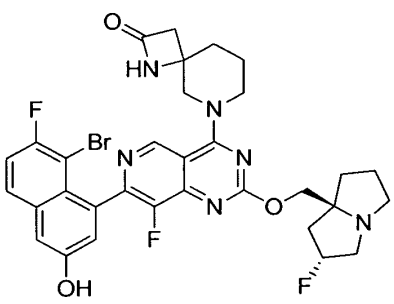
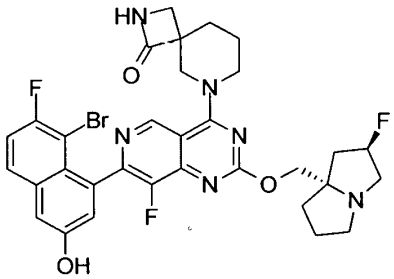
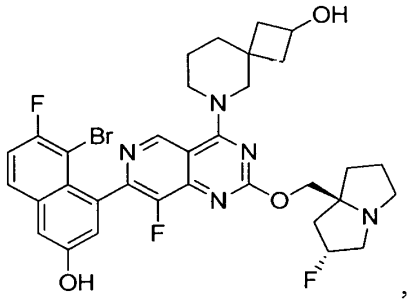
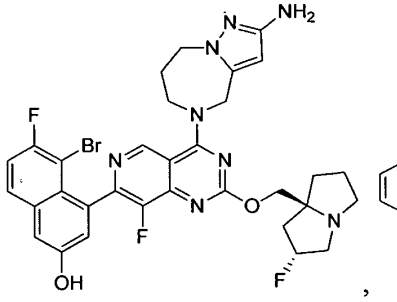
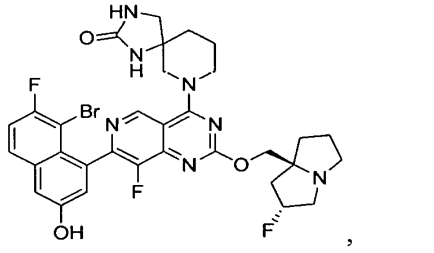

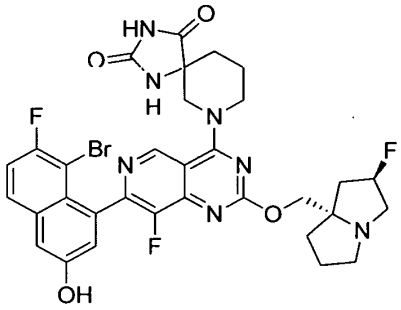
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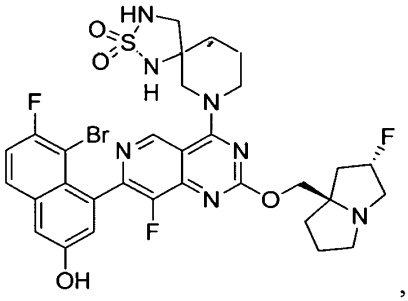
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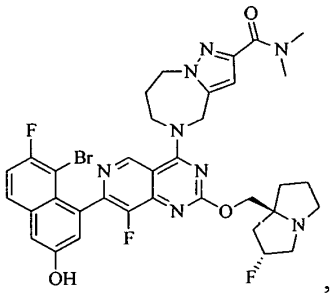
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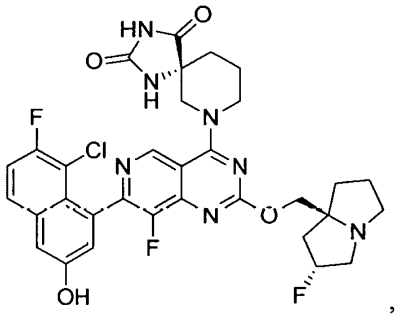
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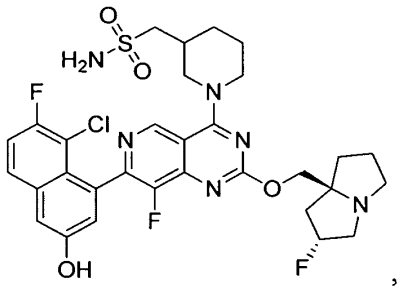
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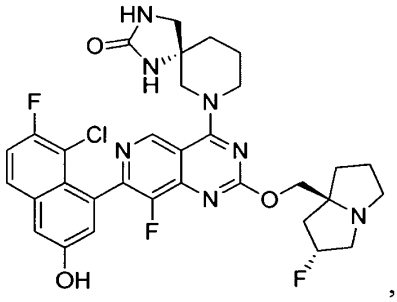
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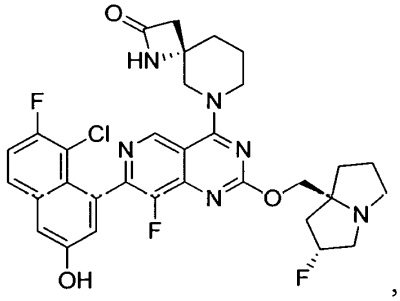
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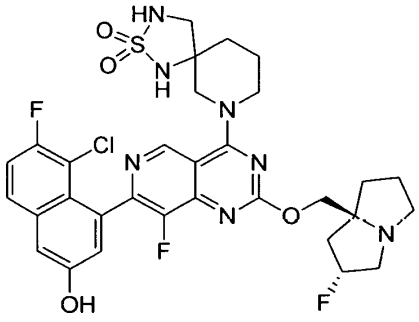
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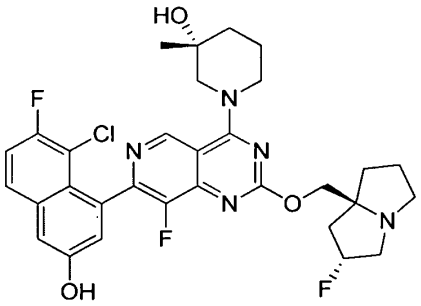
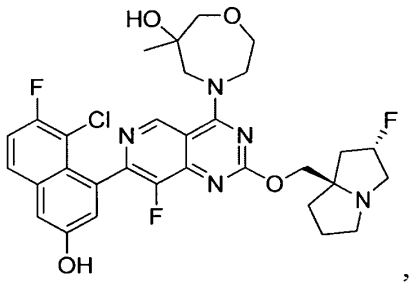
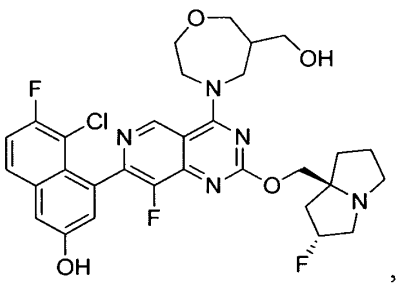
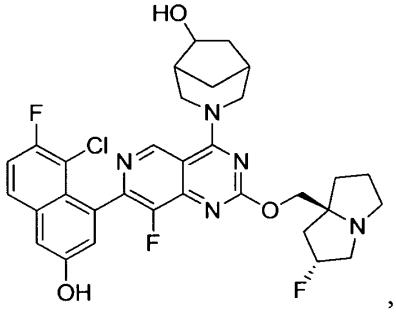
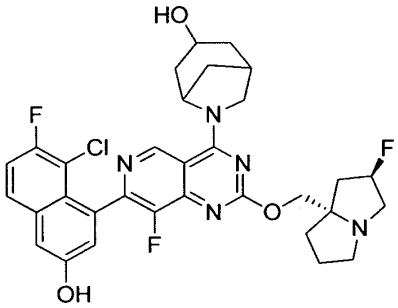
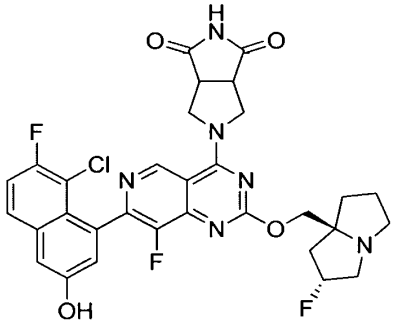
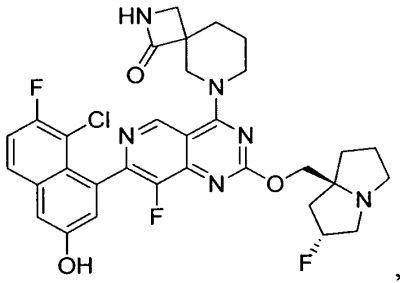
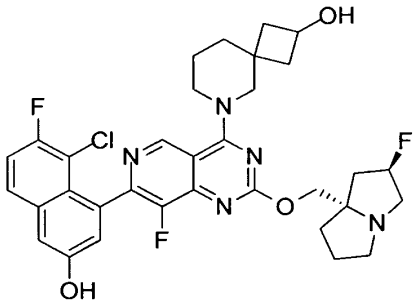

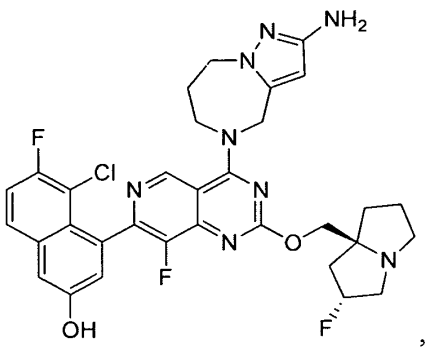
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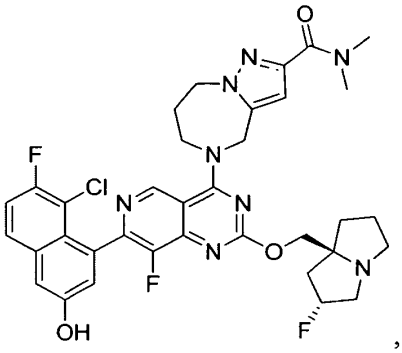
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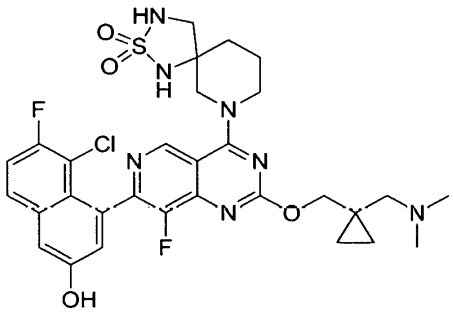
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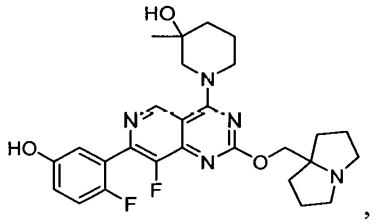
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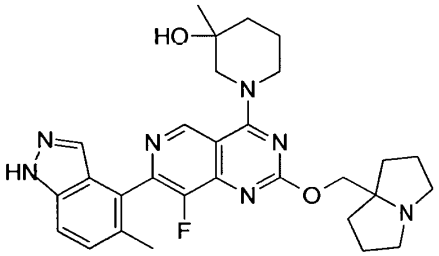
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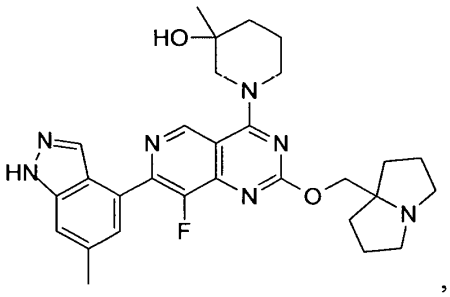
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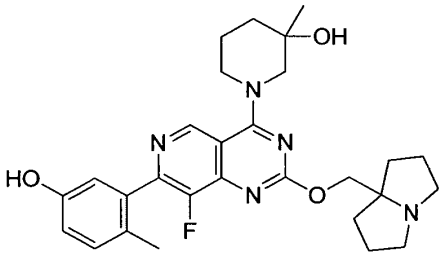
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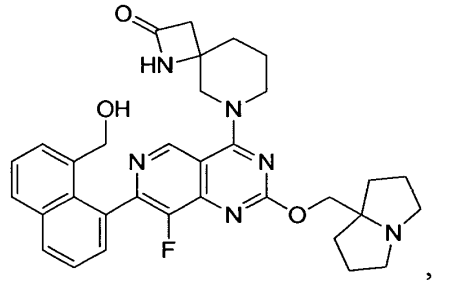
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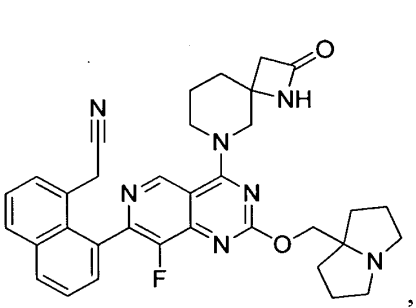
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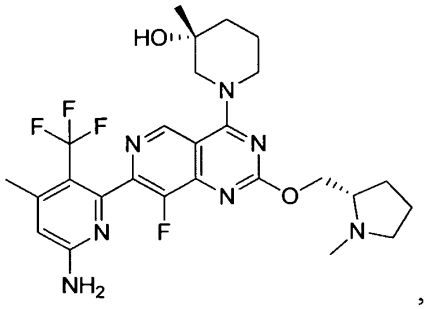
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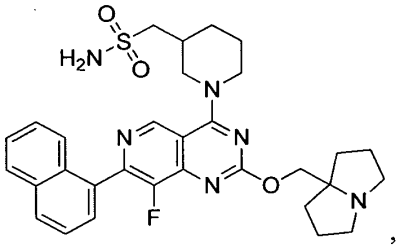
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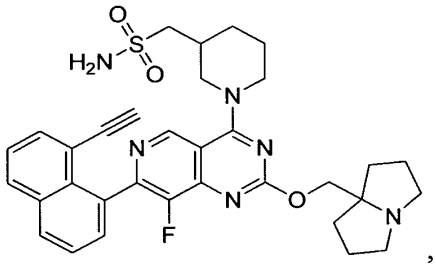
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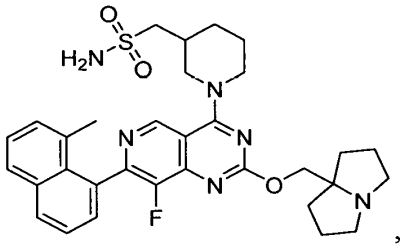
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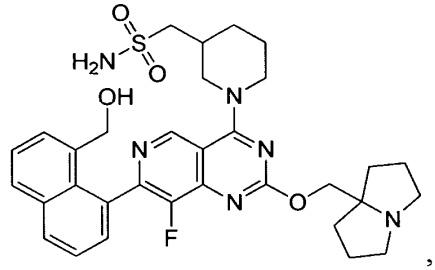
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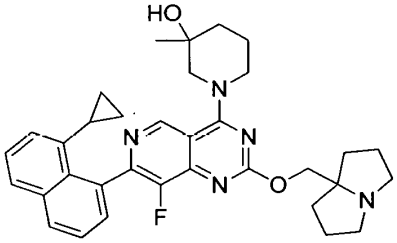
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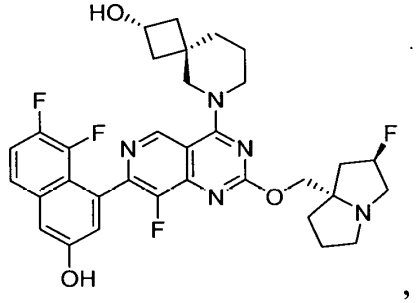
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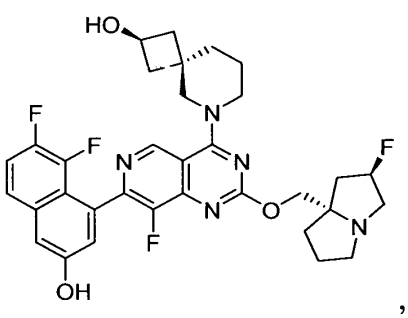
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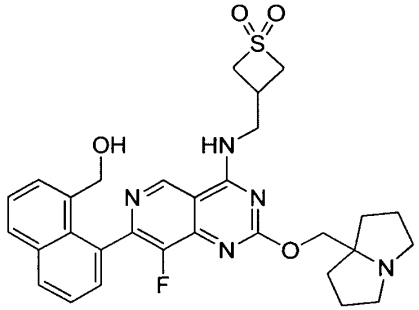
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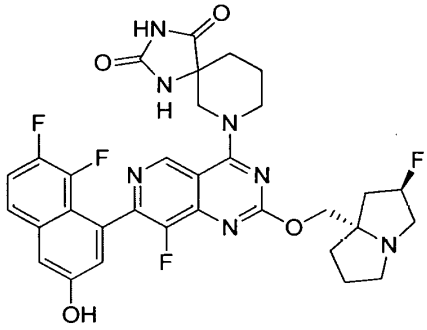
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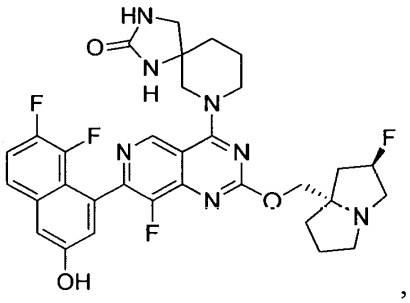
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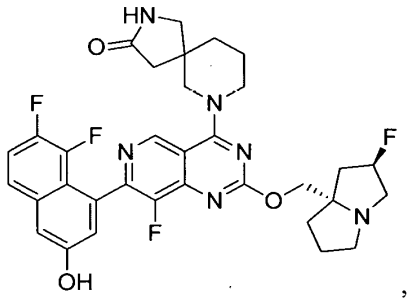
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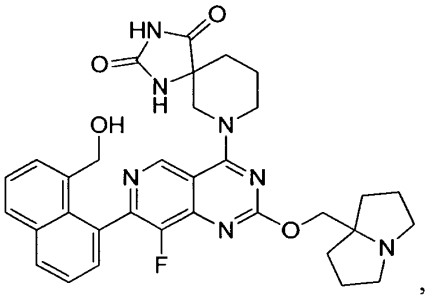
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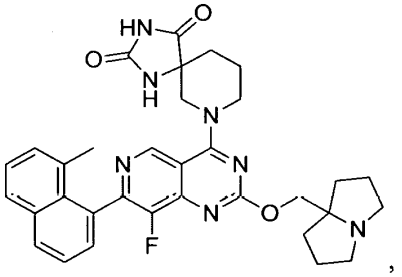
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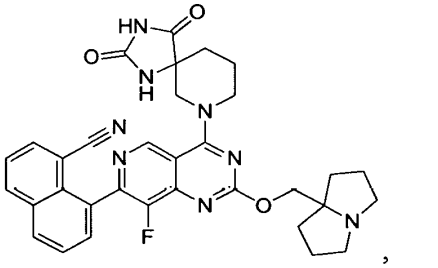
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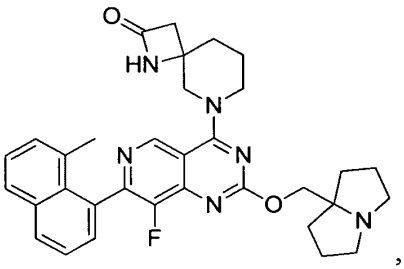
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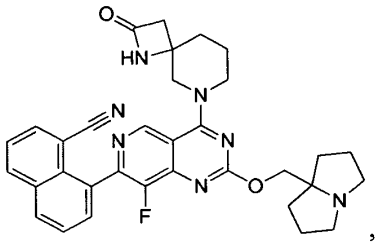
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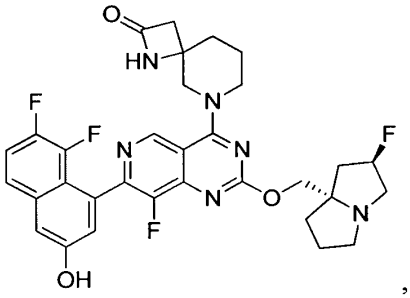
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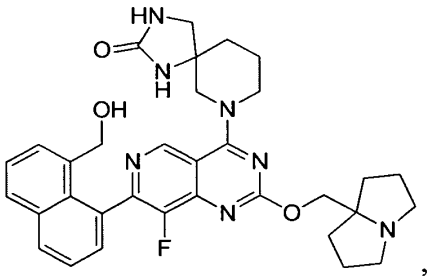
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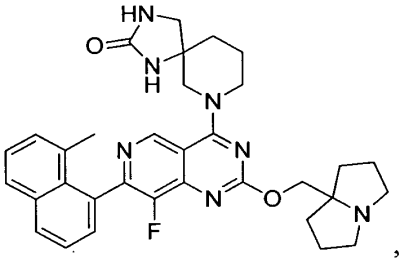
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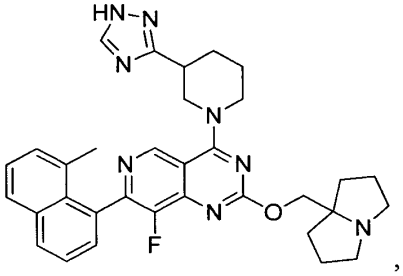
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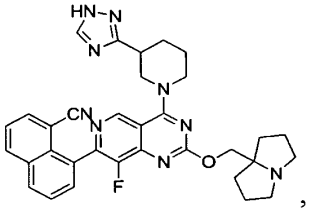
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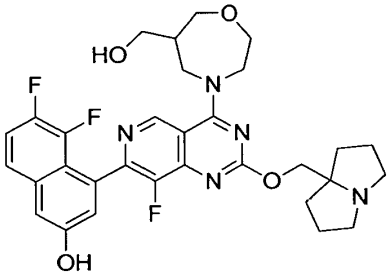
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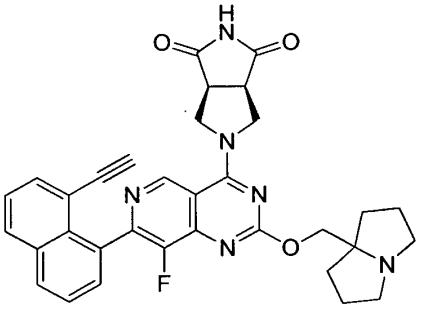
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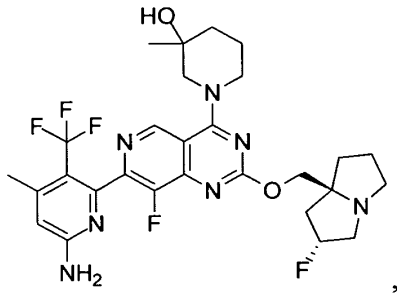
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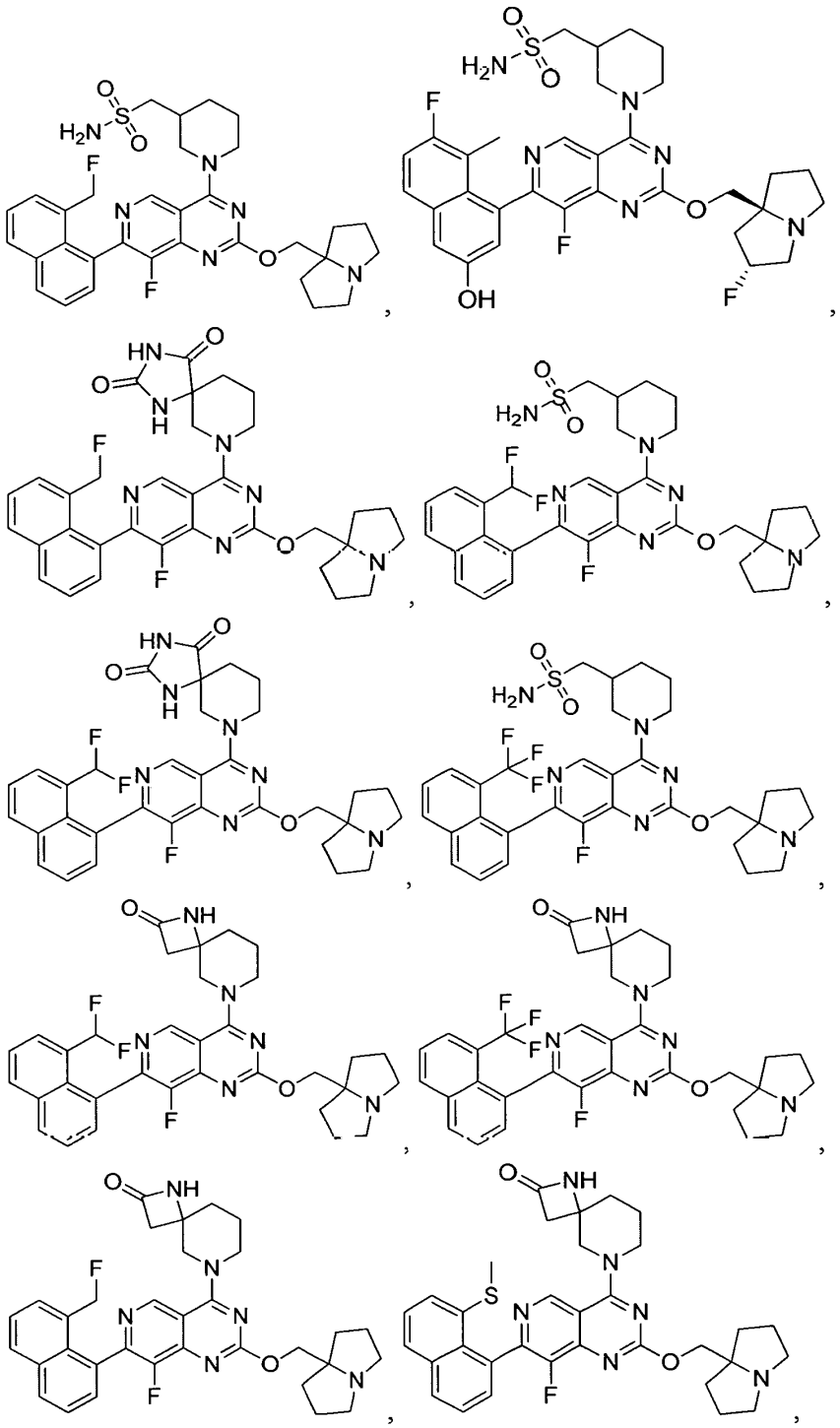

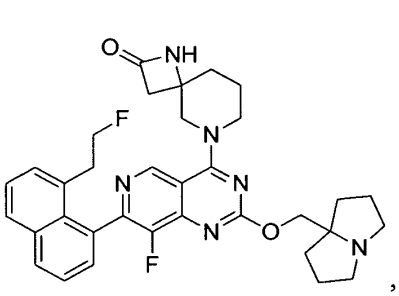
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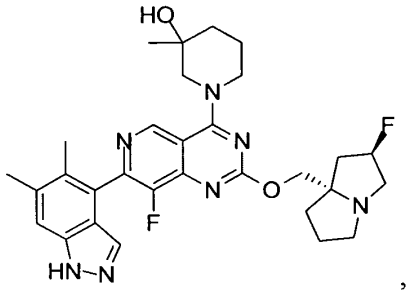
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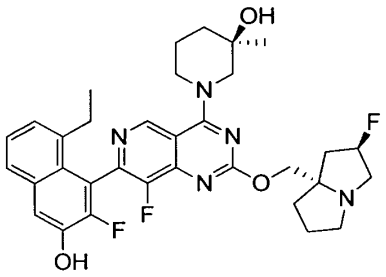
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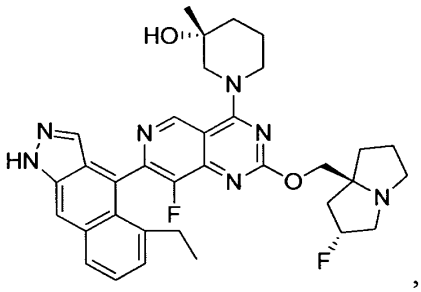
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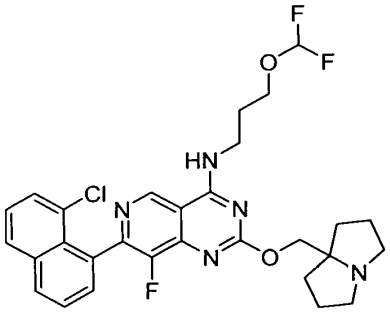
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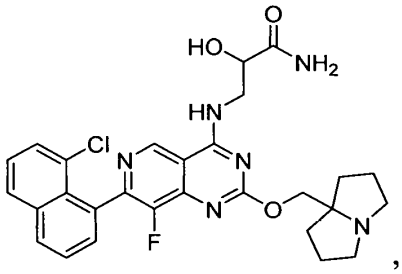
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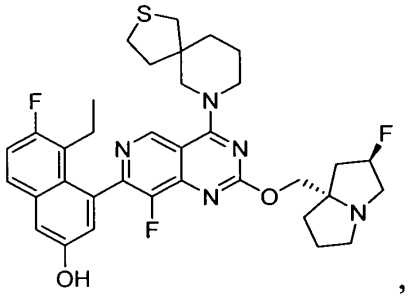
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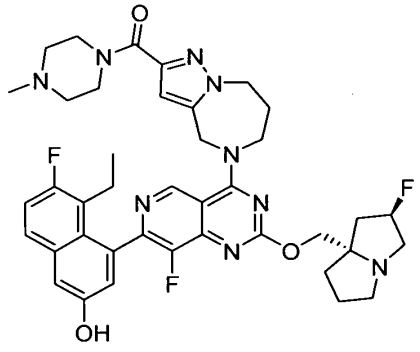
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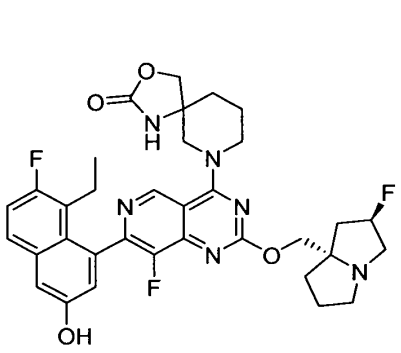
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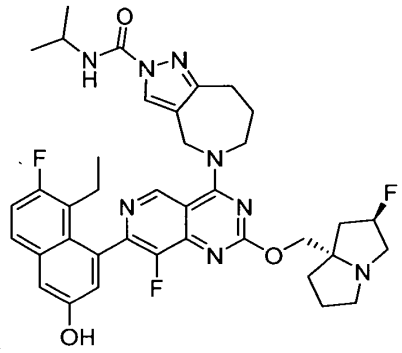
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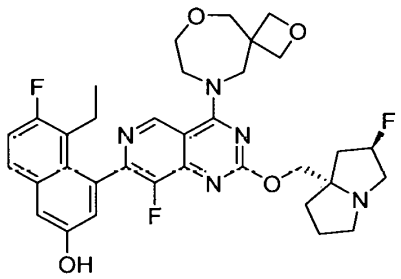
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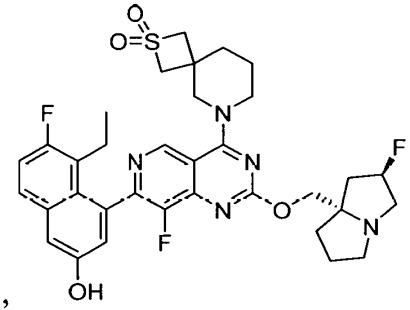
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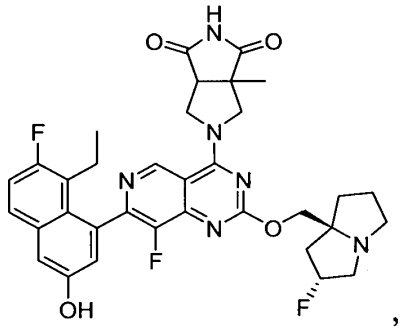
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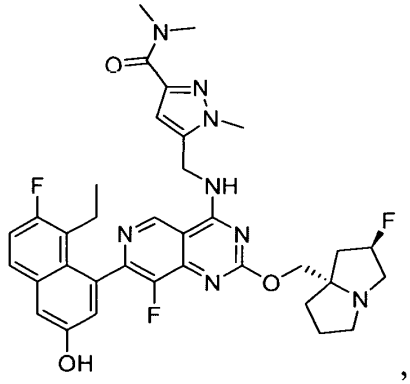
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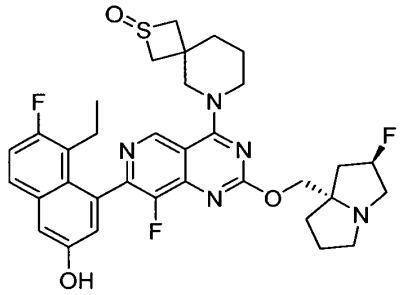
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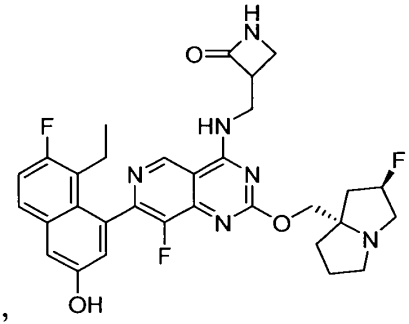
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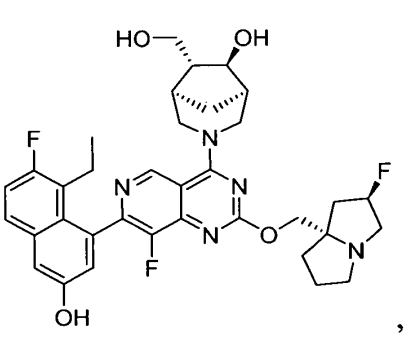
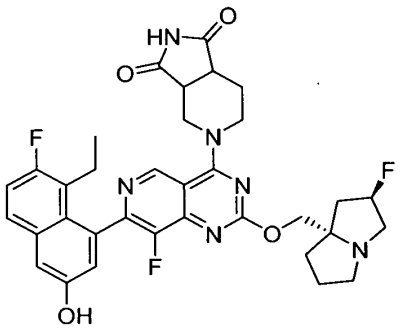
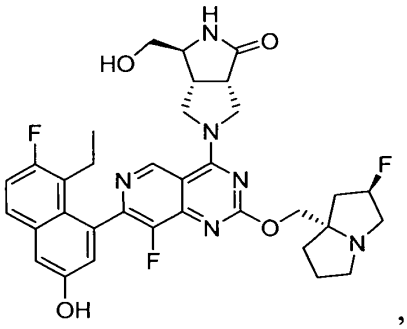
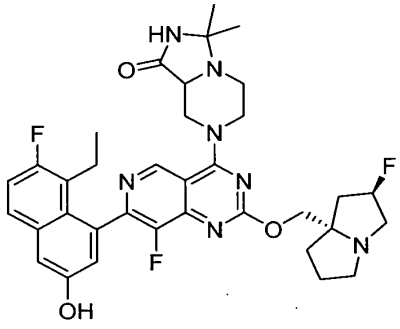
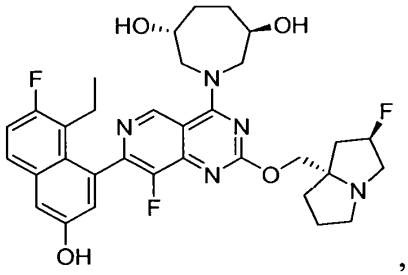
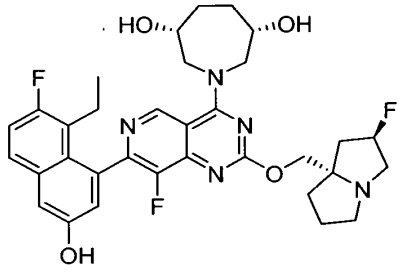
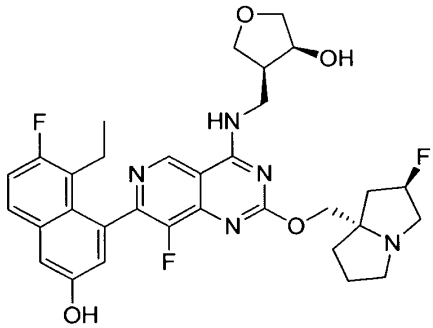
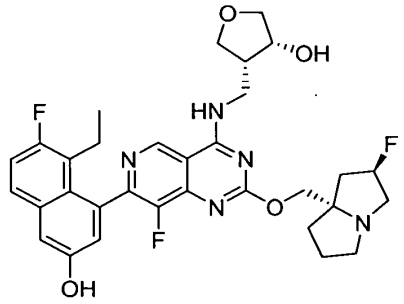

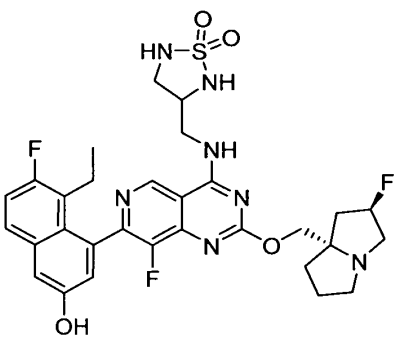
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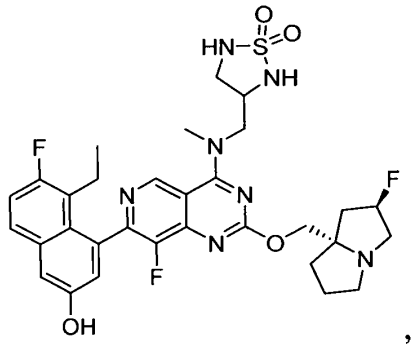
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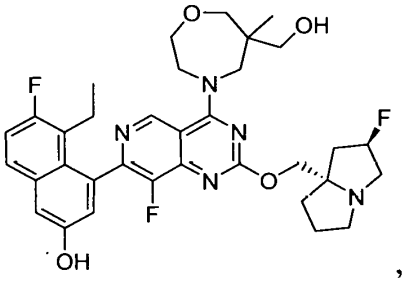
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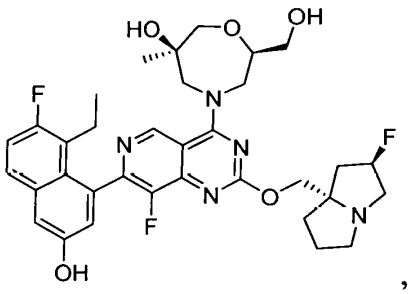
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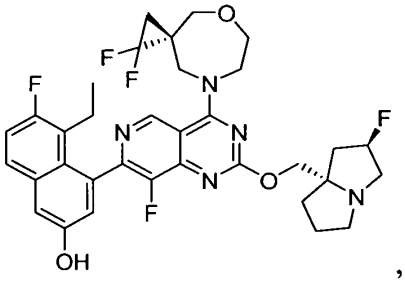
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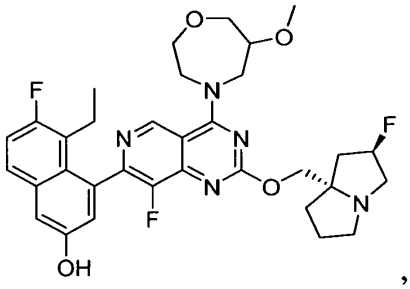
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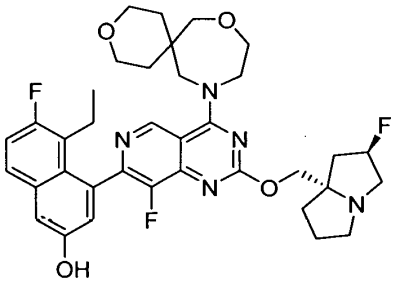
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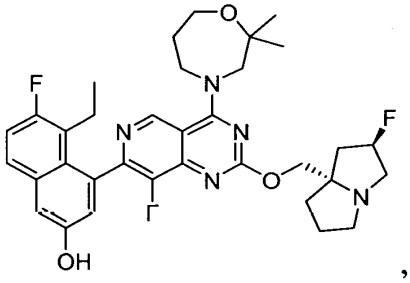
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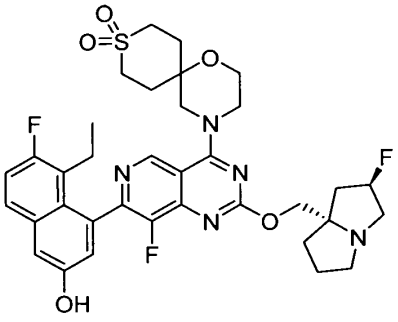
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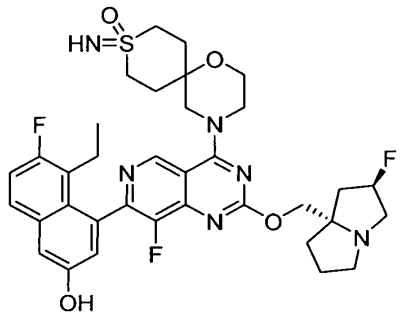
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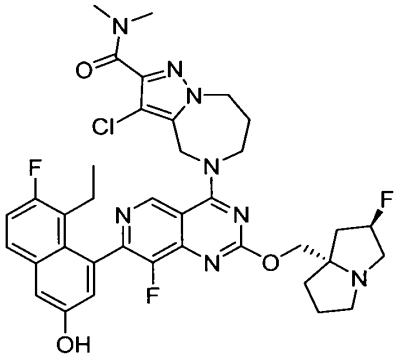
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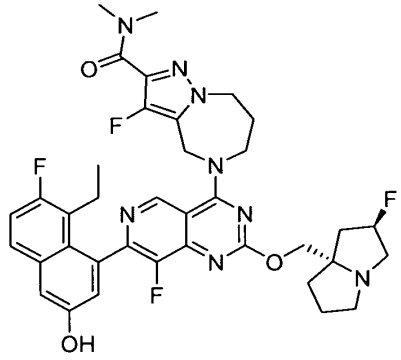
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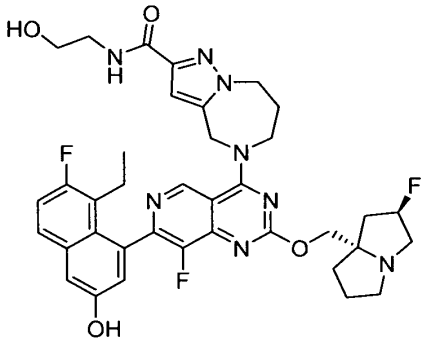
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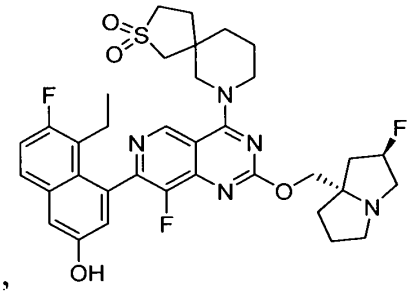
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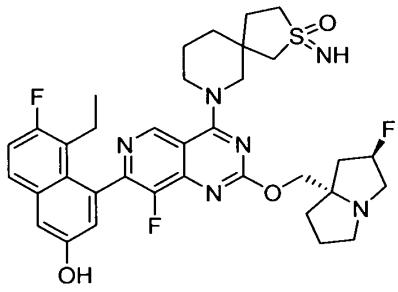
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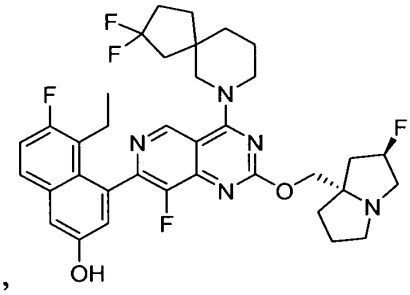
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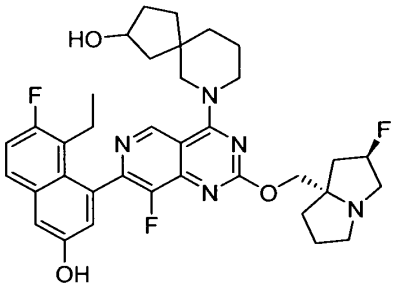
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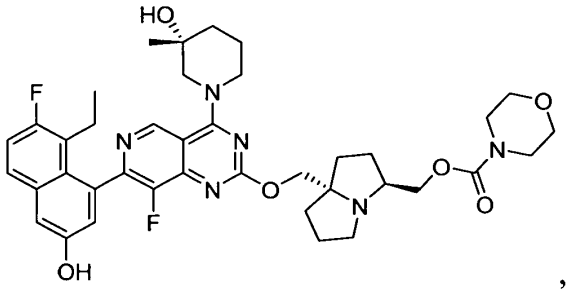
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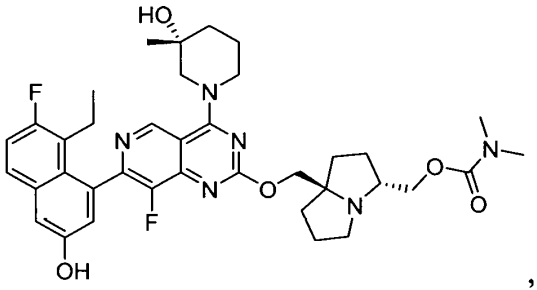
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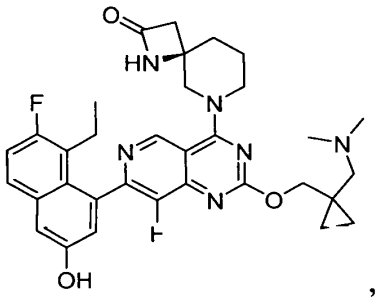
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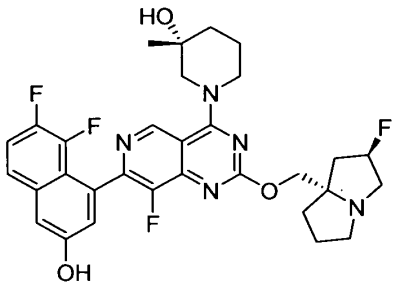
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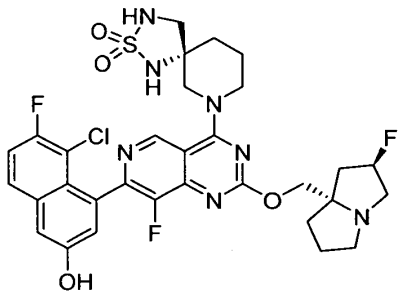
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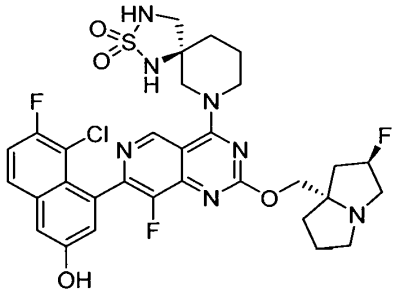
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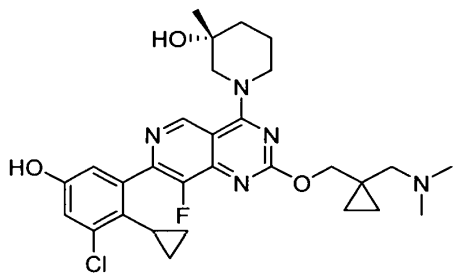
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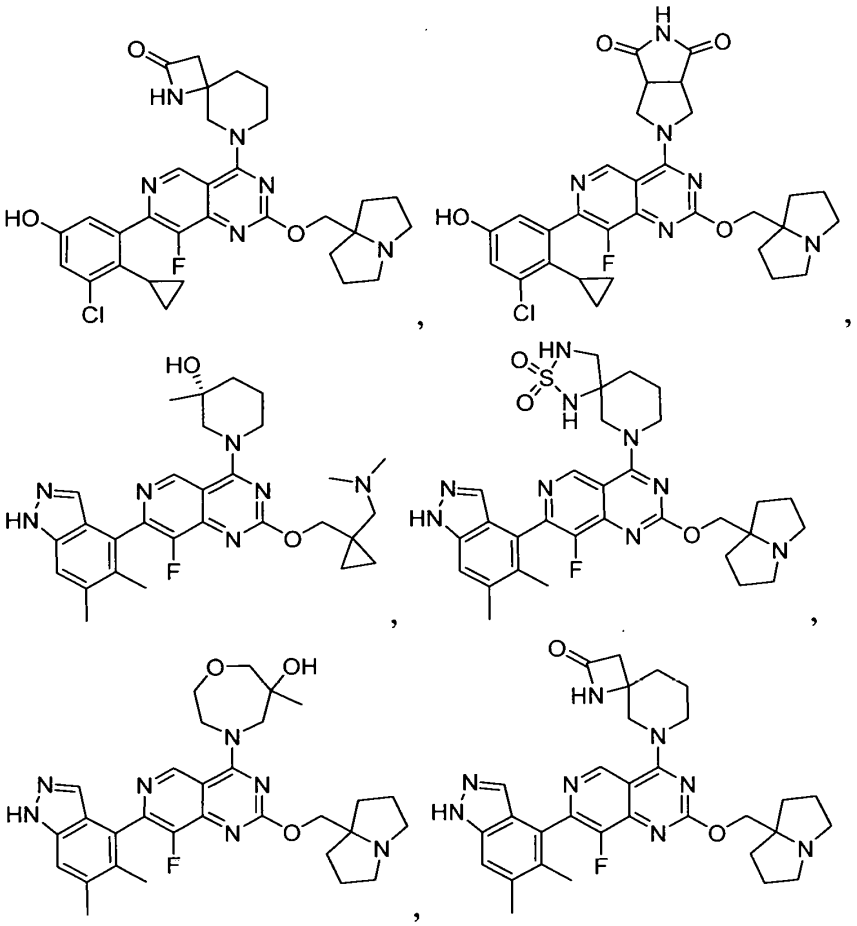

and pharmaceutically acceptable salts thereof.

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,

osteochronfroma (osteocartilaginous 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, intravitreous 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.