KRAS INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Provisional Patent Application No. 63/564,090, filed March 12, 2024; U.S. Provisional Patent Application No. 63/669,038, filed July 09, 2024; U.S. Provisional Patent Application No. 63/709,182, filed October 18, 2024; the disclosure of each of which is hereby incorporated by reference in its entirety for all purposes.

TECHNICAL FIELD

The disclosure relates to substituted pyridopyrimidine compounds that act as Kirsten rat sarcoma virus (KRAS) inhibitors. The disclosure also provides compounds of formula (I), stereoisomers of the compounds, and tautomers of the compounds, and pharmaceutically acceptable salts thereof and uses of the compounds, stereoisomers, tautomers, and salts for the treatment of abnormal cell growth, such as cancer, in a subject.

BACKGROUND

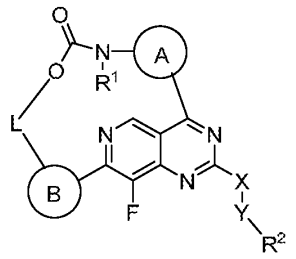
Kirsten rat sarcoma virus (KRAS) is a GTPase, a class of enzymes that convert nucleotide guanosine triphosphate (GTP) into guanosine diphosphate (GDP). KRAS plays an important role in the signal transduction cascade in biochemical pathways responsible for cell growth and differentiation.

While current kinase inhibitors can be effective treatments for cancer, their use may be limited by poor selectivity for KRAS. There remains a need to identify potent KRAS inhibitors for the treatment of patients with cancer or other proliferative diseases or conditions driven by KRAS alterations.

BRIEF SUMMARY

In brief, the present disclosure provides compounds, including stereoisomers, tautomers, or pharmaceutically acceptable salts thereof, which can be used alone or in combination with other therapeutic agents.

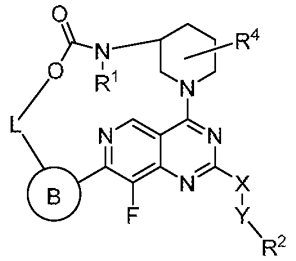
In one embodiment, a compound having a structure of Formula (I) is provided:



(I)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein R^1, R^2, L, X, Y, A, and B are as defined herein.

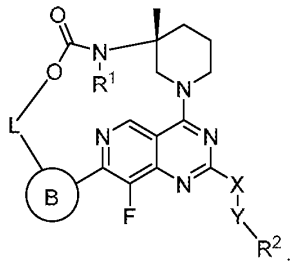
In some embodiments, a compound having a structure of Formula (IA) is provided:



(IA)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein the variables are as defined herein.

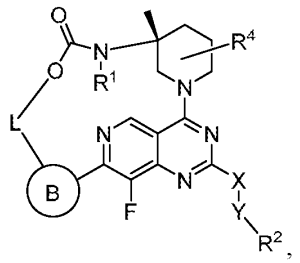
In some embodiments, a compound having a structure of Formula (IA-2) is provided:



(IA-2)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein the variables are as defined herein.

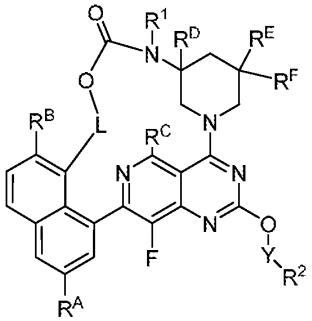
In some embodiments, a compound having a structure of Formula (IA-3) is provided:



(IA-3)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein the variables are as defined herein.

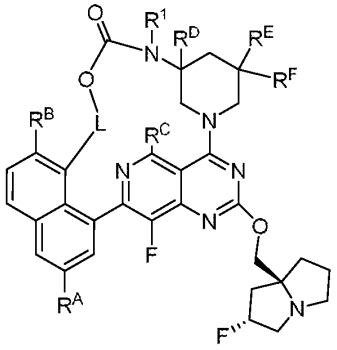
In some embodiments, a compound having a structure of Formula (III) is provided:



(III)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein the variables are as defined herein.

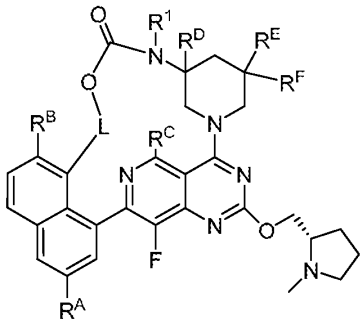
In some embodiments, a compound having a structure of Formula (IIIA) is provided:



(IIIA)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein the variables are as defined herein.

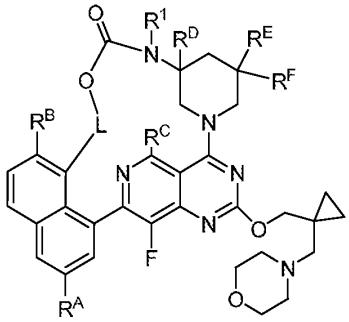
In some embodiments, a compound having a structure of Formula (IIIB) is provided:



(IIIB)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein the variables are as defined herein.

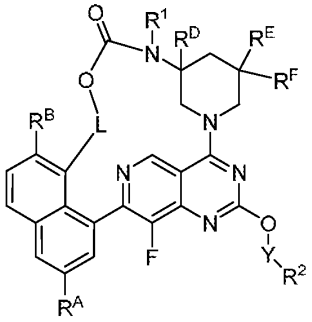
In some embodiments, a compound having a structure of Formula (IIIC) is provided:



(IIIC)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein the variables are as defined herein.

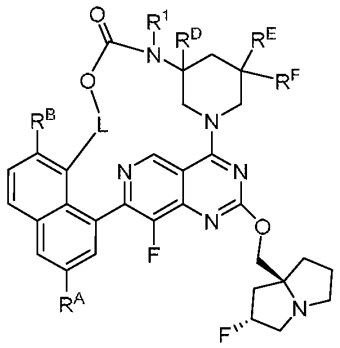
In some embodiments, a compound having a structure of Formula (III-1) is provided:



(III-1)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein the variables are as defined herein.

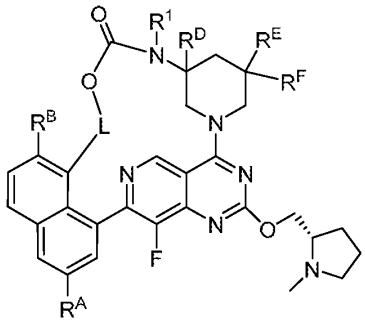
In some embodiments, a compound having a structure of Formula (III-1A) is provided:



(III-1A)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein the variables are as defined herein.

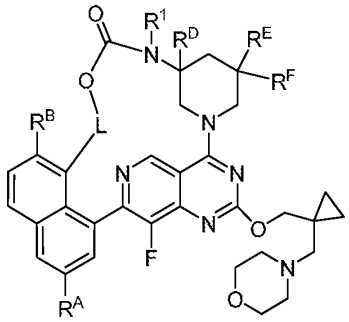
In some embodiments, a compound having a structure of Formula (III-1B) is provided:



(III-1B)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein the variables are as defined herein.

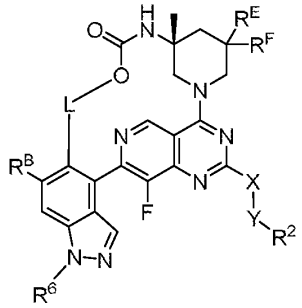
In some embodiments, a compound having a structure of Formula (III-1C) is provided:



(III-1C)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein the variables are as defined herein.

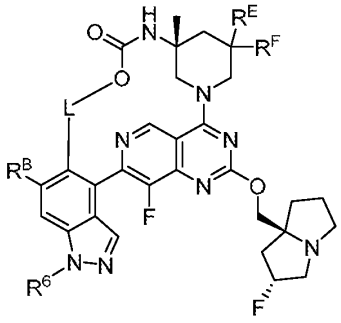
In some embodiments, a compound having a structure of Formula (IV) is provided:



(IV)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein the variables are as defined herein.

In some embodiments, a compound having a structure of Formula (IVA) is provided:



(IVA)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein the variables are as defined herein.

Pharmaceutical compositions comprising one or more of the foregoing compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA)

and an additional therapeutic agent are also provided.

In other embodiments, methods of treatment by administering the foregoing compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) or the pharmaceutical compositions comprising a compound of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA), to a subject in need thereof to treat a disease are provided.

Various aspects and embodiments now will be described more fully hereinafter. Such aspects and embodiments may take many different forms, and the exemplary ones disclosed herein should not be construed as limiting; rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey its scope to those skilled in the art.

DETAILED DESCRIPTION

I. Definitions

For convenience, certain terms employed in the specification, examples and claims are collected here. Unless defined otherwise, all technical and scientific terms used in this disclosure have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

Where a range of values is provided, it is intended that each intervening value between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the disclosure. For example, if a range of 1 mM to 8 mM is stated, it is intended that 2 mM, 3 mM, 4 mM, 5 mM, 6 mM, and 7 mM are also explicitly disclosed, as well as the range of non-integer values greater than or equal to 1 mM and the range of non-integer values less than or equal to 8 mM.

The singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a "polymer" includes a single polymer as well as two or more of the same or different polymers, reference to an "excipient" includes a single excipient as well as two or more of the same or different excipients, and the like.

The term “about”, particularly in reference to a given quantity, is meant to encompass deviations of plus or minus five percent.

The compositions of the present disclosure can comprise, consist essentially of, or consist of, the components disclosed.

All percentages, parts and ratios are based upon the total weight of the compositions and all measurements made are at about 25 °C., unless otherwise specified.

As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated:

"Amino" refers to the $-NH_2$, -NHR, or $-NR_2$ radical,

"Cyano" refers to the -CN radical,

"Hydroxyl" refers to the -OH radical,

"Imino" refers to the =NH or =NR substituent,

"Nitro" refers to the $-NO_2$ radical,

"Oxo" refers to the =O substituent,

"Thio" refers to the -S substituent,

"Trifluoromethyl" refers to the $-CF_3$ radical,

Hydrazido or hydrazino refers to N-N substituent,

wherein each R of “amino” or “imino” is a compatible substituent as described in this disclosure and wherein an R group is chiral, isomers are contemplated and included herein.

"Alkyl" refers to a linear, saturated, acyclic, monovalent hydrocarbon radical or branched, saturated, acyclic, monovalent hydrocarbon radical, having from one to twelve carbon atoms, preferably one to eight carbon atoms or one to six carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl and the like. An optionally substituted alkyl radical is an alkyl radical that is optionally substituted, valence permitting, by one, two, three, four, or five substituents independently selected from the group consisting of halo, cyano, nitro, aryl, cycloalkyl, heterocyclyl, heteroaryl, oxo, trimethylsilyl, $-OR'$, $-OC(O)R'$, $-N(R')_2$, $C(O)R''$, $-C(O)OR'$, $-C(O)N(R')_2$, $-N(R')C(O)OR'''$, $N(R')C(O)R'''$, $-N(R')S(O)_tR'''$ (where t is 1 or 2), $-S(O)_tOR'''$ (where t is 1 or 2), $-S(O)_pR'''$ (where p is 0, 1, or 2) and $-S(O)_tN(R')_2$ (where t is 1 or 2), where each R' is independently hydrogen, alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, or heteroaryl; each R'' is independently hydrogen, cycloalkyl, aryl, heterocyclyl, or heteroaryl; and each R''' is independently alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl.

"Alkylene" refers to a divalent radical of an alkyl group.

"Deuteroalkylene" refers to a divalent radical of a deuteroalkyl group.

"Alkenyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon double bonds (*e.g.*, 1, 2, 3, or 4 carbon–carbon double bonds), and optionally one or more carbon–carbon triple bonds (*e.g.*, 1, 2, 3, or 4 carbon–carbon triple bonds) ("C2–20 alkenyl").

"Alkenylene" refers to a divalent radical of an alkenyl group.

"Alkynyl" refers to a radical of a straight–chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon–carbon triple bonds (*e.g.*, 1, 2, 3, or 4 carbon–carbon triple bonds), and optionally one or more carbon–carbon double bonds (*e.g.*, 1, 2, 3, or 4 carbon–carbon double bonds) ("C2–20 alkynyl").

"Alkynylene" refers to a divalent radical of an alkynyl group.

"Alkylalcohol" refers to an alkyl group substituted with an alcohol (-OH) group.

"Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined above containing one to twelve carbon atoms. The alkyl part of the optionally substituted alkoxy radical is optionally substituted as defined above for an alkyl radical.

"Alkoxyalkyl" refers to a radical of the formula $-R_a-O-R_b$ where R_a is alkylene and R_b is alkyl as defined above. Alkyl and alkylene parts of the optionally substituted alkoxyalkyl radical are optionally substituted as defined above for an alkyl radical and alkylene chain, respectively.

"Aralkyl" refers to a radical of the formula $-R_a-R_b$, where R_a is alkylene and R_b is aryl as described herein. Alkylene and aryl portions of optionally substituted aralkyl are optionally substituted as described herein for alkylene and aryl, respectively.

"Aryl" refers to an aromatic monocyclic or multicyclic hydrocarbon ring system radical containing from 6 to 18 carbon atoms, where the multicyclic aryl ring system is a bicyclic, tricyclic, or tetracyclic ring system. Aryl radicals include, but are not limited to, groups such as fluorenyl, phenyl and naphthyl. An optionally substituted aryl is an aryl radical that is optionally substituted by one, two, three, four, or five substituents independently selected from the group consisting of alkyl, akenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, aryl, heteroaryl, heteroarylalkyl, $-R''-OR'$, $-R''-OC(O)-R'$, $-R''-N(R')_2$, $-R''-C(O)R'$, $-R''-C(O)OR'$, $-R''-C(O)N(R')_2$, $-R''-N(R')C(O)OR'''$, $-R''-N(R')C(O)R'''$, $-R''-N(R')S(O)_tR'''$ (where t is 1 or 2), $-R''-S(O)_tOR'''$ (where t is 1 or 2), $-R''-S(O)_pR'''$ (where p is 0, 1, or 2), and $-R''-S(O)_tN(R')_2$ (where t is 1 or 2), where each R' is independently hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl; each

R″ is independently a direct bond or a linear or branched alkylene or alkenylene chain; and each R‴ is independently alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclyl, or heteroaryl.

"Arylene" refers to a divalent radical of an aryl group.

"Arylalkoxy" refers to a group of formula –O-R, where R is aralkyl. An optionally substituted arylalkoxy is an arylalkoxy that is optionally substituted as described herein for aralkyl. In some embodiments, arylalkoxy is benzyloxy.

"Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical having from three to fifteen carbon atoms, preferably having from three to ten carbon atoms, and which is saturated or unsaturated, and which attaches to the rest of the molecule by a single bond. A polycyclic hydrocarbon radical is bicyclic, tricyclic, or tetracyclic ring system. An unsaturated cycloalkyl contains one, two, or three carbon-carbon double bonds and/or one carbon-carbon triple bond. Monocyclic cycloalkyl radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyl radicals include, for example, adamantyl, norbornyl, decalinyl, and the like. An optionally substituted cycloalkyl is a cycloalkyl radical that is optionally substituted by one, two, three, four, or five substituents independently selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, nitro, oxo, aryl, aralkyl, cycloalkyl, heterocyclyl, heteroaryl, -R″-OR′, -R″-OC(O)-R′, -R″-N(R′)$_2$, -R″-C(O)R′, -R″-C(O)OR′, -R″-C(O)N(R′)$_2$, -R″-N(R′)C(O)OR‴, -R″-N(R′)C(O)R‴, -R″-N(R′)S(O)$_t$R‴ (where t is 1 or 2), -R″-S(O)$_t$OR‴ (where t is 1 or 2), -R″-S(O)$_p$R‴ (where p is 0, 1, or 2) and -R″-S(O)$_t$N(R′)$_2$ (where t is 1 or 2) where each R′ is independently hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl; each R″ is independently a direct bond or a linear or branched alkylene or alkenylene chain; and each R‴ is independently alkyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, or heteroaryl.

"Deuterated compounds" are compounds where one or more hydrogen atoms have been replaced with a deuterium atom. Deuterated drugs may be derivatives of an active compound. Deuterated drugs may be prodrugs. Deuteration may alter the physical properties, metabolic properties, activity or safety of a drug.

"Deuteroalkyl" refers to an alkyl group where 1 or more hydrogen atoms of an alkyl are replaced with deuterium.

"Derivatives" are related chemical species that can be derived from a similar compound via chemical reactions. They may encompass slight chemical modifications, substitution of atoms with deuterated atoms, substitution of atoms with stable or radioactive

isotopes or other modifications that imbue a compound with desirable properties.

"Fused" refers to any ring system described herein which is fused to an existing ring structure in the compounds of the invention. When the fused ring system is a heterocyclyl or a heteroaryl, any carbon atom on the existing ring structure which becomes part of the fused ring system may be replaced with a nitrogen atom.

"Halo" refers to the halogen substituents: bromo, chloro, fluoro, and iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is further substituted by one or more halogen substituents. The number of halo substituents included in haloalkyl is from one and up to the total number of the hydrogen atoms available for replacement with the halo substituents (e.g., perfluoroalkyl). Non-limiting examples of haloalkyl include trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl, 2-fluoroethyl, 3-bromo 2-fluoropropyl, 1-bromomethyl, 2-bromoethyl and the like. For an optionally substituted haloalkyl, the hydrogen atoms bonded to the carbon atoms of the alkyl part of the haloalkyl radical may be optionally replaced with substituents as defined above for an optionally substituted alkyl.

"Haloalkenyl" refers to an alkenyl radical, as defined above, that is further substituted by one or more halo substituents. The number of halo substituents included in haloalkenyl is from one and up to the total number of the hydrogen atoms available for replacement with the halo substituents (e.g., perfluoroalkenyl). Non-limiting examples of haloalkenyl include 2,2-difluoroethenyl, 3-chloroprop-1-enyl, and the like. For an optionally substituted haloalkenyl, the hydrogen atoms bonded to the carbon atoms of the alkenyl part of the haloalkenyl radical may be optionally replaced with substituents as defined above for an optionally substituted alkenyl group.

"Haloalkynyl" refers to an alkynyl radical, as defined above, that is further substituted by one or more halo substituents. The number of halo substituents included in haloalkynyl is from one and up to the total number of the hydrogen atoms available for replacement with the halo substituents (e.g., perfluoroalkynyl). Non-limiting examples of haloalkynyl include 3-chloroprop-1-ynyl and the like. The alkynyl part of the haloalkynyl radical may be additionally optionally substituted as defined above for an alkynyl group.

"Heteroalkyl" refers to a non-cyclic stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P, S, and Si may be placed at any interior position of the heteroalkyl

group or at the position at which the alkyl group is attached to the remainder of the molecule. Exemplary heteroalkyl groups include, but are not limited to: $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $-O-CH_3$, and $-O-CH_2-CH_3$. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$.

"Heteroalkylene" refers to a divalent radical of a heteroalkyl.

"Heteroarylalkyl" refers to a radical of the formula $-R_a-R_b$, where R_a is alkylene and R_b is heteroaryl as described herein. Alkylene and heteroaryl portions of optionally substituted heteroarylalkyl are optionally substituted as described herein for alkylene and heteroaryl, respectively.

"Heterocyclyl" refers to a stable 3- to 18-membered nonaromatic ring system radical having the carbon count of two to twelve and containing a total of one to six heteroatoms independently selected from the group consisting of nitrogen, oxygen, phosphorus, and sulfur. A heterocyclyl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system. A bicyclic, tricyclic, or tetracyclic heterocyclyl is a fused, spiro, and/or bridged ring system. The heterocyclyl radical may be saturated or unsaturated. Heterocyclyl includes ring systems wherein the heterocyclyl ring is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring. An unsaturated heterocyclyl contains one, two, or three carbon-carbon double bonds and/or one carbon-carbon triple bond. An optionally substituted heterocyclyl is a heterocyclyl radical that is optionally substituted by one, two, three, four, or five substituents independently selected from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, oxo, thioxo, nitro, aryl, aralkyl, cycloalkyl, heterocyclyl-, heteroaryl, $-R''-OR'$, $-R''-OC(O)-R'$, $-R''-N(R')_2$, $-R''-C(O)R'$, $-R''-C(O)OR'$, $-R''-C(O)N(R')_2$, $-R''-N(R')C(O)OR'''$, $-R''-N(R')C(O)R'''$, $-R''-N(R')S(O)_tR'''$ (where t is 1 or 2), $-R''-S(O)_tOR'''$ (where t is 1 or 2), $-R''-S(O)_pR'''$ (where p is 0, 1, or 2), and $-R''-S(O)_tN(R')_2$ (where t is 1 or 2), where each R' is independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl; each R'' is independently a direct bond or a linear or branched alkylene or alkenylene chain; and each R''' is independently alkyl, alkenyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl. The nitrogen, carbon, or sulfur atoms in the heterocyclyl radical may be optionally oxidized (when the substituent is oxo and is present on the heteroatom); the nitrogen atom may be optionally quaternized (when the substituent is alkyl, alkenyl, aryl, aralkyl, cycloalkyl, heterocyclyl, heteroaryl, $-R''-OR'$, $-R''-OC(O)-R'$, $-R''-N(R')_2$, $-R''-C(O)R'$, $-R''-C(O)OR'$, -

R″-C(O)N(R′)$_2$, -R″-N(R′)C(O)OR‴, -R″-N(R′)C(O)R‴, -R″-N(R′)S(O)$_t$R‴ (where t is 1 or 2), -R″-S(O)$_t$OR‴ (where t is 1 or 2), -R″-S(O)$_p$R‴ (where p is 0, 1, or 2), and -R″-S(O)$_t$N(R′)$_2$ (where t is 1 or 2), where R″ is a linear or branched alkylene or alkenylene chain, and R′ and R‴ are as defined above). Examples of optionally substituted heterocyclyl radicals include, but are not limited to, azetidinyl, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2oxopyrrolidinyl, oxazolidinyl-, piperidinyl, piperazinyl, 4piperidonyl, pyrrolidinyl, pyrazolidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1---oxothiomorpholinyl, and 1,1---dioxo-thiomorpholinyl. "Heterocyclylene" refers to a heterocyclyl in which one hydrogen atom is replaced with a valency. An optionally substituted heterocyclylene is optionally substituted as described herein for heterocyclyl.

"Heteroaryl" refers to a 5- to 18-membered ring system radical containing at least one aromatic ring, having the carbon count of one to seventeen carbon atoms, and containing a total of one to ten heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The heteroaryl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system. The bicyclic, tricyclic, or tetracyclic heteroaryl radical is a fused and/or bridged ring system. "Heteroaryl" also includes ring systems wherein the heteroaryl ring is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring. An optionally substituted heteroaryl is a heteroaryl radical that is optionally substituted by one, two, three, four, or five substituents independently selected from the group consisting of alkyl, alkenyl, alkoxy, halo, haloalkyl, haloalkenyl, cyano, oxo, thioxo, nitro, oxo, aryl, aralkyl, cycloalkyl, heterocyclyl, heteroaryl, or heteroarylalkyl-, -R″-OR′, -R″-OC(O)-R′, -R″-N(R′)$_2$, -R″-C(O)R′, -R″-C(O)OR′, -R″-C(O)N(R′)$_2$, -R″-N(R′)C(O)OR‴, -R″-N(R′)C(O)R‴, -R″-N(R′)S(O)$_t$R‴ (where t is 1 or 2), -R″-S(O)$_t$OR‴ (where t is 1 or 2), -R″-S(O)$_t$R‴ (where p is 0, 1, or 2), and -R″-S(O)$_t$N(R′)$_2$ (where t is 1 or 2), where each R′ is independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl; each R″ is independently a direct bond or a linear or branched alkylene or alkenylene chain; and each R‴ is alkyl, alkenyl, haloalkyl, cycloalkyl, aryl, heterocyclyl, or heteroaryl. The nitrogen, carbon, or sulfur atoms in the heterocyclyl radical may be optionally oxidized (when the substituent is oxo and is present on the heteroatom), provided that at least one ring in heteroaryl remains aromatic; the nitrogen atom may be optionally quaternized (when the substituent is alkyl, alkenyl, aryl, aralkyl, cycloalkyl,

heterocyclyl, heteroaryl, -R″-OR′, -R″-OC(O)-R′, -R″-N(R′)$_2$, -R″-C(O)R′, -R″-C(O)OR′, -R″-C(O)N(R′)$_2$, -R″-N(R′)C(O)OR‴, -R″-N(R′)C(O)R‴, -R″-N(R′)S(O)$_t$R‴ (where t is 1 or 2), -R″-S(O)$_t$OR‴ (where t is 1 or 2), -R″-S(O)$_p$R‴ (where p is 0, 1, or 2), and -R″-S(O)$_t$N(R′)$_2$ (where t is 1 or 2), where R″ is a linear or branched alkylene or alkenylene chain, and R′ and R‴ are as defined above), provided that at least one ring in heteroaryl remains aromatic. Examples of optionally substituted heteroaryl radicals include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzthiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, 1,4benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo-[1,2a]pyridinyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, naphthyl, naphthyridinyl, oxadiazolyl-, 2oxoazepinyl, oxazolyl, oxiranyl-, 1-phenyl-1*H*pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl and thiophenyl- (*i.e.*, thienyl).

"Heteroarylene" is a divalent radical of a heteroaryl group.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, salts, compositions, dosage forms, etc., which are--within the scope of sound medical judgment--suitable for use in contact with the tissues of human beings and/or other mammals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. In some aspects, "pharmaceutically acceptable" means approved by a regulatory agency of the federal or a state government, or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals (e.g., mammals), and more particularly, in humans.

"Prodrugs" are compounds that after administration are metabolized or otherwise chemically transformed into an active moiety. Prodrugs may be derivatives of an active compound. Prodrugs may or may not be active prior to conversion into an active form *in vivo*.

The term "treating" is used herein, for instance, in reference, for example, to methods of treating inflammatory diseases or to a gastrointestinal disease, and generally includes the administration of a compound or composition which reduces the frequency of, or delays the

onset of, symptoms of a medical condition (e.g., autoimmune disease, inflammatory disorder, gastrointestinal disorder) in a subject relative to a subject not receiving the compound or composition. This can include reversing, reducing, or arresting the symptoms, clinical signs, and underlying pathology of a condition in a manner to improve or stabilize a subject's condition (e.g., regression of symptoms of an autoimmune or inflammatory disease such as improvement in the MAYO score in the treatment of ulcerative colitis). In the case of oncology, "treating" can be ameliorative (slowing or reducing symptoms) or curative (reversing or eliminating symptoms).

The embodiments disclosed herein encompass all pharmaceutically acceptable compounds of the compound of (I), (II), (IA)-(IE), or (IA-1)-(IE-1) being isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. These radiolabeled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. Certain isotopically-labelled compounds of (I)-(IL), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of (I)-(IL) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Preparations and Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

The term "cyclyl" refers to any cyclic group. In some embodiments, the term "cyclyl"includes aryl, heteroaryl, carbocyclyl, cycloalkyl, and heterocyclyl, as defined herein.

Unless otherwise indicated, an "optionally substituted" group may have a suitable

substituent at each substitutable position of the group. When a functional group is "optionally substituted," there may be more than one (e.g., 1, 2, 3, or 4) optional substituent regardless of whether it is indicated that the functional group is optionally substituted with "one or more substituents" and each optional substituent may be the same or different. In some embodiments, the term "one or more substituents" refers to 1, 2, 3, or 4 substituents. Combinations of substituents envisioned under this invention are preferably those that result in the formation of stable or chemically feasible compounds.

Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group (such as an alkyl, alkenyl, alkynyl, alkylene, alkenylene, alkynylene or the carbon atom of a carbocyclyl, aryl, heterocyclyl or heteroaryl) are independently, for example,

halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$;

$-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$, which may be substituted with R°; -CH=CHPh, which may be substituted

with $-NO_2$; -CN; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$;

$-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$;

$-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$;

$-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$;

$-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$-, SC(S)SR°; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$;

$-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$;$-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$;

$-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$;

$-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; $-SiR_3$; $-(C_{1-4}$ straight or branched alkylene)$O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene)$C(O)O-N(R^\circ)_2$, where each R° may be substituted as defined below and is independently hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently, for example, deuterium, halogen, $-(CH_2)_{0-2}R^\bullet$, -(haloR$^\bullet$), $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$; -O(haloR$^\bullet$), -CN, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, -(C_{1-4} straight or branched alkylene)$C(O)OR^\bullet$, or $-SSR^\bullet$, where each R$^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} alkyl, C_{1-4} alkenyl, C_{1-4} alkynyl, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, where each independent occurrence of R* is selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, and carbocyclyl, which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(C(R^*)_2)_{2-3}O-$, where each independent occurrence of R* is selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, and carbocyclyl, which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on the alkyl, alkenyl, alkynyl, or carbocyclyl group of R* include halogen, -R$^\bullet$, -(haloR$^\bullet$), -OH, -OR$^\bullet$, -O(haloR$^\bullet$), -CN, -C(O)OH, -C(O)OR$^\bullet$, $-NH_2$, -NHR$^\bullet$, $-NR^\bullet_2$, or $-NO_2$, where each R$^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$,

$-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; where each $R^\dagger$ is independently hydrogen, C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, which may be substituted as defined below, unsubstituted -OPh, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, it should be understood that a substitutable nitrogen can be substituted with four substituents (or have four bonds to less than four substituents) such that the nitrogen atom will be positively charged or its cation, i.e., N^+. Such substitution of a substitutable nitrogen can be of a ring nitrogen, for example, a ring nitrogen of a heterocyclic group containing nitrogen as a ring atom. In particular embodiments, where one of the substituents of a cationic nitrogen atom is a hydroxyl group, the hydroxyl group can be deprotonated and represented by a negatively charged oxygen atom, i.e., O^-. In such cases, a general formula for the substitution can be represented by $RN^+(O^-)(R')R''$, where R, R' and R'' represent carbon or other atoms, groups and/or moieties to which the nitrogen atom is bound.

Suitable substituents on the alkyl, alkenyl, alkynyl, or carbocyclyl group of $R^\dagger$ are independently, for example,

halogen, $-R^\bullet$, -(haloR$^\bullet$), -OH, $-OR^\bullet$, -O(haloR$^\bullet$), -CN, -C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, where each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

The embodiments disclosed herein encompass the *in vivo* metabolic products of the disclosed compounds. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the disclosure includes compounds produced by a process comprising administering a compound of this disclosure to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabeled compound of the disclosure in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological

samples.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoroacetic acid (TFA), undecylenic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine,

piperidine, N ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

A "pharmaceutical composition" refers to a formulation of a compound of the disclosure and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, e.g., humans. Such a medium includes all pharmaceutically acceptable carriers, diluents and excipients therefor.

"Effective amount" or "therapeutically effective amount" refers to that amount of a compound of the disclosure which, when administered to a mammal, preferably a human, is sufficient to effect treatment in the mammal, preferably a human. The amount of a compound which constitutes a "therapeutically effective amount" will vary depending on the compound, the condition and its severity, the manner of administration, and the age of the mammal to be treated, but can be determined routinely by one of ordinary skill in the art having regard to his own knowledge and to this disclosure.

A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another. The present disclosure also contemplates "diastereomers", which refers to non-mirror image of non-identical stereoisomers. Diastereomers occur when two or more stereoisomers of a compound have different configurations at one or more of the equivalent stereocenters and are not mirror images of each other.

A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present disclosure includes tautomers of any said compounds.

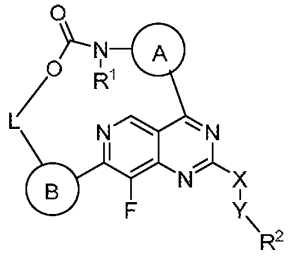
“Abnormal cell growth”, as used herein, unless otherwise indicated, means cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). Abnormal cell growth may be benign (not cancerous) or malignant (cancerous).

By reserving the right to proviso out or exclude any individual members of any such group, including any sub-ranges or combinations of sub-ranges within the group, that can be claimed according to a range or in any similar manner, less than the full measure of this disclosure can be claimed for any reason. Further, by reserving the right to proviso out or exclude any individual substituents, analogs, compounds, ligands, structures, or groups thereof, or any members of a claimed group, less than the full measure of this disclosure can be claimed for any reason.

Throughout this disclosure, various patents, patent applications and publications are referenced. The disclosures of these patents, patent applications and publications in their entireties are incorporated into this disclosure by reference in order to more fully describe the state of the art as known to those skilled therein as of the date of this disclosure. This disclosure will govern in the instance that there is any inconsistency between the patents, patent applications and publications cited and this disclosure.

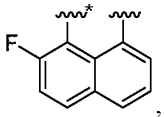
II. Compounds

The compounds described herein are KRAS inhibitors. In one embodiment, a compound having a structure of Formula (I), or a stereoisomer of the compound, tautomer of the compound, or a pharmaceutically acceptable salt thereof is provided:



(I)

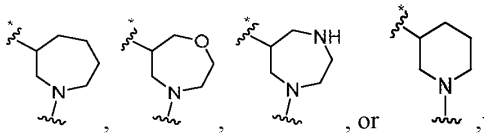
wherein A is 4-11 membered heterocyclylene, wherein the 4-11 membered heterocyclylene is optionally substituted; B is an arylene or 5-14 membered heteroarylene, wherein the arylene or 5-14 membered heteroarylene is optionally substituted, wherein the 5-14 membered heteroarylene is not indazolylene; R^1 is a hydrogen or C_1-C_3 alkyl; R^2 is a hydrogen, 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, -(C_1-C_3 alkylene)-heteroaryl, aryl fused to 4-8 membered heterocyclyl, or amine, wherein the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, 4-8 membered heterocyclyl, or amine is optionally substituted; L is C_1-C_8 alkylene, C_2-C_8 alkenylene, C_2-C_8 alkynylene, or C_1-C_8 heteroalkylene, wherein the C_1-C_8 alkylene, C_1-C_8 alkenylene, C_1-C_8 alkynylene, or C_1-C_8 heteroalkylene is optionally substituted; X is -O-, -NR^3-, or a direct bond, wherein R^3 is a hydrogen or C_1-C_3 alkyl; and Y is C_1-C_5 alkylene, C_1-C_5 deuteroalkylene, or a direct bond, wherein the C_1-C_5 alkylene or C_1-C_5 deuteroalkylene is optionally substituted, wherein:

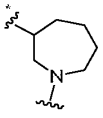
when B is , L is not C_2 alkylene, wherein ~* indicates the location of a bond to L and ~ indicates the location of a bond to the pyridine group.

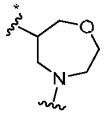
In some embodiments, A is 4-10 membered heterocyclylene. In some other embodiments, A is 5-8 membered heterocyclylene. In some other embodiments, A is 5-10 membered heterocyclylene. In some other embodiments, A is 6-8 membered heterocyclylene.

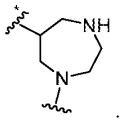
In some embodiments, the 4-11 membered heterocyclylene of A is pyrrolidinylene, piperidinylene, morpholinylene, azepanylene, oxazepanylene, or diazepanylene. In some embodiments, wherein the 4-11 membered heterocyclylene of A is azepanylene, piperidinylene, or oxazepanylene. In some embodiments, the 4-11 membered heterocyclylene of A is pyrrolidinylene. In some embodiments, the 4-11 membered heterocyclylene of A is piperidinylene. In some embodiments, the 4-11 membered heterocyclylene of A is morpholinylene. In some embodiments, the 4-11 membered heterocyclylene of A is azepanylene. In some embodiments, the 4-11 membered heterocyclylene of A is oxazepanylene. In some embodiments, the 4-11 membered heterocyclylene of A is or diazepanylene.

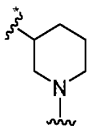
In some embodiments, the 4-11 membered heterocyclylene of A has one of the following structures:



, , , or , wherein ~* indicates the location of a bond to the carbamate group, and ~ indicates the location of a bond to the pyrimidine group. In some embodiments, the 4-11 membered heterocyclyleneof A is 

. In some embodiments, the 4-11 membered heterocyclylene of A is 

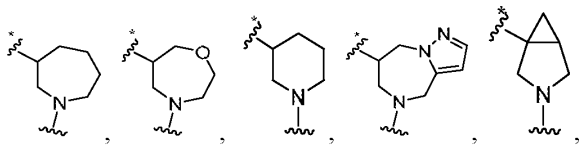
. In some embodiments, the 4-11 membered heterocyclylene of A is 

. In some embodiments, the 4-11 membered heterocyclylene of A is 

.

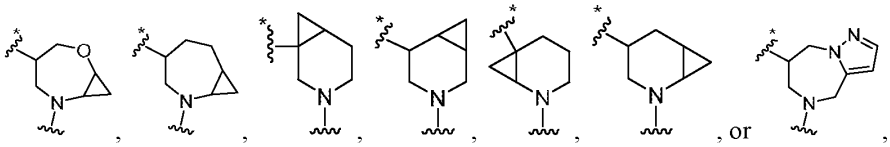
In some embodiments, the 4-11 membered heterocyclylene of A has one of the

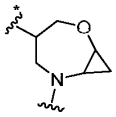
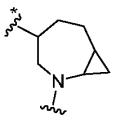
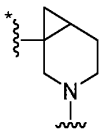
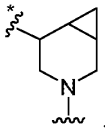
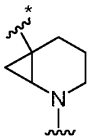
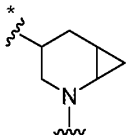
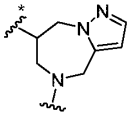
following structures:



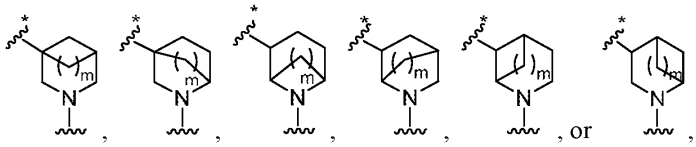
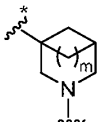
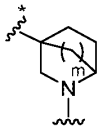
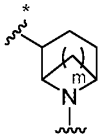
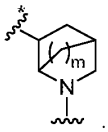
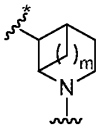
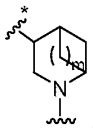
, wherein ~* indicates the location of a bond to the carbamate group and ~ indicates the location of a bond to the pyrimidine group, wherein the 4-11 membered heterocycloalkylene is optionally substituted.

In some embodiments, the 4-11 membered heterocyclylene of A is a fused bicyclic heterocyclylene or a bridged bicyclic heterocyclylene. In some embodiments, A is a fused bicyclic heterocyclylene. In some embodiments, the fused bicyclic heterocyclylene has one of the following structures:



, or , wherein ~* indicates the location of a bond to the carbamate group, and ~ indicates the location of a bond to the pyrimidine group. In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is .

In some embodiments, A is a bridged bicyclic heterocyclylene. In some embodiments, the bridged bicyclic hetrocyclylene has one of the following structures:

, wherein m is 1 or 2 and * indicates the location of a bond to a carbamate group and ~ indicates the location of a bond to the pyrimidine group. In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, A is . In some embodiments, when A is a bridged bicyclic heterocyclylene, m is 1. In some embodiments, when A is a bridged bicyclic heterocyclylene, m is 2.

In some embodiments, the 4-11 membered heterocyclylene of A is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from C_1-C_4 alkyl, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, C_1-C_4 alkylene-CN, halo, amine, hydroxyl, and -C(=O)CH_3.

In some embodiments, the 4-11 membered heterocyclylene of A is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, and -C(=O)CH_3.

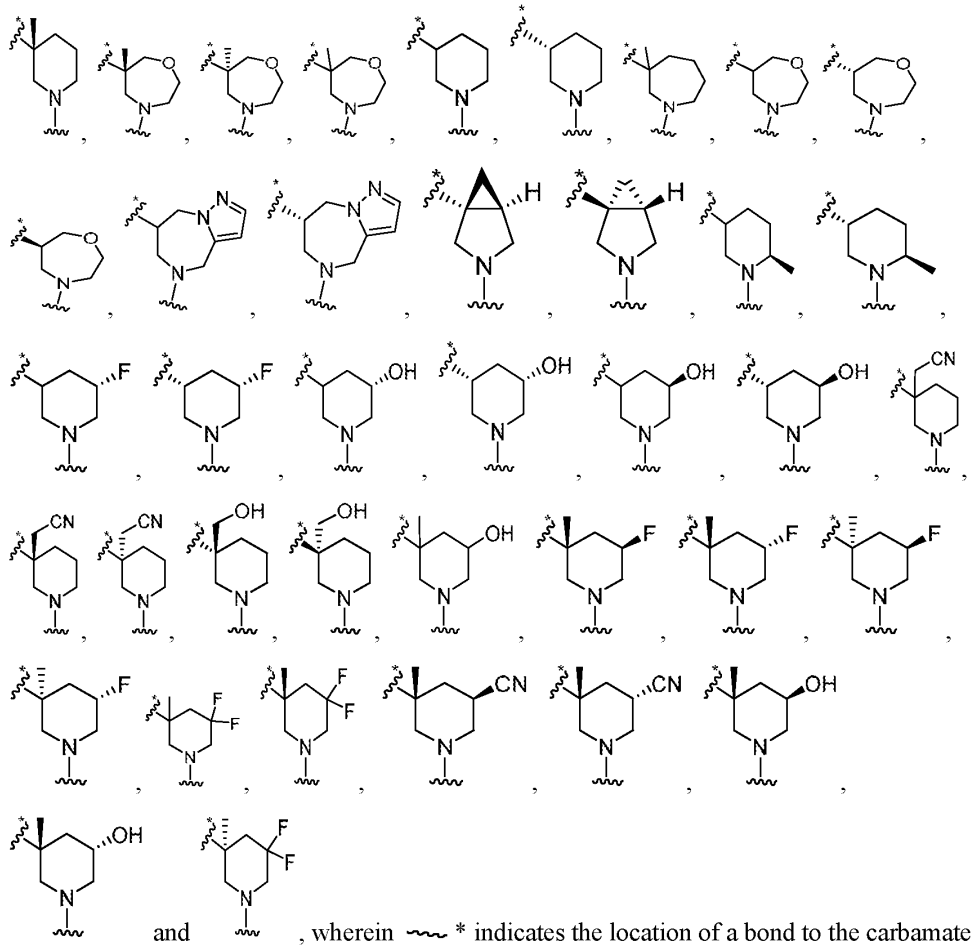
In some embodiments, the 4-11 membered heterocyclylene of A is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from -CH_3, -CD_3, -D, -F, -CN, -CH_3CN, -NH_2, -CH_2OCH_3, -OCH_3, -CF_2H, -CF_3, -OH, -C_1-C_3 alkylalcohol, and C_1-C_3 alkoxyl. . In some embodiments, the 4-11 membered heterocyclylene of A is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from -CH_3, -F, -CN, -NH_2, -CH_2OCH_3, -OCH_3, -CF_2H, -CF_3, -OH, -C_1-C_3 alkylalcohol, and C_1-C_3 alkoxyl. In some embodiments, C_1-C_3 alkylalcohol is C_1 alkylalcohol. In some embodiments, C_1-C_3 alkylalcohol is C_2 alkylalcohol. In some embodiments, C_1-C_3 alkylalcohol is C_3 alkylalcohol. In some embodiments, C_1-C_3

alkylalcohol is $-CH_2OH$, $-(CH_2)_2OH$, $-CH(CH_3)OH$, $-(CH_2)_3OH$, or $-C(CH_3)_2OH$. In some embodiments, C_1-C_3 alkoxyl is C_1 alkoxyl. In some embodiments, C_1-C_3 alkoxyl is C_2 alkoxyl. In some embodiments, C_1-C_3 alkoxyl is C_3 alkoxyl. In some embodiments, C_1-C_3 alkoxyl is $-OCH_3$, $-CH_2OCH_3$, $-OCH_2CH_3$, $-O(CH_2)_2CH_3$, $-CH_2OCH_2CH_3$, or $-(CH_2)_2OCH_3$.

In some embodiments, the 4-11 membered heterocyclylene of A is substituted with one or more substituents each independently selected from from $-CH_3$, -F, -OH, $-CH_2CN$, and $-CH_2OH$.

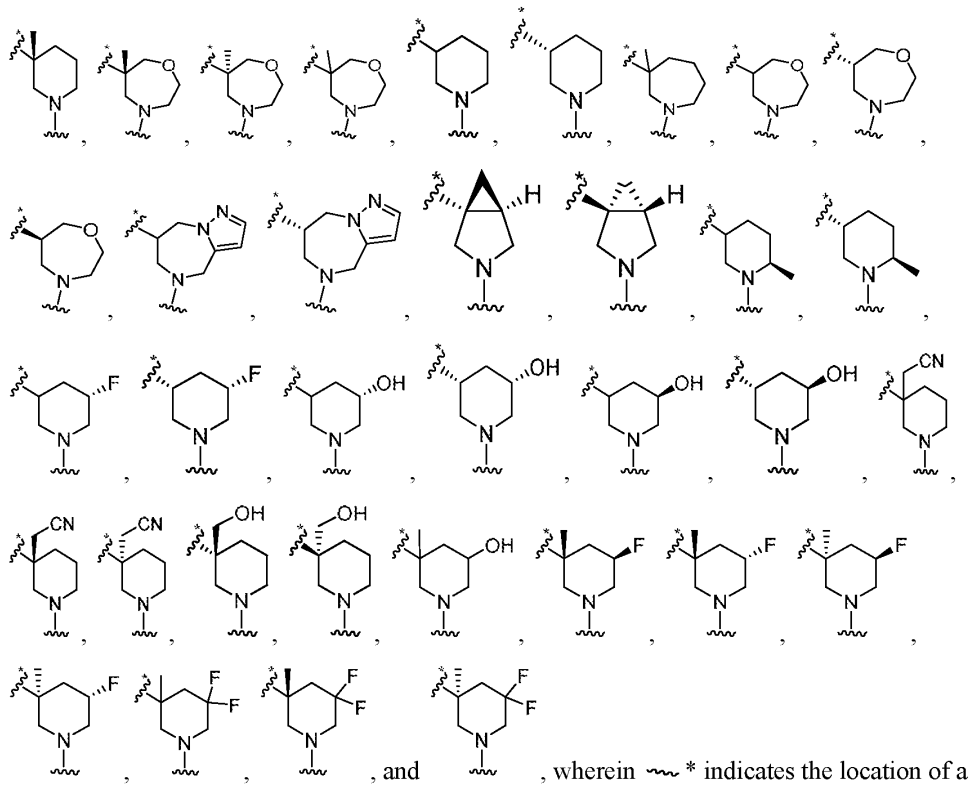
In some embodiments, the 4-11 membered heterocyclylene of A is substituted with one or more substituents each independently selected from $-C_1$-C_4 alkyl, -OH, -halo and -CN.

In some embodiments, the A is selected from the group consisting of:



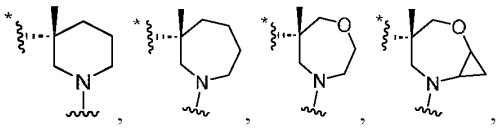
and , wherein ~~* indicates the location of a bond to the carbamate group and ~~ indicates the location of a bond to the pyrimidine group.

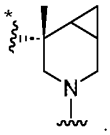
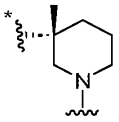
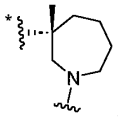
In some embodiments, the A is selected from the group consisting of:

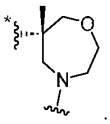
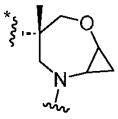
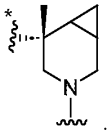


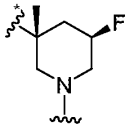
, and , wherein ~~* indicates the location of a bond to the carbamate group and ~~ indicates the location of a bond to the pyrimidine group.

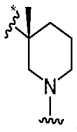
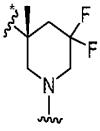
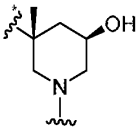
In some embodiments, A is a 6-11 membered bicyclic heterocyclylene. In some embodiments, A is a 7-11 membered bicyclic heterocyclylene. In some embodiments, A is a 6-10 membered bicyclic heterocyclylene. In some embodiments, A is a 7-10 membered bicyclic heterocyclylene. In some embodiments, A is a 6 membered bicyclic heterocyclylene. In some embodiments, A is a 7 membered bicyclic heterocyclylene. In some embodiments, A is an 8 membered bicyclic heterocyclylene. In some embodiments, A is a 9 membered bicyclic heterocyclylene. In some embodiments, A is a 10 membered bicyclic heterocyclylene. In some embodiments, A is an 11 membered bicyclic heterocyclylene.

In some embodiments, A is  , or


. In some embodiments, A is 
. In some embodiments, A is 
.

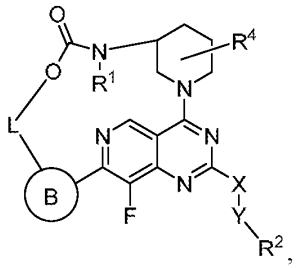
In some embodiments, A is 
. In some embodiments, A is 
. In some embodiments, A is 
.

In some embodiments, A is selected from the group consisting of: 
,

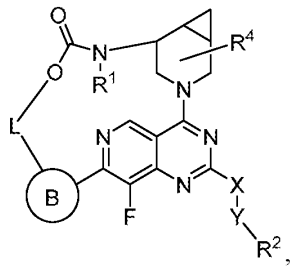

, 
, and 
, wherein ~~ * indicates the location of a bond to the carbamate group and ~~ indicates the location of a bond to the pyrimidine group.

In some embodiments, B is an arylene or 5-10 membered heteroarylene, wherein the arylene or 5-10 membered heteroarylene is optionally substituted, wherein the 5-10 membered heteroarylene is not indazolylene.

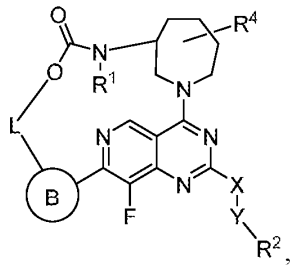
In some embodiments, the compound has one of the following structures of Formula (IA)-(IE):



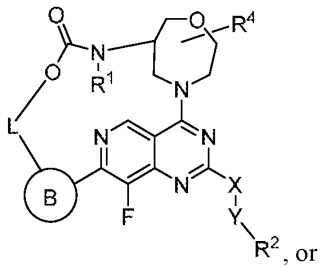
(IA)



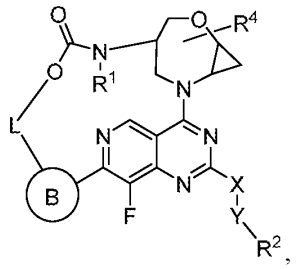
(IB)



(IC)



(ID)

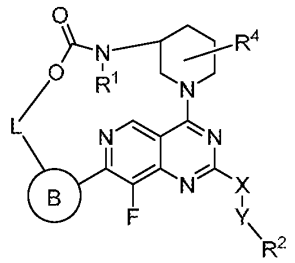


(IE)

wherein:

R^4 is a hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, or -C(=O)CH_3, wherein the remaining variables are as defined herein.

In some embodiments, the compound has the following structure of Formula (IA):

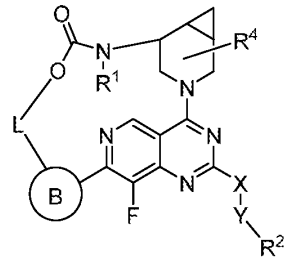


(IA)

wherein:

R^4 is a hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, or -$C(=O)CH_3$, wherein the remaining variables are as defined herein.

In some embodiments, the compound has the following structure of Formula (IB):

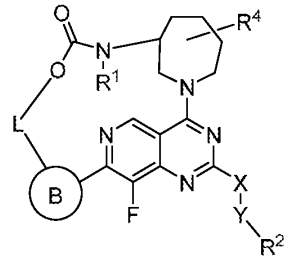


(IB)

wherein:

R^4 is a hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, or -$C(=O)CH_3$, wherein the remaining variables are as defined herein.

In some embodiments, the compound has the following structure of Formula (IC):

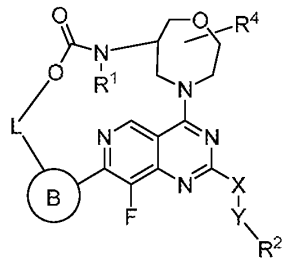


(IC)

wherein:

R^4 is a hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, or -$C(=O)CH_3$, wherein the remaining variables are as defined herein.

In some embodiments, the compound has the following structure of Formula (ID):

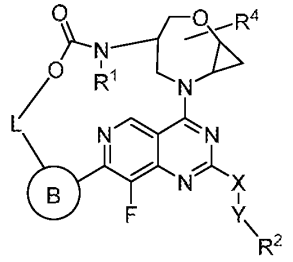


(ID)

wherein:

R^4 is a hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, or -$C(=O)CH_3$, wherein the remaining variables are as defined herein.

In some embodiments, the compound has the following structure of Formula (IE):



(IE)

wherein:

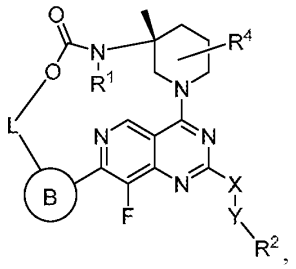
R^4 is a hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, or -$C(=O)CH_3$, wherein the remaining variables are as defined herein.

In some embodiments, R^4 is -H, -CH_3, -F, -Cl, -CN, -NH_2, -CH_2OCH_3, -OCH_3, -CF_2H, -CF_3, -OH, -C_1-C_3 alkylalcohol, C_1-C_3 alkoxyl, or -$C(=O)CH_3$. In some embodiments, -C_1-C_3 alkylalcohol of R^4 is C_1 alkylalcohol. In some embodiments, R^4 is -H. In some embodiments, R^4 is -CH_3. In some embodiments, R^4 is -F. In some embodiments, R^4 is -Cl. In some embodiments, R^4 is -CN. In some embodiments, R^4 is -NH_2. In some embodiments, R^4 is -CH_2OCH_3. In some embodiments, R^4 is -OCH_3. In some embodiments, R^4 is -CF_2H. In some embodiments, R^4 is -CF_3. In some embodiments, R^4 is -OH. In some embodiments, R^4 is -C_1-C_3 alkylalcohol. In some embodiments, R^4 is C_1-C_3 alkoxyl. In some embodiments, R^4 is -$C(=O)CH_3$.

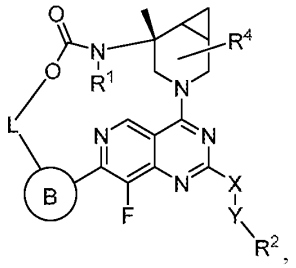
In some embodiments, -C_1-C_3 alkylalcohol of R^4 is C_2 alkylalcohol. In some embodiments, -C_1-C_3 alkylalcohol of R^4 is C_3 alkylalcohol. In some embodiments, -C_1-C_3 alkylalcohol of R^4 is -CH_2OH, -$(CH_2)_2OH$, -$CH(CH_3)OH$, -$(CH_2)_3OH$, or -$C(CH_3)_2OH$.

In some embodiments, -C_1-C_3 alkoxyl of R^4 is C_1 alkoxyl. In some embodiments, -C_1-C_3 alkoxyl of R^4 is C_2 alkoxyl. In some embodiments, -C_1-C_3 alkoxyl of R^4 is C_3 alkoxyl. In some embodiments, -C_1-C_3 alkoxyl of R^4 is $-OCH_3$, $-CH_2OCH_3$, $-OCH_2CH_3$, $-O(CH_2)_2CH_3$, $-CH_2OCH_2CH_3$, or $-(CH_2)_2OCH_3$.

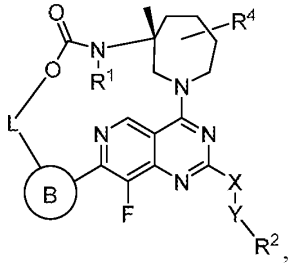
In some embodiments, the compound has one of the following structures of Formula (IA-1)-(IE-1):



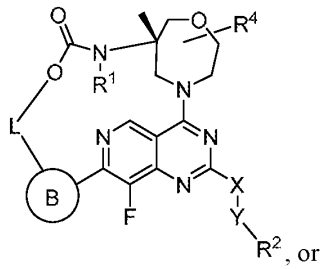
(IA-1)



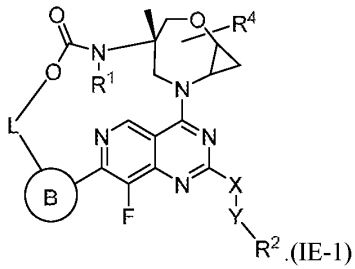
(IB-1)



(IC-1)



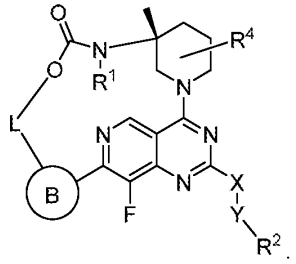
(ID-1)



(IE-1)

wherein the variables are as defined herein.

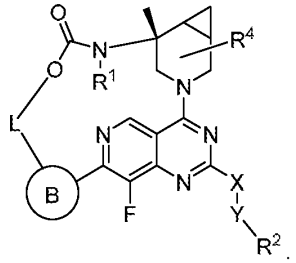
In some embodiments, the compound has the following structure of Formula (IA-1):



(IA-1)

wherein the variables are as defined herein.

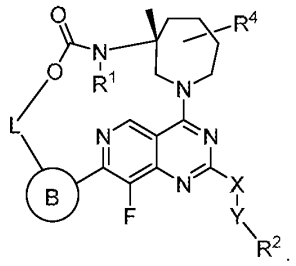
In some embodiments, the compound has the following structure of Formula (IB-1):



(IB-1)

wherein the variables are as defined herein.

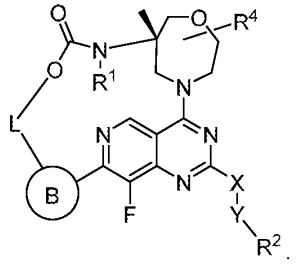
In some embodiments, the compound has the following structure of Formula (IC-1):



(IC-1)

wherein the variables are as defined herein.

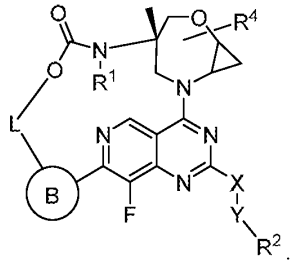
In some embodiments, the compound has the following structure of Formula (ID-1):



(ID-1)

wherein the variables are as defined herein.

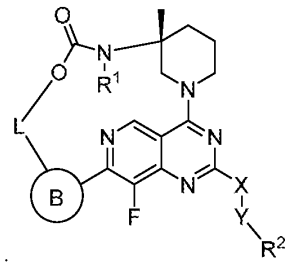
In some embodiments, the compound has the following structure of Formula (IE-1):



(IE-1)

wherein the variables are as defined herein.

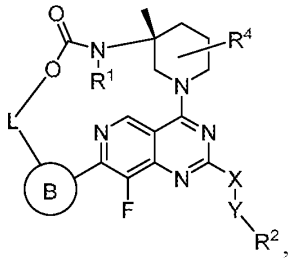
In some embodiments, the compound has the following structure of Formula (IA-2):



(IA-2)

wherein the variables are as defined herein.

In some embodiments, the compound has the following structure of Formula (IA-3):



(IA-3)

or a stereoisomer of the compound, tautomer of the compound, or a pharmaceutically acceptable salt thereof, wherein:

R^4 is -H;

B is an arylene or heteroarylene, wherein the arylene or heteroarylene is optionally substituted;

R^1 is a hydrogen or C_1-C_3 alkyl;

R^2 is a hydrogen, 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, -(C_1-C_3 alkylene)-heteroaryl, aryl fused to 4-8 membered heterocyclyl, or amine, wherein the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, 4-8 membered heterocyclyl, or amine is optionally substituted;

L is C_1-C_8 alkylene, C_1-C_8 alkenylene, C_1-C_8 alkynylene, or C_1-C_8 heteroalkylene. wherein the C_1-C_8 alkylene, C_1-C_8 alkenylene, C_1-C_8 alkynylene, or C_1-C_8 heteroalkylene is optionally substituted;

X is -O-, -NR^3-, or a direct bond, wherein R^3 is a hydrogen or C_1-C_3 alkyl; and

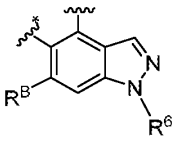
Y is C_1-C_5 alkylene, C_1-C_5 deuteroalkylene, or a direct bond, wherein the C_1-C_5 alkylene or C_1-C_5 deuteroalkylene is optionally substituted,

or a stereoisomer of the compound, salt of the compound or tautomer of the

compound thereof.

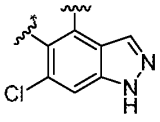
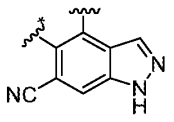
In some embodiments, B is arylene or 5-18 membered heteroarylene.

In some embodiments, B is arylene or 5-14 membered heteroarylene.

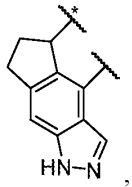
In some embodiments, B is , wherein * indicates the location of a bond to L and indicates the location of a bond to the pyridine group, wherein

R^B is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O- C_1-C_4 alkylene, halo, hydroxyl, -C(=O)CH_3, NH_2, -NH(CH_3), N(CH_3)$_2$;

R^6 is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$ wherein R^{X1}, R^{X2}: are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, and wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy can be substituted with: C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, -C(O)$NR^{X3}R^{X4}$ wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, or prodrug moiety R^5.

In some embodiments, B is  or , wherein * indicates the location of a bond to L and indicates the location of a bond to the pyridine group.

In some embodiments, B is an arylene or heteroarylene. In some embodiments, B is an arylene. In some embodiments, the arylene of B is a phenylene or naphthylene. In some specific embodiments, the arylene of B is a phenylene. In some other specific embodiments, the arylene of B is a naphthylene. In some other embodiments, B is a heteroarylene. In some embodiments, the heteroarylene is a 5-6 membered heteroarylene. In some embodiments, the heteroarylene of B is a pyridinylene or indazolylene. In some specific embodiments, the heteroarylene of B is a pyridinylene

In some embodiments, the heteroarylene of B is , wherein ~~* indicates the location of a bond to the carbamate group and ~~ indicates the location of a bond to the pyrimidine group.

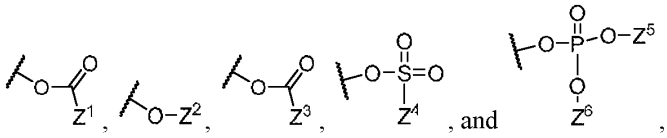
In some embodiments, the arylene or heteroarylene of B is optionally substituted with one or more substituents each independently selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, alkylene-cyclyl, heterocyclyl, aryl, heteroaryl, and a prodrug functional moiety R^5, wherein the alkylene-cyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy, wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy is optionally substituted with C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, or -C(O)$NR^{X3}R^{X4}$, wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy.

In some embodiments, the arylene or heteroarylene of B is optionally substituted with one or more substituents each independently selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, C_1-C_4 alkylene-C_6-C_{10} aryl, C_1-C_4 alkylene-(5-10 membered heteroaryl), C_1-C_4 alkylene-C_3-C_{10} cycloalkyl, C_1-C_4 alkylene-(3-10 membered heterocyclyl), 3-10 membered heterocyclyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, and a prodrug functional moiety R^5, wherein the C_1-C_4 alkylene-C_6-C_{10} aryl, C_1-C_4 alkylene-(5-10 membered heteroaryl), C_1-C_4 alkylene-C_3-C_{10} cycloalkyl, C_1-C_4 alkylene-(3-10 membered heterocyclyl), 3-10 membered heterocyclyl, C_6-C_{10} aryl, or 5-10 membered heteroaryl is optionally substituted, wherein R^{X1}, R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy and wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy is optionally substituted with C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl , heterocyclyl, or -C(O)$NR^{X3}R^{X4}$, wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy.

In some embodiments, the arylene or heteroarylene of B is optionally substituted with

one or more substituents each independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, CN and a prodrug functional moiety R^5.

In some embodiments, the arylene or heteroarylene of B is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, and a prodrug functional moiety R^5. In some embodiments, wherein the arylene or heteroarylene of B is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from $-CH_3$, -F, -Cl, -CN, $-NH_2$, $-CH_2OCH_3$, $-OCH_3$, $-CF_2H$, $-CF_3$, -OH, $-C_1$-C_3 alkylalcohol, C_1-C_3 alkoxyl, a prodrug functional moiety R^5. In some embodiments, $-C_1$-C_3 alkylalcohol is C_1 alkylalcohol. In some embodiments, $-C_1$-C_3 alkylalcohol is C_2 alkylalcohol. In some embodiments, $-C_1$-C_3 alkylalcohol is C_3 alkylalcohol. In some embodiments, $-C_1$-C_3 alkylalcohol is $-CH_2OH$, $-(CH_2)_2OH$, $-CH(CH_3)OH$, $-(CH_2)_3OH$, or $-C(CH_3)_2OH$. In some embodiments, $-C_1$-C_3 alkoxyl is C_1 alkoxyl. In some embodiments, $-C_1$-C_3 alkoxyl is C_2 alkoxyl. In some embodiments, $-C_1$-C_3 alkoxyl is C_3 alkoxyl. In some embodiments, $-C_1$-C_3 alkoxyl is $-OCH_3$, $-CH_2OCH_3$, $-OCH_2CH_3$, $-O(CH_2)_2CH_3$, $-CH_2OCH_2CH_3$, or $-(CH_2)_2OCH_3$.

In some embodiments, the prodrug functional moiety R^5 is selected from the group consisting of , wherein:

Z^1 and Z^4 are each independently

(i) $-NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, C_{1-4} heteroalkyl, or aryl wherein the alkyl, haloalkyl, alkoxy, heteroalkyl, aryl is optionally substituted with C_{1-4} alkyl, C_{1-4} haloalkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, or $-C(O)NR^{X3}R^{X4}$, wherein the heteroaryl is optionally substituted with C_{1-4} alkyl, R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy;

(ii) optionally substituted monocyclic, fused or bridged bicyclic 4-11 membered N-containing heterocyclyl or 4-11 membered N-containing heteroaryl, wherein the point of attachment is on N;

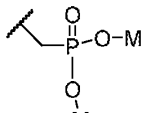
(iii) optionally substituted C_{1-8} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, or C_{1-6} heteroalkylene;

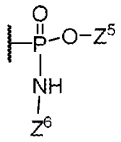
(iv) optionally substituted 4-8 membered cycloalkyl, 4-10 membered aryl; or

(v) -OM, wherein M is a metal;

Z^2 is

(i) R″, (R)—O—(R), (R)—S—(R), (R)—O—(R)-X, (R)—S—(R)-X, wherein the X is optionally substituted cycloalkyl, heterocyclyl, aryl, heteroaryl, (R)—O—C(O)—R′, or (R)—O—C(O)—O—R′, wherein R″ is optionally substituted C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} heteroalkyl, wherein R is optionally substituted C_{1-8} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, or C_{1-6} heteroalkylene; wherein R′ is optionally substituted -$NR^{X1}R^{X2}$, C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-8} haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, wherein R^{X1} and R^{X2} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy;

(ii) , where M is a metal;

(iii) 

(iv) optionally substituted 4-10 membered aryl, 4-11 membered heteroaryl, 4-8 membered cycloalkyl, 4-10 membered heterocyclyl;

Z^3 is

(i) R″, which is optionally substituted C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} heteroalkyl; or

(ii) amino acid residue wherein amino acid residue is valine, leucine, isoleucine, phenylalanine, glycine, glutamate, aspartate, proline, lysine, tryptophan or serine; or

(iii) optionally substituted 4-10 membered aryl, 4-11 membered heteroaryl, 4-8 membered cycloalkyl or 4-10 membered heterocyclyl;

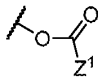
Z^5 and Z^6 are each independently

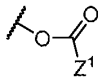
(i) hydrogen; or

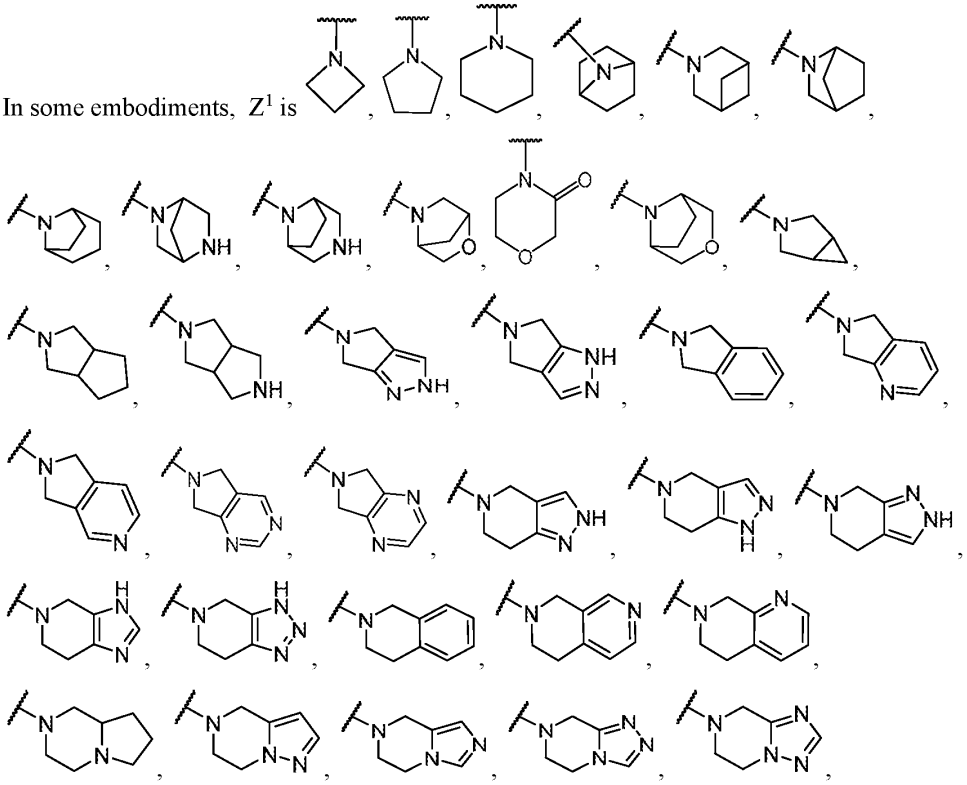
(ii) R″, (R)—O—(R), (R)—S—(R), (R)—O—(R)-X, (R)—S—(R)-X, wherein the X is optionally substituted cycloalkyl, heterocyclyl, aryl, heteroaryl, (R)—O—C(O)—R′, or (R)—O—C(O)—O—R′, wherein R″ is optionally substituted C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} heteroalkyl, wherein R is optionally substituted C_{1-8} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, or C_{1-6} heteroalkylene; wherein R′ is optionally substituted -$NR^{X1}R^{X2}$, C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-8} haloalkyl, cycloalkyl, heterocyclyl, aryl,

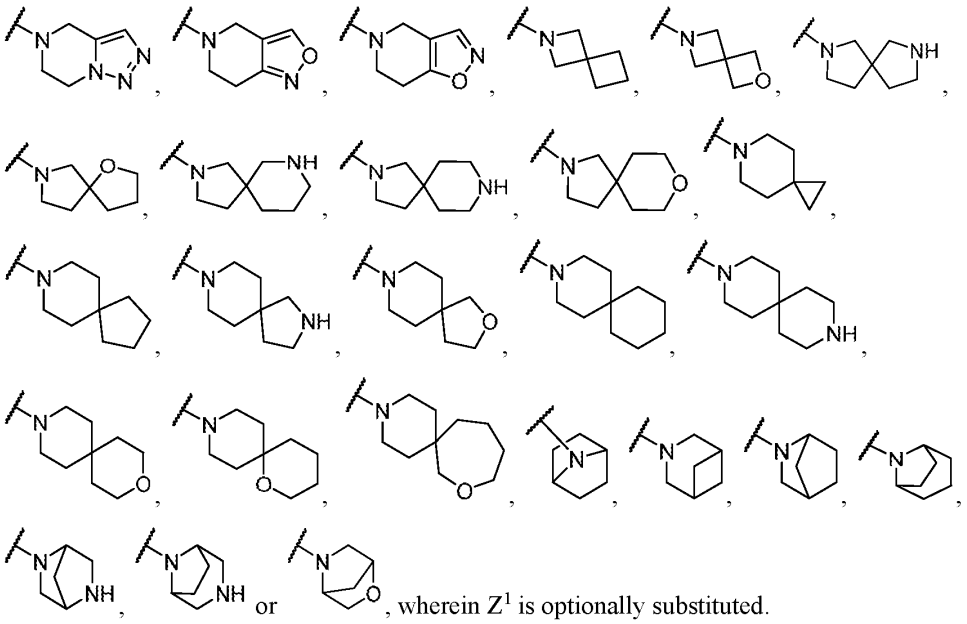
heteroaryl, wherein R^{X1} and R^{X2} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy; or

(iii) optionally substituted 4-10 membered aryl, 4-11 membered heteroaryl, 4-8 membered cycloalkyl or 4-10 membered heterocyclyl.

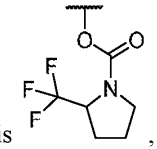
In some embodiments, the prodrug functional moiety R^5 is , wherein Z^1 is monocyclic, fused or bridged bicyclic 4-11 membered N-containing heterocyclyl or 4-11 membered N-containing heteroaryl optionally substituted with 0 to 4 substituents, wherein the point of attachment is on N.

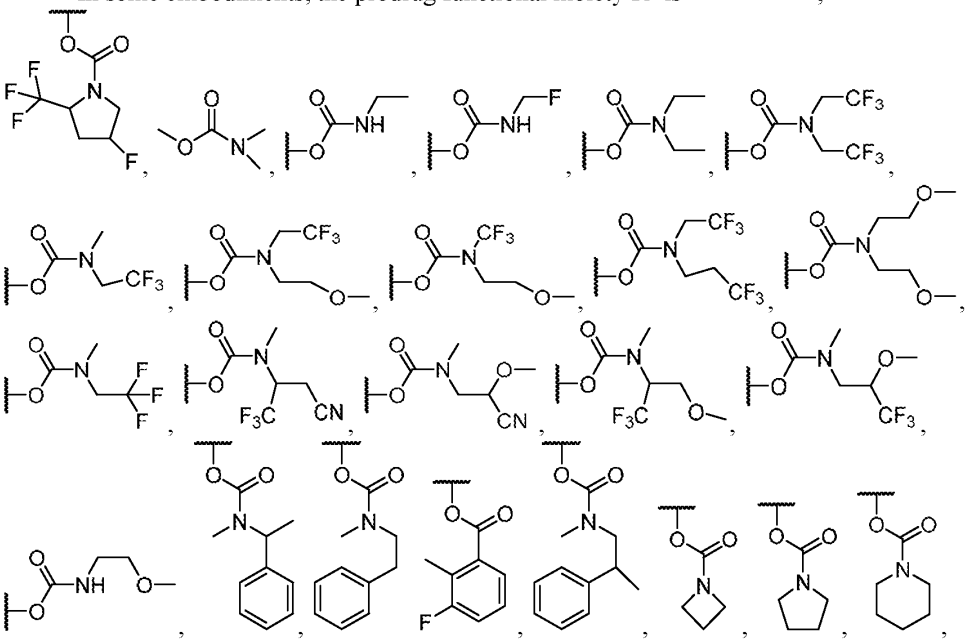
In some embodiments, the prodrug functional moiety R^5 is , wherein Z^1 is monocyclic, fused or bridged bicyclic 4-11 membered N-containing heterocyclyl or 4-11 membered N-containing heteroaryl optionally substituted with 2 to 3 substituents, wherein the point of attachment is on N.

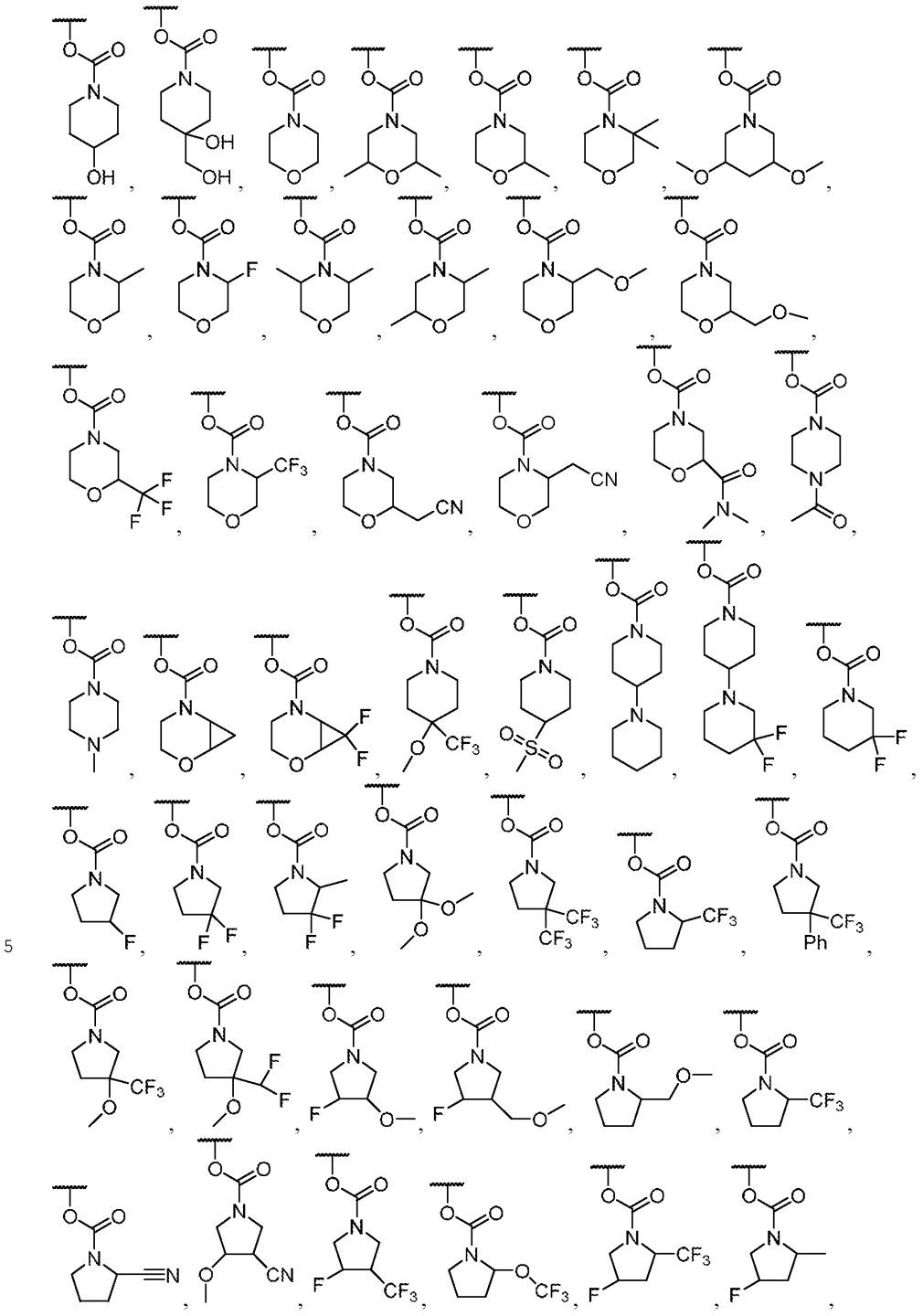
In some embodiments, Z^1 is 

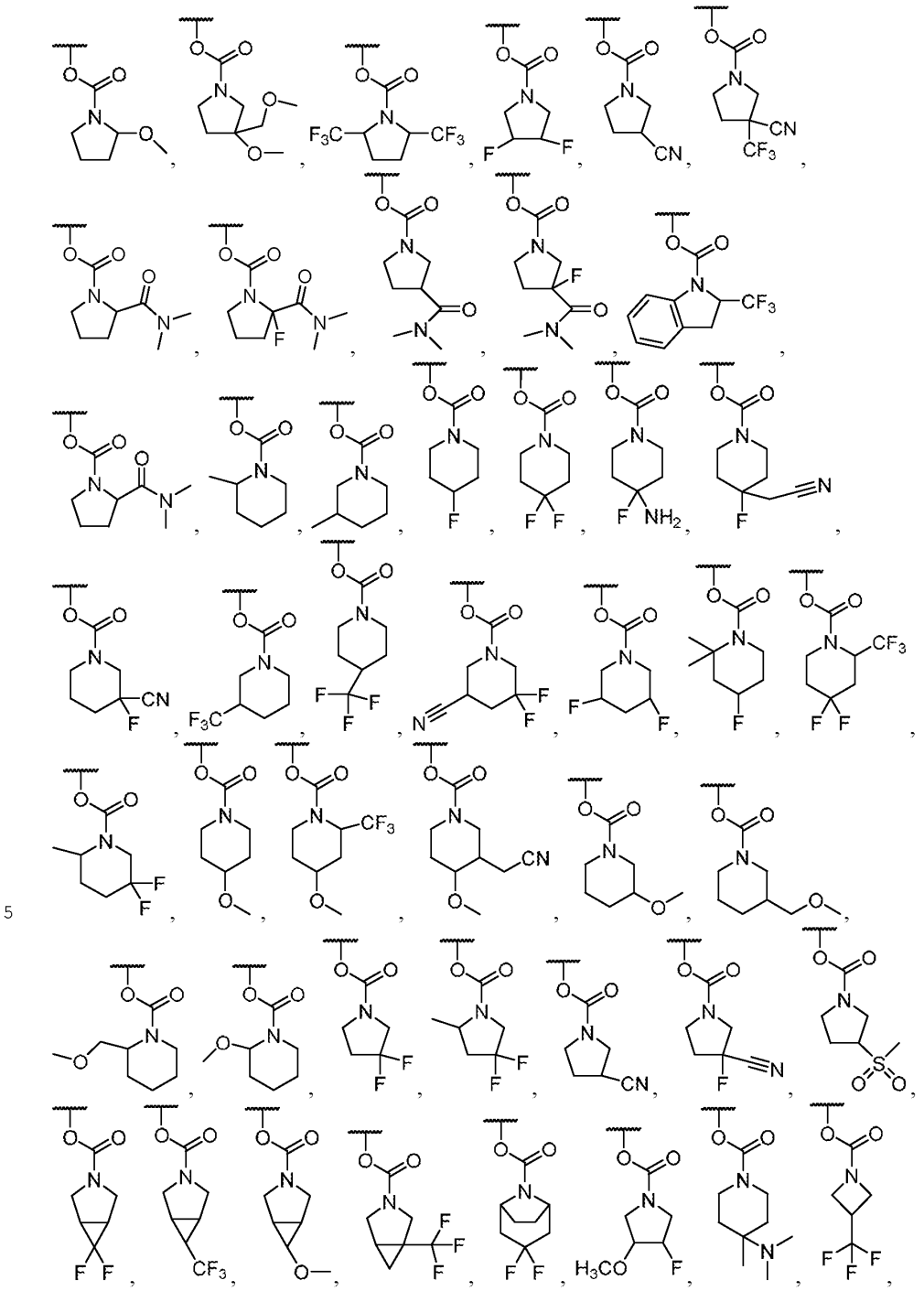


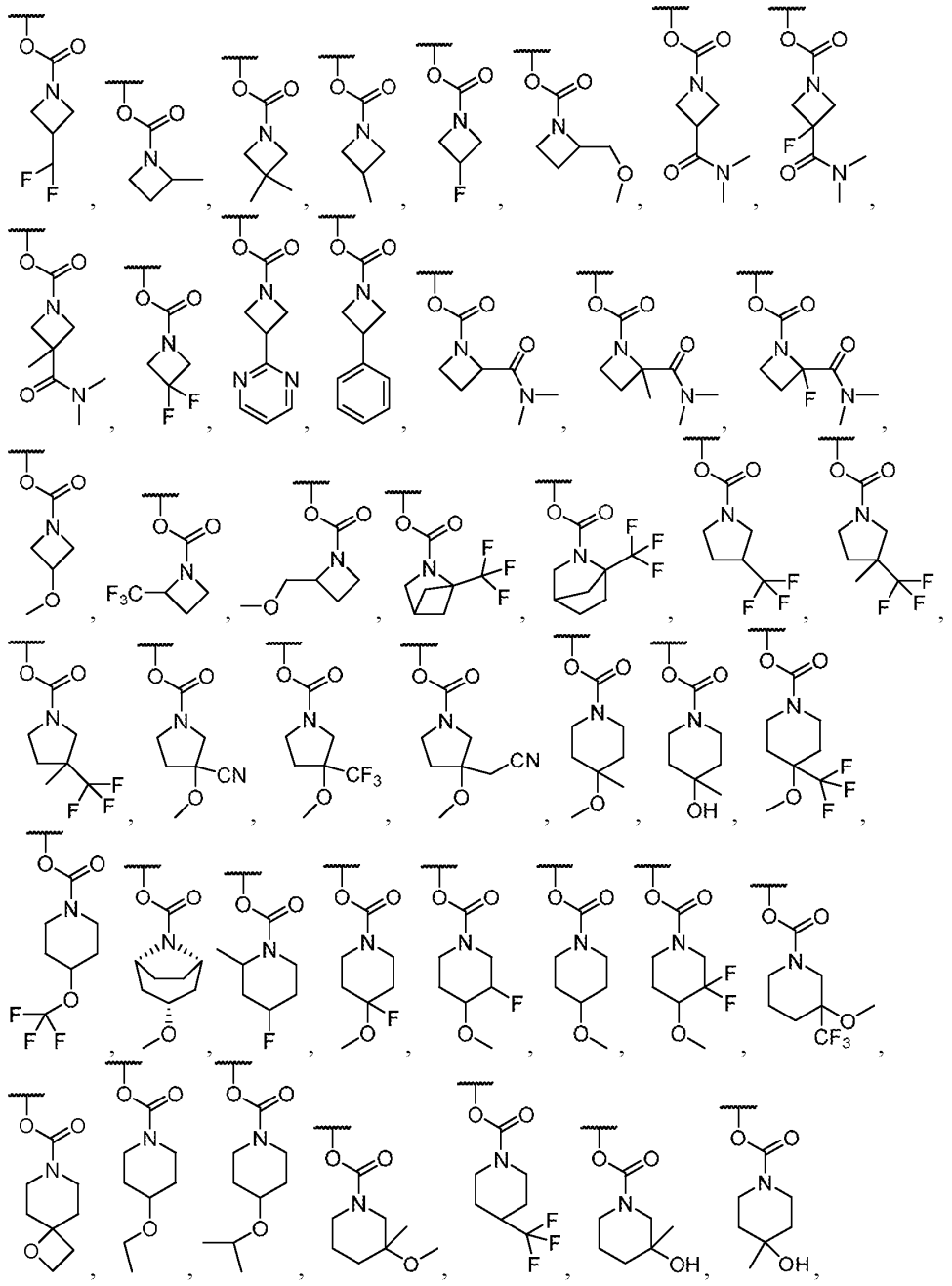
, wherein Z^1 is optionally substituted.

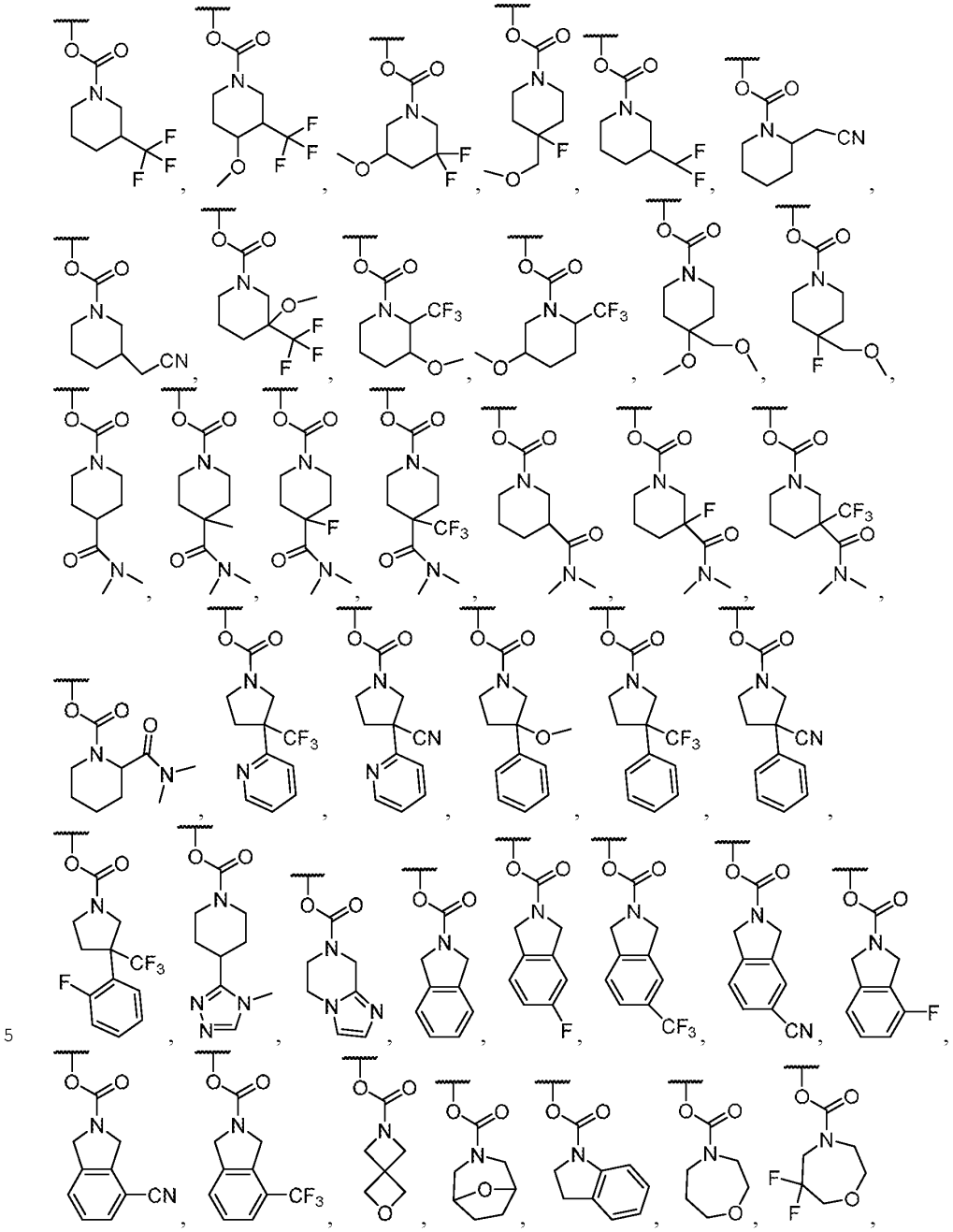
In some embodiments, the prodrug functional moiety R^5 is ,

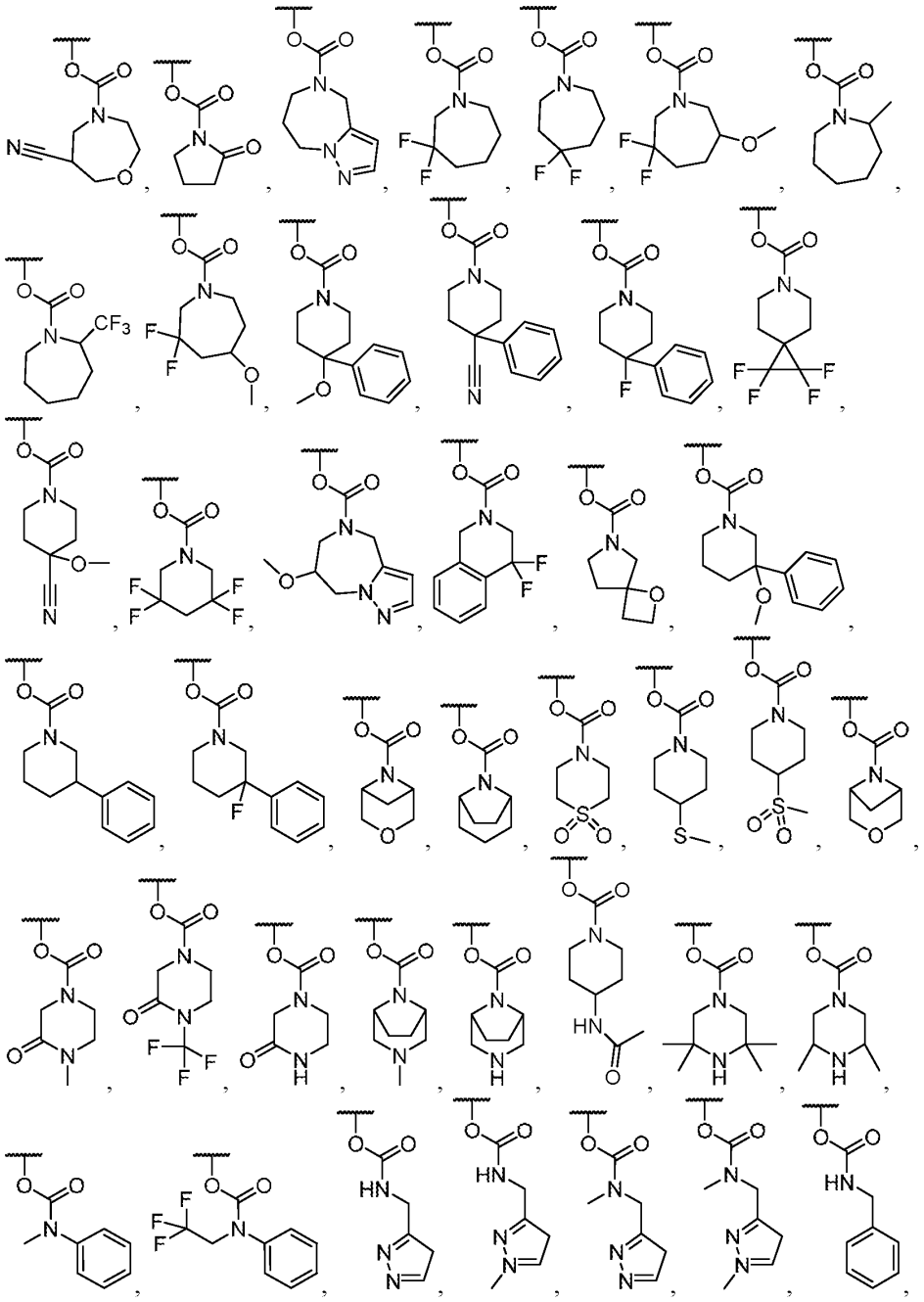


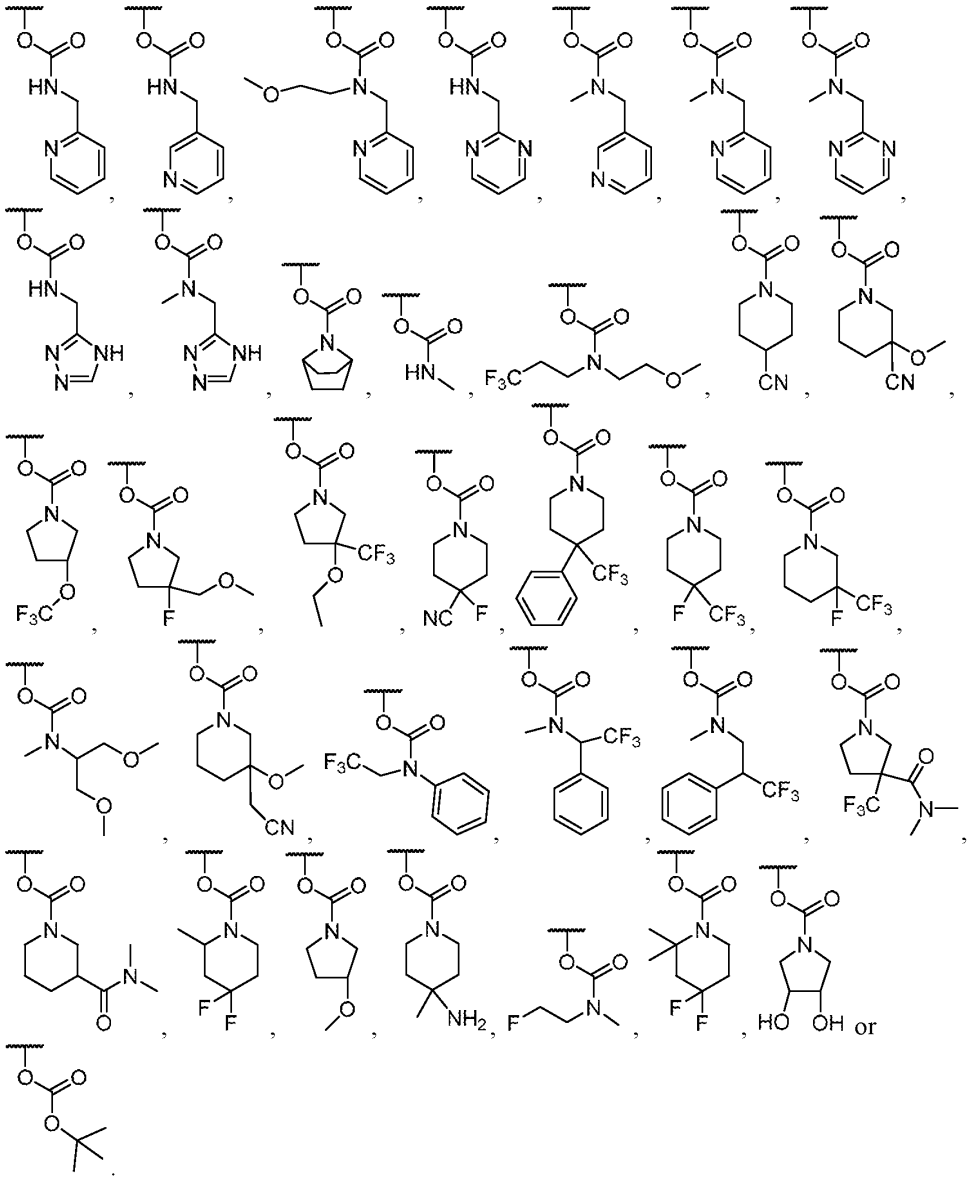


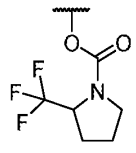


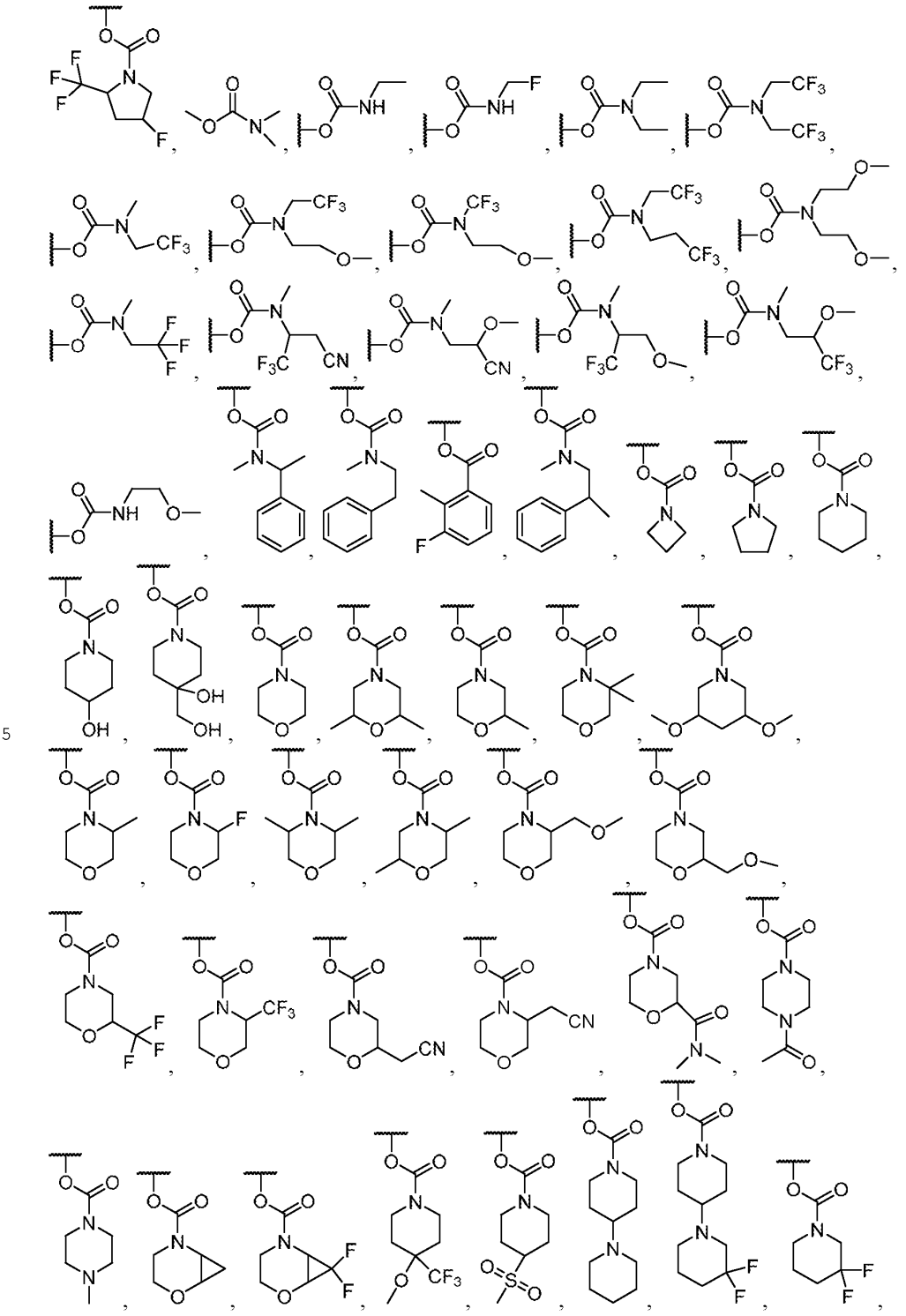


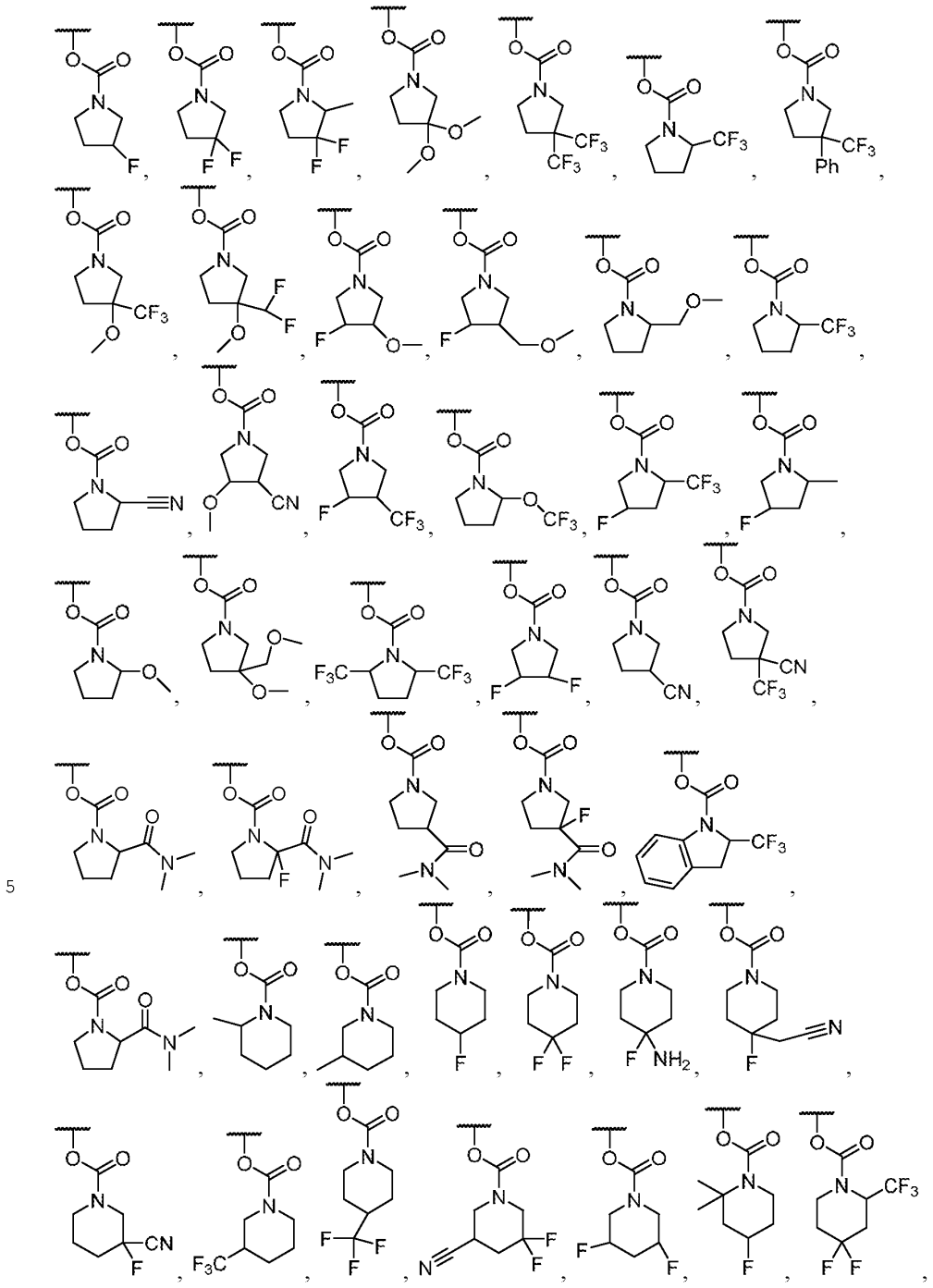


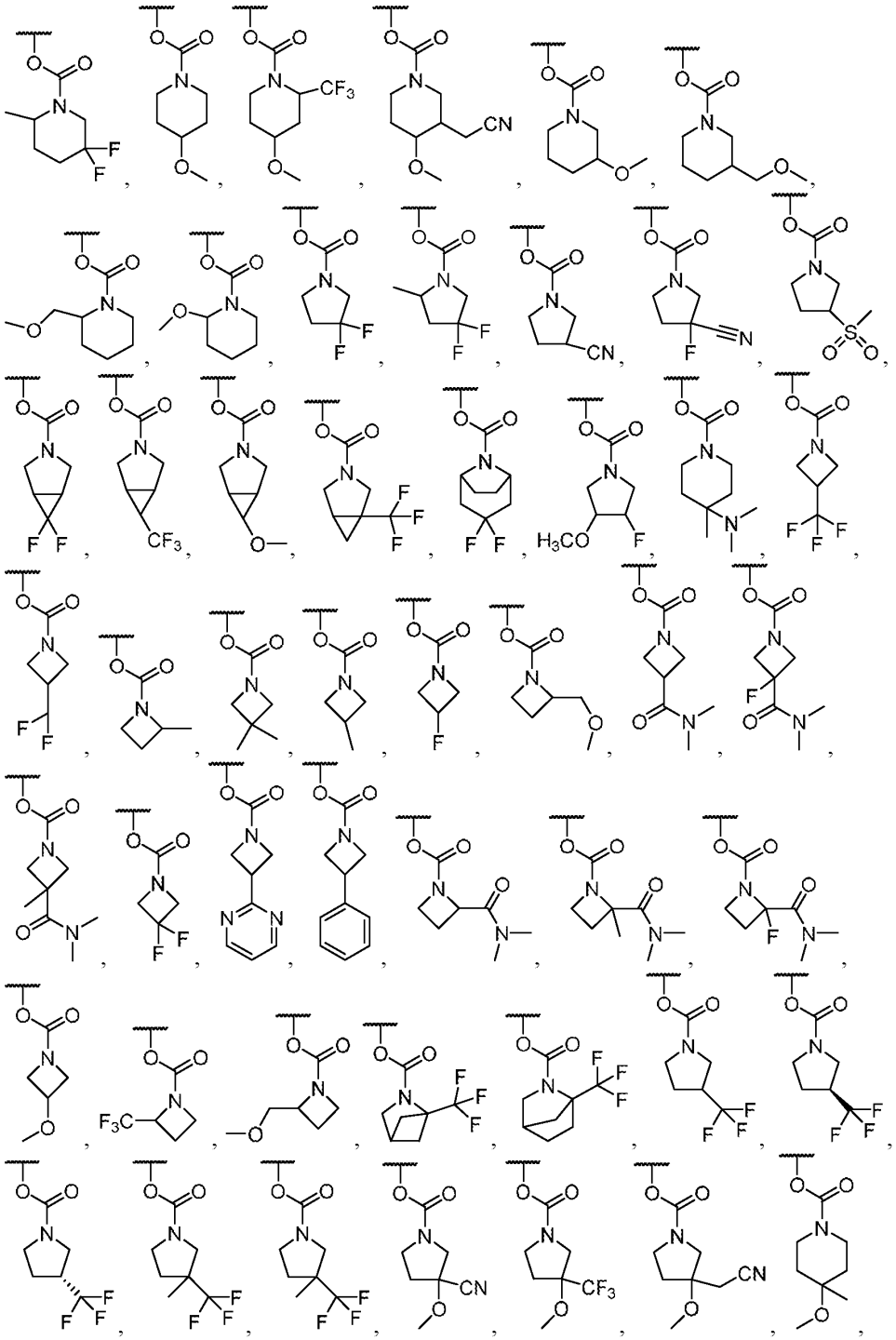


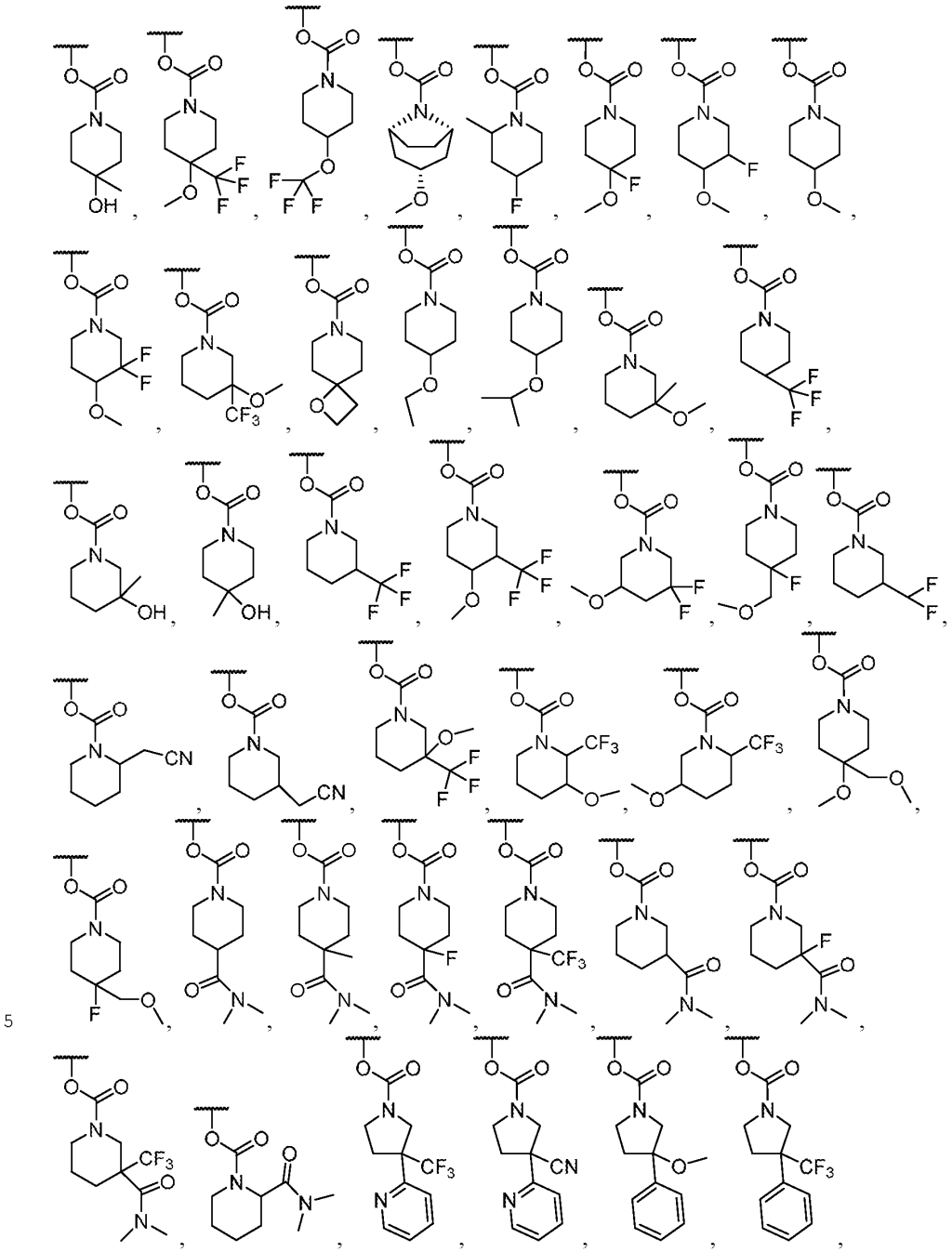


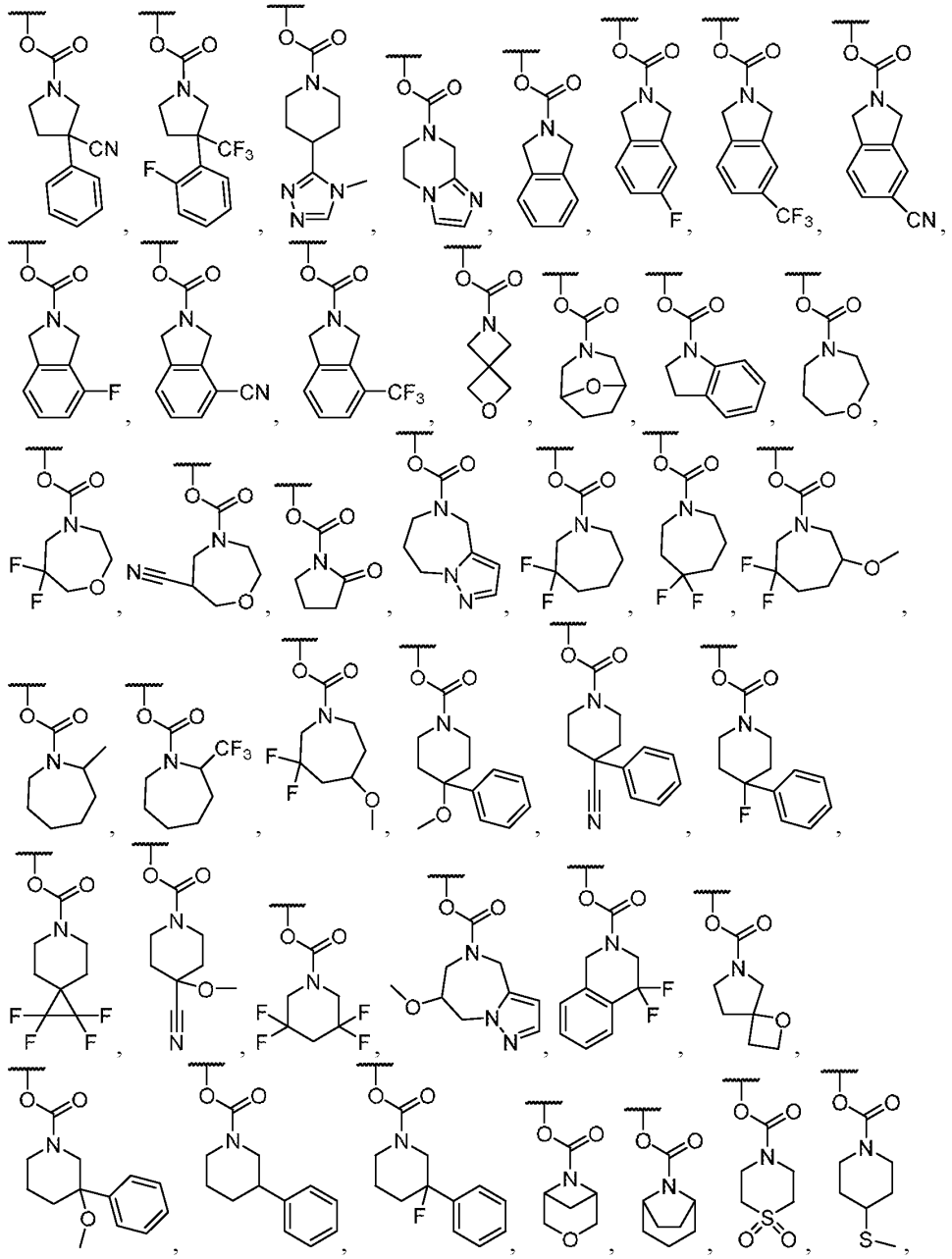
In some embodiments, the prodrug functional moiety R^5 is ,

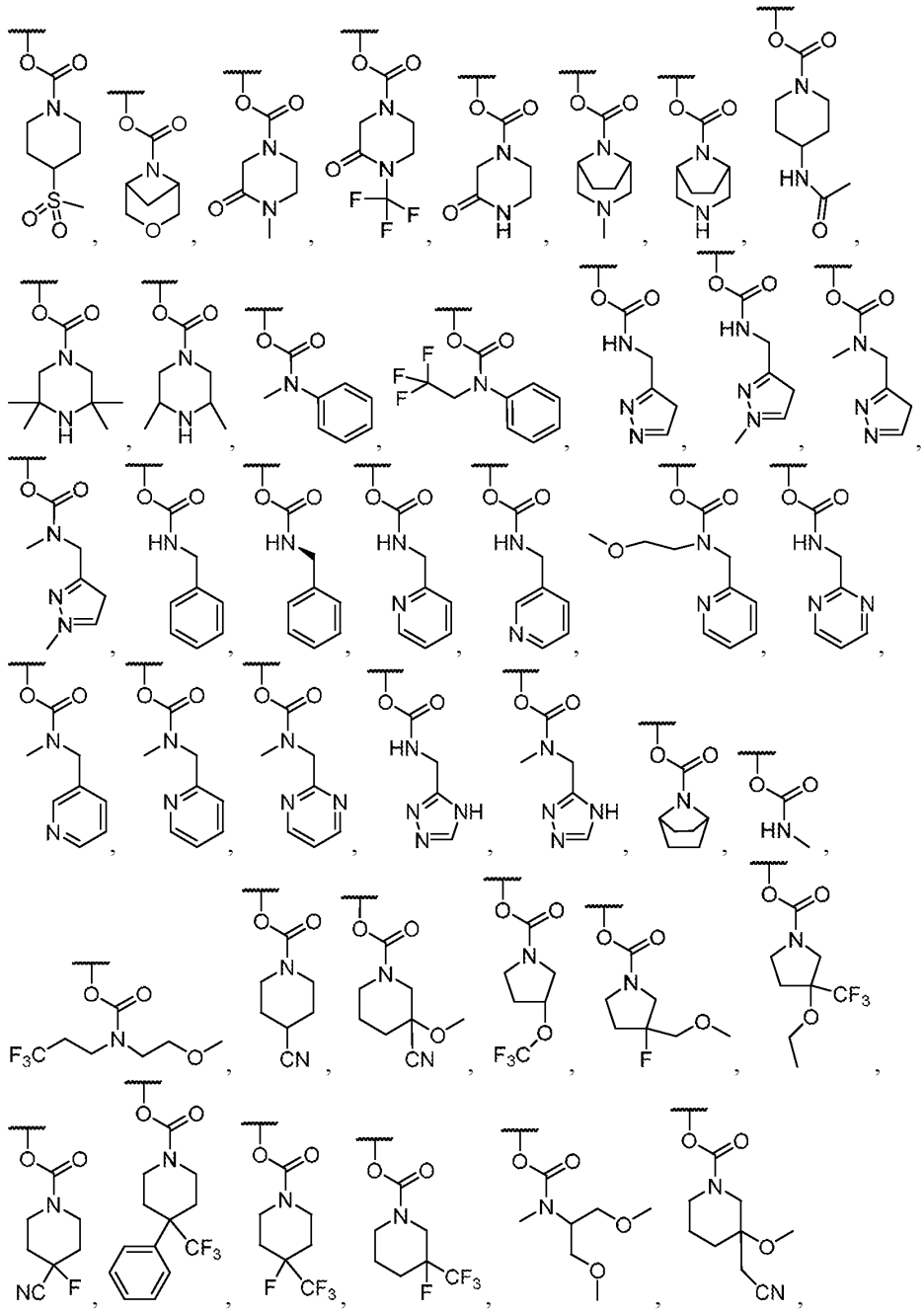


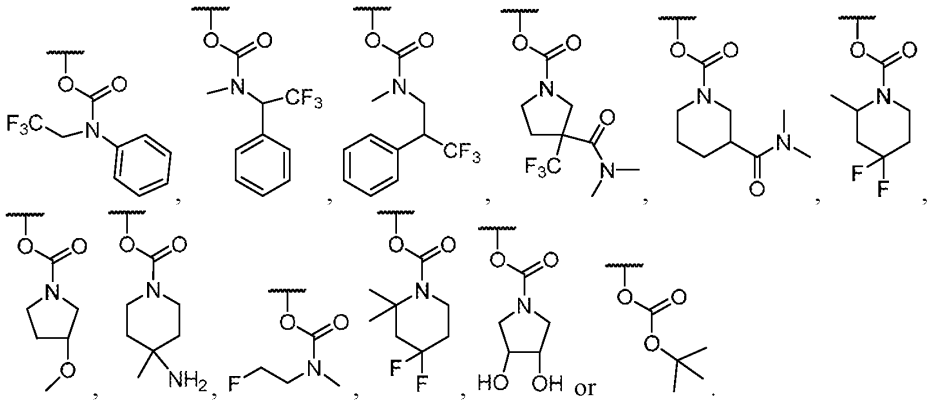


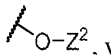


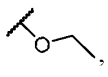


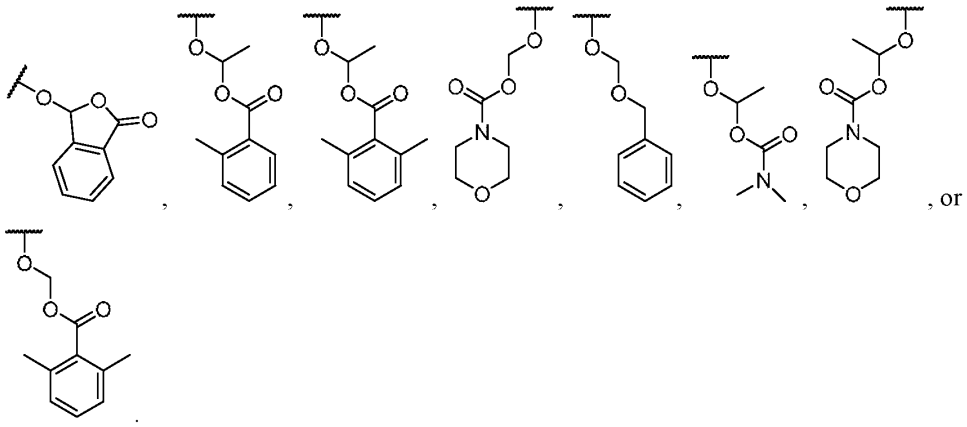


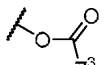


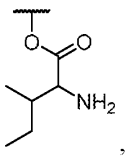


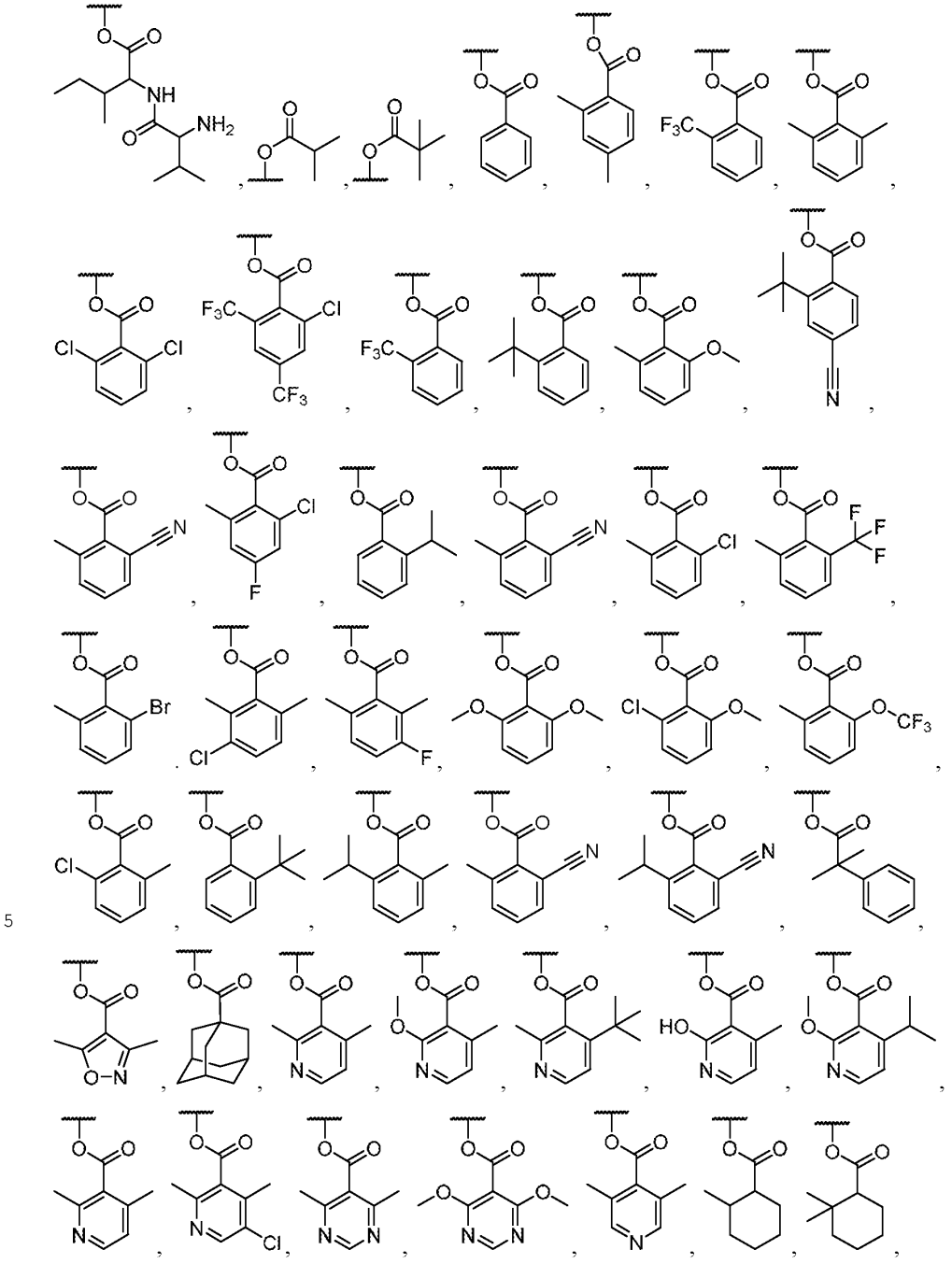
In some embodiments, the prodrug functional moiety R^5 is , wherein Z^2 is C_{1-3} alkyl, (C_{1-3} alkylene)—O—(C_{1-3} alkyl), (C_{1-3} alkylene)—O—C(O)—X, wherein the alkyl and X are optionally substituted.

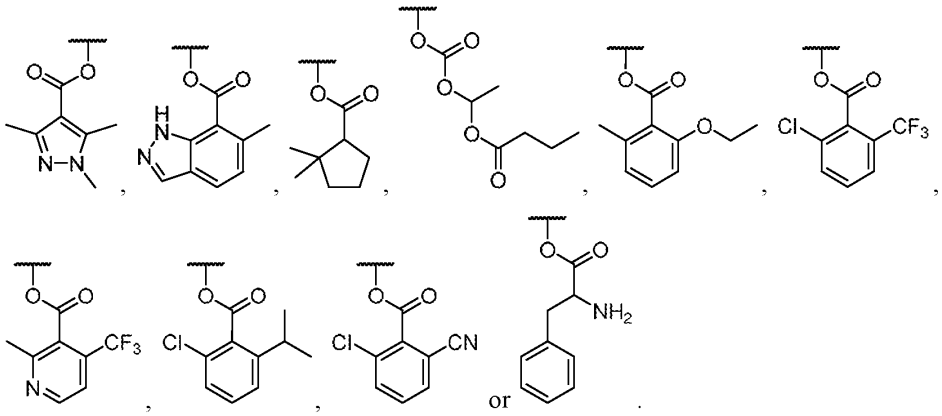
In some embodiments, the prodrug functional moiety R^5 is ,

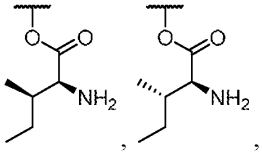


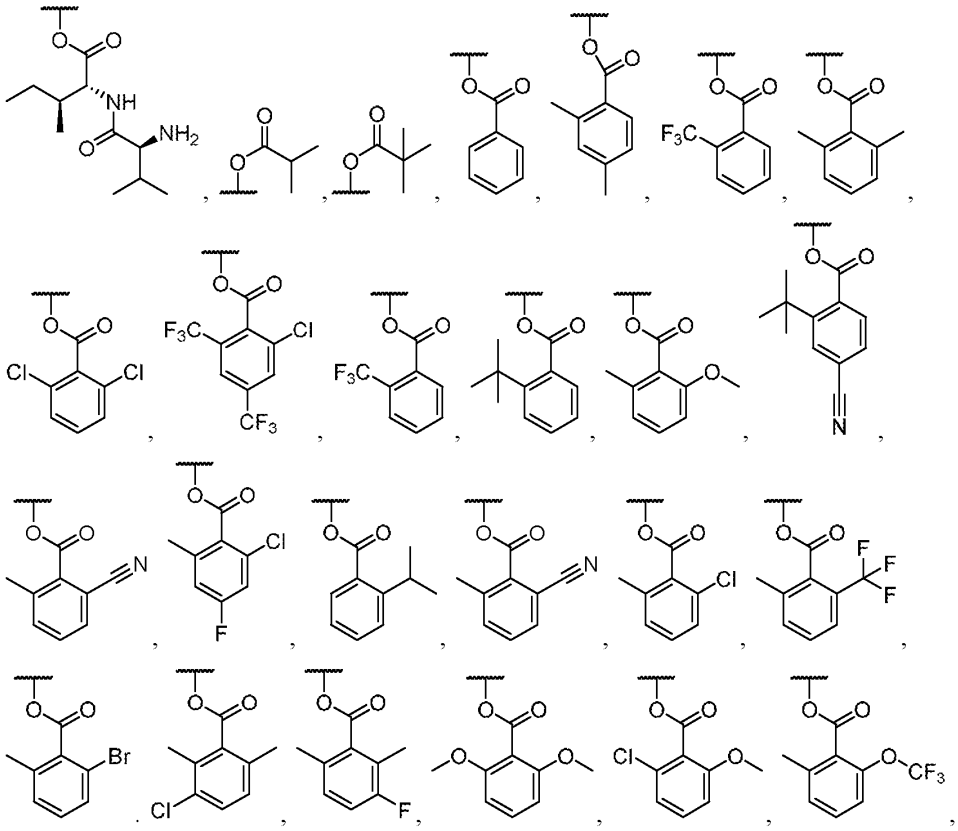
In some embodiments, the prodrug functional moiety R^5 is ,wherein Z^3 is optionally substituted 4-10 membered aryl, 4-11 membered heteroaryl, 4-8 membered cycloalkyl, 4-10 membered heterocyclyl.

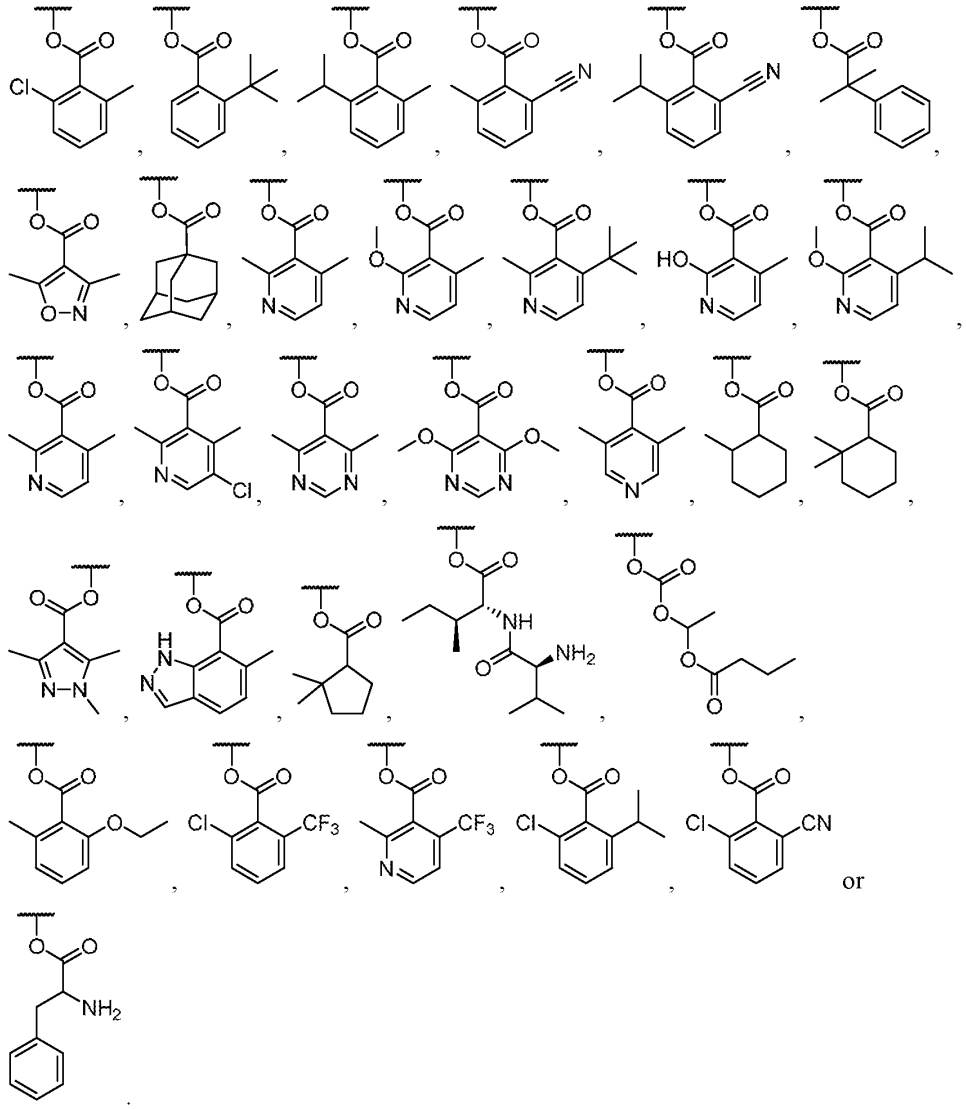
In some embodiments, the prodrug functional moiety R^5 is ,





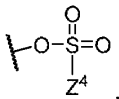
In some embodiments, the prodrug functional moiety R^5 is 

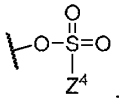




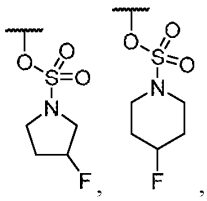
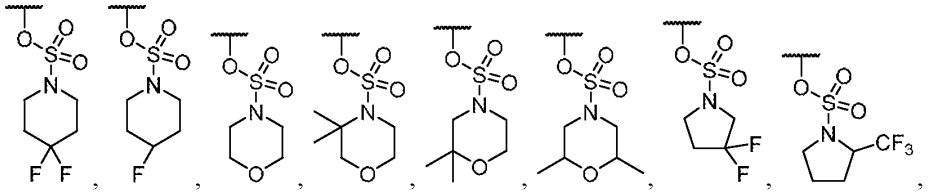
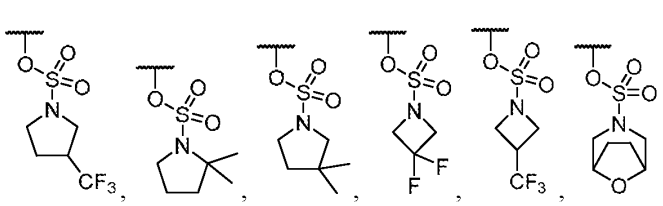
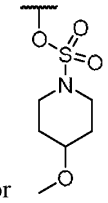
or

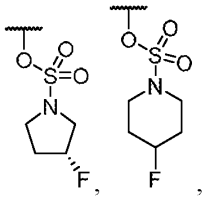
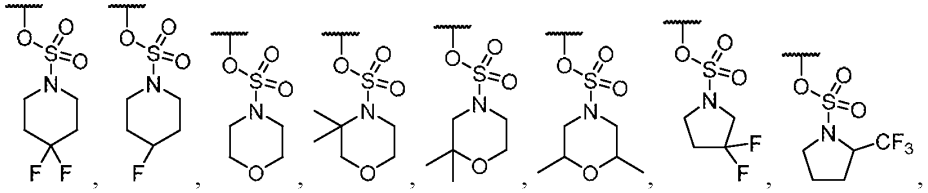
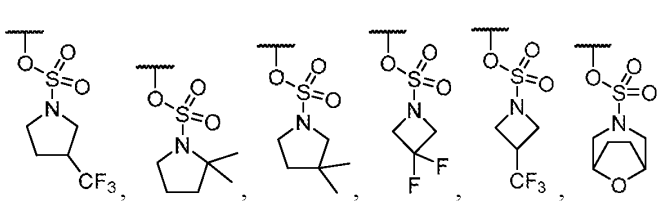
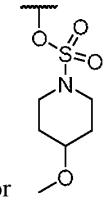
.

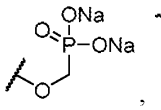
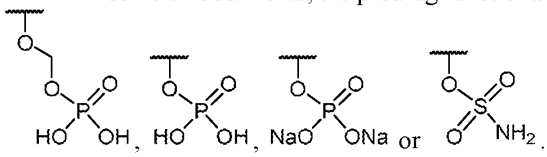
In some embodiments, the prodrug functional moiety R^5 is , wherein Z^4 is monocyclic, fused or bridged bicyclic 4-11 membered N-containing heterocyclyl or 4-11 membered N-containing heteroaryl optionally substituted with 0 to 4 substituents, wherein the point of attachment is on N.

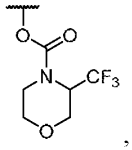
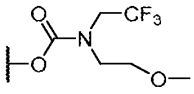
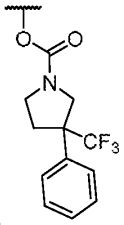
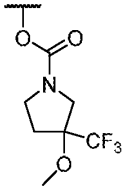
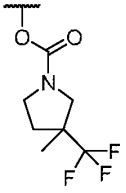
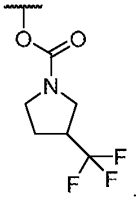
In some embodiments, the prodrug functional moiety R^5 is ,wherein Z^4 is

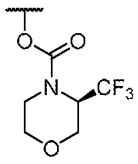
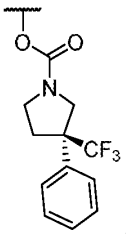
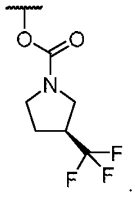
monocyclic, fused or bridged bicyclic 4-11 membered N-containing heterocyclyl or 4-11 membered N-containing heteroaryl optionally substituted with 2 to 3 substituents, wherein the point of attachment is on N.

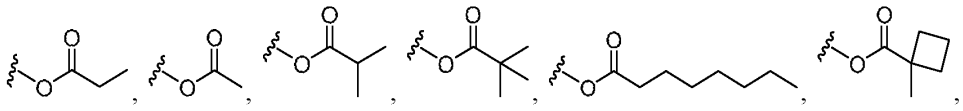
In some embodiments, the prodrug functional moiety R^5 is , , ,  or .

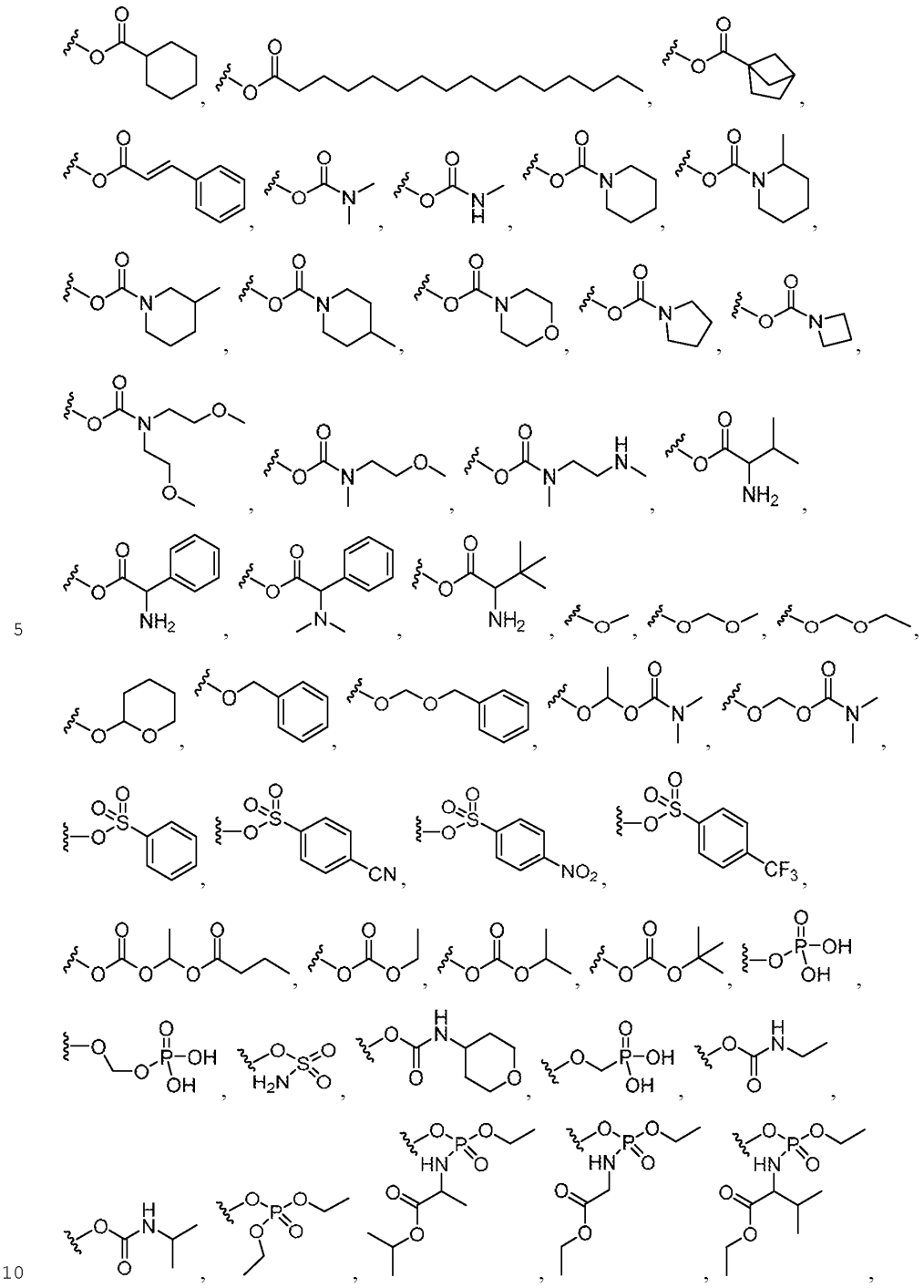
In some embodiments, the prodrug functional moiety R^5 is , , ,  or .

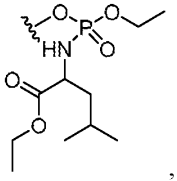
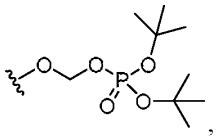
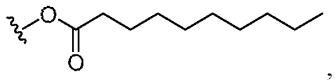
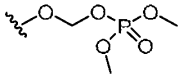
In some embodiments, the prodrug functional moiety R^5 is  ,  ,  or .

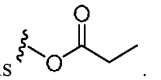
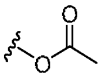
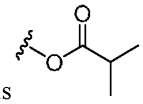
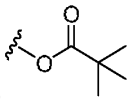
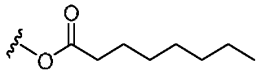
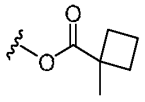
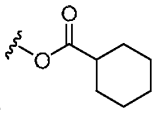
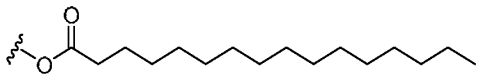
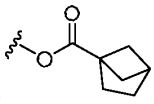
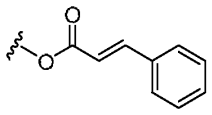
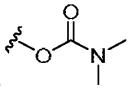
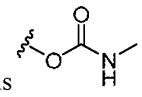
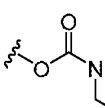
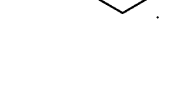
In some embodiments, the prodrug functional moiety R^5 is selected from the group consisting of  ,  ,  ,  ,  and  .

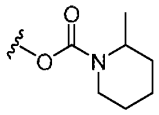
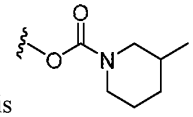
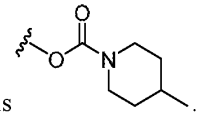
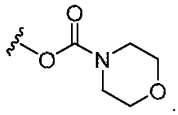
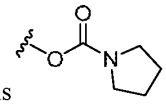
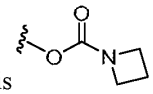
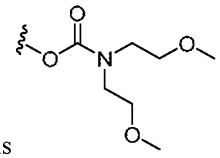
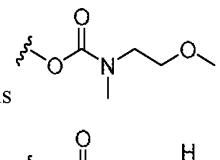
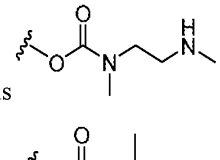
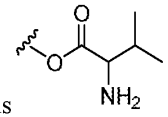
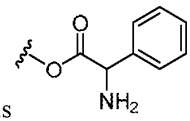
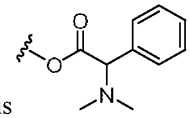
In some embodiments, the prodrug functional moiety R^5 is  ,  , or  .

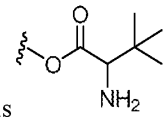
In some embodiments, the prodrug functional moiety R^5 has one of the following structures:  ,

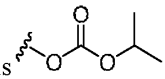
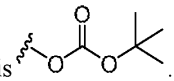
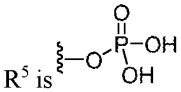
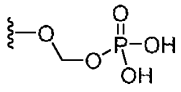
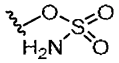
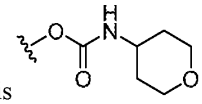
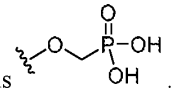
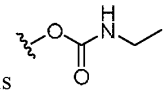
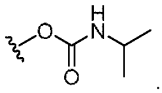
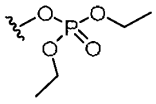
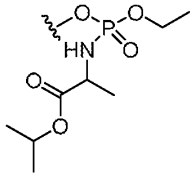
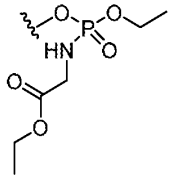
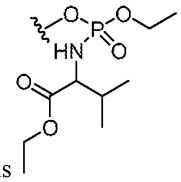


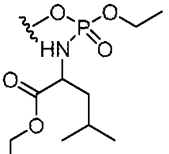
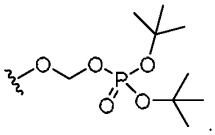
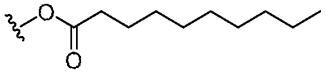
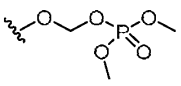
, , , or .

In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is .

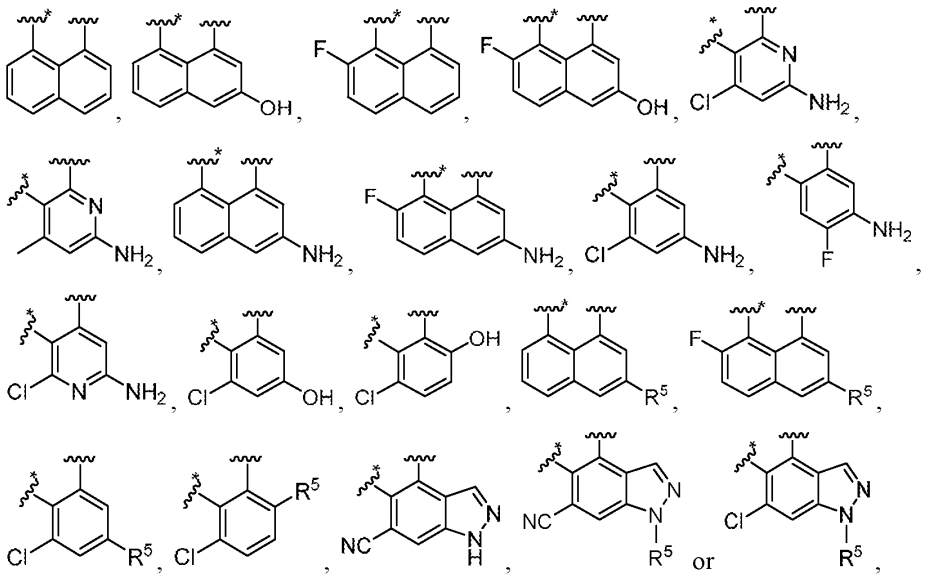
prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is

moiety R^5 is . In some embodiments, the prodrug functional

prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is .

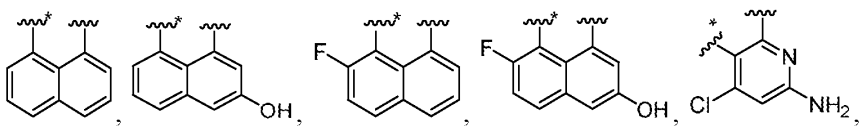
In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is . In some embodiments, the prodrug functional moiety R^5 is .

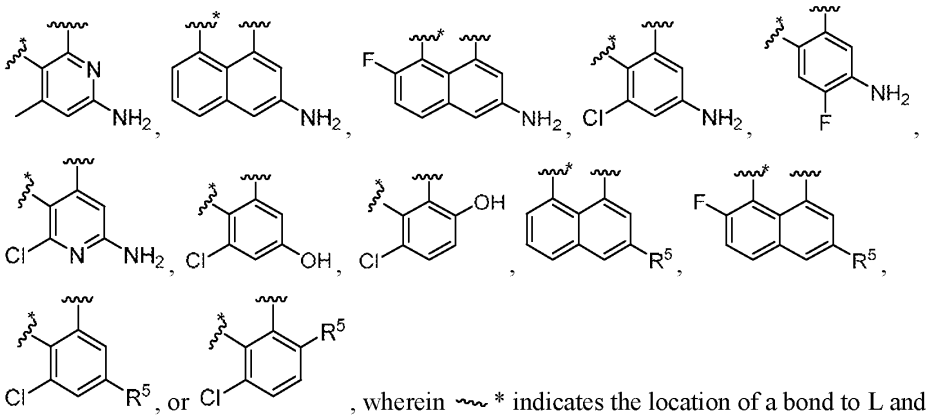
In some embodiments, B has one of the following structures:



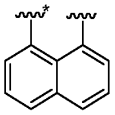
wherein ~* indicates the location of a bond to L and ~ indicates the location of a bond to the pyridine group.

In some embodiments, B has one of the following structures:

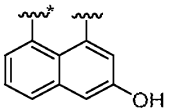




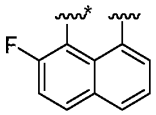
, wherein ~~* indicates the location of a bond to L and ~~ indicates the location of a bond to the pyridine group. In some embodiments, B is



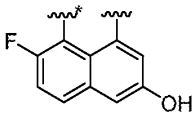
. In some embodiments, B is



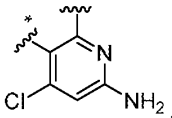
. In some embodiments, B is



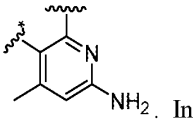
. In some embodiments, B is



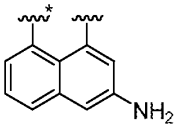
. In some embodiments, B is



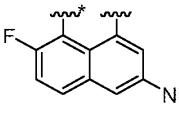
. In some embodiments, B is



. In some embodiments, B is

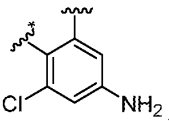


. In some embodiments, B is

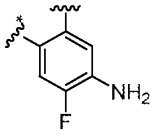


. In some embodiments, B

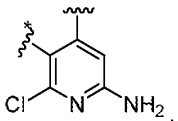
is



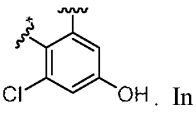
. In some embodiments, B is



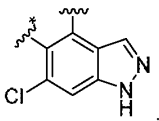
. In some embodiments, B is



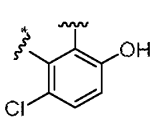
. In some embodiments, B is



. In some embodiments, B is



. In some embodiments, B is

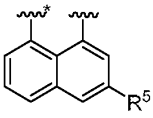
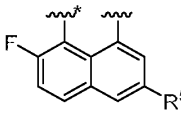
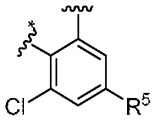
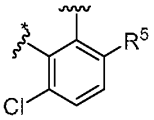
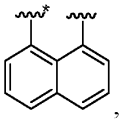
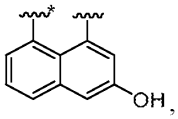
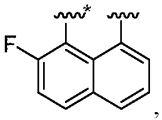
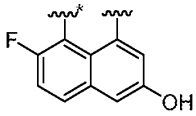


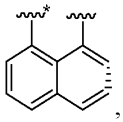
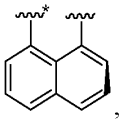
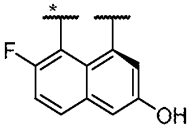
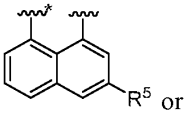
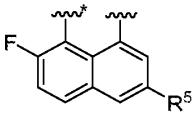
. In some embodiments, B is

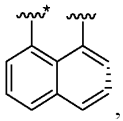
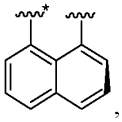
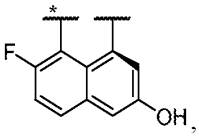
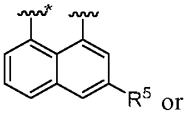
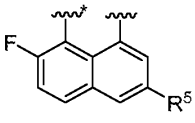
. In some embodiments, B is



. In some embodiments, B is

. In some embodiments, B is . In some embodiments, B is . In some embodiments, B is . In some embodiments, B is , , , or .

In some embodiments, B is , , ,  or , wherein B is further optionally substituted, wherein ~~* indicates the location of a bond to L and ~~ indicates the location of a bond to the pyridine group.

In some embodiments, B is , , ,  or , wherein ~~* indicates the location of a bond to L and ~~ indicates the location of a bond to the pyridine group.

In one embodiment, L is C_1-C_8 alkylene, C_2-C_8 alkenylene, C_2-C_8 alkynylene, or C_1-C_8 heteroalkylene. In some embodiments, L is C_1-C_8 alkylene. In some embodiment, L is C_2-C_8 alkenylene. In some embodiments, L is C_2-C_8 alkynylene. In some embodiment, L is C_1-C_8 heteroalkylene. In some other embodiments, L is C_1-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, or C_1-C_6 heteroalkylene. In some other embodiments, L is C_1-C_4 alkylene, C_2-C_4 alkenylene, C_2-C_4 alkynylene, or C_1-C_4 heteroalkylene. In some other embodiments, L is C_2-C_4 alkylene, C_2-C_4 alkenylene, C_2-C_4 alkynylene, or C_2-C_4 heteroalkylene. In some other embodiments, L is C_2-C_6 alkylene, C_2-C_6 alkenylene, C_2-C_6 alkynylene, or C_2-C_6

heteroalkylene.

In some embodiments, the C_1-C_8 alkylene, C_2-C_8 alkenylene, C_2-C_8 alkynylene, or C_1-C_8 heteroalkylene of L is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from halo, -D, C_1-C_4 alkyl, and C_3-C_5 cycloalkyl. In some embodiments, the C_1-C_8 alkylene of L is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from halo, -D, C_1-C_4 alkyl, C_3-C_5 cycloalkyl. In some other embodiments, the C_2-C_8 alkenylene of L is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from halo, -D, C_1-C_4 alkyl, and C_3-C_5 cycloalkyl. In some other embodiments, the C_2-C_8 alkynylene of L is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from halo, -D, C_1-C_4 alkyl, and C_3-C_5 cycloalkyl. In some other embodiments, the C_1-C_8 heteroalkyl of L is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from halo, -D, C_1-C_4 alkyl, or C_3-C_5 cycloalkyl. In some specific embodiments, the C_1-C_8 alkylene, C_2-C_8 alkenylene, C_2-C_8 alkynylene, or C_1-C_8 heteroalkylene of L is substituted with -F, -D, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CF_2H$, or one or more carbon atoms of the C_1-C_8 alkylene, C_2-C_8 alkenylene, C_2-C_8 alkynylene, or C_1-C_8 heteroalkylene are substituted with a substituent each independently selected from , and . In some specific embodiments, the C_1-C_8 alkylene of L is substituted with -F, -D, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CF_2H$, or one or more carbon atoms of the C_1-C_8 alkylene are substituted with a substituent each independently selected from  and . In some other specific embodiments, the C_2-C_8 alkenyl of L is substituted with -F, -D, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-CF_2H$, or one or more carbon atoms of the C_2-C_8 alkenylene are substituted with a substituent each independently selected from  and . In some other specific embodiments, the C_2-C_8 alkynylene of L is substituted with -F, -D, $-CH_3$, $-CH_2CH_3$, $-CF_3$, or $-CF_2H$, or one or more carbon atoms of the C_2-C_8 alkynylene are substituted with a substituent each independently selected from  and . In some other specific embodiments, the C_1-C_8 heteroalkyl of L is substituted with -F, -D, $-CH_3$, $-CH_2CH_3$, $-CF_3$, or $-CF_2H$, or one or more carbon aroms of the C_1-C_8 heteroalkylene is

substituted with a substituent each independently selected from  and .

In some embodiments, L is selected from the group consisting of: C_1-C_8 alkylene, C_2-C_8 alkenylene, and C_2-C_8 alkynylene, wherein the C_1-C_8 alkylene, C_2-C_8 alkenylene, and C_2-C_8 alkynylene are optionally substituted with one or more substituents each independently selected from halo and -D.

In some embodiments, L is selected from the group consisting of: C_1-C_6 alkylene, C_2-C_6 alkenylene, and C_2-C_6 alkynylene, wherein the C_1-C_6 alkylene, C_2-C_6 alkenylene, and C_2-C_6 alkynylene are optionally substituted with one or more substituents each independently selected from halo and -D.

In some embodiments, L is selected from the group consisting of: C_2-C_4 alkylene, C_2-C_4 alkenylene, and C_2-C_4 alkynylene, wherein the C_2-C_4 alkylene, C_2-C_4 alkenylene, and C_2-C_4 alkynylene are optionally substituted with one or more substituents each independently selected from halo and -D.

In some embodiments, L is selected from the group consisting of: $–(CH_2)_4$-, $–(CH_2)_3$-, $–(CH_2)_2$-, *–CH_2CH=CH–**, *–$(CH_2)_2CH$=CH–**, *–$(CH_2)_2C\equiv C$–**, *–$CH_2C\equiv C$–**, –CH_2CHFCH_2–, –$CH_2CF_2CH_2$–, *–$CH(CH_3)CH_2CH_2$–**, *–$(CH_2)CH(CH_2)$- **, *–$(CH_2)_2CH(CH_2)$- **, *–$(CH_2)C(CH)_2$-**, and *–$(CH_2)_2C(CH_2)$-**, wherein * indicates the location of the bond to the carbamate group and ** indicates the location of the bond to B group. In some embodiments, L is $–(CH_2)_4$-. In some embodiments, L is $–(CH_2)_3$-. In some embodiments, L is $–(CH_2)_2$-. In some embodiments, L is *–CH_2CH=CH–**. In some embodiments, L is*–$(CH_2)_2CH$=CH–**. In some embodiments, L is *–$(CH_2)_2C\equiv C$–**. In some embodiments, L is *–$CH_2C\equiv C$–**. In some embodiments, L is –CH_2CHFCH_2–. In some embodiments, L is –$CH_2CF_2CH_2$–. In some embodiments, L is *–$CH(CH_3)CH_2CH_2$–**. In some embodiments, L is *–$(CH_2)CH(CH_2)$- **. In some embodiments, L is *–$(CH_2)_2CH(CH_2)$- **. In some embodiments, L is *–$(CH_2)C(CH)_2$-**. In some embodiments, L is *–$(CH_2)_2C(CH_2)$-**.

In some specific embodiments, L is $–(CH_2)_3$-, $–(CH_2)_2$-, *–$(CH_2)CH(CH_2)$- **, *–$(CH_2)_2CH(CH_2)$-**, *–$(CH_2)C(CH)_2$-**, or *–$(CH_2)_2C(CH_2)$- **, wherein * indicates the location of the bond to the carbamate group and ** indicates the location of the bond to B group. In some other specific embodiments, L is $–(CH_2)_3$- or $–(CH_2)_2$-. In some embodiments, L is $–(CH_2)_3$-. In some embodiments, L is $–(CH_2)_2$-. In some embodiments, L is *–$(CH_2)CH(CH_2)$- **. In some embodiments, L is *–$(CH_2)_2CH(CH_2)$- **. In some

embodiments, L is *–$(CH_2)C(CH)_2$-**. In some embodiments, L is *–$(CH_2)_2C(CH_2)$- **.

In some embodiments, L is –$(CH_2)_3$-.

In one embodiment, R^2 is a hydrogen, 4-8 membered cycloalkyl, 4-10 membered heterocycloalkyl, heteroaryl, or amine. In some embodiments, R^2 is a hydrogen. In some embodiments, R^2 is 4-8 membered cycloalkyl. In some embodiments, the 4-8 membered cycloalkyl of R^2 is a cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl. In some embodiments, the 4-8 membered cycloalkyl of R^2 is a cyclopropyl. In some embodiments, the 4-8 membered cycloalkyl of R^2 is cyclobutyl. In some embodiments, the 4-8 membered cycloalkyl of R^2 is cyclopentyl. In some embodiments, the 4-8 membered cycloalkyl of R^2 is cyclohexyl. In some embodiments, the 4-8 membered cycloalkyl of R^2 is cycloheptyl. In some embodiments, the 4-8 membered cycloalkyl of R^2 is cyclooctyl.

In some other embodiments, R^2 is 4-10 membered heterocyclyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, oxanyl, piperazinyl, morpholinyl, dioxanyl, azepanyl, oxepanyl, homopiperazinyl, or oxazepanyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is azetidinyl, pyrrolidinyl, morpholinyl, or piperidinyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is azetidinyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is pyrrolidinyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is tetrahydrofuranyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is piperidinyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is oxanyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is piperazinyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is morpholinyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is dioxanyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is azepanyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is oxepanyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is homopiperazinyl. In some embodiments, the 4-10 membered heterocyclyl of R^2 is oxazepanyl.

In some other embodiments, R^2 is heteroaryl (e.g., 5-6 membered heteroaryl). In some embodiments, the heteroaryl of R^2 is imidazolyl, pyrazolyl, or pyridinyl. In some embodiments, the heteroaryl of R^2 is imidazolyl. In some embodiments, the heteroaryl of R^2 is pyrazolyl. In some embodiments, the heteroaryl of R^2 is pyridinyl.

In some other embodiments, R^2 is a bicyclic heterocyclyl. In some embodiments, the bicyclic of R^2 is a fused bicyclic heterocyclyl, a spiro bicyclic heterocyclyl, or a bridged bicyclic heterocyclyl. In some embodiments, the bicyclic heterocyclyl of R^2 is a fused

bicyclic heterocyclyl. In some embodiments, the fused bicyclic of R^2 is hexahydro-1H-pyrrolizinyl, octahydro-6λ^2-pyrrolo[3,4-b]pyridinyl, octahydro-1H-cyclopenta[b]pyridinyl, hexahydro-1H-pyrrolo[2,1-c][1,4]oxazinyl, 2-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.1.0]hexanyl, or 1,2,3,4-tetrahydroisoquinolinyl. In some embodiments, the fused bicyclic heterocyclyl of R^2 is hexahydro-1H-pyrrolizinyl. In some embodiments, the fused bicyclic heterocyclyl of R^2 is octahydro-6λ^2-pyrrolo[3,4-b]pyridinyl. In some embodiments, the fused bicyclic heterocyclyl of R^2 is octahydro-1H-cyclopenta[b]pyridinyl. In some embodiments, the fused bicyclic heterocyclyl of R^2 is hexahydro-1H-pyrrolo[2,1-c][1,4]oxazinyl. In some embodiments, the fused bicyclic heterocyclyl of R^2 is 2-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.1.0]hexanyl. In some embodiments, the fused bicyclic heterocyclyl of R^2 is 1,2,3,4-tetrahydroisoquinolinyl.

In some embodiments, the bicyclic heterocyclyl of R^2 is a spiro bicyclic heterocyclyl. In some embodiments, the spiro bicyclic heterocyclyl of R^2 is tetrahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizinyl] or 5-azaspiro[2.4]heptanyl. In some embodiments, the spiro bicyclic heterocyclyl of R^2 is tetrahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizinyl]. In some embodiments, the spiro bicyclic heterocyclyl of R^2 is 5-azaspiro[2.4]heptanyl.

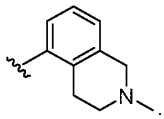
In some embodiments, the bicyclic heterocyclyl of R^2 is a bridged bicyclic heterocyclyl. In some embodiments, the bridged bicyclic heterocyclyl of R^2 is 2-oxa-5-azabicyclo[2.2.1]heptanyl.

In some embodiments, the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, or amine of R^2 is substituted with one or more substituents each independently selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, C_1-C_4 alkylene-C_6-C_{10} aryl, C_1-C_4 alkylene-(5-10 membered heteroaryl), C_1-C_4 alkylene-C_3-C_{10} cycloalkyl, C_1-C_4 alkylene-(3-10 membered heterocyclyl), 3-10 membered heterocyclyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_1-C_4 alkylene- $NR^{X1}R^{X2}$, $=CH_2$, $=CF_2$ or =CFH, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy.

In some embodiments, the 4-8 membered cycloalkyl, 4-10 membered heterocycloalkyl, heteroaryl, or amine of R^2 is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from halo, deuterium, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, hydroxyl, $=CH_2$, $=CF_2$, =CFH, heteroaryl, -and (CH_2)p-4-6 membered heterocycloalkyl, wherein p is an integer between 1 and 3. In some specific embodiments, the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, or amine of R^2 is

substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from -CH_3, -F, -CN, -NH_2, -CH_2OCH_3, -OCH_3, -CF_2H, -CF_3, -OH, =CH_2, =CF_2, =CFH, heteroaryl, -C_1-C_3 alkylalcohol, C_1-C_3 alkoxyl, and deuterium.

In some embodiments, R^2 is aryl (e.g., phenyl) fused to 4-8 membered heterocyclyl, wherein the 4-8 membered heterocyclyl is optionally substituted. In some embodiments, the aryl (e.g., phenyl) fused to 4-8 membered hetererocyclyl is



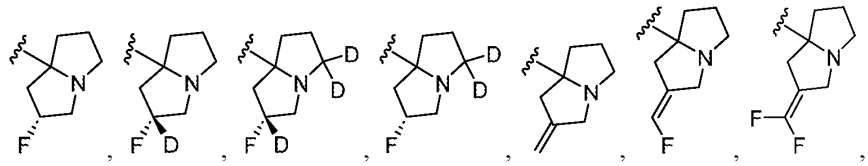
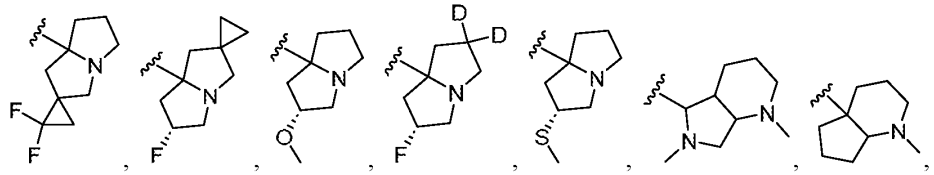
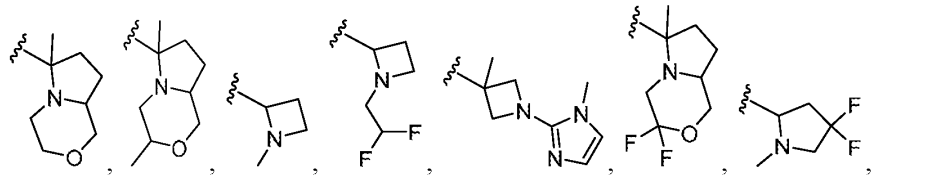
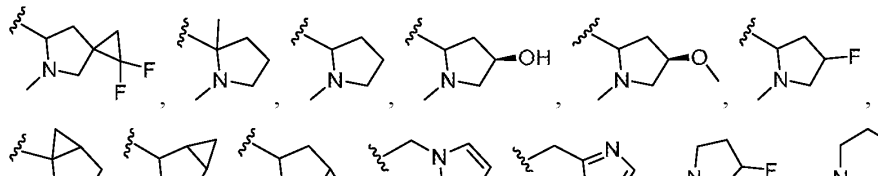
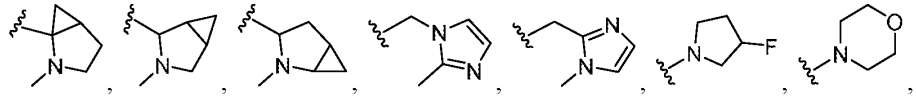
In some embodiments, the 4-8 membered cycloalkyl, 4-10 membered heterocycloalkyl, heteroaryl, or amine of R^2 is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from halo, deuterium, C_1-C_4 alkyl, C_1-C_4 alkylene-NR^X, C_1-C_4 alkylene-(4-10 membered heterocyclyl), C_1-C_4 heteroalkyl, hydroxyl, =CH_2, =CF_2, =CFHand heteroaryl, each R^X is independently hydrogen or C_1-C_4 alkyl. In some specific embodiments, the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, or amine of R^2 is substituted with one or more substituents (e.g., 1, 2, 3, 4, or 5 substituents) each independently selected from -CH_3, -F, -CN, -NH_2, -CH_2OCH_3, -OCH_3, -CF_2H, -CF_3, -OH, =CH_2, =CF_2, =CFH, heteroaryl, -C_1-C_3 alkylalcohol, C_1-C_3 alkoxyl, deuterium, -$CH_2N(CH_3)_2$, and -CH_2-(6-membered heterocyclyl).

In some embodiments , the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, or amine of R^2 is substituted with one or more substituents each independently selected from the group consisting of -CH_3, -F, =CF_2, =CFH, =CH_2, and -OH.

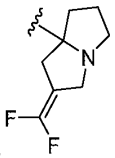
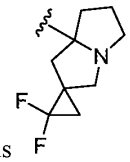
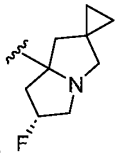
In some other embodiments, R^2 is an amine. In some embodiments, the amine of R^2 is -NH_2, -$NH(CH_3)$, or -$N(CH_3)_2$. In some embodiments, the amine of R^2 is -NH_2. In some embodiments, the amine of R^2 is -$NH(CH_3)$. In some embodiments, the amine of R^2 is -$N(CH_3)_2$.

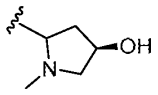
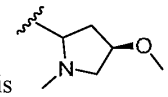
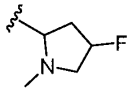
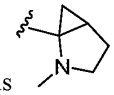
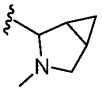
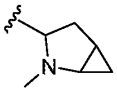
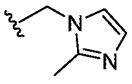
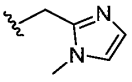
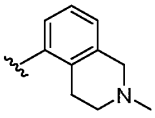
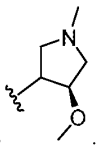
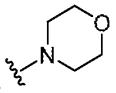
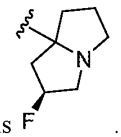
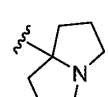
In some embodiments, R^2 is selected from the group consisting of 4-10 membered heterocyclyl, 5-6 membered heteroaryl, and amine, wherein the 4-10 membered heterocyclyl, 5-6 membered heteroaryl, and amine are optionally substituted with one or more substituents each independently selected from the group consisting of -CH_3, -F, =CF_2, =CFH, =CH_2, and -OH.

In some embodiments, R^2 has one of the following structures:

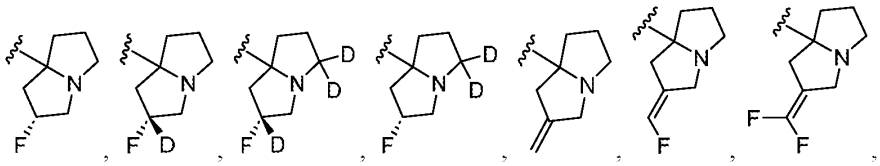






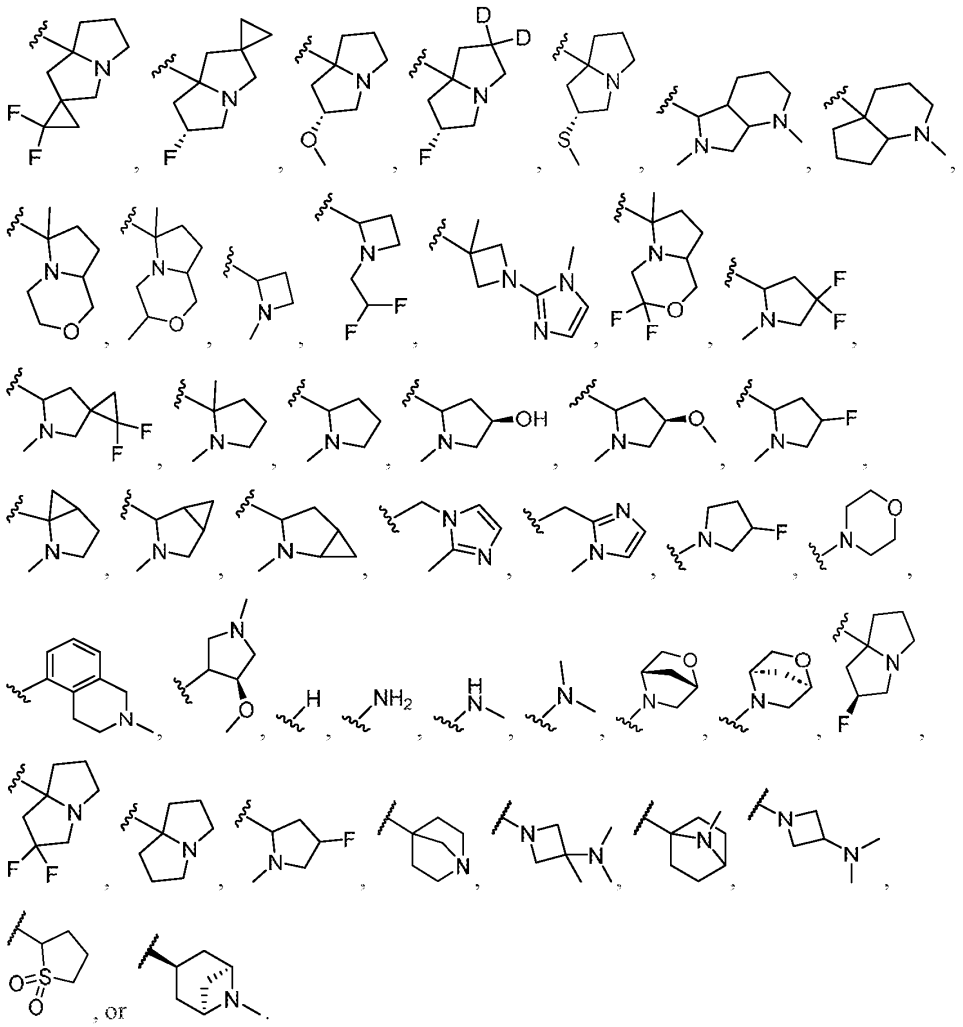
, or . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is .

In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is .

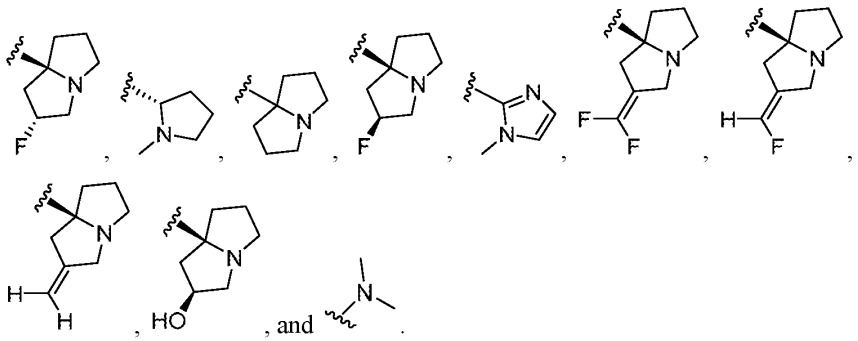
. In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is . In some embodiments, R^2 is .

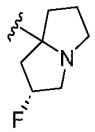
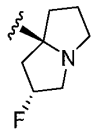
In some embodiments, R^2 has one of the following structures:





In some embodiment, R^2 is selected from the group consisting of:



In some embodiments, R^2 is  . In some other embodiments, R^2 is  .

In one embodiment, R^1 is a hydrogen or C_1-C_3 alkyl. In some embodiments, R^1 is a hydrogen. In some embodiments, R^1 is C_1-C_3 alkyl.

In some embodiments, R^1 is a hydrogen, $-CH_2CH_3$, or $-CH_3$. In some other specific embodiments, R^1 is $-CH_2CH_3$. In some other specific embodiments, R^1 is $-CH_3$.

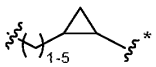
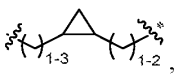
In one embodiment, X is -O-, $-NR^3$-, or a direct bond.

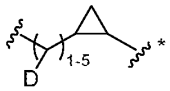
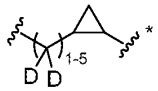
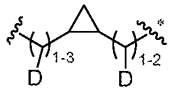
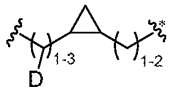
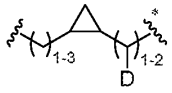
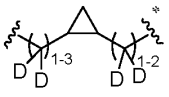
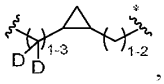
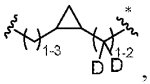
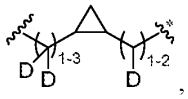
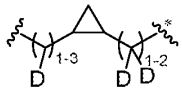
In one embodiment, X is -O- or a direct bond. In some embodiments, X is -O-. In some other embodiments, X is $-NR^3$-. In some embodiments, when X is $-NR^3$-, R^3 is a hydrogen or C_1-C_3 alkyl. In some embodiments, when X is $-NR^3$-, R^3 is a hydrogen or $-CH_3$. In some other embodiments, X is a direct bond.

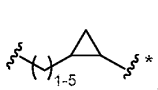
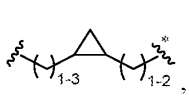
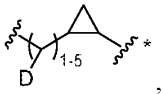
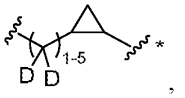
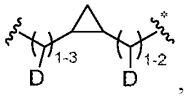
In one embodiment, Y is C_1-C_5 alkylene, C_1-C_5 deuteroalkylene, or a direct bond.

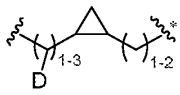
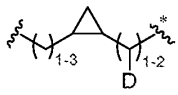
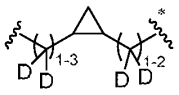
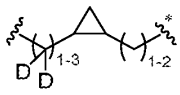
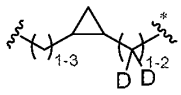
In some embodiments, Y is $-CH_2$-, $-CD_2$-, $-CH(CH_3)$-, $-CD(CH_3)$-, $-CD(CD_3)$-, or a direct bond. In some specific embodiments, Y is $-CH_2$-. In some specific embodiments, Y is $-CD_2$-. In some specific embodiments, Y is $-CH(CH_3)$-. In some specific embodiments, Y is $-CD(CH_3)$-. In some specific embodiments, Y is $-CD(CD_3)$-. In some specific embodiments, Y is a direct bond.

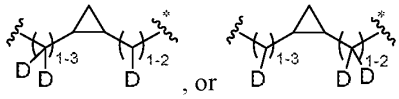
In some embodiments, Y is $-CH_2$-, $-CD_2$-, $-CH_2$-CH_2-, or a direct bond. In some specific embodiments, Y is $-CH_2$-. In some specific embodiments, Y is $-CD_2$-. In some specific embodiments, Y is $-CH_2$-CH_2-. In some specific embodiments, Y is a direct bond.

In some embodiments, the C_1-C_5 alkylene or C_1-C_5 deuteroalkylene of Y is substituted with methyl, dimethyl, or cyclopropyl. In some embodiments, one or more carbons of the C_1-C_5 alkylene or C_1-C_5 deuteroalkylene are substituted with cyclopropyl. In some embodiments, the C_1-C_5 alkylene of Y is substituted with methyl, dimethyl, or cyclopropyl. For example, Y is C_1-C_5 alkylene substituted with a cyclopropyl. In some specific embodiments, Y is  , wherein * indicates the location of a bond to R^2, and ~ indicates the location of a bond to X. In another example, Y is  , wherein * indicates the location of a bond to R^2, and ~ indicates the location of a bond to X. In some embodiments, the C_1-C_5 deuteroalkylene of Y is further substituted with methyl, dimethyl, or cyclopropyl. For example, Y is the C_1-C_5 deuteroalkyl substituted with a

cyclopropyl. In some specific embodiments, Y is  or , wherein ~~* indicates the location of a bond to R^2, and ~~ indicates the location of a bond to X. In another example, Y is , wherein ~~* indicates the location of a bond to R^2, and ~~ indicates the location of a bond to X. In another example, Y is , wherein ~~* indicates the location of a bond to R^2, and ~~ indicates the location of a bond to X. In another example, Y is , wherein ~~* indicates the location of a bond to R^2, and ~~ indicates the location of a bond to X. In another example, Y is , wherein ~~* indicates the location of a bond to R^2, and ~~ indicates the location of a bond to X. In another example, Y is , wherein ~~* indicates the location of a bond to R^2, and ~~ indicates the location of a bond to X. In another example, Y is , wherein ~~* indicates the location of a bond to R^2, and ~~ indicates the location of a bond to X. In another example, Y is , wherein ~~* indicates the location of a bond to R^2, and ~~ indicates the location of a bond to X. In another example, Y is , wherein ~~* indicates the location of a bond to R^2, and ~~ indicates the location of a bond to X. In some embodiments, Y is

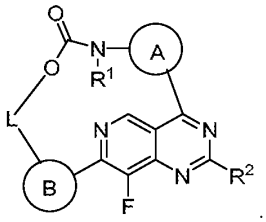
, , , , ,

, , , , ,



, wherein ~~* indicates the location of a bond to R^2, and ~~ indicates the location of a bond to X.

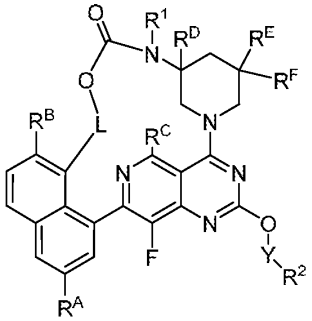
In some embodiments, when X and Y are both direct bonds, the compound has the following structure of Formula (II):



(II)

In some specific embodiments, R^2 of Formula (II) is a hydrogen.

In some embodiments, the compound has the following structure of Formula (III):



(III)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein

L is selected from the group consisting of linear C_3-C_5 alkylene and linear C_3-C_5 deuteroalkylene, wherein the linear C_3-C_5 alkylene or linear C_3-C_5 deuteroalkylene is optionally substituted with C_1-C_2 alkyl, C_1-C_2 haloalkyl, CN, halo, OH, NH_2, -$NH(CH_3)$ or $N(CH_3)_2$;

R^A is selected from the group consisting of alkylenecyclyl, heterocyclyl, aryl, or heteroaryl, H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy, wherein the alkylene-cyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted, wherein the C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy is optionally substituted with C_{1-4} alkyl, halo, OH, CN,

aryl, heteroaryl, cycloalkyl , heterocyclyl, -C(O)$NR^{X3}R^{X4}$ wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, or prodrug moiety R^5;

R^B is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, and wherein the alkyl, haloalkyl, alkoxy can be substituted with C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl , heterocyclyl, or -C(O)$NR^{X3}R^{X4}$, wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy;

R^C is selected from the group consisting of H, D, C_1-C_2 alkyl, C_1-C_2 alkoxy, halo, CN, NH_2, -$NH(CH_3)$, and $N(CH_3)_2$;

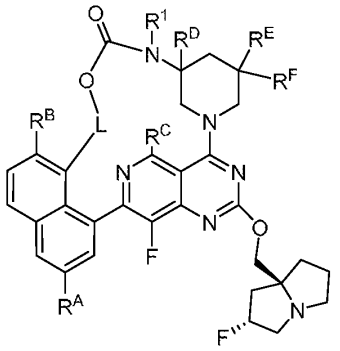
R^D is selected from the group consisting of H, D, C_1-C_3 alkyl, C_1-C_2 deuteroalkyl, C_1-C_3 haloalkyl, C_1-C_3 alkylalcohol, (C_1-C_3 alkylene)-O-(C_1-C_3 alkyl), and CN;

R^E and R^F are each independently selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, and $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, and wherein the alkyl, haloalkyl, alkoxy can be substituted with: C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, -C(O)$NR^{X3}R^{X4}$, wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy;

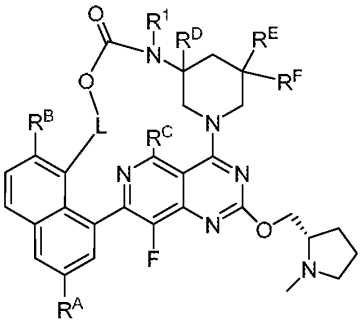
R^1 is selected from the group consisting of H, D, C_1-C_2 alkyl, C_1-C_2 alkoxy, halo, CN, NH_2, -$NH(CH_3)$, and $N(CH_3)_2$;

Y is selected from the group consisting of C_1-C_5 alkylene, C_1-C_5 deuteroalkylene, or a direct bond, wherein the C_1-C_5 alkylene or C_1-C_5 deuteroalkylene is optionally substituted;R^2 is selected from the group consisting of hydrogen, 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, -(C_1-C_3 alkylene)-heteroaryl, aryl fused to 4-8 membered heterocyclyl, and amine, wherein the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, 4-8 membered heterocyclyl, or amine is optionally substituted.

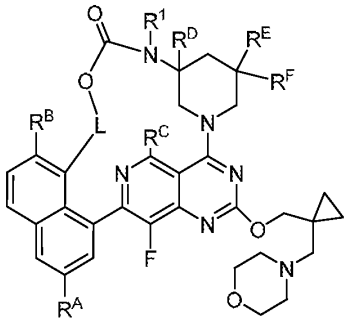
In some embodiments, the compound has one of the following structures of Formula (IIIA), (IIIB) or (IIIC):



(IIIA)



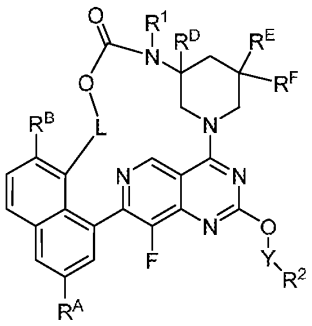
(IIIB)



(IIIC)

wherein the variables are as defined herein.

In some embodiments, the compound has the following structure of Formula (III-1):



(III-1)

wherein

L is selected from the group consisting of linear C_3-C_5 alkylene and linear C_3-C_5 deuteroalkylene, wherein the linear C_3-C_5 alkylene or linear C_3-C_5 deuteroalkylene is optionally substituted with C_1-C_2 alkyl, C_1-C_2 haloalkyl, CN, halo, OH, NH_2, -$NH(CH_3)$ or $N(CH_3)_2$;

R^A is selected from the group consisting of alkylenecyclyl, heterocyclyl, aryl, or heteroaryl, H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy, wherein the alkylene-cyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted, wherein the C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy is optionally substituted with C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl , heterocyclyl, -$C(O)NR^{X3}R^{X4}$ wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, or prodrug moiety R^5;

R^B is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, and wherein the alkyl, haloalkyl, alkoxy can be substituted with C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, or -$C(O)NR^{X3}R^{X4}$, wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy;

R^D is selected from the group consisting of H, D, C_1-C_3 alkyl, C_1-C_2 deuteroalkyl, C_1-C_3 haloalkyl, C_1-C_3 alkylalcohol, (C_1-C_3 alkylene)-O-(C_1-C_3 alkyl), and CN;

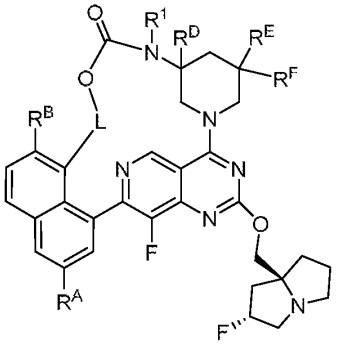
R^E and R^F are each independently selected from the group consisting of H, C_1-C_4

alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, and $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, and wherein the alkyl, haloalkyl, alkoxy can be substituted with: C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, -$C(O)NR^{X3}R^{X4}$, wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy;

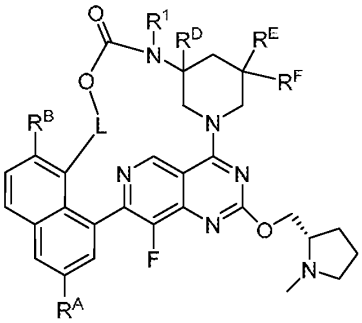
R^1 is selected from the group consisting of H, D, C_1-C_2 alkyl, C_1-C_2 alkoxy, halo, CN, NH_2, -$NH(CH_3)$, and $N(CH_3)_2$;

Y is selected from the group consisting of C_1-C_5 alkylene, C_1-C_5 deuteroalkylene, or a direct bond, wherein the C_1-C_5 alkylene or C_1-C_5 deuteroalkylene is optionally substituted;R^2 is selected from the group consisting of hydrogen, 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, -(C_1-C_3 alkylene)-heteroaryl, aryl fused to 4-8 membered heterocyclyl, and amine, wherein the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, 4-8 membered heterocyclyl, or amine is optionally substituted.

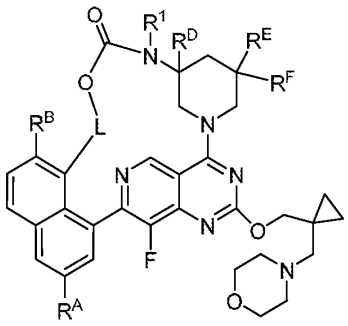
In some embodiments, the compound has one of the following structures of Formula (IIIA), (IIIB) or (IIIC):



(III-1A)



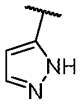
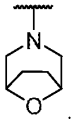
(III-1B)



(III-1C)

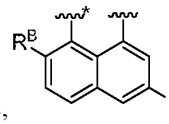
wherein the variables are as defined herein.

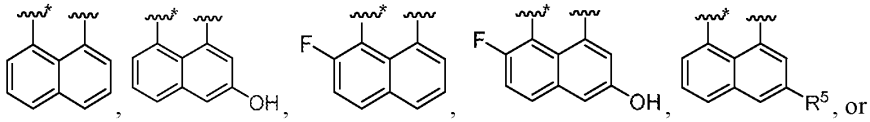
In some embodiments, L is selected from the group consisting of unsubstituted linear C_3-alkylene, unsubstituted linear C_4-alkylene, linear C_3-alkylene substituted with -CH_3, CN, F, or Cl, or linear C_4-alkylene substituted with -CH_3, CN, F, or Cl.

In some embodiments, R^A is selected from the group consisting of H, OH, C_1-C_4 alkylalcohol, F, Cl, C_1-C_2 alkyl, C_1-C_2 haloalkyl, CN, NH_2, -$NH(CH_3)$, $N(CH_3)_2$, -$NHC(O)NHCH_3$, -CHF_2, R^5 prodrug moiety,  and .

In some embodiments, R^B is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 heteroalkyl, halo, NH_2, -$NH(CH_3)$, $N(CH_3)_2$, and OH.

In some embodiments, R^B is selected from the group of H, CH_3, F, and Cl.

In some embodiments,  has the structure of the following:

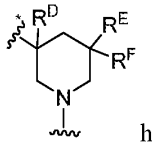
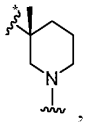


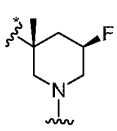
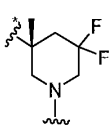
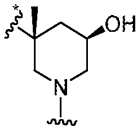
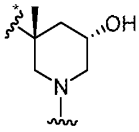
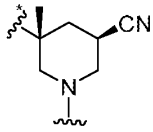
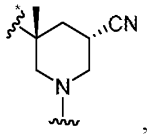
wherein ~* indicates the location of a bond to L and ~ indicates the location of a bond to the pyrimidine group.

In some embodiments, R^C is selected from the group consisting of H, -CH_3, and -OCH_3.

In some embodiments, R^D is selected from the group consisting of -CH_3, C_1-haloalkyl, -CF_3, -CH_2CH_2OH, -CH_2OH, -CH_2CHF_2, and -CH_2-O-CH_3.

In some embodiments, R^E and R^F are each independently selected from the group consisting of H, D, F, Cl, CH_3, C_1 haloalkyl, and -OCH_3.

In some embodiments,  has the structure of the following: ,

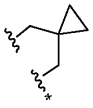
, , , , , or ,

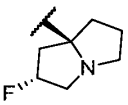
wherein ~ * indicates the location of a bond to the carbamate group and ~ indicates the location of a bond to the pyrimidine group.

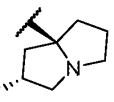
In some embodiments, R^1 is selected from the group consisting of H, CH_3, and C_1 haloalkyl.

In some embodiments, Y is C_1-C_3 alkylene optionally substituted with C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, cyclopropyl, and $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, or C_{1-4} haloalkyl.

In some embodiments, wherein Y is substituted C_3 alkylene, wherein the substituted C_3 alkylene is

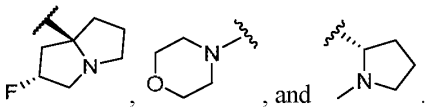
, wherein ~ represents the point of attachment to X and ~* represents the point of attachment to R^2.

In some embodiments, R^2 is selected from the group consisting of ,

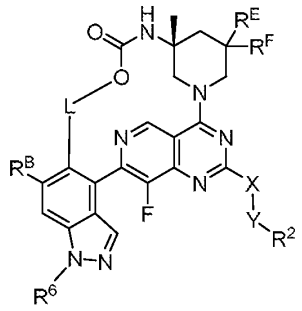
, morpholinyl, or pyrrolidinyl, wherein , morpholinyl, or pyrrolidinyl is optionally substituted with C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, cyclopropyl, or $NR^{X1}R^{X2}$,

wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, or C_{1-4} haloalkyl.

In some embodiments, R^2 is selected from the group consisting of:



In some embodiments, the compound has the following structure of Formula (IV):



(IV)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein

L is selected from the group consisting of : C_1-C_8 alkylene, C_2-C_8 alkenylene, C_2-C_8 alkynylene, C_1-C_8 heteroalkylene, wherein the C_1-C_8 alkylene, C_1-C_8 alkenylene, C_1-C_8 alkynylene, or C_1-C_8 heteroalkylene is optionally substituted, —O-(C_1-C_8 alkylene)—, —O-(C_2-C_8 alkenylene)—, —O-(C_2-C_8 alkynylene)—, —O-(C_1-C_8 heteroalkylene)—, —S-(C_1-C_8 alkylene)—, —S-(C_2-C_8 alkenylene)—, —S-(C_2-C_8 alkynylene)—, —S-(C_1-C_8 heteroalkylene)—, —NR-(C_1-C_8 alkylene)—, —NR-(C_2-C_8 alkenylene)—, —NR-(C_2-C_8 alkynylene)—, and —NR-(C_1-C_8 heteroalkylene)—;

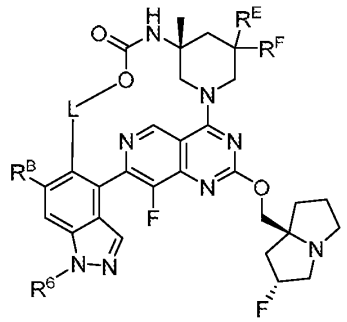
R^B is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O- C_1-C_4 alkylene, halo, hydroxyl, -C(=O)CH_3, NH_2, -NH(CH_3), N(CH_3)$_2$;

R^6 is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$ **w**herein R^{X1}, R^{X2}: are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, and wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy can be substituted with: C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, -C(O)$NR^{X3}R^{X4}$ wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, or prodrug moiety R^5;

X, Y, and R^2 are as defined in claim 17;

R^E and R^F are each independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 heteroalkyl, halo, $NR^{X1}R^{X2}$, hydroxyl, or CN, wherein R^{X1} and R^{X2} are each independently H or C_{1-4} alkyl.

In some embodiments, the compound has the following structure of Formula (IVA):



(IVA)

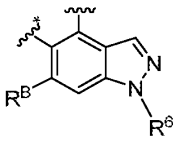
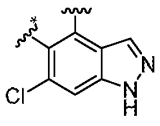
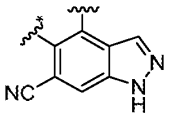
wherein the variables are as defined herein.

In some embodiments, L is linear C_2-C_5 alkylene optionally substituted with C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, or CN.

In some embodiments, R^B is H, F, Cl, $-CH_3$, $-CD_3$, $-CF_3$, $-CH_2CH_3$, OH, CN, or NH_2.

In some embodiments, R^6 is H, F, Cl, $-CH_3$, $-CD_3$, $-CF_3$, $-CH_2CH_3$, OH, CN, or NH_2.

In some embodiments, R^B is CN or Cl.

In some embodiments,  has the structure of following:  or  wherein 〰* indicates the location of a bond to L and 〰 indicates the location of a bond to the pyridine group.

In some embodiments, R^E and R^F are each independently H, F, Cl, $-CH_3$, $-CD_3$, $-CF_3$, $-CH_2CH_3$, OH, CN, or NH_2.

In some embodiments of Formula (I), (IA-3), (II), (III), or (IV) or a subformula thereof (e.g., Formula (IA), Formula (IA-2), Formula (IIIA), Formula (IIIB), Formula (IIIC), Formula (III-1), Formula (III-1A), Formula (III-1B), Formula (III-1C), Formula (IVA)), each of the optional substituent mentioned herein may be selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 deuteroalkyl, -D, C_1-C_6 heteroalkyl, CN, C_1-C_6 alkylene-CN, C_1-C_6 alkylalcohol, C_1-C_6 alkylene-O-C_1-C_6 alkyl, halo, hydroxyl, -C(=O)-C_1-C_6 alkyl, $NR^{X1}R^{X2}$, C_1-C_6 alkylene-phenyl, C_1-C_6 alkylene-(5-10 membered heteroaryl), C_1-C_6 alkylene-(C_{3-10} cycloalkyl), C_1-C_6 alkylene-(5-10 membered heterocyclyl), 5-10 membered heterocyclyl, C_{3-10} cycloalkyl, phenyl, naphthyl, 5-10 membered heteroaryl, and a prodrug functional moiety R^5 (as defined herein), wherein the 5-10 membered heterocyclyl, C_{3-10} cycloalkyl, phenyl, naphthyl, or 5-10 membered heteroaryl is optionally substituted with C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 deuteroalkyl, -D, C_1-C_6 heteroalkyl, CN, C_1-C_6 alkylene-CN, C_1-C_6 alkylalcohol, C_1-C_6 alkylene-O-C_1-C_6 alkyl, halo, hydroxyl, -C(=O)-C_1-C_6 alkyl, or $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, or C_1-C_6 alkylene-(C_{1-6} alkoxy), and wherein the C_{1-6} alkyl, C_{1-6} haloalkyl, or C_1-C_6 alkylene-C_{1-6} alkoxy is optionally substituted with C_{1-6} alkyl, halo, OH, or CN.

In some embodiments of Formula (I), (IA-3), (II), (III), or (IV) or a subformula thereof (e.g., Formula (IA), Formula (IA-2), Formula (IIIA), Formula (IIIB), Formula (IIIC), Formula (III-1), Formula (III-1A), Formula (III-1B), Formula (III-1C), Formula (IVA)), each of the optional substituent mentioned herein may be selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 deuteroalkyl, -D, C_1-C_6 heteroalkyl, CN, C_1-C_6 alkylene-CN, C_1-C_6 alkylalcohol, C_1-C_6 alkylene-O-C_1-C_6 alkyl, halo, hydroxyl, -C(=O)-C_1-C_6 alkyl, $NR^{X1}R^{X2}$, 5-10 membered heterocyclyl, C_{3-10} cycloalkyl, phenyl, naphthyl, 5-10 membered heteroaryl, and a prodrug functional moiety R^5 (as defined herein), wherein R^{X1} and R^{X2} are each independently H, C_{1-6} alkyl, or C_{1-6} haloalkyl.

In some embodiments of Formula (I), (IA-3), (II), (III), or (IV) or a subformula thereof (e.g., Formula (IA), Formula (IA-2), Formula (IIIA), Formula (IIIB), Formula (IIIC), Formula (III-1), Formula (III-1A), Formula (III-1B), Formula (III-1C), Formula (IVA)), each of the optional substituent mentioned herein may be selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 deuteroalkyl, -D, C_1-C_6 heteroalkyl, CN, C_1-C_6 alkylene-CN, C_1-C_6 alkylalcohol, C_1-C_6 alkylene-O-C_1-C_6 alkyl, halo, hydroxyl, -C(=O)-C_1-C_6 alkyl, $NR^{X1}R^{X2}$, 5-10 membered heterocyclyl, C_{3-10} cycloalkyl, phenyl, naphthyl, and 5-10 membered heteroaryl, wherein R^{X1} and R^{X2} are each

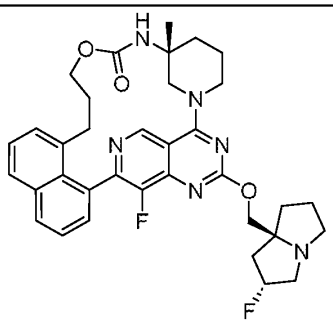
independently H, C_{1-6} alkyl, or C_{1-6} haloalkyl.

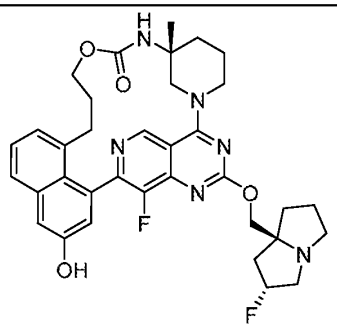
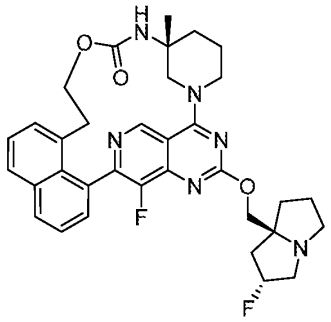
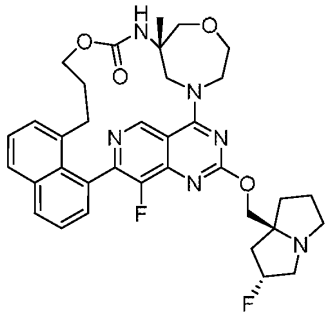
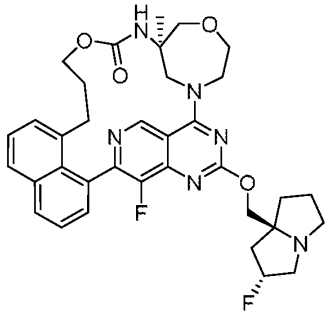
In some embodiments of Formula (I), (IA-3), (II), (III), or (IV) or a subformula thereof (e.g., Formula (IA), Formula (IA-2), Formula (IIIA), Formula (IIIB), Formula (IIIC), Formula (III-1), Formula (III-1A), Formula (III-1B), Formula (III-1C), Formula (IVA)), each of the optional substituent mentioned herein may be selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 deuteroalkyl, -D, C_1-C_6 heteroalkyl, CN, C_1-C_6 alkylene-CN, C_1-C_6 alkylalcohol, C_1-C_6 alkylene-O-C_1-C_6 alkyl, halo, hydroxyl, -C(=O)-C_1-C_6 alkyl, $NR^{X1}R^{X2}$, cyclopropyl, and a prodrug functional moiety R^5 (as defined herein), wherein R^{X1} and R^{X2} are each independently H, C_{1-6} alkyl, or C_{1-6} haloalkyl.

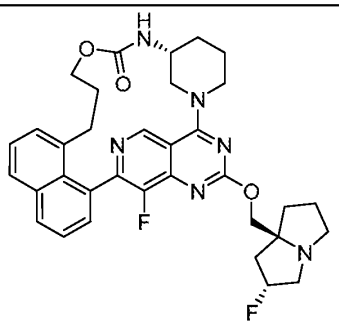
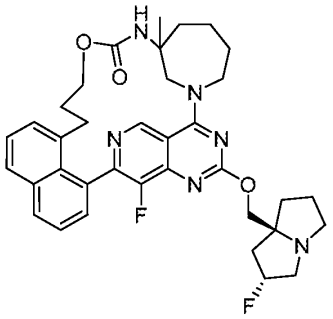
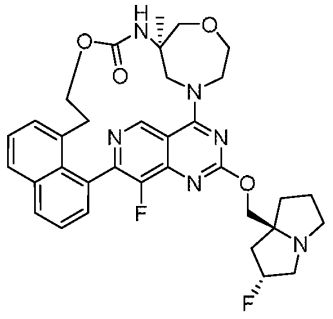
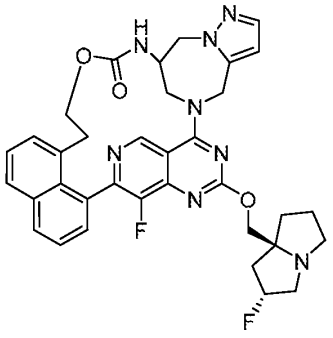
In some embodiments of Formula (I), (IA-3), (II), (III), or (IV) or a subformula thereof (e.g., Formula (IA), Formula (IA-2), Formula (IIIA), Formula (IIIB), Formula (IIIC), Formula (III-1), Formula (III-1A), Formula (III-1B), Formula (III-1C), Formula (IVA)), each of the optional substituent mentioned herein may be selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 deuteroalkyl, -D, C_1-C_6 heteroalkyl, CN, C_1-C_6 alkylene-CN, C_1-C_6 alkylalcohol, C_1-C_6 alkylene-O-C_1-C_6 alkyl, halo, hydroxyl, -C(=O)-C_1-C_6 alkyl, $NR^{X1}R^{X2}$, and cyclopropyl, wherein R^{X1} and R^{X2} are each independently H, C_{1-6} alkyl, or C_{1-6} haloalkyl.

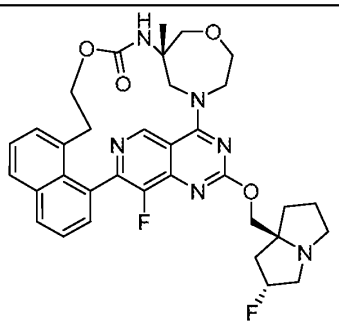
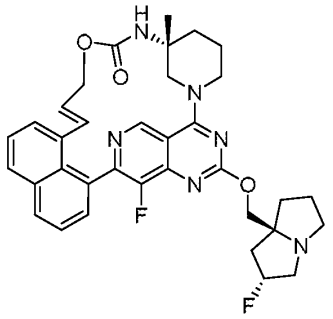
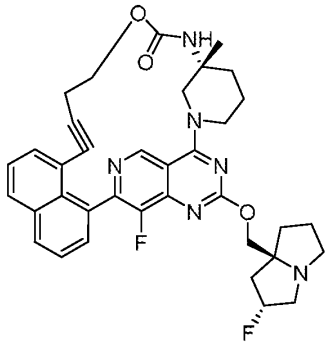
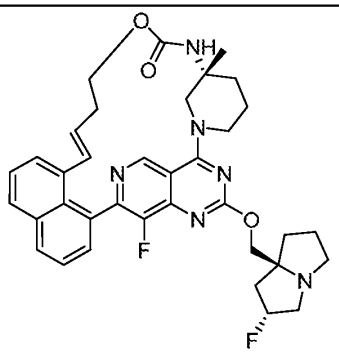
In one embodiment, the compound of formula of (I), (II), (IA)-(IE), or (IA-1)-(IE-1) has one of the following structures shown in Table 1 below.

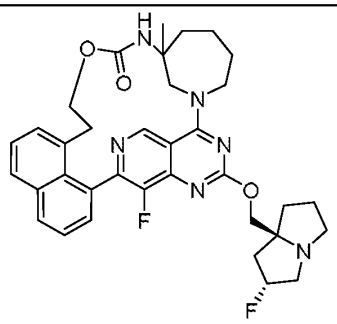
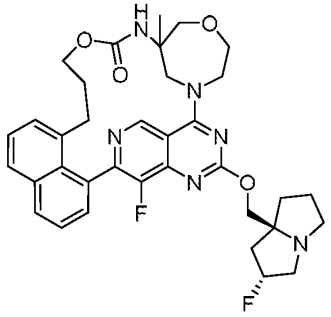
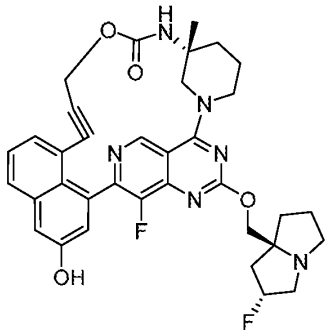
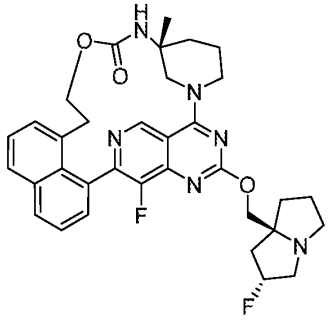
Table 1: List of Compounds of (I), (II), (IA)-(IE), or (IA-1)-(IE-1)

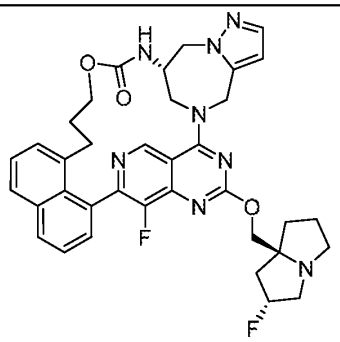
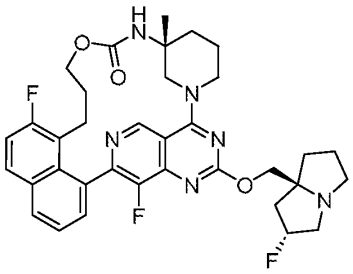
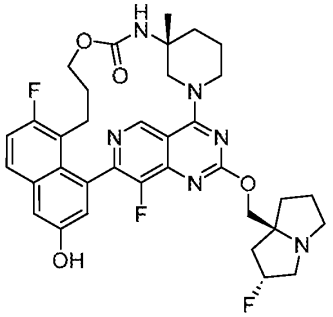
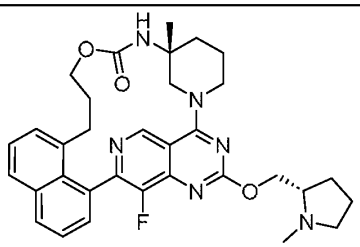
Cmp. ID	Structure
1	

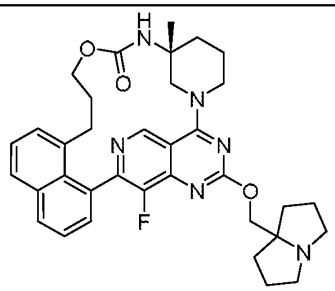
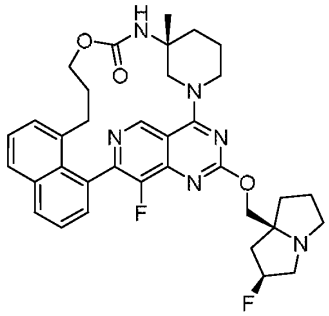
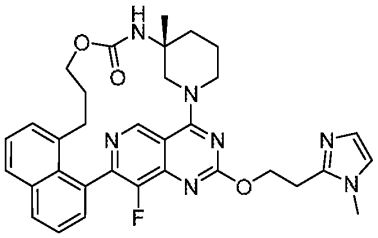
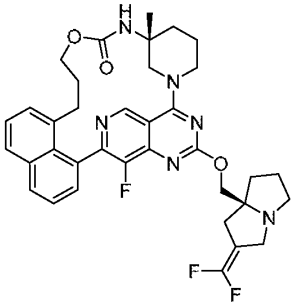
2	
3	
4	
5	

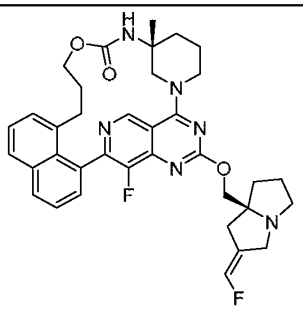
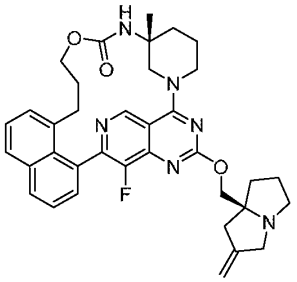
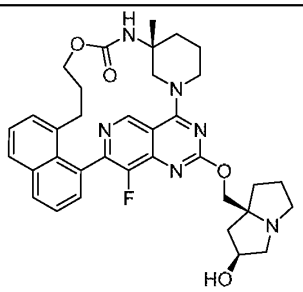
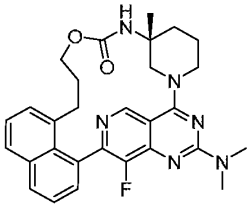
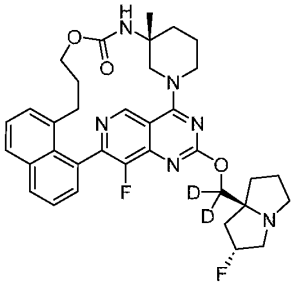
6	
7	
8	
9	

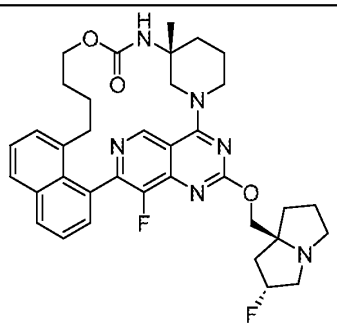
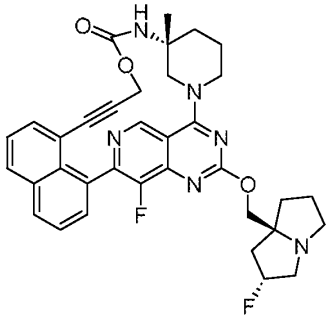
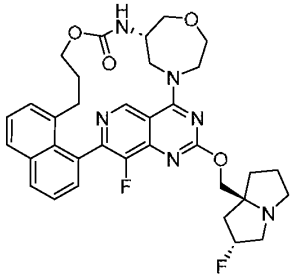
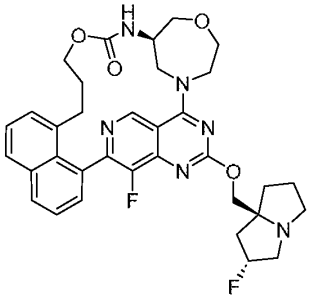
10	
11	
12	
13	

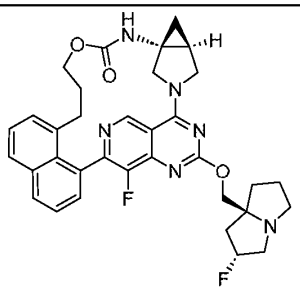
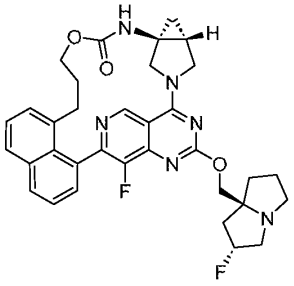
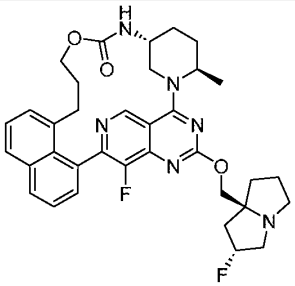
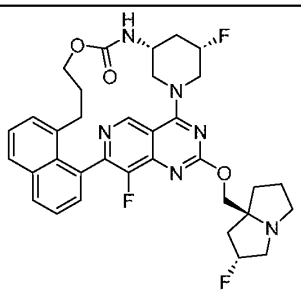
14	
15	
16	
17	

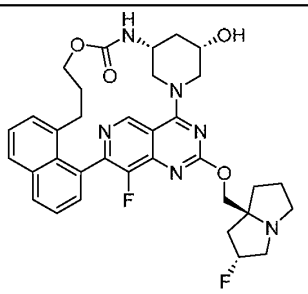
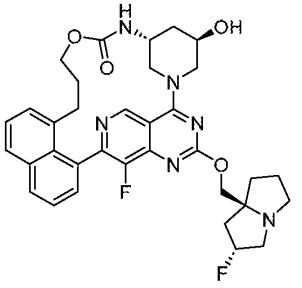
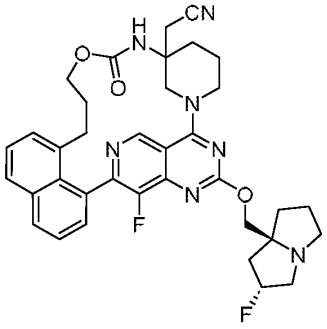
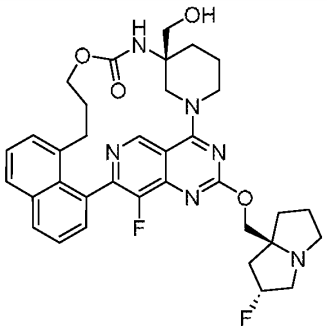
18	
19	
20	
21	

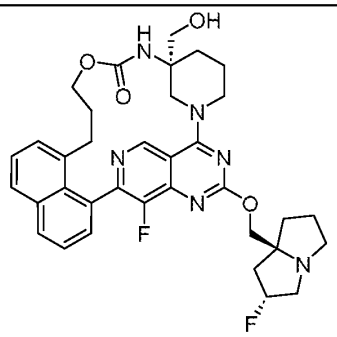
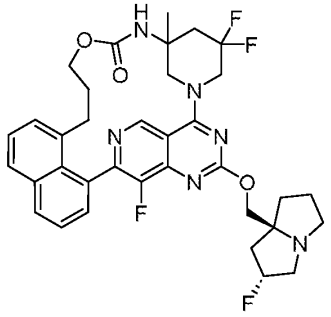
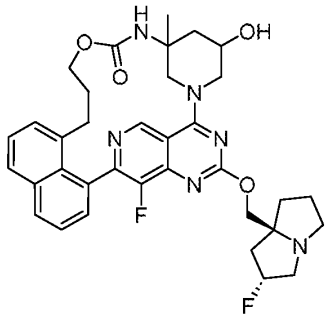
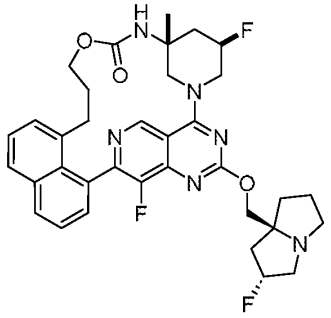
22	
23	
24	
25	

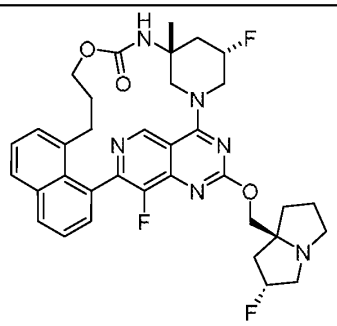
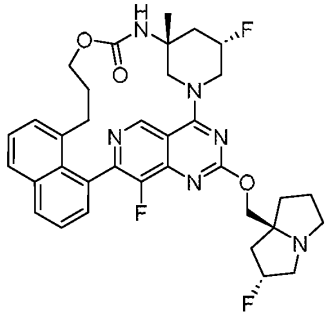
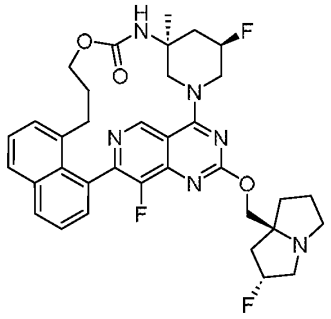
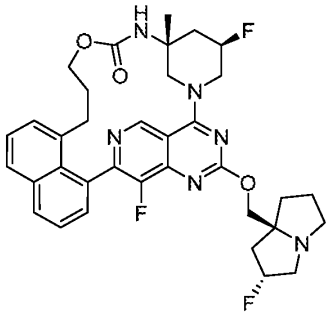
26	
27	
28	
29	
30	

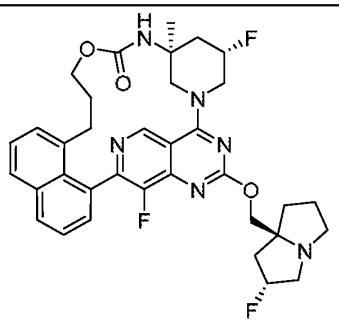
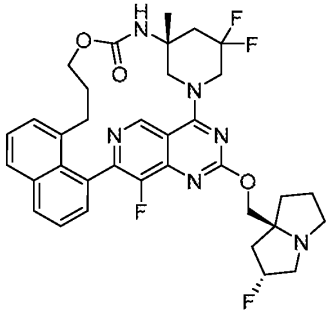
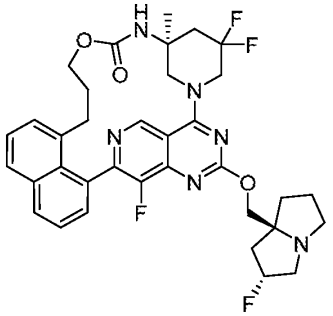
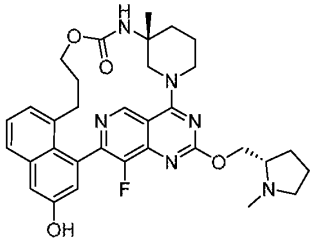
31	
32	
33	
34	

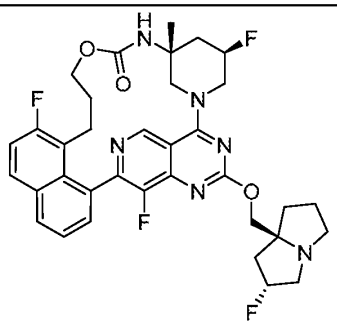
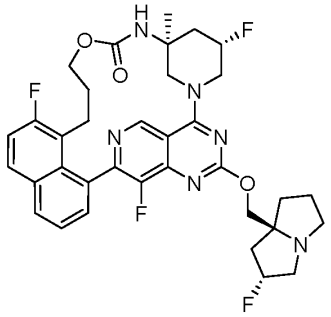
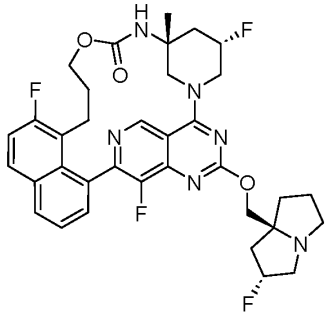
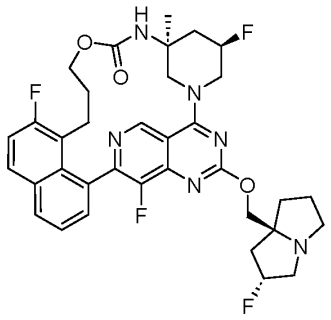
35	
36	
37	
38	

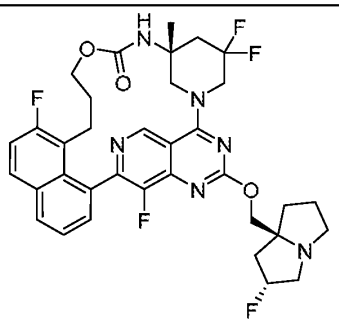
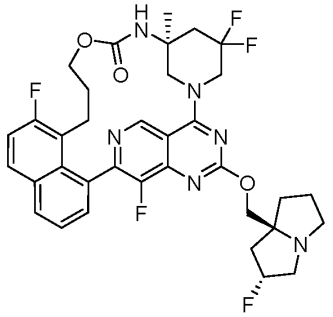
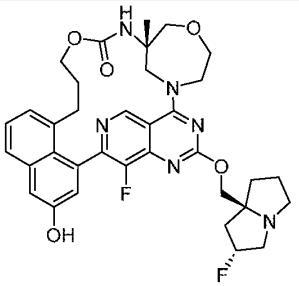
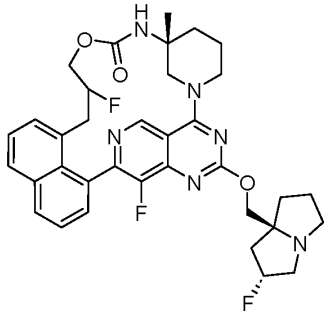
39	
40	
41	
42	

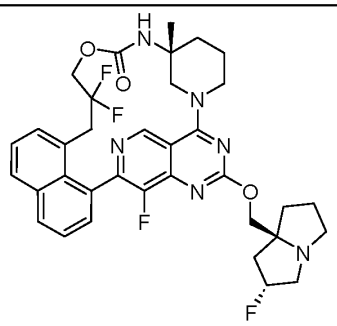
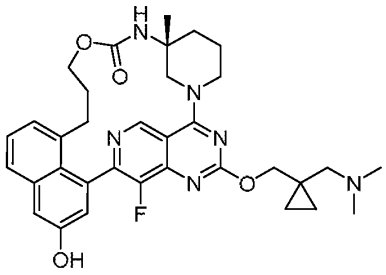
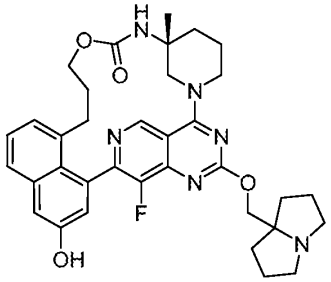
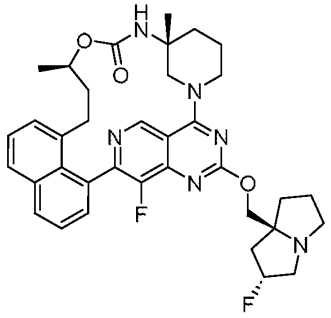
43	
44	
45	
46	

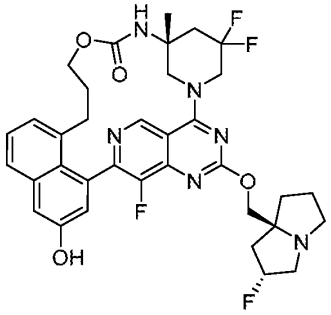
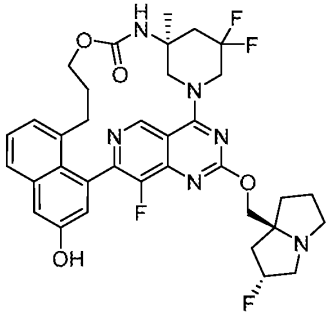
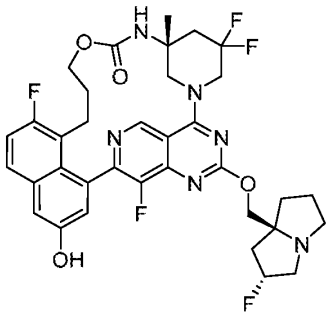
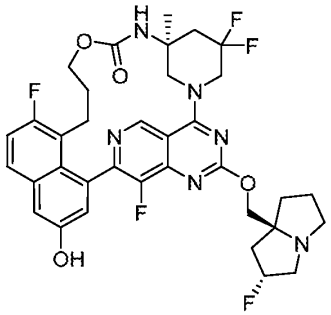
47	
48	
49	
50	

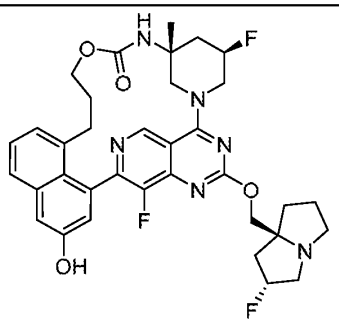
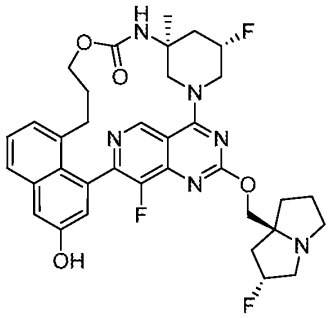
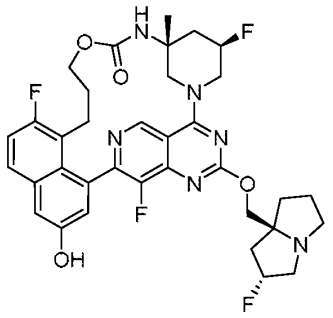
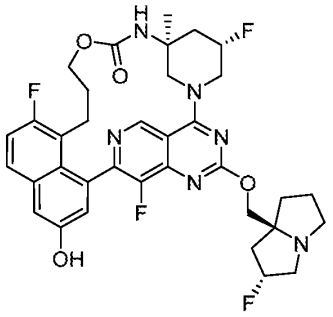
51	
52	
53	
54	

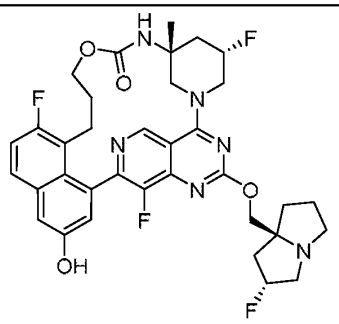
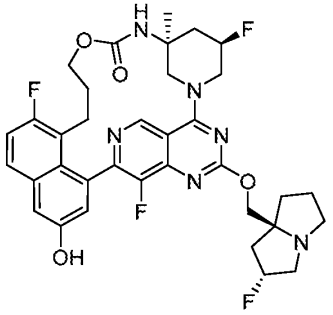
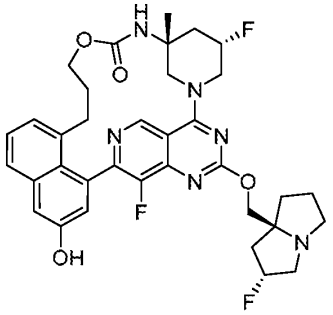
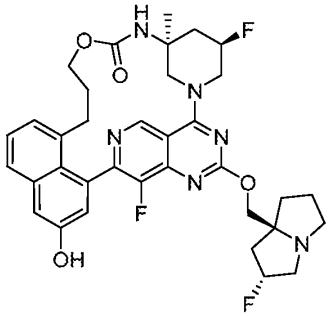
55	
56	
57	
58	

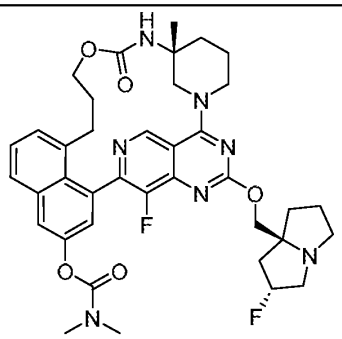
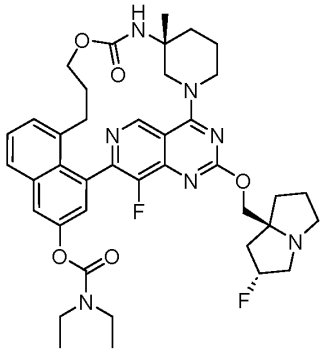
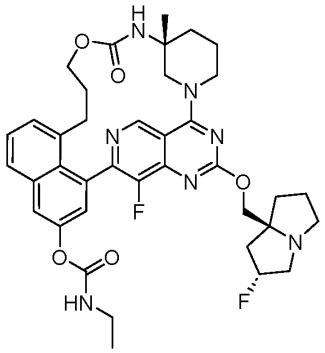
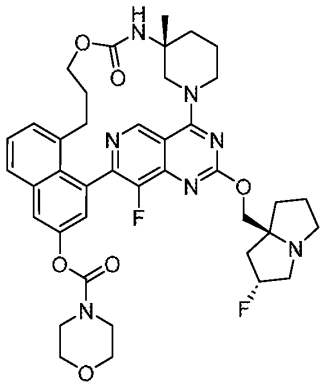
59	
60	
61	
62	

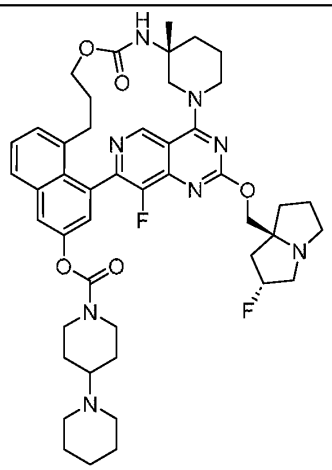
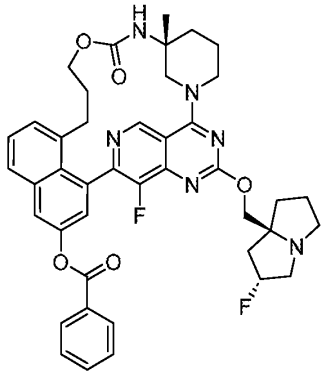
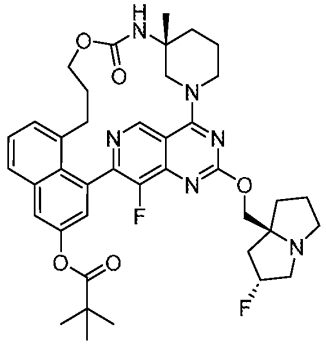
63	
64	
65	
66	

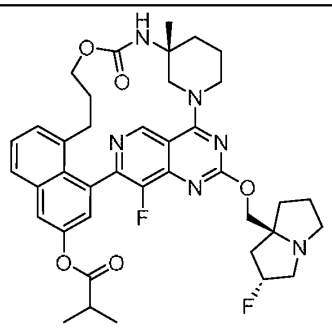
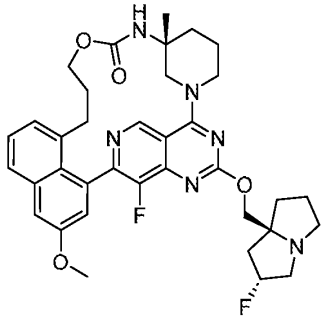
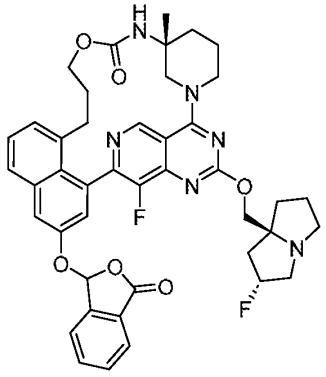
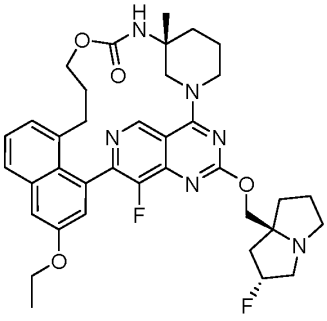
67	
68	
69	
70	

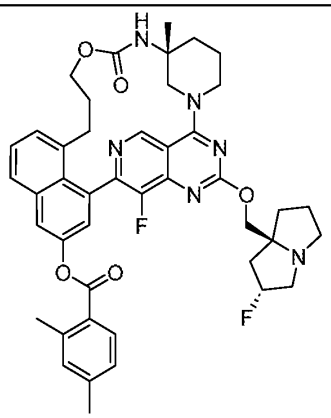
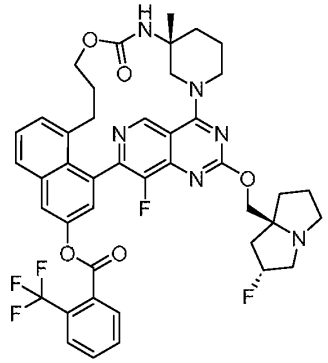
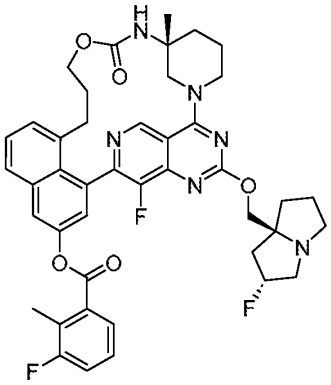
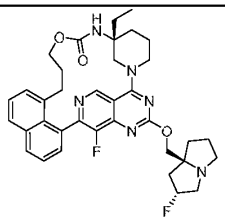
71	
72	
73	
74	

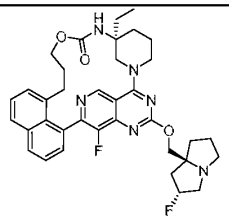
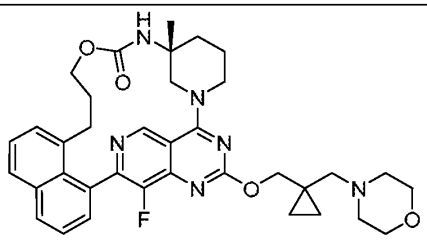
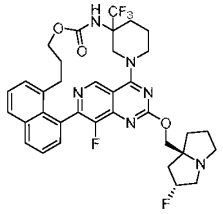
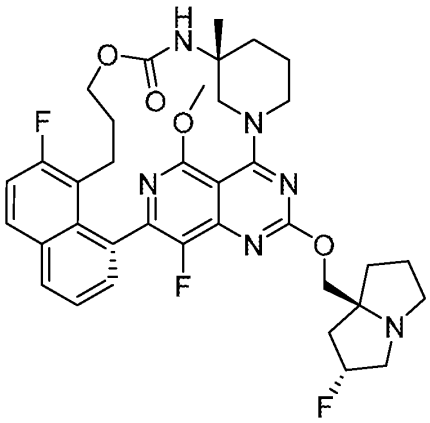
75	
76	
77	
78	

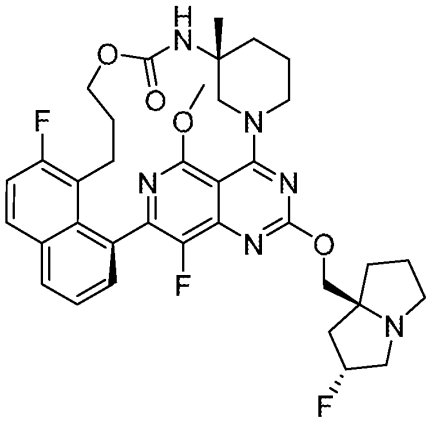
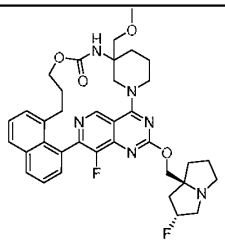
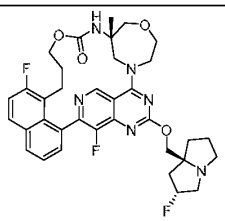
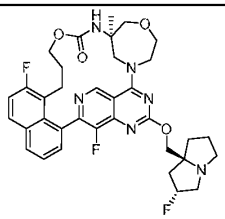
79	
80	
81	
82	

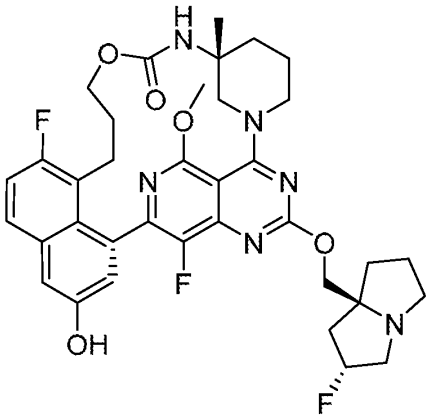
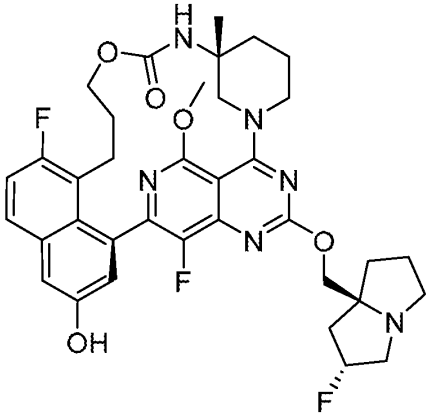
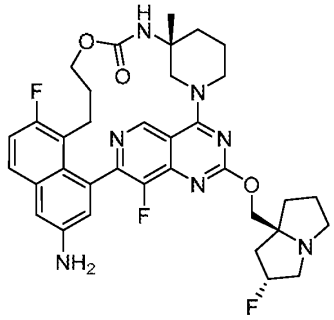
83	
84	
85	

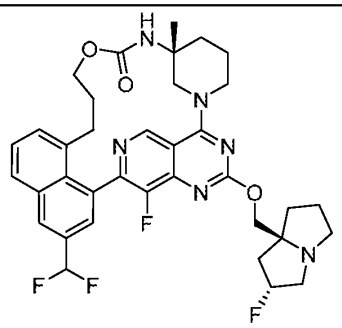
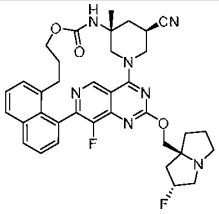
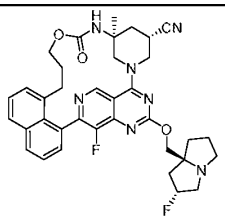
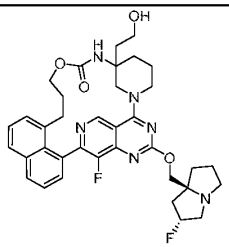
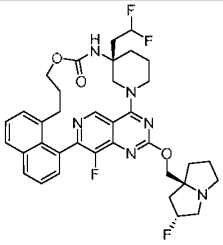
86	
87	
88	
89	

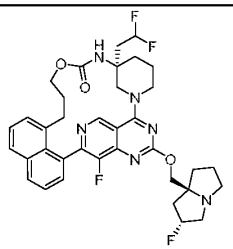
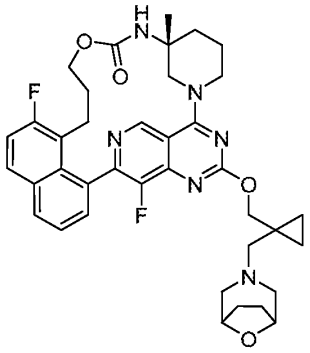
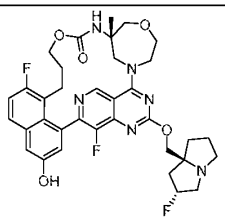
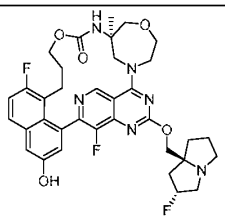
90	
91	
92	
93	

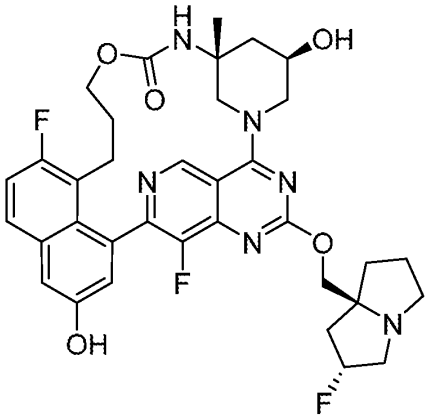
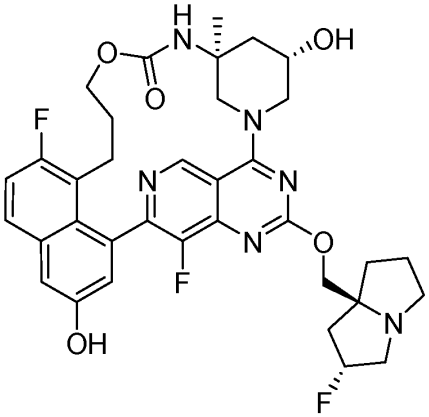
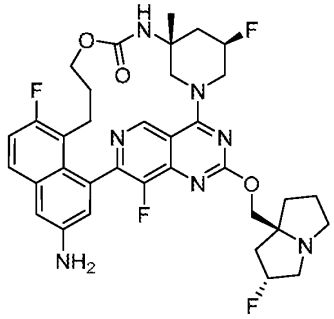
94	
95	
96	
97	

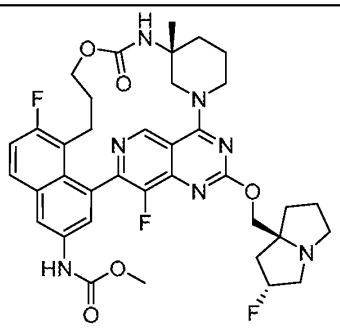
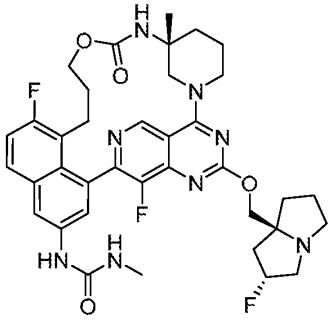
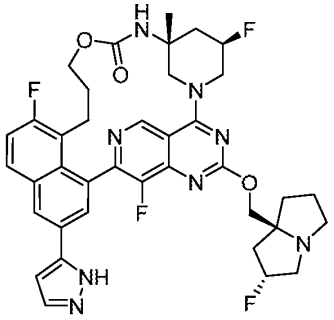
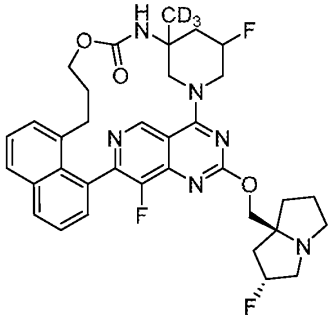
98	
99	
100	
101	

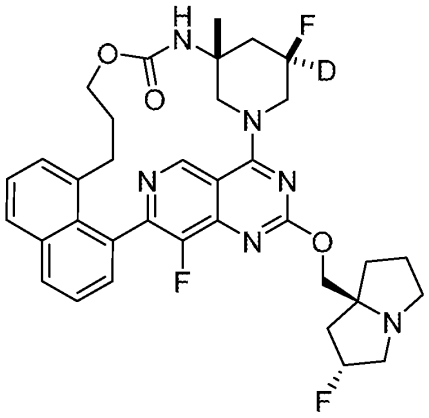
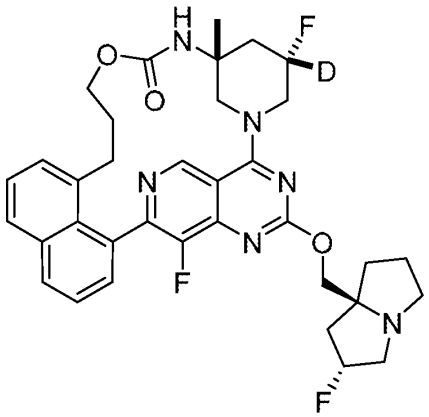
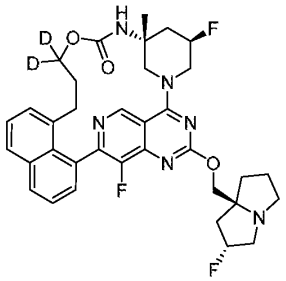
102	
103	
104	

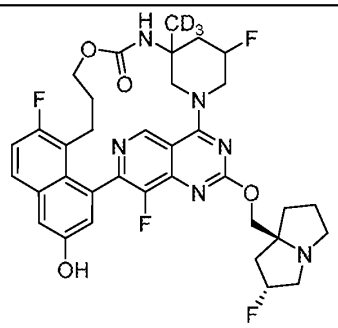
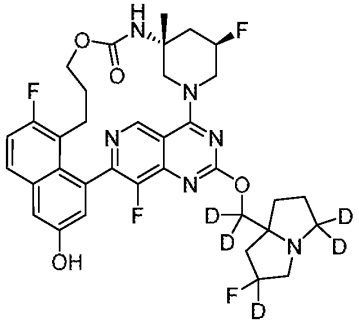
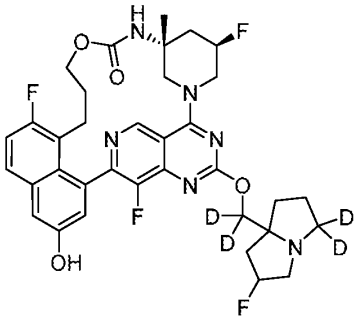
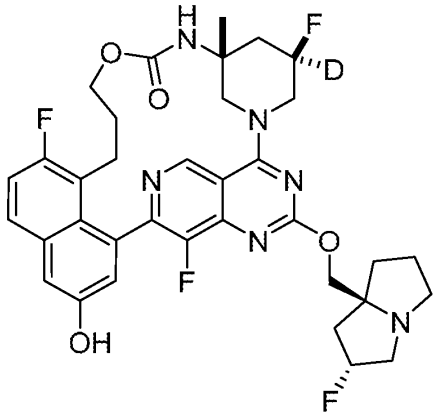
105	
106	
107	
108	
109	

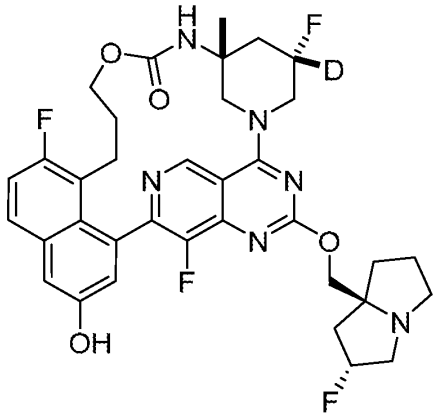
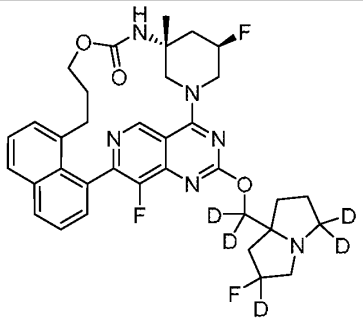
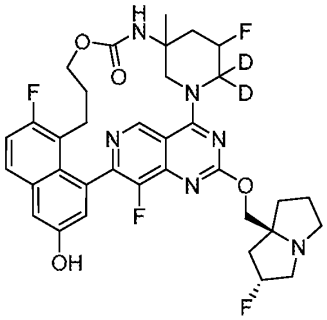
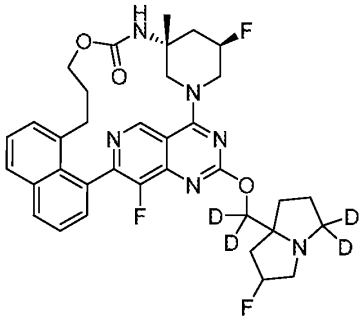
110	
111	
114	
115	

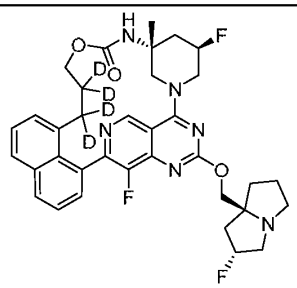
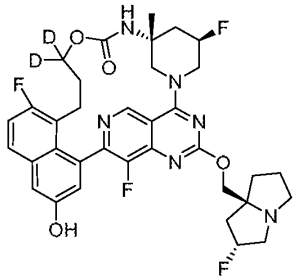
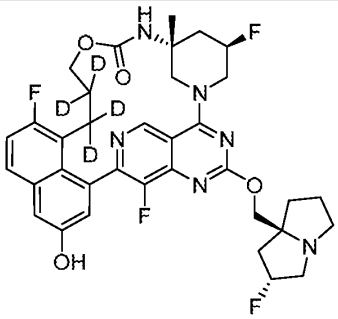
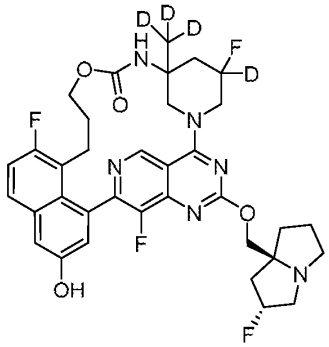
117	
118	
119	

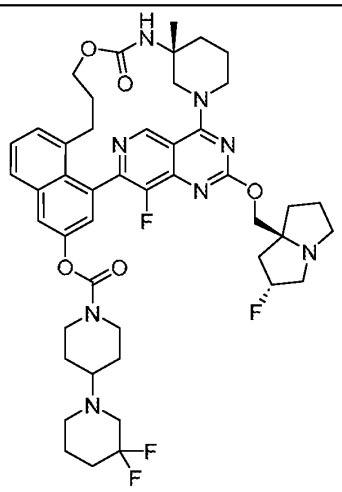
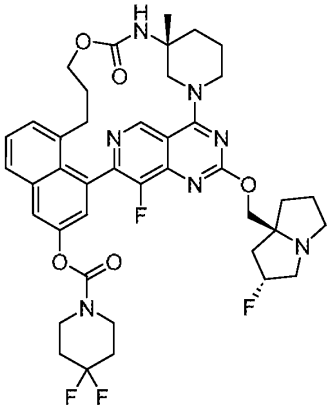
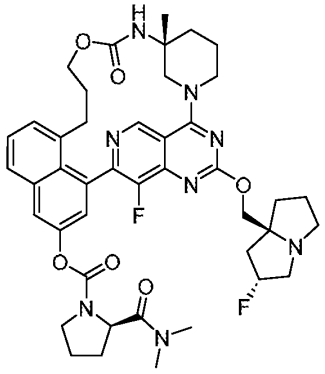
120	
121	
122	
123	

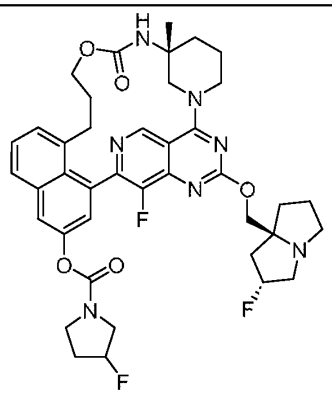
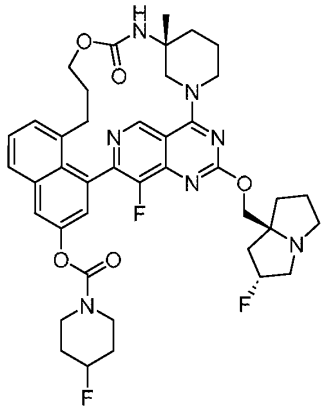
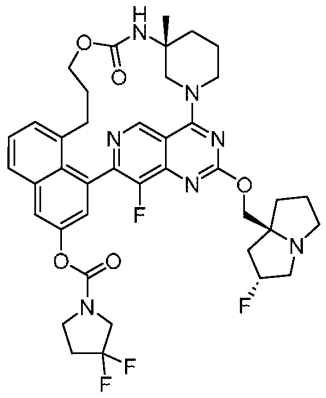
124	
125	
126	

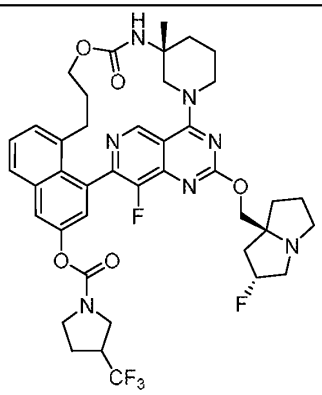
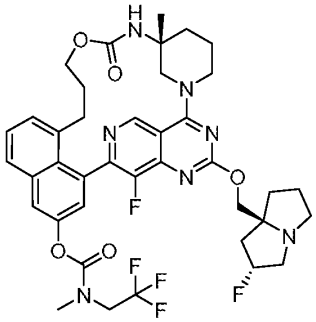
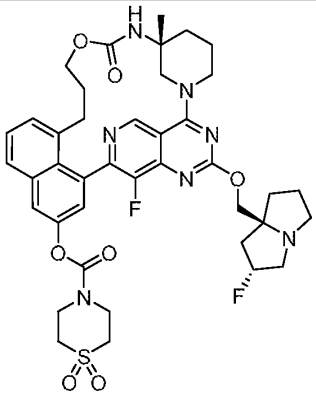
127	
128	
129	
130	

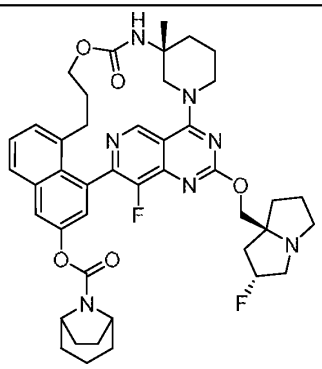
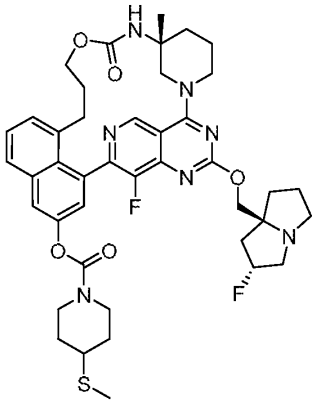
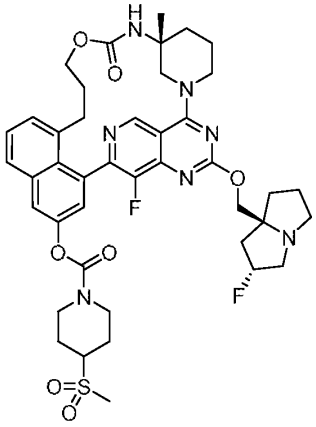
131	
132	
133	
134	

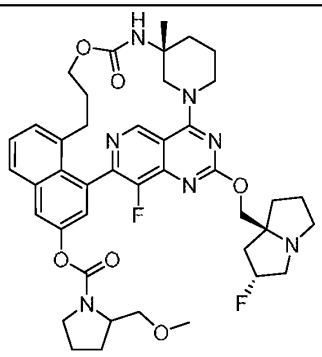
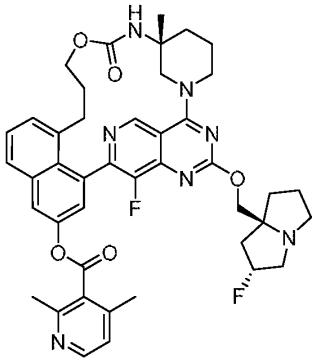
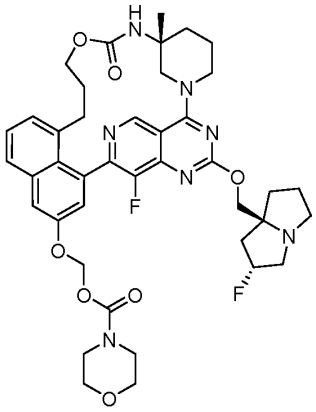
135	
136	
137	
138	

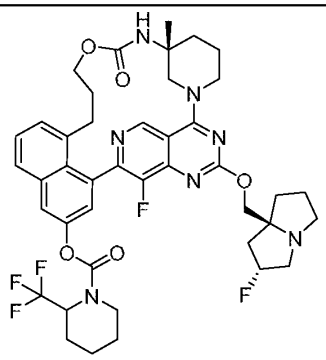
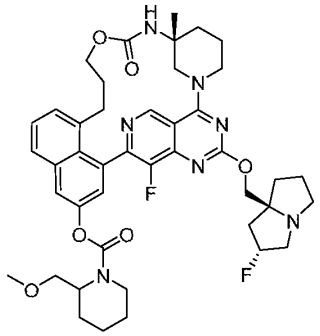
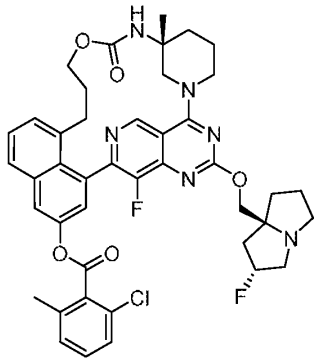
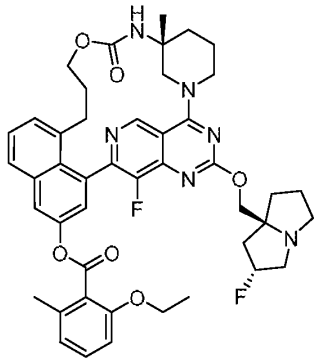
139	
140	
141	

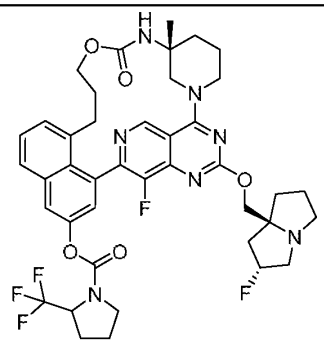
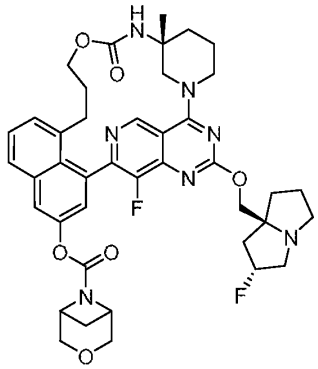
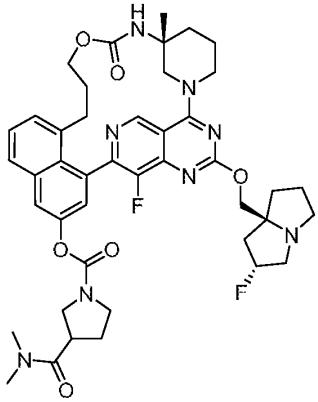
142	
143	
144	

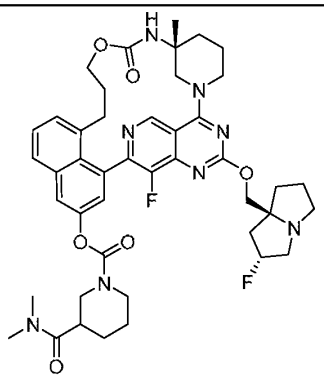
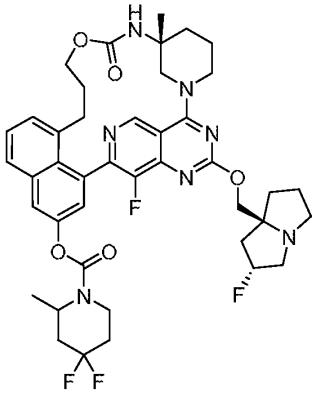
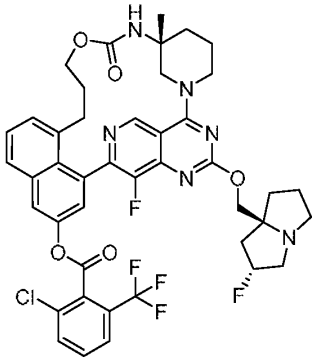
145	
146	
147	

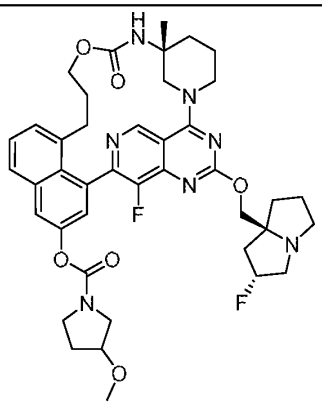
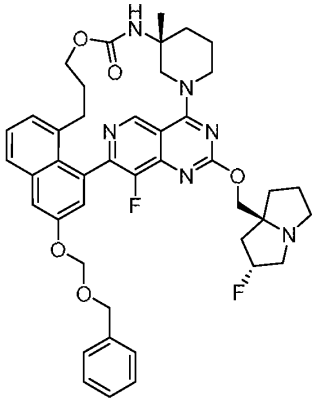
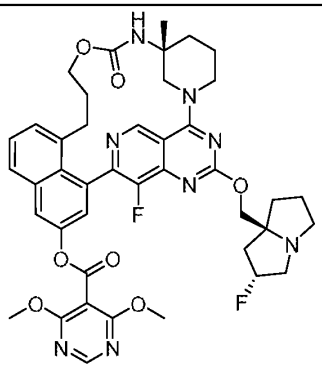
148	
149	
150	

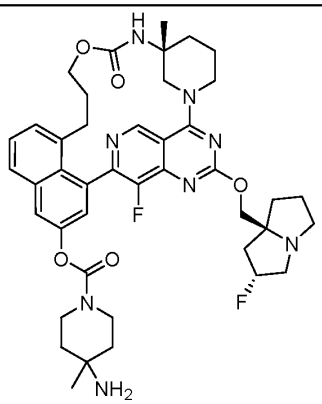
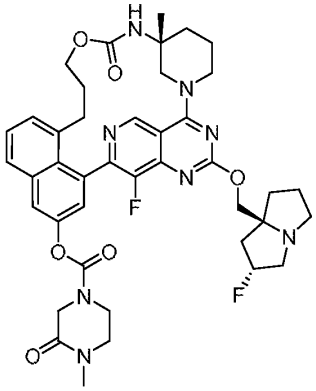
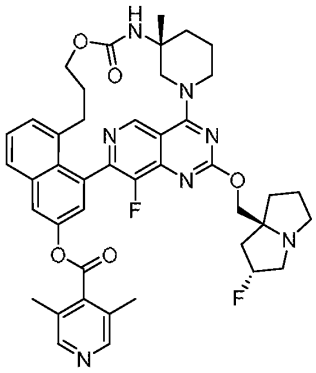
151	
152	
153	

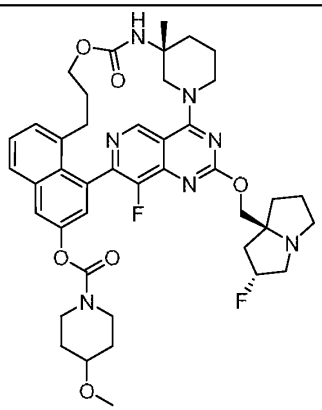
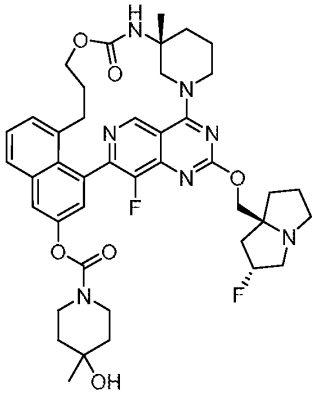
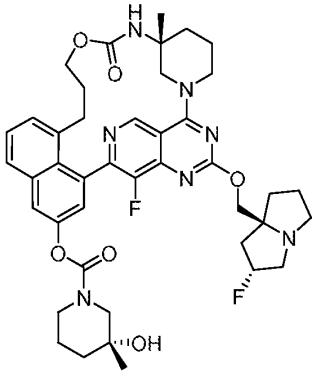
154	
155	
156	
157	

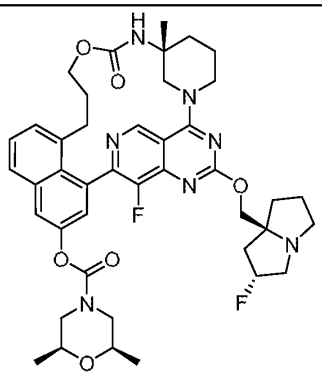
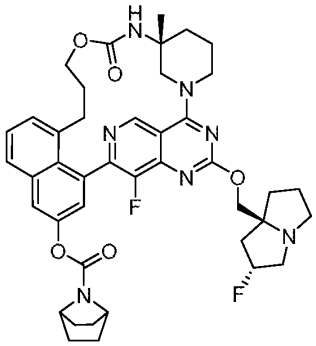
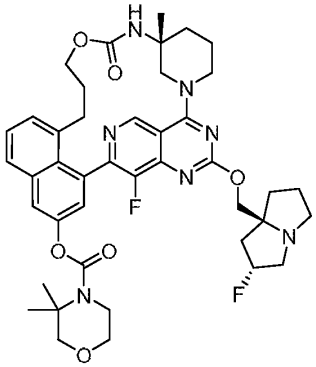
158	
159	
160	

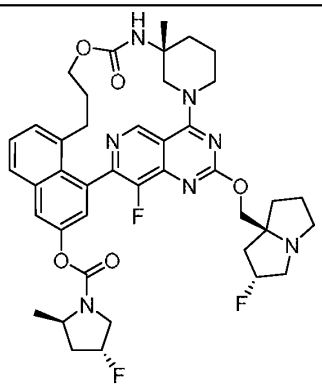
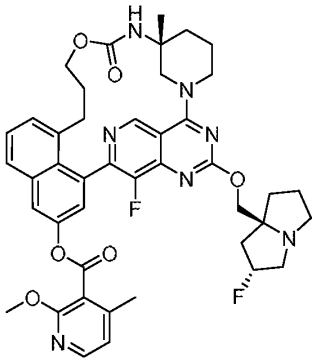
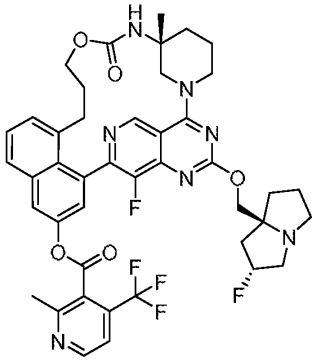
161	
162	
163	

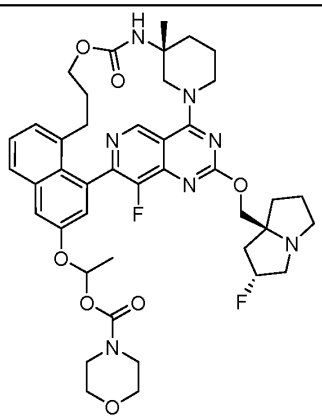
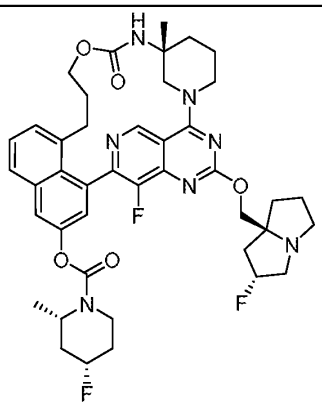
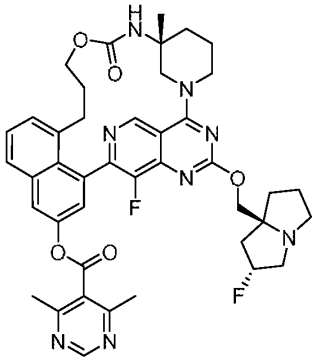
164	
165	
166	

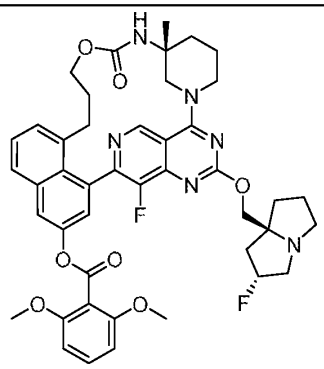
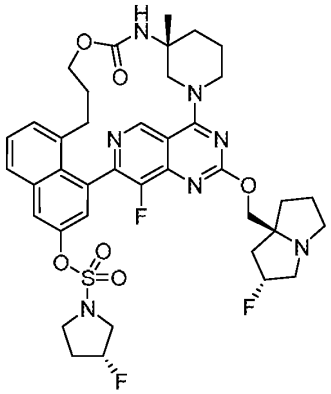
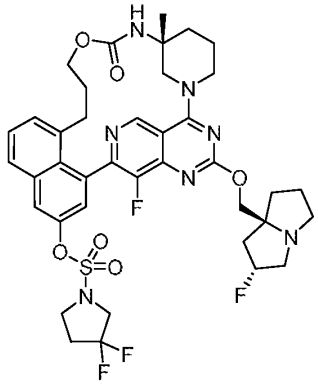
167	
168	
169	

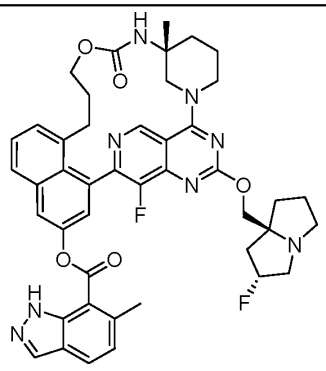
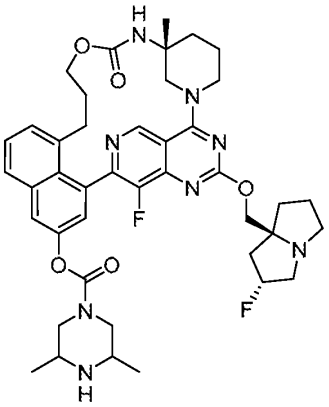
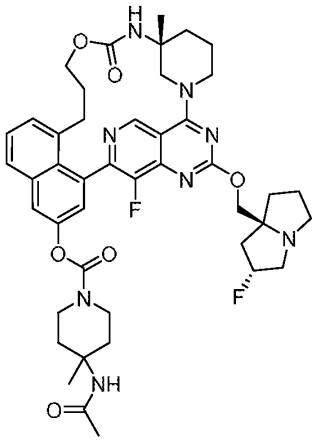
170	
171	
172	

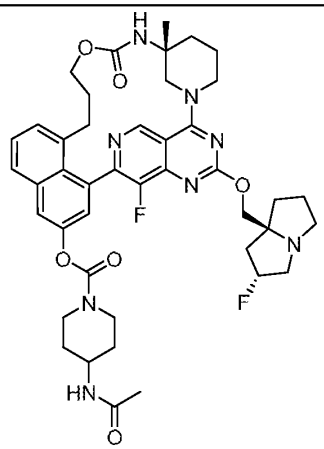
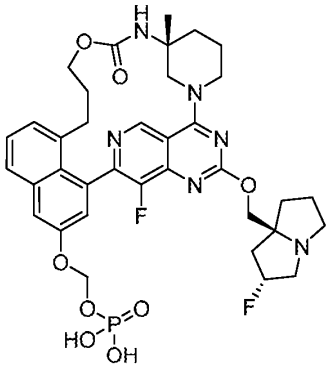
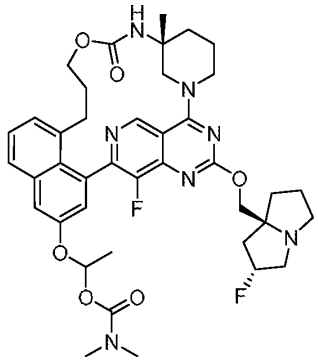
173	
174	
175	

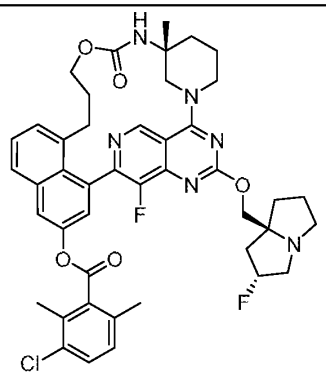
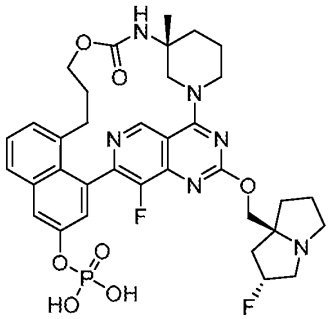
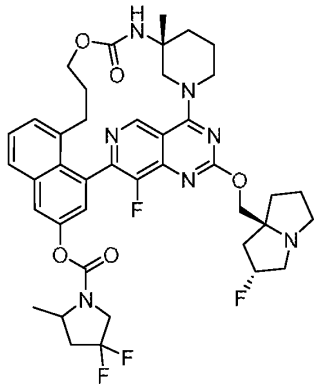
176	
177	
178	

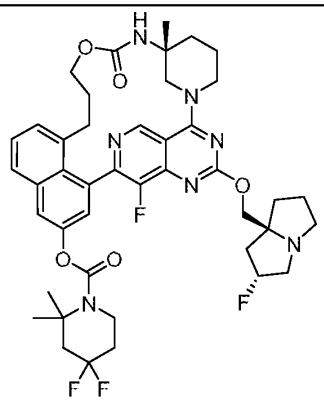
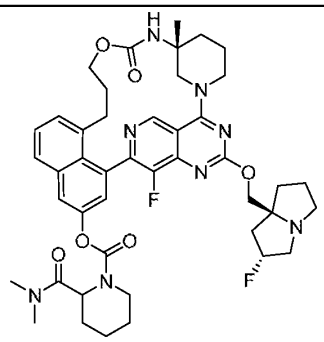
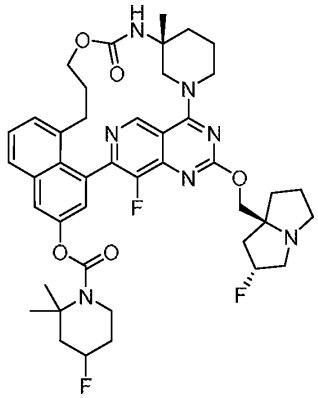
179	
180	
181	

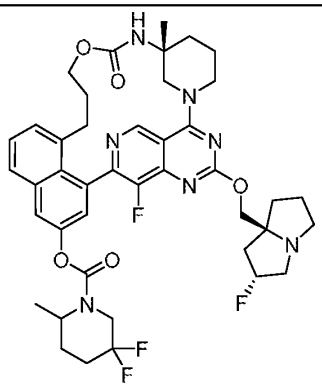
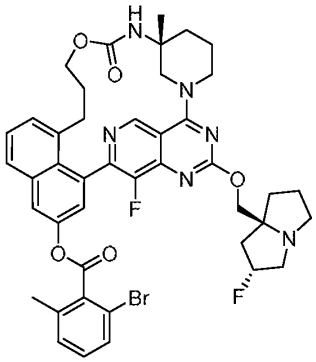
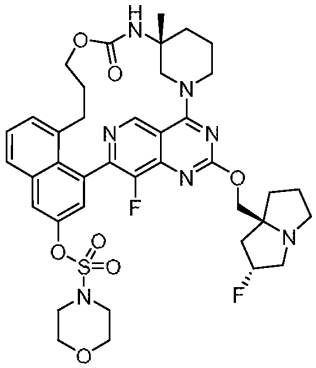
182	
183	
184	

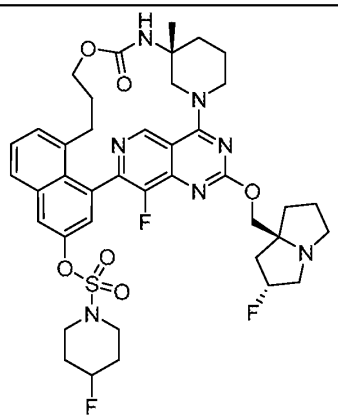
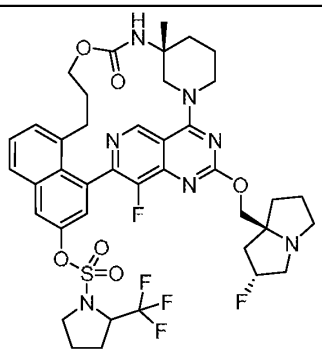
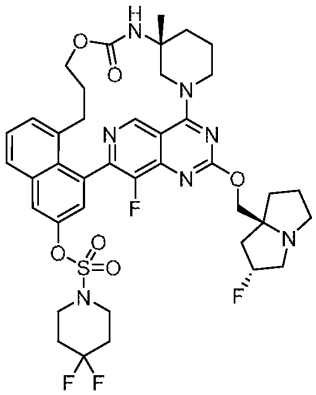
185	
186	
187	

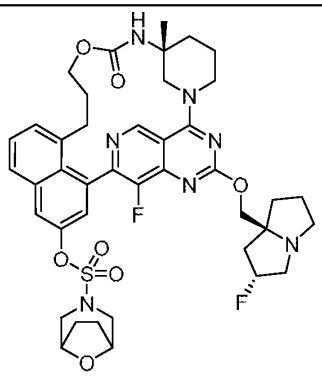
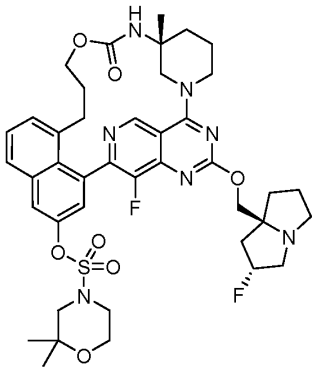
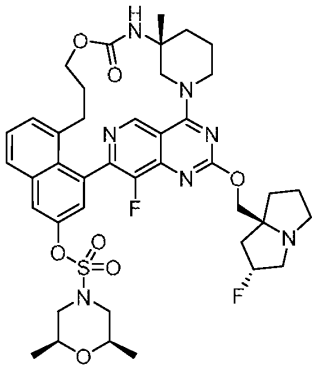
188	
189	
190	

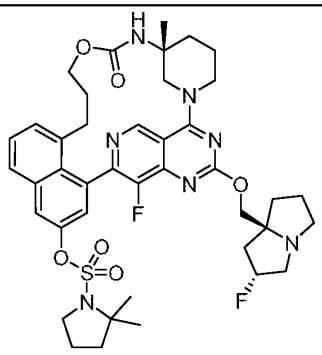
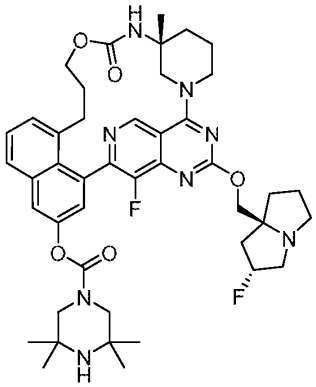
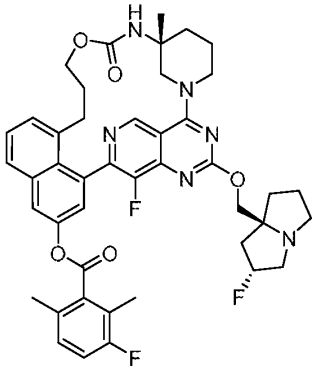
191	
192	
193	

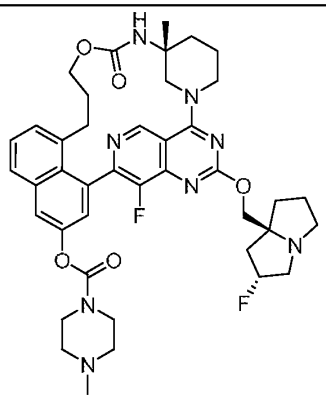
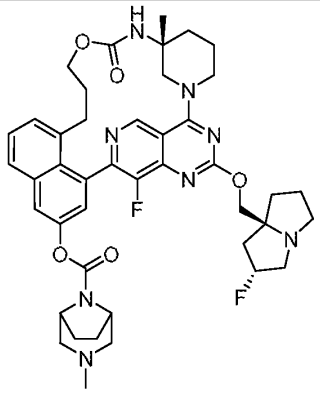
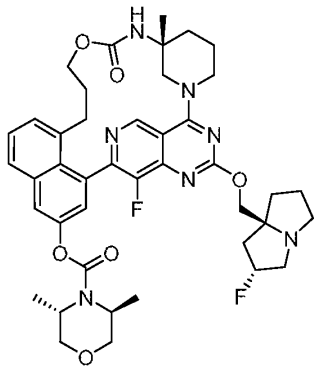
194	
195	
196	

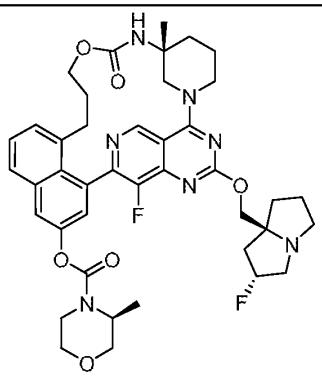
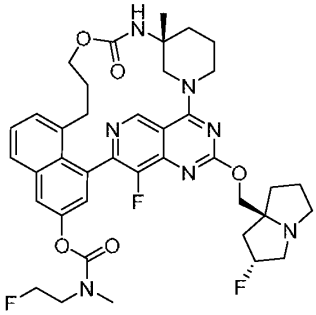
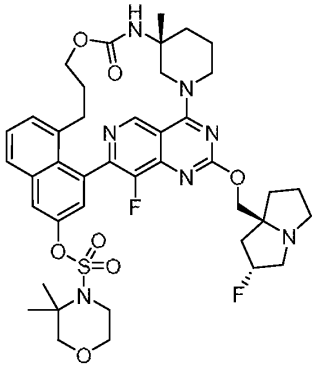
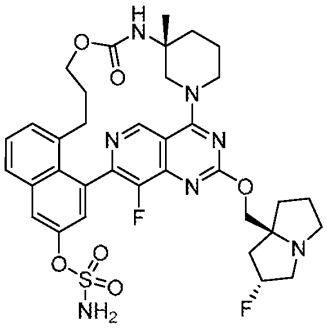
197	
198	
199	

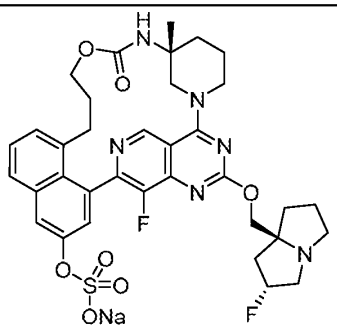
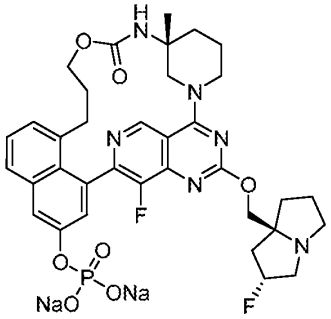
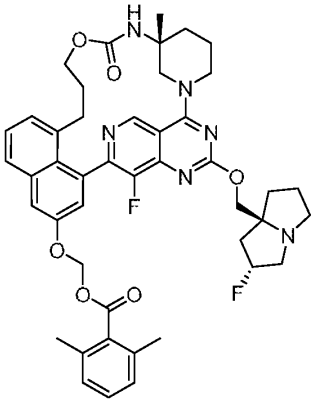
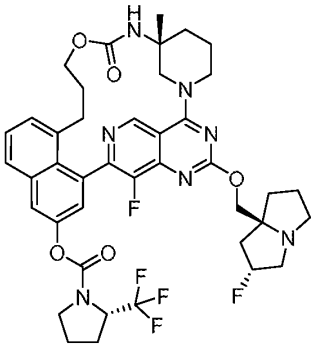
200	
201	
202	

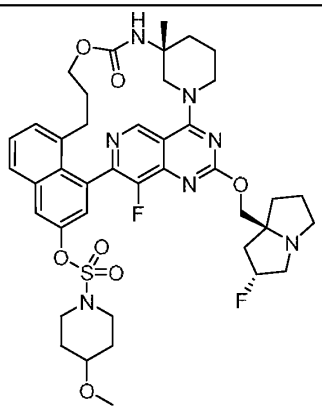
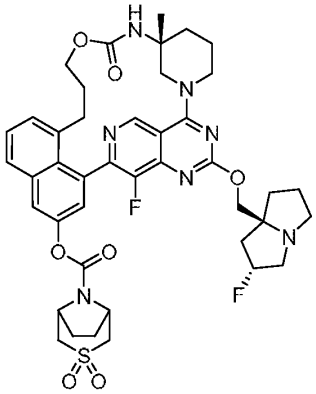
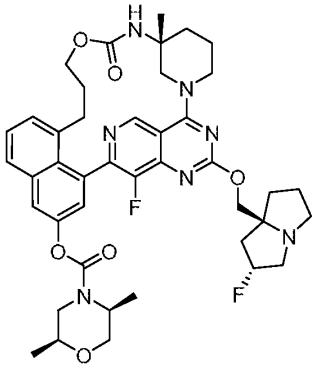
203	
204	
205	

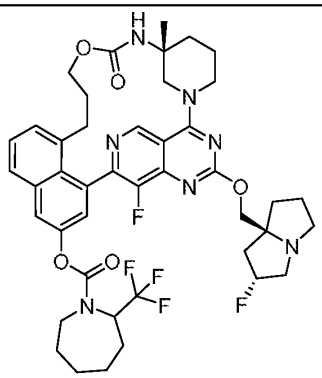
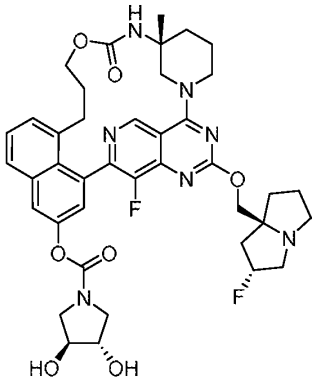
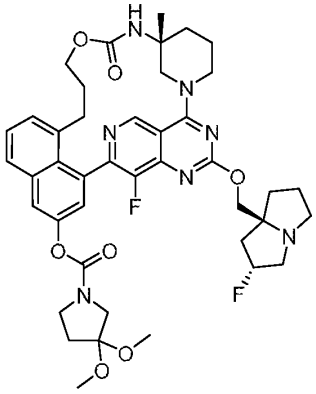
206	
207	
208	

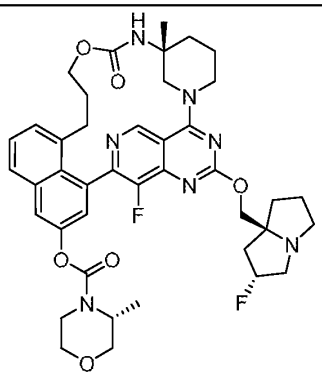
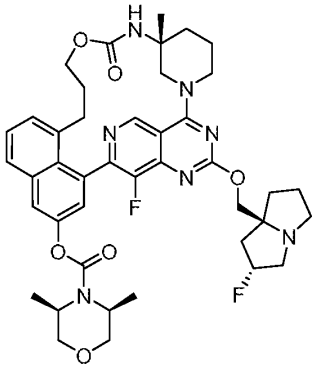
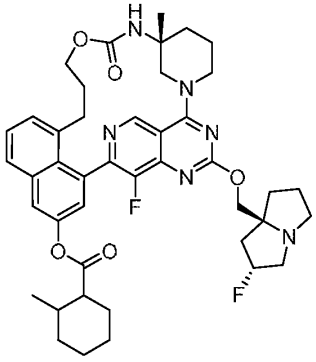
209	
210	
211	

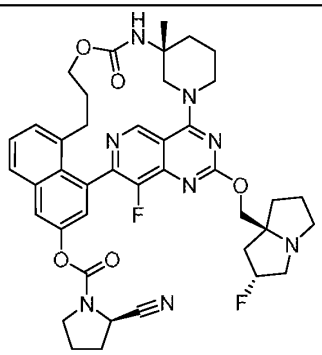
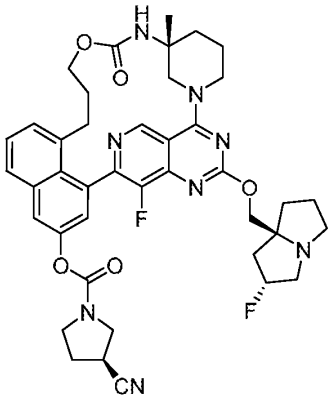
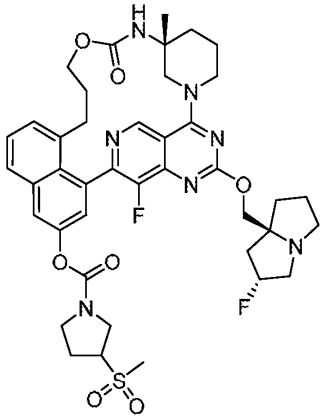
212	
213	
214	
215	

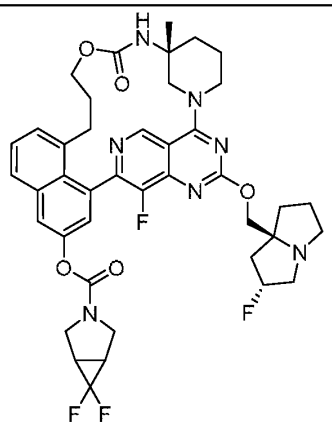
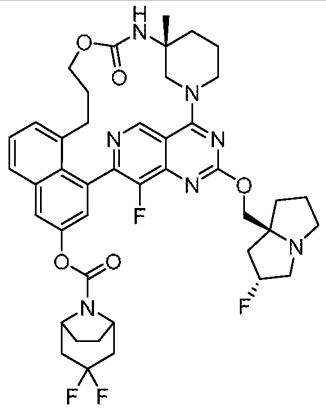
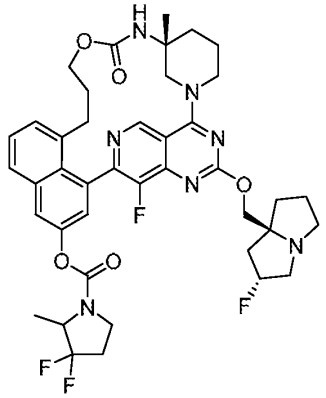
216	
217	
218	
219	

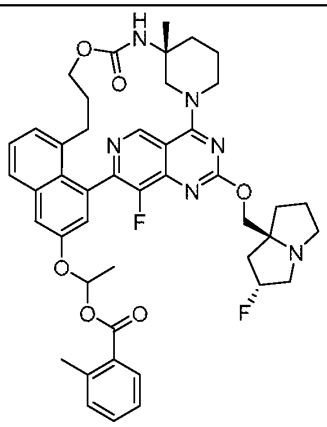
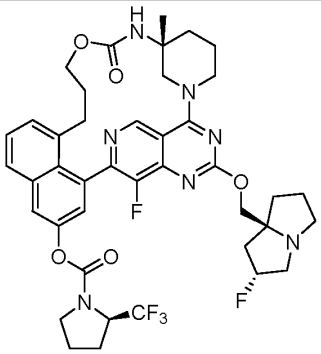
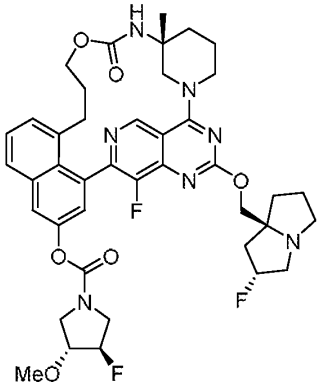
220	
221	
222	

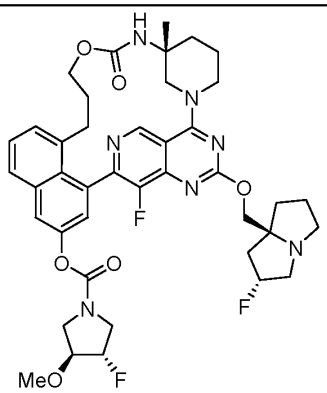
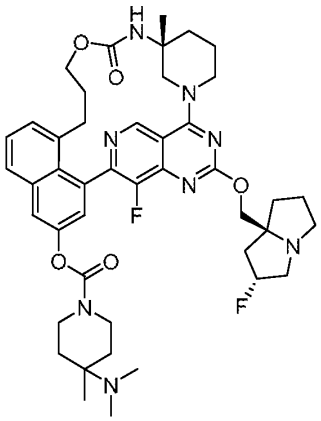
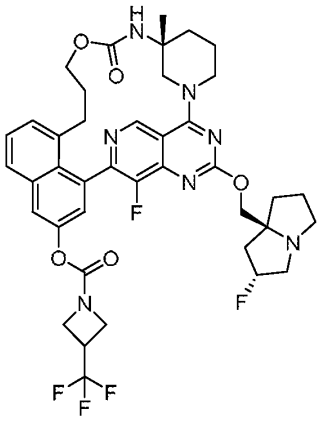
223	
224	
225	

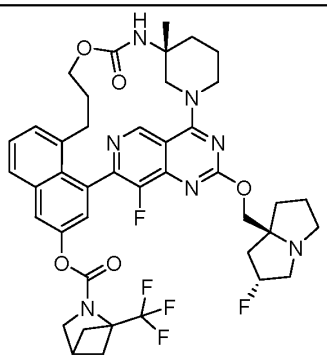
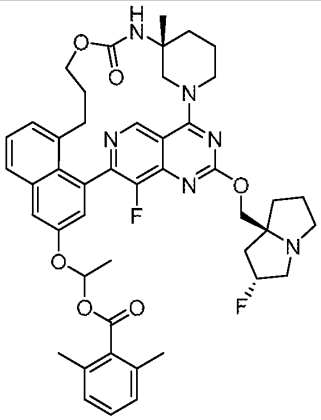
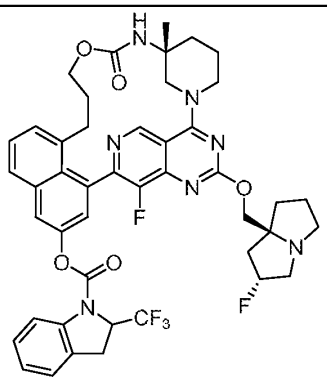
226	
227	
228	

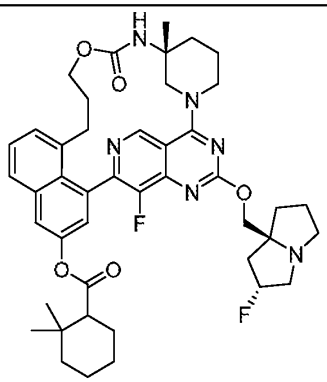
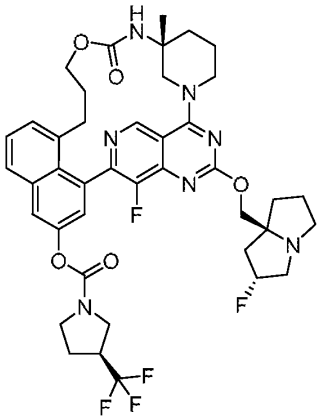
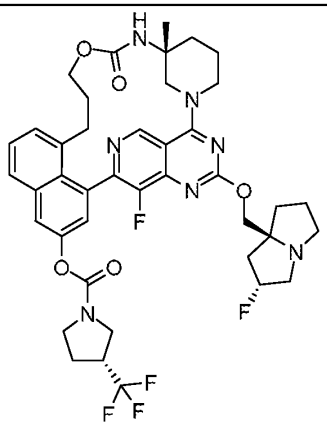
229	
230	
231	

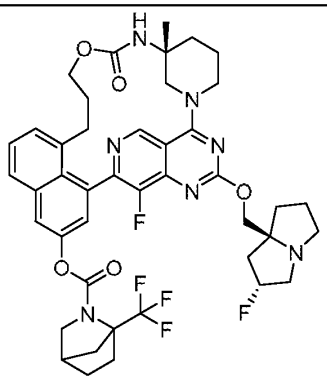
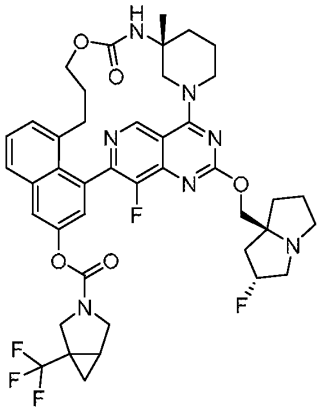
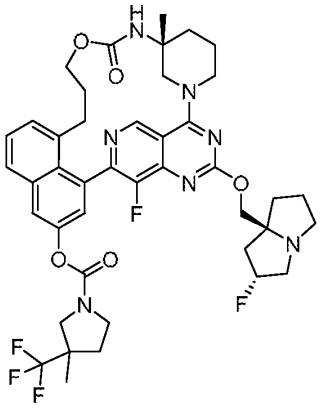
232	
233	
234	

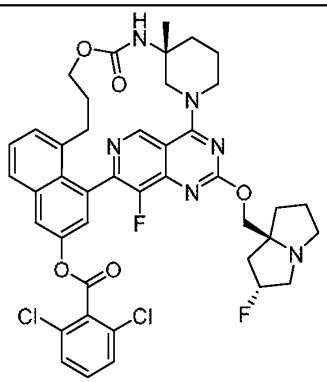
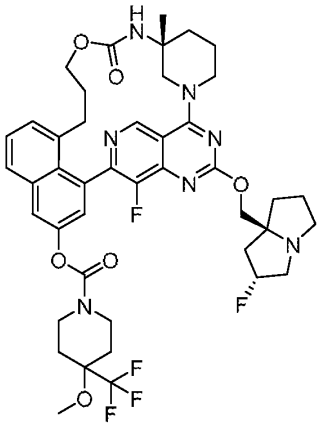
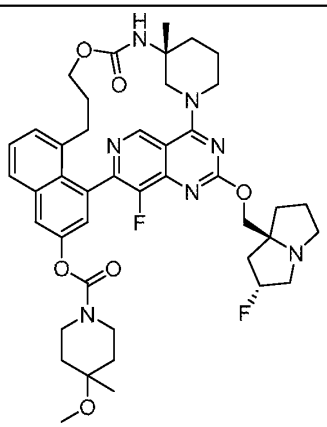
235	
236	
237	

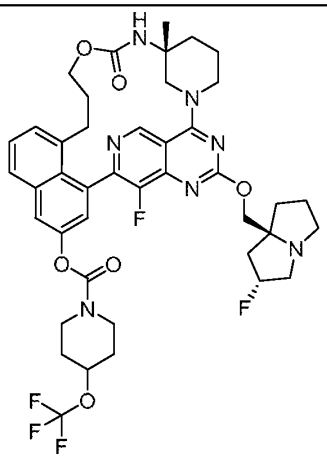
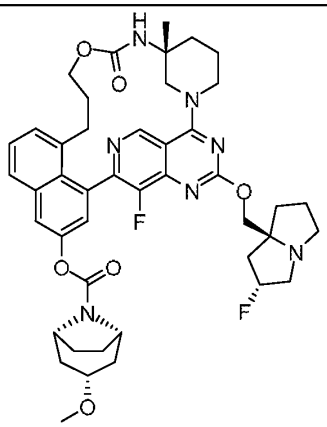
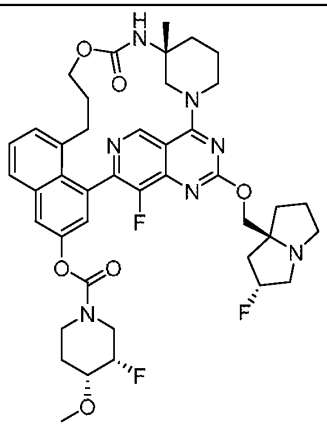
238	
239	
240	

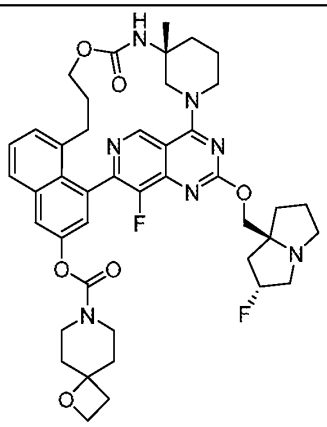
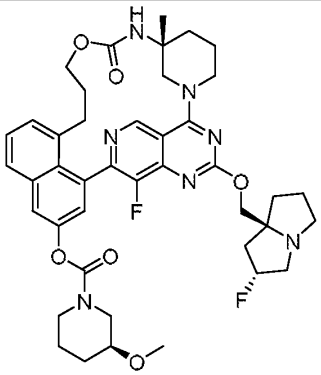
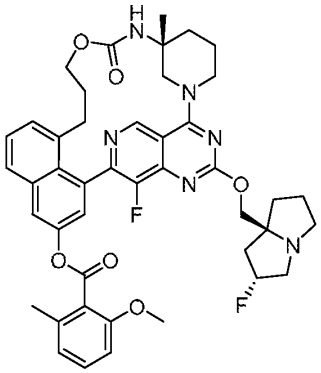
241	
242	
243	

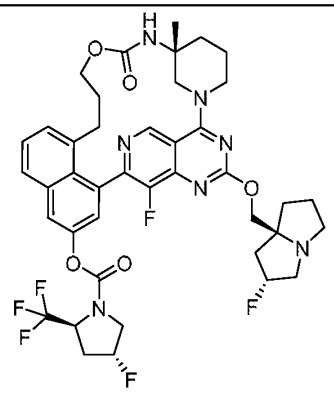
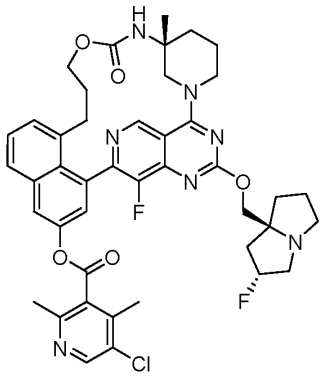
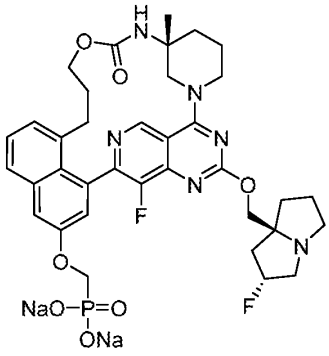
244	
245	
246	

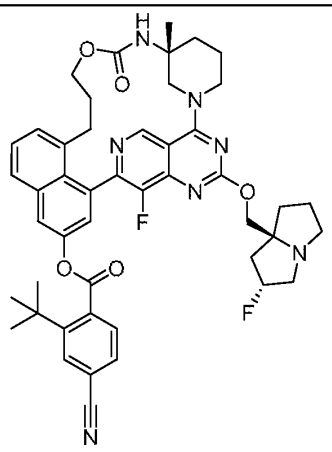
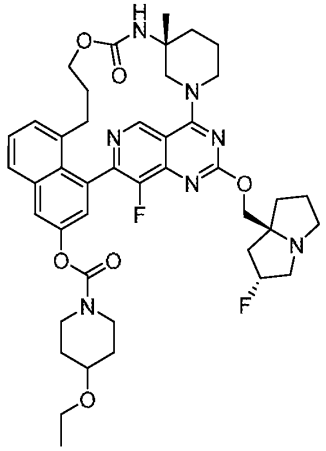
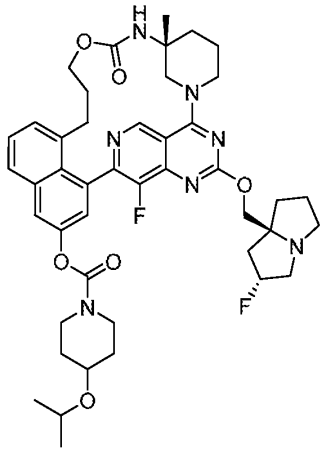
247	
248	
249	

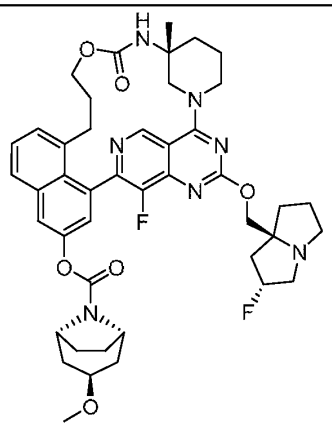
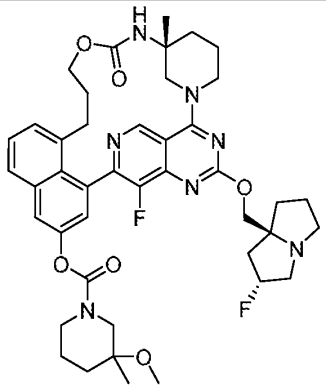
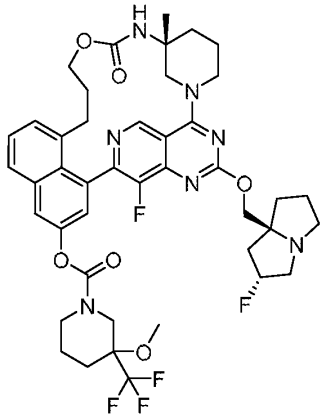
250	
251	
252	

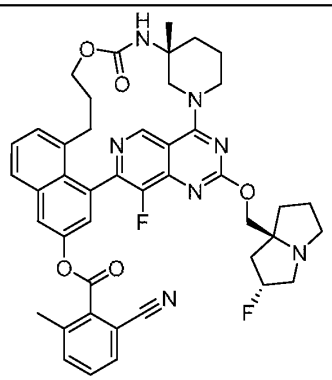
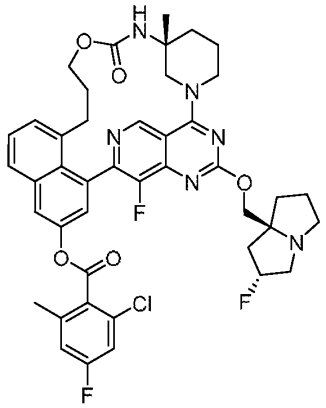
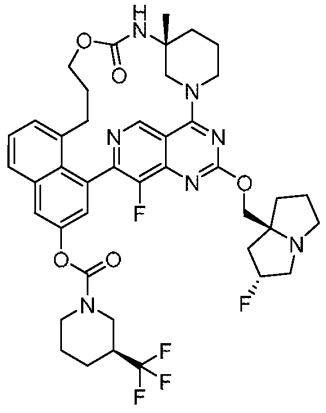
253	
254	
255	

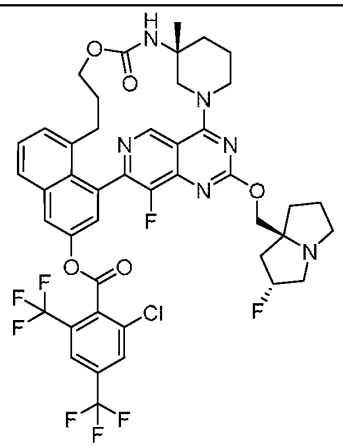
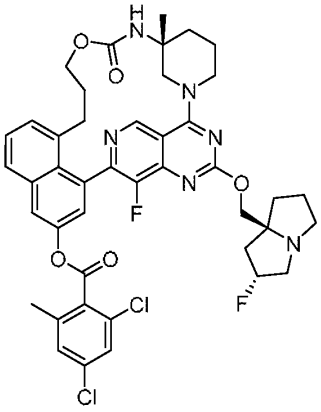
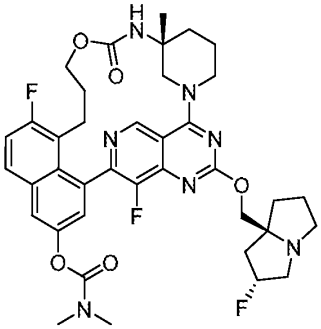
256	
257	
258	

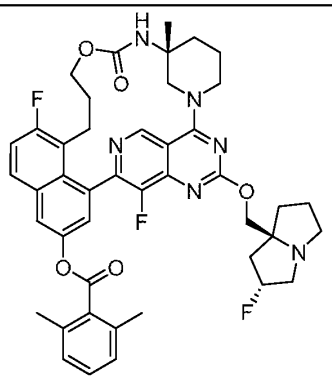
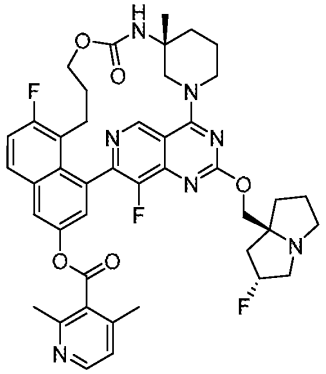
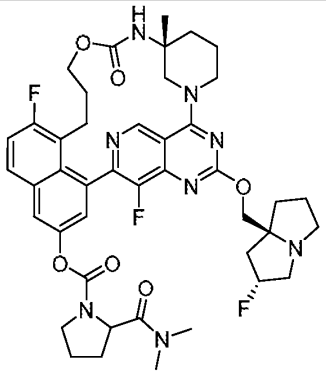
259	
260	
261	

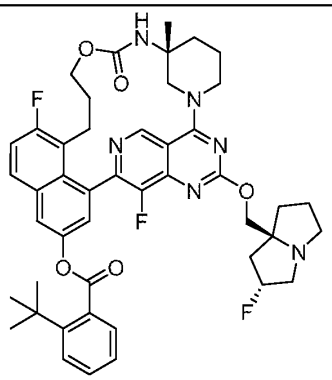
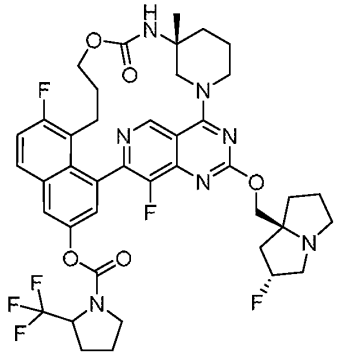
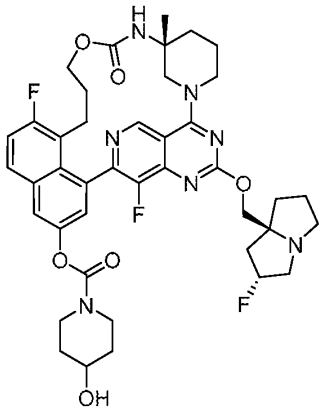
262	
263	
264	

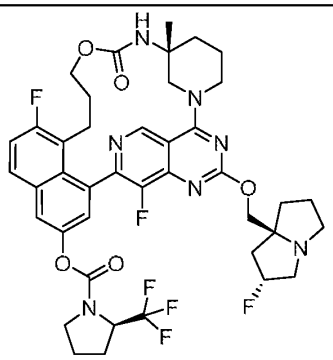
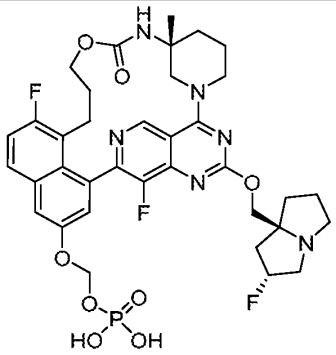
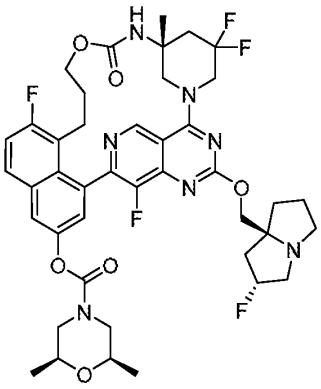
265	
266	
267	

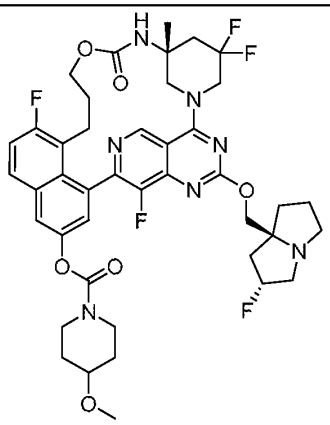
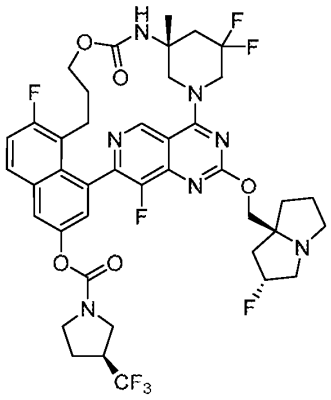
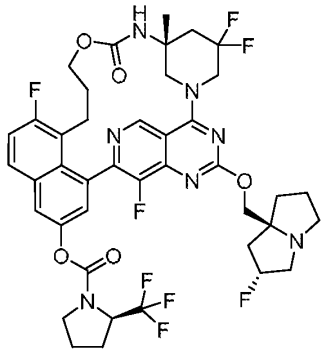
268	
269	
270	

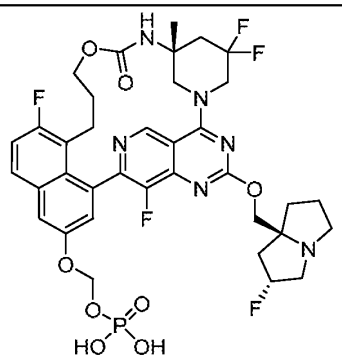
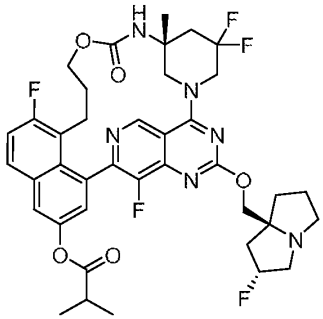
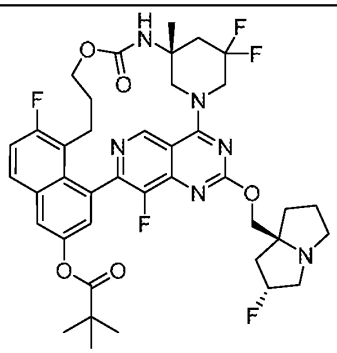
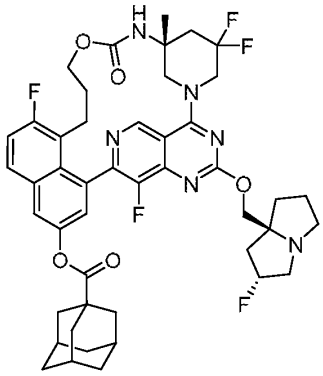
271	
272	
273	

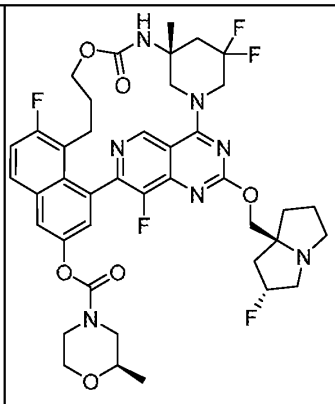
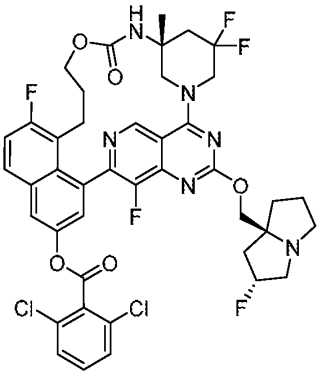
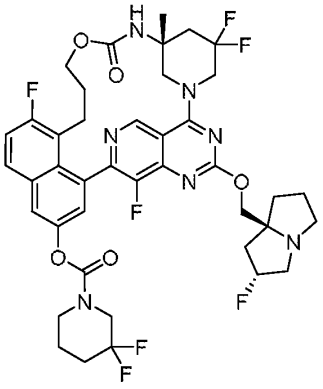
274	
275	
276	

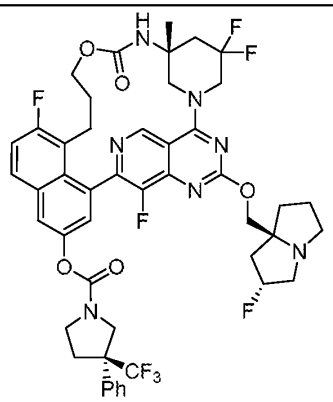
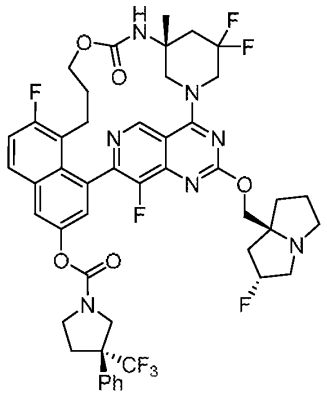
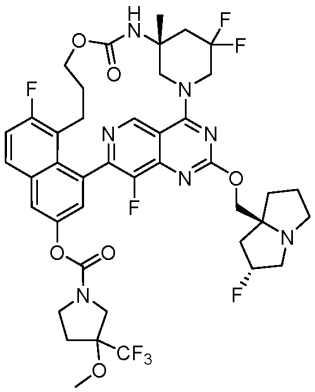
277	
278	
279	

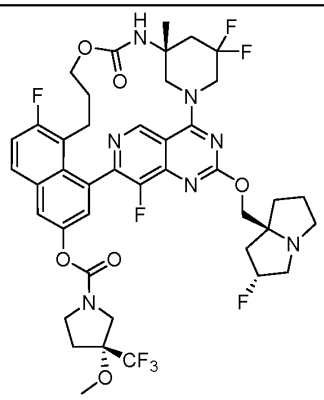
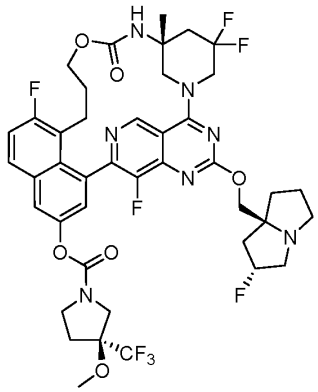
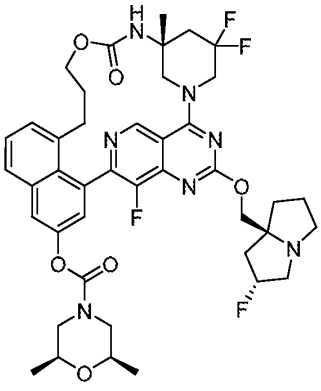
281	
282	
283	

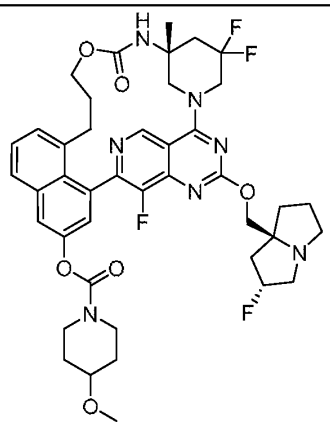
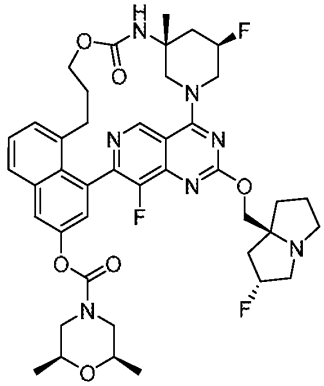
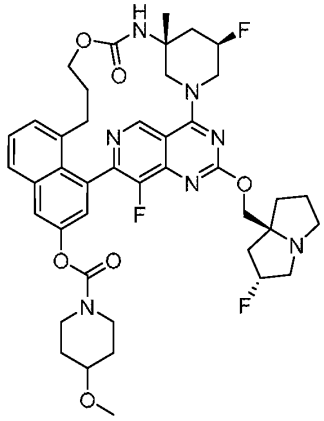
284	
285	
286	

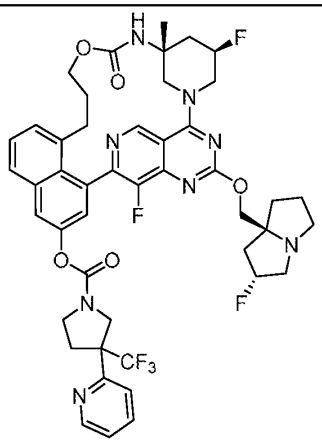
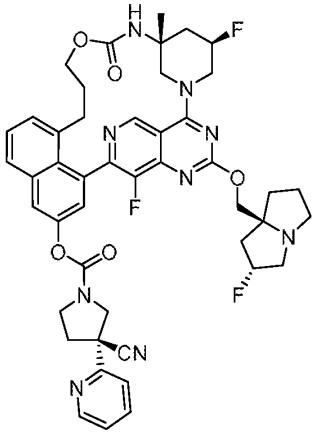
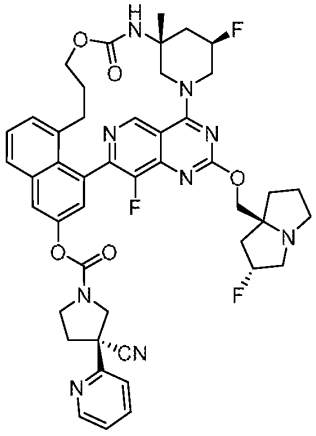
287	
288	
289	
290	

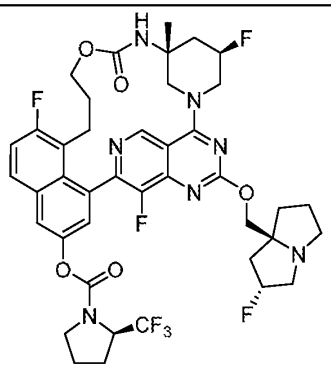
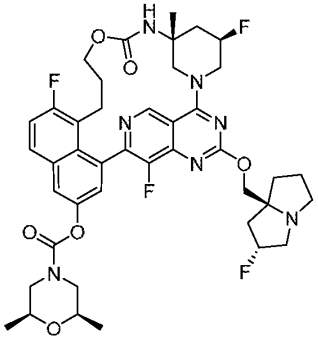
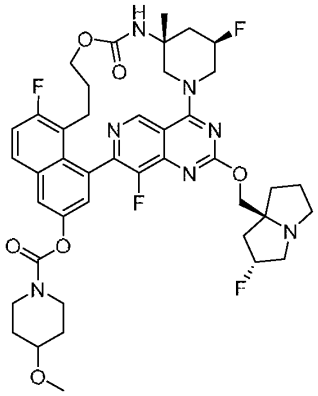
291	
292	
293	

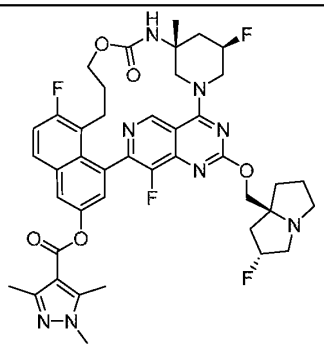
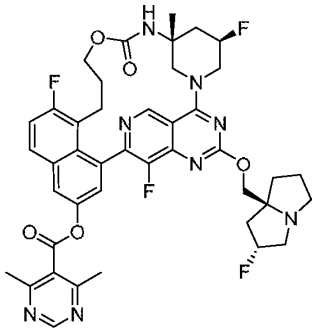
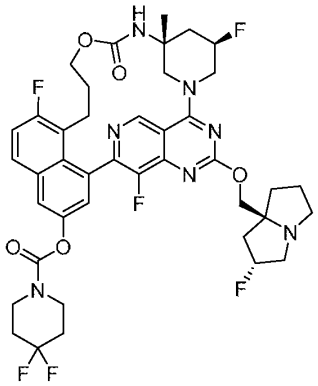
294	
295	
296	

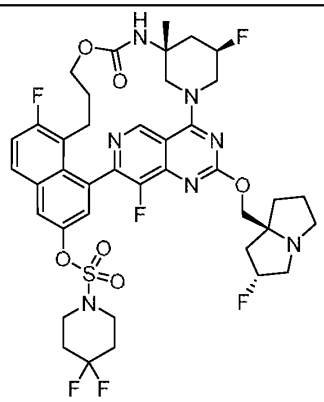
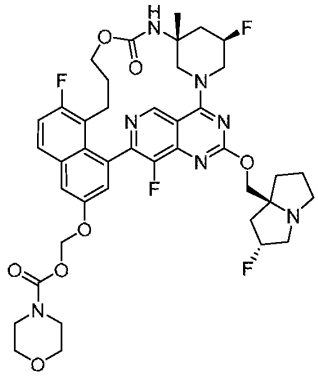
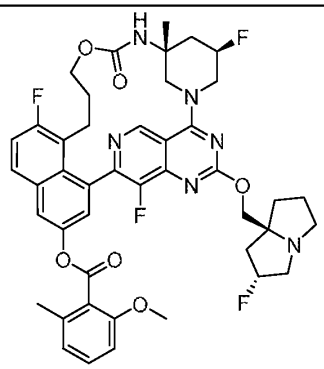
297	
298	
299	

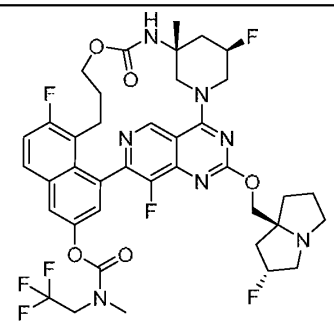
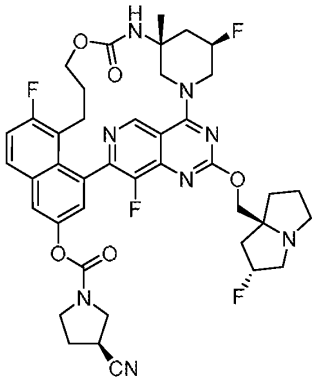
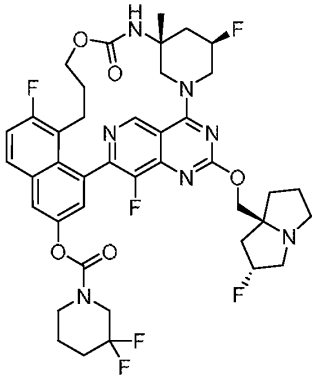
300	
301	
302	

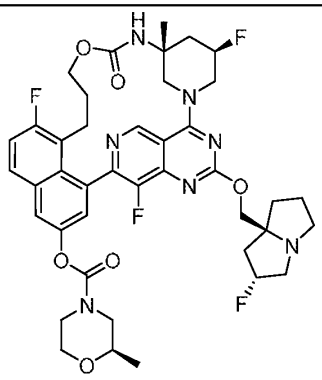
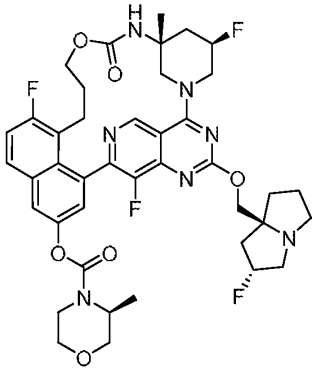
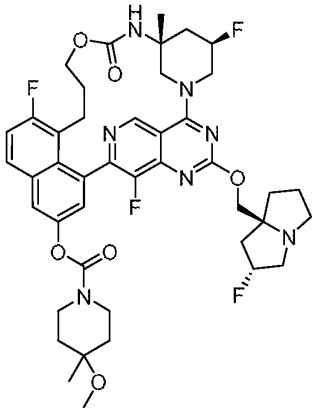
303	
304	
305	

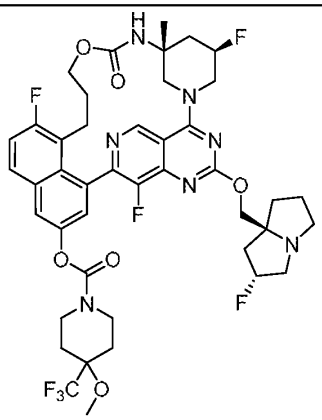
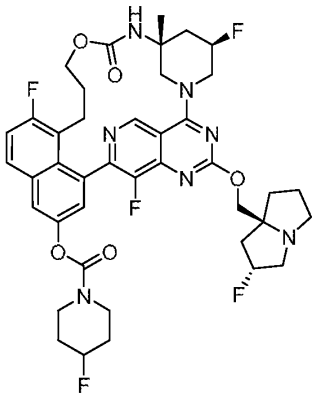
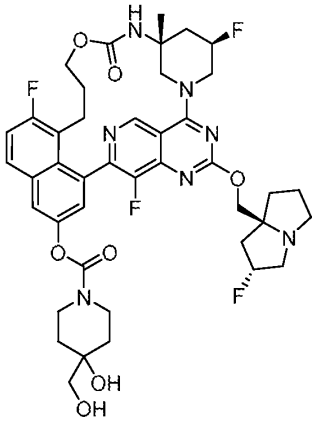
306	
307	
308	

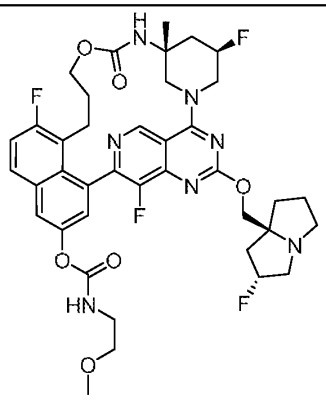
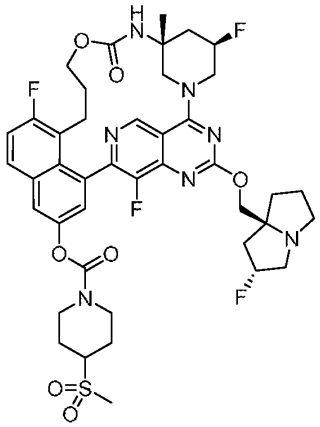
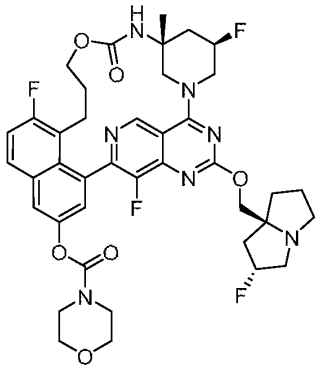
309	
310	
311	

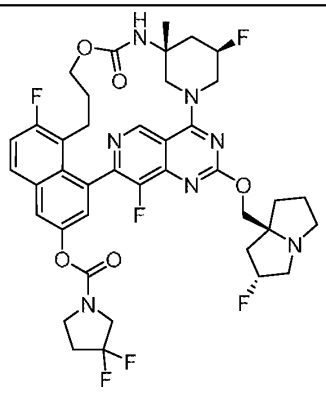
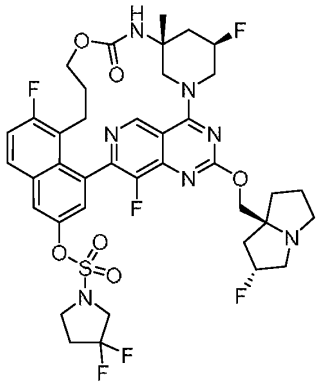
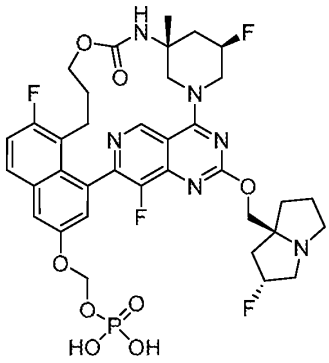
312	
313	
314	

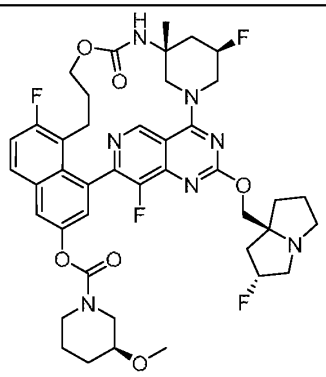
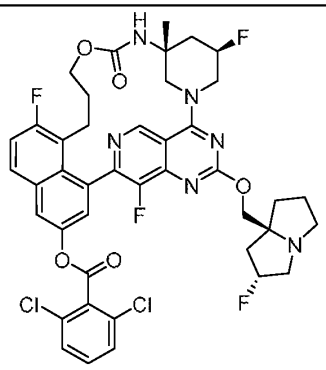
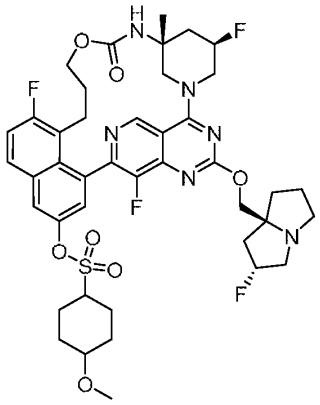
315	
316	
317	

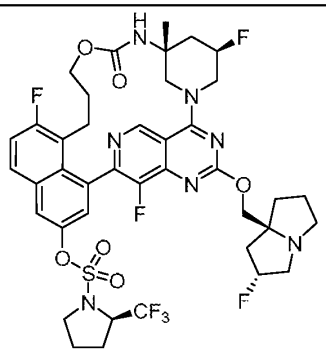
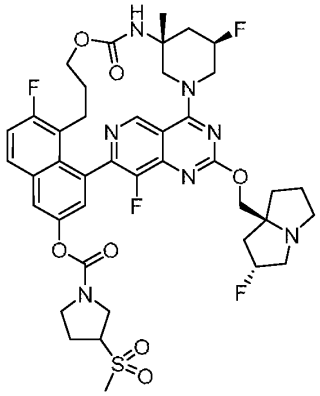
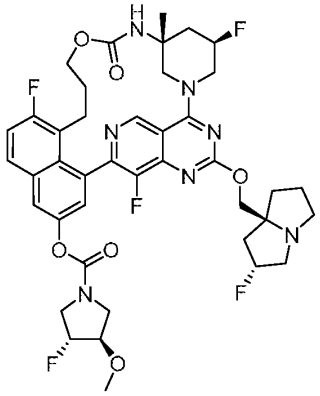
318	
319	
320	

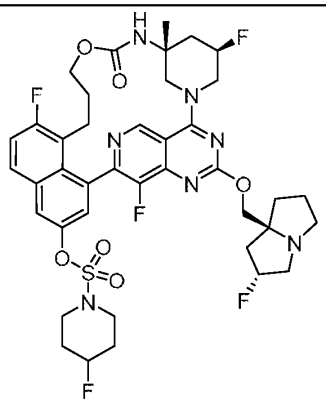
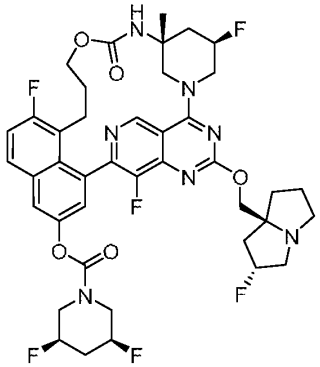
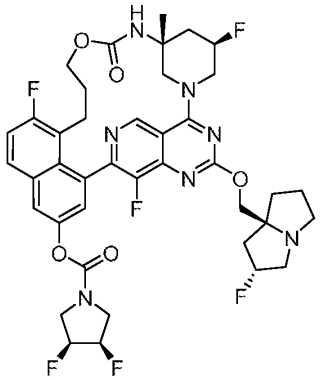
321	
322	
323	

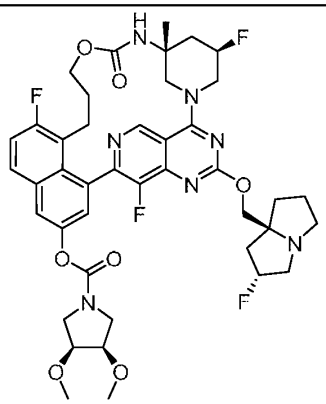
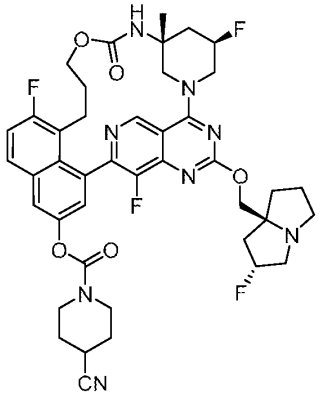
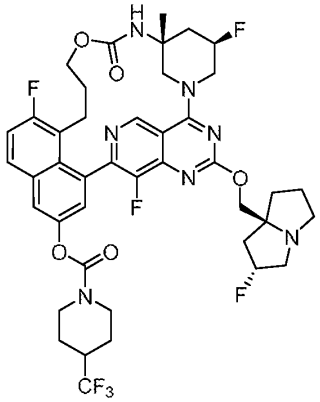
324	
325	
326	

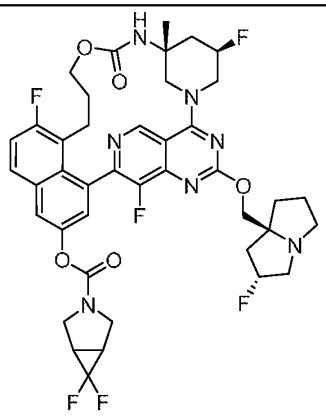
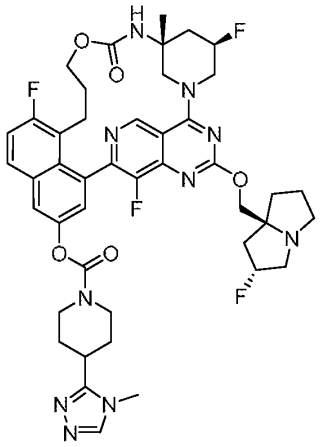
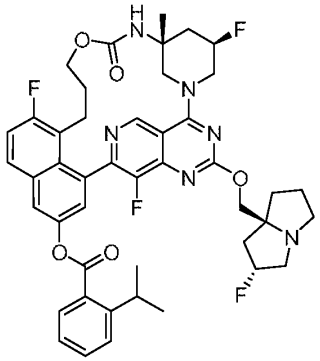
327	
328	
329	

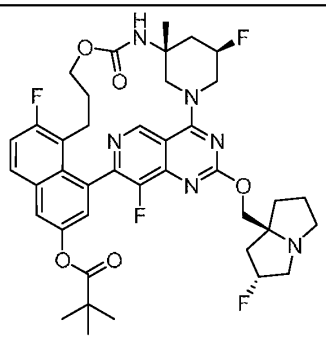
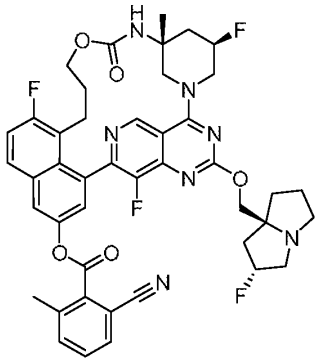
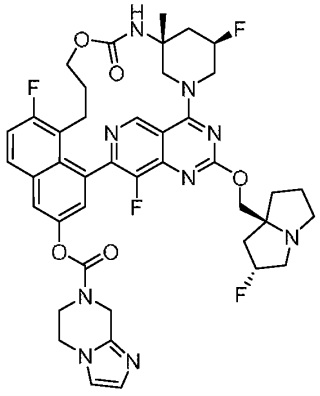
330	
331	
332	

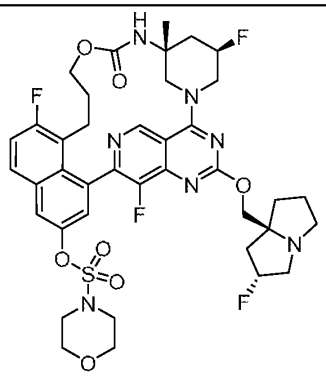
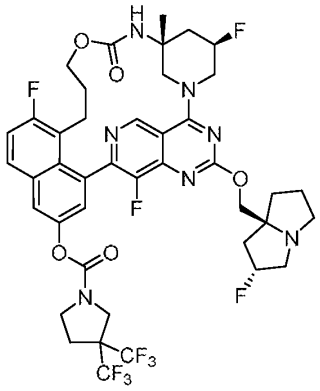
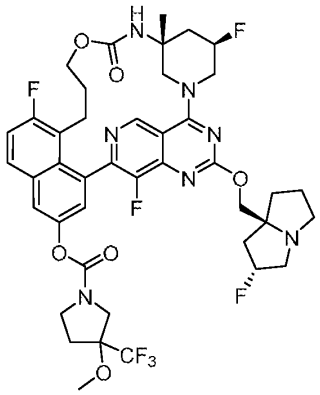
333	
334	
335	

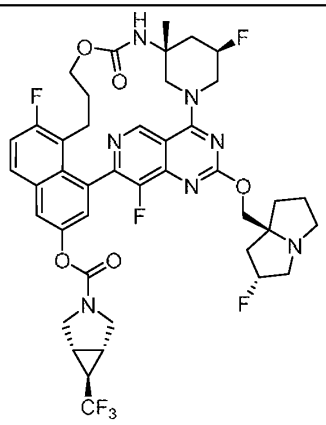
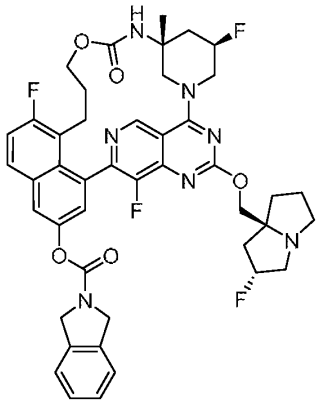
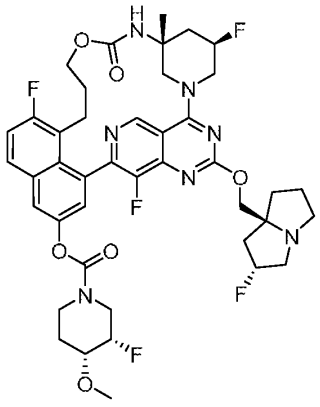
336	
337	
338	

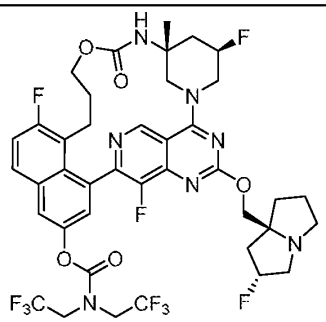
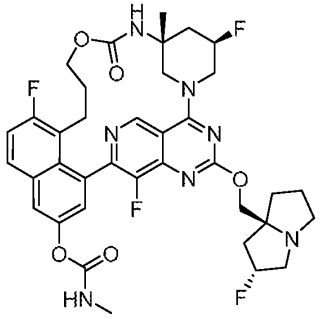
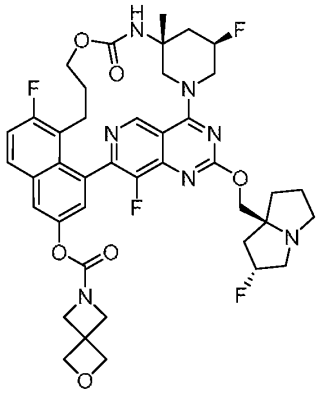
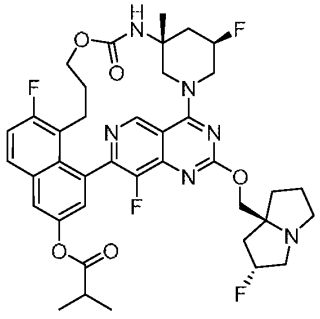
339	
340	
341	

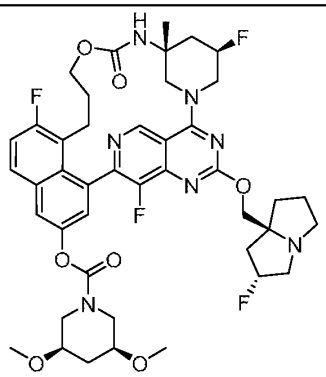
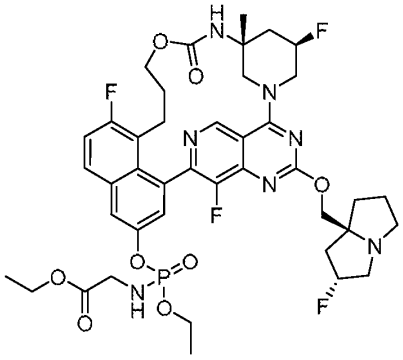
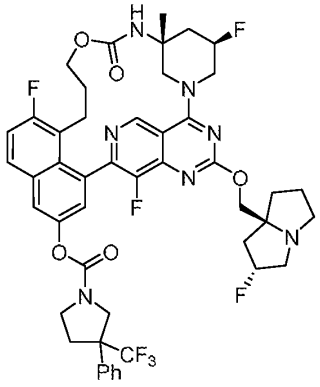
342	
343	
344	

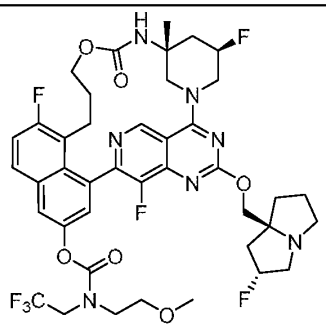
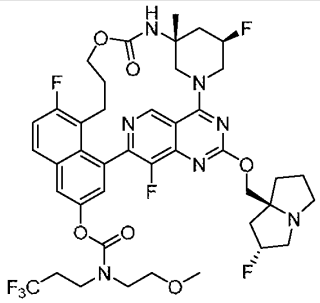
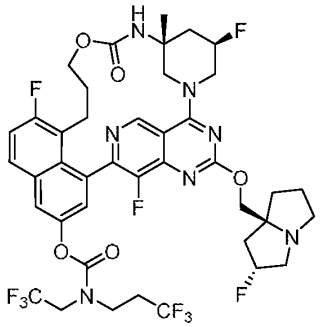
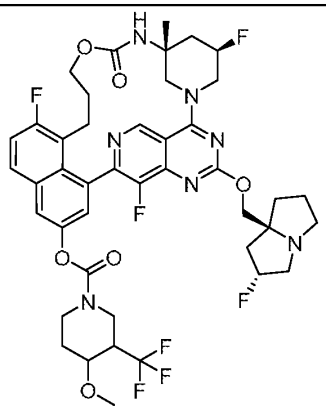
345	
346	
347	

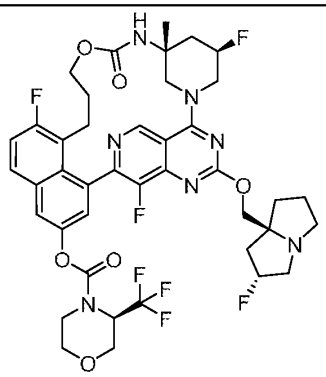
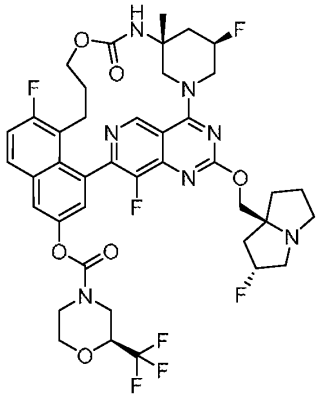
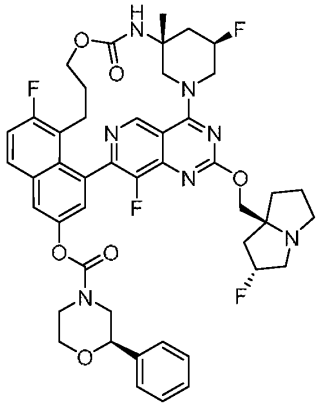
348	
349	
350	

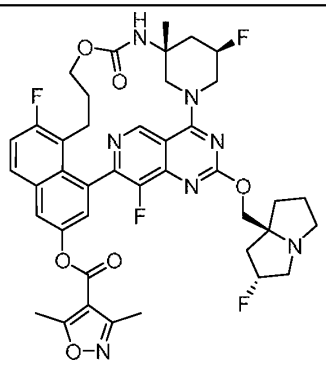
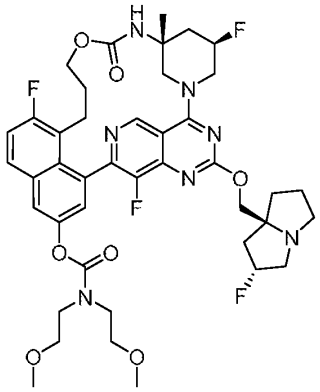
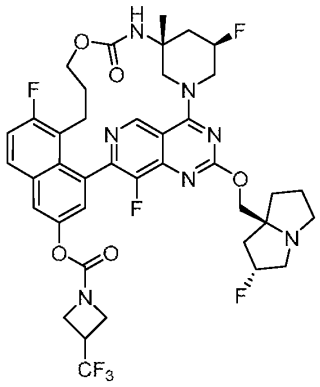
351	
352	
353	

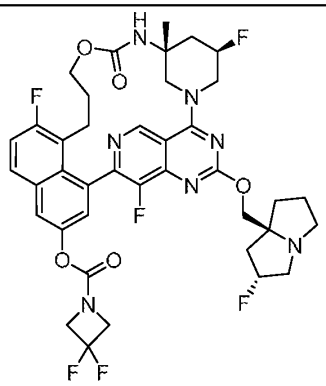
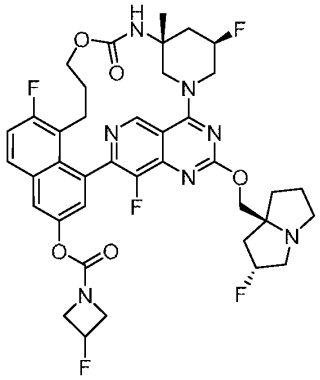
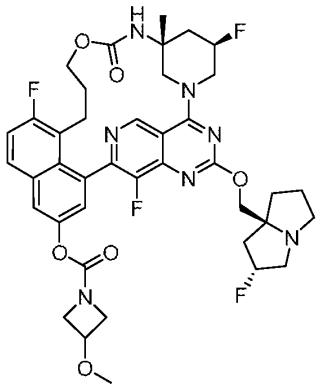
354	
355	
356	
357	

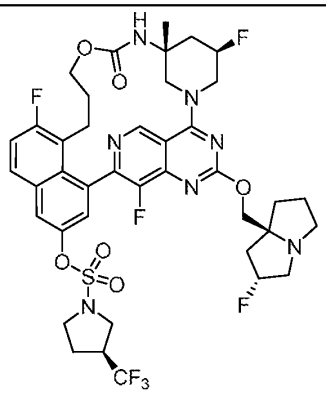
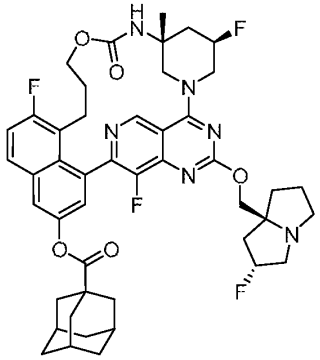
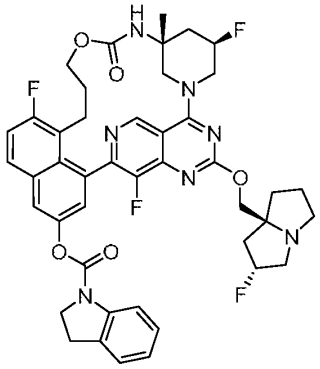
358	
359	
360	

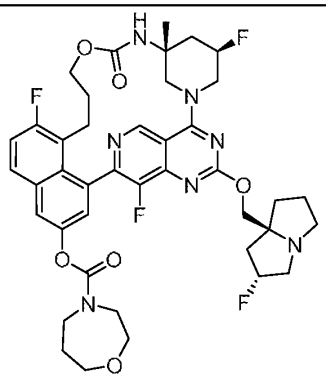
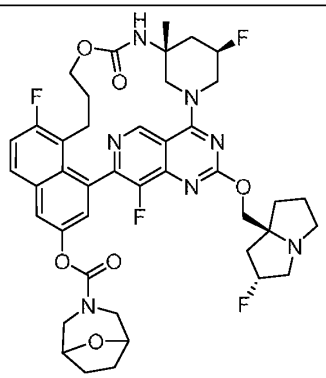
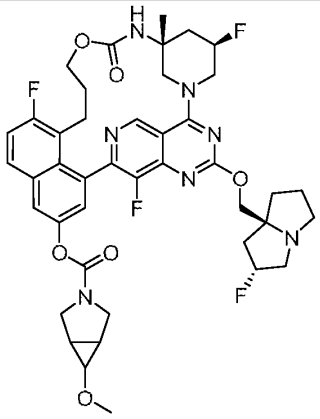
361	
362	
363	
364	

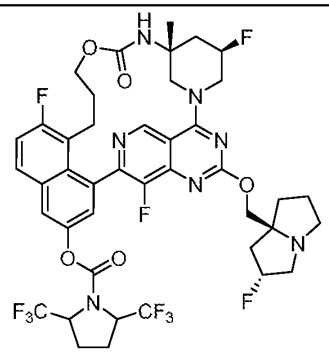
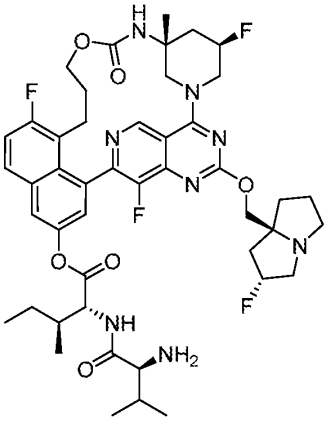
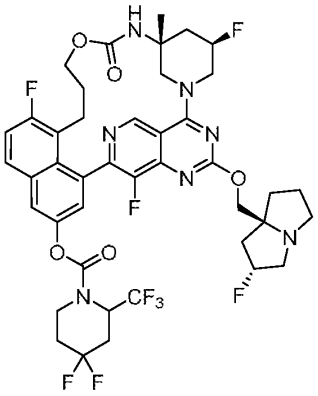
365	
366	
367	

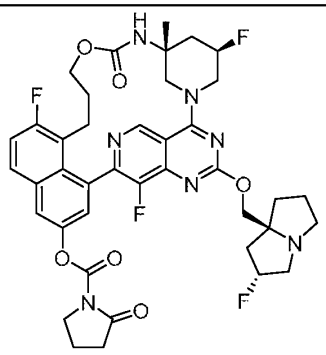
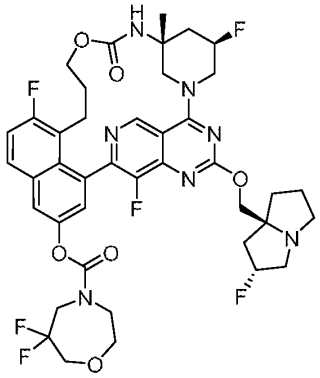
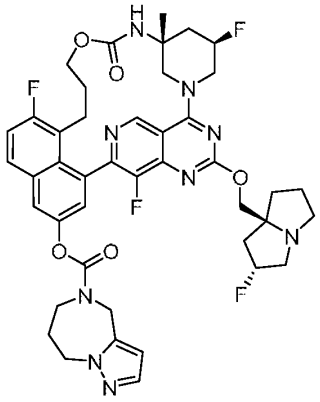
368	
369	
370	

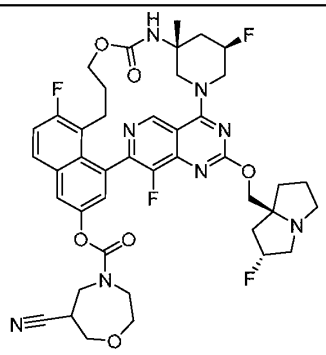
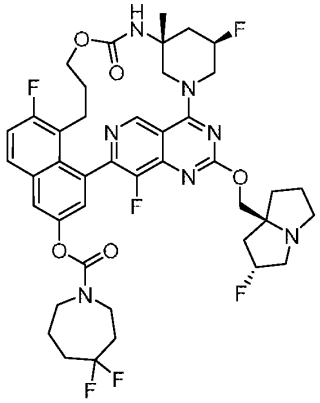
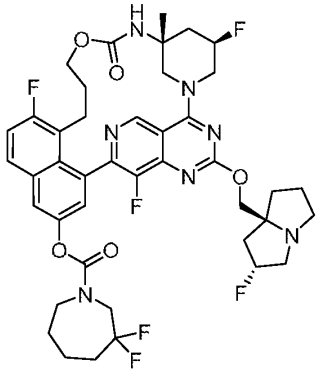
371	
372	
373	

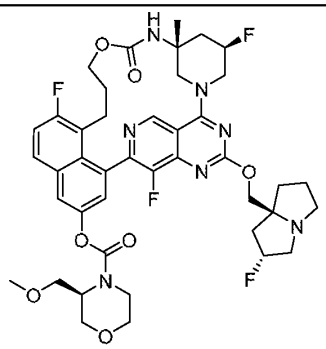
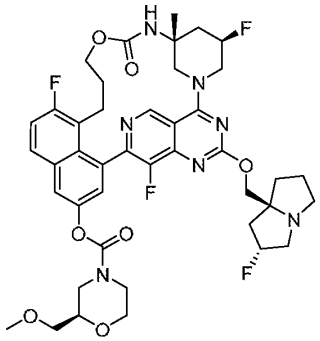
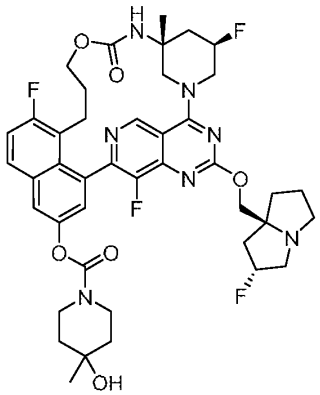
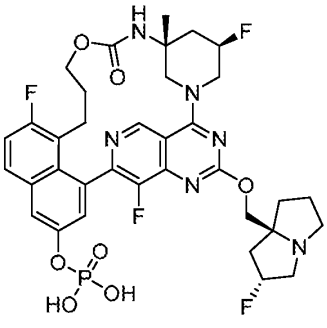
374	
375	
376	

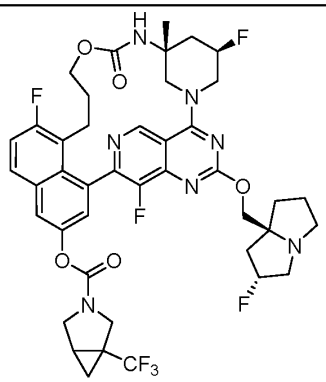
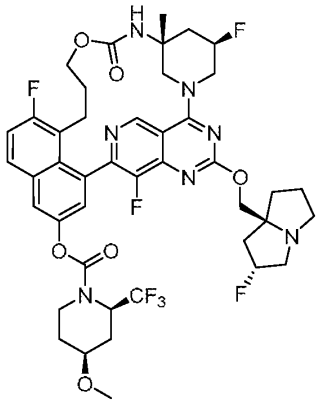
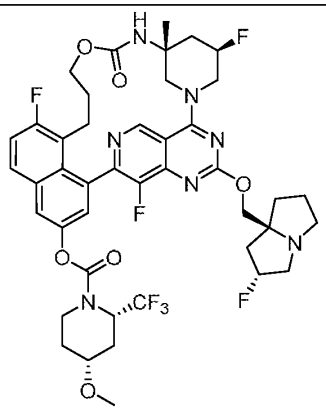
377	
378	
379	

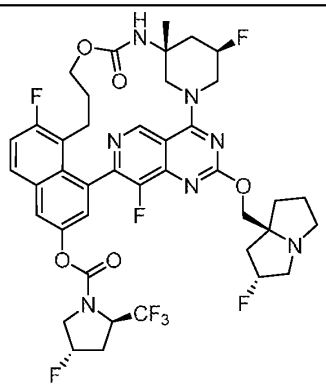
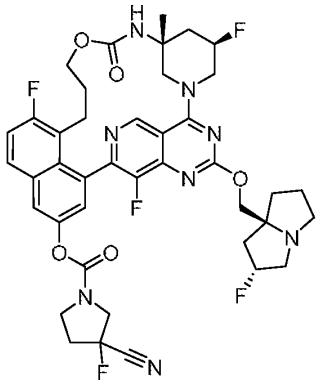
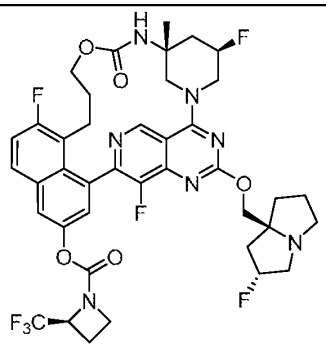
380	
381	
382	

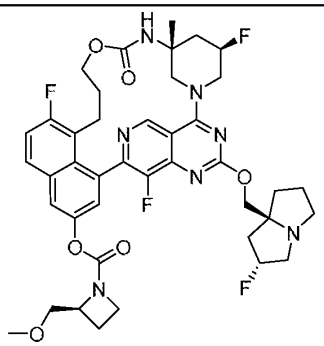
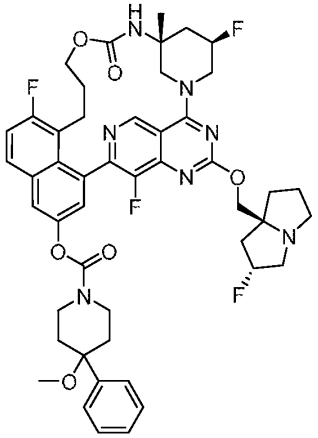
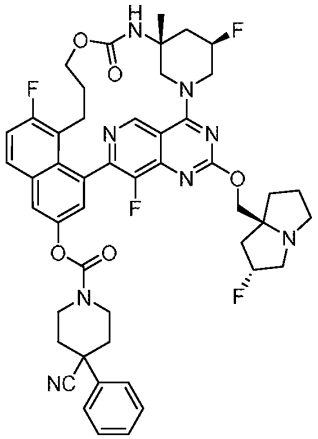
383	
384	
385	

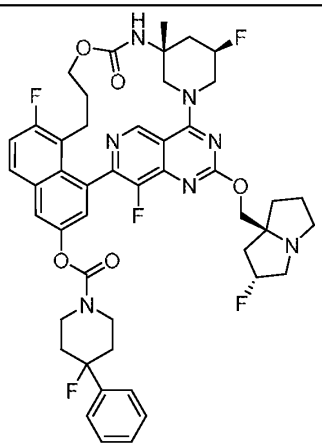
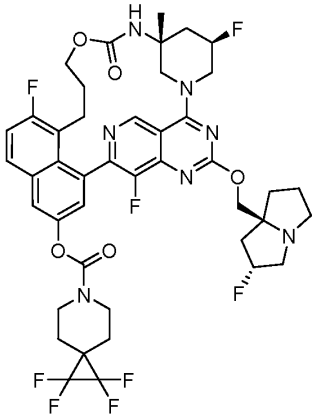
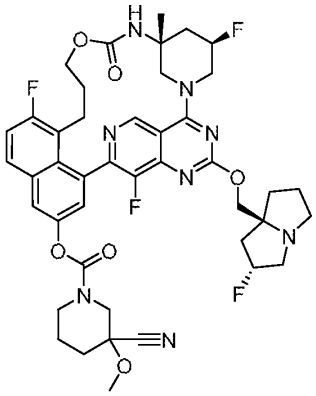
386	
387	
388	

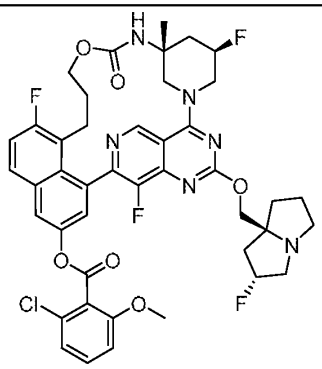
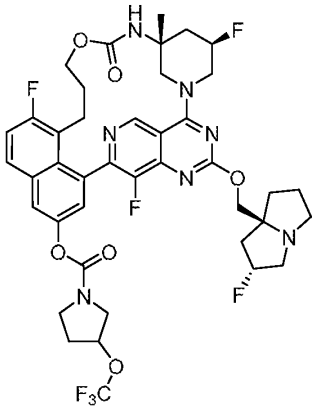
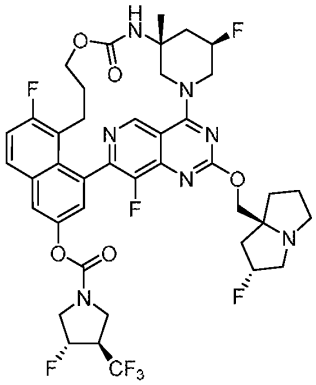
389	
390	
391	
392	

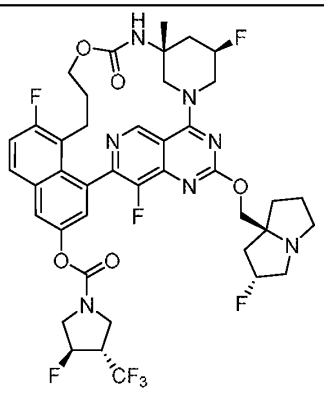
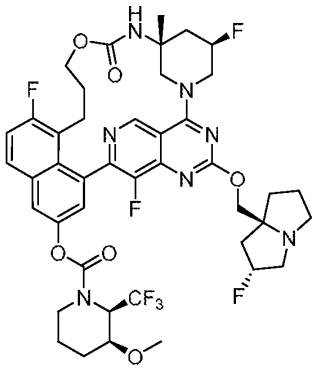
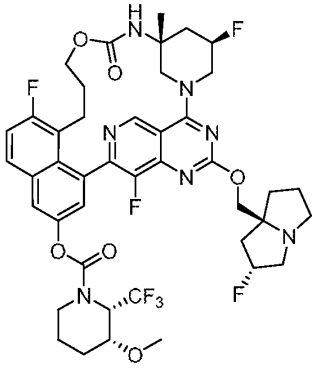
393	
394	
395	

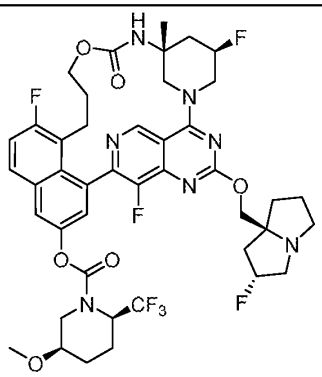
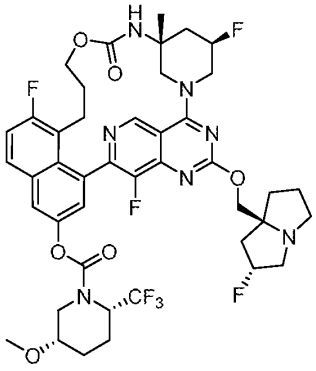
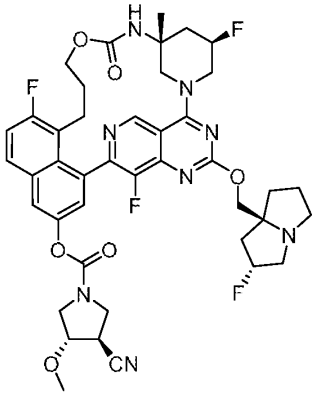
396	
397	
398	

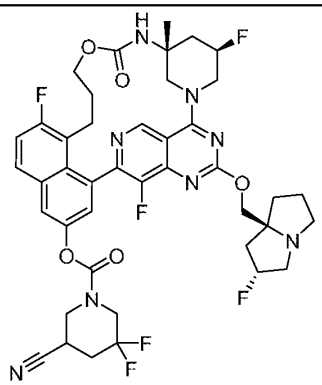
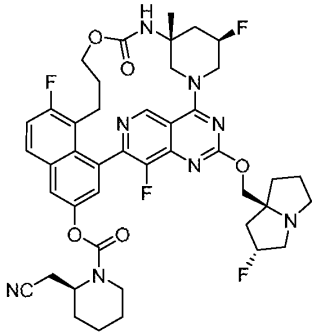
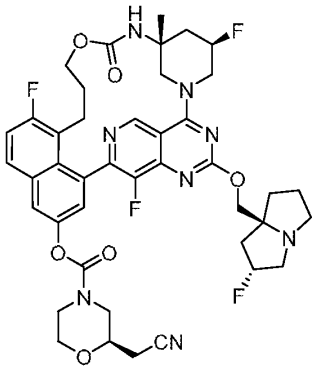
399	
400	
401	

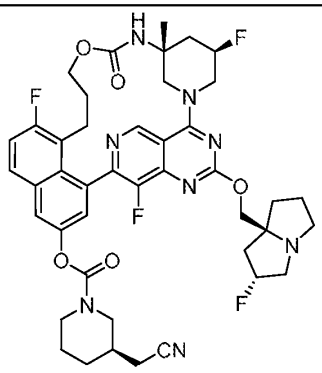
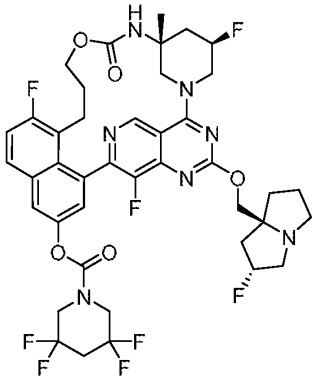
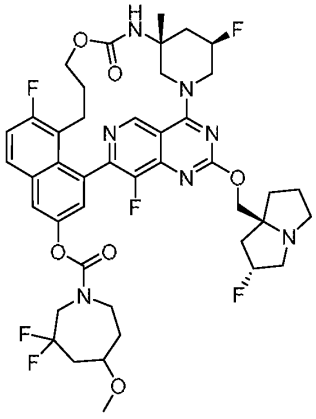
402	
403	
404	

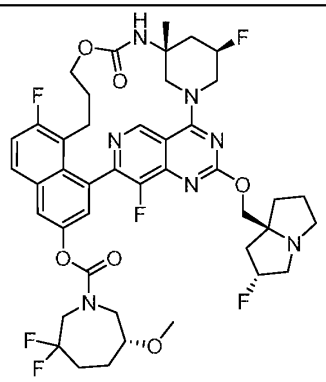
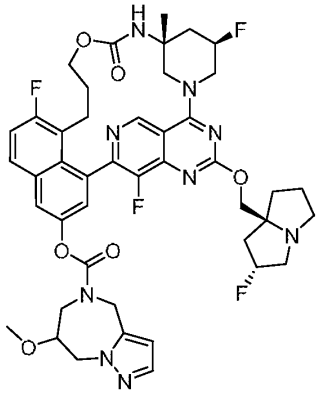
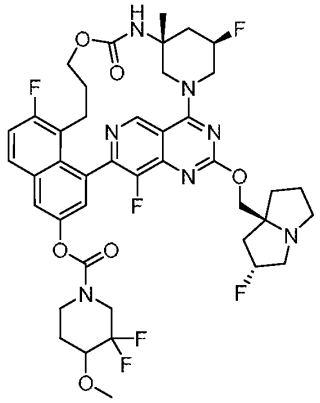
405	
406	
407	

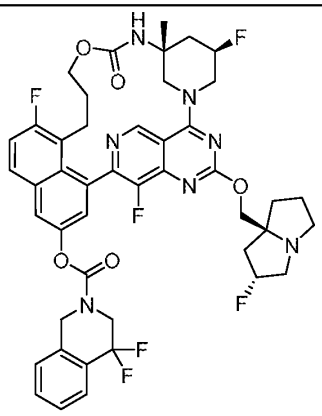
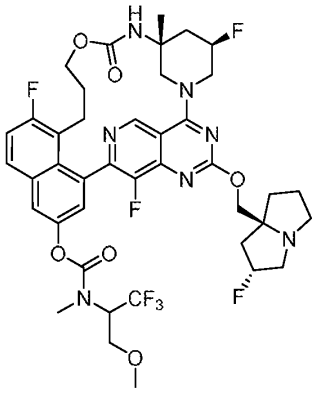
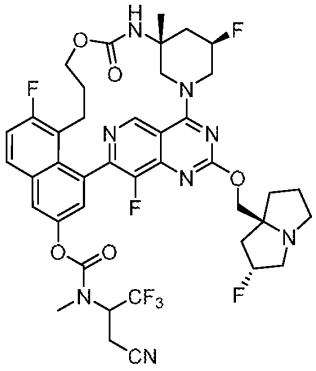
408	
409	
410	

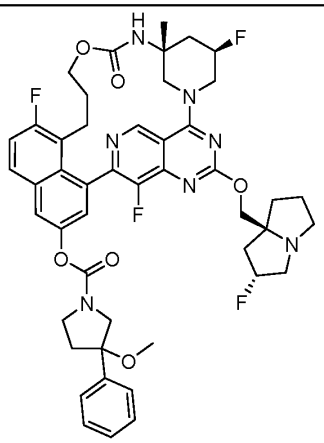
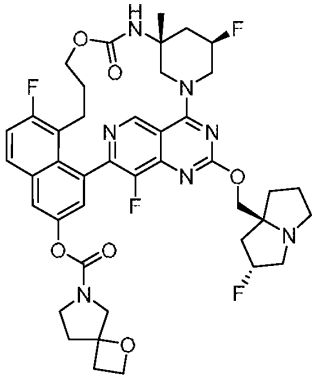
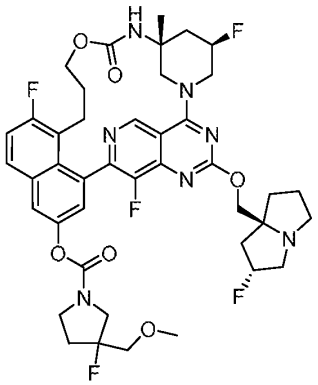
411	
412	
413	

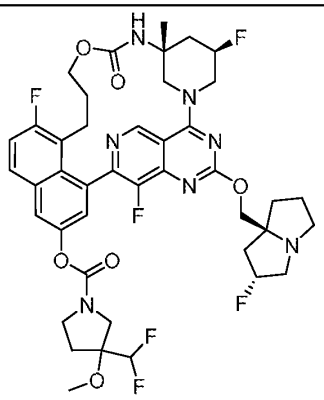
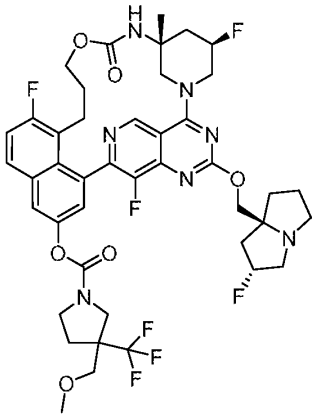
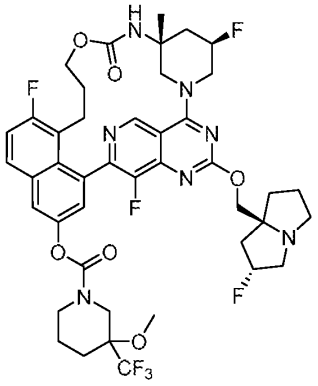
414	
415	
416	

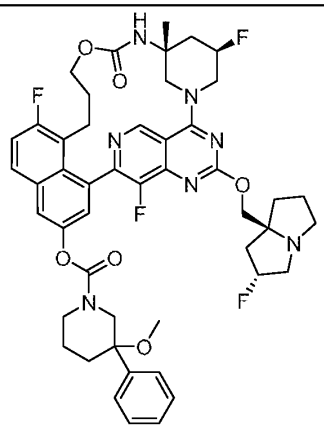
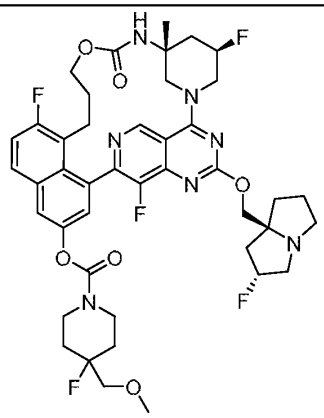
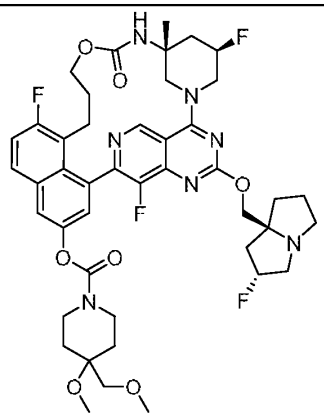
417	
418	
419	

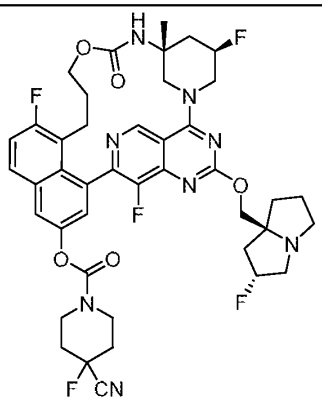
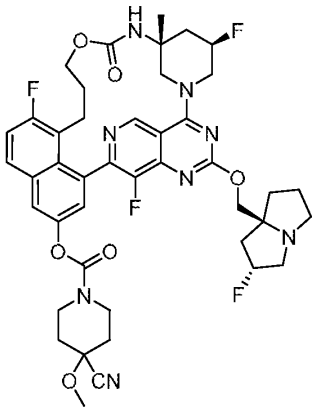
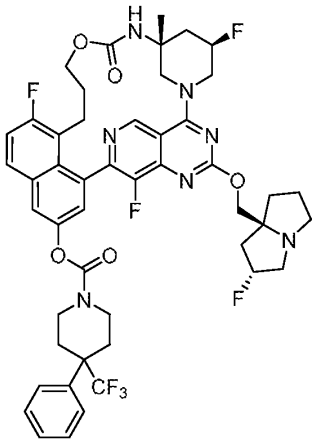
420	
421	
422	

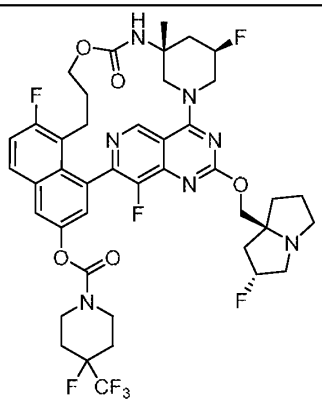
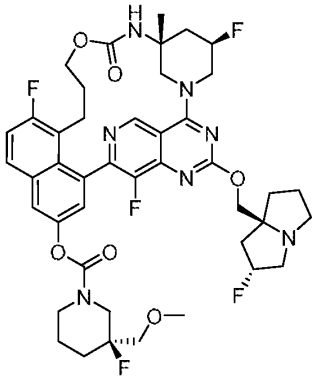
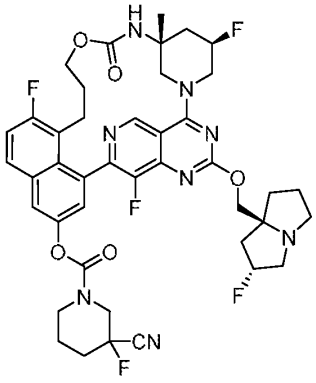
423	
424	
425	

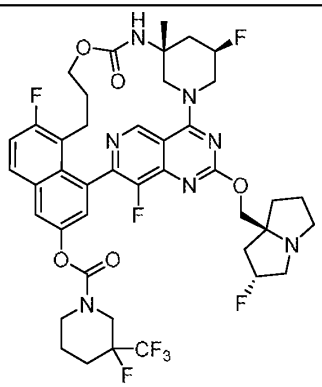
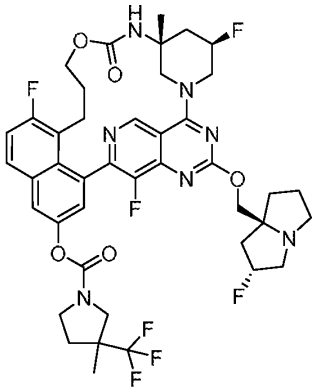
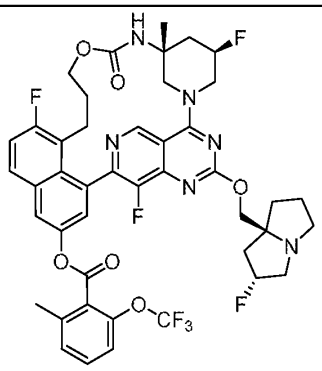
426	
427	
428	

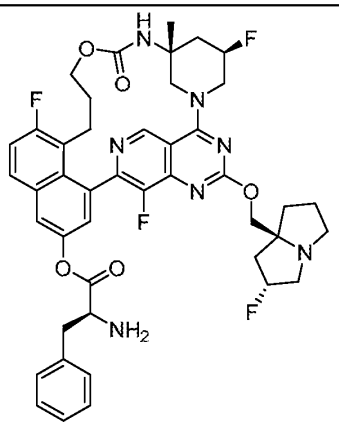
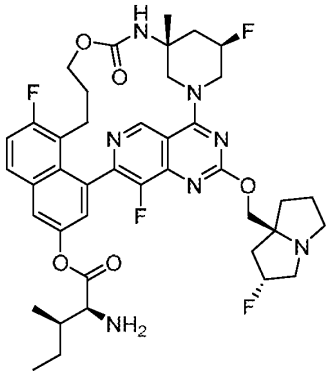
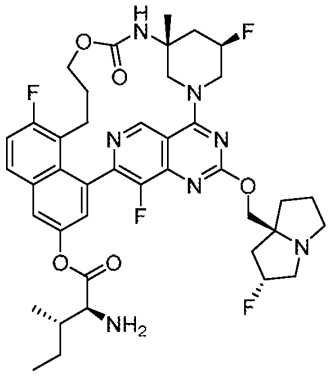
429	
430	
431	

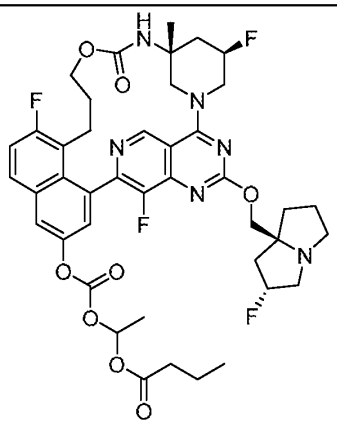
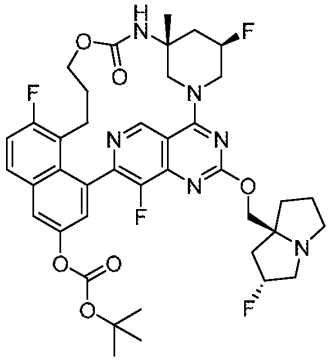
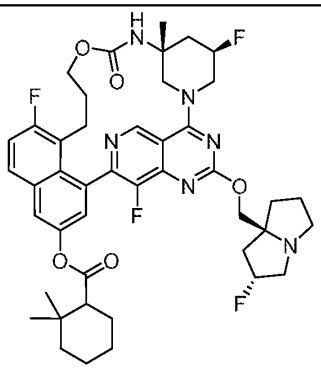
432	
433	
434	

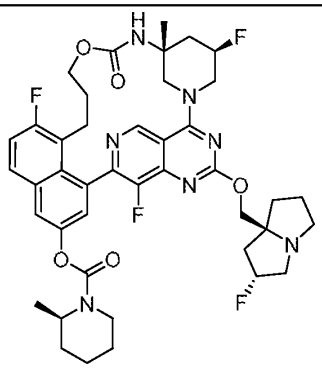
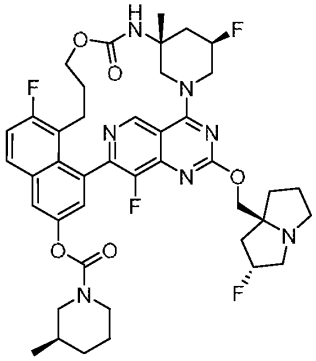
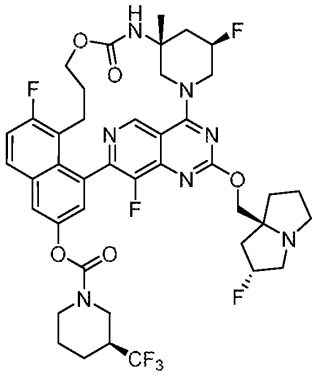
435	
436	
437	

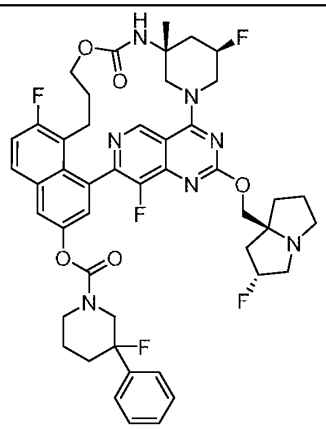
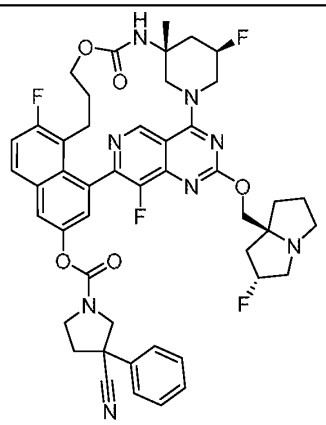
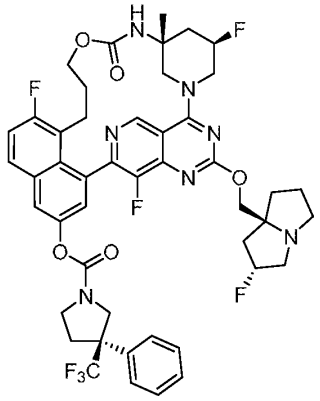
438	
439	
440	

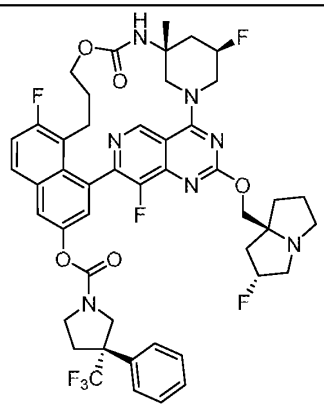
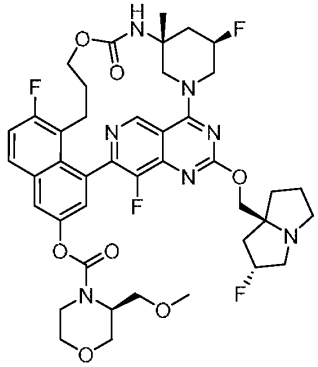
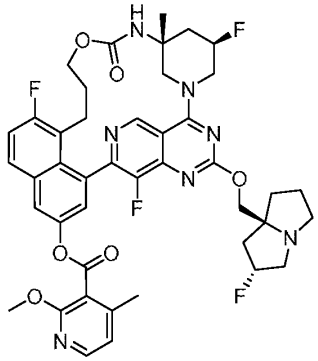
441	
442	
443	

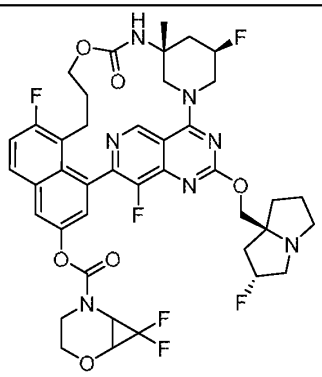
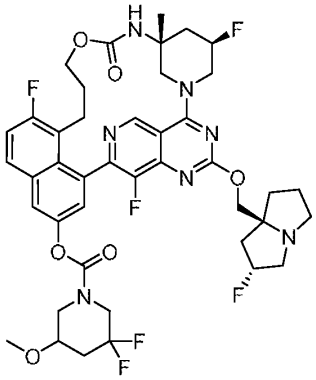
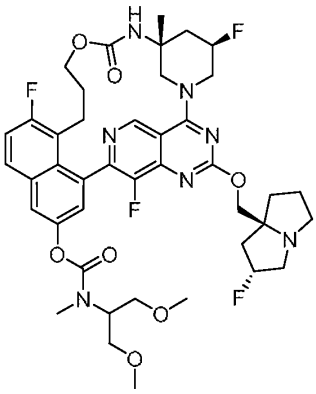
444	
445	
446	

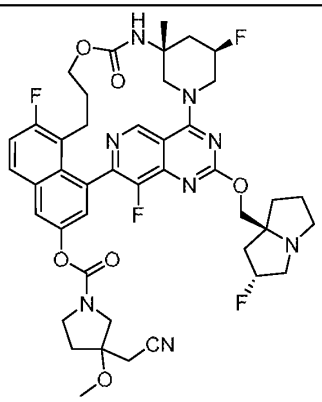
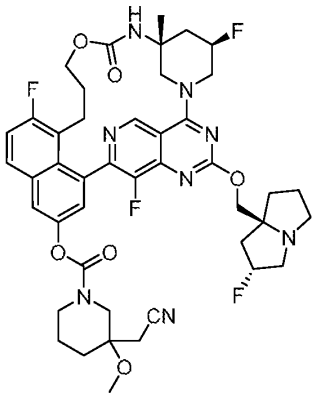
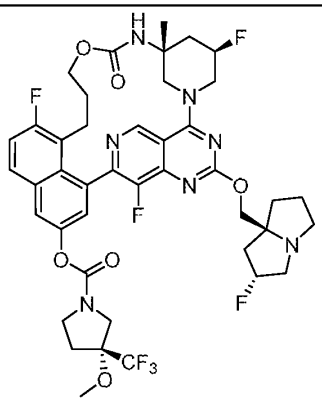
447	
448	
449	

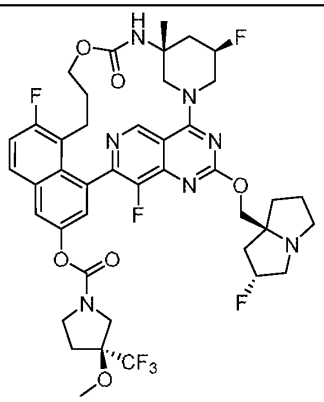
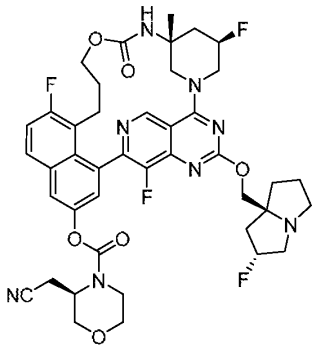
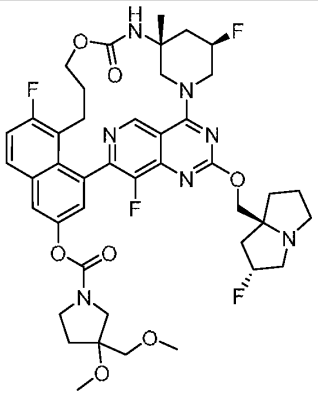
450	
451	
452	

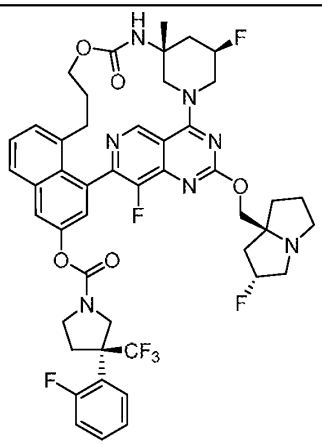
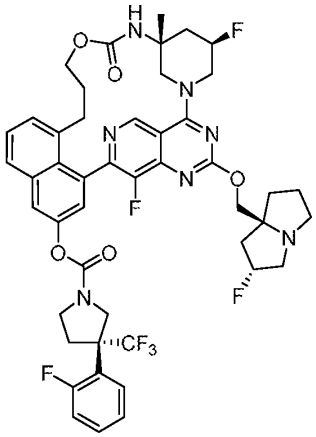
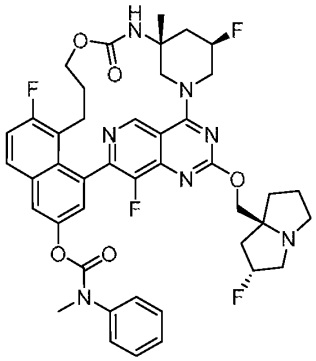
453	
454	
455	

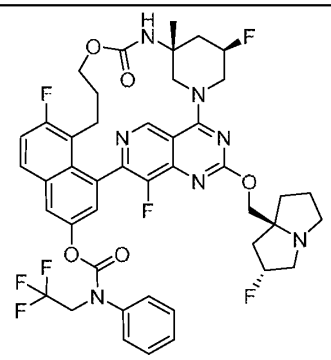
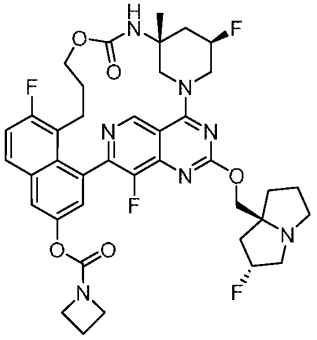
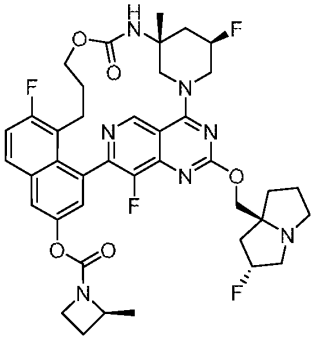
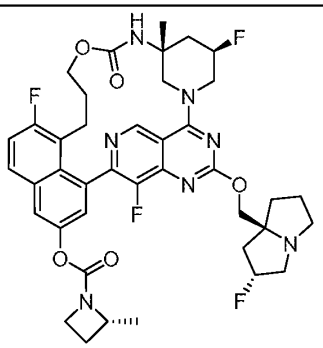
456	
457	
458	

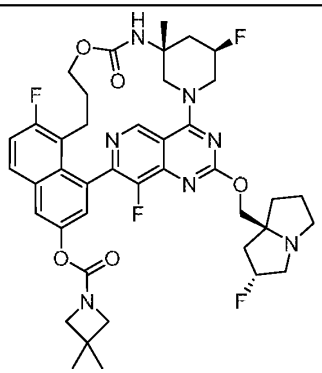
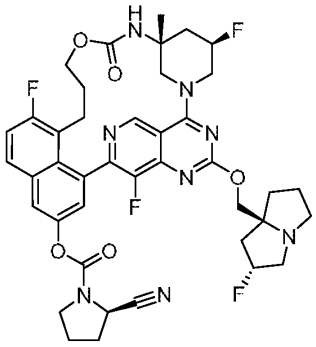
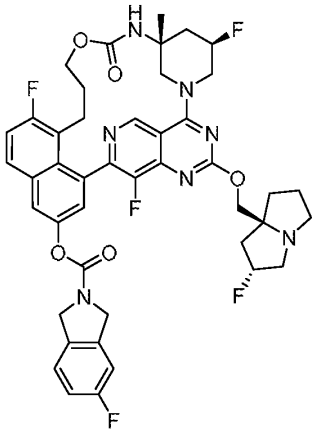
459	
460	
461	

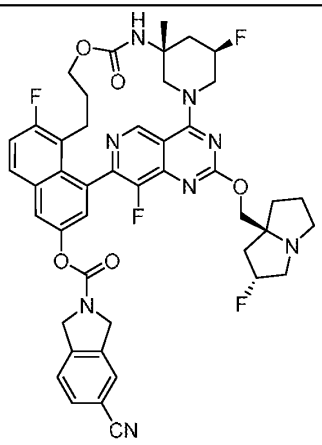
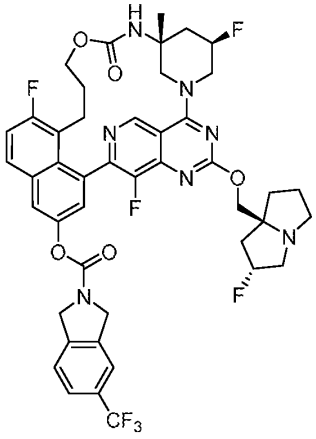
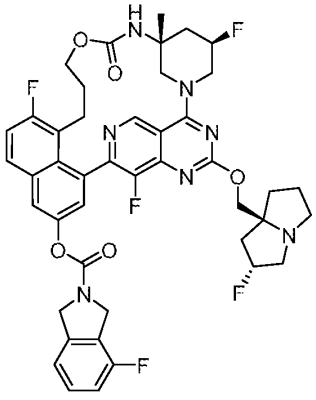
462	
463	
464	

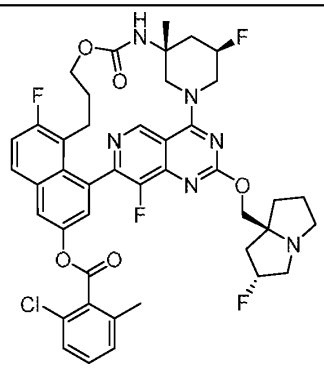
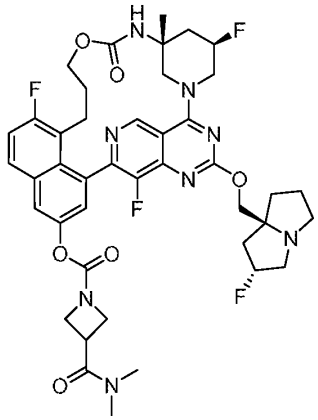
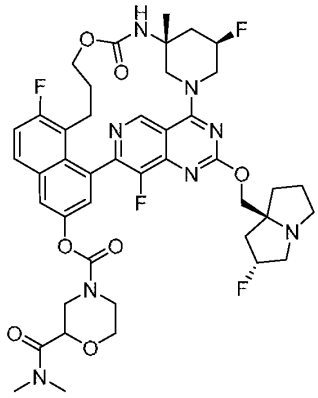
465	
466	
467	

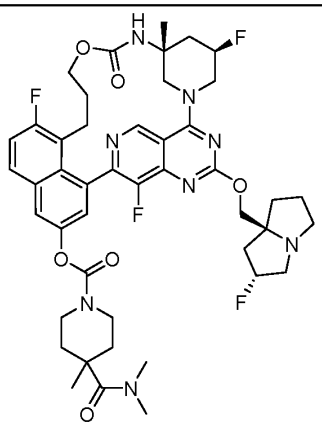
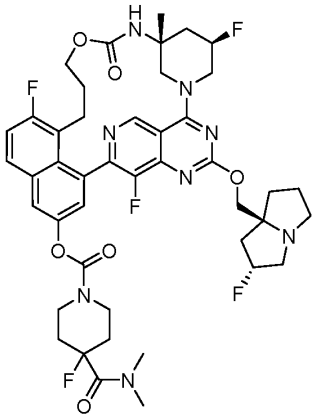
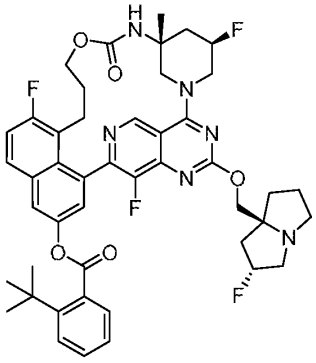
468	
469	
470	

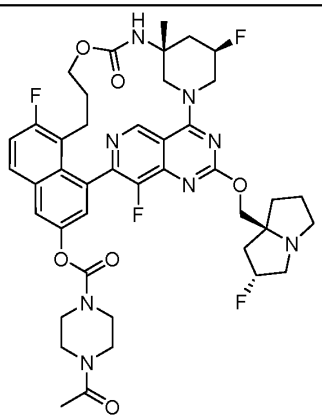
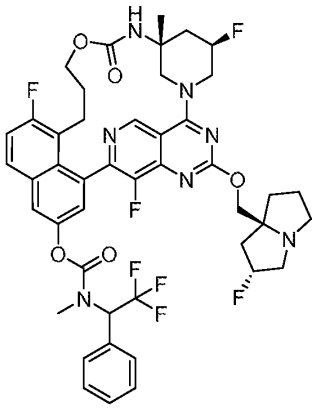
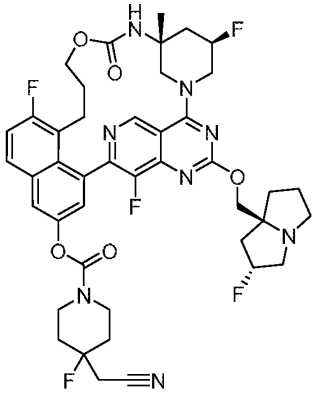
471	
472	
473	
474	

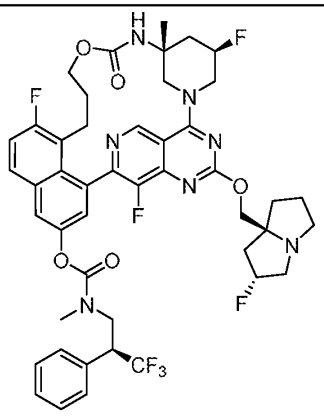
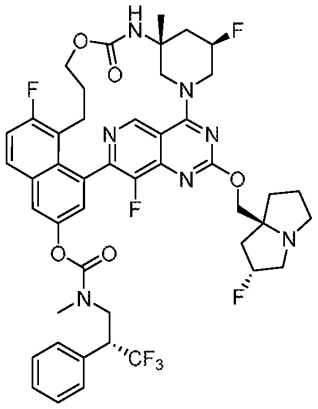
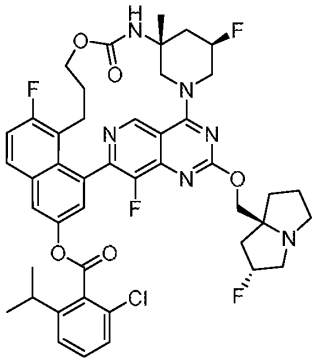
475	
476	
477	

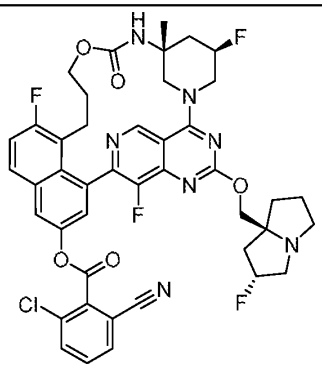
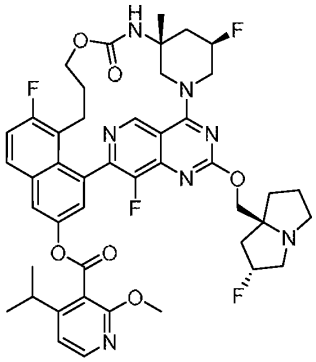
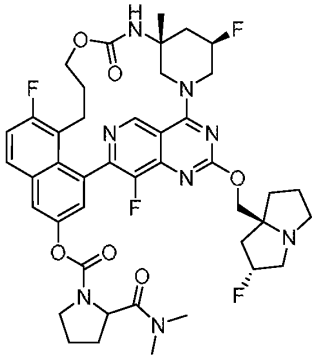
478	
479	
480	

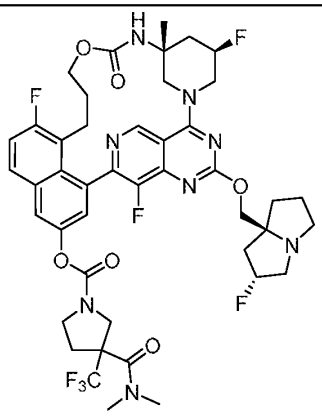
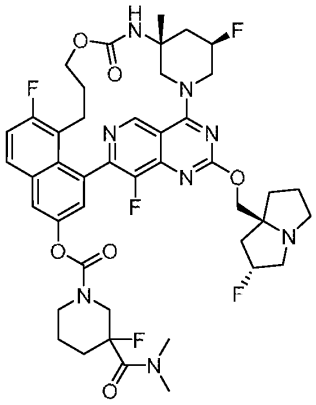
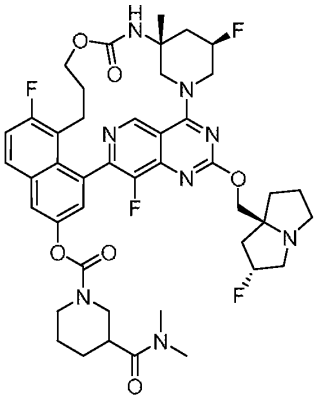
481	
482	
483	

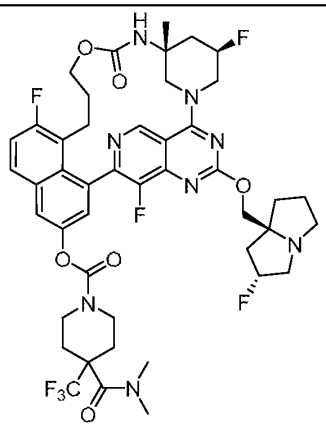
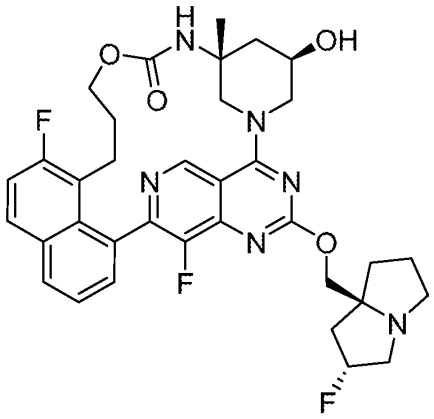
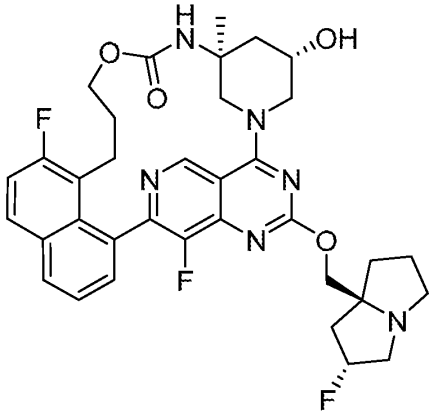
484	
485	
486	

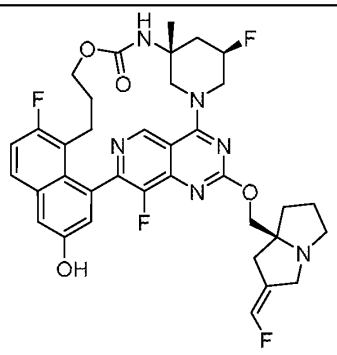
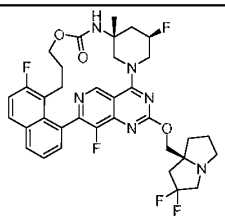
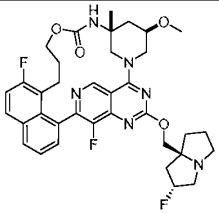
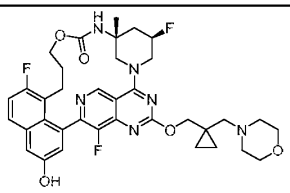
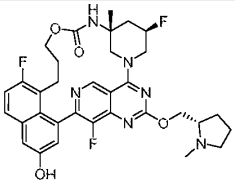
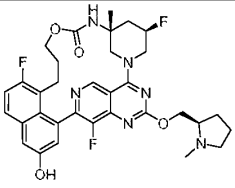
487	
488	
489	

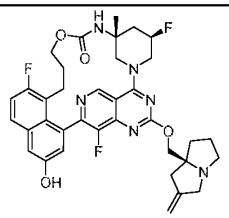
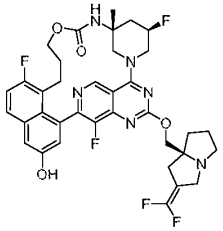
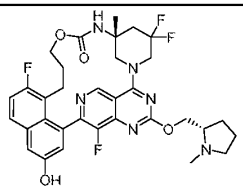
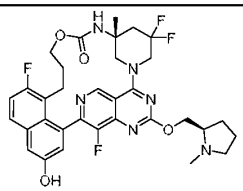
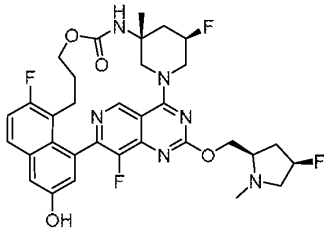
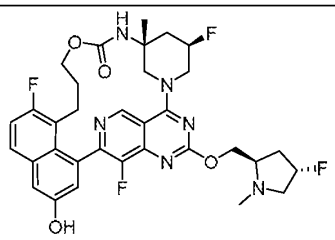
490	
491	
492	

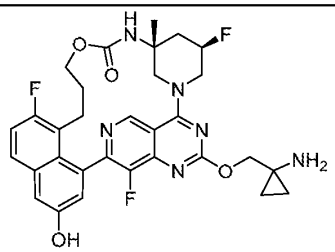
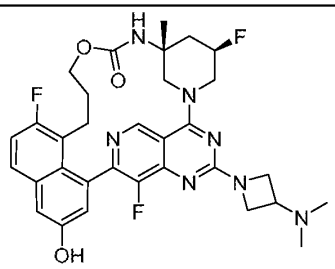
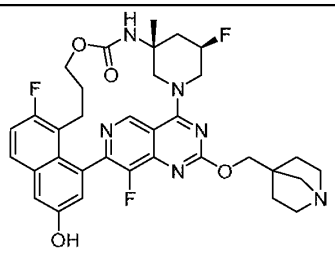
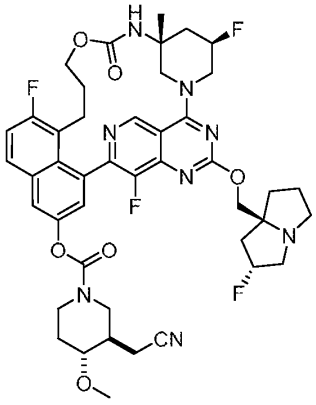
493	
494	
495	

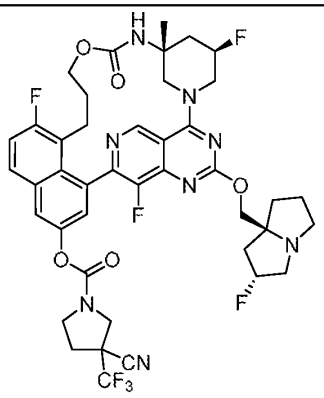
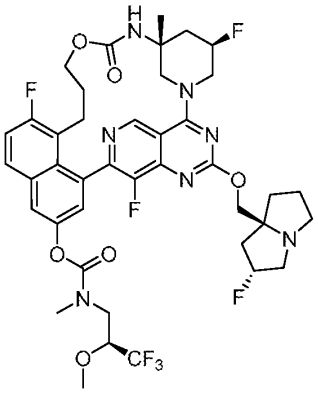
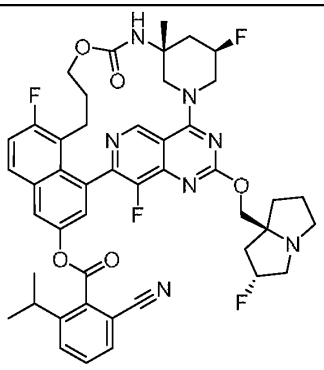
496	
497	
498	

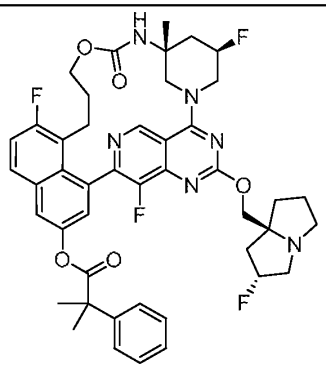
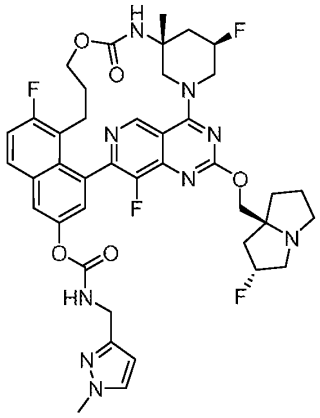
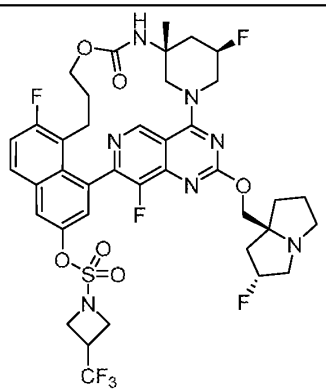
499	
500	
501	

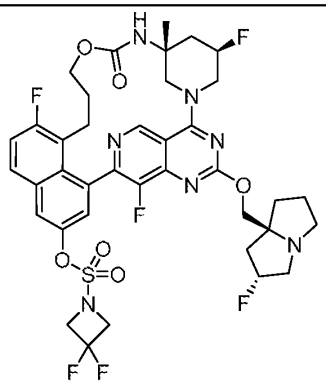
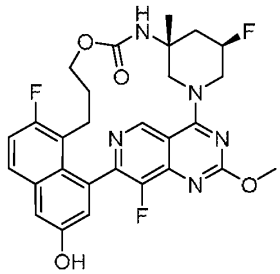
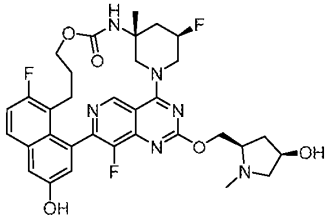
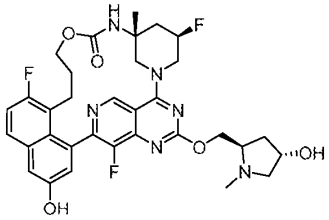
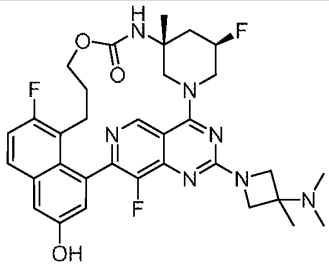
502	
503	
504	
505	
506	
507	

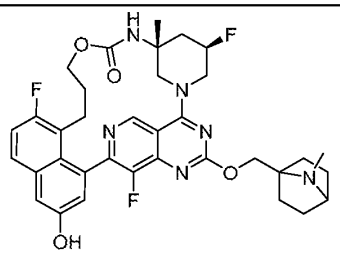
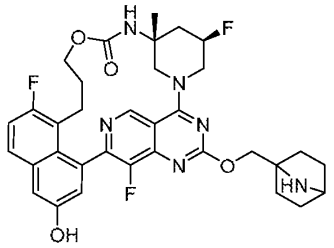
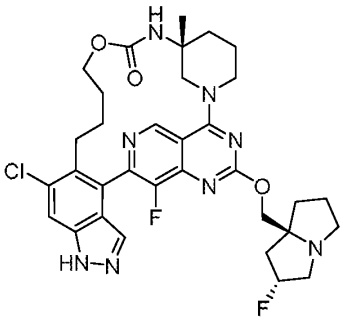
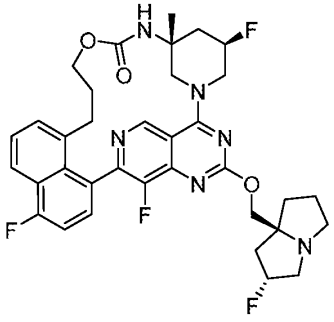
508	
509	
510	
511	
512	
513	

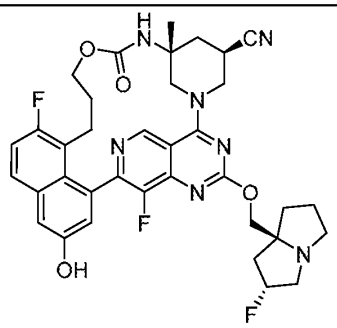
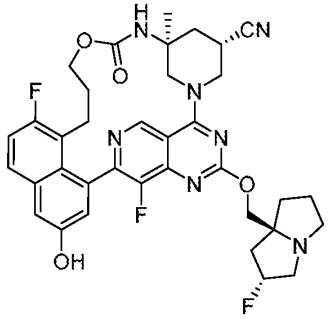
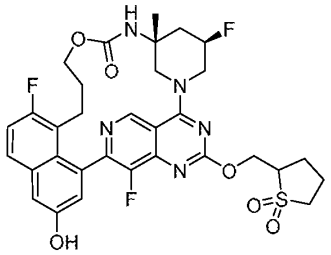
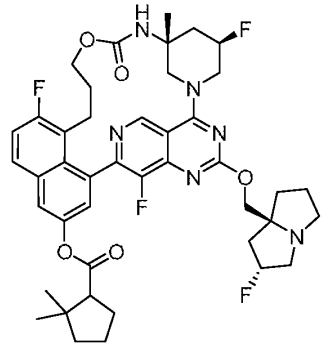
514	
515	
516	
518	

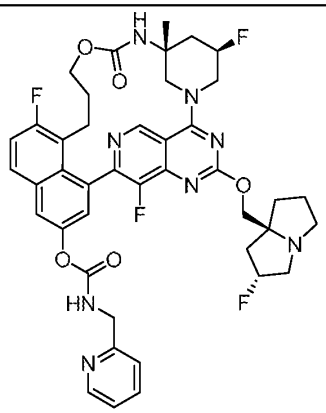
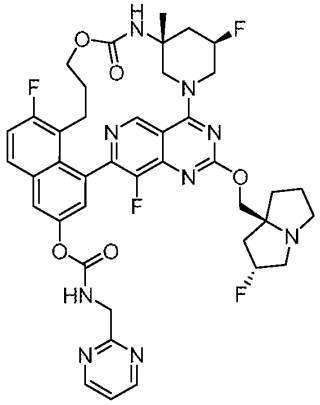
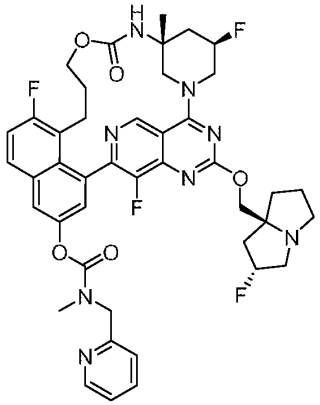
519	
520	
521	

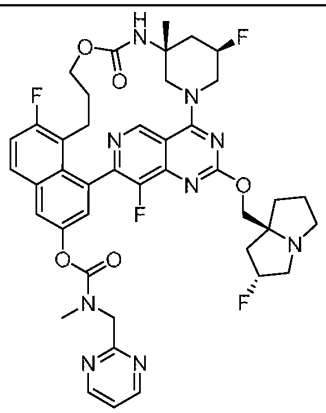
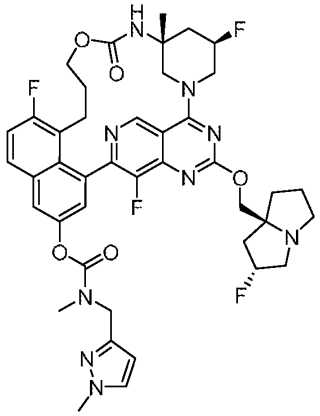
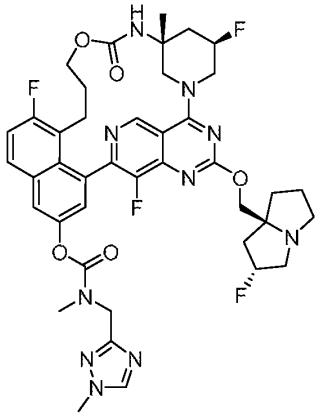
522	
523	
524	

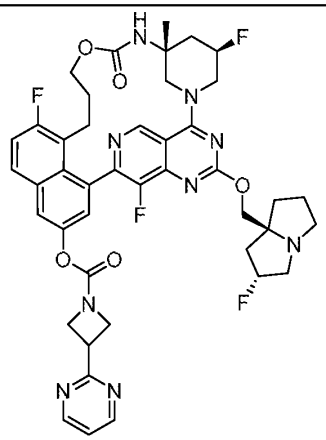
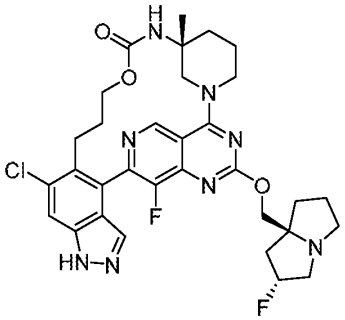
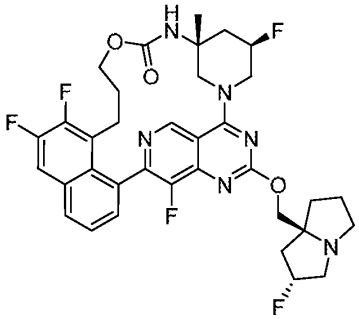
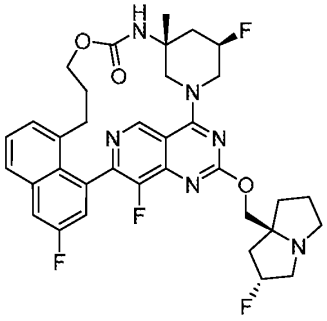
525	
526	
527	
528	
529	

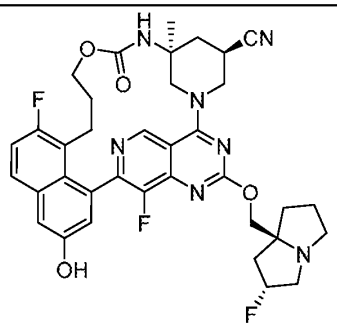
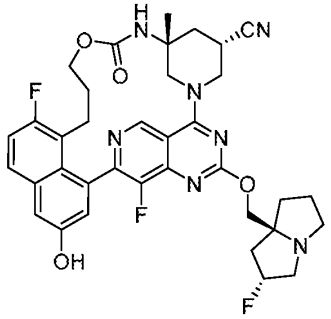
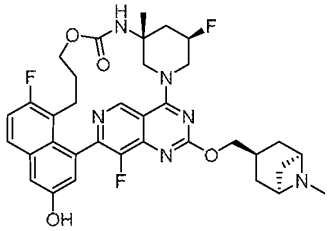
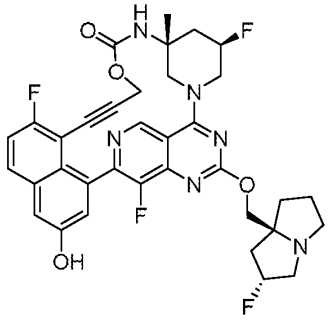
530	
531	
532	
533	

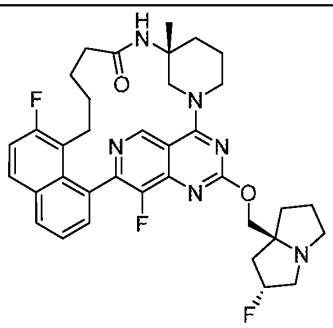
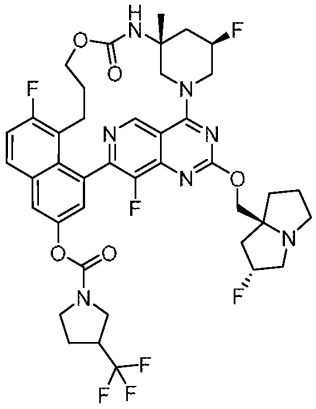
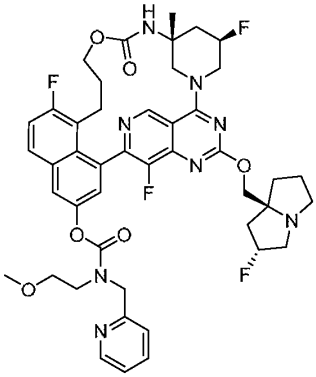
534	
535	
536	
537	

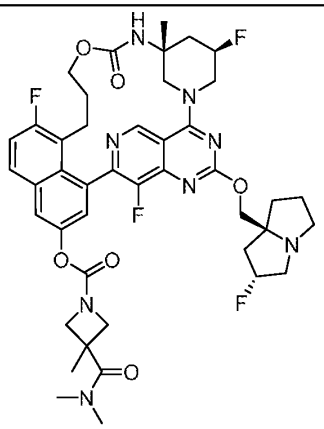
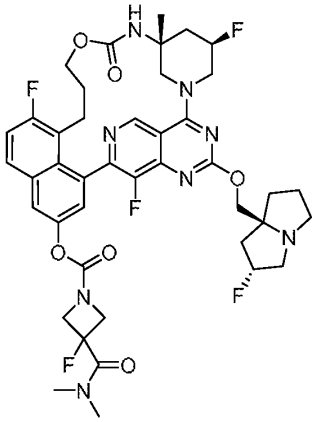
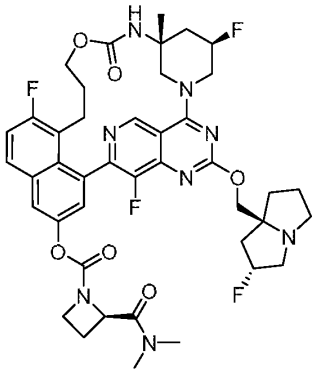
538	
539	
540	

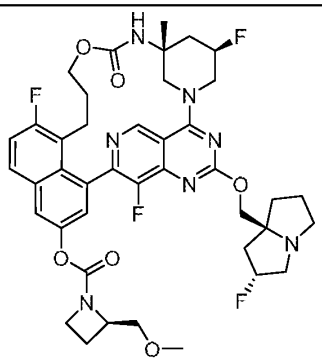
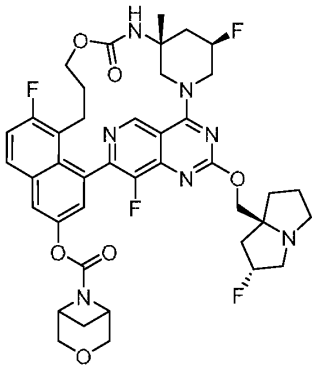
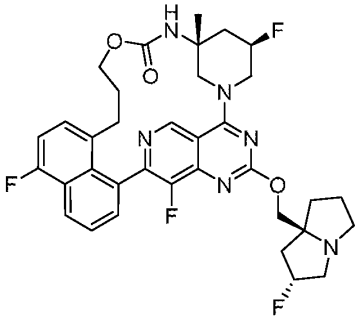
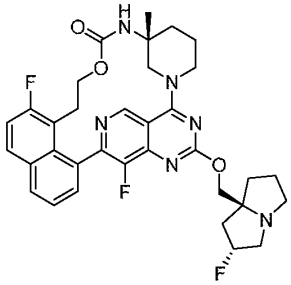
541	
542	
543	

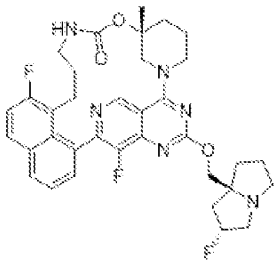
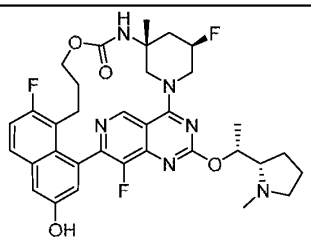
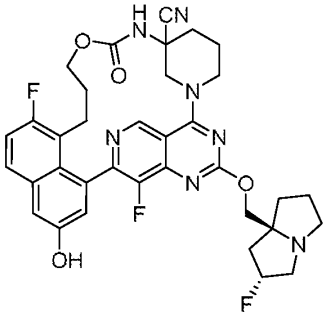
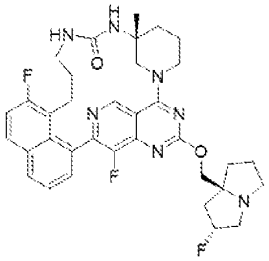
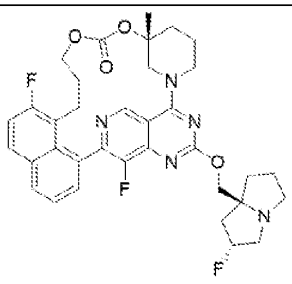
544	
545	
546	
547	

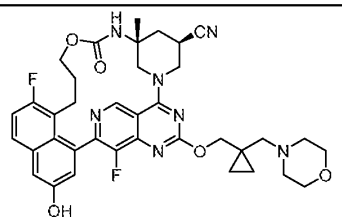
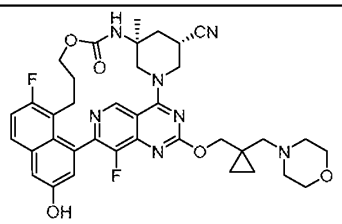
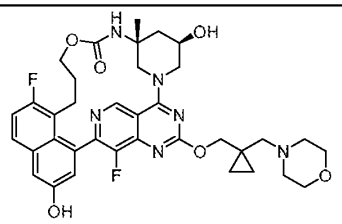
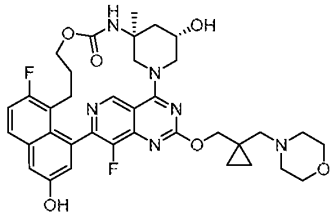
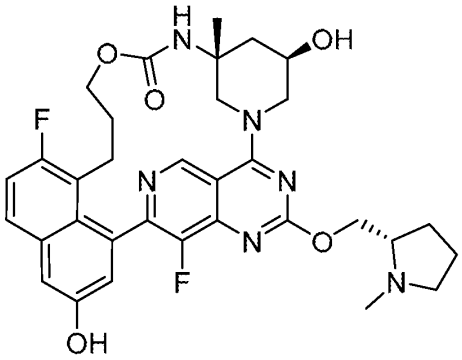
548	
549	
550	
551	

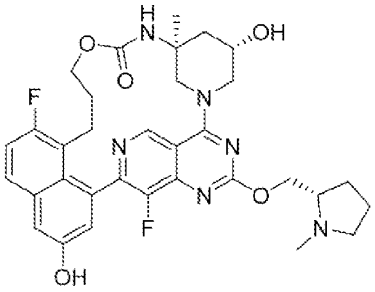
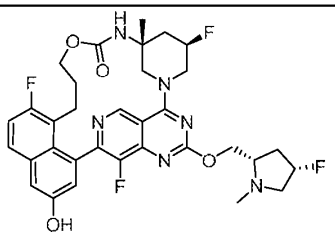
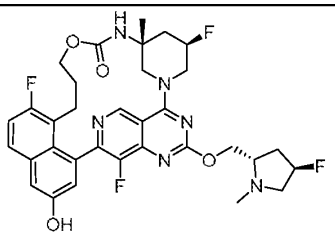
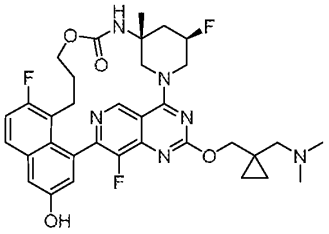
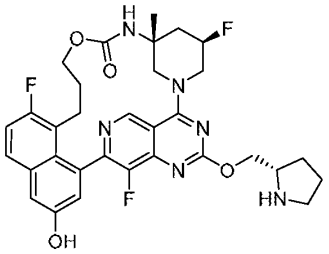
552	
553	
554	

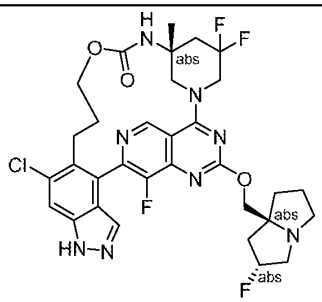
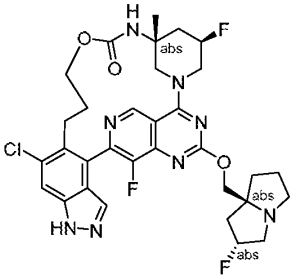
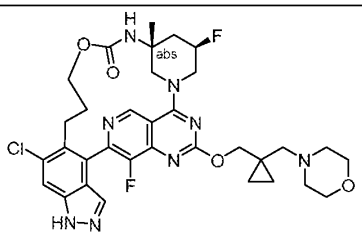
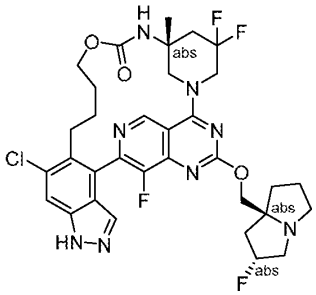
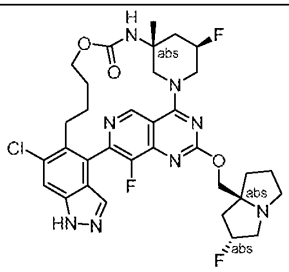
555	
556	
557	

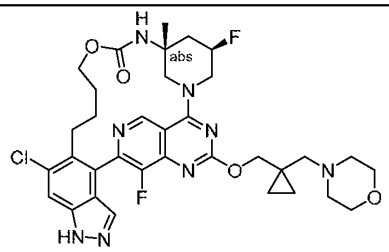
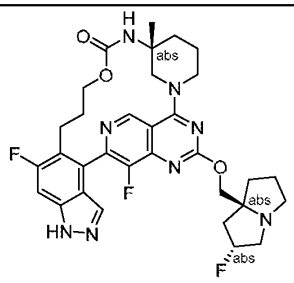
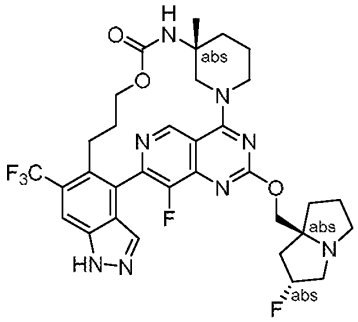
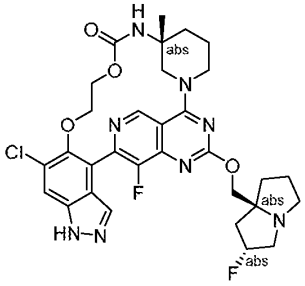
558	
559	
560	
561	

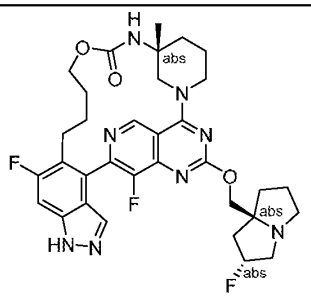
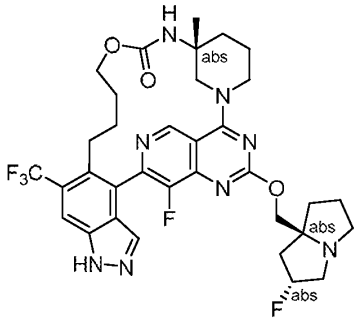
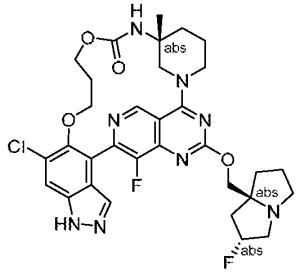
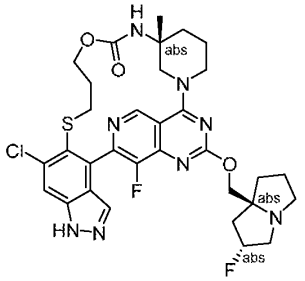
562	
563	
564	
565	
566	

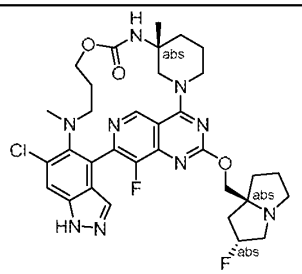
567	
568	
569	
570	
571	

572	
573	
574	
575	
576	

577	
578	
579	
580	
581	

582	
583	
584	
585	

586	
587	
588	
589	

590	

As can be appreciated, the compounds described herein provide new therapies for disease without the need for exotic chemistry or specialized reagents or manufacturing techniques.

III Pharmaceutical compositions

Other embodiments are directed to pharmaceutical compositions. In an embodiment, the pharmaceutical composition comprises any one (or more) of the foregoing compounds and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is formulated for oral administration. In other embodiments, the pharmaceutical composition is formulated for injection. In still more embodiments, the pharmaceutical compositions comprise a compound as disclosed herein and an additional therapeutic agent (*e.g.*, anticancer agent). Non-limiting examples of such additional therapeutic agents are described herein below.

Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, optical, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the compound is delivered in a targeted drug delivery system, for example, in a liposome coated with an organ specific antibody. In such embodiments, the liposomes are targeted to and

taken up selectively by the organ. In yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

In treatment methods according to embodiments of the disclosure, an effective amount of at least one compound of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) is administered to a subject suffering from or diagnosed as having such a disease, disorder, or medical condition. Effective amounts or doses may be ascertained by methods such as modeling, dose escalation studies or clinical trials, *e.g.*, the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating physician.

The compounds according to the disclosure are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.001 to 0.1 mg, 0.01 to 0.1 mg, 0.5 to 5 mg, 0.5 to 10 mg, 0.01-10 mg, 0.1 to 10 mg, 10 to 5000 mg, 100 to 5000 mg, 1000 mg to 4000 mg per day, or 1000 to 3000 mg per day are examples of dosages that are used in some embodiments. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

In some embodiments, compounds of the disclosure are administered in a single dose. In an embodiment, the single dose is administered orally. In another embodiment, the single dose is administered by injection. However, other routes are used as appropriate. In some embodiments, compounds of the disclosure are administered in multiple doses. In some embodiments, dosing is about once, twice, three times, four times, five times, six times, or more than six times per day. In other embodiments, dosing is about once a month, once every two weeks, once a week, or once every other day. In another embodiment compounds of the disclosure and another agent (*e.g.*, an additional anti-cancer agent) are administered together about once per day to about 6 times per day. In another embodiment the administration of compounds of the disclosure and an agent continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

Administration of compounds of the disclosure may continue as long as necessary. In

some embodiments, compounds of the disclosure are administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, compounds of the disclosure are administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, compounds of the disclosure are administered chronically on an ongoing basis, *e.g.*, for the treatment of chronic effects.

In some embodiments, the compounds of the disclosure are administered in individual dosage forms. It is known in the art that due to intersubject variability in compound pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy.

In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. In specific embodiments, pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the disclosed compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are used as suitable to formulate the pharmaceutical compositions described herein: Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

Provided herein are pharmaceutical compositions comprising one or more compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA),and a pharmaceutically acceptable carrier. Also provided herein are pharmaceutical compositions comprising one or more compounds selected from compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) and pharmaceutically acceptable diluent(s), excipient(s), and carrier(s). In certain embodiments, the compounds described are administered as pharmaceutical compositions in which one or more compounds selected from compounds of

Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) are mixed with other active ingredients, as in combination therapy. Encompassed herein are all combinations of actives set forth in the combination therapies section below and throughout this disclosure. In specific embodiments, the pharmaceutical compositions include one or more compounds of Formula (I), (II), (IA)-

(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA).

A pharmaceutical composition, as used herein, refers to a mixture of one or more compounds selected from compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, the pharmaceutical composition facilitates administration of the compound to an organism. In some embodiments, therapeutically effective amounts of one or more compounds selected from compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) provided herein are administered in a pharmaceutical composition to a mammal having a disease, disorder or medical condition to be treated. In specific embodiments, the mammal is a human. In certain embodiments, therapeutically effective amounts vary depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds described herein are used singly or in combination with one or more therapeutic agents as components of mixtures.

In one embodiment, one or more compounds selected from compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) are formulated in aqueous solutions. In specific embodiments, the aqueous solution is selected from, by way of example only, a physiologically compatible buffer, such as Hank's solution, Ringer's solution, or physiological saline buffer. In other embodiments, one or more compounds selected from compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) are formulated for transmucosal administration. In specific embodiments, transmucosal formulations include penetrants that are appropriate to the barrier to be permeated. In still other embodiments wherein the compounds described herein are formulated for other parenteral injections, appropriate formulations include aqueous or non-aqueous solutions. In specific embodiments, such solutions include physiologically compatible buffers and/or excipients.

In another embodiment, compounds described herein are formulated for oral administration. Compounds described herein are formulated by combining the active compounds with, *e.g.*, pharmaceutically acceptable carriers or excipients. In various embodiments, the compounds described herein are formulated in oral dosage forms that

include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like.

In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating agents include, by way of example only, cross linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a pharmaceutically acceptable salt thereof such as sodium alginate.

In one embodiment, the oral dosage forms, such as a pill, capsule or tablet, comprises one or more suitable layers or coatings. In specific embodiments, concentrated sugar solutions are used for coating the dosage form. The sugar solutions, optionally contain additional components, such as by way of example only, gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs and/or pigments are also optionally added to the coatings for identification purposes. Additionally, the dyestuffs and/or pigments are optionally utilized to characterize different combinations of active compound doses.

In certain embodiments, therapeutically effective amounts of at least one of the compounds described herein are formulated into other oral dosage forms. Oral dosage forms include push fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other embodiments, soft capsules, contain one or more active compound that is dissolved or suspended in a suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

In still other embodiments, the compounds described herein are formulated for

parental injection, including formulations suitable for bolus injection or continuous infusion. In specific embodiments, formulations for injection are presented in unit dosage form (*e.g.*, in ampoules) or in multi dose containers. Preservatives are, optionally, added to the injection formulations. In still other embodiments, the pharmaceutical compositions are formulated in a form suitable for parenteral injection as sterile suspensions, solutions or emulsions in oily or aqueous vehicles. Parenteral injection formulations optionally contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In specific embodiments, pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water soluble form. In additional embodiments, suspensions of one or more compounds selected from compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles for use in the pharmaceutical compositions described herein include, by way of example only, fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In certain specific embodiments, aqueous injection suspensions contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension contains suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, in other embodiments, the active ingredient is in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

Pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent or excipient, and one or more compounds selected from compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) as an active ingredient. The active ingredient is in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of N-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. All tautomers of the compounds described herein are included within the scope of the compounds presented herein. Additionally, the compounds described herein encompass unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, carriers, adjuvants, such as

preserving, stabilizing, wetting or emulsifying agents, solution promoters, pharmaceutically acceptable salts for regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

Methods for the preparation of compositions comprising the compounds described herein include formulating the compound(s) with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid composition. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels, ointments, suspensions and creams. The form of the pharmaceutical compositions described herein include liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions also optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

In some embodiments, pharmaceutical compositions comprising one or more compounds selected from compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) illustratively takes the form of a liquid where the agents are present in solution, in suspension or both. Typically when the composition is administered as a suspension, a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

In certain embodiments, aqueous suspensions contain one or more polymers as suspending agents. Polymers include water-soluble polymers such as cellulosic polymers, *e.g.*, hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Certain pharmaceutical compositions described herein comprise a mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

Pharmaceutical compositions also, optionally, include solubilizing agents to aid in the solubility of one or more compounds selected from compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA). The term "solubilizing agent" generally includes agents that result in

formation of a micellar solution or a true solution of the agent. Certain acceptable nonionic surfactants, for example polysorbate 80, are useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, *e.g.*, polyethylene glycol 400, and glycol ethers.

Furthermore, pharmaceutical compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

Compositions also, optionally, include one or more pharmaceutically acceptable salts in an amount required to bring osmolality of the composition into an acceptable range. Such pharmaceutically acceptable salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable pharmaceutically acceptable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

Other pharmaceutical compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

Compositions may include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, *e.g.*, polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, *e.g.*, octoxynol 10, octoxynol 40.

Compositions may include one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

In certain embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

In alternative embodiments, other delivery systems for hydrophobic pharmaceutical compounds are employed. Liposomes and emulsions are examples of delivery vehicles or

carriers useful herein. In certain embodiments, organic solvents such as N-methylpyrrolidone are also employed. In additional embodiments, the compounds described herein are delivered using a sustained release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained release materials are useful herein. In some embodiments, sustained release capsules release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization are employed.

In certain embodiments, the formulations described herein comprise one or more antioxidants, metal chelating agents, thiol containing compounds and/or other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

In some embodiments, the concentration of one or more compounds selected from compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) provided in the pharmaceutical compositions is greater than 90%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25%, 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25%, 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 1.25% , 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v, or v/v. In another embodiment, the amount of a compound selected from compounds of (I), (II), (IA)-(IE), or (IA-1)-(IE-1) in the pharmaceutical compositions is an amount between about any two of the values recited in the preceding sentence, for example, between about 2-70 w/w%, 3.5-80 w/w%, 1-30 w/w%, etc.

In some embodiments, the concentration of one or more compounds selected from

compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) provided in the pharmaceutical compositions of the present disclosure is in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40 %, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12%, approximately 1% to approximately 10% w/w, w/v or v/v.

In some embodiments, the amount the one or more compounds selected from compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) provided in the pharmaceutical compositions of the present disclosure is equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g, or 0.0001 g.

In some embodiments, the amount of the one or more compounds selected from compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) provided in the pharmaceutical compositions of the present disclosure is in the range of 0.0001-10 g, 0.0005-9 g, 0.001-8 g, 0.005-7 g, 0.01-6 g, 0.05-5 g, 0.1-4 g, 0.5-4 g, or 1-3 g.

Packaging materials for use in packaging pharmaceutical compositions described herein include those found in, *e.g.*, U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. For example, the container(s) includes one or more compounds described herein,

optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprise a compound with an identifying description or label or instructions relating to its use in the methods described herein.

For example, a kit typically includes one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included. A label is optionally on or associated with the container. For example, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself, a label is associated with a container when it is present within a receptacle or carrier that also holds the container, *e.g.*, as a package insert. In addition, a label is used to indicate that the contents are to be used for a specific therapeutic application. In addition, the label indicates directions for use of the contents, such as in the methods described herein. In certain embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack for example contains metal or plastic foil, such as a blister pack. Alternatively, the pack or dispenser device is accompanied by instructions for administration, or the pack or dispenser is accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In some embodiments, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

As mentioned above, the compounds and compositions of the disclosure will find utility in a broad range of diseases and conditions mediated by protein kinases, including diseases and conditions mediated by kinase. Such diseases may include by way of example and not limitation, cancers such as lung cancer, NSCLC (non small cell lung cancer), oat-cell

cancer, bone cancer, pancreatic cancer, skin cancer, dermatofibrosarcoma protuberans, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, colon-rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (*e.g.*, uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, hepatocellular cancer, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (*e.g.*, cancer of the thyroid, pancreas, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer (particularly hormone-refractory), chronic or acute leukemia, solid tumors of childhood, hypereosinophilia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (*e.g.*, renal cell carcinoma, carcinoma of the renal pelvis), pediatric malignancy, neoplasms of the central nervous system (*e.g.*, primary CNS lymphoma, spinal axis tumors, medulloblastoma, brain stem gliomas or pituitary adenomas), Barrett's esophagus (pre-malignant syndrome), neoplastic cutaneous disease, psoriasis, mycoses fungoides, and benign prostatic hypertrophy, diabetes related diseases such as diabetic retinopathy, retinal ischemia, and retinal neovascularization, hepatic cirrhosis, angiogenesis, cardiovascular disease such as atherosclerosis, immunological disease such as autoimmune disease and renal disease.

In some embodiments, a pharmaceutical composition has a compound described above and a pharmaceutically acceptable carrier including, for example, any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

In one embodiment, a pharmaceutical composition comprising the compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) and a therapeutic agent is disclosed. In some embodiments, the compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) or the pharmaceutical composition comprising the compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) for use in treating a disease associated with mutations in KRAS is also disclosed.

A method of treating a disease associated with G12D, G12V, G12C, G12S, G12A, G12R, Q61H, and/or G13D mutation in KRAS, and/or wild-type KRAS mutations,

comprising: administering the compounds of Formula (I), (II), (IA)-(IE), (IA-1)-(IE-1), (IA-2): (IA-3), (II), (III), (III-1), (III-1A), (III-1B), (III-1C)), (IIIA)-(IIIC), (IV) or (IVA) or the pharmaceutical composition to a subject in need thereof. The subject is an animal. In some embodiments, the subject is a human. In some embodiments, the disease associated with mutations in KRAS is a cancer. In some embodiments, the cancer is pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC), colorectal cancer, endometrial endometrioid adenocarcinoma, rectal adenocarcinoma, gastric cancer, or lung cancer. In some embodiments, the cancer is a pancreatic cancer. In some embodiments, the cancer is a pancreatic ductal adenocarcinoma (PDAC). In some embodiments, the cancer is a colorectal cancer. In some embodiments, the cancer is an endometrial endometrioid adenocarcinoma. In some embodiments, the cancer is a rectal adenocarcinoma. In some embodiments, the cancer is a gastric cancer. In some embodiments, the cancer is a lung cancer.

IV. Methods of Preparation

Preparation methods for the above compounds and compositions are described herein below and/or known in the art.

It will be appreciated by those skilled in the art that in the process described herein the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (for example, t-butyldimethylsilyl, t-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for amino, amidino and guanidino include t-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include —C(O)—R″ (where R″ is alkyl, aryl or arylalkyl), p-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or arylalkyl esters. Protecting groups may be added or removed in accordance with standard techniques, which are known to one skilled in the art and as described herein. The use of protecting groups is described in detail in Green, T. W. and P. G. M. Wutz, Protective Groups in Organic Synthesis (1999), 3rd Ed., Wiley. As one of skill in the art would appreciate, the protecting group may also be a polymer resin such as a Wang resin, Rink resin or a 2-chlorotrityl-chloride resin.

It will also be appreciated by those skilled in the art, although such protected derivatives of compounds of this invention may not possess pharmacological activity as such, they may be administered to a mammal and thereafter metabolized in the body to form compounds of the invention which are pharmacologically active. Such derivatives may

therefore be described as "prodrugs". All prodrugs of compounds of this invention are included within the scope of the invention. In some embodiments, for example, a phosphate bearing compound of (I), (II), (IA)-(IE), or (IA-1)-(IE-1) is a prodrug and the structure of such example is described in the disclosure.

Furthermore, all compounds of the invention which exist in free base or acid form can be converted to their pharmaceutically acceptable salts by treatment with the appropriate inorganic or organic base or acid by methods known to one skilled in the art. Salts of the compounds of the invention can be converted to their free base or acid form by standard techniques.

EXAMPLES

The following section describes abbreviations used in the examples and includes examples for making intermediate compounds I1-I22 (Examples 1-21) and examples for making compounds 1-78 (Examples 22-52).

Abbreviations:

Sat.: Saturated

Aq.: Aqueous

DIPEA: N,N-Diisopropylethylamine

MeCN: Acetonitrile

TFA: 2,2,2-Trifluoroacetic acid

DCM: Dichloromethane

Pd/C: Palladium on activated carbon

DMF: N,N-Dimethylformamide

MeOH: Methanol

Quant.: Quantitative

K_2CO_3: Potassium Carbonate

Cs_2CO_3: Cesium Carbonate

Na_2SO_4: Sodium Sulfate

$MgSO_4$: Magnesium Sulfate

LCMS: Liquid chromatography mass spectrometry

EtOAc: Ethyl acetate

THF: Tetrahydrofuran

DMSO: Dimethyl sulfoxide

HPLC: High-performance liquid chromatography

n-BuLi: n-butyl lithium

MTBE: Methyl tert-butyl ether

Bop-Cl: Bis(2-oxo-3-oxazolidinyl)phosphonic chloride

LiHMDS: Lithium bis(trimethylsilyl)amide

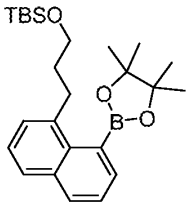
DMAP: 4-Dimethylaminopyridine

TBS: tert-Butyldimethylsilyl

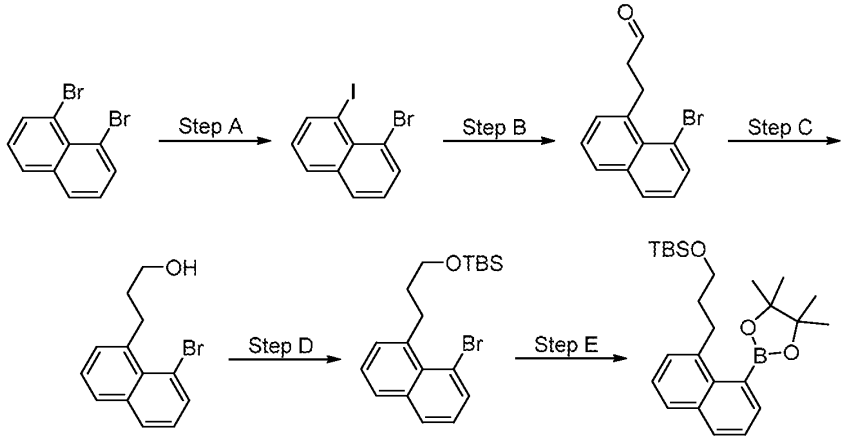
Syntheses of intermediate compounds

Example 1

Intermediate I1



tert-butyldimethyl(3-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)silane



Step A. 1-bromo-8-iodonaphthalene. To a 500 mL three-necked round-bottom flask equipped with a magnetic stir bar was added 1,8- dibromonaphthalene 1 (20.0 g, 69.9 mmol) followed by the addition of THF (160 mL). The flask was evacuated and backfilled with nitrogen three times. The solution was cooled to -70 °C. n-BuLi (2.5 M, 28.0 mL) was added dropwise. After 15 min, a solution of molecular iodine (17.8 g, 69.9 mmol) in THF (160 mL) was added dropwise. The mixture was warmed to 25 °C under an atmosphere of nitrogen for

1.5 h in the dark. The mixture was quenched by slow addition of saturated aqueous ammonium chloride (300 mL), transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (100 mL x 3). The organic layers were combined and washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. To the crude product was added MTBE (50 mL) and this slurry was stirred at 25 °C for 10 min. The suspension was filtered and the filter cake was washed with MTBE (10 mL). The solid was concentrated under vacuum to give 1-bromo-8-iodonaphthalene (14.0 g, 60% yield) as a light yellow solid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 8.40 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.99 - 7.89 (m, 1H), 7.85 - 7.73 (m, 2H), 7.26 - 7.21 (m, 1H), 7.05 (t, *J* = 8.0 Hz, 1H).

Step B. 3-(8-bromonaphthalen-1-yl)propanal. To a 500 mL three-necked round-bottom equipped with a magnetic stir bar was added 1-bromo-8-iodo-naphthalene (14.0 g, 42.0 mmol), $Pd(OAc)_2$ (0.50 g, 2.20 mmol), $NaHCO_3$ (8.83 g, 105 mmol), and tetrabutylammonium chloride (11.7 g, 42.1 mmol) followed by the addition of DMF (200 mL). The flask was purged with nitrogen three times and allyl alcohol (14.3 mL, 210 mmol) was added to the mixture at 25 °C. The mixture was stirred at 40 °C under an atmosphere of nitrogen for 20 h. The mixture was quenched by slow addition of H_2O (150 mL), transferred to a separatory funnel and the aqueous layer extracted with ethyl acetate (300 mL x 3). The combined organic layers were washed with brine (400 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (0-4% EtOAc in petroleum ether) to give 3-(8-bromonaphthalen-1-yl)propanal (3.70 g, 33% yield) as a yellow oil.

^{1}H NMR: (400 MHz, $CDCl_3$) δ = 9.90 (s, 1H), 7.86 (ddd, *J* = 1.2, 8.0, 15.6 Hz, 2H), 7.78 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.47 - 7.38 (m, 2H), 7.31 - 7.25 (m, 1H), 3.92 - 3.87 (m, 2H), 2.98 - 2.93 (m, 2H).

Step C. 3-(8-bromonaphthalen-1-yl)propan-1-ol. To a 250 mL three-necked round-bottom flask equipped with a magnetic stir bar was added 3-(8-bromonaphthalen-1-yl)propanal (3.60 g, 13.7 mmol) followed by the addition of EtOH (30 mL). The solution was cooled to 0°C. The flask was purged with nitrogen three times and $NaBH_4$ (1.12 g, 29.6 mmol) was added in batches to the solution. The mixture was stirred for 0.5 h at 0 °C and quenched by slow addition of saturated aqueous ammonium chloride (30 mL). The mixture was transferred to a separatory funnel and the aqueous layer extracted with ethyl acetate (30 mL x 3). The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (15% EtOAc

in petroleum ether) to give 3-(8-bromonaphthalen-1-yl)propan-1-ol (2.80 g, 77% yield) as a yellow oil.

^{1}H NMR: (400 MHz, MeOD-d_4) δ = 7.89 - 7.82 (m, 2H), 7.78 (dd, J = 1.6, 8.0 Hz, 1H), 7.45 - 7.35 (m, 2H), 7.25 (t, J = 8.0 Hz, 1H), 3.65 (q, J = 6.4 Hz, 2H), 3.61 - 3.52 (m, 1H), 3.15 (dd, J = 7.2, 8.8 Hz, 1H), 1.98 - 1.91 (m, 2H).

Step D. (3-(8-bromonaphthalen-1-yl)propoxy)(tert-butyl)dimethylsilane. To a 250 mL three-necked round-bottom flask equipped with a magnetic stir bar was added 3-(8-bromonaphthalen-1-yl)propan-1-ol (2.80 g, 10.6 mmol) and imidazole (1.44 g, 21.1 mmol) followed by the addition of THF (30 mL). The solution was cooled to 0 °C and tert-butyldimethylsilyl chloride (1.91 g, 12.7 mmol) in THF (30 mL) was added dropwise. The mixture was warmed to 20 °C and stirred for 1 h. The mixture was quenched by slow addition of H_2O (30 mL). The mixture was transferred to a separatory funnel and the aqueous layer extracted with ethyl acetate (40 mL x 3). The combined organics were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (100% petroleum ether) to give (3-(8-bromonaphthalen-1-yl)propoxy)(tert-butyl)dimethylsilane (3.20 g, 80% yield) as a colorless oil.

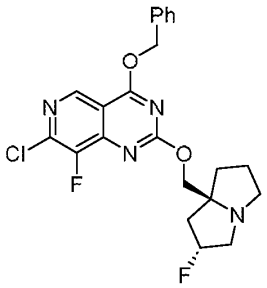
^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.87 - 7.79 (m, 2H), 7.74 - 7.71 (m, 1H), 7.43 - 7.38 (m, 2H), 7.23 (t, J = 8.0 Hz, 1H), 3.74 - 3.72 (m, 2H), 3.62 - 3.53 (m, 2H), 2.00 - 1.96 (m, 2H), 0.94 (s, 9H), 0.09 (s, 6H).

Step E. tert-butyldimethyl(3-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)silane. To a 40 mL vial equipped with a magnetic stir bar was added (3-(8-bromonaphthalen-1-yl)propoxy)(tert-butyl)dimethylsilane (3.20 g, 8.44 mmol) and 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaborolane (3.22 g, 12.7 mmol) followed by the addition of dioxane (30 mL). [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.62 g, 0.84 mmol) and potassium acetate (1.66 g, 16.9 mmol) were added into the mixture. The mixture was sparged with nitrogen for 2 min. The mixture was heated to 90 °C and stirred for 18 h. The mixture was quenched by addition of H_2O (30 mL), the mixture transferred to a separatory funnel and the aqueous layer extracted with ethyl acetate (30 mL x 3). The combined organics were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (2% EtOAc in petroleum ether) to give tert-butyldimethyl(3-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)silane (1.10 g, 30% yield) as a colorless oil. LCMS (MM-ES+APCI, Pos): m/z

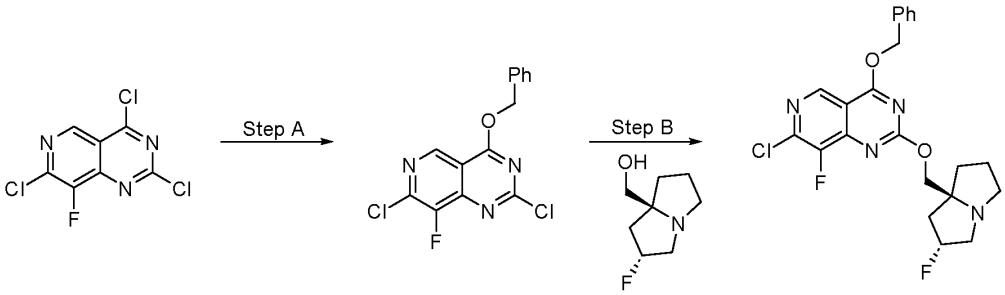
427.2 (M+H).

Example 2

Intermediate I2



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



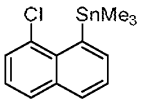
Step A. 4-(benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidine. To a solution of 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (3.00 g, 11.9 mmol) and 1,4-dioxane (30 mL) in a 250 mL round-bottomed flask was added benzyl alcohol (1.85 mL, 17.8 mmol) and N,N-diisopropylethylamine (6.20 mL, 35.7 mmol). The mixture was stirred at 85 °C for 1 h. The reaction mixture was concentrated to dryness. The residue was purified via silica gel chromatography (0 - 100 % EtOAc in hexanes) to give 4-(benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidine (1.80 g, 47 %) as a white crystalline solid. LCMS (MM-ES+APCI, Pos): m/z 324.0 (M+H).

Step B. 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidine (1.80 g, 5.55 mmol) in THF (18.5 mL) in a 100 mL round-bottomed flask was added ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (1.06 g, 6.66 mmol) and N,N-diisopropylethylamine (1.93 mL, 11.1 mmol). The mixture was stirred at 50 °C for 21 h. The reaction mixture was concentrated to dryness and

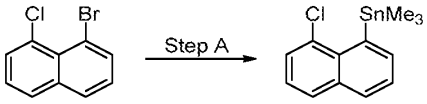
partitioned between H_2O (20 mL) and DCM (20 mL). The layers were separated and the aqueous phase was extracted with DCM (2 X 10 mL). The combined organic extracts were concentrated to dryness and purified via silica gel chromatography (0 – 20 % MeOH in CH_2Cl_2) to give 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (1.87 g, 75%) as an orange solid. LCMS (MM-ES+APCI, Pos): m/z 447.2 (M+H).

Example 3

Intermediate I3



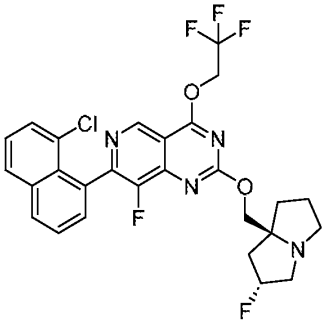
(8-chloronaphthalen-1-yl)trimethylstannane



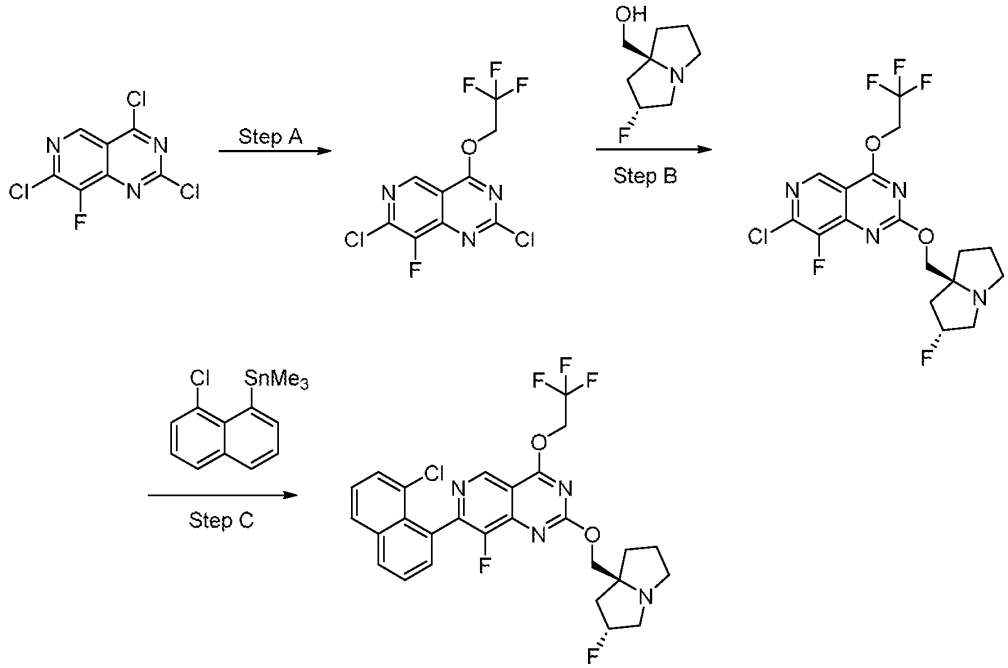
Step A. (8-chloronaphthalen-1-yl)trimethylstannane. To a solution of 1-bromo-8-chloronaphthalene (15 g, 62 mmol) in toluene (200 mL) was added $Pd(PPh_3)_4$ (7.2 g, 6.2 mmol) and hexamethylditin (25 mL, 122 mmol). The flask was evacuated and backfilled with nitrogen three times. The mixture was heated to 110 °C for 16 h and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (100% petroleum ether) to give (8-chloronaphthalen-1-yl)trimethylstannane (19 g, 94% yield) as a colorless oil. ^1H NMR: (400 MHz, $CDCl_3$) δ 7.88 - 7.83 (m, 2H), 7.81 - 7.77 (m, 1H), 7.62 (dd, J = 1.2, 7.2 Hz, 1H), 7.48 (dd, J = 6.8, 8.0 Hz, 1H), 7.41 - 7.36 (m, 1H), 0.43 (s, 9H).

Example 4

Intermediate I4



7-(8-chloronaphthalen-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



Step A. 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. A flask containing 2,4,7-trichloro-8-fluoropyrido[4,3-d]pyrimidine (12 g, 48 mmol) in DCM (120 mL) was evacuated and backfilled with nitrogen three times. The mixture was cooled to 0 °C and a solution of 2,2,2-trifluoroethanol (3.2 mL, 44 mmol) and DIPEA (12 mL, 71 mmol) in DCM (40 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h and diluted with H_2O (150 mL). The aqueous layer was extracted with DCM (150 mL × 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10 – 15% EtOAc in petroleum ether) to give 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (14.2 g, 86% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 315.9 (M+H).

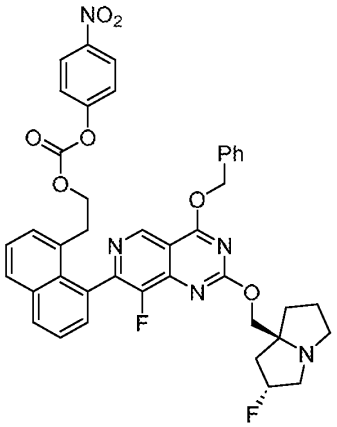
Step B. 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. To a solution of 2,7-dichloro-8-fluoro-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (13 g, 41 mmol) in THF (160 mL) was added (2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (7.50 g, 47.1 mmol)

and DIPEA (15 mL, 83 mmol). The mixture was stirred at rt for 16 h and diluted with H_2O (200 mL). The mixture was extracted with ethyl acetate (200 mL × 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure. The residue was purified by silica gel chromatography (10 – 100% EtOAc in petroleum ether) to give 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (16.2 g, 78% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 439.0 (M+H).

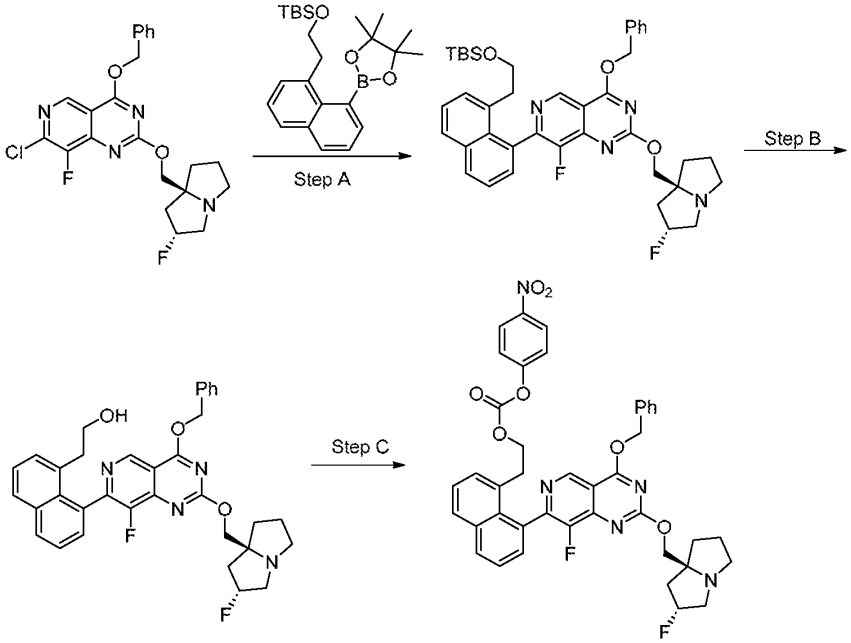
Step C. 7-(8-chloronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. To a solution of 7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (9.0 g, 19 mmol) and (8-chloronaphthalen-1-yl)trimethylstannane, Intermediate I3 (12 g, 38 mmol), in toluene (140 mL) was added $Pd(dppf)Cl_2$ (1.4 g, 1.9 mmol), CuI (1.4 g, 7.1 mmol) and BINAP (2.7 g, 4.4 mmol). The flask was evacuated and backfilled with nitrogen three times and heated to 90 °C for 16 h. The suspension was filtered through a pad of Celite and the pad washed with ethyl acetate (200 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (50 – 75% EtOAc in petroleum ether). The residue was purified by preparative HPLC (20 - 50% MeCN in 0.1% aqueous formic acid). Fractions containing the product were lyophilized to obtain 7-(8-chloronaphthalen-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 (4.5 g, 40% yield) was obtained as a white solid. LCMS (MM-ES+APCI, Pos): m/z 565.2 (M+H).

Example 5

Intermediate I5



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



Step A. 4-(benzyloxy)-7-(8-(2-((tert-butyldimethylsilyl)oxy)ethyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (2.00 g, 4.16 mmol) and tert-butyldimethyl(2-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-

1-yl)ethoxy)silane (2.2 g, 5.2 mmol) in 1,4-dioxane (20 mL) and H_2O (2 mL) was added Cs_2CO_3 (3.4 g, 10 mmol) and mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.38 g, 0.52 mmol). The solution was sparged with nitrogen for 5 min. The reaction was heated to 90 °C for 1 h and diluted with H_2O (80 mL). The mixture was extracted with ethyl acetate (40 mL × 3). The combined organic layers were washed with brine (40 mL × 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (17-33% EtOAc in petroleum ether) to give 4-(benzyloxy)-7-(8-(2-((tert-butyldimethylsilyl)oxy)ethyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (2.0 g, 51% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 697.3 (M+H).

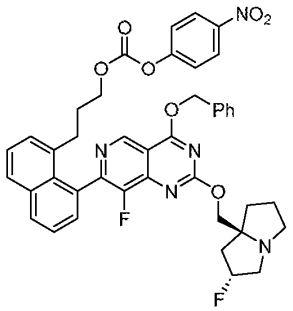
Step B. 2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethan-1-ol. To a solution of 4-(benzyloxy)-7-(8-(2-((tert-butyldimethylsilyl)oxy)ethyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (2.0 g, 2.7 mmol) in DCM (20 mL) was added TFA (1.0 mL, 14 mmol). The solution was cooled to 0 °C and stirred at this temperature for 1 h. The reaction was quenched by the addition of saturated $NaHCO_3$ (5 mL). The mixture was diluted with H_2O (10 mL) and extracted with DCM (6 mL × 3). The organic phase was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-10% MeOH in DCM) to obtain 2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethan-1-ol (1.3 g, 80% yield) was as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 583.2 (M+H).

Step C. 2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethyl (4-nitrophenyl) carbonate. To a solution of 2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethan-1-ol (0.400 g, 0.654 mmol) in THF (5 mL) at 0 °C was added triethylamine (0.28 mL 1.98 mmol) followed by a solution of 4-nitrophenyl chloroformate (0.26 g, 1.3 mmol) in THF (2 mL). The mixture was warmed to rt and stirred at this temperature for 16 h. The mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-

yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethyl (4-nitrophenyl) carbonate (0.30 g, 59% yield) as a light yellow solid. LCMS (MM-ES+APCI, Pos): m/z 748.1 (M+H).

Example 6

Intermediate I6

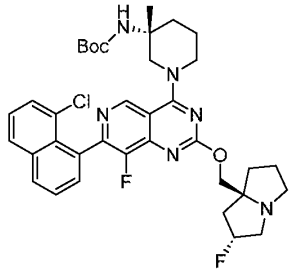


3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (4-nitrophenyl) carbonate

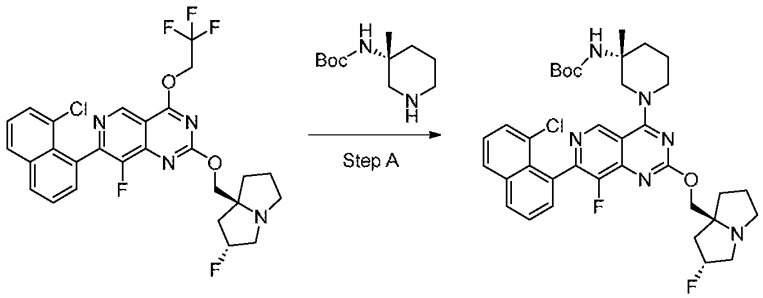
Intermediate I6 was synthesized with intermediate I1, following the general procedure of intermediate I5. LCMS (MM-ES+APCI, Pos): m/z 762.3 (M+H).

Example 7

Intermediate I7



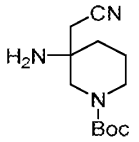
tert-butyl ((R)-1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate



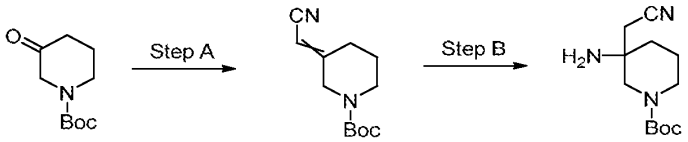
Step A. tert-butyl ((R)-1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate. A solution of tert-butyl (R)-(3-methylpiperidin-3-yl)carbamate (0.045 g, 0.21 mmol), 7-(8-chloronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine, Intermediate I4 (0.10 g, 0.18 mmol), and DIPEA (0.15 mL, 0.88 mmol) in MeCN (1.0 mL) was stirred at 80 °C for 16 h. The solution was concentrated under reduced pressure to obtain tert-butyl ((R)-1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate (0.12 g), which was taken onto the next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 679.3 (M+H).

Example 8

Intermediate I8



tert-butyl 3-amino-3-(cyanomethyl)piperidine-1-carboxylate

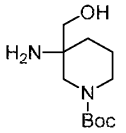


Step A. tert-butyl 3-(cyanomethylene)piperidine-1-carboxylate. To a solution of tert-butyl 3-oxopiperidine-1-carboxylate (5.0 g, 25 mmol) and diethyl (cyanomethyl)phosphonate (4.1 mL, 25.09 mmol) in THF (50 mL) was added K_2CO_3 (4.2 g, 30 mmol). The reaction was stirred at 70°C for 12 h and then it was diluted with H_2O (100 mL). The mixture was extracted with EtOAc (3 X 100 mL). The combined organic layers were washed with brine (5 X 100mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-20% EtOAc in petroleum ether) to give tert-butyl 3-(cyanomethylene)piperidine-1-carboxylate (6.0 g) which was taken onto the next step without further purification. ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 5.24 (br s, 1H), 3.97 (s, 2H), 3.50 (br d, J = 5.6 Hz, 2H), 2.70 - 2.55 (m, 2H), 1.74 (br d, J = 5.6 Hz, 2H), 1.45 (s, 9H).

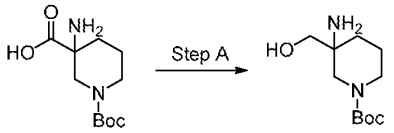
Step B. tert-butyl 3-amino-3-(cyanomethyl)piperidine-1-carboxylate. To a solution of tert-butyl 3-(cyanomethylene)piperidine-1-carboxylate (6.0 g, 27 mmol) in MeOH (12 mL) was added NH3·H2O (30%; 33 mL, 260 mmol). The reaction was heated to 90 °C for 4 h and and concentrated under reduced pressure. The residue was diluted with H_2O (100 mL) and extracted with ethyl acetate (120 mL x 3). The combined organic phase was washed with brine (100 mL x 3), dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% MeOH in DCM) to give tert-butyl 3-amino-3-(cyanomethyl)piperidine-1-carboxylate (1.3 g, 20% yield) as a colorless oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 3.59 - 3.35 (m, 2H), 3.34 - 3.10 (m, 2H), 2.46 (br s, 2H), 1.81 - 1.66 (m, 2H), 1.57 (br s, 2H), 1.47 (s, 9H).

Example 9

Intermediate I9



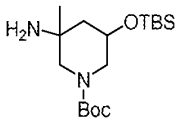
tert-butyl 3-amino-3-(hydroxymethyl)piperidine-1-carboxylate



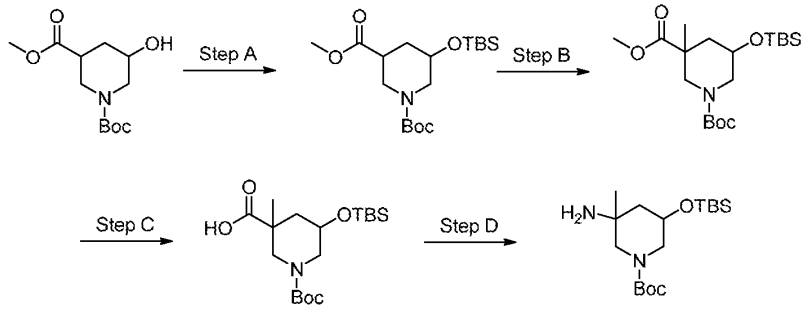
Step A. tert-butyl 3-amino-3-(hydroxymethyl)piperidine-1-carboxylate. To a solution of 3-amino-1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid (4.5 g, 18.42 mmol) in THF (45 mL) at -10 °C was added BH3·THF (1.0 M; 55 mL, 55 mmol). The solution was warmed to rt and stirred at this temperature for 12 h. The suspension was cooled to 0 °C and slowly quenched with MeOH (100 mL). The mixture was stirred at 0 °C for 2 h, warmed to rt and stirred at rt for 22 h. The mixture was treated with diethylamine (340 mL) and heated at 50 °C for 3 h. The suspension was concentrated under reduced pressure and the residue was solubilized with MeOH (5 mL). The solution was slowly added into 3:1 mixture of brine/1 N NaOH (1000 mL) and extracted with 15% IPA in DCM (500 mL). The organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10-20% MeOH in DCM) to give tert-butyl 3-amino-3-(hydroxymethyl)piperidine-1-carboxylate (3.3 g, 78% yield) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 3.97 - 2.72 (m, 6H), 1.62 (br d, J = 10.2 Hz, 4H), 1.49 (s, 9H).

Example 10

Intermediate I10



tert-butyl 3-amino-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1-carboxylate



Step A. 1-(tert-butyl) 3-methyl 5-((tert-butyldimethylsilyl)oxy)piperidine-1,3-dicarboxylate. To a solution of 1-(tert-butyl) 3-methyl 5-hydroxypiperidine-1,3-dicarboxylate (1.5 g, 5.78 mmol) in DCM (30 mL) was added tert-butyldimethylsilyl chloride (1.3 g, 8.7 mmol), DMAP (0.14 g, 1.2 mmol) and 1H-imidazole (0.98 g, 14 mmol). The mixture was stirred at rt for 16 h and diluted with saturated aqueous NH_4Cl (30 mL). The mixture was extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-15% EtOAc in petroleum ether) to give 1-(tert-butyl) 3-methyl 5-((tert-butyldimethylsilyl)oxy)piperidine-1,3-dicarboxylate (3.2 g, 67% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 318.1 (M+H, -tBu).

Step B. 1-(tert-butyl) 3-methyl 5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1,3-dicarboxylate. To a solution of 1-(tert-butyl) 3-methyl 5-((tert-butyldimethylsilyl)oxy)piperidine-1,3-dicarboxylate (0.50 g, 1.34 mmol) in THF (10 mL) at -65 °C was added LiHMDS (1.0 M in THF; 6.7 mL, 0.67 mmol) dropwise over the course of 10 min, followed by addition of iodomethane (0.42 mL, 6.69 mmol) in THF (2 mL). The reaction was warmed to rt and stirred at this temperature for 15 min. The mixture was quenched by slow addition of saturated aqueous NH_4Cl (20 mL). The mixture extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 - 20% EtOAc in petroleum ether) to give 1-(tert-butyl) 3-methyl 5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1,3-dicarboxylate (0.51 g, 49% yield) as yellow oil. LCMS (MM-ES+APCI, Pos): m/z 410.2 (M+Na).

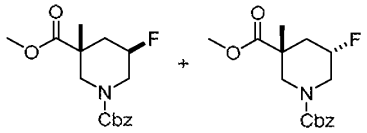
Step C. 1-(tert-butoxycarbonyl)-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-3-carboxylic acid. To a solution of 1-(tert-butyl) 3-methyl 5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1,3-dicarboxylate (1.1 g, 2.8 mmol) in THF (2 mL), H_2O (2 mL) and MeOH

(2 mL) was added LiOH (0.20 g, 8.4 mmol). The mixture was stirred at rt for 2 h and concentrated under redued pressure to obtain 1-(tert-butoxycarbonyl)-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-3-carboxylic acid (0.52 g, 49% yield), which was taken onto the next step without further purification.

Step D. tert-butyl 3-amino-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1-carboxylate. To a solution of 1-(tert-butoxycarbonyl)-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-3-carboxylic acid (0.50 g, 1.3 mmol) in THF (20 mL) was added DPPA (1.2 mL, 5.4 mmol) and DIPEA (3.26 mL, 19 mmol). The mixture was stirred at 80 °C for 2 h, and KOH (1.5 g, 27 mmol) in H_2O (8 mL) was added. The mixture was stirred at rt for 2 h and followed by dilution with H_2O (2 mL). The mixture was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (55% – 85% acetonitrile in 0.05% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain tert-butyl 3-amino-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1-carboxylate (0.14 g, 30% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 345.2 (M+H).

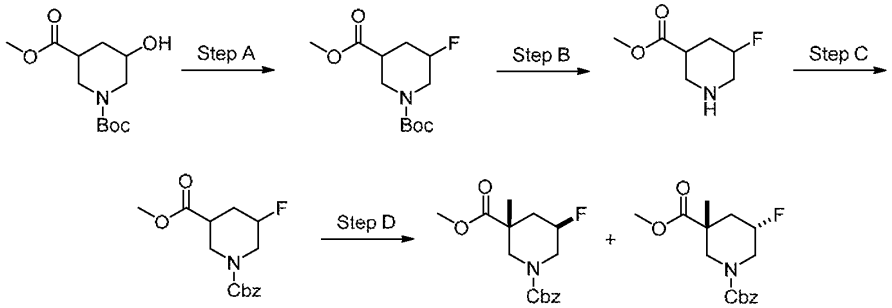
Example 11

Intermediates I11 and I12



1-benzyl 3-methyl (rel-3R,5R)-5-fluoro-3-methylpiperidine-1,3-dicarboxylate

1-benzyl 3-methyl (rel-3R,5S)-5-fluoro-3-methylpiperidine-1,3-dicarboxylate



Step A. 1-(tert-butyl) 3-methyl 5-fluoropiperidine-1,3-dicarboxylate.

To a solution of 1-(tert-butyl) 3-methyl 5-hydroxypiperidine-1,3-dicarboxylate (100 g, 390 mmol) in DCM (1000 mL) at -78 °C was added DAST (61 mL, 460 mmol) dropwise. The reaction was stirred at -78 °C for 2 h and warmed to rt and stirred for an additional 3 h. The mixture was quenched by slow addition of aqueous $NaHCO_3$ (500 mL) at 0 °C. The mixture was extracted with DCM (500 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-20% EtOAc in petroleum ether) to give 1-(tert-butyl) 3-methyl 5-fluoropiperidine-1,3-dicarboxylate (47 g, 47% yield) as a yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.81 - 4.37 (m, 1H), 4.33 - 4.18 (m, 1H), 3.72 (br d, J = 3.2 Hz, 3H), 3.14 - 2.69 (m, 2H), 2.64 - 2.23 (m, 2H), 1.89 - 1.73 (m, 1H), 1.67 - 1.58 (m, 1H), 1.47 (d, J = 3.2 Hz, 9H).

Step B. methyl 5-fluoropiperidine-3-carboxylate. A solution of 1-(tert-butyl) 3-methyl 5-fluoropiperidine-1,3-dicarboxylate (47 g, 180 mmol) in HCl in dioxane (4.0 M; 470 mL, 120 mmol) was stirred at rt for 1 h. The solution was concentrated under reduced pressure to give methyl 5-fluoropiperidine-3-carboxylate (35 g, 98% yield) as a yellow oil, which was taken onto the next step without further purification.

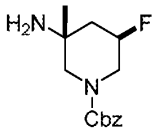
Step C. 1-benzyl 3-methyl 5-fluoropiperidine-1,3-dicarboxylate. To a solution of methyl 5-fluoropiperidine-3-carboxylate (35 g, 180 mmol) and NaHCO3 (150 g, 1800 mmol) in THF (300 mL) and H_2O (300 mL) at 0 °C was added benzyl chloroformate (28 mL, 190 mmol). The reaction was stirred at rt for 1 h and diluted with H_2O (1000 mL). The mixture was extracted with ethyl acetate (500 mL x 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-20% EtOAc in petroleum ether) to give 1-benzyl 3-methyl 5-fluoropiperidine-1,3-dicarboxylate (46 g, 88% yield) as a yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.39 - 7.35 (m, 5H), 5.15 (br d, J = 4.4 Hz, 2H), 4.63 - 4.23 (m, 2H), 3.74 - 3.66 (m, 3H), 3.18 - 2.88 (m, 2H), 2.69 - 2.22 (m, 2H), 2.05 (s, 1H), 1.94 - 1.73 (m, 1H).

Step D. 1-benzyl 3-methyl (rel-3R,5R)-5-fluoro-3-methylpiperidine-1,3-dicarboxylate and 1-benzyl 3-methyl (rel-3R,5S)-5-fluoro-3-methylpiperidine-1,3-dicarboxylate. To a solution of 1-benzyl 3-methyl 5-fluoropiperidine-1,3-dicarboxylate (46 g, 155 mmol) in THF (500 mL) at -78 °C under an atmosphere of nitrogen was added LiHMDS (1.0 M in THF; 230 mL, 230 mmol) dropwise. The mixture was stirred at -78 °C for 1 h and then MeI (29 mL, 470 mmol) was added dropwise. The reaction was warmed to rt and stirred for an additional 2 h at

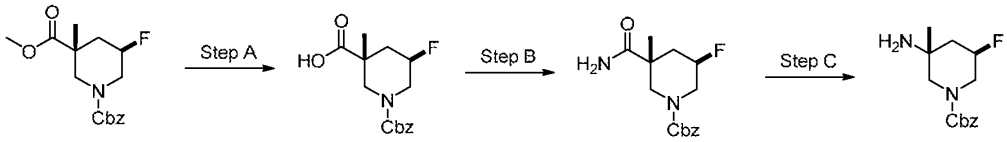
rt. The mixture was quenched by slow addition of saturated aqueous NH_4Cl (1000 mL) at 0 °C. The aqueous phase was extracted with ethyl acetate (800 mL x 3). The combined organic layers were washed with brine (1000 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-20% EtOAc in petroleum ether1) to give 1-benzyl 3-methyl (rel-3R,5R)-5-fluoro-3-methylpiperidine-1,3-dicarboxylate (27 g, 56% yield) as a yellow oil and 1-benzyl 3-methyl (rel-3R,5S)-5-fluoro-3-methylpiperidine-1,3-dicarboxylate (15 g, 31% yield) as a yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.41 - 7.34 (m, 5H), 5.19 - 5.12 (m, 2H), 4.71 (s, 1H), 4.10 - 3.89 (m, 2H), 3.70 - 3.53 (m, 3H), 3.47 - 3.03 (m, 2H), 2.52 - 2.30 (m, 1H), 1.73 - 1.64 (m, 1H), 1.28 (br d, J = 7.2 Hz, 3H). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.43 - 7.30 (m, 5H), 5.27 - 5.01 (m, 2H), 4.86 - 4.58 (m, 1H), 4.09 - 3.95 (m, 1H), 3.83 - 3.41 (m, 5H), 3.22 (br d, J = 13.2 Hz, 1H), 2.47 - 2.27 (m, 1H), 1.91 - 1.73 (m, 1H), 1.25 - 1.11 (m, 3H).

Example 12

Intermediate I13



benzyl (rel-3R,5R)-3-amino-5-fluoro-3-methylpiperidine-1-carboxylate



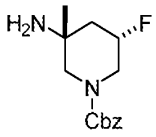
Step A. (rel-3R,5R)-1-((benzyloxy)carbonyl)-5-fluoro-3-methylpiperidine-3-carboxylic acid. To a solution of 1-benzyl 3-methyl (rel-3R,5R)-5-fluoro-3-methylpiperidine-1,3-dicarboxylate (27 g, 87 mmol) in MeOH (100 mL), THF (100 mL) and H_2O (100 mL) was added LiOH (6.3 g, 260 mmol). The reaction was stirred at 25 °C for 1 h after which the pH of mixture was adjusted to 3 with HCl (1.0 M). The mixture was extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give (rel-3R,5R)-1-((benzyloxy)carbonyl)-5-fluoro-3-methylpiperidine-3-carboxylic acid (27g, 87% yield) as a yellow oil. The product was used into the next step without further purification. LCMS (MM-ES+APCI, Neg): m/z 294.2 (M-H).

Step B. benzyl (rel-3R,5R)-3-carbamoyl-5-fluoro-3-methylpiperidine-1-carboxylate. To a solution of (rel-3R,5R)-1-((benzyloxy)carbonyl)-5-fluoro-3-methylpiperidine-3-carboxylic acid (27 g, 76 mmol), NH_4Cl (40 g, 760 mmol), HATU (57 g, 150 mmol) in DMF (300 mL) was added DIPEA (160 mL, 910 mmol). The mixture was heated to 50 °C for 12 h. The solution was diluted with H_2O (200 mL) and then extracted with ethyl acetate (300 mL x 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-100% EtOAc in petroleum ether) to give benzyl (rel-3R,5R)-3-carbamoyl-5-fluoro-3-methylpiperidine-1-carboxylate (16 g, 55% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 295.1 (M+H).

Step C. benzyl (rel-3R,5R)-3-amino-5-fluoro-3-methylpiperidine-1-carboxylate. To a solution of benzyl (rel-3R,5R)-3-carbamoyl-5-fluoro-3-methylpiperidine-1-carboxylate (16 g, 42 mmol) in MeCN (50 mL) and H_2O (200 mL) at 0 °C was added NaOH (5.0 M; 42 mL, 210 mmol) and NBS (11 g, 63 mmol). The reaction was heated to 80 °C and stirred for 30 min. The mixture was diluted with H_2O (50 mL), and then extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-100% EtOAc in petroleum ether) to give benzyl (rel-3R,5R)-3-amino-5-fluoro-3-methylpiperidine-1-carboxylate (9.0 g, 78% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 267.1 (M+H).

Example 13

Intermediate I14

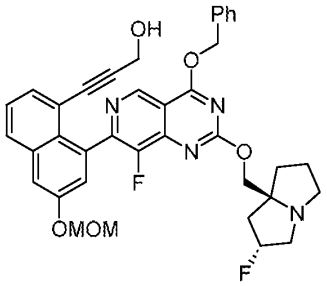


benzyl (rel-3R,5S)-3-amino-5-fluoro-3-methylpiperidine-1-carboxylate

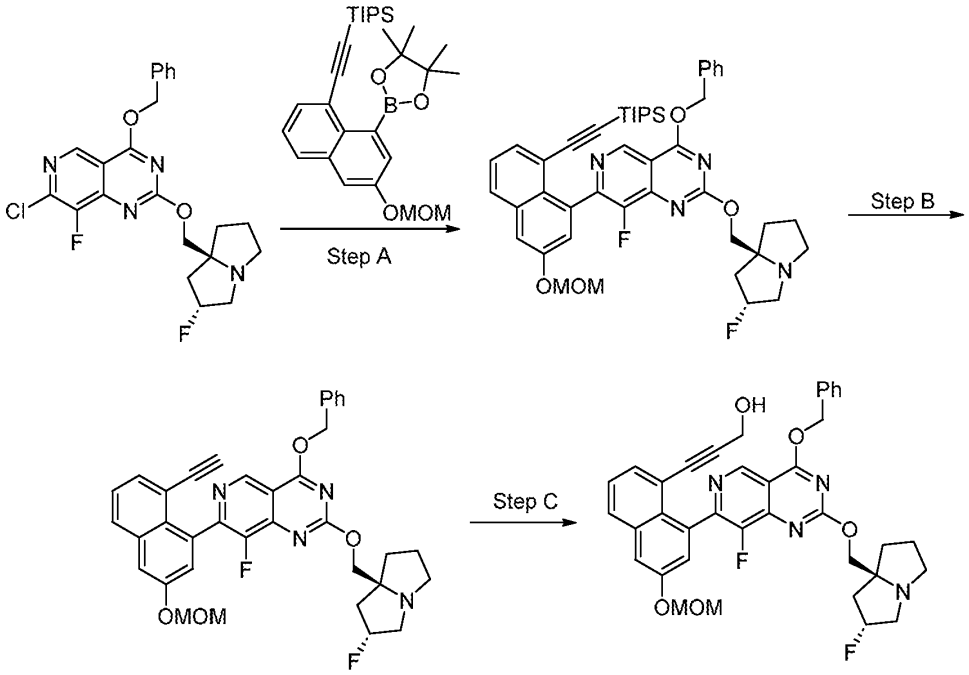
Intermediate I14 was synthesized using intermediate I12, according to the procedure of intermediate I13. LCMS (MM-ES+APCI, Pos): m/z 267.3 (M+H).

Example 14

Intermediate 15



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



Step A. 4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (8.4 g, 17 mmol) and triisopropyl((6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane (10 g, 20 mmol) in 1,4-dioxane (150 mL) and H_2O (30 mL)

was added K_2CO_3 (5.8 g, 42 mmol) and mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium (II) (1.1 g, 1.5 mmol). The flask was evacuated and backfilled with nitrogen three times. The mixture was heated at 90 °C and stirred under an atmosphere of nitrogen for 1 h. The suspension was filtered through a pad of Celite and the filter cake washed with ethyl acetate (400 mL). The combined organics were concentrated under reduced pressure and purified by silica gel chromatography (11-17% EtOAc in petroleum ether) to give 4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidine (13 g, 89% yield) as a yellow gum. LCMS (MM-ES+APCI, Pos): m/z 779.4 (M+H).

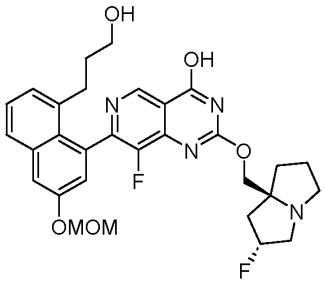
Step B. 4-(benzyloxy)-7-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidine (13 g, 15 mmol) in DMF (130 mL) was added CsF (4.6 g, 30 mmol). The reaction was stirred at rt for 1.5 h. The mixture was diluted with H_2O (500 mL) and extracted with ethyl acetate (150 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (11-100% EtOAc in petroleum ether) to give 4-(benzyloxy)-7-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (6.5 g, 64% yield) as a brown solid. LCMS (MM-ES+APCI, Pos): m/z 623.4 (M+H).

Step C. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol. A solution of 4-(benzyloxy)-7-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (4.2 g, 6.3 mmol) and paraformaldehyde (2.1 g) in THF (252 mL) was purged with nitrogen three times. The solution was cooled to -70 °C, and LiHMDS (1.0 M, 1.4 mL) was added to the mixture and stirred for 2 h. The mixture was warmed to rt and was stirred for an additional 1.5 h. The mixture was quenched by slow addition of H_2O (80 mL) and extracted with ethyl acetate (80 mL x 3). The combined organic layer was washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (50-75% EtOAc in petroleum

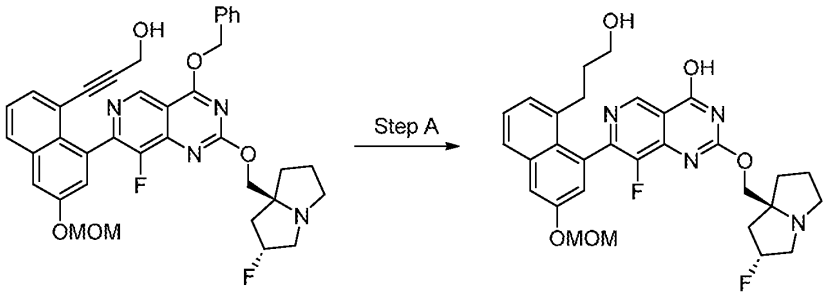
ether) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol (0.77 g, 17% yield) as a yellow gum. LCMS (MM-ES+APCI, Pos): m/z 653.2 (M+H).

Example 15

Intermediate I16



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

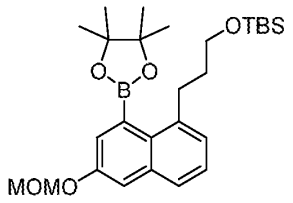


Step A. 8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-ol. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol (1.1 g, 1.6 mmol) in THF (12 mL) and MeOH (4.0 mL) was added $Pd(OH)_2$ (20 wt% Pd; 0.28 g, 0.40 mmol). The mixture was sparged with H_2 for 10 min and stirred at rt for 19 h under 1 atm of hydrogen. The mixture was filtered through a Celite plug and the filter cake was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure. The residue was purified via silica gel chromatography (5 - 20 % MeOH in DCM) to give 8-

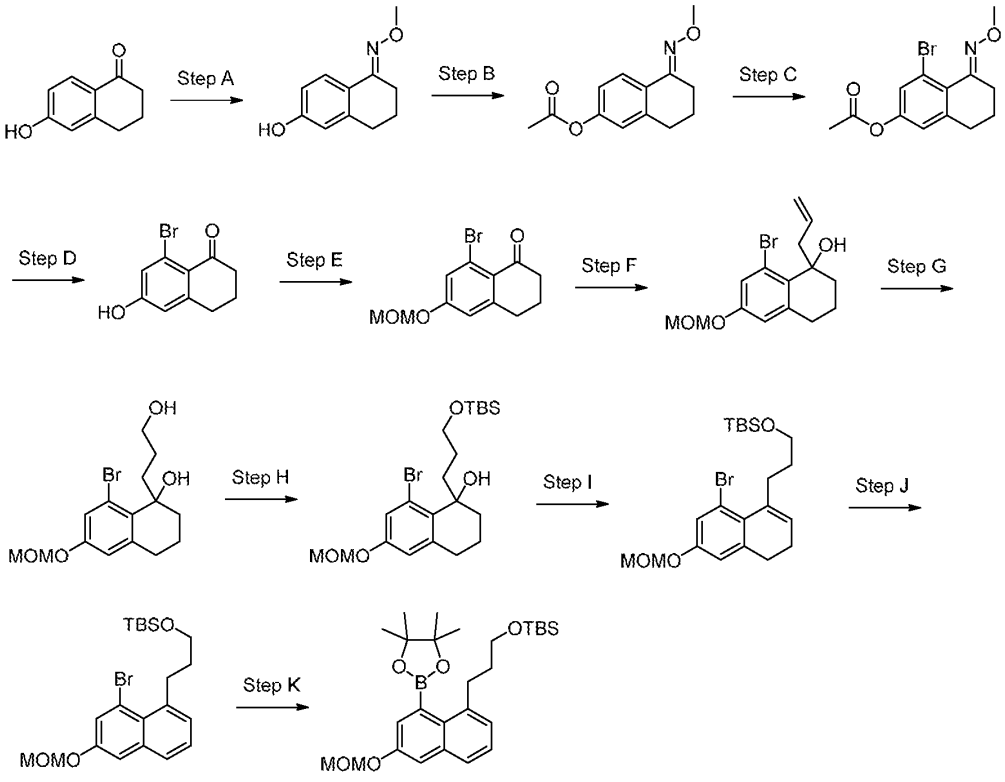
fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-ol (0.67 g, 74%) as an orange solid. LCMS (MM-ES+APCI, Pos): m/z 567.3 (M+H).

Example 16

Intermediate I17



tert-butyl(3-(6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)dimethylsilane



Step A. (E)-6-hydroxy-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime. To a solution of 6-hydroxy-3,4-dihydronaphthalen-1(2H)-one (100 g, 620 mmol) in EtOH (1000 mL) was added O-methylhydroxylamine hydrochloride (103 g, 1200 mmol) and pyridine (200

mL, 2.5 mol). The mixture was stirred at 80 °C for 2 h after which it was diluted with H_2O (500 mL). The mixture was extracted with ethyl acetate (500 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give (E)-6-hydroxy-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (115 g) as a black oil, which was taken onto the next step without further purification.

Step B. (E)-5-(methoxyimino)-5,6,7,8-tetrahydronaphthalen-2-yl acetate. To a solution of (E)-6-hydroxy-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (115 g, 601 mmol) in DCM (1200 mL) at 0 °C was added pyridine (97 mL, 1200 mol) and acetyl chloride (51 mL, 720 mmol). The mixture was warmed to rt and stirred for 1 h. The reaction was slowly diluted with water (1000 mL) and the mixture extracted with DCM (500 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-20% EtOAc in petroleum ether) to give (E)-5-(methoxyimino)-5,6,7,8-tetrahydronaphthalen-2-yl acetate (131 g, 93% yield) as white solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 6.95 - 6.84 (m, 2H), 3.98 (s, 3H), 2.78 - 2.68 (m, 4H), 2.30 (s, 3H), 1.90 - 1.77 (m, 2H).

Step C. (E)-4-bromo-5-(methoxyimino)-5,6,7,8-tetrahydronaphthalen-2-yl acetate. To a solution of (E)-5-(methoxyimino)-5,6,7,8-tetrahydronaphthalen-2-yl acetate (105 g, 450 mmol) in AcOH (1000 mL) was added NBS (96 g, 540 mmol) and $Pd(OAc)_2$ (5.05 g, 23 mmol) in portions. The reaction was heated to 90 °C and stirred at this temperature for 1 h. The mixture was cooled to rt and diluted with H_2O (1500 mL). The mixture was extracted with ethyl acetate (1000 mL x 3). The combined organic layers were washed with brine (1000 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-10% EtOAC in petroleum ether) to give (E)-4-bromo-5-(methoxyimino)-5,6,7,8-tetrahydronaphthalen-2-yl acetate (82 g, 88% yield) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.24 - 7.18 (m, 1H), 6.81 (d, J = 2.4 Hz, 1H), 4.01 - 3.91 (m, 3H), 2.67 (t, J = 6.8 Hz, 2H), 2.58 - 2.50 (m, 2H), 2.21 - 2.20 (m, 3H), 1.79 - 1.60 (m, 2H).

Step D. 8-bromo-6-hydroxy-3,4-dihydronaphthalen-1(2H)-one. To a solution (E)-4-bromo-5-(methoxyimino)-5,6,7,8-tetrahydronaphthalen-2-yl acetate (61 g, 195 mmol) in 1,4-dioxane (630 mL) was added HCl in dioxane (2.0 M; 908 mL, 1800 mmol). The reaction was heated to 110 °C and stirred for 1 h. After cooling to rt, the solution was diluted with H_2O (1000 mL) and extracted with ethyl acetate (1000 mL x 3). The combined organic layers were washed with brine (1000 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under

reduced pressure. The residue was purified by silica gel chromatography (0-20% EtOAC in petroleum ether) to give 8-bromo-6-hydroxy-3,4-dihydronaphthalen-1(2H)-one (35 g, 74% yield) as a yellow solid. ^{1}H NMR: (400 MHz, MeOH-d_4) δ 7.01 (d, J = 2.4 Hz, 1H), 6.71 - 6.67 (m, 1H), 2.93 (t, J = 6.0 Hz, 2H), 2.61 (t, J = 6.8 Hz, 2H), 2.09 - 2.01 (m, 2H).

Step E. 8-bromo-6-(methoxymethoxy)-3,4-dihydronaphthalen-1(2H)-one. To a solution of 8-bromo-6-hydroxy-3,4-dihydronaphthalen-1(2H)-one (75 g, 310 mmol) in DCM (1300 mL) at 0 °C was added DIPEA (16 mL, 930 mol) and 1-bromomethyl methyl ether (51 mL, 620 mmol). The mixture was allowed to warm to rt and stirred for 1 h. The reaction was slowly diluted with H_2O (800 mL) and then extracted with DCM (300 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-12% EtOAc in petroleum ether) to give 8-bromo-6-(methoxymethoxy)-3,4-dihydronaphthalen-1(2H)-one (71 g, 80% yield) as yellow solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 2.4 Hz, 1H), 6.87 - 6.83 (m, 1H), 5.20 (s, 2H), 3.48 (s, 3H), 2.94 (t, *J* = 6.0 Hz, 2H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.11 - 2.04 (m, 2H).

Step F. 1-allyl-8-bromo-6-(methoxymethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol. Two solutions were prepared and pumped through a flow reactor. Solution one, containing 8-bromo-6-(methoxymethoxy)-3,4-dihydronaphthalen-1(2H)-one (70 g, 250 mmol) in THF (700 mL), was pumped at 61.3 mL/min at -10 °C. A second line pumped allylmagnesium bromide (1.0 M in diethyl ether; 500 mL) at 61.3 mL/min at -10 °C. The two pumps were started at the same time and were combined in three tandem flow reactors (FLR3, GL, CSTRs, 500 mL, -10 °C) with residence time of 5 min each. The mixture was collected at the end in a bottle containing NH_4Cl solution (1.0 M; 1000 mL). The reaction was run for 15 min after which it was diluted with saturated NH_4Cl solution (3000 mL). The solution was extracted with ethyl acetate (500 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-10% EtOAc in petroleum ether) to give 1-allyl-8-bromo-6-(methoxymethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol (75 g, 93% yield) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 2.4 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 5.96 - 5.75 (m, 1H), 5.23 – 4.98 (m, 4H), 3.59 - 3.43 (m, 3H), 3.41 (s, 1H), 3.15 - 2.54 (m, 4H), 2.38 - 2.09 (m, 2H), 1.85 - 1.68 (m, 2H).

Step G. 8-bromo-1-(3-hydroxypropyl)-6-(methoxymethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol. Three solutions were prepared and pumped through a flow reactor.

Solution one, containing 1-allyl-8-bromo-6-(methoxymethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol (71 g, 217 mmol) in THF (710 mL) was pumped at 26.4 mL/min. A second line pumped BH_3·THF (1.0 M; 220 mL, 430 mmol) was pumped at 16.3 mL/min. A third line pumped a solution of NaOH (26 g, 650 mmol) and H_2O_2 (30 mL, 1300 mmol) was pumped at 14.6 mL/min. The first two pumps started at the same time and the third pump started 3 min later. Solution one and two were combined in PFA coil reactor (213 mL, rt). The resonance time for this step was 5 min. The combined solution was pumped into a second flow reactor (FLR2, GL, CSTRs, 284 mL, 0 °C) along with solution three. The residence time for flow reactor 2 was 5 min. The mixture was collected at the end and was stirred with a saturated solution of sodium sulfite (3000 mL) for 30 min at 0 °C. The mixture was extracted with ethyl acetate (500 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-45% EtOAc in petroleum ether) to give 8-bromo-1-(3-hydroxypropyl)-6-(methoxymethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol (62 g, 83% yield) as a yellow solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.14 (d, J = 2.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 5.13 (s, 2H), 3.69 (t, J = 6.4 Hz, 2H), 3.49 - 3.44 (m, 3H), 2.96 - 2.70 (m, 2H), 2.36 - 2.24 (m, 1H), 2.17 - 1.90 (m, 2H), 1.88 - 1.65 (m, 5H).

Step H. 8-bromo-1-(3-((tert-butyldimethylsilyl)oxy)propyl)-6-(methoxymethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol. To a solution of 8-bromo-1-(3-hydroxypropyl)-6-(methoxymethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol (61 g, 177 mmol) and imidazole (24 g, 353 mmol) in DCM (610 mL) at 0 °C was added TBSCl (35 mL, 230 mol). The mixture was warmed to rt and stirred for 1 h. The reaction was concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-2% EtOAc in petroleum ether) to give 8-bromo-1-(3-((tert-butyldimethylsilyl)oxy)propyl)-6-(methoxymethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol (68 g, 82% yield) as yellow solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.14 (d, J = 2.4 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 5.12 (s, 2H), 3.67 - 3.62 (m, 2H), 3.54 (br s, 1H), 3.49 - 3.45 (m, 3H), 2.89 - 2.70 (m, 2H), 2.45 - 2.18 (m, 1H), 2.13 - 1.99 (m, 2H), 1.89 - 1.61 (m, 5H), 0.96 - 0.84 (m, 9H), 0.05 (m, 6H).

Step I. (3-(8-bromo-6-(methoxymethoxy)-3,4-dihydronaphthalen-1-yl)propoxy)(tert-butyl)dimethylsilane. To a solution of 8-bromo-1-(3-((tert-butyldimethylsilyl)oxy)propyl)-6-(methoxymethoxy)-1,2,3,4-tetrahydronaphthalen-1-ol (68 g, 148 mmol) in toluene (730 mL) was added burgess reagent (53 g, 222 mmol). The reaction was heated to 90 °C for 12 h and then concentrated under reduced pressure. The residue was purified by silica gel

chromatography (0-5% EtOAc in petroleum ether) to give (3-(8-bromo-6-(methoxymethoxy)-3,4-dihydronaphthalen-1-yl)propoxy)(tert-butyl)dimethylsilane (55 g, 84% yield) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.17 (m, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.09 - 5.98 (m, 1H), 5.14 (d, J = 3.2 Hz, 2H), 3.72 (t, J = 7.2 Hz, 1H), 3.58 (t, J = 6.8 Hz, 1H), 3.48 (d, J = 2.8 Hz, 3H), 2.89 (t, J = 7.6 Hz, 1H), 2.63 - 2.43 (m, 4H), 2.12 - 1.97 (m, 1H), 1.75 (m, 1H), 1.66 - 1.59 (m, 1H), 0.93 - 0.82 (m, 9H), 0.11 - 0.05 (m, 6H).

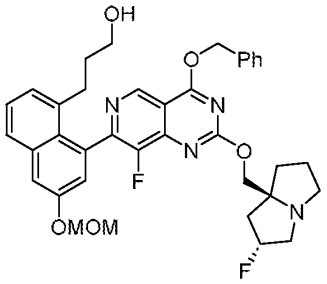
Step J. (3-(8-bromo-6-(methoxymethoxy)naphthalen-1-yl)propoxy)(tert-butyl)dimethylsilane. To a solution of (3-(8-bromo-6-(methoxymethoxy)-3,4-dihydronaphthalen-1-yl)propoxy)(tert-butyl)dimethylsilane (54 g, 122 mmol) in DCM (540 mL) at 0 °C was added DDQ (33 g, 147 mmol). The mixture was warmed to rt and stirred for 1 h after which it was concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-5% EtOAc in petroleum ether) to give (3-(8-bromo-6-(methoxymethoxy)naphthalen-1-yl)propoxy)(tert-butyl)dimethylsilane (26 g, 49% yield) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.65 - 7.60 (m, 2H), 7.39 - 7.31 (m, 2H), 7.28 (d, J = 7.2 Hz, 1H), 5.27 (s, 2H), 3.71 (t, J = 6.4 Hz, 2H), 3.60 - 3.45 (m, 5H), 2.12 - 1.89 (m, 2H), 1.13 - 0.84 (m, 9H), 0.12 - 0.07 (m, 6H).

Step K. tert-butyl(3-(6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)dimethylsilane. Three solutions were prepared and pumped through a flow reactor. Solution one, containing (3-(8-bromo-6-(methoxymethoxy)naphthalen-1-yl)propoxy)(tert-butyl)dimethylsilane (20 g, 45.5 mmol) in THF (200 mL) was pumped at 98.3 mL/min. A second line pumped n-BuLi (2.5 M in hexanes; 85 mL, 213 mmol) was pumped at 19.9 mL/min. A third line pumped 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (21.2 g, 137 mmol) in THF (200 mL) was pumped at 104 mL/min. The first two pumps started at the same time and the third pump started 0.09 min later. Solutions one and two were combined in PFA coil reactor (10 mL, -40 °C). The resonance time for this step was 0.09 min. The combined solution was pumped into a second PFA coil reactor (10 mL, -40 °C) along with solution three. The resonance time for this step was 0.05 min. The mixture was collected at the end in a bottle containing NH_4Cl solution (1.0 M; 1000 mL). The reaction was run for 15 min after which it was diluted with saturated NH_4Cl solution (200 mL). The solution was extracted with ethyl acetate (300 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-8% EtOAc in petroleum ether). The material was repurified by preparative MPLC (0% – 1% EtOH in hexanes) to give

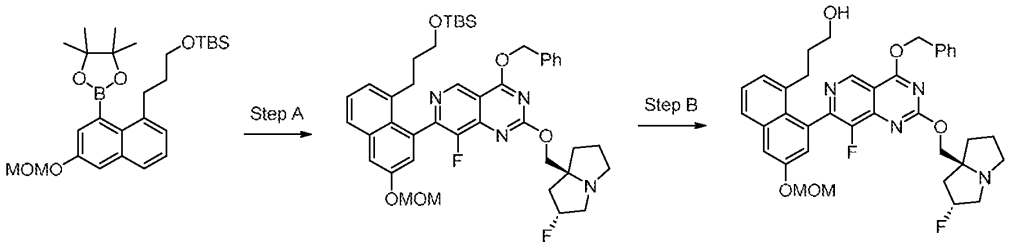
tert-butyl(3-(6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)dimethylsilane (7.3 g, 32 % yield) as a yellow solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.2 Hz, 1H), 7.42 (d, J = 2.8 Hz, 1H), 7.40 - 7.34 (m, 2H), 7.29 - 7.24 (m, 1H), 5.30 (s, 2H), 3.65 (t, J = 6.4 Hz, 2H), 3.52 (s, 3H), 3.23 (t, J = 7.2 Hz, 2H), 1.99 (m, 2H), 1.44 (s, 12H), 0.97 - 0.74 (m, 9H), 0.06 - 0.02 (m, 6H).

Example 17

Intermediate I18



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



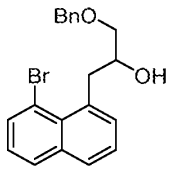
Step A. 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl)-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of Intermediate I2 (4.7 g, 10 mmol) and Intermediate I17 (5.0 g, 10 mmol) in 1,4-dioxane (50 mL) and H_2O (5 mL) was added K_2CO_3 (2.8 g, 21 mmol) and mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.75 g, 1.0 mmol). The reaction was sparged with nitrogen for 5 min after which it was heated to 90 °C for 4 h. The solution was diluted with H_2O (30 mL) and then extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced

pressure. The residue was purified by silica gel chromatography (0-40% EtOAc in petroleum ether) to give 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl)-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (6.3 g, 68% yield) as a yellow gum. LCMS (MM-ES+APCI, Pos): m/z 771.5 (M+H).

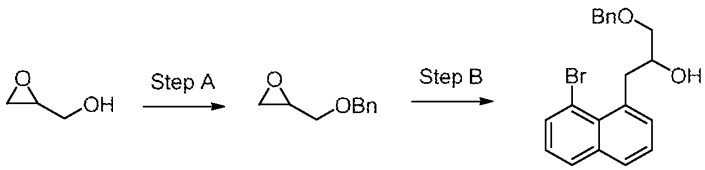
Step B. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propan-1-ol. To a solution of 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl)-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (6.3 g, 7.0 mmol) in THF (70 mL) was added triethylamine-trihydrofluoride (3.4 mL, 21 mmol). The reaction was stirred at rt for 2 h after which it was diluted with H_2O (30 mL). The pH of mixture was adjusted to 8 with saturated aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced. The residue was purified by silica gel chromatography (0-80% EtOAc in petroleum ether) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propan-1-ol (1.04 g, 92% yield) as an off-white solid. LCMS (MM-ES+APCI, Pos): m/z 657.3 (M+H).

Example 18

Intermediate I19



1-(benzyloxy)-3-(8-bromonaphthalen-1-yl)propan-2-ol

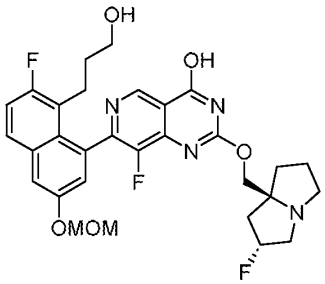


Step A. 2-((benzyloxy)methyl)oxirane. To a solution of oxiran-2-ylmethanol (9.0 mL, 135 mmol) in THF (100 mL) at 0 °C was added NaH (60% in mineral oil; 6.5 g, 162 mmol) portion wise. The mixture was warmed to rt and was stirred for 1 h, then benzyl bromide (24 mL, 203 mmol) was added and the reaction was stirred for an additional 2 h. The mixture was quenched by slow addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-10% EtOAc in petroleum ether) to give 2-((benzyloxy)methyl)oxirane (7.0 g, 31% yield) as a yellow oil. ^1H NMR: (400 MHz, $CDCl_3$) δ 7.40 - 7.24 (m, 5H), 4.57 (q, J = 12.0 Hz, 2H), 3.75 (dd, J = 3.2, 11.2 Hz, 1H), 3.42 (dd, J = 5.6, 11.2 Hz, 1H), 3.25 - 3.13 (m, 1H), 2.86 - 2.73 (m, 1H), 2.60 (dd, J = 2.8, 5.2 Hz, 1H).

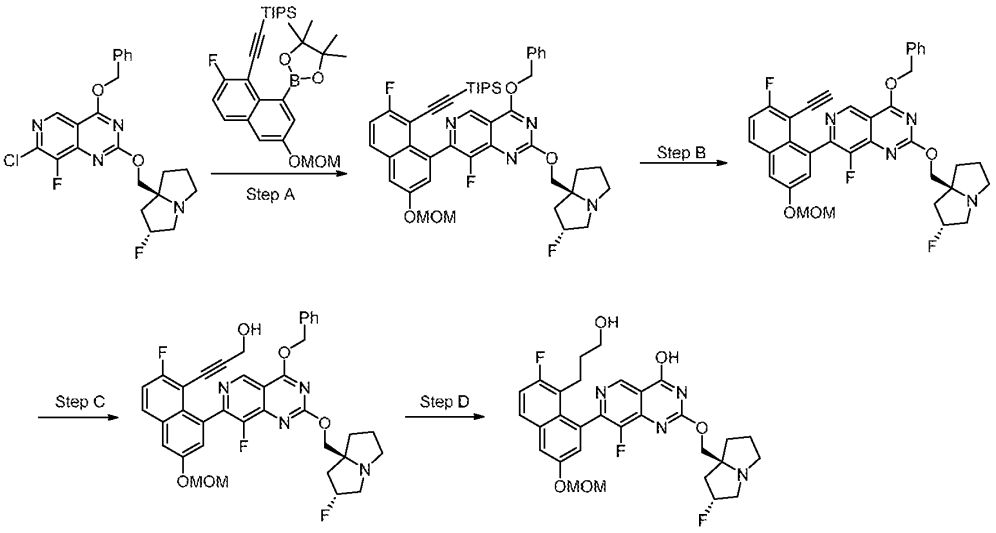
Step B. 1-(benzyloxy)-3-(8-bromonaphthalen-1-yl)propan-2-ol. A solution of 1,8-dibromonaphthalene (9.2 g, 32 mmol) in THF (100 mL) was evacuated and backfilled with nitrogen three times. The solution was cooled to -78 °C and then n-BuLi (2.5 M in hexanes; 12.9 mL, 32 mmol) was added dropwise. The mixture was cooled to -78 °C and stirred for 30 min, after which 2-((benzyloxy)methyl)oxirane (6.04 mL, 39 mmol) was added dropwise. The mixture was warmed to 0 °C and stirred for 1.5 h at this temperature. The reaction was quenched by slow addition of saturated aqueous NH_4Cl (20 mL). The mixture was stirred for 30 min and then extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-10% EtOAc in petroleum ether) to give 1-(benzyloxy)-3-(8-bromonaphthalen-1-yl)propan-2-ol (3.7 g, 29% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 392.9 / 394.9 (M+Na).

Example 19

Intermediate I20



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



Step A. 4-(benzyloxy)-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]pyrimidine. A solution of ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (7.46 g, 14.5 mmol), 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (5.00 g, 11.2 mmol), mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2'-amino-1,1'-biphenyl)]palladium(II) (1.1 g, 1.5 mmol), and potassium phosphate (7.1 g, 34 mmol) in THF (40 mL) and H_2O (10 mL) was sparged with argon for 10 min. The solution was heated to 80 °C for 2 h. The reaction solution was diluted with H_2O (50 mL) and extracted with DCM (50 mL x 3). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (20 - 100% EtOAc in hexanes) to give 4-(benzyloxy)-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]pyrimidine (7.191 g, 81%). LCMS (MM-ES+APCI, Pos): m/z 797.3 (M+H).

Step B. 4-(benzyloxy)-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]pyrimidine. To a solution of 4-(benzyloxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-

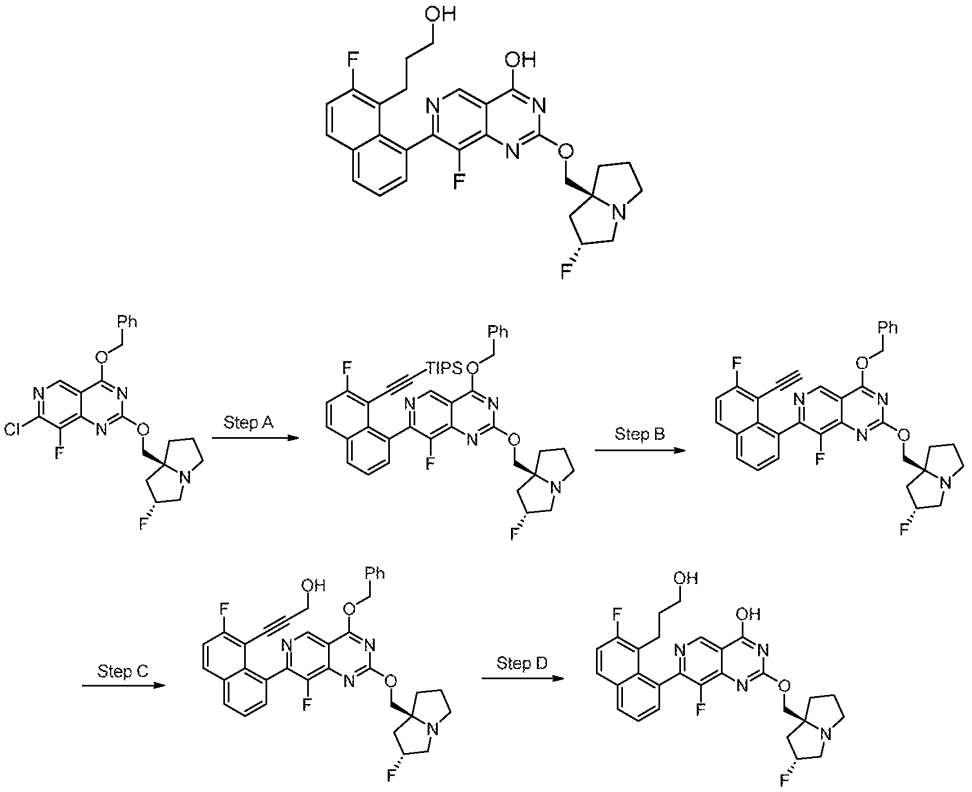
7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (6.51 g, 8.16 mmol) in THF (40 mL) at 0 °C was added TBAF (1.0 M in THF; 9.4 mL, 9.4 mmol). The reaction was stirred at this temperature for 40 min and diluted with H_2O (100 mL). The slurry was filtered by vacuum filtration and the pad was washed with H_2O (100 mL). The precipitate was dried under reduced pressure to obtain 4-(benzyloxy)-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]pyrimidine (5.0 g, 86 %). LCMS (MM-ES+APCI, Pos): m/z 641.2 (M+H).

Step C. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol. To a solution of 4-(benzyloxy)-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]pyrimidine (4.99 g, 7.783 mmol) in THF (70.0 mL) at -78 °C was added LiHMDS (1.0 M in THF; 8.95 mL, 8.95 mmol). This mixture was stirred at -78 °C for 50 minutes and paraformaldehyde (2.3 g, 78 mmol) was added in one portion. The mixture was warmed to rt and stirred for 1 h. The solution was diluted with saturated $NaHCO_3$ solution (50 mL) and extracted with DCM (50 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 - 10% MeOH in DCM) to afford 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol (2.97 g, 57%). LCMS (MM-ES+APCI, Pos): m/z 671.3 (M+H).

Step D. 8-fluoro-7-(7-fluoro-8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-ol. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol (2.97 g, 4.43 mmol) in THF (33 mL) and MeOH (11 mL) was added $Pd(OH)_2$ (20% wt; 933 mg, 1.33 mmol). The mixture was sparged with H_2 for 10 min and was stirred at rt for 2.5 days under 1 atm of H_2. The mixture was filtered through Celite and the pad was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure. The residue was purified via silica gel chromatography (0 - 15 % MeOH in DCM) to give 8-fluoro-7-(7-fluoro-8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-ol (1.49 g, 57%). LCMS (MM-ES+APCI, Pos): m/z 585.3 (M+H).

Example 20

Intermediate I21



Step A. 4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine. A solution of ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (6.7 g, 15 mmol), 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (6.0 g, 13 mmol), mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2'-amino-1,1'-biphenyl)]palladium(II) (0.98 g, 1.3 mmol), K_2CO_3 (5.6 g, 40 mmol) in 1,4-dioxane (100 mL) and H_2O (10 mL) was stirred at 80 °C for 16 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (30 - 50% EtOAc in petroleum ether) to give 4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (8.5 g, 86%

yield). LCMS (MM-ES+APCI, Pos): m/z 737.6 (M+H).

Step B. 4-(benzyloxy)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine. To a solution of 4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (8.5 g, 12 mmol) in DMF (50 mL) was added CsF (8.8 g, 58 mmol). The reaction was stirred at rt for 16 h. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (80 - 100% EtOAc in petroleum ether) to give 4-(benzyloxy)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (4.5 g, 67% yield). LCMS (MM-ES+APCI, Pos): m/z 581.4 (M+H).

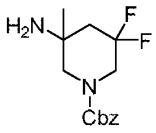
Step C. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)prop-2-yn-1-ol. To a solution of 4-(benzyloxy)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (4.0 g, 6.9 mmol) in THF (200 mL) at -60 °C was added LiHMDS (1.0 M in THF; 10 mL, 10 mmol). The reaction was stirred for 5 min and then paraformaldehyde (2.0 g) was added. The reaction was stirred at -65 °C for 2 h, warmed to rt and stirred for an additional 2 h. The mixture was diluted with H_2O (200 mL) and extracted with EtOAc (200 mL x 3). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (50 - 70% EtOAc in petroleum ether) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)prop-2-yn-1-ol (1.2 g, 29% yield). LCMS (MM-ES+APCI, Pos): m/z 611.4 (M+H).

Step D. 8-fluoro-7-(7-fluoro-8-(3-hydroxypropyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol. A solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)prop-2-yn-1-ol (0.500 g, 0.491 mmol) and Pd/C (10% wt; 3.5 g, 3.3 mmol) in MeOH (100 mL) and THF (10 mL) was stirred at 35 °C for 2 h under an atmosphere of H_2. The reaction mixture was filtered over Celite and the filtrate was concentrated under reduced pressure to give 8-fluoro-7-(7-fluoro-8-(3-hydroxypropyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (0.33 g, 77% yield), which was used directly in the

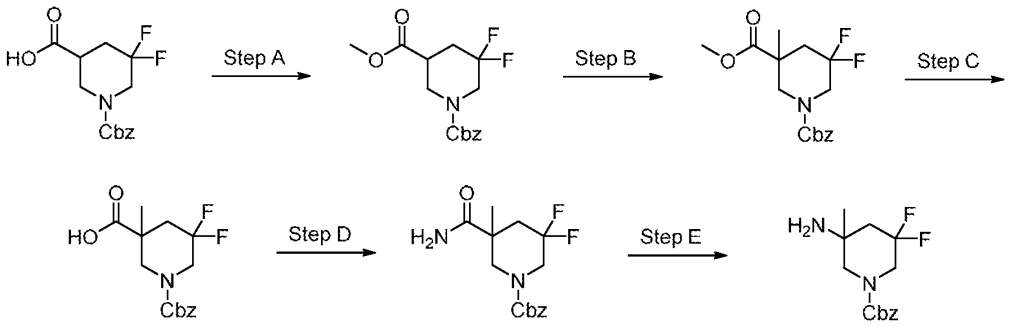
next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 525.3 (M+H).

Example 21

Intermediate I22



benzyl 3-amino-5,5-difluoro-3-methylpiperidine-1-carboxylate



Step A. 1-benzyl 3-methyl 5,5-difluoropiperidine-1,3-dicarboxylate. To a solution of 1-((benzyloxy)carbonyl)-5,5-difluoropiperidine-3-carboxylic acid (1.8 g, 6.0 mmol) and K_2CO_3 (1.7 g, 12 mmol) in DMF (20 mL) was added MeI (1.1 mL, 18 mmol). The reaction was heated to 50 °C and stirred for 12 h. The mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-17% EtOAc in petroleum ether) to give 1-benzyl 3-methyl 5,5-difluoropiperidine-1,3-dicarboxylate (1.8 g, 96% yield) as a colorless oil. ^{1}H NMR: (400 MHz, CDCl3) δ = 7.42 - 7.32 (m, 5H), 5.16 (br s, 2H), 4.64 - 4.26 (m, 2H), 3.73 (s, 3H), 3.20 - 2.78 (m, 3H), 2.60 - 2.40 (m, 1H).

Step B. 1-benzyl 3-methyl 5,5-difluoro-3-methylpiperidine-1,3-dicarboxylate. To a solution of 1-benzyl 3-methyl 5,5-difluoropiperidine-1,3-dicarboxylate (1.8 g, 5.8 mmol) followed by in THF (20 mL) at -78 °C was added LiHMDS (1.0 M in THF; 8.62 mL) drop wise. The reaction was stirred at -78 °C under an atmosphere of nitrogen for 1 h after which MeI (1.1 mL, 17 mmol) was added dropwise. The reaction warmed to rt and stirred for 2 h. The mixture was quenched by slow addition of saturated aqueous NH_4Cl (20 mL) and then

extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-17% EtOAc in petroleum ether) to give 1-benzyl 3-methyl 5,5-difluoro-3-methylpiperidine-1,3-dicarboxylate (1.45 g, 77% yield) as a yellow oil. ^{1}H NMR: (400 MHz, CDCl3) δ = 7.47 - 7.29 (m, 5H), 5.19 (s, 2H), 3.69 (br s, 7H), 2.49 (br s, 1H), 2.12 - 1.95 (m, 1H), 1.28 (br d, J = 7.2 Hz, 3H).

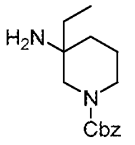
Step C. 1-((benzyloxy)carbonyl)-5,5-difluoro-3-methylpiperidine-3-carboxylic acid. To a solution of 1-benzyl 3-methyl 5,5-difluoro-3-methylpiperidine-1,3-dicarboxylate (0.75 g, 2.3 mmol) in MeOH (5 mL), THF (5 mL), and H_2O (5 mL) was added LiOH (0.16 g, 6.8 mmol). The reaction was stirred at rt for 1 h. The pH of solution was adjusted to 3 with HCl (1 M) and the mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-33% EtOAc in petroleum ether) to give 1-((benzyloxy)carbonyl)-5,5-difluoro-3-methylpiperidine-3-carboxylic acid (0.70 g, 98% yield) as a yellow oil. 1H NMR: (400 MHz, CDCl3) δ = 7.41 - 7.31 (m, 5H), 3.91 - 3.40 (m, 4H), 2.61 - 2.41 (m, 1H), 2.05 - 1.95 (m, 1H), 1.33 (br s, 3H).

Step D. benzyl 3-carbamoyl-5,5-difluoro-3-methylpiperidine-1-carboxylate. To a solution of 1-((benzyloxy)carbonyl)-5,5-difluoro-3-methylpiperidine-3-carboxylic acid (0.50 g, 1.6 mmol) in DMF (8 mL) was added NH_4Cl (0.85 g, 16 mmol), DIPEA (3.3 mL, 19 mmol) and HATU (1.2 g, 3.2 mmol). The reaction was heated to 50 °C for 12 h. The mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-33% EtOAc in petroleum ether) to give benzyl 3-carbamoyl-5,5-difluoro-3-methylpiperidine-1-carboxylate (0.42 g, 50% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 313.1 (M+H).

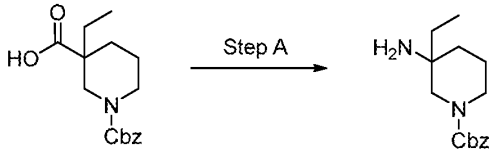
Step E. benzyl 3-amino-5,5-difluoro-3-methylpiperidine-1-carboxylate. To solution of benzyl 3-carbamoyl-5,5-difluoro-3-methylpiperidine-1-carboxylate (0.42 g, 0.79 mmol) in MeCN (5 mL) at 0 °C was added NaOH (5.0 M; 1.7 mL) and NBS (0.21 g, 1.2 mmol). The reaction was stirred at rt for 12 h. The mixture was slowly poured into water (10 mL), and then extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (100% EtOAc) to give benzyl 3-

amino-5,5-difluoro-3-methylpiperidine-1-carboxylate (0.17 g, 65% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 285.1 (M+H).

Intermediate I23

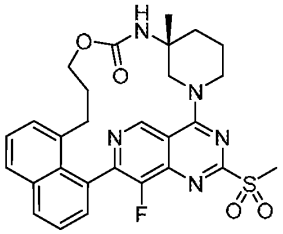


benzyl 3-amino-3-ethylpiperidine-1-carboxylate

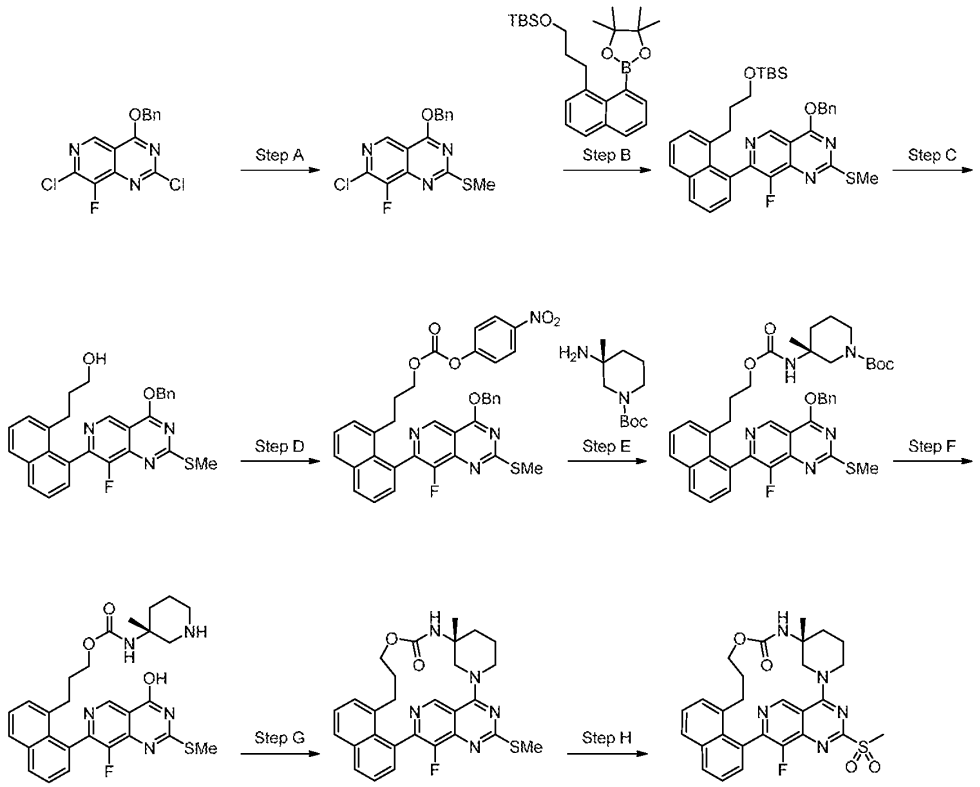


Step A. benzyl 3-amino-3-ethylpiperidine-1-carboxylate. To solution of 1-((benzyloxy)carbonyl)-3-ethylpiperidine-3-carboxylic acid (0.50 g, 1.7 mmol) and DIPEA (3.0 mL, 17.16 mmol) in 1,4-dioxane (8.0 mL) was added DPPA (1.5 mL, 6.9 mmol). The mixture was heated to 100 °C and stirred for 2 h. After cooling to rt, HCl (6.0 M; 8.0 mL) was added to the reaction and it was stirred for an additional 14 h. The mixture was diluted with H_2O (10 mL) and washed with EtOAc (10 mL x 3). The aqueous phase was neutralized to pH 9 with aqueous Na_2CO_3 and then it was extracted with DCM (10 mL x 3). The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to obtain benzyl 3-amino-3-ethylpiperidine-1-carboxylate (180 mg, 38% yield, which was taken onto the next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 263.1 (M+H).

Intermediate I24



(1^3R)-2^8-fluoro-1^3-methyl-2^2-(methylsulfonyl)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 4-(benzyloxy)-7-chloro-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidine. To solution of 4-(benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidine (38 g, 120 mmol) in DCM (380 mL) was added sodium methanethiolate (9.1 g, 130 mmol). The mixture was stirred at rt for 3 h. The mixture was quenched by slow addition of H_2O (500 mL) and extracted with ethyl acetate (400 mL x 3). The combined organic layers were washed with brine (400 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The suspension was filtered, and the filter cake was washed with 10% MeOH in DCM (500 mL). The solid was concentrated under vacuum to give 4-benzyloxy-7-chloro-8-fluoro-2-methylsulfanyl-pyrido [4, 3-d] pyrimidine (29 g, 64% yield). LCMS (MM-ES+APCI, Pos): m/z 336.0 (M+1).

Step B. 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl)naphthalen-1-yl)-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidine. To a solution of 4-benzyloxy-7-chloro-8-fluoro-2-methylsulfanyl-pyrido[4,3-d]pyrimidine (10 g, 30 mmol) and Intermediate 1 (25 g, 60 mmol) in dioxane (200 mL) and H_2O (20 mL) was added K_3PO_4 (19 g, 89 mmol) and [1,1′-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (1.9 g, 3.0 mmol). The mixture was purged with nitrogen for 2 min, then heated to 90 °C for 1 h. The mixture was

quenched by slow addition of H_2O (300 mL) and extracted with ethyl acetate (300 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10 – 20% EtOAc in petroleum ether) to give 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl)naphthalen-1-yl)-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidine (5.9 g, 24% yield). LCMS (MM-ES+APCI, Pos): m/z 600.4 (M+1).

Step C. 3-(8-(4-(benzyloxy)-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propan-1-ol. To a solution of 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl)naphthalen-1-yl)-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidine (5.9 g, 9.8 mmol) in MeOH (60 mL) was added TEA-HF (3.6 g, 98 mmol). The mixture was stirred at 60 °C for 2 h. The reaction mixture was concentrated under reduced pressure, then diluted with ethyl acetate (300 mL) and extracted with H_2O (300 mL × 3). The combined organic layers were washed with brine (100 mL), and concentrated under reduced pressure to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propan-1-ol (2.4 g, 47% yield). LCMS (MM-ES+APCI, Pos): m/z 486.3 (M+1).

Step D. 3-(8-(4-(benzyloxy)-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (4-nitrophenyl) carbonate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propan-1-ol (2.4 g, 4.9 mmol) in DCM (20 mL) and pyridine (1.4 mL, 17 mmol) was added a solution of 4-nitrophenyl carbonochloridate (2.8 g, 14 mmol) in DCM (20 mL). The mixture was stirred at rt for 12 h then quenched by slow addition of H_2O (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20 – 30% EtOAc in petroleum ether) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (4-nitrophenyl) carbonate (2.1 g, 63% yield). LCMS (MM-ES+APCI, Pos): m/z 651.2 (M+1).

Step E. tert-butyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (4-nitrophenyl) carbonate (2.0 g, 3.0 mmol) and tert-butyl (3R)-3-amino-3-methyl-piperidine-1-carboxylate (0.95 g, 4.5 mmol) in DMF (20 mL) was added DIPEA (1.6 mL, 8.9 mmol). The mixture was stirred at rt for 12 h, then

quenched by slow addition of H_2O (100 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure affording the residue. The residue was purified by silica gel column chromatography (20 – 30% EtOAc in petroleum ether) to give tert-butyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (2.5 g, 82% yield). LCMS (MM-ES+APCI, Pos): m/z 726.4 (M+1).

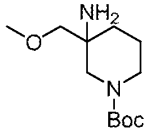
Step F. 3-(8-(8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (R)-(3-methylpiperidin-3-yl)carbamate. To a solution of tert-butyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(methylthio)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (2.5 g, 2.4 mmol) in DCM (21 mL) was added TFA (7.0 mL, 94 mmol). The mixture was stirred at rt for 1 h then quenched by slow addition of H_2O (50 mL) followed by aqueous $NaHCO_3$ until pH 7 was reached. The resulting mixture was extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (18 – 48% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain 3-(8-(8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (R)-(3-methylpiperidin-3-yl)carbamate (800 mg, 56% yield). LCMS (MM-ES+APCI, Pos): m/z 536.2 (M+1).

Step G. (1^3R)-2^8-fluoro-1^3-methyl-2^2-(methylthio)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(8-(8-fluoro-4-hydroxy-2-(methylthio)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (R)-(3-methylpiperidin-3-yl)carbamate (650 mg, 1.1 mmol) in DCM (650 mL) was added DIPEA (0.95 mL, 5.5 mmol) and BOP-Cl (0.84 g, 3.3 mmol). The mixture was stirred at rt for 16 h, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50 – 100% EtOAc in petroleum ether) to give (1^3R)-2^8-fluoro-1^3-methyl-2^2-(methylthio)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.24 g, 42% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 518.3 (M+1).

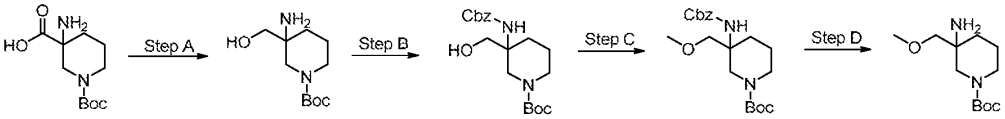
Step H. (1^3R)-2^8-fluoro-1^3-methyl-2^2-(methylsulfonyl)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of (1^3R)-2^8-fluoro-1^3-methyl-2^2-(methylthio)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.30 g, 0.57 mmol) in DCM (5

mL) at 0 °C was added m-CPBA (0.35 g, 1.7 mmol) portionwise. The mixture was stirred at rt for 1 h. The mixture was quenched by slow addition of aqueous Na_2SO_3 (50 mL) at 0 °C. The mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30 – 50% EtOAc in petroleum ether) and the pure fractions lyophilized to give (1^3R)-2^8-fluoro-1^3-methyl-2^2-(methylsulfonyl)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.067 g, 19% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 550.2 (M+1).

Intermediate I25



tert-butyl 3-amino-3-(methoxymethyl)piperidine-1-carboxylate



Step A. tert-butyl 3-amino-3-(hydroxymethyl)piperidine-1-carboxylate. To a solution of 3-amino-1-(tert-butoxycarbonyl)piperidine-3-carboxylic acid (4.5 g, 18 mmol) in THF (300 mL) at 0 °C was added BH_3·THF (1.0 M; 37 mL). The reaction was heated to 80 °C for 4 h. After cooling to 0 °C, the reaction was quenched with MeOH (10 mL) and then it was stirred for an additional 16 h at rt. The mixture was concentrated under reduced pressure. The residue was purified via silica gel chromatography (0-15% MeOH in DCM) to give tert-butyl 3-amino-3-(hydroxymethyl)piperidine-1-carboxylate (2.6 g, 61% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 231.1 (M+H).

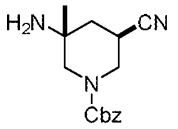
Step B. tert-butyl 3-(((benzyloxy)carbonyl)amino)-3-(hydroxymethyl)piperidine-1-carboxylate. To a solution of tert-butyl 3-amino-3-(hydroxymethyl)piperidine-1-carboxylate (1.0 g, 4.3 mmol) and DIPEA (2.3 mL, 13 mmol) in DCM (20 mL) at 0 °C was added CbzCl (0.68 mL, 4.8 mmol). The mixture was warmed to rt and stirred for 16 h after which it was concentrated under recued pressure. The residue was purified by silica gel chromatography (0- 60% EtOAc in petroleum ether) to give tert-butyl 3-(((benzyloxy)carbonyl)amino)-3-(hydroxymethyl)piperidine-1-carboxylate (1.1 g, 61% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 265.1 (M+H - Boc).

Step C. tert-butyl 3-(((benzyloxy)carbonyl)amino)-3-(methoxymethyl)piperidine-1-

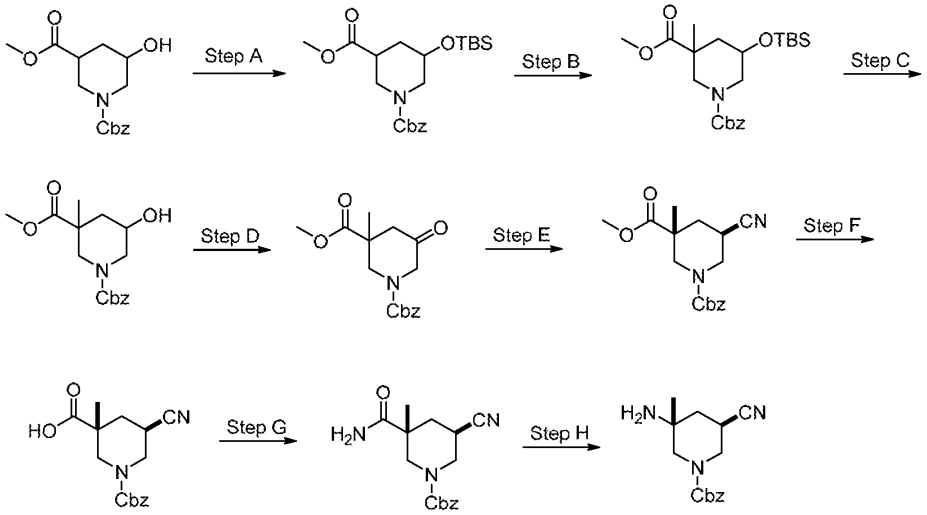
carboxylate. To a solution of tert-butyl 3-(((benzyloxy)carbonyl)amino)-3-(hydroxymethyl)piperidine-1-carboxylate (1.0 g, 2.5 mmol) in MeCN (10 mL) was added Ag_2O (2.2 g, 9.5 mmol) and MeI (4.7 mL, 75 mmol). The mixture was heated to 40 °C for 48 h. The suspension was filtered and the filter cake was washed with MeCN (30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-30% EtOAc in petroleum ether) to give tert-butyl 3-(((benzyloxy)carbonyl)amino)-3-(methoxymethyl)piperidine-1-carboxylate (0.15 g, 14% yield) as a colorless oil. LCMS (MM-ES+APCI, Pos): m/z 279.1 (M+H - Boc).

Step D. tert-butyl 3-amino-3-(methoxymethyl)piperidine-1-carboxylate. To a solution of tert-butyl 3-(((benzyloxy)carbonyl)amino)-3-(methoxymethyl)piperidine-1-carboxylate (0.20 g, 0.45 mmol) in THF (5.0 mL) was added 10 % Pd/C (0.048 g, 0.045 mmol). The mixture was stirred under an atmosphere of H_2 for 16 h. The suspension was filtered and the filter cake was washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure to give tert-butyl 3-amino-3-(methoxymethyl)piperidine-1-carboxylate (110 mg) as a colorless oil, which was taken onto the next step without further purification.

Intermediate I26



benzyl (rel-3R,5R)-3-amino-5-cyano-3-methylpiperidine-1-carboxylate



Step A. 1-benzyl 3-methyl 5-((tert-butyldimethylsilyl)oxy)piperidine-1,3-dicarboxylate. To a solution of 1-benzyl 3-methyl 5-hydroxypiperidine-1,3-dicarboxylate (5.0 g, 17 mmol) and TBSCl (3.9 g, 26 mmol) in DCM (50 mL) was added imidazole (2.3 g, 34 mmol) and DMAP

(1.0 g, 8.5 mmol). The mixture was stirred at rt for 2 h and then the solution was diluted with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-90% EtOAc in petroleum ether) to give 1-benzyl 3-methyl 5-((tert-butyldimethylsilyl)oxy)piperidine-1,3-dicarboxylate (12 g, 79% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 408.1 (M+H).

Step B. 1-benzyl 3-methyl 5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1,3-dicarboxylate. To a solution of 1-benzyl 3-methyl 5-((tert-butyldimethylsilyl)oxy)piperidine-1,3-dicarboxylate (3.5 g, 8.6 mmol) in THF (70 mL) at -65 °C was added LiHMDS (1.0 M; 26 mL) dropwise. A solution of MeI (1.5 mL, 25 mmol) in THF (10 mL) was added to the reaction. The reaction was warmed to rt and stirred for 30 min after which it was diluted with saturated aqueous NH_4Cl (20 mL) and then extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-90% EtOAc in petroleum ether) to give 1-benzyl 3-methyl 5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1,3-dicarboxylate (8.0 g, 86% yield) as colorless oil. LCMS (MM-ES+APCI, Pos): m/z 422.2 (M+H).

Step C. 1-benzyl 3-methyl 5-hydroxy-3-methylpiperidine-1,3-dicarboxylate. To solution of 1-benzyl 3-methyl 5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1,3-dicarboxylate (8.0 g, 19 mmol) in THF (80 mL) was added $NEt_3 \cdot HF$ (16 mL, 95 mmol). The mixture was stirred at rt for 2 h after which it was diluted with H_2O (100 mL) and then extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-17% EtOAc in petroleum ether) to give 1-benzyl 3-methyl 5-hydroxy-3-methylpiperidine-1,3-dicarboxylate (5.8 g, 99% yield) as colorless oil.

Step D. 1-benzyl 3-methyl 3-methyl-5-oxopiperidine-1,3-dicarboxylate. To a solution of 1-benzyl 3-methyl 5-hydroxy-3-methylpiperidine-1,3-dicarboxylate (3.8 g, 12 mmol) in DCM (60 mL) at 0 °C was added DMP (7.9 g, 19 mmol) was added. The mixture was allowed to warm to rt and stirred for 1 h. The mixture was diluted with NaOH (1.0 M; 15 mL) and then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (9-50% EtOAc in petroleum ether)

to give 1-benzyl 3-methyl 3-methyl-5-oxopiperidine-1,3-dicarboxylate (2.9 g, 77% yield) as colorless oil.

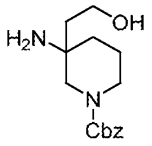
Step E. 1-benzyl 3-methyl (rel-3R,5R)-5-cyano-3-methylpiperidine-1,3-dicarboxylate. To a solution of 1-benzyl 3-methyl 3-methyl-5-oxopiperidine-1,3-dicarboxylate (2.9 g, 9.5 mmol) and 1-((isocyanomethyl)sulfonyl)-4-methylbenzene (3.0 g, 15 mmol) in DME (290 mL) and MeOH (3.5 mL) was added aqueous t-BuOK (1.0 M; 19 mL). The mixture was stirred at rt for 12 h after which it was diluted with H_2O (50 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-50% EtOAc in petroleum ether) to give 1-benzyl 3-methyl (rel-3R,5R)-5-cyano-3-methylpiperidine-1,3-dicarboxylate (1.1 g, 35% yield) as yellow oil. 1H NMR: (400 MHz, MeOH-d4) δ 7.43 - 7.25 (m, 5H), 5.20 - 5.08 (m, 2H), 4.53 - 4.20 (m, 2H), 3.56 (br d, J = 16.0 Hz, 3H), 3.19 - 2.94 (m, 2H), 2.93 - 2.78 (m, 1H), 2.56 - 2.43 (m, 1H), 1.68 (br t, J = 12.8 Hz, 1H), 1.31 - 1.12 (m, 3H).

Step F. (rel-3R,5R)-1-((benzyloxy)carbonyl)-5-cyano-3-methylpiperidine-3-carboxylic acid. To a solution of 1-benzyl 3-methyl (rel-3R,5R)-5-cyano-3-methylpiperidine-1,3-dicarboxylate (1.0 g, 3.2 mmol) in H_2O (10 mL) and THF (10 mL) was added LiOH (0.38 g, 16 mmol). The mixture was heated to 70 °C for 1 h after which it was diluted with H_2O (20 mL) and extracted with EtOAc (10 mL x 3). The aqueous phase was adjusted to pH 3 with aqueous HCl (1 M) and was then extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give (rel-3R,5R)-1-((benzyloxy)carbonyl)-5-cyano-3-methylpiperidine-3-carboxylic acid (0.90 g) as yellow oil, which was used in the next step without further purification.

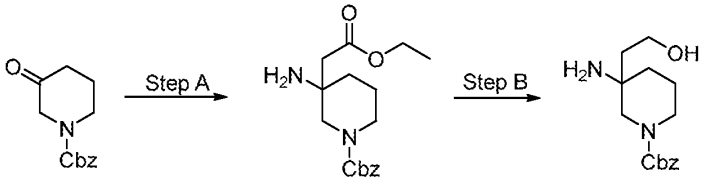
Step G. benzyl (rel-3R,5R)-3-carbamoyl-5-cyano-3-methylpiperidine-1-carboxylate. To a solution of (rel-3R,5R)-1-((benzyloxy)carbonyl)-5-cyano-3-methylpiperidine-3-carboxylic acid (0.90 g, 3.0 mmol) in DMF (20 mL) was added NH_4Cl (1.6 g, 30 mmol), DIPEA (6.2 mL, 36 mmol) and HATU (2.3 g, 6.0 mmol). The mixture was heated to 50 °C for 12 after which it was diluted with H_2O (30 mL) and extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-25% EtOAc in petroleum ether) to give benzyl (rel-3R,5R)-3-carbamoyl-5-cyano-3-methylpiperidine-1-carboxylate (0.60 g, 67% yield) as a light yellow oil.

Step H. benzyl (rel-3R,5R)-3-amino-5-cyano-3-methylpiperidine-1-carboxylate. To a solution of benzyl (rel-3R,5R)-3-carbamoyl-5-cyano-3-methylpiperidine-1-carboxylate (0.50 g, 1.7 mmol) in MeCN (5.0 mL) at 0 °C was added NBS (0.44 g, 2.5 mmol) followed by a solution of NaOH (0.3 g, 8.3 mmol) in H_2O (20 mL). The mixture was heated to 60 °C for 8 h after which it was diluted with H_2O (10 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50-100% EtOAc in petroleum ether) to give benzyl (rel-3R,5R)-3-amino-5-cyano-3-methylpiperidine-1-carboxylate (0.30 g, 55% yield) as colorless oil.

Intermediate I27



benzyl 3-amino-3-(2-hydroxyethyl)piperidine-1-carboxylate

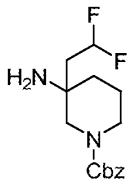


Step A. benzyl 3-amino-3-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate. To a solution of benzyl 3-oxopiperidine-1-carboxylate (2.0 g, 8.6 mmol) in EtOH (20 mL) was added NH_4OAc (2.0 g, 26 mmol) and 3-ethoxy-3-oxopropanoic acid (1.7 g, 13 mmol). The mixture was heated to 80 °C for 16 h after which it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-100% EtOAc in petroleum ether) to give benzyl 3-amino-3-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (1.8 g, 32% yield) as yellow oil. LCMS (MM-ES+APCI, Pos): m/z 321.0 (M+H).

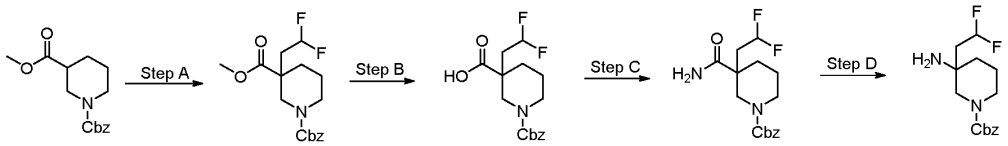
Step B. benzyl 3-amino-3-(2-hydroxyethyl)piperidine-1-carboxylate. To a solution of benzyl 3-amino-3-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (1.8 g, 2.7 mmol) in THF (10 mL) at 0 °C was added $LiAlH_4$ (2.5 M solution in THF; 2.7 mL). The mixture was stirred at 0 °C for 2 h after which it was quenched by slow addition of $Na_2SO_4 \cdot 10H_2O$ (3.2 mL, 13.7 mmol). The mixture was warmed to rt and stirred for 16 h. The suspension was filtered and the filter cake was washed with THF (20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC (10% – 40% MeCN in 0.05% aqueous NH_4OH). The fractions containing the product were lyophilized to obtain benzyl 3-amino-3-

(2-hydroxyethyl)piperidine-1-carboxylate (0.40 g, 53% yield) as yellow oil. LCMS (MM-ES+APCI, Pos): m/z 279.2 (M+H).

Intermediate I28



benzyl 3-amino-3-(2,2-difluoroethyl)piperidine-1-carboxylate



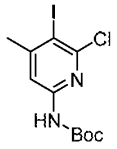
Step A. 1-benzyl 3-methyl 3-(2,2-difluoroethyl)piperidine-1,3-dicarboxylate. To a solution of 1-benzyl 3-methyl piperidine-1,3-dicarboxylate (3.0 g, 11 mmol) in THF (30 mL) at -78 °C was added LiHMDS (1.0 M in THF; 16mL). The reaction was stirred for 1 h at -78 °C, after which 1,1-difluoro-2-iodoethane (3.1 g, 16 mmol) was added. The reaction mixture was stirred at -78 °C for 1 h and then at rt for 12 h. The mixture was diluted with saturated aqueous NH_4Cl (50 mL) at 0 °C and was then extracted with EtOAc (50 mL x 3). The combined organic phase was washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (17-25% EtOAc in petroleum ether) to give 1-benzyl 3-methyl 3-(2,2-difluoroethyl)piperidine-1,3-dicarboxylate (2.0 g, 54% yield) as yellow liquid. LCMS (MM-ES+APCI, Pos): m/z 342.2 (M+H).

Step B. 1-((benzyloxy)carbonyl)-3-(2,2-difluoroethyl)piperidine-3-carboxylic acid. To a solution of 1-benzyl 3-methyl 3-(2,2-difluoroethyl)piperidine-1,3-dicarboxylate (1.9 g, 5.6 mmol) in THF (10 mL) and H_2O (10 mL) was added $LiOH.H_2O$ (1.2 g, 28 mmol). The mixture was stirred at rt for 12 h, after which it was diluted with H_2O (10 mL) and extracted with EtOAc (20 mL). The pH of aqueous phase was adjusted to 3 with HCl (4.0 M). The aqueous phase was concentrated under reduced pressure. To the slurry was added DCM (40 mL) and the mixture was stirred for 1 h. The slurry was filtered and then the organic phase of the filtrate was concentrated under reduced pressure to give 1-((benzyloxy)carbonyl)-3-(2,2-difluoroethyl)piperidine-3-carboxylic acid (1.6 g, 88% yield) as yellow gum. LCMS (MM-ES+APCI, Pos): m/z 326.2 (M+H).

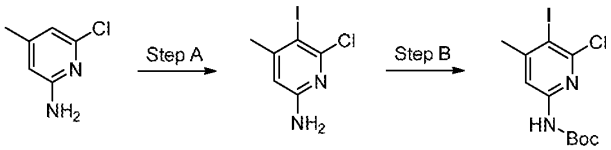
Step C. benzyl 3-carbamoyl-3-(2,2-difluoroethyl)piperidine-1-carboxylate. To a solution of 1-((benzyloxy)carbonyl)-3-(2,2-difluoroethyl)piperidine-3-carboxylic acid (1.5 g, 4.6 mmol), DIPEA (2.4 mL, 14 mmol), and HATU (2.6 g, 6.9 mmol) in DMF (10 mL) was added NH_4Cl (0.49 g, 9.2 mmol). The mixture was stirred at rt for 1 h after which it was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (17-25% EtOAc in petroleum ether) to give benzyl 3-carbamoyl-3-(2,2-difluoroethyl)piperidine-1-carboxylate (1.1 g, 74% yield) as colorless gum. LCMS (MM-ES+APCI, Pos): m/z 327.1 (M+H).

Step D. benzyl 3-amino-3-(2,2-difluoroethyl)piperidine-1-carboxylate. To a solution of benzyl 3-carbamoyl-3-(2,2-difluoroethyl)piperidine-1-carboxylate (1.0 g, 3.1 mmol) in MeCN (5 mL) at 0 °C was added NBS (0.82 g, 4.6 mmol). The mixture was stirred at rt for 30 min and then a solution of NaOH (0.61 g, 15 mmol) in H_2O (20 mL) was added. The mixture was heated to 60 °C for 30 min and then it was diluted with H_2O (10 mL) and extracted with EtOAc (50 mL x 3). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50-100% EtOAc in petroleum ether) to give benzyl 3-amino-3-(2,2-difluoroethyl)piperidine-1-carboxylate (0.35 g, 38% yield) as yellow gum. LCMS (MM-ES+APCI, Pos): m/z 299.1 (M+H).

Intermediate I29



tert-butyl (6-chloro-5-iodo-4-methylpyridin-2-yl)carbamate

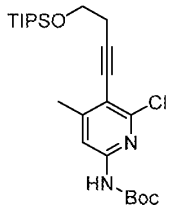


Step A. 6-chloro-5-iodo-4-methylpyridin-2-amine. To a solution of 6-chloro-4-methylpyridin-2-amine (3.0 g, 21 mmol) in DMF (100 mL) was added NIS (5.7 g, 25 mmol). The mixture was stirred at 80 °C for 2 h and then it was diluted with H_2O (50 mL) and extracted with EtOAc (100 mL x 3). The organics were washed with brine (50 mL x 2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was

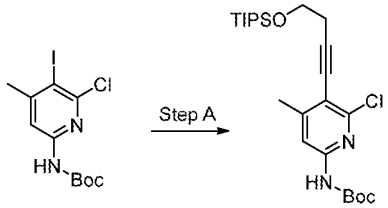
purified by silica gel column chromatography (0-20% EtOAc in petroleum ether) to give 6-chloro-5-iodo-4-methylpyridin-2-amine (4.0 g, 62% yield) as a yellow solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 4.53 (br s, 2H), 2.39 - 2.33 (m, 3H).

Step B. tert-butyl (6-chloro-5-iodo-4-methylpyridin-2-yl)carbamate. To a solution of 6-chloro-5-iodo-4-methylpyridin-2-amine (6.0 g, 20 mmol) and NEt_3 (8.2 mL, 59 mmol) in DCM (60 mL) was added DMAP (0.24 g, 2.0 mmol) and di-tert-butyl dicarbonate (5.2 g, 24 mmol). The mixture was stirred at rt for 16 h and then it was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x 3). The organic phases were washed with brine (50 mL x 2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-16% EtOAc in petroleum ether) to give tert-butyl (6-chloro-5-iodo-4-methylpyridin-2-yl)carbamate (2.0 g, 27% yield) as a yellow solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.19 (s, 1H), 2.49 (s, 3H), 1.52 (s, 9H).

Intermediate I30



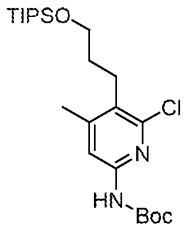
tert-butyl (6-chloro-4-methyl-5-(4-((triisopropylsilyl)oxy)but-1-yn-1-yl)pyridin-2-yl)carbamate



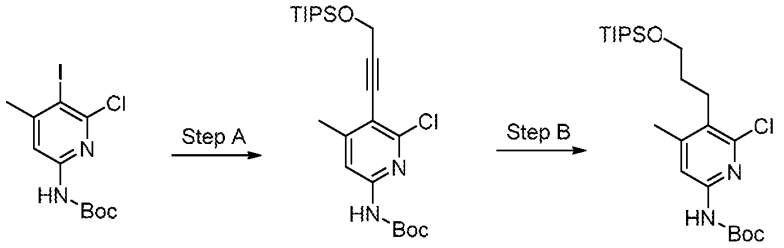
Step A. tert-butyl (6-chloro-4-methyl-5-(4-((triisopropylsilyl)oxy)but-1-yn-1-yl)pyridin-2-yl)carbamate. To a solution of tert-butyl (6-chloro-5-iodo-4-methylpyridin-2-yl)carbamate (2.0 g, 5.4 mmol) and (but-3-yn-1-yloxy)triisopropylsilane (1.8 g, 8.1 mmol) in DMF (20 mL) was added $Pd(PPh_3)_2Cl_2$ (0.38 g, 0.54 mmol), CuI (0.10 g, 0.54 mmol) and NEt_3 (2.2 mL, 16 mmol). The flask was then evacuated and backfilled with nitrogen three times and then it was heated to 65 °C for 16 h. After cooling to rt, the reaction was diluted with H_2O (50 mL) and extracted with EtOAc (100 mL x 3). The organic phases were washed with brine (50 mL x 2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-10% EtOAc in petroleum ether)

to give tert-butyl (6-chloro-4-methyl-5-(4-((triisopropylsilyl)oxy)but-1-yn-1-yl)pyridin-2-yl)carbamate (1.6 g, 62% yield) as yellow oil.

Intermediate I31



tert-butyl (6-chloro-4-methyl-5-(3-((triisopropylsilyl)oxy)propyl)pyridin-2-yl)carbamate

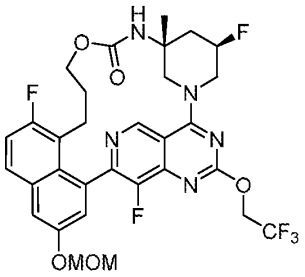


Step A. tert-butyl (6-chloro-4-methyl-5-(3-((triisopropylsilyl)oxy)prop-1-yn-1-yl)pyridin-2-yl)carbamate. To a solution tert-butyl (6-chloro-5-iodo-4-methylpyridin-2-yl)carbamate (4.0 g, 10 mmol) and triisopropyl(prop-2-yn-1-yloxy)silane (6.7 g, 31 mmol) in DMF (40 mL) was added $Pd(PPh_3)_2Cl_2$ (0.74 g, 1.1 mmol), CuI (0.20 g, 1.1 mmol) and NEt_3 (4.4 mL, 32 mmol). The flask was evacuated and backfilled with nitrogen three times and then it was heated to 65 °C for 16 h. After cooling to rt, the reaction was diluted with H_2O (100 mL) and extracted with EtOAc (150 mL x 3). The organic phases were washed with brine (50 mL x 3), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-3% EtOAc in petroleum ether) to give tert-butyl (6-chloro-4-methyl-5-(3-((triisopropylsilyl)oxy)prop-1-yn-1-yl)pyridin-2-yl)carbamate (3.8 g, 63% yield). LCMS (MM-ES+APCI, Pos): m/z 397.2 (M+H).

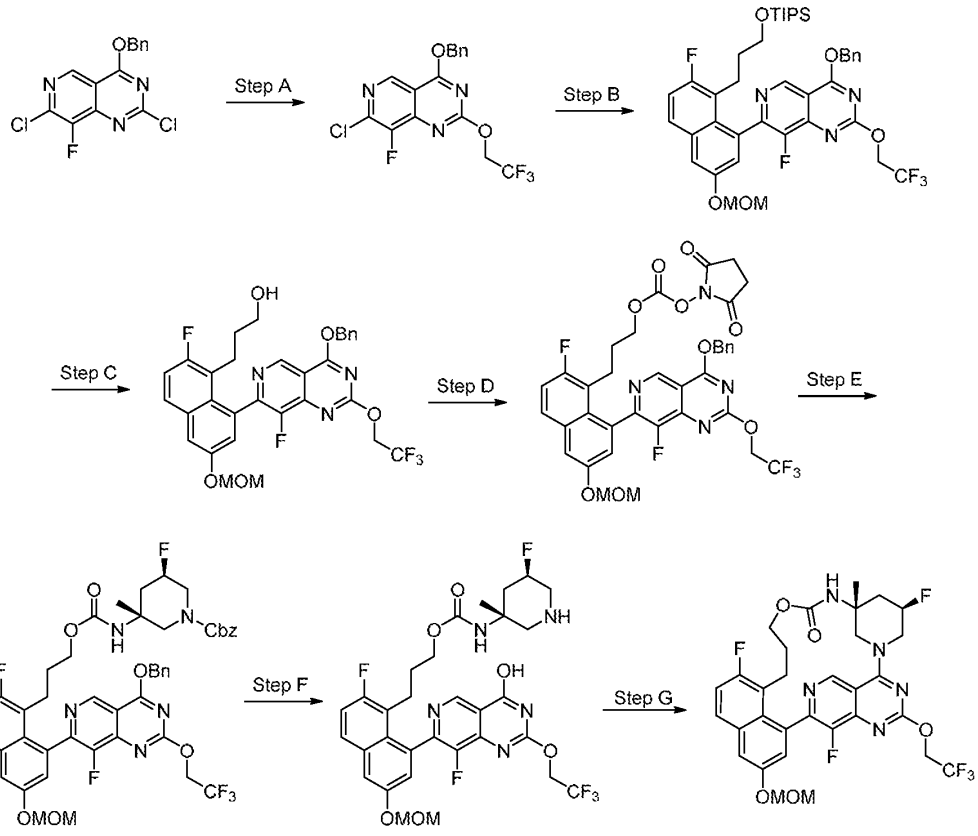
Step B. tert-butyl (6-chloro-4-methyl-5-(3-((triisopropylsilyl)oxy)propyl)pyridin-2-yl)carbamate. A solution of tert-butyl (6-chloro-4-methyl-5-(3-((triisopropylsilyl)oxy)prop-1-yn-1-yl)pyridin-2-yl)carbamate (2.0 g, 4.3 mmol) in MeOH (50 mL) and THF (50 mL) was passed through a fixed bed (5 mL, FLR1; 10% Ru/SiO_2) at 0.3 mL/min at 45 °C. The reactor was pressurized with hydrogen 1 MPa at a flow rate of 20 mL/min. The solution was collected from the reactor and then concentrated under reduced pressure to afford tert-butyl (6-chloro-4-methyl-5-(3-((triisopropylsilyl)oxy)propyl)pyridin-2-yl)carbamate (2.0 g, 88%

yield) as brown oil. LCMS (MM-ES+APCI, Pos): m/z 457.3 (M+H).

Intermediate I33



(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-3^3-(methoxymethoxy)-1^3-methyl-2^2-(2,2,2-trifluoroethoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 4-(benzyloxy)-7-chloro-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidine (0.50 g, 1.4 mmol) and 2,2,2-trifluoroethan-1-ol (0.20 mL, 2.8 mmol) in MeCN (6 mL) was added

DIPEA (0.49 mL, 2.8 mmol). The reaction was heated to 40 °C for 12 h and then it was diluted with H_2O (40 mL). The suspension was stirred for 10 min and then it was filtered. The filter cake was washed with H_2O (10 mL) and petroleum ether (10 mL). The precipitate was further dried under vacuum to obtain 4-(benzyloxy)-7-chloro-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (0.50 g, 89% yield). LCMS (MM-ES+APCI, Pos): m/z 388.0 (M+H).

Step B. 4-(benzyloxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-7-chloro-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (0.50 g, 1.3 mmol) and (3-(2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)triisopropylsilane (0.77 g, 1.3 mmol) in dioxane (6 mL) and H_2O (0.6 mL) was added mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.094 g, 0.13 mmol) and Cs2CO3 (0.82 g, 1.5 mmol). The mixture was sparged with N_2 for 2 m in and then it was heated to 90 °C for 1 h. The solution was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-25% EtOAc in petroleum ether) to give 4-(benzyloxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidine (0.83 g, 77% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 772.3 (M+H).

Step C. 3-(8-(4-(benzyloxy)-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propan-1-ol. To a solution of 4-(benzyloxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin (0.83 g, 0.97 mmol) in THF (10 mL) was added NEt_3-3HF (0.47 mL, 2.9 mmol). The mixture was stirred at 50 °C for 48 h and then it was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-25% EtOAc in petroleum ether) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propan-1-ol (0.45 g, 72% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 616.2 (M+H).

Step D. 3-(8-(4-(benzyloxy)-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propan-1-ol (0.20 g, 0.31 mmol) and pyridine (0.073 mL, 0.92 mmol) in DCM (3 mL) was added N,N′-disuccinimidyl carbonate (0.23 g, 0.92 mmol). The mixture was stirred at rt for 1 h and then it was diluted with H_2O (10 mL) and extracted with DCM (15 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.23 g, 99% yield).

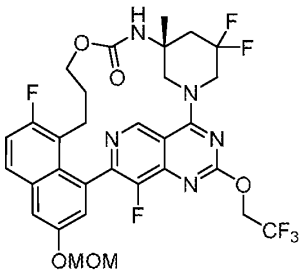
Step E. benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.23 g, 0.30 mmol) and DIPEA (0.11 mL, 0.61 mmol) in DCM (3 mL) was added benzyl (R)-3-amino-3-methylpiperidine-1-carboxylate (0.10 g, 0.36 mmol). The mixture was stirred 35 °C for 2 h and then it was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-100% EtOAc in petroleum ether) to give benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.22 g, 73% yield) as white solid. LCMS (MM-ES+APCI, Pos): m/z 908.5 (M+H).

Step F. 3-(2-fluoro-8-(8-fluoro-4-hydroxy-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate. To a solution of benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.22 g, 0.24 mmol) in THF (4 mL) was added 10% Pd/C (0.25 g, 0.24 mmol). The flask was evacuated and backfilled with H_2 three times. The mixture was stirred at rt under an atmosphere of H_2 for 2 h. The suspension was filtered through Celite, and the filter cake was washed with THF (30

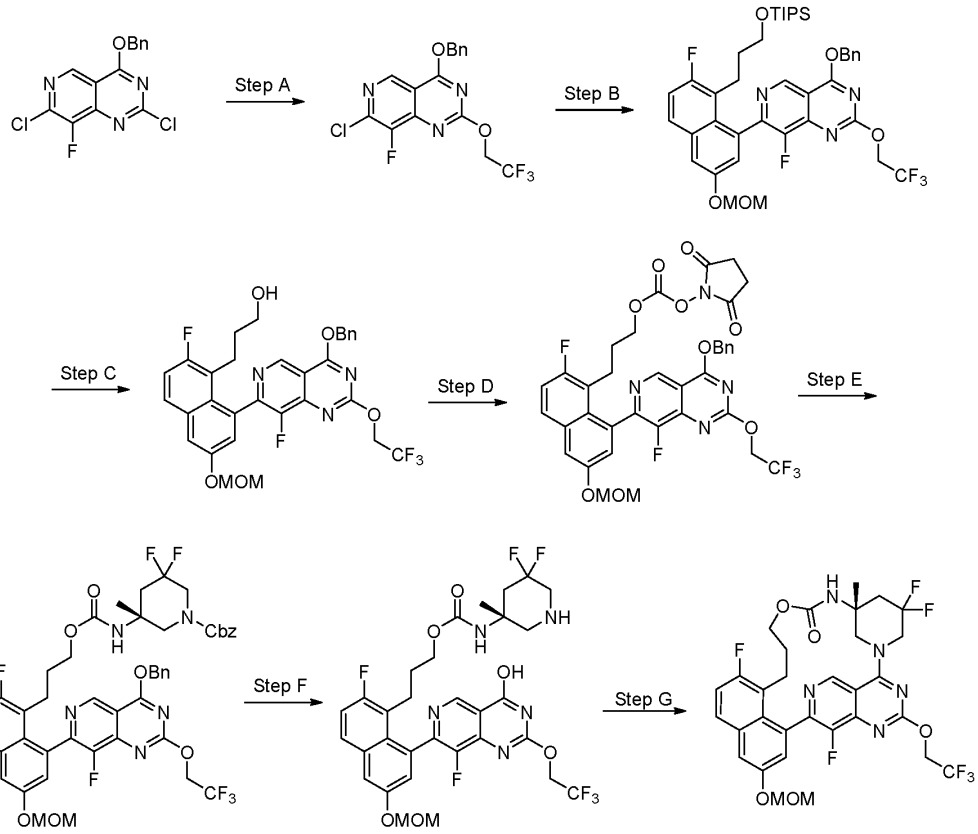
mL x 3). The filtrate was concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-4-hydroxy-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.16 g, 99% yield) as a white solid.

Step G. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-3^3-(methoxymethoxy)-1^3-methyl-2^2-(2,2,2-trifluoroethoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(2-fluoro-8-(8-fluoro-4-hydroxy-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.16 g, 0.23 mmol) and DIPEA (0.20 mL, 1.2 mmol) in MeCN (80 mL) was added BrOP (0.27 g, 0.70 mmol). The mixture was stirred at rt for 12 h and then it was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced. The residue was purified by silica gel chromatography (0-50% EtOAc in petroleum ether) to give (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-3^3-(methoxymethoxy)-1^3-methyl-2^2-(2,2,2-trifluoroethoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(2-fluoro-8-(8-fluoro-4-hydroxy-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.50 g, 30% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 666.3 (M+H).

Intermediate I34

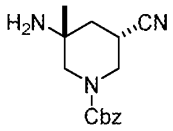


(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-3^3-(methoxymethoxy)-1^3-methyl-2^2-(2,2,2-trifluoroethoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one

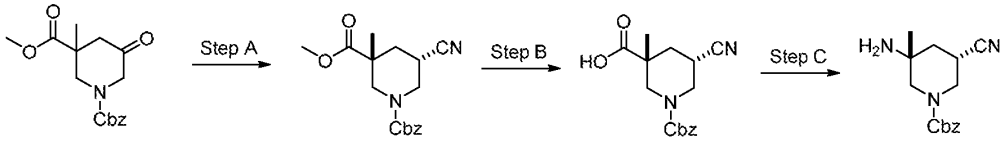


Steps A-G were performed following the procedure of Intermediate I33.

Intermediate I35



benzyl (rel-3R,5S)-3-amino-5-cyano-3-methylpiperidine-1-carboxylate



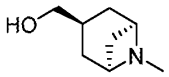
Step A. 1-benzyl 3-methyl (rel-3R,5S)-5-cyano-3-methylpiperidine-1,3-dicarboxylate. To a solution of 1-benzyl 3-methyl 3-methyl-5-oxopiperidine-1,3-dicarboxylate (5.0 g, 16 mmol) and 1-((isocyanomethyl)sulfonyl)-4-methylbenzene (5.1 g, 26 mmol) in DME (500 mL) and MeOH (6 mL) was added t-BuOK (3.7 g, 33 mmol). The reaction was stirred for 12 h and then it was diluted with H_2O (50 mL) and then extracted with ethyl acetate (30 mL x 3). The

combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-50% EtOAc in petroleum ether) to give 1-benzyl 3-methyl (rel-3R,5S)-5-cyano-3-methylpiperidine-1,3-dicarboxylate (1.0 g, 19% yield) as a yellow oil. ^{1}H NMR: (400 MHz, MeOH-d_4) δ 7.47 - 7.32 (m, 5H), 5.26 - 5.11 (m, 2H), 3.95 (br d, J = 13.2 Hz, 1H), 3.83 - 3.62 (m, 5H), 3.42 - 3.34 (m, 1H), 3.15 - 3.06 (m, 1H), 2.36 (dd, J = 7.2, 14.0 Hz, 1H), 1.96 (dd, J = 4.4, 13.9 Hz, 1H), 1.18 (br s, 3H).

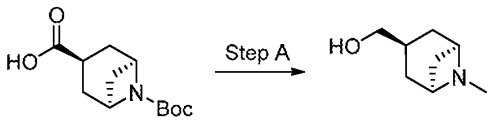
Step B. (rel-3R,5S)-1-((benzyloxy)carbonyl)-5-cyano-3-methylpiperidine-3-carboxylic acid. To a solution of 1-benzyl 3-methyl (rel-3R,5S)-5-cyano-3-methylpiperidine-1,3-dicarboxylate (1.0 g, 3.2 mmol) in THF (10 mL) and H_2O (2.5 mL) was added LiOH (0.30 g, 13 mmol). The mixture was stirred for 12 h and then it was diluted with H_2O (5 mL). The pH of mixture was adjusted to 7 with 1 M HCl. The resulting mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (rel-3R,5S)-1-((benzyloxy)carbonyl)-5-cyano-3-methylpiperidine-3-carboxylic acid (0.90 g, 94% yield) as a yellow oil, which was used into the next step without further purification.

Step C. benzyl (rel-3R,5S)-3-amino-5-cyano-3-methylpiperidine-1-carboxylate. To a solution of (rel-3R,5S)-1-((benzyloxy)carbonyl)-5-cyano-3-methylpiperidine-3-carboxylic acid (0.90 g, 3.0 mmol) in THF (80 mL) was added DPPA (2.6 mL, 12 mmol) and DIPEA (7.3 mL, 42 mmol). The mixture was heated to 75 °C and stirred for 4 h. The solution was cooled to rt then a solution of KOH (3.3 g, 60 mmol) in H_2O (25 mL) was added dropwise. The mixture was stirred for 12 h and then it was diluted with H_2O (100 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25-75% EtOAc in petroleum ether) to give benzyl (rel-3R,5S)-3-amino-5-cyano-3-methylpiperidine-1-carboxylate (0.50 g, 61% yield) as a colorless oil. ^{1}H NMR: (400 MHz, MeOH-d_4) δ 7.47 - 7.25 (m, 5H), 5.23 - 5.05 (m, 2H), 4.19 - 4.06 (m, 1H), 3.75 - 3.56 (m, 1H), 3.28 - 3.11 (m, 1H), 2.99 (ddd, J = 4.0, 9.6, 14.0 Hz, 2H), 2.00 - 1.89 (m, 1H), 1.81 - 1.68 (m, 1H), 1.05 (br s, 3H).

Intermediate I36

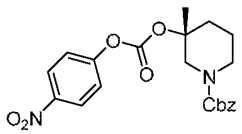


((1R,3r,5S)-6-methyl-6-azabicyclo[3.1.1]heptan-3-yl)methanol

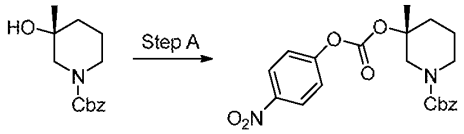


Step A. ((1R,3r,5S)-6-methyl-6-azabicyclo[3.1.1]heptan-3-yl)methanol. To a solution of (1R,3r,5S)-6-(tert-butoxycarbonyl)-6-azabicyclo[3.1.1]heptane-3-carboxylic acid (0.10 g, 410 mmol) in THF (7.5 mL) at 0°C was added $LiAlH_4$ (2.5 M in THF; 1.0 mL). The reaction was heated to 70°C for 1 h. After cooling to 0°C the reaction was quenched with H_2O (10 mL). The mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give ((1R,3r,5S)-6-methyl-6-azabicyclo[3.1.1]heptan-3-yl)methanol (0.020 g, 34% yield), which was used in the next step without further purification.

Intermediate I37

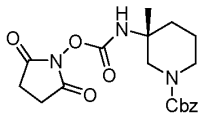


benzyl (R)-3-methyl-3-(((4-nitrophenoxy)carbonyl)oxy)piperidine-1-carboxylate

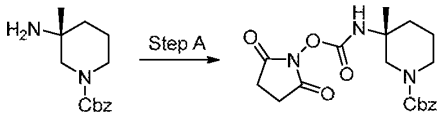


Step A. benzyl (R)-3-methyl-3-(((4-nitrophenoxy)carbonyl)oxy)piperidine-1-carboxylate. To a solution of benzyl (R)-3-hydroxy-3-methylpiperidine-1-carboxylate (0.60 g, 2.4 mmol) and pyridine (0.39 mL, 4.8 mmol) in DCM (6 mL) at 0°C was added 4-nitrophenyl carbonochloridate (1.5 g, 7.2 mmol). The reaction was stirred at rt for 12 h and then it was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (44-74% MeCN in 0.1% aqueous NH_4HCO_3) to give benzyl (R)-3-methyl-3-(((4-nitrophenoxy)carbonyl)oxy)piperidine-1-carboxylate (0.47 g, 47% yield). LCMS (MM-ES+APCI, Pos): m/z 415.2 (M+H).

Intermediate I38

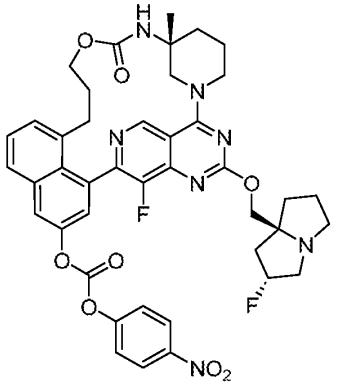


benzyl (R)-3-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate

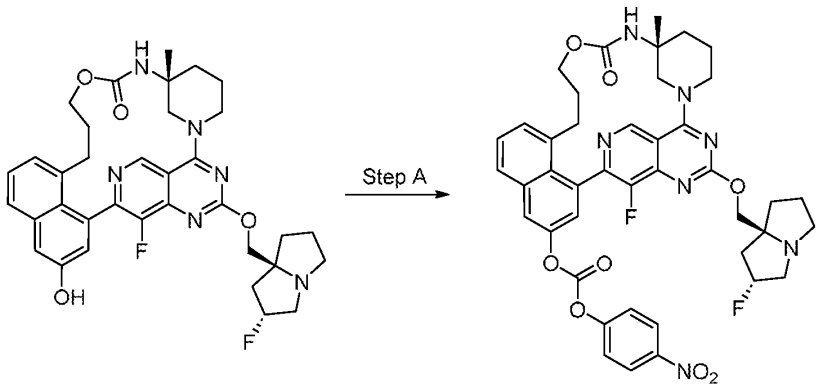


Step A. benzyl (R)-3-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of benzyl (R)-3-amino-3-methylpiperidine-1-carboxylate (0.10 g, 0.40 mmol) and pyridine (0.16 mL, 2.0 mmol) in DCM (1 mL) was added N,N'-disuccinimidyl carbonate (0.21 g, 0.81 mmol). The reaction was stirred at 30 °C for 2 h and then it was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give benzyl (R)-3-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.15 g, 96% yield). LCMS (MM-ES+APCI, Pos): m/z 390.0 (M+H).

Intermediate I39

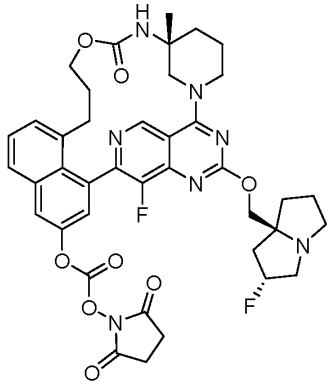


(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (4-nitrophenyl) carbonate

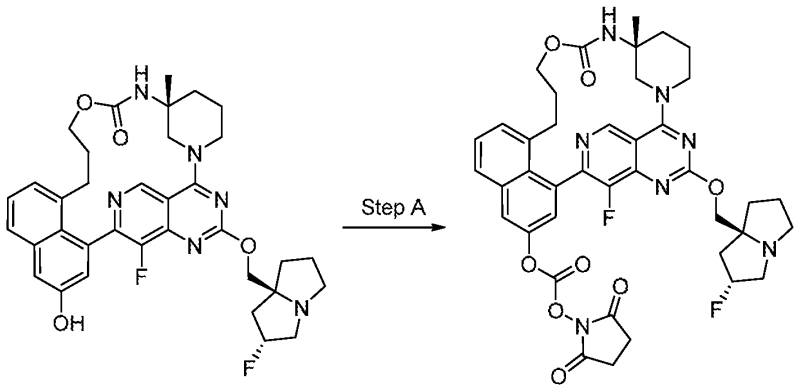


Step A. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (4-nitrophenyl) carbonate. To a solution of (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.051 g, 0.078 mmol) and DIPEA (0.027 mL, 0.16 mmol) in DCM (0.5 mL) was added 4-nitrophenyl carbonochloridate (0.019 g, 0.093 mmol). The reaction was stirred at rt for 1 h. The mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (4-nitrophenyl) carbonate (0.060 g, 96% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): 810.7 (M+H).

Intermediate I40

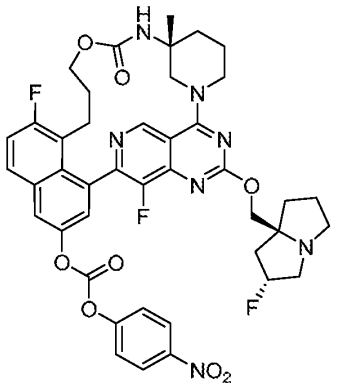


2,5-dioxopyrrolidin-1-yl ((1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) carbonate

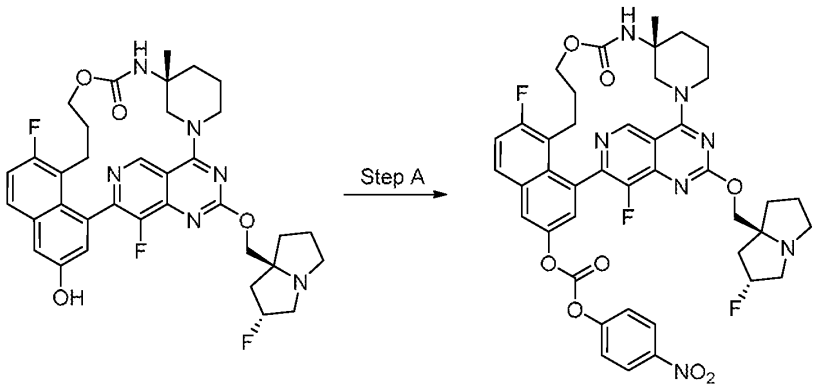


Intermediate I40 was synthesized using N,N -disuccinimidyl carbonate according to Intermediate I39 procedures.

Intermediate I41

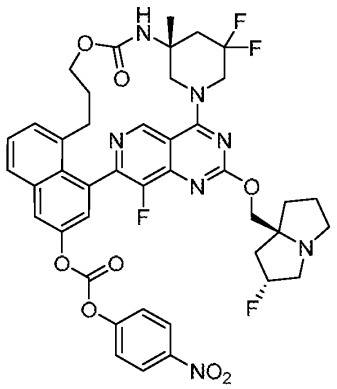


(1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (4-nitrophenyl) carbonate

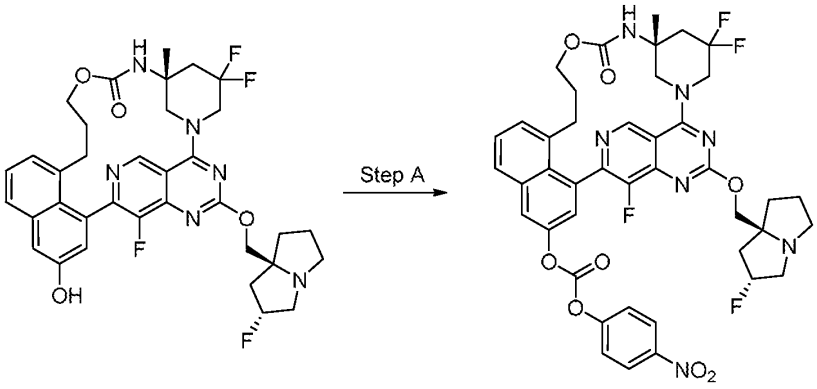


Intermediate I41 was synthesized according to Intermediate I39 procedures.

Intermediate I42

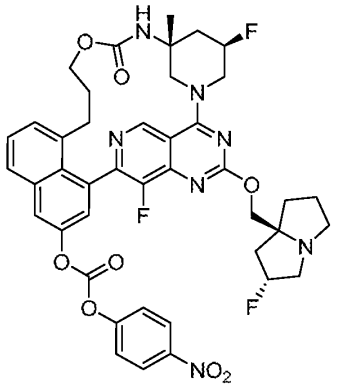


4-nitrophenyl ((1^{3}R)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) carbonate

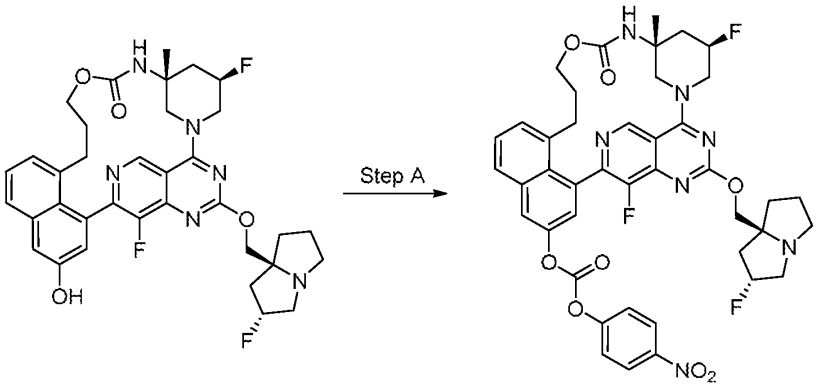


Intermediate I42 was synthesized according to Intermediate I39 procedures.

Intermediate I43

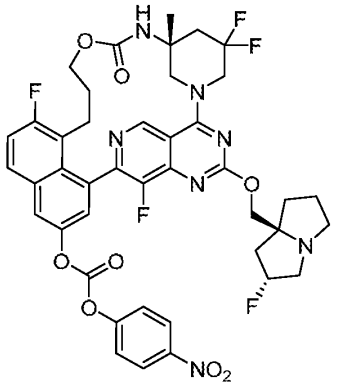


(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (4-nitrophenyl) carbonate

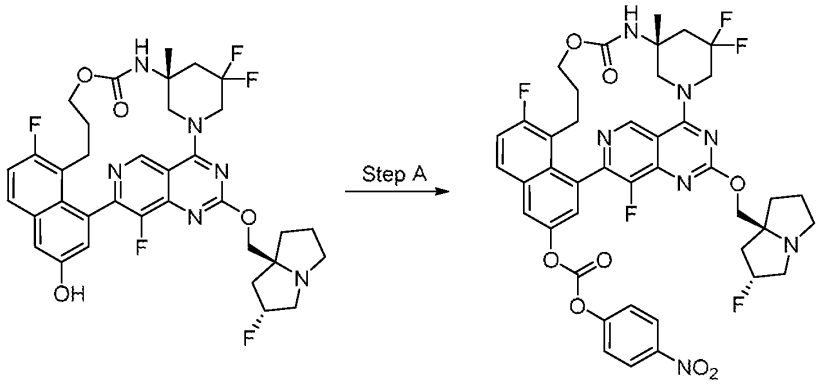


Intermediate I43 was synthesized according to Intermediate I39 procedures.

Intermediate I44

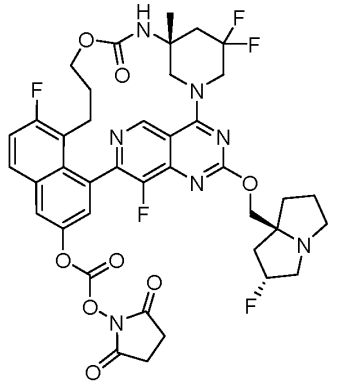


4-nitrophenyl ((1^{3}R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) carbonate



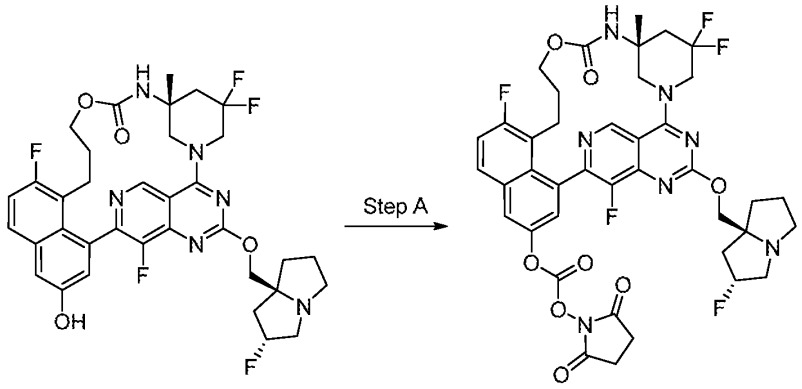
Intermediate I44 was synthesized according to Intermediate I39 procedures.

Intermediate I45



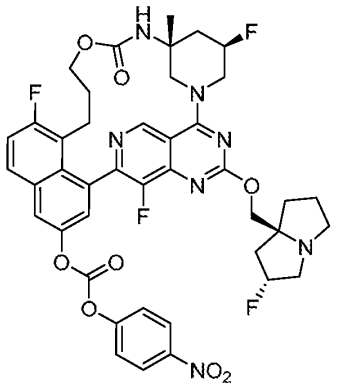
2,5-dioxopyrrolidin-1-yl ((1^{3}R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-

pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) carbonate

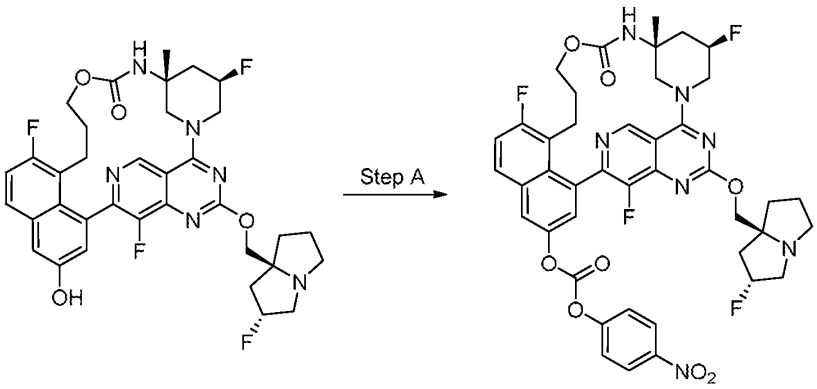


Intermediate I45 was synthesized using N,N -disuccinimidyl carbonate according to Intermediate I39 procedures.

Intermediate I46

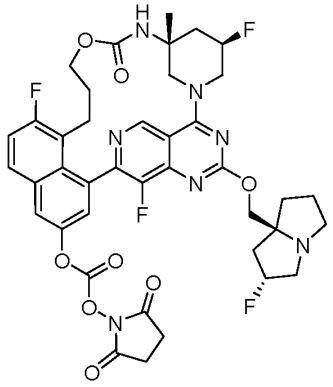


4-nitrophenyl ((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) carbonate

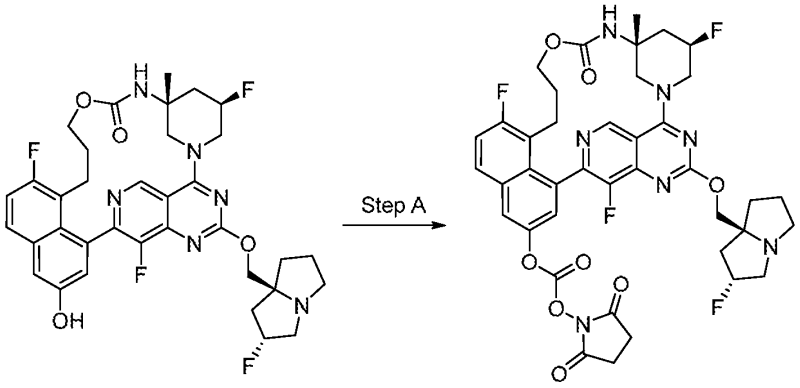


Intermediate I43 was synthesized according to Intermediate I39 procedures.

Intermediate I47



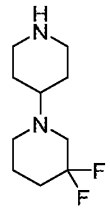
2,5-dioxopyrrolidin-1-yl ((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) carbonate



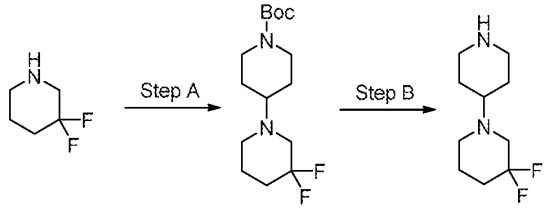
Intermediate I47 was synthesized using N,N -disuccinimidyl carbonate according to

Intermediate I39 procedures.

Intermediate I48



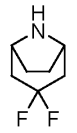
3,3-difluoro-1,4'-bipiperidine



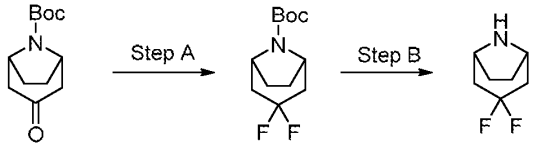
Step A. tert-butyl 3,3-difluoro-[1,4'-bipiperidine]-1'-carboxylate. To a solution of tert-butyl 4-oxopiperidine-1-carboxylate (0.25 g, 1.3 mmol) and 3,3-difluoropiperidine (0.20 g, 1.3 mmol) in DMF (3 mL) was added DIPEA (0.22 mL, 1.3 mmol). The mixture was sparged with nitrogen for 5 min and then it was heated to 50 °C for 2 h. Then, to the reaction was added AcOH (0.072 mL, 1.3 mmol) and $NaBH(OAc)_3$ (0.66 g, 3.1 mmol). The mixture was sparged with nitrogen for 5 min and then it was heated to 50 °C for 10 h. The mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (17% EtOAc in petroleum ether) to give tert-butyl 3,3-difluoro-[1,4'-bipiperidine]-1'-carboxylate (0.10 g, 26% yield) as a colorless oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.15 (br s, 2H), 2.78 - 2.63 (m, 4H), 2.60 - 2.46 (m, 3H), 1.88 (dt, J = 6.8, 13.6 Hz, 2H), 1.79 - 1.66 (m, 5H), 1.46 (s, 9H), 1.43 - 1.39 (m, 1H).

Step B. 3,3-difluoro-1,4'-bipiperidine. To a solution of tert-butyl 3,3-difluoro-[1,4'-bipiperidine]-1'-carboxylate (0.050 g, 0.16 mmol) in DCM (1 mL) was added 2 M HCl in dioxane (1.0 mL). The reaction was stirred at rt for 1 h. The mixture was concentrated under reduced pressure to give 3,3-difluoro-1,4'-bipiperidine (0.30 g, 76% yield) as a white solid.

Intermediate I49



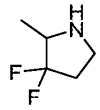
(rel-1R,5S)-3,3-difluoro-8-azabicyclo[3.2.1]octane



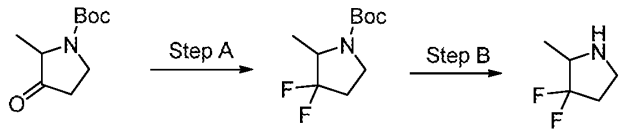
Step A. tert-butyl (rel-1R,5S)-3,3-difluoro-8-azabicyclo[3.2.1]octane-8-carboxylate. To a solution of tert-butyl (rel-1R,5S)-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (0.50 g, 2.2 mmol) in DCM (4 mL) was added DAST (6.0 mL, 45 mmol). The reaction was stirred at rt for 16 h and then it was quenched with sat. aq. $NaHCO^3$ solution (10 mL) at 0 °C. The mixture was extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (9-25% EtOAc in petroleum ether) to give tert-butyl (rel-1R,5S)-3,3-difluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (0.22 g, 40% yield) as brown oil. LCMS (MM-ES+APCI, Pos): 192.1 (M+H-tBu).

Step B. (rel-1R,5S)-3,3-difluoro-8-azabicyclo[3.2.1]octane. To a solution of tert-butyl (rel-1R,5S)-3,3-difluoro-8-azabicyclo[3.2.1]octane-8-carboxylate (0.22 g, 0.89 mmol) in DCM (10 mL) was added 2 M HCl in 1,4-dioxane (5 mL). The reaction was stirred for 2 h and then it was concentrated under reduced pressure to give (rel-1R,5S)-3,3-difluoro-8-azabicyclo[3.2.1]octane (160 mg), which was taken onto the next step without further purification.

Intermediate I50



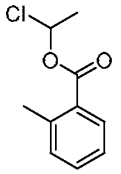
3,3-difluoro-2-methylpyrrolidine



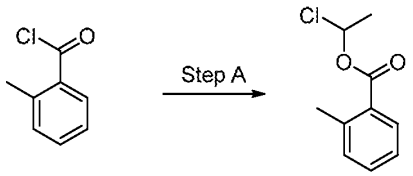
Step A. tert-butyl 3,3-difluoro-2-methylpyrrolidine-1-carboxylate. To a solution of tert-butyl 2-methyl-3-oxopyrrolidine-1-carboxylate (0.50 g, 2.5 mmol) in DCM (6 mL) was added DAST (10 mL, 76 mmol). The reaction was stirred at rt for 12 h and then it was quenched with ice water (100 mL). The resulting mixture extracted with DCM (25 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (9% EtOAc in petroleum ether) to give tert-butyl 3,3-difluoro-2-methylpyrrolidine-1-carboxylate (0.20 g, 36% yield) as a yellow oil. ^{1}H NMR : (400 MHz, $CDCl_3$) δ 4.07 - 3.83 (m, 1H), 3.52 (br t, J = 6.4 Hz, 2H), 2.38 - 2.21 (m, 2H), 1.49 (s, 9H), 1.29 - 1.22 (m, 3H).

Step B. 3,3-difluoro-2-methylpyrrolidine. To a solution of tert-butyl 3,3-difluoro-2-methylpyrrolidine-1-carboxylate (0.20 g, 0.90 mmol) in DCM (1 mL) was added 2 M HCl in 1,4-dioxane (1 mL). The reaction was stirred for 30 min and then it was concentrated under reduced pressure to give 3,3-difluoro-2-methylpyrrolidine (100 mg), which was taken onto the next step without further purification.

Intermediate I51



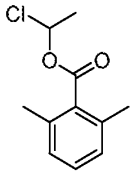
1-chloroethyl 2-methylbenzoate



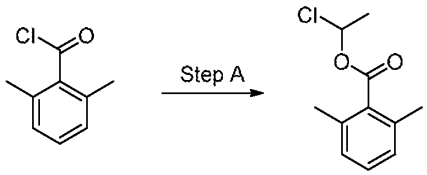
Step A. 1-chloroethyl 2-methylbenzoate. To a solution of 2-methylbenzoyl chloride (0.42 mL, 3.2 mmol) and $ZnCl_2$ (0.0088 g, 0.065 mmol) in DCM (5 mL) at -10 °C was added a solution of acetaldehyde (5 M in THF, 0.65 mL) in DCM (1.5 mL). The mixture was allowed

to warm to rt and was stirred for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-2% EtOAc in petroleum ether) to give 1-chloroethyl 2-methylbenzoate (0.45 g, 70% yield) as colorless oil. ^{1}H NMR: (400 MHz, DMSO-d6) δ 7.87 (d, J = 7.6 Hz, 1H), 7.59 - 7.51 (m, 1H), 7.41 - 7.32 (m, 2H), 6.80 (q, J = 5.6 Hz, 1H), 2.54 (s, 3H), 1.88 (d, J = 5.6 Hz, 3H).

Intermediate I52



1-chloroethyl 2,6-dimethylbenzoate

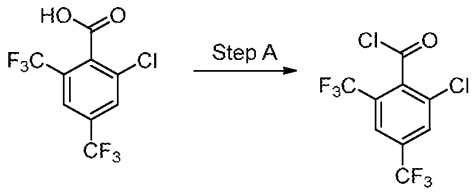


Intermediate I52 was synthesized according to Intermediate I51 procedures. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.27 - 7.19 (m, 1H), 7.06 (d, *J* = 7.6 Hz, 2H), 6.85 - 6.76 (m, 1H), 2.36 (s, 6H), 1.89 (d, *J* = 6.0 Hz, 3H).

Intermediate I53



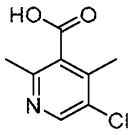
2-chloro-4,6-bis(trifluoromethyl)benzoyl chloride



Step A. 2-chloro-4,6-bis(trifluoromethyl)benzoyl chloride. To a solution of 2-chloro-4,6-

bis(trifluoromethyl)benzoic acid (0.020 g, 0.068 mmol) in DCM (1 mL) at 0 °C was added oxalyl chloride (0.0066 mL, 0.075 mmol) followed by DMF (0.1 mL). The reaction was allowed to warm to rt and was stirred for 1 h. The mixture was concentrated under reduced pressure to obtain 2-chloro-4,6-bis(trifluoromethyl)benzoyl chloride (0.020 g, 94% yield), which was taken onto the next step without further purification.

Intermediate I54



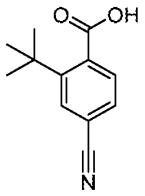
5-chloro-2,4-dimethylnicotinic acid



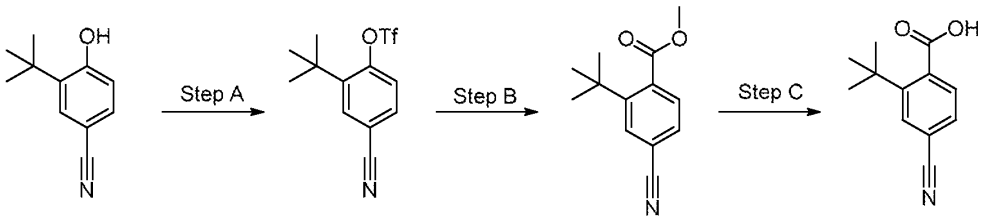
Step A. 3-bromo-5-chloro-2,4-dimethylpyridine. To a solution of 5-bromo-4,6-dimethylpyridin-3-amine (1.0 g, 5.0 mmol) in MeCN (10 mL) was added CuCl (0.74 g, 7.5 mmol) and *t*-BuONO (1.2 mL, 10 mmol). The reaction was stirred at 50 °C for 1 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-17% EtOAc in petroleum ether) to give 3-bromo-5-chloro-2,4-dimethylpyridine (0.70 g, 64% yield) as a colorless liquid. GCMS (MM-ES+APCI, Pos): 218.8 / 220.8 (M+H).

Step B. 5-chloro-2,4-dimethylnicotinic acid. To a solution of 3-bromo-5-chloro-2,4-dimethylpyridine (0.30 g, 1.4 mmol) in THF (5 mL) at -78 °C was added *n*-BuLi (2.5 M in THF, 0.82 mL). The reaction was stirred at -78 °C for 1 h, then CO_2 (0.060 g, 1.4 mmol) was added. The reaction mixture was allowed to stir at -78 °C for 1 h and then it was slowly diluted with H_2O (5 mL). The mixture was extracted with ethyl acetate (10 mL x 3). The pH of aqueous phase was adjusted to 4 with 1 M HCl, and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC (0 – 20% MeCN in 0.1% aqueous formic acid). The fractions containing the product were lyophilized to obtain 5-chloro-2,4-dimethylnicotinic acid (0.035 g, 14% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): 186.0 (M+H).

Intermediate I55



2-(tert-butyl)-4-cyanobenzoic acid



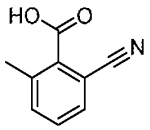
Step A. 2-(tert-butyl)-4-cyanophenyl trifluoromethanesulfonate. To a solution of 3-(tert-butyl)-4-hydroxybenzonitrile (0.35 g, 2.0 mmol) and pyridine (0.32 mL, 4.0 mmol) in DCM (0.5 mL) at 0 °C was added Tf_2O (0.66 mL, 4.0 mmol). The mixture was stirred at 0 °C for 1 h and then it was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-9% EtOAc in petroleum ether) to give 2-(tert-butyl)-4-cyanophenyl trifluoromethanesulfonate (0.50 g, 82% yield) as yellow oil. ^1H NMR: (400 MHz, $CDCl_3$) δ 7.71 (d, J = 2.0 Hz, 1H), 7.54 (dd, J = 2.0, 8.8 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 1.37 (s, 9H).

Step B. methyl 2-(tert-butyl)-4-cyanobenzoate. Two solutions were prepared and pumped through a flow reactor. Solution 1 containing 2-(tert-butyl)-4-cyanophenyl trifluoromethanesulfonate (0.50 g, 1.6 mmol) and $Pd(dppf)Cl_2$ (0.13 g, 0.16 mmol) in DMF (5 mL), MeOH (5 mL), and EtOAc (0.50 mL) was pumped at 1 mL/min at 3.5 MPa. Solution 2 containing DMF (5 mL) and MeOH (5 mL) was pumped at 0.1 mL/min. The two pumps were combined in a flow reactor (FLR1, SS, Coils reactor) along with CO(g) which was pumped at 30 mL/min at 4.0 MPa. After 60 min in the reactor, the mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography eluting (0-9% EtOAc in petroleum ether) to give methyl 2-(tert-butyl)-4-cyanobenzoate (0.30 g, 85% yield)

as a colorless oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 1.2 Hz, 1H), 7.54 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 3.95 (s, 3H), 1.42 (s, 9H).

Step C. 2-(tert-butyl)-4-cyanobenzoic acid. To a solution of methyl 2-(tert-butyl)-4-cyanobenzoate (0.050 g, 0.23 mmol) in EtOAc (0.5 mL) was added LiI (0.092 g, 0.69 mmol). The mixture was heated to 70 °C and stirred for 12 h. The mixture was quenched with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The aqueous phase pH was adjusted to 1 with 1 M HCl (5mL) and then it was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 2-(tert-butyl)-4-cyanobenzoic acid (0.040 g, 86% yield,) as yellow oil, which was taken onto the next step without further purification.

Intermediate I56

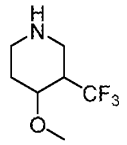


2-cyano-6-methylbenzoic acid

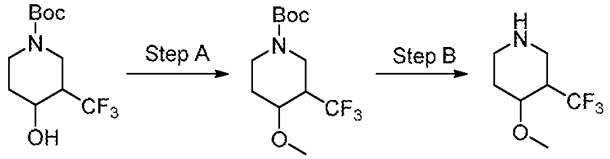


Step A. 2-cyano-6-methylbenzoic acid. To a solution of 2-bromo-3-methylbenzonitrile (0.20 g, 1.0 mmol) in THF (2 mL) at -78 °C was added n-BuLi (2.5 M in THF; 0.49 mL). The reaction was stirred at -78 °C for 30 min and then dry ice was added to the reaction. The mixture was allowed to warm to rt and was stirred for 16 h. The mixture was diluted with sat. aq. NH4Cl (2 mL) and then it was extracted with ethyl acetate (4 mL). The pH of aqueous layer was adjusted to 3 with 1 M HCl, which was then lyophilized to give 2-cyano-6-methylbenzoic acid (0.10 mg, 46% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): 162.2 (M+H).

Intermediate I57



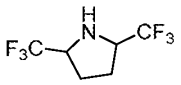
4-methoxy-3-(trifluoromethyl)piperidine



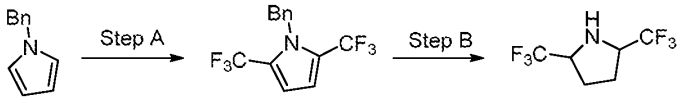
Step A. tert-butyl 4-methoxy-3-(trifluoromethyl)piperidine-1-carboxylate. To a solution of tert-butyl 4-hydroxy-3-(trifluoromethyl)piperidine-1-carboxylate (0.20 g, 0.74 mmol) in THF (5 mL) at 0 °C was added NaH (60% in mineral oil; 0.059 g, 1.5 mmol). The mixture was stirred for 1 h and then CH_3I (0.093 mL, 1.5 mmol). The reaction was stirred for 1 h and then it was diluted with H_2O (10 mL) extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (17-25% EtOAc in petroleum ether) to obtain tert-butyl 4-methoxy-3-(trifluoromethyl)piperidine-1-carboxylate (0.20 g, 95% yield) as a colorless liquid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.16 - 3.75 (m, 3H), 3.38 (s, 3H), 3.22 (br d, J = 12.4 Hz, 1H), 3.11 - 3.02 (m, 1H), 2.38 - 2.19 (m, 1H), 2.05 - 1.92 (m, 1H), 1.47 (s, 9H).

Step B. 4-methoxy-3-(trifluoromethyl)piperidine. A solution of tert-butyl 4-methoxy-3-(trifluoromethyl)piperidine-1-carboxylate (0.10 g, 0.35 mmol) in 2 M HCl in dioxane (0.88 mL) was stirred for 1 h. The mixture was concentrated under reduced pressure to give 4-methoxy-3-(trifluoromethyl)piperidine (0.060 g, 93% yield) as a colorless oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.80 (br d, J = 1.6 Hz, 1H), 3.87 (br s, 1H), 3.46 (br d, J = 9.2Hz, 1H), 3.38 (s, 3H), 3.34 (br s, 1H), 3.20 (br s, 1H), 3.05 (br s, 1H), 2.68 - 2.28 (m, 1H), 2.23 - 1.95 (m, 2H).

Intermediate I58



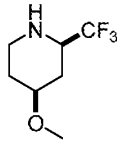
2,5-bis(trifluoromethyl)pyrrolidine



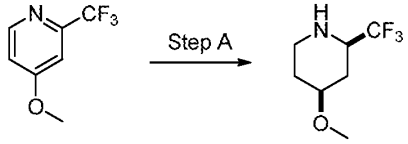
Step A. 1-benzyl-2,5-bis(trifluoromethyl)-1H-pyrrole. To a solution of 1-benzyl-1H-pyrrole (2.0 g, 13 mmol) in MeCN (200 mL) was added sodium 2,2,2-trifluoroacetate (10 g, 76 mmol), $Fe(OTf)_2$ (0.45 g, 1.3 mmol,), 4,4'-dimethoxy-2,2'-bipyridine (0.28 g, 1.3 mmol) and $K_2S_2O_8$ (10 g, 38 mmol). The mixture was stirred at rt under an atmosphere of nitrogen for 16 h while irradiated with a 395 nm LED. The suspension was filtered and the filter cake was washed with MeCN (100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% hexanes) to give 1-benzyl-2,5-bis(trifluoromethyl)-1H-pyrrole (2.0 g, 54% yield) as colorless oil. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.36 - 7.30 (m, 2H), 7.27 (d, J = 7.2 Hz, 1H), 6.95 (s, 2H), 6.86 (d, J = 7.2 Hz, 2H), 5.43 (s, 2H).

Step B. 2,5-bis(trifluoromethyl)pyrrolidine. A solution of 1-benzyl-2,5-bis(trifluoromethyl)-1H-pyrrole (0.40 g, 1.4 mmol) in THF (20 mL) was pumped at a rate of 0.3 mL/min through a fixed bed (FLR1, SS, Fixed bed, 6.350 (1/4'') mm, 1 mL, 100 °C) of $Pd(OH)_2/Al_2O_3$ (3.5 g). The H_2 back pressure regulator was adjusted to 3 MPa, and the flow rate was adjusted to 30 mL/min. The solution was collected and concentrated under reduced pressure to afford 2,5-bis(trifluoromethyl)pyrrolidine (0.28 g, 99% yield) as a colorless oil, which was taken onto the next step without further purification.

Intermediate I59



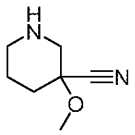
(rel-2R,4S)-4-methoxy-2-(trifluoromethyl)piperidine



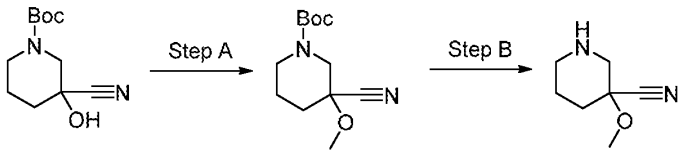
Step A. (rel-2R,4S)-4-methoxy-2-(trifluoromethyl)piperidine. A solution of 4-methoxy-2-(trifluoromethyl)pyridine (0.10 g, 0.57 mmol) in MeOH (30 mL) was pumped at a rate of 0.4 mL/min through a fixed bed (FLR1, SS, Fixed bed, 6.350 (1/4") mm, 1 mL, 95 °C) of 10%

Ru/SiO_2 (3.3 g). The H_2 back pressure regulator was adjusted to 2.5 MPa, and the flow rate of adjusted to 30 mL/min. The solution was collected and concentrated under reduced pressure to afford (rel-2R,4S)-4-methoxy-2-(trifluoromethyl)piperidine (0.030 g, 29% yield) as yellow oil. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 3.50 - 3.35 (m, 1H), 3.34 - 3.25 (m, 1H), 3.22 (s, 3H), 3.05 (br d, J = 12.0 Hz, 1H), 2.63 - 2.55 (m, 1H), 2.14 (br d, J = 11.6 Hz, 1H), 1.95 (br d, J = 11.2 Hz, 1H), 1.28 - 1.06 (m, 2H).

Intermediate I60



3-methoxypiperidine-3-carbonitrile

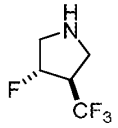


Step A. tert-butyl 3-cyano-3-methoxypiperidine-1-carboxylate. To a solution of tert-butyl 3-cyano-3-hydroxypiperidine-1-carboxylate (0.10 g, 0.44 mmol) in DCM (1 mL) at 0 °C was added trimethyloxonium tetrafluoroborate (0.098 g, 0.66 mmol). The mixture was allowed to warm to rt and was stirred for 10 min. The solution was cooled to 0 °C, then 1,8-bis(dimethylamino)naphthalene (0.14 g, 0.66 mmol, 1.5 eq) was added. The reaction was allowed to warm to rt and was stirred for 12 h. The mixture was diluted with H_2O (5 mL) and sat. NH_4Cl solution (2 mL) and then extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-5% EtOAc in petroleum ether) to give tert-butyl 3-cyano-3-methoxypiperidine-1-carboxylate (0.070 g, 66% yield) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.92 (br d, *J* = 13.2 Hz, 1H), 3.70 - 3.16 (m, 6H), 2.27 - 2.10 (m, 1H), 1.94 - 1.75 (m, 2H), 1.68 (dt, *J* = 3.6, 8.4 Hz, 1H), 1.53 - 1.47 (m, 9H).

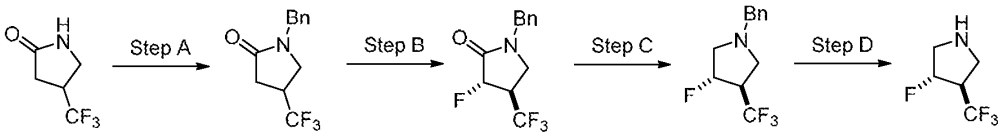
Step B. 3-methoxypiperidine-3-carbonitrile. To a solution of tert-butyl 3-cyano-3-methoxypiperidine-1-carboxylate (0.050 g, 0.21 mmol) in DCM (0.50 mL) was added 2 M HCl in dioxane (0.50 mL). The reaction was stirred for 1 h and then it was concentrated under reduced pressure to give 3-methoxypiperidine-3-carbonitrile (0.035 g, 95%), which

was taken onto the next step without further purification.

Intermediate I61



(rel-3S,4R)-3-fluoro-4-(trifluoromethyl)pyrrolidine



Step A. 1-benzyl-4-(trifluoromethyl)pyrrolidin-2-one. To a solution of 4-(trifluoromethyl)pyrrolidin-2-one (1.0 g, 6.5 mmol) in THF (10 mL) at 0 °C was added NaH (60% in mineral oil; 0.52 g, 13 mmol). The mixture was stirred for 1 h at this temperature and then benzyl bromide (2.2 g, 13 mmol) was added. The reaction was warmed to rt and was stirred for 1 h. The mixture was diluted with sat. aq. NH_4Cl solution (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (17-25% EtOAc in petroleum ether) to give1-benzyl-4-(trifluoromethyl)pyrrolidin-2-one (1.5 g, 85% yield). ^1H NMR: (400 MHz, $CDCl_3$) δ 7.39 - 7.29 (m, 3H), 7.24 (d, J = 6.8 Hz, 2H), 4.23 - 4.07 (m, 2H), 3.50 - 3.33 (m, 2H), 3.16 - 3.00 (m, 1H), 2.82 - 2.53 (m, 2H).

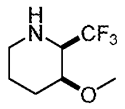
Step B. (rel-3S,4R)-1-benzyl-3-fluoro-4-(trifluoromethyl)pyrrolidin-2-one. To a solution of 1-benzyl-4-(trifluoromethyl)pyrrolidin-2-one (0.6 g, 2.2 mmol) in THF (48 mL) at -78 °C was added LDA (2.5 M in THF; 1.3 mL). The mixture was stirred at -78 °C for 30 min, then N-(benzene sulfonyl)-N-fluoro-benzene sulfonamide (1.05 g, 3.33 mmol, 1.5 eq) was added N-fluorobenzenesulfonimide (1.1 g, 3.3 mmol). The reaction was stirred at -78 °C for 30 min and warmed to rt and stirred for 1 h. The solution was diluted with 1 M aq. NH_4Cl solution and then extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (rel-3S,4R)-1-benzyl-3-fluoro-4-(trifluoromethyl)pyrrolidin-2-one (0.34 g, 50% yield). LCMS (MM-ES+APCI, Pos): 261.9 (M+H).

Step C. (rel-3S,4R)-1-benzyl-3-fluoro-4-(trifluoromethyl)pyrrolidine. To a solution of (rel-

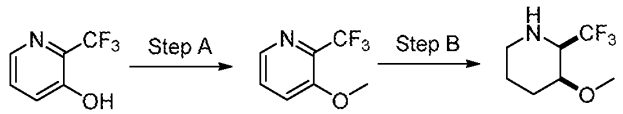
3S,4R)-1-benzyl-3-fluoro-4-(trifluoromethyl)pyrrolidin-2-one (0.34 g, 1.1 mmol) at 0 °C was added BH_3·THF (1.0 M; 5.9 mL). The reaction was stirred at rt for 1 h and then it was quenched with MeOH (10 mL). The mixture was warmed to 70 °C and was stirred for 1 h. The solution was concentrated under reduced pressure to give (rel-3S,4R)-1-benzyl-3-fluoro-4-(trifluoromethyl)pyrrolidine (0.27 g, 98% yield). LCMS (MM-ES+APCI, Pos): 248.0 (M+H).

Step D. (rel-3S,4R)-3-fluoro-4-(trifluoromethyl)pyrrolidine. To a solution of (rel-3S,4R)-1-benzyl-3-fluoro-4-(trifluoromethyl)pyrrolidine (0.27 g, 1.1 mmol) in THF (10 mL) was added 10% Pd/C (2.3 g). The flask was evacuated and backfilled with H_2 three times and then it was stirred at rt under an atmosphere of H_2 for 1 h. The suspension was filtered and the filter cake was washed with THF (10 mL). The mixture was concentrated under reduced pressure to give (rel-3S,4R)-3-fluoro-4-(trifluoromethyl)pyrrolidine (0.15 g, 87% yield), which was taken onto the next step without further purification.

Intermediate I62



(rel-2R,3S)-3-methoxy-2-(trifluoromethyl)piperidine

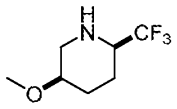


Step A. 3-methoxy-2-(trifluoromethyl)pyridine. To a solution of 2-(trifluoromethyl)pyridin-3-ol (0.30 g, 1.8 mmol) and K_2CO_3 (0.51 g, 3.7 mmol) in DMF (3 mL) was added MeI (0.23 mL, 3.7 mmol). The reaction ws stirred for 16 h and then it was diluted with H2O (2 mL) and extracted with EtOAc (2 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-25% EtOAc in petroleum ether) to give 3-methoxy-2-(trifluoromethyl)pyridine (0.25 g, 76% yield) as a white solid. LCMS (MM-ES+APCI, Pos): 178.2 (M+H).

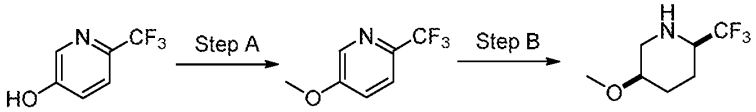
Step B. (rel-2R,3S)-3-methoxy-2-(trifluoromethyl)piperidine. A solution of give 3-methoxy-2-(trifluoromethyl)pyridine (0.25 g, 1.3 mmol) in THF (10 mL) and 2,2,2-trifluoroethanol (10 mL) was pumped at a rate of 0.3 mL/min through a fixed bed (FLR1, SS, Fixed bed, 6.350 (1/4") mm, 5 mL, 100 °C) of 10% Ru/SiO_2 (2.7 g). The H_2 back pressure regulator was

adjusted to 2.5 MPa, and the flow rate of adjusted to 30 mL/min. The solution was collected and concentrated under reduced pressure to afford (rel-2R,3S)-3-methoxy-2-(trifluoromethyl)piperidine (0.080 g, 42% yield) as yellow oil. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 3.87 (dq, J = 6.8, 9.6 Hz, 1H), 3.50 - 3.46 (m, 1H), 3.34 (s, 1H), 3.26 (s, 3H), 2.90 (br d, J = 13.2 Hz, 1H), 2.54 (s, 1H), 2.10 - 1.93 (m, 2H), 1.60 - 1.50 (m, 1H), 1.49 (br s, 1H).

Intermediate I63

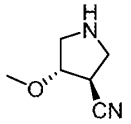


(rel-2R,5R)-5-methoxy-2-(trifluoromethyl)piperidine

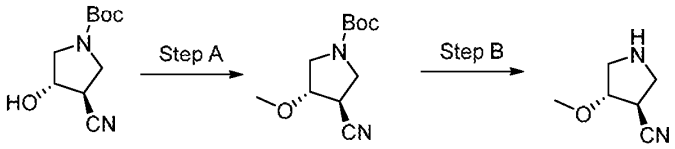


Steps A-B were performed with 6-(trifluoromethyl)pyridin-3-ol following the procedures for Intermediate I62. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.35 (s, 3H), 3.29 - 3.21 (m, 2H), 3.12 (br s, 1H), 2.73 (br d, *J* = 12.4 Hz, 1H), 2.13 (br d, *J* = 14.0 Hz, 1H), 1.74 - 1.68 (m, 2H), 1.68 - 1.52 (m, 2H).

Intermediate I64

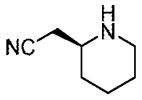


(3S,4S)-4-methoxypyrrolidine-3-carbonitrile

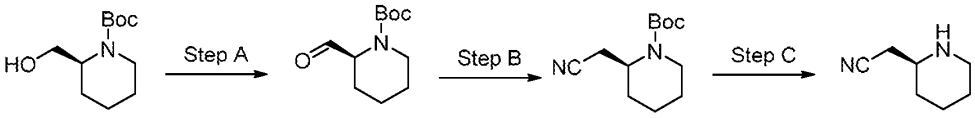


Steps A-B were performed with tert-butyl (3S,4S)-3-cyano-4-hydroxypyrrolidine-1-carboxylate following the procedures for Intermediate I60.

Intermediate I65



(S)-2-(piperidin-2-yl)acetonitrile

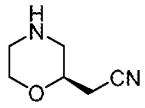


Step A. tert-butyl (S)-2-formylpiperidine-1-carboxylate. To a solution of tert-butyl (S)-2-(hydroxymethyl)piperidine-1-carboxylate (0.50 g, 2.3 mmol) in DCM (5 mL) at 0 °C was added DMP (1.5 g, 3.5 mmol). The reaction was stirred at rt for 2 h and then it was diluted with H_2O (10 mL). The pH of mixture was adjusted to 9 with 3 M NaOH and then it was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-20% EtOAc in petroleum ether) to give tert-butyl (S)-2-formylpiperidine-1-carboxylate (0.30 g, 61% yield) as colorless oil.

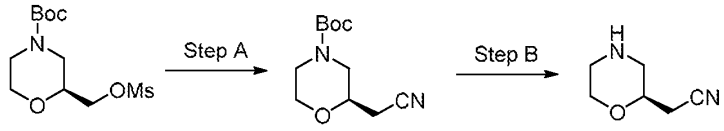
Step B. tert-butyl (S)-2-(cyanomethyl)piperidine-1-carboxylate. To a solution of tert-butyl (S)-2-formylpiperidine-1-carboxylate (0.30 g, 1.4 mmol) and tosylmethyl isocyanide (0.44 g, 2.3 mmol) in DME (30 mL) and MeOH (0.5 mL) was added KOtBu (0.32 g, 2.8 mmol). The reaction was stirred for 12 h and then it was diluted with H_2O (15 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-20% EtOAc in petroleum ether) to give tert-butyl (S)-2-(cyanomethyl)piperidine-1-carboxylate (0.060 g, 19% yield). ^1H NMR: (400 MHz, $CDCl_3$) δ 4.63 (br d, J = 6.8 Hz, 1H), 4.17 - 3.98 (m, 1H), 2.82 - 2.69 (m, 1H), 2.62 (d, J = 7.6 Hz, 2H), 1.88 - 1.79 (m, 1H), 1.78 - 1.65 (m, 3H), 1.53 - 1.47 (m, 10H).

Step C. (S)-2-(piperidin-2-yl)acetonitrile. To a solution of tert-butyl (S)-2-(cyanomethyl)piperidine-1-carboxylate (0.060 g, 0.27 mmol) in DCM (0.50 mL) was added 2 M HCl in dioxane (0.50 mL). The reaction was stirred for 1 h and then it was concentrated under reduced pressure to give (S)-2-(piperidin-2-yl)acetonitrile (0.040 g, 93%), which was taken onto the next step without further purification.

Intermediate I66



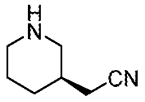
(R)-2-(morpholin-2-yl)acetonitrile



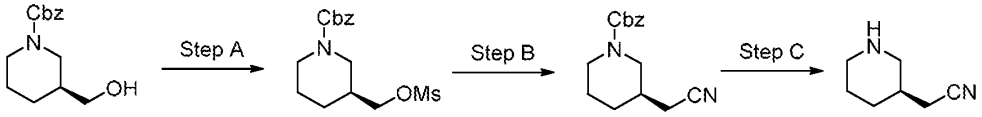
Step A. tert-butyl (R)-2-(cyanomethyl)morpholine-4-carboxylate. To a solution of tert-butyl (S)-2-(((methylsulfonyl)oxy)methyl)morpholine-4-carboxylate (0.30 g, 1.0 mmol) in DMF (5 mL) was added NaCN (0.060 g, 1.2 mmol). The reaction was heated to 80 °C for 16 h and then it was diluted with H_2O (10 mL). The pH of mixture was adjusted to 11 with sat. aq. NaOH solution and then it was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-100% EtOAc in hexanes to give tert-butyl (R)-2-(cyanomethyl)morpholine-4-carboxylate (0.060 g, 26% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.08 - 3.78 (m, 3H), 3.72 - 3.63 (m, 1H), 3.57 (dt, J = 2.8, 11.6 Hz, 1H), 2.97 (br t, J = 11.6 Hz, 1H), 2.85 - 2.66 (m, 1H), 2.64 - 2.48 (m, 2H), 1.48 (s, 9H).

Step B. (R)-2-(morpholin-2-yl)acetonitrile. To a solution of tert-butyl (R)-2-(cyanomethyl)morpholine-4-carboxylate (0.060 g, 0.27 mmol) in DCM (2 mL) was added 2 M HCl in dioxane (2.7 mL). The reaction was heated to 40 °C for 1 h and then it was concentrated under reduced pressure to give (R)-2-(morpholin-2-yl)acetonitrile (0.040 g, 93% yield) as a white solid, which was taken onto the next step without further purification.

Intermediate I67



(R)-2-(piperidin-3-yl)acetonitrile



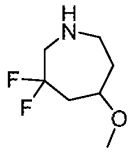
Step A. benzyl (S)-3-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate. To a solution of benzyl (S)-3-(hydroxymethyl)piperidine-1-carboxylate (0.30 g, 1.2 mmol) and NEt_3 (0.33 mL, 2.4 mmol) in DCM (4 mL) at 0 °C was added methanesulfonic anhydride (0.36 g, 2.1 mmol). The reaction was stirred at rt for 30 min and then it was diluted with H_2O (3 mL) and extracted with ethyl acetate (3 mL x 3). The combined organic layers were washed with brine

(5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-50% EtOAc in petroleum ether) to give benzyl (S)-3-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate (0.36 g, 91% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.44 - 7.29 (m, 5H), 5.14 (s, 2H), 4.19 - 3.99 (m, 3H), 3.92 (br d, J = 12.6 Hz, 1H), 3.11 - 2.80 (m, 5H), 2.05 - 1.92 (m, 1H), 1.90 - 1.79 (m, 1H), 1.77 - 1.65 (m, 1H), 1.56 - 1.45 (m, 1H), 1.41 - 1.30 (m, 1H).

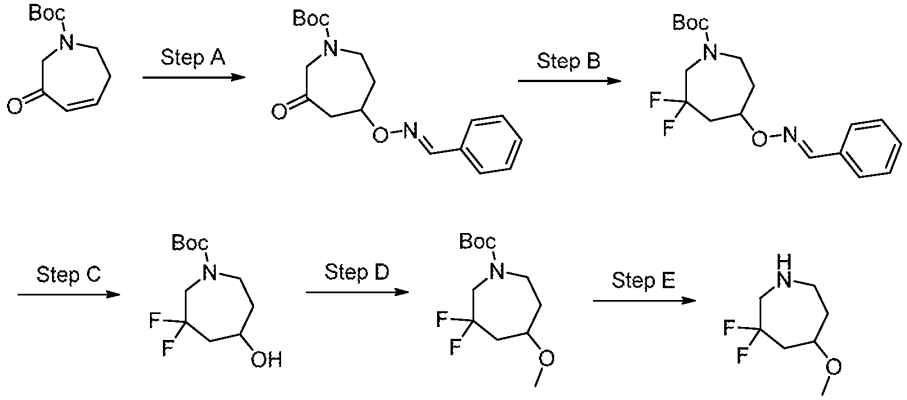
Step B. benzyl (R)-3-(cyanomethyl)piperidine-1-carboxylate. To a solution of benzyl (S)-3-(((methylsulfonyl)oxy)methyl)piperidine-1-carboxylate (0.36 g, 1.1 mmol) in DMF (5 mL) was added NaCN (0.064 g, 1.3 mmol) and KI (0.091g, 0.55 mmol). The reaction was heated to 45 °C for 2 h and then 70 °C for 12 h. The mixture was diluted with H_2O (10 mL). The pH of mixture was adjusted to 11 with sat. aq. NaOH solution and then it was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-100% EtOAc in hexanes) to give benzyl (R)-3-(cyanomethyl)piperidine-1-carboxylate (0.23 g, 81% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.41 - 7.30 (m, 6H), 5.14 (br d, J = 2.4 Hz, 2H), 4.17 - 4.02 (m, 1H), 3.97 (td, J = 4.0, 13.2 Hz, 1H), 3.01 - 2.90 (m, 1H), 2.90 - 2.69 (m, 1H), 2.43 - 2.32 (m, 1H), 2.32 - 2.24 (m, 1H), 2.03 - 1.87 (m, 2H), 1.73 (td, J = 34.0, 13.2 Hz, 1H), 1.53 (br d, J = 11.6 Hz, 1H), 1.40 (ddd, J = 3.2, 10.8, 13.2 Hz, 1H).

Step C. (R)-2-(piperidin-3-yl)acetonitrile. To a solution of benzyl (R)-3-(cyanomethyl)piperidine-1-carboxylate (0.080 g, 0.31 mmol) in THF (3 mL) was added 10% Pd/C (0.030 g, 0.028 mmol). The flask was then evacuated and backfilled with H_2 three times and then it was stirred under an atmosphere of H_2 for 2 h. The suspension was filtered through Celite, and the filter cake was washed with THF (200 mL x 3). The filtrate was concentrated under reduced pressure to give (R)-2-(piperidin-3-yl)acetonitrile (0.038 g, 99% yield) as colorless oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.12 (br d, J = 12.0 Hz, 1H), 2.99 (td, J = 3.6, 12.0 Hz, 1H), 2.58 (dt, J = 2.8, 11.6 Hz, 1H), 2.49 - 2.40 (m, 1H), 2.39 - 2.31 (m, 1H), 2.29 (dd, J = 2.8, 6.8 Hz, 2H), 1.97 - 1.90 (m, 1H), 1.88 - 1.82 (m, 1H), 1.74 - 1.68 (m, 1H), 1.55 - 1.46 (m, 1H), 1.32 - 1.24 (m, 1H).

Intermediate I68



3,3-difluoro-5-methoxyazepane



Step A. tert-butyl (E)-5-((benzylideneamino)oxy)-3-oxoazepane-1-carboxylate. To a solution of tert-butyl 3-oxo-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate (0.50 g, 2.4 mmol), (E)-benzaldehyde oxime (0.43 g, 3.6 mmol) in MeCN (10 mL) was added DBU (0.014 mL, 0.095 mmol). The reaction was stirred for 16 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5-20% EtOAc in petroleum ether) to give tert-butyl (E)-5-((benzylideneamino)oxy)-3-oxoazepane-1-carboxylate (0.40 g, 48% yield). ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.57 (dd, J = 2.8, 6.8 Hz, 2H), 7.41 - 7.35 (m, 3H), 4.72 - 4.53 (m, 1H), 4.42 - 4.22 (m, 1H), 3.97 - 3.61 (m, 2H), 3.42 - 3.19 (m, 1H), 3.11 - 2.97 (m, 1H), 2.96 - 2.82 (m, 1H), 2.38 - 2.07 (m, 2H), 1.54 - 1.45 (m, 9H).

Step B. tert-butyl (E)-5-((benzylideneamino)oxy)-3,3-difluoroazepane-1-carboxylate. To a solution of give tert-butyl (E)-5-((benzylideneamino)oxy)-3-oxoazepane-1-carboxylate (0.400 g, 1.1 mmol) in DCM (10 mL) was added bis(2-methoxyethyl)aminosulfur trifluoride (1.3 mL, 5.7 mmol). The reaction was heated to 50 °C for 12 h and then it was quenched with aq. $NaHCO_3$ (10 mL). The resulting mixture was extracted with DCM (8 mL x 3). The combined organic layers were washed with brine (6 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica

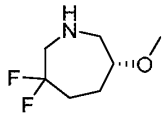
gel column chromatography (0-9% EtOAc in petroleum ether) to give tert-butyl (E)-5-((benzylideneamino)oxy)-3,3-difluoroazepane-1-carboxylate (0.250 g, 62% yield) as colorless oil. LCMS (MM-ES+APCI, Pos): 299.2 (M+H-tBu).

Step C. tert-butyl 3,3-difluoro-5-hydroxyazepane-1-carboxylate. To a solution tert-butyl (E)-5-((benzylideneamino)oxy)-3,3-difluoroazepane-1-carboxylate (0.25 g, 0.71 mmol) in MeOH (10 mL) was added 10% Pd/C (0.25 g,). The flask was then evacuated and backfilled with H_2 three times and then it was stirred under an atmosphere of H_2 for 1 h. The suspension was filtered and the filtrate was concentrated under reduced pressure to give tert-butyl 3,3-difluoro-5-hydroxyazepane-1-carboxylate (0.15 g) as colorless oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.09 (br t, J = 8.4 Hz, 1H), 3.91 - 3.60 (m, 3H), 3.45 - 3.22 (m, 1H), 2.48 - 2.16 (m, 2H), 2.11 - 1.97 (m, 1H), 1.96 - 1.77 (m, 1H), 1.47 (br s, 9H).

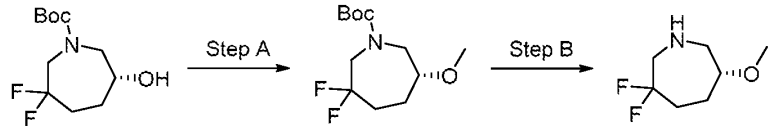
Step D. tert-butyl 3,3-difluoro-5-methoxyazepane-1-carboxylate. To a solution of tert-butyl 3,3-difluoro-5-hydroxyazepane-1-carboxylate (0.15 g, 0.60 mmol) in THF (3 mL) at 0 °C was added NaH (60% in mineral oil; 0.036 g, 0.90 mmol). The mixture was stirred at rt for 1 h and then CH_3I (0.074 mL, 1.2 mmol) was added. The reaction was stirred at rt for 2 h and then it was diluted with H_2O (5 mL) and then extracted with ethyl acetate (4 mL x 3). The combined organic layers were washed with brine (4 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (9-25% EtOAc in petroleum ether) to tert-butyl 3,3-difluoro-5-methoxyazepane-1-carboxylate (0.10 g, 60% yield) as colorless oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.95 - 3.61 (m, 2H), 3.60 - 3.23 (m, 6H), 2.47 - 2.14 (m, 2H), 2.12 - 1.98 (m, 1H), 1.94 - 1.67 (m, 1H), 1.47 (s, 9H).

Step E. 3,3-difluoro-5-methoxyazepane. To a solution of tert-butyl 3,3-difluoro-5-methoxyazepane-1-carboxylate (0.045 g, 0.16 mmol) in MeOH (0.5 mL) was added 2 M HCl in dioxane (1.0 mL). The mixture was stirred at 40 °C for 1 h and then it was concentrated under reduced pressure to give 3,3-difluoro-5-methoxyazepane (0.030 g). LCMS (MM-ES+APCI, Pos): 166.2 (M+H).

Intermediate I69

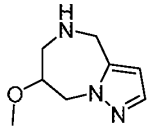


(R)-3,3-difluoro-6-methoxyazepane

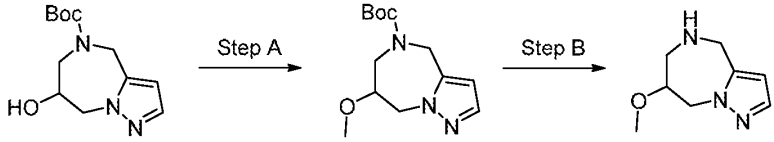


Steps A-B were performed with tert-butyl (R)-3,3-difluoro-6-hydroxyazepane-1-carboxylate following the procedures for Intermediate I60. ^{1}H NMR: (400 MHz, MeOH-d_4) δ 3.84 - 3.66 (m, 3H), 3.66 - 3.52 (m, 2H), 3.43 - 3.36 (m, 3H), 2.55 - 2.32 (m, 1H), 2.28 - 2.09 (m, 2H), 1.95 (br s, 1H).

Intermediate I70

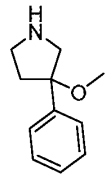


7-methoxy-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepine

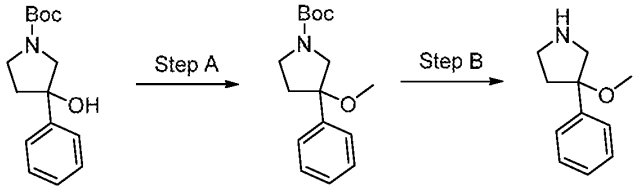


Steps A-B were performed with tert-butyl 7-hydroxy-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate following the procedures for Intermediate I60. ^{1}H NMR: (400 MHz, D_2O) δ 7.44 (d, J = 1.6 Hz, 1H), 6.43 (s, 1H), 4.81 (dd, J = 5.6, 15.6 Hz, 1H), 4.60 (d, J = 15.6 Hz, 1H), 4.50 (d, J = 15.6 Hz, 1H), 4.29 (d, J = 15.6 Hz, 1H), 3.97 (t, J = 4.4Hz, 1H), 3.83 (dd, J = 4.4, 14.0 Hz, 1H), 3.46 (d, J = 14.0 Hz, 1H), 3.30 (s, 3H).

Intermediate I71



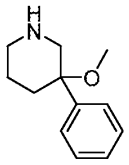
3-methoxy-3-phenylpyrrolidine



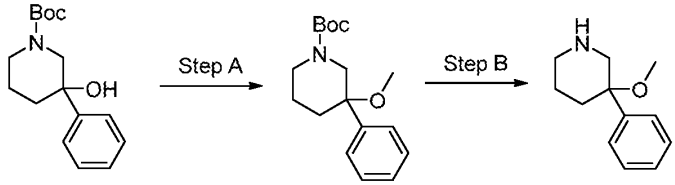
Steps A-B were performed with tert-butyl 3-hydroxy-3-phenylpyrrolidine-1-

carboxylatefollowing the procedures for Intermediate I60.

Intermediate I72

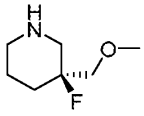


3-methoxy-3-phenylpiperidine

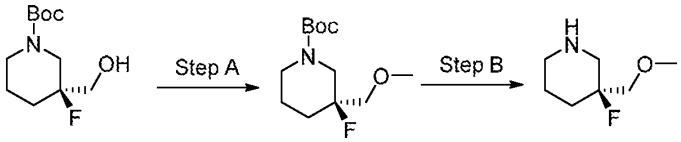


Steps A-B were performed with tert-butyl 3-hydroxy-3-phenylpiperidine-1-carboxylate following the procedures for Intermediate I62.

Intermediate I73

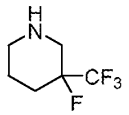


(S)-3-fluoro-3-(methoxymethyl)piperidine

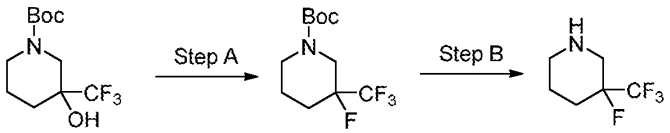


Steps A-B were performed with tert-butyl (S)-3-fluoro-3-(hydroxymethyl)piperidine-1-carboxylate following the procedures for Intermediate I60.

Intermediate I74



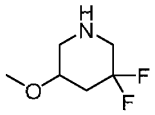
3-fluoro-3-(trifluoromethyl)piperidine



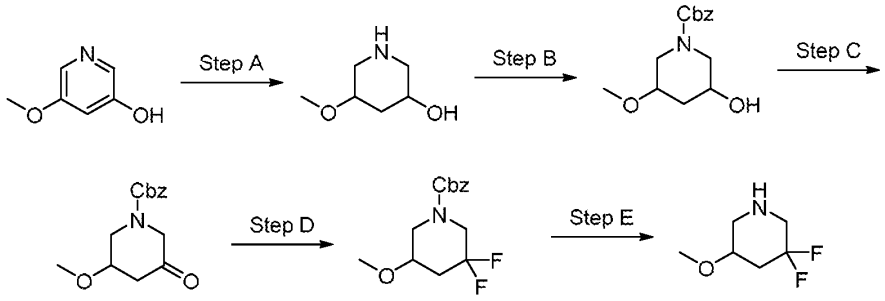
Step A. tert-butyl 3-fluoro-3-(trifluoromethyl)piperidine-1-carboxylate. To a solution of tert-butyl 3-hydroxy-3-(trifluoromethyl)piperidine-1-carboxylate (0.10 g, 0.37 mmol) in DCM (1 mL) at -78 °C was added DAST (0.20 mL, 1.5 mmol). The reaction was stirred at -78 °C for 2 h and then it was warmed to 0 °C and stirred for 2 h. The mixture was quenched with ice water (5 mL) and then extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (17% EtOAc in petroleum ether) to tert-butyl 3-fluoro-3-(trifluoromethyl)piperidine-1-carboxylate (0.050 g, 50% yield) as colorless oil. ^{1}H NMR: (400 MHz, MeOH-d_4) δ 4.29 - 4.07 (m, 1H), 3.96 - 3.90 (m, 1H), 3.19 - 2.91 (m, 1H), 2.89 - 2.70 (m, 1H), 2.08 - 1.96 (m, 1H), 1.89 - 1.74 (m, 1H), 1.72 - 1.55 (m, 2H), 1.36 (s, 9H). ^{19}F NMR: (376 MHz, MeOH-d_4) δ -83.92 (br d, J = 31.5 Hz, 3F), -178.92 - -179.75 (m, 1F).

Step B. 3-fluoro-3-(trifluoromethyl)piperidine. To a solution of tert-butyl 3-fluoro-3-(trifluoromethyl)piperidine-1-carboxylate (0.050 g, 0.18 mmol) in DCM (0.5 mL) was added 2 M HCl in dioxane (0.092 mL). The mixture was stirred for 2 h and then it was concentrated under reduced pressure to give 3-fluoro-3-(trifluoromethyl)piperidine (0.035 g, 89% yield).

Intermediate I75



3,3-difluoro-5-methoxypiperidine



Step A. 5-methoxypiperidin-3-ol. A solution of 5-methoxypyridin-3-ol (3.0 g, 24 mmol) in HFIP (90 mL) was pumped at a rate of 0.3 mL/min through a fixed bed (FLR1, SS, Fixed bed, 6.350(1/4") mm, 1 mL, 85 °C) of 5% $Pd(OH)_2/Al_2O_3$ (4.7 g). The H_2 back pressure regulator was adjusted to 2.5 MPa, and the flow rate of adjusted to 30 mL/min. The solution

was collected and concentrated under reduced pressure to afford 5-methoxypiperidin-3-ol (3.0 g, 95% yield). LCMS (MM-ES+APCI, Pos): 132.0 (M+H).

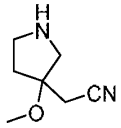
Step B. benzyl 3-hydroxy-5-methoxypiperidine-1-carboxylate. To a solution of 5-methoxypiperidin-3-ol (3.0 g, 23 mmol) in THF (30 mL) at 0 °C was added Na_2CO_3 (7.3 g, 69 mmol) and CbzCl (3.9 mL, 27 mmol). The reaction was stirred at rt for 2 h and then it was diluted with H_2O (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (13 – 43% MeCN in 0.1% aqueous NH_4HCO_3) to give benzyl 3-hydroxy-5-methoxypiperidine-1-carboxylate (2.3 g, 37% yield) as yellow oil. LCMS (MM-ES+APCI, Pos): 266.0 (M+H).

Step C. benzyl 3-methoxy-5-oxopiperidine-1-carboxylate. To a solution of benzyl 3-hydroxy-5-methoxypiperidine-1-carboxylate (2.0 g, 7.3 mmol) in DCM (20 mL) at 0 °C. was added DMP (3.7 g, 8.7 mmol). The reaction was stirred at rt for 16 h. The mixture was filtered and the filter cake was washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-33% EtOAc in hexanes) to give benzyl 3-methoxy-5-oxopiperidine-1-carboxylate (1.8 g, 94% yield) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.42 - 7.31 (m, 5H), 5.17 (br s, 2H), 4.27 - 4.09 (m, 1H), 4.06 - 3.96 (m, 1H), 3.85 (br d, J = 9.6 Hz, 2H), 3.77 - 3.64 (m, 1H), 3.51 - 3.17 (m, 3H), 2.82 - 2.50 (m, 2H).

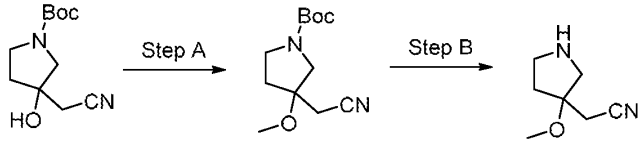
Step D. benzyl 3,3-difluoro-5-methoxypiperidine-1-carboxylate. To a solution of benzyl 3-methoxy-5-oxopiperidine-1-carboxylate (0.50 g, 1.9 mmol) in DCM (5 mL) at 0 °C was added DAST 0.75 mL, 5.7 mmol). The reaction was heated to 40 °C for 16 h and then it was quenched with water (10 mL). The pH of mixture was adjusted to 9 with sat. aq. $NaHCO_3$ solution and then extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-14% EtOAc in hexanes). The residue was purified by preparative HPLC (18 – 48% MeCN in 0.1% aqueous TFA) to give benzyl 3,3-difluoro-5-methoxypiperidine-1-carboxylate (0.160 g, 28% yield) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.43 - 7.30 (m, 5H), 5.17 (s, 2H), 4.30 - 3.99 (m, 2H), 3.58 - 3.20 (m, 5H), 3.09 - 2.83 (m, 1H), 2.49 (br d, J = 10.4 Hz, 1H), 2.00 - 1.76 (m, 1H). ^{19}F NMR: (376 MHz, $CDCl_3$) δ -98.50 - -102.13 (m, 2F).

Step E. 3,3-difluoro-5-methoxypiperidine. A solution of benzyl 3,3-difluoro-5-methoxypiperidine-1-carboxylate (0.20 g, 0.70 mmol) in THF (5 mL) and MeOH (5 mL) was pumped at a rate of 0.4 mL/min through a fixed bed (FLR1, SS, Fixed bed, 6.35(1/4'') mm, 5mL, 45 °C) of 5% Pd/Al_2O_3 (4.7 g). The H_2 back pressure regulator was adjusted to 1.5 MPa, and the flow rate of adjusted to 30 mL/min. The solution was collected and concentrated under reduced pressure to afford 3,3-difluoro-5-methoxypiperidine (0.10 g, 94% yield), which was taken onto the next step without further purification.

Intermediate I76

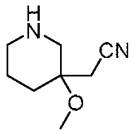


2-(3-methoxypyrrolidin-3-yl)acetonitrile

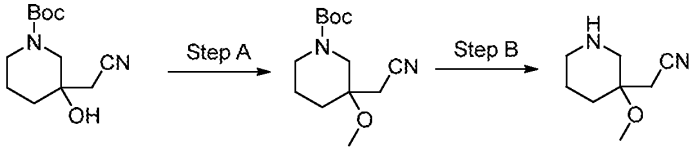


Steps A-B were performed with tert-butyl 3-(cyanomethyl)-3-hydroxypyrrolidine-1-carboxylate following the procedures for Intermediate I60.

Intermediate I77

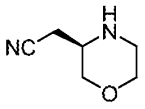


2-(3-methoxypiperidin-3-yl)acetonitrile

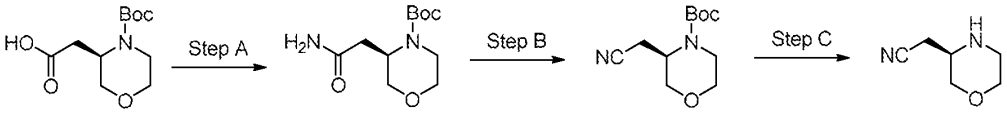


Steps A-B were performed with tert-butyl 3-(cyanomethyl)-3-hydroxypiperidine-1-carboxylate following the procedures for Intermediate I60.

Intermediate I78



(R)-2-(morpholin-3-yl)acetonitrile

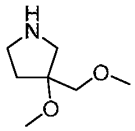


Step A. tert-butyl (R)-3-(2-amino-2-oxoethyl)morpholine-4-carboxylate. To a solution of (R)-2-(4-(tert-butoxycarbonyl)morpholin-3-yl)acetic acid (0.20 g, 0.82 mmol) in THF (5 mL) was added EDCI (0.31 g, 1.6 mmol), NEt_3 (1.1 mL, 8.2 mmol), and 1-hydroxy-1H-benzotriazole, ammonium salt (0.50 g, 3.3 mmol). The reaction was stirred for 1 h and then it was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-100% EtOAC in petroleum ether) to give tert-butyl (R)-3-(2-amino-2-oxoethyl)morpholine-4-carboxylate (0.15 g, 75% yield) as a yellow solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ = 7.35 (br s, 1H), 6.83 (br s, 1H), 4.22 - 4.12 (m, 1H), 3.77 (br dd, J = 2.8, 11.6 Hz, 1H), 3.65 - 3.60 (m, 2H), 3.42 (dd, J = 3.2, 11.2 Hz, 1H), 3.21 - 3.07 (m, 2H), 3.04 - 2.95 (m, 1H), 2.27 - 2.12 (m, 1H), 1.39 (s, 9H).

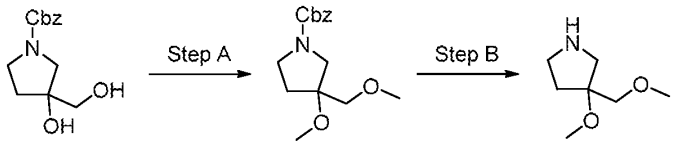
Step B. tert-butyl (R)-3-(cyanomethyl)morpholine-4-carboxylate. To a solution of tert-butyl (R)-3-(2-amino-2-oxoethyl)morpholine-4-carboxylate (0.15 g, 0.61 mmol) in DCM (2 mL) was added 1-methoxy-N-triethylammoniosulfonyl-methanimidate azanide (0.29 g, 1.2 mmol). The reaction was stirred for 1 h and then it was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-25% EtOAC in petroleum ether) to give tert-butyl (R)-3-(cyanomethyl)morpholine-4-carboxylate (0.11 g, 79% yield) as a yellow solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ = 4.23 (br s, 1H), 3.78 (br dd, J = 2.8, 11.2 Hz, 1H), 3.69 - 3.58 (m, 2H), 3.47 (dd, J = 3.2, 12.0 Hz, 1H), 3.32 - 3.27 (m, 1H), 3.15 - 2.92 (m, 2H), 2.87 - 2.75 (m, 1H), 1.42 (s, 9H).

Step C. (R)-2-(morpholin-3-yl)acetonitrile. To a solution of tert-butyl (R)-3-(cyanomethyl)morpholine-4-carboxylate (0.11 g, 0.49 mmol) in DCM (1.0 mL) was added 2 M HCl in dioxane (1.0 mL). The mixture was stirred for 1 h and then it was concentrated under reduced pressure to give (R)-2-(morpholin-3-yl)acetonitrile (0.060 g, 76% yield).

Intermediate I79



3-methoxy-3-(methoxymethyl)pyrrolidine



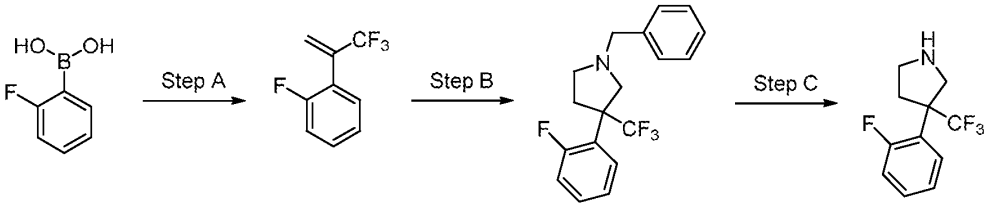
Step A. benzyl 3-methoxy-3-(methoxymethyl)pyrrolidine-1-carboxylate. To a solution of benzyl 3-hydroxy-3-(hydroxymethyl)pyrrolidine-1-carboxylate (0.080 g, 0.32 mmol) in THF (2 mL) at 0 °C was added NaH (60% in mineral oil; 0.032 g, 0.80 mmol). The mixture was stirred for 30 min, then MeI (0.050 mL, 0.80 mmol) was added. The reaction was stirred at rt for 1 h and then it was diluted with H_2O (6 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (50% EtOAC in petroleum ether) to give benzyl 3-methoxy-3-(methoxymethyl)pyrrolidine-1-carboxylate (0.080 g, 90% yield) as a colorless oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.41 - 7.28 (m, 5H), 5.19 - 5.08 (m, 2H), 3.65 - 3.35 (m, 9H), 3.30 (d, J = 3.2 Hz, 3H), 2.13 - 2.01 (m, 1H), 1.99 - 1.82 (m, 1H).

Step B. 3-methoxy-3-(methoxymethyl)pyrrolidine. To a solution of benzyl 3-methoxy-3-(methoxymethyl)pyrrolidine-1-carboxylate (0.080 g, 0.29 mmol) in MeOH (3 mL) was added 10% Pd/C (0.15 g, 0.14 mmol). The flask was evacuated and backfilled with H_2 three times. The mixture was stirred under an atmosphere of H_2 for 1 h. The suspension was filtered and the filter cake was washed with MeOH (10 mL). The filtrate was concentrated under reduced pressure to give 3-methoxy-3-(methoxymethyl)pyrrolidine (0.040 g, 96% yield) as a yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.93 - 8.13 (m, 1H), 3.67 - 3.40 (m, 8H), 3.39 - 3.28 (m, 4H), 2.31 - 2.22 (m, 1H), 2.15 - 2.02 (m, 1H).

Intermediate I80



3-(2-fluorophenyl)-3-(trifluoromethyl)pyrrolidine



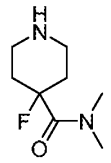
Step A. 1-fluoro-2-(3,3,3-trifluoroprop-1-en-2-yl)benzene. To a solution of (2-fluorophenyl)boronic acid (0.50 g, 3.6 mmol) in THF (10 mL) was added 2-bromo-3,3,3-trifluoroprop-1-ene (1.3 g, 7.2 mmol), $Pd(PPh_3)_2Cl_2$ (0.13 g, 0.18 mmol) and 2 M aq. K_2CO_3 (7.2 mL). The reaction was heated to 60 °C for 12 h and then it was diluted with H_2O (10 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-1% EtOAc in hexanes) to give 1-fluoro-2-(3,3,3-trifluoroprop-1-en-2-yl)benzene (0.29 g, 43% yield) as a colorless liquid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.41 - 7.33 (m, 2H), 7.19 - 7.11 (m, 2H), 6.19 (d, J = 1.2 Hz, 1H), 5.79 (d, J = 0.8 Hz, 1H). ^{19}FNMR: (377 MHz $CDCl_3$) δ = -65.85 - -66.00 (m, 3F), -114.37 (q, J = 4.5 Hz, 1F).

Step B. 1-benzyl-3-(2-fluorophenyl)-3-(trifluoromethyl)pyrrolidine. To a solution of 1-fluoro-2-(3,3,3-trifluoroprop-1-en-2-yl)benzene (0.40 g, 2.1 mmol) in DCM (4 mL) at 0 °C was added N-benzyl-1-methoxy-N-((trimethylsilyl)methyl)methanamine (2.0 g, 8.4 mmol) and TFA (0.016 mL, 0.21 mmol). The mixture was stirred for 12 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-2% EtOAc in hexanes) to give 1-benzyl-3-(2-fluorophenyl)-3-(trifluoromethyl)pyrrolidine (0.55 g, 68% yield) as a colorless liquid. LCMS (MM-ES+APCI, Pos): 324.1 (M+H).

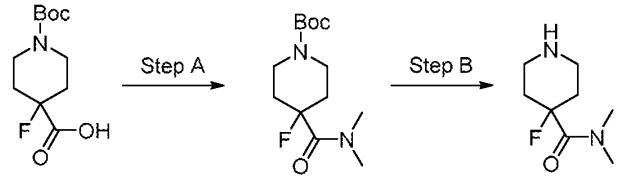
Step C. 3-(2-fluorophenyl)-3-(trifluoromethyl)pyrrolidine. To a solution of 1-benzyl-3-(2-fluorophenyl)-3-(trifluoromethyl)pyrrolidine (0.50 g, 1.3 mmol) in THF (5 mL) was added

10% Pd/C (0.14 g, 0.13 mmol). The mixture was stirred at rt under an atmosphere of H_2 (30 Psi) for 12 h. The mixture was filtered and the filtrate was concentrated under reduced pressure to give 3-(2-fluorophenyl)-3-(trifluoromethyl)pyrrolidine (0.35 g, 99 % yield). LCMS (MM-ES+APCI, Pos): 234.0 (M+H).

Intermediate I81



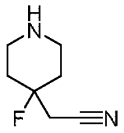
4-fluoro-N,N-dimethylpiperidine-4-carboxamide



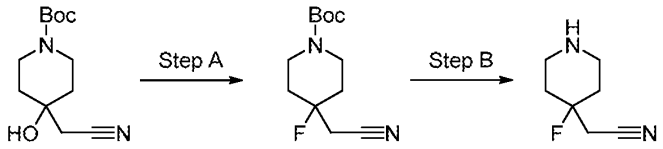
Step A. tert-butyl 4-(dimethylcarbamoyl)-4-fluoropiperidine-1-carboxylate. To a solution of 1-(tert-butoxycarbonyl)-4-fluoropiperidine-4-carboxylic acid (0.20 g, 0.81 mmol) dimethylamine HCl (0.079 g, 0.97 mmol) in DCM (2 mL) was added EDCI (0.23 g, 1.2 mmol) and DMAP (0.20 g, 1.6 mmol). The reaction was stirred for 1 h and then it was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25% EtOAc in petroleum ether) to give tert-butyl 4-(dimethylcarbamoyl)-4-fluoropiperidine-1-carboxylate (0.12 g, 54% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): 219.2 (M+H-tBu).

Step B. 4-fluoro-N,N-dimethylpiperidine-4-carboxamide. To a solution of tert-butyl 4-(dimethylcarbamoyl)-4-fluoropiperidine-1-carboxylate (0.12 g, 0.44 mmol) in DCM (1.0 mL) was added 2 M HCl in dioxane (1.0 mL). The mixture was stirred for 1 h and then it was concentrated under reduced pressure to give 4-fluoro-N,N-dimethylpiperidine-4-carboxamide (0.090 g, 98% yield), which was taken onto the next step without further purification.

Intermediate I82

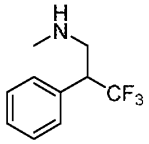


2-(4-fluoropiperidin-4-yl)acetonitrile

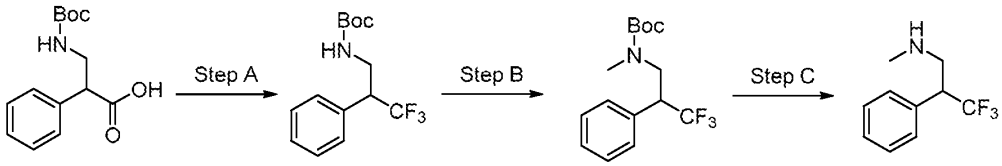


Steps A-B were performed with tert-butyl 4-(cyanomethyl)-4-hydroxypiperidine-1-carboxylate following the procedures for Intermediate I74.

Intermediate I83



3,3,3-trifluoro-N-methyl-2-phenylpropan-1-amine



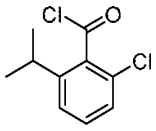
Step A. tert-butyl (3,3,3-trifluoro-2-phenylpropyl)carbamate. To a solution of 3-((tert-butoxycarbonyl)amino)-2-phenylpropanoic acid (0.90 g, 3.4 mmol) and 1-trifluoromethyl-1,2-benziodoxol-3(1H)-one (1.4 g, 4.2 mmol) in EtOAc (10 mL) was (4,4'-di-*tert*-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-κ*N*)phenyl-κ*C*]iridium(III) hexafluorophosphate (0.038 g, 0.034 mmol), $CuCl_2$ (0.091 g, 0.68 mmol), bis(2-pyridyl)methanone (0.16 g, 0.85 mmol) and 1,1,3,3-tetramethylguanidine (0.21 mL, 1.7 mmol). The vial was sparged with nitrogen for one minute and the reaction was stirred for 16 h. The mixture was diluted with H_2O (15 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica

gel column chromatography (0-5% EtOAc in petroleum ether). The residue was purified by preparative TLC (9% EtOAc in petroleum ether) to give tert-butyl (3,3,3-trifluoro-2-phenylpropyl)carbamate (0.060 g, 6% yield) as yellow oil. LCMS (MM-ES+APCI, Pos): 234.2 (M+H-tBu).

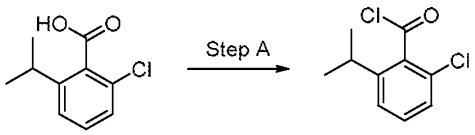
Step B. tert-butyl methyl(3,3,3-trifluoro-2-phenylpropyl)carbamate. To a solution of tert-butyl (3,3,3-trifluoro-2-phenylpropyl)carbamate (0.023 g, 0.080 mmol) in THF (1 mL) at 0 °C was added NaH (60% in mineral oil; 0.0070 g, 0.18 mmol). The mixture was stirred at rt for 30 min and then MeI (0.015 mL, 0.24 mmol). The reaction was stirred for 1 h and then it was diluted with H_2O (5 mL) and extracted with ethyl acetate (8 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (9% EtOAc in petroleum ether) to give tert-butyl methyl(3,3,3-trifluoro-2-phenylpropyl)carbamate (0.015 g, 59% yield) as colorless oil. LCMS (MM-ES+APCI, Pos): 248.1 (M+H-tBu).

Step C. 3,3,3-trifluoro-N-methyl-2-phenylpropan-1-amine. To a solution of tert-butyl methyl(3,3,3-trifluoro-2-phenylpropyl)carbamate (0.015 g, 0.047 mmol) in DCM (0.3 mL) was added 2 M HCl in dioxane (0.3 mL). The mixture was stirred for 3 h and then it was concentrated under reduced pressure to give 3,3,3-trifluoro-N-methyl-2-phenylpropan-1-amine (0.011 g, 98% yield), which was taken onto the next step without further purification. ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 10.15 - 9.28 (m, 2H), 7.44 (s, 5H), 4.36 - 4.17 (m, 1H), 3.70 - 3.57 (m, 1H), 3.45 - 3.28 (m, 1H), 2.49 (br s, 3H).

Intermediate I84



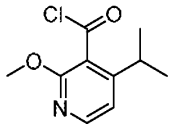
2-chloro-6-isopropylbenzoyl chloride



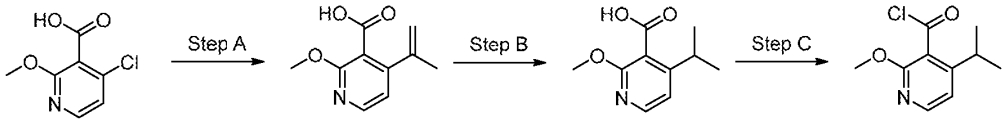
Step A. 2-chloro-6-isopropylbenzoyl chloride. To a solution of 2-chloro-6-isopropylbenzoic acid (0.050 g, 0.20 mmol) in DCM (2 mL) at 0 °C was added oxalyl chloride (0.026 mL, 0.30

mmol) and DMF (0.0076 mL, 0.099 mmol). The reaction was stirred at 0 °C for 1 h. The mixture was concentrated under reduced pressure to give 2-chloro-6-isopropylbenzoyl chloride (0.040 g) as a yellow oil, which was used directly without further purification.

Intermediate I85



4-isopropyl-2-methoxynicotinoyl chloride



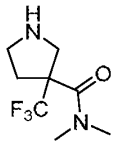
Step A. 2-methoxy-4-(prop-1-en-2-yl)nicotinic acid. To a solution of 4-chloro-2-methoxynicotinic acid (0.50 g, 2.7 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (0.54 g, 3.2 mmol) in dioxane (10 mL) and water (2 mL) was added Cs_2CO_3 (2.6 g, 8.0 mmol), $Pd(dppf)Cl_2$ (0.59 g, 0.80 mmol). The reaction was heated to 110 °C for 3 h and then it was diluted with H_2O (30 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (38 – 48% MeCN in 0.225% aqueous formic acid) to give 2-methoxy-4-(prop-1-en-2-yl)nicotinic acid (0.080 g, 15% yield) as a white solid. LCMS (MM-ES+APCI, Pos): 194.2 (M+H).

Step B. 4-isopropyl-2-methoxynicotinic acid. To a solution of 2-methoxy-4-(prop-1-en-2-yl)nicotinic acid (0.080 g, 0.41 mmol) in MeOH (3 mL) was added 10% Pd/C (0.44 g). The reaction was stirred at rt for 2 h under an atmosphere of H_2. The suspension was filtered and the pad was washed with MeOH (20mL). The filtrate was concentrated under reduced pressure to give 4-isopropyl-2-methoxynicotinic acid (0.050 g, 59% yield) as a white solid. LCMS (MM-ES+APCI, Pos): 196.2 (M+H).

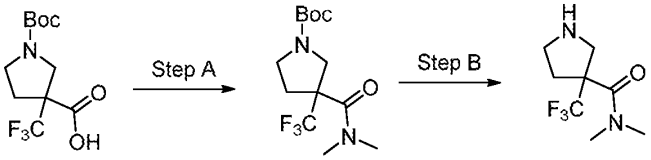
Step C. 4-isopropyl-2-methoxynicotinoyl chloride. To a solution of 4-isopropyl-2-methoxynicotinic acid (0.020 g, 0.098 mmol) in DCM (2 mL) was added oxalyl chloride (0.013 mL, 0.15 mmol) and DMF (0.00076 mL, 0.0098 mmol). The reaction was stirred for 1 h. The mixture was concentrated under reduced pressure to 4-isopropyl-2-methoxynicotinoyl

chloride (0.020 g, 95% yield) as a yellow oil, which was used directly without further purification. LCMS (MM-ES+APCI, Pos): 210.4 (M+H-Cl+OMe).

Intermediate I86

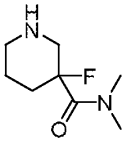


N,N-dimethyl-3-(trifluoromethyl)pyrrolidine-3-carboxamide

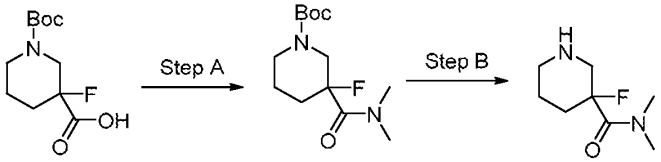


Steps A-B were performed with 1-(tert-butoxycarbonyl)-3-(trifluoromethyl)pyrrolidine-3-carboxylic acid following the procedures for Intermediate I81.

Intermediate I87

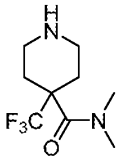


3-fluoro-N,N-dimethylpiperidine-3-carboxamide

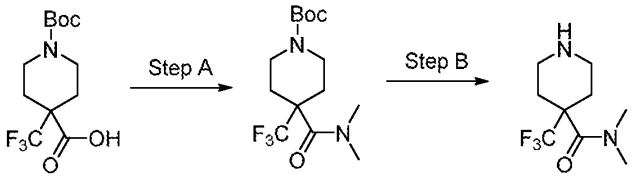


Steps A-B were performed with 1-(tert-butoxycarbonyl)-3-fluoropiperidine-3-carboxylic acid following the procedures for Intermediate I81. ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 10.23 - 9.69 (m, 2H), 3.68 - 3.56 (m, 1H), 3.54 - 3.39 (m, 2H), 3.21 (d, J = 3.6 Hz, 3H), 3.12 - 3.04 (m, 1H), 3.00 (s, 3H), 2.35 - 2.19 (m, 2H), 2.18 - 2.02 (m, 1H), 1.95 - 1.84 (m, 1H).

Intermediate I88

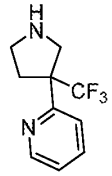


N,N-dimethyl-4-(trifluoromethyl)piperidine-4-carboxamide

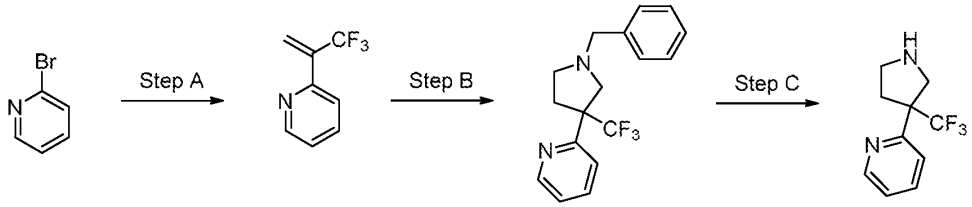


Steps A-B were performed with 1-(tert-butoxycarbonyl)-4-(trifluoromethyl)piperidine-4-carboxylic acid following the procedures for Intermediate I81.

Intermediate I89

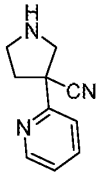


2-(3-(trifluoromethyl)pyrrolidin-3-yl)pyridine

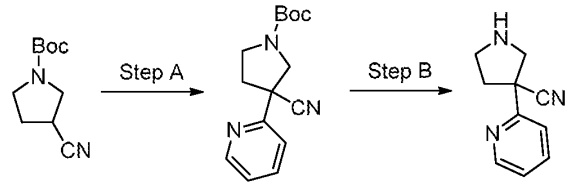


Steps A-B were performed with 2-bromopyridine and 4,4,5,5-tetramethyl-2-(3,3,3-trifluoroprop-1-en-2-yl)-1,3,2-dioxaborolane following the procedures for Intermediate I80. LCMS (MM-ES+APCI, Pos): 217.2 (M+H).

Intermediate I90



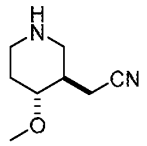
3-(pyridin-2-yl)pyrrolidine-3-carbonitrile



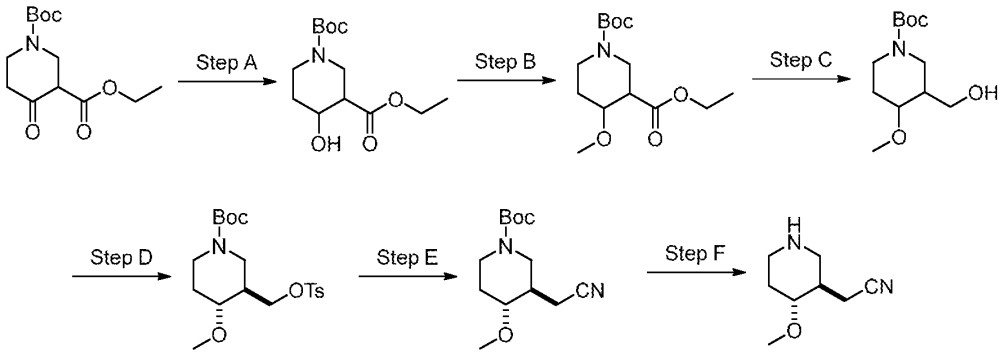
Step A. tert-butyl 3-cyano-3-(pyridin-2-yl)pyrrolidine-1-carboxylate. A solution of tert-butyl 3-cyanopyrrolidine-1-carboxylate (1.0 g, 5.1 mmol), 2-fluoropyridine (0.48 mL, 5.6 mmol) in THF (20 mL) at 0 °C was added NaHMDS (2.5 M in THF; 3.1 mL). The mixture was stirred at 0 °C for 30 min then it was stirred at rt for 15.5 h. The mixture was diluted with saturated aqueous NH_4Cl solution (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (11-17% EtOAc in petroleum ether) to give tert-butyl 3-cyano-3-(pyridin-2-yl)pyrrolidine-1-carboxylate (1.0 g, 72% yield) as a light yellow oil. ^{1}H NMR: (400 MHz, MeOH-d_4) δ 8.62 (br d, J = 4.0 Hz, 1H), 7.83 - 7.73 (m, 1H), 7.70 - 7.61 (m, 1H), 7.30 (br t, J = 6.0 Hz, 1H), 4.12 - 4.04 (m, 1H), 3.92 (d, J = 11.2 Hz, 1H), 3.78 - 3.66 (m, 2H), 2.86 - 2.65 (m, 1H), 2.62 - 2.49 (m, 1H), 1.48 (br d, J = 4.8 Hz, 9H).

Step B. 3-(pyridin-2-yl)pyrrolidine-3-carbonitrile. A solution of tert-butyl 3-cyano-3-(pyridin-2-yl)pyrrolidine-1-carboxylate (0.50 g, 1.8 mmol) in 2 M HCl in dioxane (4.6 mL) was stirred for 1 h. The mixture was concentrated under reduced pressure to give 3-(pyridin-2-yl)pyrrolidine-3-carbonitrile (0.19 g, 50% yield) as a white solid. LCMS (MM-ES+APCI, Pos): 174.1 (M+H).

Intermediate I91



2-((rel-3R,4R)-4-methoxypiperidin-3-yl)acetonitrile



Step A. 1-(tert-butyl) 3-ethyl 4-hydroxypiperidine-1,3-dicarboxylate. A solution of 1-(tert-butyl) 3-ethyl 4-oxopiperidine-1,3-dicarboxylate (5.0 g, 18 mmol) in EtOH (50 mL) and THF (50 mL) was pumped at a rate of 0.3 mL/min through a fixed bed (FLR1, SS, Fixed bed, 6.35(1/4'') mm, 5mL, 60 °C) of 5% $Pd(OH)_2/Al_2O_3$ (4.2 g). The H_2 back pressure regulator was adjusted to 1.5 MPa, and the flow rate adjusted to 30 mL/min. The solution was collected and concentrated under reduced pressure to afford 1-(tert-butyl) 3-ethyl 4-hydroxypiperidine-1,3-dicarboxylate (4.5 g, 79% yield). LCMS (MM-ES+APCI, Pos): 218.0 (M+H-tBu).

Step B. 1-(tert-butyl) 3-ethyl 4-methoxypiperidine-1,3-dicarboxylate. Four batches. To a solution of 1-(tert-butyl) 3-ethyl 4-hydroxypiperidine-1,3-dicarboxylate (4.0 g, 15 mmol) in MeCN (40 mL) was added $CaSO_4$ (12 g, 88 mmol), Ag_2O (14 g, 60 mmol) and MeI (3.6 mL, 60 mmol). The reaction was heated to 40 °C for 16 h. The suspension was filtered through a pad of Celite. The Celite pad was washed with ethyl acetate (100 mL). The mixture was diluted water (100 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-25% EtOAC in hexanes) to give 1-(tert-butyl) 3-ethyl 4-methoxypiperidine-1,3-dicarboxylate (1.6 g, 38% yield) as colorless oil.

Step C. tert-butyl 3-(hydroxymethyl)-4-methoxypiperidine-1-carboxylate. To a solution of 1-(tert-butyl) 3-ethyl 4-methoxypiperidine-1,3-dicarboxylate (2.0 g, 7.0 mmol) in THF (20 mL) at 0 °C was added $LiAlH_4$ (2.5 M in THF; 7.0 mL). The mixture was allowed to warm to rt and stirred for 2 h. The mixture was quenched at 0 °C by slow addition of $Na_2SO_4 \cdot 10H_2O$ (4 g). The mixture was allowed to warm to rt and was stirred for 2 h. The suspension was filtered and the filter cake was washed with THF (40 mL). The filtrate was concentrated under reduced pressure to give tert-butyl 3-(hydroxymethyl)-4-methoxypiperidine-1-

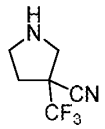
carboxylate (1.7 g, 99% yield) as colorless oil.

Step D. tert-butyl (rel-3S,4R)-4-methoxy-3-((tosyloxy)methyl)piperidine-1-carboxylate. To a solution of tert-butyl 3-(hydroxymethyl)-4-methoxypiperidine-1-carboxylate (1.7 g, 6.9 mmol) in DCM (20 mL) was added triethylamine (2.9 mL, 21 mmol) and TosCl (2.6 g, 14 mmol). The mixture was stirred at 40 °C for 16 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-33% EtOAC in hexanes). The residue was purified by preparative HPLC (46 – 76% MeCN in 0.1% aqueous TFA) to give tert-butyl (rel-3S,4R)-4-methoxy-3-((tosyloxy)methyl)piperidine-1-carboxylate (0.60 g, 128% yield) as a brown solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 4.27 - 4.13 (m, 1H), 4.13 - 3.83 (m, 3H), 3.30 - 3.13 (m, 4H), 2.93 - 2.70 (m, 2H), 2.46 (s, 3H), 2.05 - 1.94 (m, 1H), 1.78 (tdd, J = 4.4, 9.2, 13.6 Hz, 1H), 1.44 (s, 9H), 1.39 - 1.25 (m, 1H).

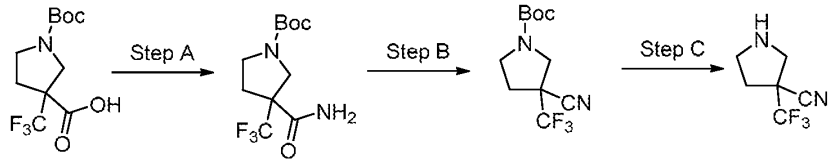
Step E. tert-butyl (rel-3R,4R)-3-(cyanomethyl)-4-methoxypiperidine-1-carboxylate. To a solution of tert-butyl (rel-3S,4R)-4-methoxy-3-((tosyloxy)methyl)piperidine-1-carboxylate (0.25 g, 0.58 mmol) in DMF (3 mL) was added K_2CO_3 (0.24 g, 1.7 mmol), NaI (0.017 g, 0.12 mmol) and tetrabutylammonium cyanide (0.17 g, 0.64 mmol). The mixture was heated to 80 °C for 16 h and then it was diluted with water (15 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-33% EtOAc in hexanes) to give tert-butyl (rel-3R,4R)-3-(cyanomethyl)-4-methoxypiperidine-1-carboxylate (0.14 g, 95% yield) as yellow oil.

Step F. 2-((rel-3R,4R)-4-methoxypiperidin-3-yl)acetonitrile. To a solution of tert-butyl (rel-3R,4R)-3-(cyanomethyl)-4-methoxypiperidine-1-carboxylate (0.060 g, 0.24 mmol) in DCM (2 mL) was added 2 M HCl dioxane (3.5 mL). The mixture was stirred at 40 °C for 1 h and then it was concentrated under reduced pressure to give 2-((rel-3R,4R)-4-methoxypiperidin-3-yl)acetonitrile (0.035 g, 78% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): 155.0 (M+H).

Intermediate I92

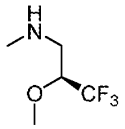


3-(trifluoromethyl)pyrrolidine-3-carbonitrile

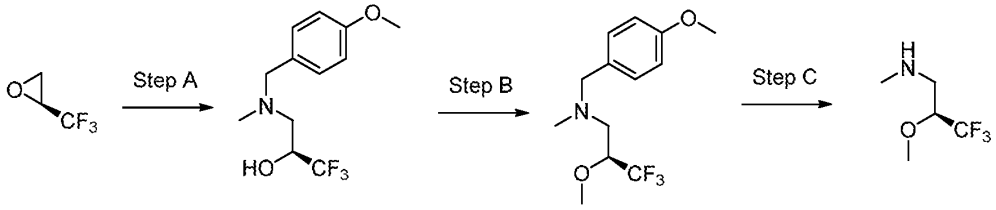


Steps A-C were performed with 1-(tert-butoxycarbonyl)-3-(trifluoromethyl)pyrrolidine-3-carboxylic acid following the procedures for Intermediate I78.

Intermediate I93



(S)-3,3,3-trifluoro-2-methoxy-N-methylpropan-1-amine



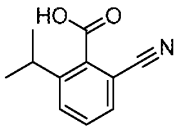
Step A. (S)-1,1,1-trifluoro-3-((4-methoxybenzyl)(methyl)amino)propan-2-ol. To a solution of lithium trifluoromethanesulfonate (0.056 g, 0.36 mmol) in MeCN (6 mL) at -10 °C was added (S)-2-(trifluoromethyl)oxirane (0.20 g, 1.8 mmol). The solution was stirred at -10 °C for 5 min and then 1-(4-methoxyphenyl)-N-methylmethanamine (0.35 g, 2.3 mmol) was added. The reaction was allowed to warm to rt and was stirred for 16 h. The mixture was concentrated under reduced pressure. The residue was purified by preparative TLC (100% EtOAc) to obtain (S)-1,1,1-trifluoro-3-((4-methoxybenzyl)(methyl)amino)propan-2-ol (0.12 g, 023% yield) as a colorless oil. LCMS (MM-ES+APCI, Pos): 264.3 (M+H).

Step B. (S)-3,3,3-trifluoro-2-methoxy-N-(4-methoxybenzyl)-N-methylpropan-1-amine. To a solution of (S)-1,1,1-trifluoro-3-((4-methoxybenzyl)(methyl)amino)propan-2-ol (0.070 g, 0.24 mmol) in THF (3 mL) was added KOH (0.021 g, 0.37 mmol). The reaction was stirred at rt for 30 min and then MeI (0.023 mL, 0.37 mmol) was added. The mixture was stirred for 3 h and then it was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated

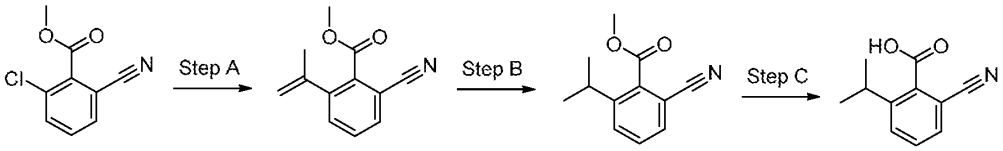
under reduced pressure. The residue was purified by preparative TLC (33% EtOAc in petroleum ether) to give (S)-3,3,3-trifluoro-2-methoxy-N-(4-methoxybenzyl)-N-methylpropan-1-amine (0.050 g, 74% yield) as a colorless oil. LCMS (MM-ES+APCI, Pos): 278.1 (M+H).

Step C. (S)-3,3,3-trifluoro-2-methoxy-N-methylpropan-1-amine. A flask containing (S)-3,3,3-trifluoro-2-methoxy-N-(4-methoxybenzyl)-N-methylpropan-1-amine (0.050 g, 0.18 mmol) and 20% $Pd(OH)_2$ (0.065 g, 0.093 mmol) in EtOH (3 mL) was evacuated and backfilled with H_2 three times. The mixture was stirred under an atmosphere of H_2 for 1 h. The suspension was filtered through a pad of Celite. The Celite pad was washed with EtOH (5 mL). To the filtrate was added 12 M HCl (0.1 ml). The mixture was stirred for 1 h and then it was concentrated under reduced pressure to give (S)-3,3,3-trifluoro-2-methoxy-N-methylpropan-1-amine (30 mg), which was used into the next step without further purification.

Intermediate I94



2-cyano-6-isopropylbenzoic acid



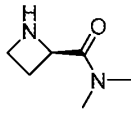
Step A. methyl 2-cyano-6-(prop-1-en-2-yl)benzoate. To a solution of methyl 2-chloro-6-cyanobenzoate (0.30 g, 1.5 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (0.31 g, 1.8 mmol) in dioxane (4 mL) and H_2O (0.8 mL) was added Cs_2CO_3 (1.0 g, 3.1 mmol) and $Pd(dppf)Cl_2$ (0.11 g, 0.15 mmol). The flask was evacuated and backfilled with nitrogen three times. The mixture was stirred at 110 °C under an atmosphere of nitrogen for 2 h. The mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (4 mL x 3). The combined organic layers were washed with brine (3 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (9-25% EtOAc in petroleum ether) to give methyl 2-cyano-6-(prop-1-en-2-yl)benzoate (0.22 g, 64% yield) as a colorless oil. LCMS

(MM-ES+APCI, Pos): 202.2 (M+H).

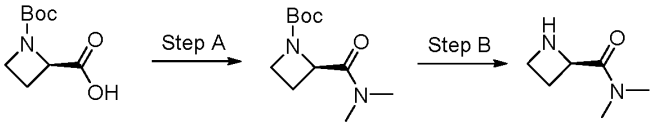
Step B. methyl 2-cyano-6-isopropylbenzoate. To a solution of methyl 2-cyano-6-(prop-1-en-2-yl)benzoate (0.20 g, 0.89 mmol) in MeOH (5 mL) was added 10% Pd/C (0.20 g). The suspension was degassed under vacuum and purged with H_2. The reaction was stirred for 1 h under an atmosphere of H_2. The slurry was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (9-20% EtOAc in petroleum ether) to give methyl 2-cyano-6-isopropylbenzoate (0.050 g, 27% yield) as a colorless oil. LCMS (MM-ES+APCI, Pos): 203.9 (M+H).

Step C. 2-cyano-6-isopropylbenzoic acid. To a solution of methyl 2-cyano-6-isopropylbenzoate (0.050 g, 0.24 mmol) in ethyl acetate (2 mL) was added LiI (0.028 mL, 0.72 mmol). The mixture was stirred at 70 °C for 12 h and then it was diluted with ethyl acetate (5 mL). The mixture was washed with H_2O (5 mL x 2). The aqueous phase was combined and lyophilized to obtain 2-cyano-6-isopropylbenzoic acid (0.040 g) as a white solid. LCMS (MM-ES+APCI, Pos): 190.2 (M+H).

Intermediate I95



(R)-N,N-dimethylazetidine-2-carboxamide



Step A. tert-butyl (R)-2-(dimethylcarbamoyl)azetidine-1-carboxylate. To a solution of (R)-1-(tert-butoxycarbonyl)azetidine-2-carboxylic acid (0.10 g, 0.50 mmol) and dimethylamine·HCl (0.068 mL, 0.75 mmol) in DCM (1 mL) was added HATU (0.28 g, 0.75 mmol) and DIPEA (0.26 mL, 1.5 mmol). The mixture was stirred at rt for 1 h and then it was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-25% EtOAc in petroleum ether) to give tert-butyl (R)-2-(dimethylcarbamoyl)azetidine-1-carboxylate (0.11 g, 97% yield) as a yellow solid. ^{1}H NMR:

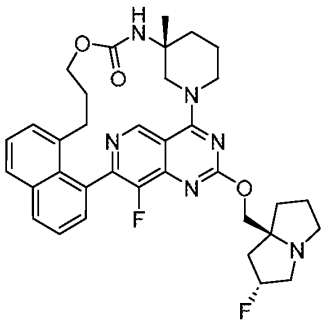
(400 MHz, $CDCl_3$) δ = 4.97 (dd, J = 5.2, 8.8 Hz, 1H), 4.09 - 4.01 (m, 1H), 3.87 (dt, J = 5.6, 8.4 Hz, 1H), 3.00 (d, J = 7.2 Hz, 6H), 2.49 - 2.38 (m, 1H), 2.24 - 2.15 (m, 1H), 1.43 (s, 9H);

Step B. (R)-N,N-dimethylazetidine-2-carboxamide. To a solution of tert-butyl (R)-2-(dimethylcarbamoyl)azetidine-1-carboxylate (0.11 g, 0.48 mmol) in DCM (2.0 mL) was added 2 M HCl in dioxane (2.0 mL). The reaction was stirred at rt for 12 h and then it was concentrated under reduced pressure to give (R)-N,N-dimethylazetidine-2-carboxamide (0.050 g, 63% yield), which was taken into the next step without further purification.

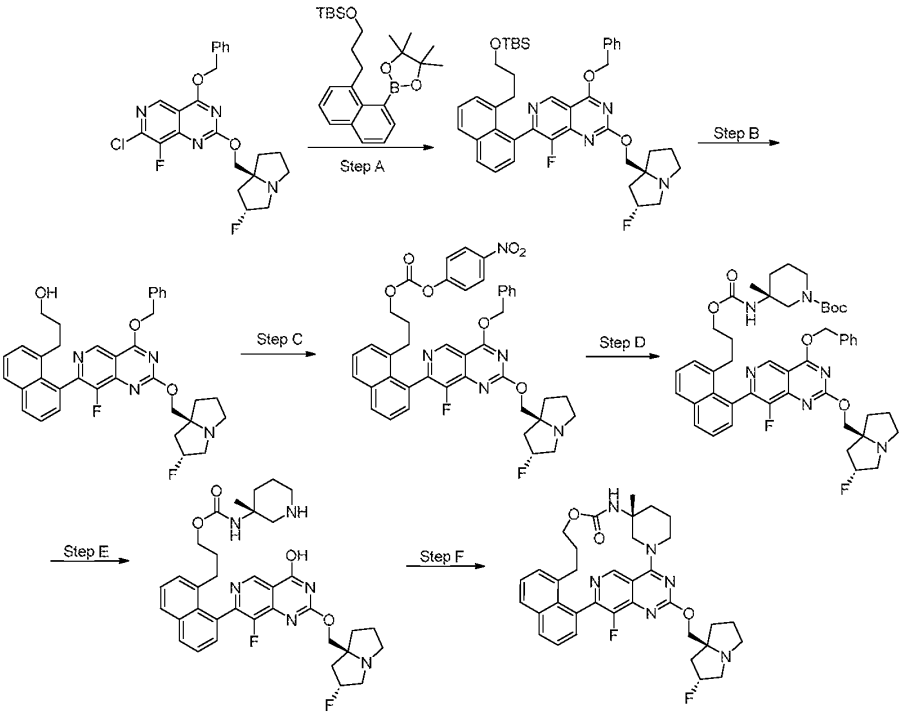
Synthesis of compounds of Formula (I), (IA)-(IE), or (IA-1)-(IE-1)

Example 22

Compound 1



(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a 40 mL vial equipped with a magnetic stir bar was added 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (1.00 g, 2.24 mmol) and tert-butyldimethyl(3-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)silane (0.96 g, 2.24 mmol) followed by the addition of dioxane (10 mL) and H_2O (1 mL). Mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.16 g, 0.22 mmol) and Cs_2CO_3 (1.46 g, 4.48 mmol) was added into the mixture at 25 °C. The mixture was sparged with nitrogen for 2 min and stirred at 90 °C for 1 h. The mixture was quenched by addition of H_2O (10 mL), the mixture transferred to separatory funnel and the aqueous layer extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (0-100% EtOAc in hexanes) to give 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.57 g, 28% yield) as a light yellow oil. LCMS (MM-ES+APCI, Pos): m/z 711.3 (M+H).

Step B. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propan-1-ol. To a 40 mL vial equipped with a magnetic stir bar was added 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.57 g, 0.63 mmol) followed by the addition of DCM (10 mL). TFA (0.50 mL, 6.73 mmol) was added to the mixture at 0 °C. The mixture was stirred at 0 °C for 1 h. The pH of the mixture was adjusted to 7 with saturated aqueous sodium bicarbonate (5 mL). The mixture was transferred to a separatory funnel and the aqueous layer extracted with DCM (5 mL x 3). The combined organics were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (0-100% EtOAc in petroleum ether) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propan-1-ol (0.35 g, 84% yield) as a light yellow oil. LCMS (MM-ES+APCI, Pos): m/z 597.3 (M+H).

Step C. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (4-nitrophenyl) carbonate. To a 40 mL vial equipped with a magnetic stir bar was added 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propan-1-ol (0.35 g, 0.53 mmol) and pyridine (0.13 mL, 1.59 mmol) followed by the addition of DCM (4 mL) at 0 °C. 4-Nitrophenyl chloroformate (0.56 g, 2.78 mmol) was dissolved in DCM (2 mL) and added dropwise at 0 °C to the reaction. The mixture was warmed to 25 °C and stirred for 3 h. The mixture was quenched by slow addition of H_2O (10 mL), transferred to separatory funnel and the aqueous layer extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (0-30% EtOAc in petroleum ether) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (4-nitrophenyl) carbonate (0.19 g, 45% yield) as a white gum. LCMS (MM-ES+APCI, Pos): m/z 762.3 (M+H).

Step D. tert-butyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a 8 mL vial equipped with a magnetic stir bar was added 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-

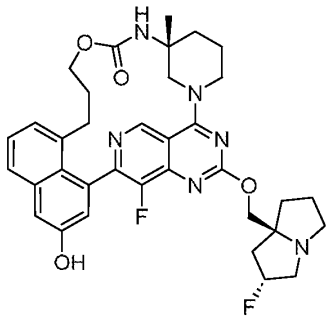
1-yl)propyl (4-nitrophenyl) carbonate (0.19 g, 0.24 mmol) and tert-butyl (R)-3-amino-3-methylpiperidine-1-carboxylate (0.103 g, 0.48 mmol) followed by the addition of DMF (2 mL). N,N-diisopropylethylamine (0.08 mL, 0.48 mmol) was added into the mixture at 25 °C and stirred for 16 h. The mixture was quenched by slow addition of H_2O (10 mL). The mixture was transferred to a separatory funnel and the aqueous layer extracted with ethyl acetate (5 mL x 3). The combined organic layers washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (0-60% EtOAc in petroleum ether) to give tert-butyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.18 g, 83% yield) as a white gum. LCMS (MM-ES+APCI, Pos): m/z 837.4 (M+H).

Step E. 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate. To a 40 mL vial equipped with a magnetic stir bar was added tert-butyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.18 g, 0.20 mmol) followed by the addition of DCM (3 mL). TFA (0.30 mL, 4.04 mmol) was added to the mixture at 25 °C and stirred for 1 h. The mixture was quenched by slow addition of saturated sodium bicarbonate (5mL), transferred to a separatory funnel and the aqueous layer extracted with DCM (3 mL x 3). The combined organic layers were washed with brine (3 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate (0.17 g) as a yellow solid. The crude product was used in the next step without further purification. Step F. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (compound 1). To a 250 mL round-bottom flask equipped with a magnetic stir bar was added 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate (0.13 g, 0.20 mmol) and N,N-diisopropylethylamine (0.17 mL, 1.01 mmol) followed by the addition of DCM (130 mL). BOP-Cl (0.15 g, 0.60 mmol) was added to the mixture at 0 °C. The mixture was stirred at 25 °C

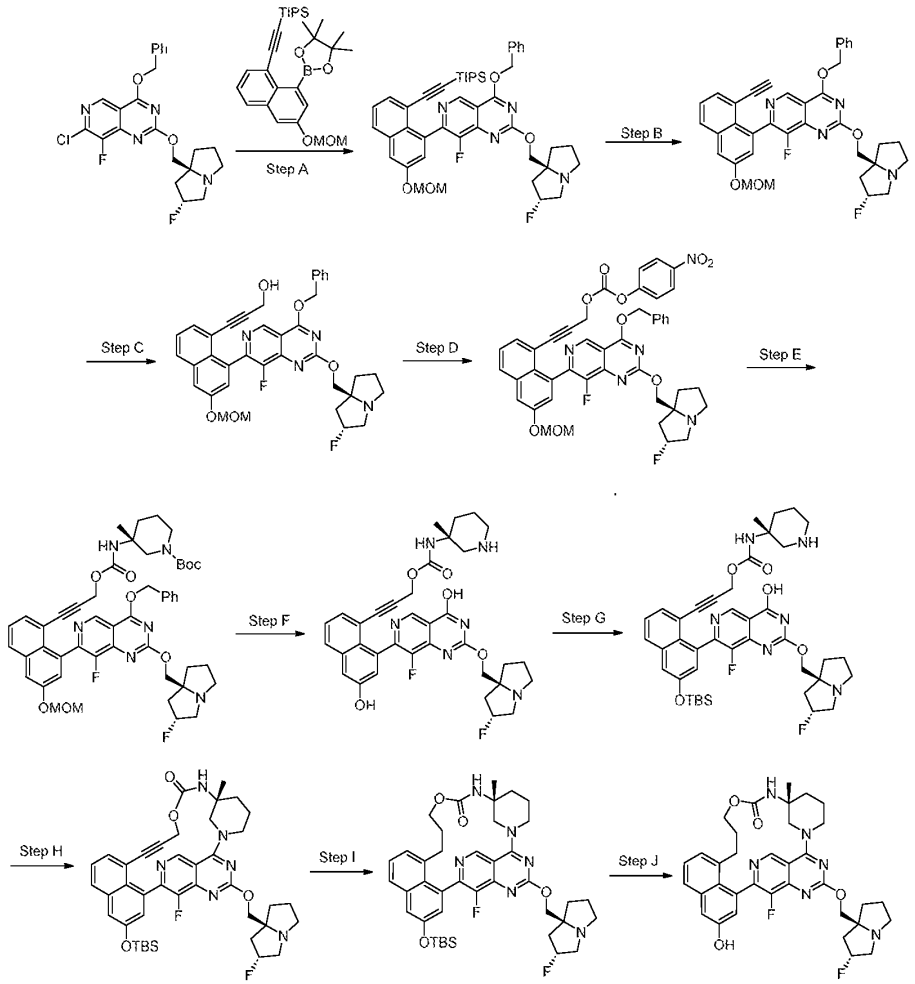
for 2 h. The mixture was quenched by slow addition of saturated aqueous sodium bicarbonate (2 mL), transferred to separatory funnel and the aqueous layer as extracted with DCM (10 mL x 3). The combined organics were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC (38%–68% acetonitrile in 0.05% aqueous ammonia hydroxide). After lyophilization, (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.016 g, 13% yield) was obtained as a white solid. LCMS (MM-ES+APCI, Pos): m/z 629.3 (M+H).

Example 23

Compound 2



(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidine. To a 500 mL round-bottom flask equipped with a magnetic stir bar was added 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (8.40 g, 16.8 mmol) and triisopropyl((6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane (10.0 g, 20.2 mmol) followed by the addition of dioxane (150 mL) and H_2O (30 mL). K_2CO_3 (5.80 g, 42.0 mmol) and mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium (II) (1.10 g, 1.51 mmol) were added into the mixture at 25 °C. The flask was evacuated and backfilled with nitrogen three times. The mixture was heated at 90 °C and stirred under an atmosphere of nitrogen for 1 h. The

suspension was filtered through a pad of Celite and the celite washed with ethyl acetate (400 mL). The combined organics were concentrated under reduced pressure and purified by silica gel column chromatography (11-17% EtOAc in petroleum ether) to give the desired product 4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidine (13.0 g, 89% yield) as a yellow gum. LCMS (MM-ES+APCI, Pos): m/z 779.4 (M+H).

Step B. 4-(benzyloxy)-7-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a 500 mL round-bottom flask equipped with a magnetic stir bar was added 4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidine (13.0 g, 15.0 mmol) followed by the addition of DMF (130 mL). CsF (4.55 g, 30.0 mmol) was added to the mixture at 25 °C and stirred at 25 °C for 1.5 h. The mixture was quenched by slow addition of H_2O (500 mL), transferred to a separatory funnel and the aqueous layer extracted with ethyl acetate (150 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (11-100% EtOAc in petroleum ether) to give 4-(benzyloxy)-7-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (6.45 g, 64% yield) as a brown solid. LCMS (MM-ES+APCI, Pos): m/z 623.4 (M+H).

Step C. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol. To a three-necked round-bottom flask equipped with a magnetic stir bar was added 4-(benzyloxy)-7-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (4.20 g, 6.25 mmol) and paraformaldehyde (2.10 g) followed by the addition of THF (252 mL). The flask was purged with nitrogen three times. The solution was cooled to -70 °C, LiHMDS (1.0 M, 1.43 mL) added to the mixture and stirred for 2 h. The mixture was allowed to warm to 25 °C and stirred for an additional 1.5 h. The mixture was quenched by slow addition of H_2O (80 mL) and transferred to a separatory funnel. The aqueous layer was extracted with ethyl acetate (80 mL x 3). The combined organics were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude

product was purified by silica gel column chromatography (50-75% EtOAc in petroleum ether) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol (0.77 g, 17% yield) as a yellow gum. LCMS (MM-ES+APCI, Pos): m/z 653.2 (M+H).

Step D. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-yl (4-nitrophenyl) carbonate. To a 40 mL vial equipped with a magnetic stir bar was added 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol (0.770 g, 1.05 mmol) followed by the addition of DCM (8 mL) and pyridine (3.41 mL, 42.26 mmol). A solution of 4-nitrophenyl chloroformate (0.62 g, 3.08 mmol) in DCM (4 mL) was added to the mixture at 25 °C and stirred for 16 h. The mixture was quenched by slow addition of H_2O (8 mL), extracted with DCM (8 mL x 5), combined organic layers washed with brine (8 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (50-100% EtOAc in petroleum ether) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-yl (4-nitrophenyl) carbonate (0.61 g, 66% yield) as a yellow gum. LCMS (MM-ES+APCI, Pos): m/z 818.3 (M+H).

Step E. tert-butyl (R)-3-((((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-yl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a 40 mL vial equipped with a magnetic stir bar was added 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-yl (4-nitrophenyl) carbonate (0.61 g, 0.69 mmol) and tert-butyl (R)-3-amino-3-methylpiperidine-1-carboxylate (0.23 mg, 1.07 mmol) followed by the addition of DMF (8 mL). N,N-diisopropylethylamine (0.37 mL, 2.13 mmol) and DMAP (0.082 mg, 0.67 mmol) were added into the mixture at 25 °C and stirred for 3 h. The mixture was quenched by slow addition of H_2O (30 mL) and the aqueous layer extracted with ethyl acetate (8 mL x 3). The combined organics were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (50-80% EtOAc in petroleum ether) to give tert-butyl (R)-3-

((((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-yl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.40 g, 59% yield) as a yellow gum. LCMS (MM-ES+APCI, Pos): m/z 893.5 (M+H).

Step F. 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)prop-2-yn-1-yl ((R)-3-methylpiperidin-3-yl)carbamate. To a 50 mL round-bottom flask equipped with a magnetic stir bar was added tert-butyl (R)-3-((((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-yl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.40 g, 0.41 mmol) followed by the addition of DCM (10 mL). TFA (2 mL, 26.93 mmol) was added to the mixture and the reaction stirred at 25 °C for 0.5 h. The mixture was quenched by slow addition of saturated aqueous sodium bicarbonate (20 mL) and the aqueous layer extracted with ethyl acetate (10 mL x 3) followed by $CHCl_3$/MeOH: 3/1 (10 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)prop-2-yn-1-yl ((R)-3-methylpiperidin-3-yl)carbamate (0.270 g) as a yellow solid, which was taken onto the next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 659.4 (M+H).

Step G. 3-(6-((tert-butyldimethylsilyl)oxy)-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)prop-2-yn-1-yl ((R)-3-methylpiperidin-3-yl)carbamate. To a 50 mL round-bottom equipped with a magnetic stir bar was added 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)prop-2-yn-1-yl ((R)-3-methylpiperidin-3-yl)carbamate (0.13 g, 0.20 mmol) followed by the addition of DCM (5 mL). Tert-butyldimethylsilyl chloride (0.04 g, 0.26 mmol) and imidazole (0.03 g, 0.41 mmol) was added into the mixture and stirred at 25 °C for 1 h. The mixture was quenched by slow addition of H_2O (10 mL) and the aqueous layer extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 3-(6-((tert-butyldimethylsilyl)oxy)-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)prop-2-yn-1-yl ((R)-3-methylpiperidin-3-yl)carbamate (0.13 g, 82% yield)

as a yellow solid, which was taken onto the next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 773.5 (M+H).

Step H. (1^3R)-3^3-((tert-butyldimethylsilyl)oxy)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one. To a 100 mL round-bottom flask equipped with a magnetic stir bar was added 3-(6-((tert-butyldimethylsilyl)oxy)-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)prop-2-yn-1-yl ((R)-3-methylpiperidin-3-yl)carbamate (0.05 g, 0.065 mmol) followed by the addition of DCM (50 mL). N,N-diisopropylethylamine (0.03 mL, 0.19 mmol) and BOP-Cl (0.02 g, 0.097 mmol) were added to the mixture and the reaction stirred at 25 °C for 2 h. The mixture was concentrated under reduced pressure and purified by preparative TLC (100% EtOAc) to obtain desired product (1^3R)-3^3-((tert-butyldimethylsilyl)oxy)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one (0.02 g, 41% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 755.6 (M+H).

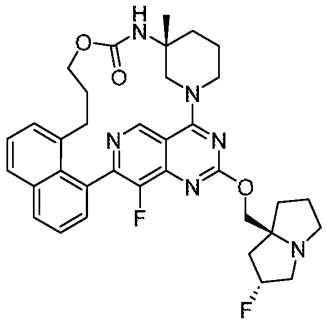
Step I. (1^3R)-3^3-((tert-butyldimethylsilyl)oxy)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a 10 mL round-bottom flask equipped with a magnetic stir bar was added Pd/C (0.02 g, 10 wt%) followed by the addition of MeOH (2 mL). (1^3R)-3^3-((tert-butyldimethylsilyl)oxy)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one (0.020 g, 0.0265 mmol) in MeOH (2 mL) was added into the mixture. The flask was then evacuated and backfilled with H_2 three times. The mixture was stirred at 20 °C under an atmosphere of H_2 for 1 h. The suspension was filtered and the filter cake was washed with ethyl acetate (5 mL x 4). The filtrate was concentrated under reduced pressure to afford (1^3R)-3^3-((tert-butyldimethylsilyl)oxy)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.015 g, 75% yield) which was used into the next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 759.5 (M+H).

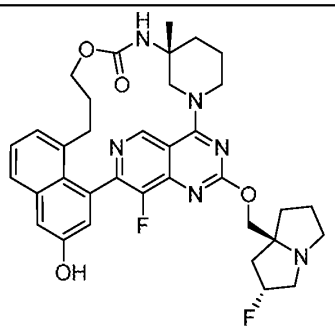
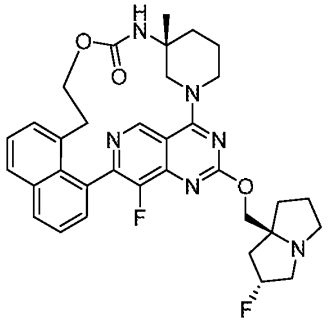
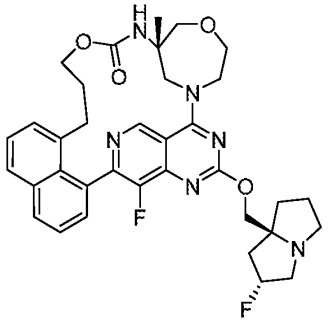
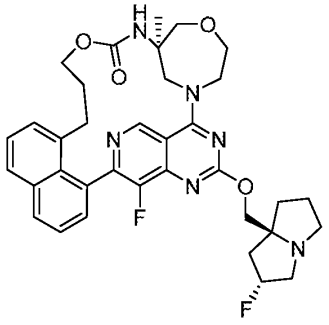
Step J. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-

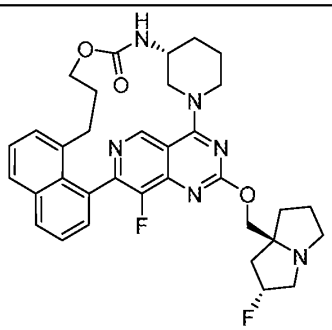
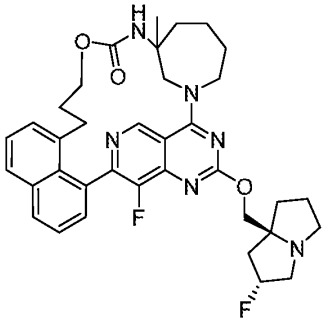
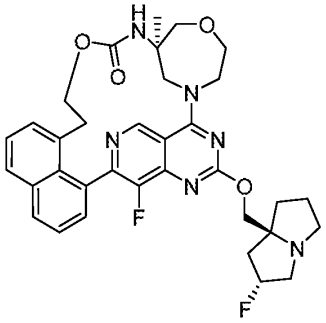
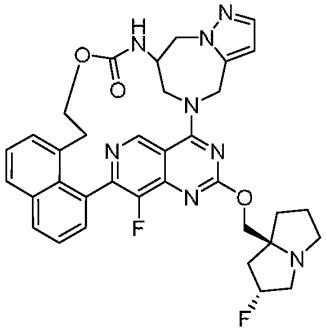
piperidina-3(1,8)-naphthalenacyclononaphan-8-one (compound 2). To a 10 mL round-bottom flask equipped with a magnetic stir bar was added (1^3R)-3^3-((tert-butyldimethylsilyl)oxy)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.015 g, 0.019 mmol) in THF (2 mL). $HF{\cdot}NEt_3$ (0.013 mL, 0.08 mmol) was added into the mixture. The mixture was stirred at 20 °C for 1 h. The suspension was filtered and the filter cake was washed with ethyl acetate (5 mL x 4). The filtrate was concentrated under reduced pressure and purified by preparative HPLC (10% – 40% acetonitrile in 0.225% aqueous formic acid). After lyophilization, (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.002 g, 15% yield) was obtained as a white solid. LCMS (MM-ES+APCI, Pos): m/z 645.4 (M+H).

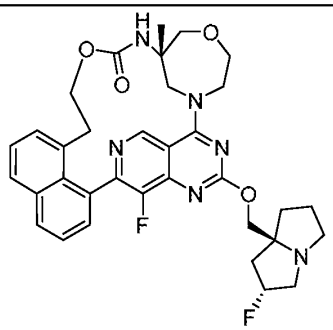
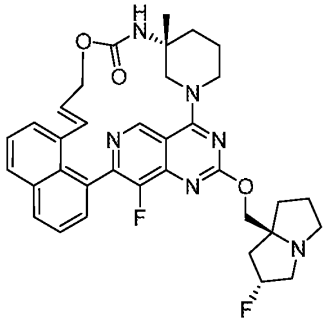
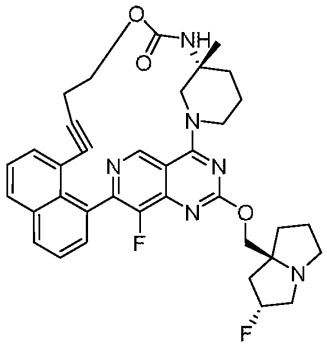
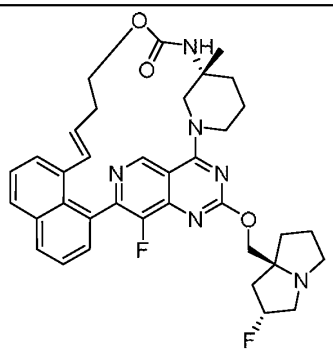
The compounds herein (such as a compound of Formula (I), Formula (IA)-(IE) or Formula (IA-1)-(IE-1)) may be prepared from an intermediate as prepared in "Syntheses of intermediates compounds", an intermediate that is commercially available, an intermediate as prepared elsewhere in this application or an intermediate that can be synthesized via a method known to those skilled in the art. Exemplary full syntheses are provided in Examples 22, 23, 26, 32 and 33 (Compound 19, Compound 20, Compound 16, Compound 9 and Compound 6). Compounds prepared in accordance with Example 22 and 23 are provided in **Table 2** below.

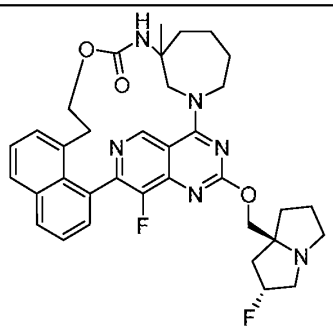
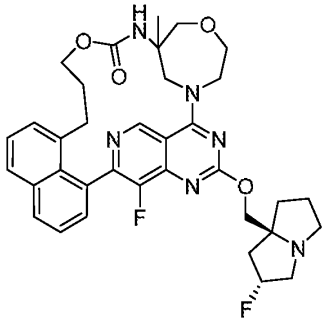
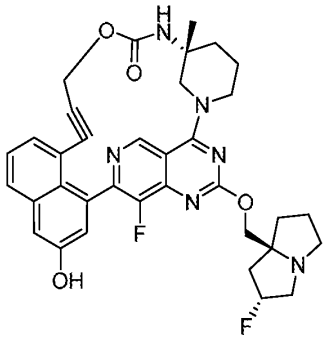
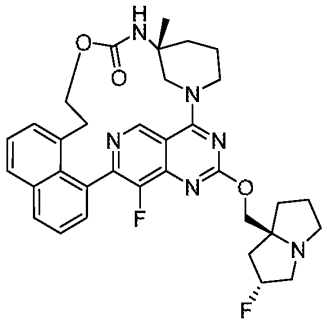
Table 2: A list of compounds 1-18 and compounds 21-30.

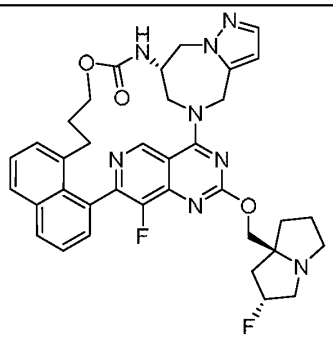
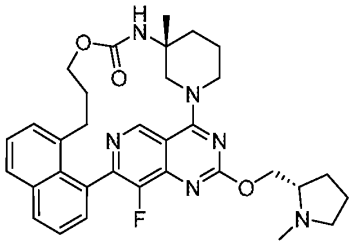
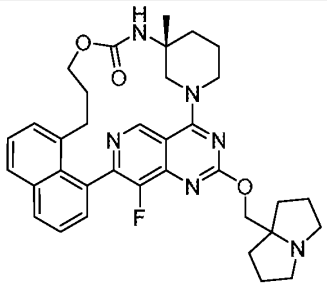
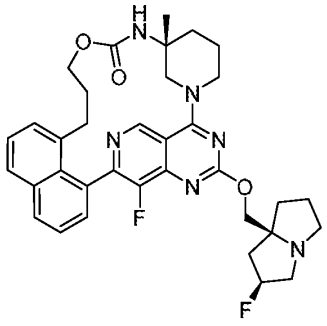
Cmp. ID	Structure	LCMS
1		629.3

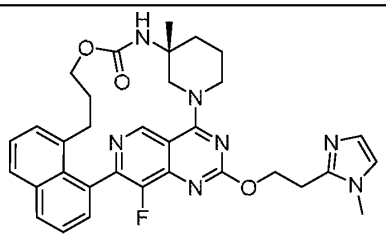
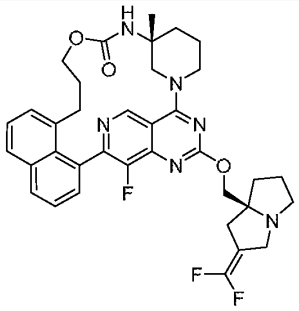
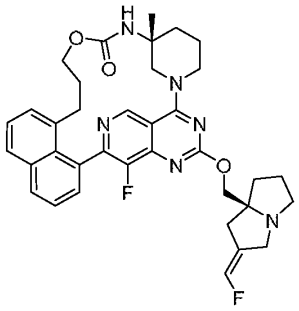
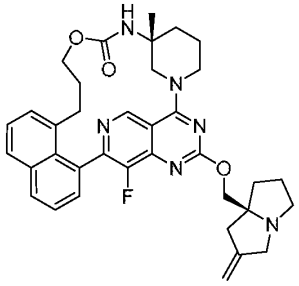
2		645.4
3		615.2
4		645.3
5		645.4

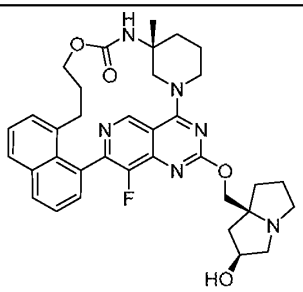
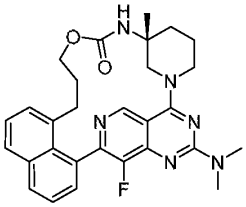
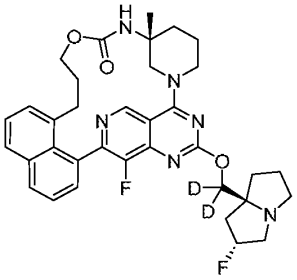
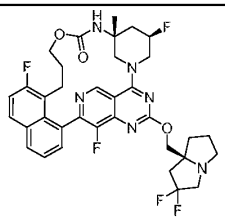
6		615.3
7		643.3
8		631.3
9		653.3

10		631.3
11		627.4
12		639.4
13		641.4

14		629.3
15		645.3
16		641.4
17		615.2

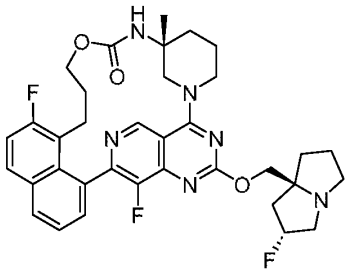
18		667.3
21		585.4
22		611.4
23		629.3

24		596.2
25		659.3
26		641.3
27		623.4

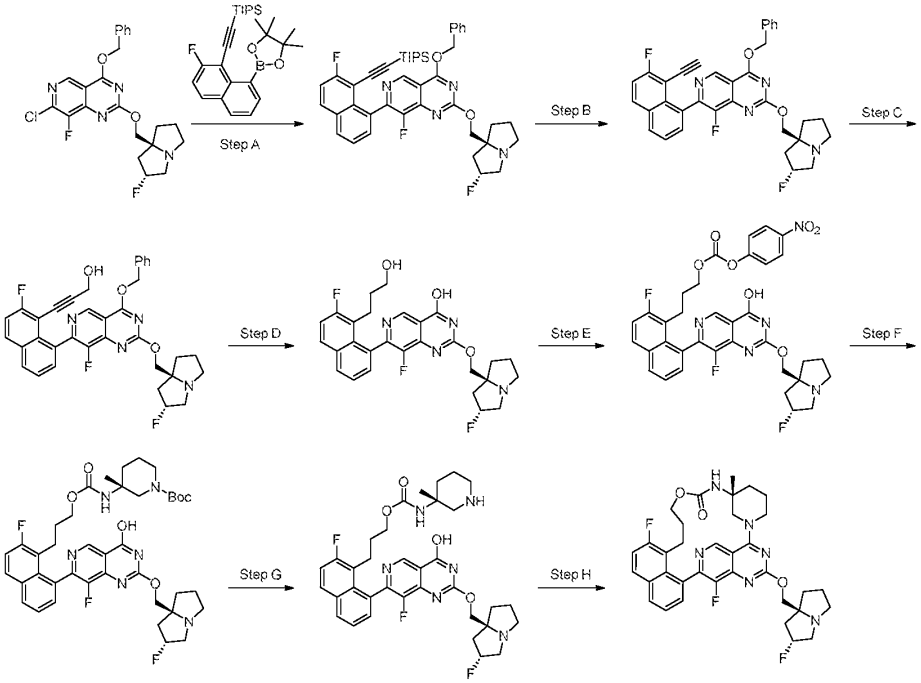
28		627.3
29		515.4
30		631.3
503		683.4

Example 24

Compound 19



(1^3R)-2^8,3^7-difluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine. A solution of ((2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (6.7 g, 15 mmol), 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (6.0 g, 13 mmol), mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2'-amino-

1,1'-biphenyl)]palladium(II) (0.98 g, 1.3 mmol), potassium carbonate (5.6 g, 40 mmol) in 1,4-dioxane (100 mL) and H_2O (10 mL) was stirred at 80 °C for 16 h. The reaction mixture was cooled to rt and diluted with H_2O (50 mL). The solution was extracted with EtOAc (3x 50 mL). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (30 - 50% EtOAc in petroleum ether) to give 4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (8.5 g, 86% yield). LCMS (MM-ES+APCI, Pos): m/z 737.6 (M+H).

Step B. 4-(benzyloxy)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine. To a solution of 4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (8.5 g, 12 mmol) in DMF (50 mL) was added CsF (8.8 g, 58 mmol). The reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (80 - 100% EtOAc in petroleum ether) to give 4-(benzyloxy)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (4.5 g, 67% yield). LCMS (MM-ES+APCI, Pos): m/z 581.4 (M+H).

Step C. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)prop-2-yn-1-ol. To a solution of 4-(benzyloxy)-7-(8-ethynyl-7-fluoronaphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (4.0 g, 6.9 mmol) in THF (200 mL) cooled to -60 °C was added LiHMDS (10 mL, 10 mmol,1 M in THF). Paraformaldehyde (2.0 g, 6.9 mmol) was added to the mixture, and the reaction was stirred at -65 °C for 2 h. The reaction mixture was warmed to rt and stirred for 2 h. The reaction mixture was diluted with H_2O (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (50 - 70% EtOAc in petroleum ether) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)prop-2-yn-1-ol (1.2 g, 29% yield). LCMS (MM-ES+APCI, Pos): m/z 611.4 (M+H).

Step D. 8-fluoro-7-(7-fluoro-8-(3-hydroxypropyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol. To a

solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)prop-2-yn-1-ol (0.50 g, 0.49 mmol) in MeOH (100 mL) and THF (10 mL) was added Pd/C (3.5 g, 3.3 mmol, 10% w/w) under N_2. The mixture was stirred at 35 °C for 2 h under an atmosphere of H_2 at 15 psi. The reaction mixture was filtered over Celite and the filtrate was concentrated under reduced pressure to give 8-fluoro-7-(7-fluoro-8-(3-hydroxypropyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (0.33 g, 77% yield) which was used directly in the next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 525.3 (M+H).

Step E. 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propyl (4-nitrophenyl) carbonate. To a 40 mL vial equipped with a magnetic stir bar was added 8-fluoro-7-(7-fluoro-8-(3-hydroxypropyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (0.28 g, 0.53 mmol), pyridine (0.13 g, 1.60 mmol), and DCM (10 mL). The solution was cooled to 0 °C, and (4-nitrophenyl) carbonochloridate (0.32 g, 1.60 mmol) was added to the mixture. The reaction was warmed to room temperature and stirred for 2 h. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (50 - 100% EtOAc in petroleum ether) to give 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propyl (4-nitrophenyl) carbonate (0.25 g, 68% yield). LCMS (MM-ES+APCI, Pos): m/z 690.5 (M+H).

Step F. *tert*-butyl (*R*)-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (4-nitrophenyl) carbonate (0.25 g, 0.36 mmol) and *tert*-butyl (3*R*)-3-amino-3-methyl-piperidine-1-carboxylate (0.093 g, 0.44 mmol) in DMF (5 mL) was added DIPEA (0.14 g, 1.1 mmol) and DMAP (0.044 g, 0.36 mmol). The mixture was stirred at rt for 16 h and was diluted with H_2O (50 mL). The solution was extracted with EtOAc (3 x 50 mL) and the combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (60 - 100% EtOAc in petroleum ether) to give *tert*-butyl (*R*)-3-

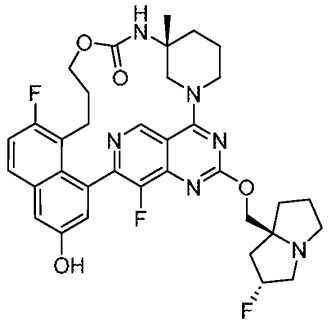
(((3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.20 g, 72% yield). LCMS (MM-ES+APCI, Pos): m/z 765.6 (M+H).

Step G. 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propyl ((*R*)-3-methylpiperidin-3-yl)carbamate. To a solution of *tert*-butyl (*R*)-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.20 g, 0.26 mmol) in DCM (5 mL) was added TFA (1.5 g, 13 mmol). The mixture was stirred at rt for 1 h. The reaction mixture was poured into sat. $NaHCO_3$ solution (50 mL) and extracted with DCM (3 x 50 mL). The combined organic phase was washed with brine (50 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propyl ((*R*)-3-methylpiperidin-3-yl)carbamate (0.12 g, 69% yield), which was used directly in the next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 665.6 (M+1).

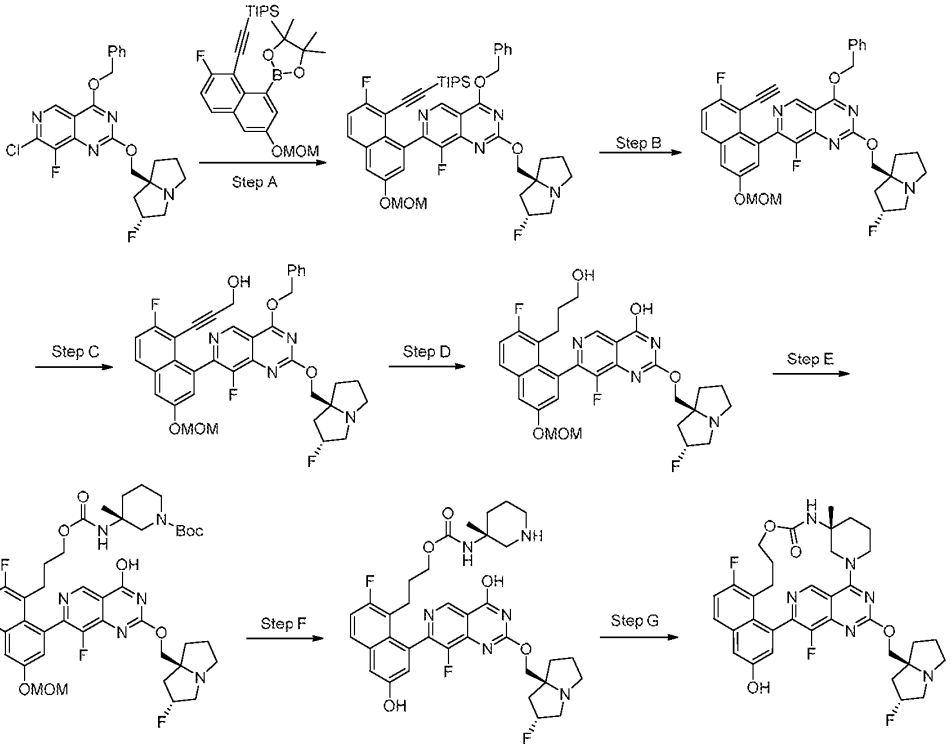
Step H. (1^3*R*)-2^8,3^7-difluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propyl ((*R*)-3-methylpiperidin-3-yl)carbamate (0.12 g, 0.181 mmol) in DCM (10 mL) was added BOP-Cl (0.07 g, 0.27 mmol) and DIPEA (0.07 g, 0.54 mmol). The mixture was stirred at rt for 16 h. The solution was diluted with H_2O (50 mL) and extracted with DCM (3 x 50 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (40-70% acetonitrile in 0.05% aqueous TFA). After lyophilization, (1^3*R*)-2^8,3^7-difluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.012 g, 10% yield) was obtained as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 647.5 (M+H).

Example 25

Compound 20



(1^3R)-2^8,3^7-difluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 4-(benzyloxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine. A solution of ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (7.5

g, 15 mmol), 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (5.0 g, 11 mmol), mesylate[(di(1-adamantyl)-*n*-butylphosphine)-2-(2'-amino-1,1'-biphenyl)]palladium(II) (1.1 g, 1.5 mmol), and potassium phosphate (7.1 g, 34 mmol) in THF (40 mL) and H_2O (10 mL) was sparged with Ar for 10 min. The solution was heated to 80 °C for 2 h. The solution was diluted with H_2O (50 mL) and extracted with DCM (3 X 50 mL). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (20 - 100% EtOAc in hexanes) to give 4-(benzyloxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (7.2 g, 81%). LCMS (MM-ES+APCI, Pos): m/z 797.3 (M+H).

Step B. 4-(benzyloxy)-7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine. To a solution of 4-(benzyloxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (6.5 g, 8.2 mmol) in THF (40 mL) at 0 °C was added TBAF (1.0 M in THF, 9.4 mL, 9.4 mmol). The reaction was stirred at 0 °C for 40 min and quenched with the addition of H_2O (100 mL). The slurry was filtered by vacuum filtration and the solids washed with H_2O (100 mL). The precipitate was dried under reduced pressure to obtain 4-(benzyloxy)-7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (5.0 g, 86 %). LCMS (MM-ES+APCI, Pos): m/z 641.2 (M+H).

Step C. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol. To a solution of 4-(benzyloxy)-7-(8-ethynyl-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidine (5.0 g, 7.8 mmol) in THF (70.0 mL) at -78 °C was added LiHMDS (1.0 M in THF; 9.0 mL, 9.0 mmol). The mixture was stirred at -78 °C for 50 minutes, and paraformaldehyde (2.3 g, 78 mmol) was added in one portion. The mixture was warmed to rt and stirred for 1 h. To the reaction mixture was added sat. $NaHCO_3$ solution (50 mL) and the mixture extracted with DCM (3 X 50 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (0 - 10% MeOH in DCM) to afford 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-

d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol (3.0 g, 57%). LCMS (MM-ES+APCI, Pos): m/z 671.3 (M+H).

Step D. 8-fluoro-7-(7-fluoro-8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol (3.0 g, 4.4 mmol) in THF (33 mL) and MeOH (11 mL) was added dihydroxypalladium (20% wt; 0.93 g, 1.3 mmol). The mixture was sparged with hydrogen gas for 10 min and stirred at room temperature for 2.5 days under 1 atm of hydrogen pressure. The reaction mixture was filtered through a celite plug. The pad was washed with MeOH (50 mL) and the filtrate was concentrated under reduced pressure. The residue was purified be silica gel chromatography (0 - 15 % MeOH in DCM) to give 8-fluoro-7-(7-fluoro-8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (1.5 g, 57%). LCMS (MM-ES+APCI, Pos): m/z 585.3 (M+H).

Step E. tert-butyl (*R*)-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of 8-fluoro-7-(7-fluoro-8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-ol (1.5 g, 2.5 mmol) and *N*'*N*'-disuccinimidyl carbonate (1.3 g, 5.1 mmol) in DCM (15 mL) was added DIPEA (1.8 mL, 10 mmol). The reaction was heated to 30 °C and stirred at this temperature for 15.5 h followed by addition of tert-butyl (*R*)-3-amino-3-methylpiperidine-1-carboxylate (1.6 g, 7.6 mmol) in DCM (3.0 mL). The reaction was stirred for 35 min. and concentrated under reduced pressure. The residue was purified via silica gel chromatography (0-10% MeOH in DCM) to give tert-butyl (*R*)-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (2.3 g, 71%). LCMS (MM-ES+APCI, Pos): m/z 825.5 (M+H).

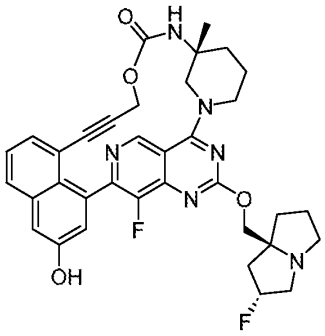
Step F. 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl ((*R*)-3-methylpiperidin-3-yl)carbamate. To a solution of tert-butyl (*R*)-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-

d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (2.1 g, 2.5 mmol) in DCM (10.0 mL) was added HCl (4.0 M in 1,4-dioxane; 0.45 mL). The reaction was stirred for 30 min at rt and then quenched by addition of sat. $NaHCO_3$ solution (10 mL). The mixture was stirred for 10 min and was extracted with 25% IPA in $CHCl_3$ (3 X 10 mL). The combined organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl ((*R*)-3-methylpiperidin-3-yl)carbamate (1.4 g, 78%). LCMS (MM-ES+APCI, Pos): m/z 681.3 (M+H).

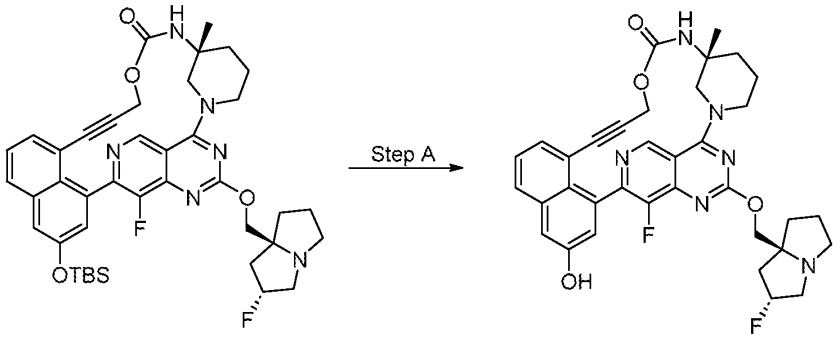
Step G. (1^3R)-2^8,3^7-difluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of bromotri(1-pyrrolidinyl)phosphoniumhexafluorophosphate (1.9 g, 4.0 mmol) and DIPEA (1.7 mL, 10 mmol) in MeCN (70 mL) was added a solution of 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl ((*R*)-3-methylpiperidin-3-yl)carbamate (1.4 g, 2.0 mmol) in MeCN (5.0 mL) and DMSO (5.0 mL) at 60 °C over 30 min via syringe pump. The reaction was stirred at this temperature for 1 h and concentrated under reduced pressure. The residue was dissolved in EtOAc (100 mL) and washed with H_2O (2 X 50 mL) and brine (50 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (0-15% MeOH in DCM) to obtain (1^3R)-2^8,3^7-difluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.15 g, 11%). LCMS (MM-ES+APCI, Pos): m/z 663.3 (M+H).

Example 26

Compound 16 (exemplary synthesis)



(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one

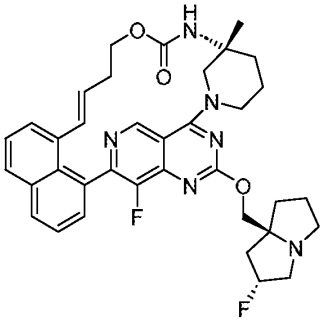


Step A. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one. To solution of (1^3R)-3^3-((tert-butyldimethylsilyl)oxy)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one (0.010 g, 0.013 mmol) and THF (1 mL) was added HF·NEt_3 (0.0086 mL, 0.053 mmol). The reaction was stirred at rt for 30 min. The mixture was quenched by slow addition of triethylamine (1 mL) and H_2O (3 mL). The aqueous layer was extracted with ethyl acetate (2 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC (10 – 40% acetonitrile in 0.1% aqueous formic acid). The fractions containing the product were lyophilized to obtain (1^3R)-2^8-fluoro-

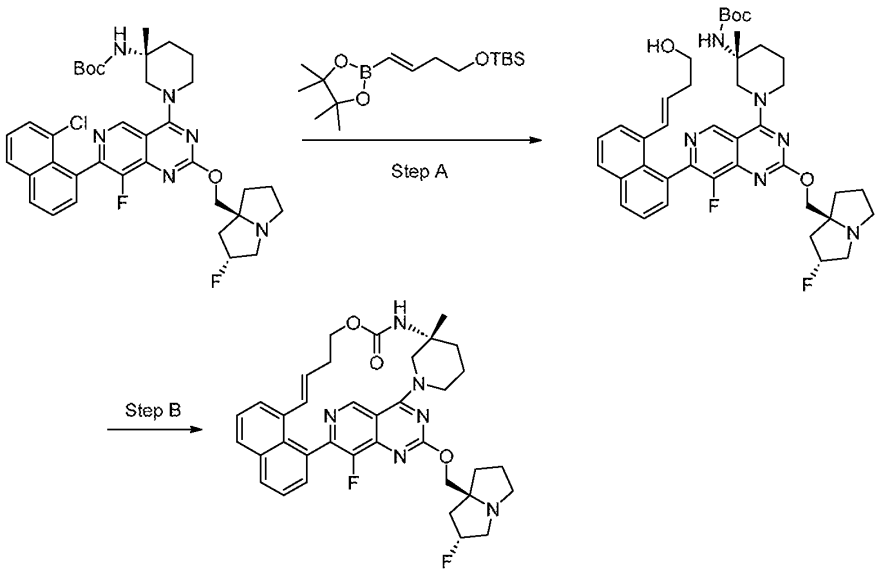
2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one (0.0021 g, 25% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 641.4 (M+H).

Example 27

Compound 13 (alternative synthesis)



(1^3R,*E*)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxa-10-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclodecaphan-4-en-9-one



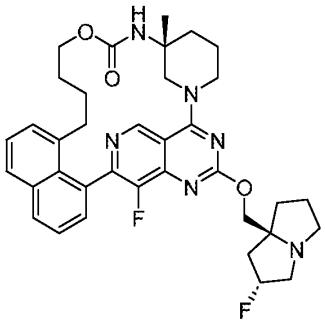
Step A. tert-butyl ((R)-1-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-

7a(5H)-yl)methoxy)-7-(8-((E)-4-hydroxybut-1-en-1-yl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate. A solution of (E)-tert-butyldimethyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl)oxy)silane (0.055 g, 0.18 mmol), tert-butyl ((R)-1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate (0.60 g, 0.088 mmol), Na_2CO_3 (0.028 g, 0.26 mmol), and bis(di-tert-butyl (4-dimethylaminophenyl)phosphine)dichloropalladium(II) (0.012 g, 0.018 mmol) in 1,4-dioxane (0.50 mL) and H_2O (0.10 mL) was sparged with argon for 10 min. The reaction was heated to 100 °C for 2 h after which it was concentrated under reduced pressure. The residue was purified via preparative HPLC (10 - 95% acetonitrile in 0.05% aqueous NH_4HCO_3). The fractions containing the product were concentrated under reduced pressure to remove the volatiles and then extracted with DCM (5 mL x 3). The organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure to obtain tert-butyl ((R)-1-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-((E)-4-hydroxybut-1-en-1-yl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate (0.015 g, 24% yield). LCMS (MM-ES+APCI, Pos): m/z 715.4 (M+H).

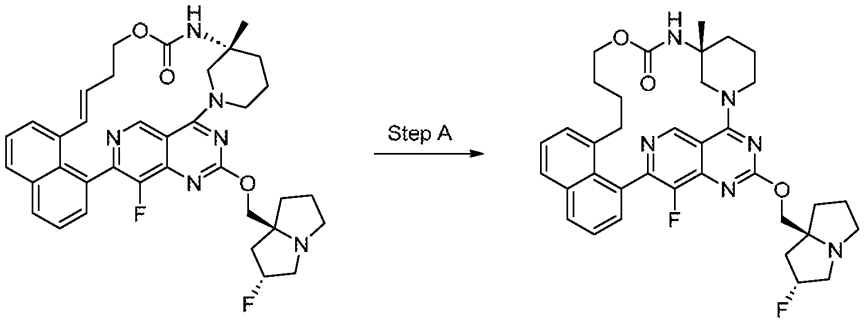
Step B. (1^3R,*E*)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxa-10-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclodecaphan-4-en-9-one. To a solution of tert-butyl ((R)-1-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-((E)-4-hydroxybut-1-en-1-yl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate (0.0075 g, 0.105 mmol) in DCM (0.10 mL) was added TFA (0.004 mL, 0.052 mmol). The reaction was stirred for 1 h. The solution was diluted with DCM (0.5 mL) and triethylamine (0.015 mL, 0.105 mmol). After stirring for 5 min, DMAP (0.001 g, 0.010 mmol) and p-nitrophenol chloroformate (0.002 g, 0.011 mmol) were added. The reaction was stirred for an additional 30 min and then concentrated under reduced pressure. The reaction was purified via preparative HPLC (10 - 100% acetonitrile in 0.05% aqueous NH_4HCO_3). The fractions containing the product were concentrated to remove volatiles and extracted with DCM (5 mL x 3). The combined organic phase was passed through a phase separator and then concentrated in vacuo to obtain (1^3R,E)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxa-10-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclodecaphan-4-en-9-one (0.0020 g, 28% yield). LCMS (MM-ES+APCI, Pos): m/z 641.4 (M+H).

Example 28

Compound 31



(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxa-10-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclodecaphan-9-one

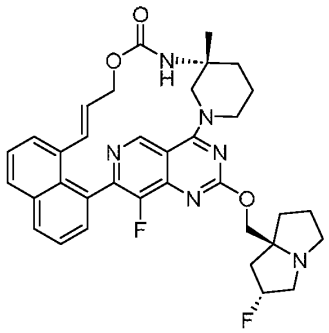


Step A. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxa-10-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclodecaphan-9-one. A slurry of (1^3R,E)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxa-10-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclodecaphan-4-en-9-one (0.010 g, 0.016 mmol) and Pd/C (10 wt%; 0.0080 g, 0.008 mmol) in MeOH (0.15 mL) was sparged with H_2 for 10 min. The reaction was stirred under an atmosphere of H_2 for 15 h. The slurry was filtered over Celite, and the pad washed with DCM (5 mL). The filtrate was concentrated under reduced pressure. The residue was purified via silica gel chromatography (0 - 20 % MeOH in DCM) to give (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxa-10-aza-2(4,7)-pyrido[4,3-d]pyrimidina-

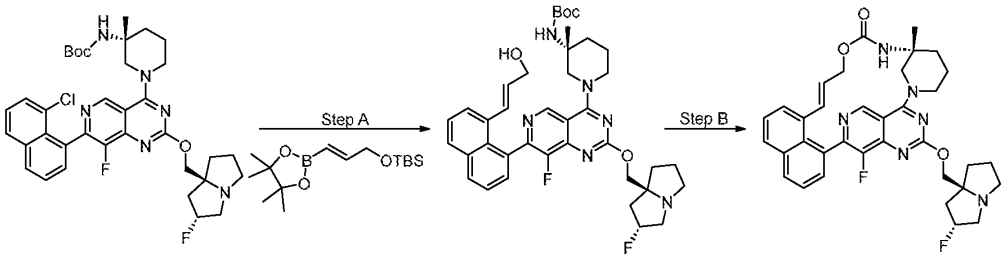
1(1,3)-piperidina-3(1,8)-naphthalenacyclodecaphan-9-one (0.008 g, 72% yield). LCMS (MM-ES+APCI, Pos): m/z 643.3 (M+H).

Example 29

Compound 11 (alternative synthesis)



(1^3R,E)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-en-8-one



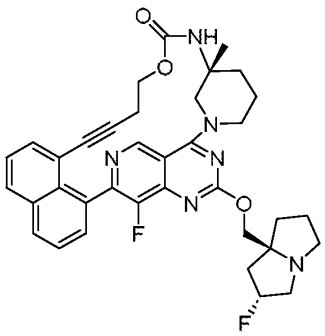
Step A. tert-butyl ((R)-1-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-((E)-3-hydroxyprop-1-en-1-yl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate. A solution of (E)-tert-butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane (0.13 g, 0.44 mmol), tert-butyl ((R)-1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate (0.15 g, 0.22 mmol), Na_2CO_3 (0.070 g, 0.66 mmol), and bis(di-tert-butyl (4-dimethylaminophenyl)phosphine)dichloropalladium(II) (0.031 g, 0.044 mmol) in 1,4-dioxane (1.0 mL) and H_2O (0.30 mL) was sparged with argon for 10 min. The reaction was heated to 100 °C for 2 h after which it was concentrated under reduced pressure. The residue was purified via silica gel chromatography (30 - 100 % EtOAc in hexanes) to give tert-butyl ((R)-1-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-((E)-3-

hydroxyprop-1-en-1-yl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate (0.066 mg, 43% yield). LCMS (MM-ES+APCI, Pos): m/z 701.4 (M+H).

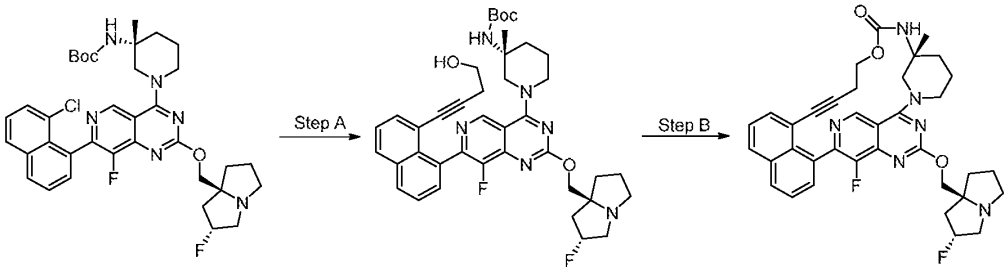
Step B. (1^3R,E)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-en-8-one. To a solution of tert-butyl ((R)-1-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-((E)-3-hydroxyprop-1-en-1-yl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate (0.066 g, 0.094 mmol) in DCM (0.25 mL) was added HCl in dioxane (4.0 M; 0.071 mL, 0.28 mmol). The reaction was stirred at rt for 1.5 h. The solution was diluted with DCM (0.5 mL) and triethylamine (0.13 mL, 0.94 mmol). The solution was stirred for 5 min and DMAP (0.012 g, 0.094 mmol) and p-nitrophenol chloroformate (0.021 g, 0.10 mmol) was added. The reaction was stirred for an additional 1 h at rt and then it was concentrated under reduced pressure. The residue was purified via preparative HPLC (5 - 100% acetonitrile in 0.1% aqueous TFA). The fractions containing the product were lyophilized. The residue was purified via preparative HPLC (5 - 60% acetonitrile in 0.1% aqueous TFA). The fractions containing the product were lyophilized to obtain (1^3R,E)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-en-8-one, trifluoroacetic acid (0.0012 g, 1.5% yield). LCMS (MM-ES+APCI, Pos): m/z 627.4 (M+H).

Example 30

Compound 12 (alternative synthesis)



(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxa-10-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclodecaphan-4-yn-9-one



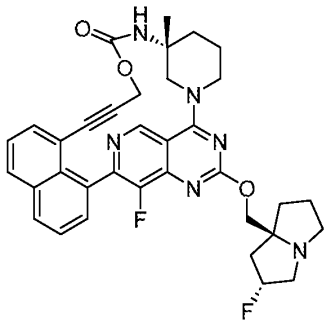
Step A. tert-butyl ((R)-1-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-(4-hydroxybut-1-yn-1-yl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate. A solution of but-3-yn-1-ol (0.047 mL, 0.62 mmol), tert-butyl ((R)-1-(7-(8-chloronaphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate (0.14 g, 0.21 mmol), Cs_2CO_3 (0.20 g, 0.62 mmol), and methanesulfonato{[4-(N,N-dimethylamino)phenyl]di-t-butylphosphino}(2'-amino-1,1'-biphenyl-2-yl)palladium(II) (0.026 g, 0.041 mmol) in DMA (1.0 mL) was sparged with argon for 10 min. The reaction was heated to 100 °C for 18 h. The reaction solution was concentrated under reduced pressure. The residue purified via preparative HPLC (5 - 100% acetonitrile in 0.1% aqueous TFA). The fractions containing the product were concentrated under reduced pressure and neutralized with saturated $NaHCO_3$ solution (10 mL) and then extracted with DCM (10 mL x 3). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure to obtain tert-butyl ((R)-1-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-(4-hydroxybut-1-yn-1-yl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate (0.0075 g, 5% yield). LCMS (MM-ES+APCI, Pos): m/z 712.8 (M+H).

Step B. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxa-10-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclodecaphan-4-yn-9-one. To a solution of tert-butyl ((R)-1-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-(4-hydroxybut-1-yn-1-yl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-yl)-3-methylpiperidin-3-yl)carbamate (0.0075 g, 0.011 mmol) in DCM (0.15 mL) was added HCl in dioxane (4.0 M; 0.016 mL, 0.063 mmol). The reaction was stirred for 2 h and concentrated under reduced pressure. The residue was dissolved in DCM (0.5 mL) and triethylamine (0.015 mL, 0.11 mmol). The solution was stirred

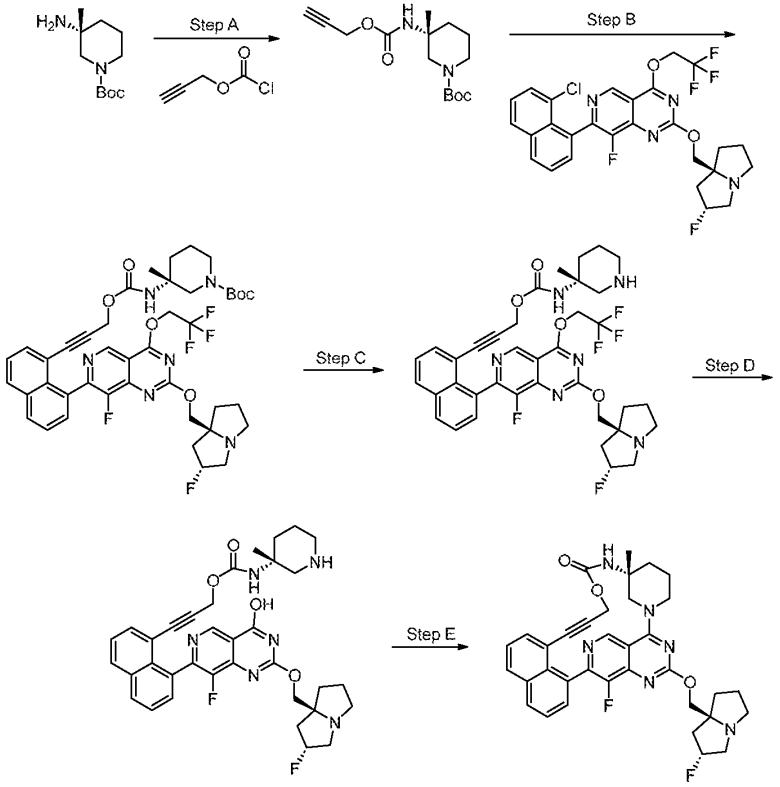
for 5 min and p-nitrophenol chloroformate (0.005 mg, 0.023 mmol) and DMAP (0.0026 g, 0.021 mmol) were added. The solution was stirred for an additional 2 h and then concentrated under reduced pressure. The residue was purified via preparative HPLC (5 - 60% acetonitrile in 0.1% aqueous TFA). The fractions containing the product were lyophilized to obtain (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxa-10-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclodecaphan-4-yn-9-one (0.00085 g, 10% yield). LCMS (MM-ES+APCI, Pos): m/z 639.4 (M+H).

Example 31

Compound 32



(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one



Step A. tert-butyl (R)-3-methyl-3-(((prop-2-yn-1-yloxy)carbonyl)amino)piperidine-1-carboxylate. To a solution of tert-butyl (R)-3-amino-3-methylpiperidine-1-carboxylate (0.80 g, 3.7 mmol) and DIPEA (1.3 mL, 7.5 mmol) in DCM (5 mL) at 0 °C was added a solution of prop-2-yn-1-yl carbonochloridate (0.53 g, 4.5 mmol) in DCM (5 mL) was added. The mixture was warmed to rt and was stirred for 2 h. The mixture was diluted with H_2O (10 mL) and extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-10% EtOAc in petroleum ether) to give tert-butyl (R)-3-methyl-3-(((prop-2-yn-1-yloxy)carbonyl)amino)piperidine-1-carboxylate (1.0 g, 90% yield) as a white solid. ^{1}H-NMR (400 MHz, methanol-d4) δ = 4.61 (br s, 2H), 4.26 - 3.77 (m, 1H), 3.66 (br d, J = 5.2 Hz, 1H), 3.24 - 2.91 (m, 2H), 2.85 (br s, 1H), 2.19 - 1.80 (m, 1H), 1.75 - 1.60 (m, 1H), 1.59 - 1.49 (m, 2H), 1.45 (s, 9H), 1.30 (s, 3H).

Step B. tert-butyl (R)-3-((((3-(8-(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-1-yl)prop-2-yn-1-yl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. A

solution of tert-butyl (R)-3-methyl-3-(((prop-2-yn-1-yloxy)carbonyl)amino)piperidine-1-carboxylate (0.030 g, 0.10 mmol), 7-(8-chloronaphthalen-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, Intermediate I4 (0.012 g, 0.020 mmol), K_2CO_3 (0.0056 g, 0.041 mmol), $Pd_2(dba)_3$ (0.0019 g, 0.0020 mmol), (4-(N,N-dimethylamino)phenyl)di-tert-butyl phosphine (0.0011 g, 0.0041 mmol) and THF (0.5 mL) was sparged with nitrogen for 5 min. The reaction was heated to 80 °C for 16 h and then diluted with H_2O (10 mL). The mixture was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-100% EtOAc in petroleum ether). The residue was purified by preparative HPLC (62-92% acetonitrile in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain tert-butyl (R)-3-((((3-(8-(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-1-yl)prop-2-yn-1-yl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.040 g, 22% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 825.5 (M+H).

Step C. 3-(8-(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-1-yl)prop-2-yn-1-yl ((R)-3-methylpiperidin-3-yl)carbamate. To a solution of tert-butyl (R)-3-((((3-(8-(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-1-yl)prop-2-yn-1-yl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.040 g, 0.045 mmol) in DCM (1 mL) was added TFA (0.30 mL, 4.0 mmol). The reaction was stirred at rt for 30 min and then it was quenched with the addition of saturated aqueous sodium bicarbonate (2 mL). The mixture was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 3-(8-(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-1-yl)prop-2-yn-1-yl ((R)-3-methylpiperidin-3-yl)carbamate (0.030 g), which was taken into the next step without further purification.

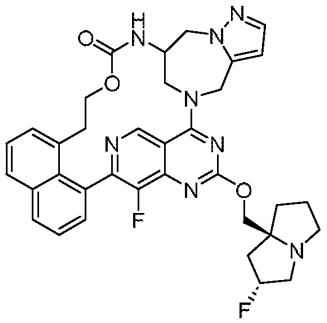
Step D. 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)prop-2-yn-1-yl ((R)-3-methylpiperidin-3-yl)carbamate. A solution of 3-(8-(8-fluoro-2-(((2R,7aS)-2-

fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)prop-2-yn-1-yl ((R)-3-methylpiperidin-3-yl)carbamate (0.030 g, 0.041 mmol) and Cs_2CO_3 (0.027 g, 0.083 mmol) in THF (1 mL) was heated to 50 °C for 10 h. The solution was diluted with H_2O (2 mL) and then extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (3 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC (40–70% acetonitrile in 0.05% aqueous ammonia hydroxide). The fractions containing the product were lyophilized to obtain 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)prop-2-yn-1-yl ((R)-3-methylpiperidin-3-yl)carbamate (0.015 g, 43% yield) was obtained as a black brown solid. LCMS (MM-ES+APCI, Pos): m/z 643.4 (M+H).

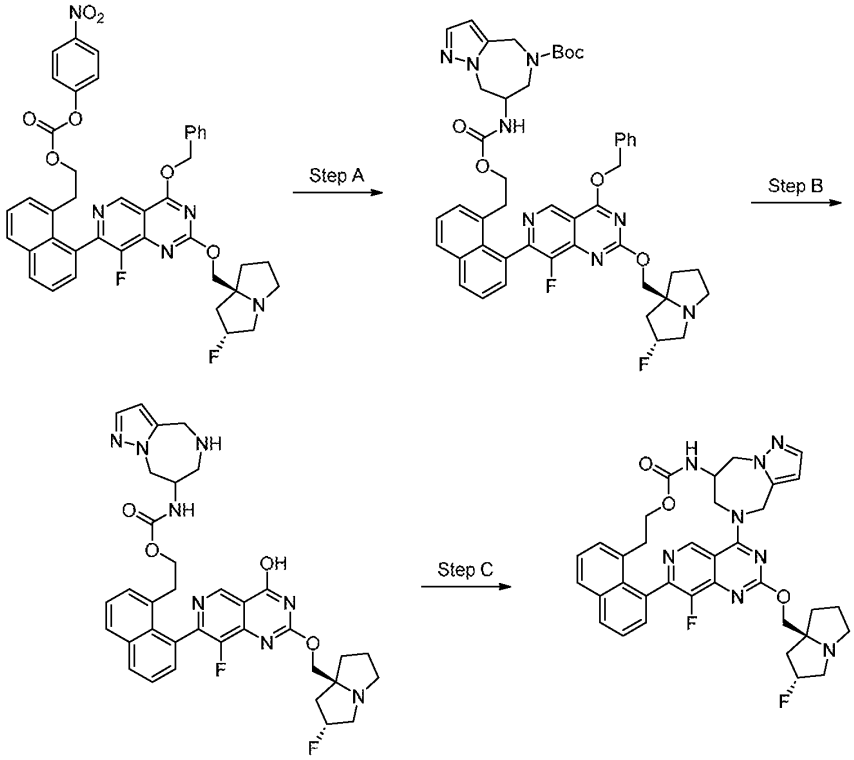
Step E. <u>(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one</u>. To a solution of 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)prop-2-yn-1-yl ((R)-3-methylpiperidin-3-yl)carbamate (0.015 g, 0.018 mmol) and DIPEA (0.016 mL, 0.089 mmol) in DCM (15 mL) was added BOP-Cl (0.014 g, 0.054 mmol). The reaction was stirred at rt for 2 h after which it was quenched with aqueous sodium bicarbonate (5 mL). The mixture was extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (3 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC (42–72% acetonitrile in aqueous 0.05% ammonia hydroxide). The fractions containing the product were lyophilized to obtain (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one (0.0029 g, 24% yield) was obtained as a white solid. LCMS (MM-ES+APCI, Pos): m/z 625.4 (M+H).

Example 32

Compound 9 (Exemplary synthesis)



2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^5,1^6,1^7,1^8-tetrahydro-1^4H-6-oxa-8-aza-1(5,7),2(4,7)-dipyrazolo[1,5-a][1,4]diazepina-3(1,8)-naphthalenacyclooctaphan-7-one



Step A. tert-butyl 7-(((2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-

yl)ethoxy)carbonyl)amino)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate. To a solution of 2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethyl (4-nitrophenyl) carbonate (0.075 g, 0.10 mmol) and tert-butyl 7-amino-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (0.025 g, 0.10 mmol) in DMF (0.50 mL) was added DIPEA (0.035 mL, 0.20 mmol). The reaction was stirred at rt for 16 h and then concentrated under reduced pressure. The residue was purified via silica gel chromatography (0 - 10 % MeOH in DCM) to give tert-butyl 7-(((2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethoxy)carbonyl)amino)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (0.075 g, 86% yield) . LCMS (MM-ES+APCI, Pos): m/z 861.4 (M+H).

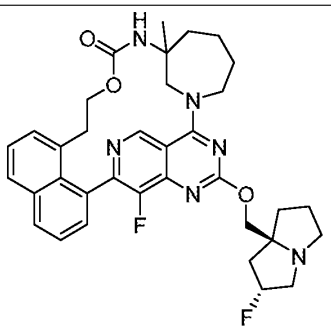
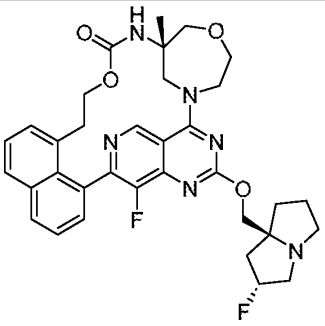
Step B. 2-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethyl (5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-7-yl)carbamate. To a solution of tert-butyl 7-(((2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethoxy)carbonyl)amino)-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate (0.075 g, 0.087 mmol) in DCM (0.50 mL) was added TFA (0.13 mL, 1.7 mmol). The reaction was stirred at rt for 1.5 h and then it was concentrated under reduced pressure to obtain 2-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethyl (5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-7-yl)carbamate (0.058 g), which was taken onto the next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 671.3 (M+H).

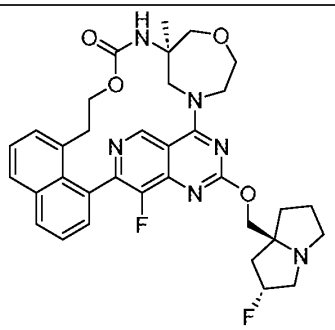
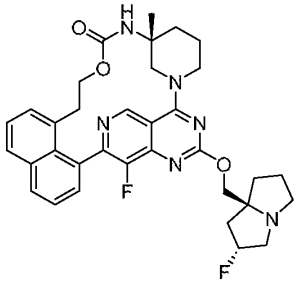
Step C. 2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^5,1^6,1^7,1^8-tetrahydro-1^4H-6-oxa-8-aza-1(5,7),2(4,7)-dipyrazolo[1,5-a][1,4]diazepina-3(1,8)-naphthalenacyclooctaphan-7-one. To a solution of 2-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethyl (5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a][1,4]diazepin-7-yl)carbamate (0.058 g, 0.087 mmol) in DCM (1.00 mL) was added DIPEA (0.46 mL, 2.6 mmol) followed by BOP-Cl (0.067 g, 0.26 mmol). The reaction was stirred at rt for 1.5 h and then it was concentrated under reduced pressure. The reaction was purified via preparative HPLC (10 - 100% acetonitrile in 0.05% aqueous NH_4HCO_3). The fractions containing the product were concentrated under reduced pressure and then extracted with 20% MeOH in DCM

(5 mL x 3). The combined organic phase was dried with Na_2SO_4, filtered, and concentrated under reduced pressure to obtain 2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^5,1^6,1^7,1^8-tetrahydro-1^4H-6-oxa-8-aza-1(5,7),2(4,7)-dipyrazolo[1,5-a][1,4]diazepina-3(1,8)-naphthalenacyclooctaphan-7-one (0.0088 g, 15% yield). LCMS (MM-ES+APCI, Pos): m/z 653.3 (M+H).

The compounds herein (such as a compound of Formula (I), Formula (IA)-(IE) or Formula (IA-1)-(IE-1)) may be prepared from an intermediate as prepared in "Syntheses of intermediates compounds", an intermediate that is commercially available, an intermediate as prepared elsewhere in this application or an intermediate that can be synthesized via a method known to those skilled in the art. Exemplary full syntheses are provided in Examples 22, 23, 26, 32 and 33 (Compound 19, Compound 20, Compound 16, Compound 9 and Compound 6). Compounds prepared in accordance with Example 32 are provided in **Table 3** below.

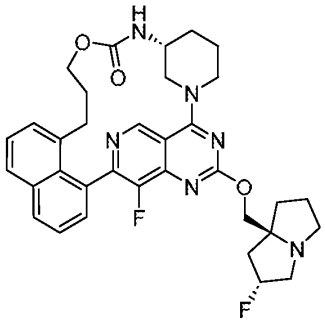
Table 3: A list of compounds prepared in accordance with Example 32

Compound ID	Structure	LCMS
14		629.3
10		631.3

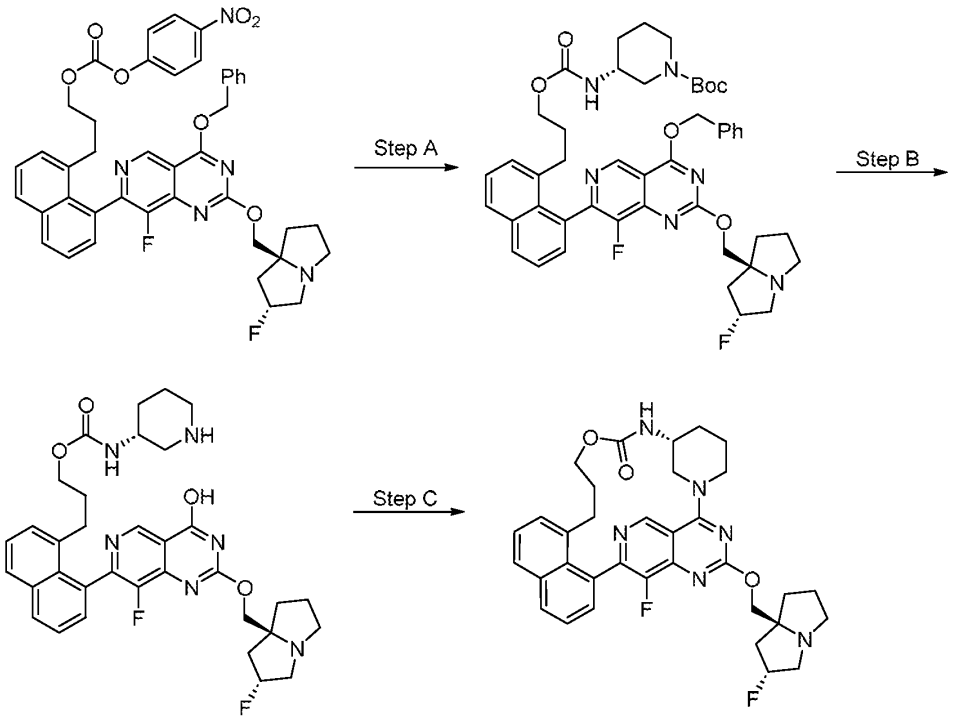
8		631.3
3		615.2

Example 33

Compound 6 (Exemplary synthesis)



(1[3]R)-2[8]-fluoro-2[2]-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. tert-butyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)piperidine-1-carboxylate. A solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (4-nitrophenyl) carbonate (0.16 g, 0.21 mmol), tert-butyl (R)-3-aminopiperidine-1-carboxylate (0.084 g, 0.42 mmol), and DIPEA (0.11 mL, 0.63 mmol) in DMF (3 mL) was stirred at rt for 1 h. The mixture was diluted with H_2O (5 mL) and then extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-25% EtOAc in petroleum ether) to give tert-butyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)piperidine-1-carboxylate (0.11 g, 62% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 823.4 (M+H).

Step B. 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-piperidin-3-

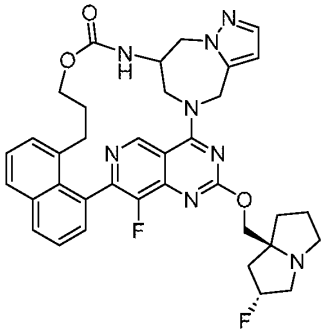
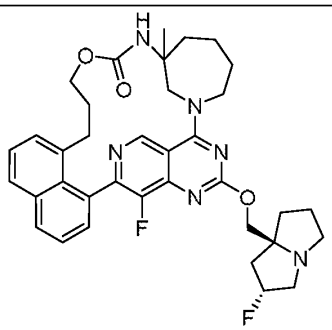
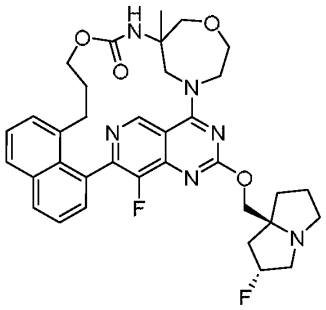
yl)carbamate. To solution of tert-butyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)piperidine-1-carboxylate (0.10 g, 0.12 mmol) in DCM (1.2 mL) was added TFA (0.40 mL, 5.4 mmol). The reaction was stirred at rt for 1 h after which it was quenched with saturated aqueous sodium bicarbonate (3 mL). The mixture was extracted with ethyl acetate (10 mL x 5). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-piperidin-3-yl)carbamate (0.060 g, 80% yield) as a white solid, which was taken onto the next step without further purification.

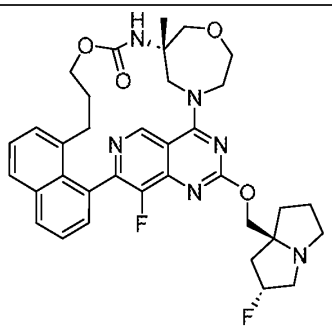
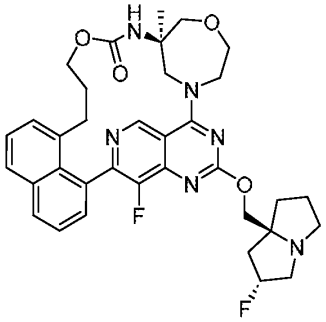
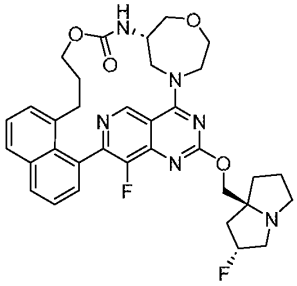
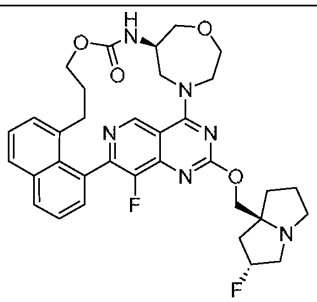
Step C. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-piperidin-3-yl)carbamate (0.060 g, 0.095 mmol), DIPEA (0.083 mL, 0.47 mmol) in DCM (60 mL) at 0 °C was added BOP-Cl (0.072 g, 0.29 mmol). The reaction was allowed to warm to rt and then it was stirred for 1 h. The mixture was concentrated under reduced pressure then diluted with saturated aqueous sodium bicarbonate (10 mL). The mixture was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC (35 – 65% acetonitrile in 0.05% aqueous ammonia hydroxide). The fractions containing the product were lyophilized to obtain ((1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.0030 g, 5% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 615.3 (M+H).

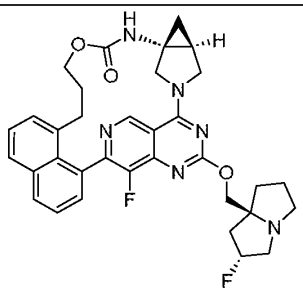
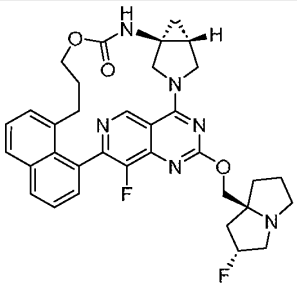
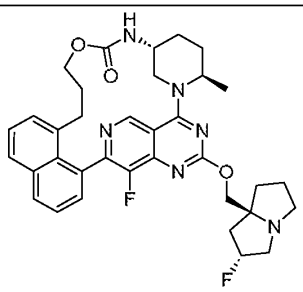
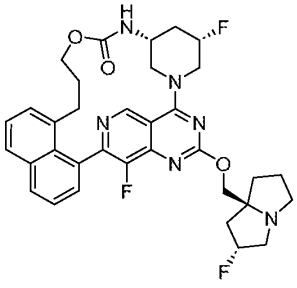
The compounds herein (such as a compound of Formula (I), Formula (IA)-(IE) or Formula (IA-1)-(IE-1)) may be prepared from an intermediate as prepared in "Syntheses of intermediates compounds", an intermediate that is commercially available, an intermediate as prepared elsewhere in this application or an intermediate that can be synthesized via a method known to those skilled in the art. Exemplary full syntheses are provided in Examples 22, 23,

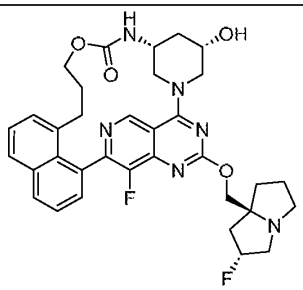
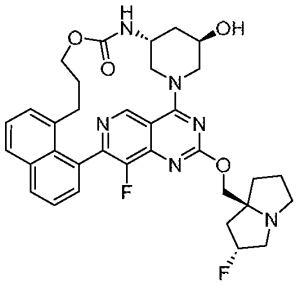
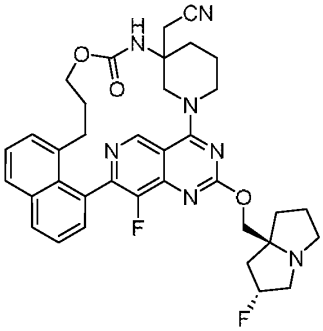
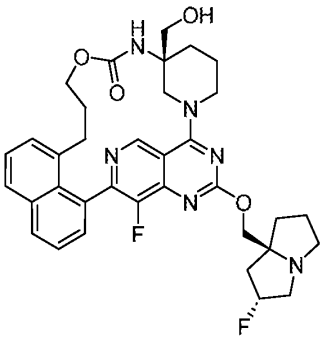
26, 32 and 33 (Compound 19, Compound 20, Compound 16, Compound 9 and Compound 6). Compounds prepared in accordance with Example 33 are provided in **Table 4** below.

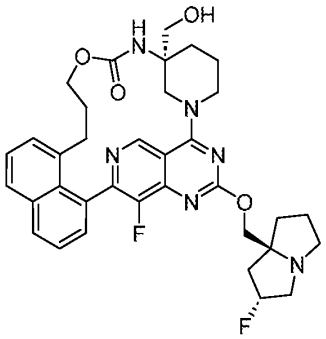
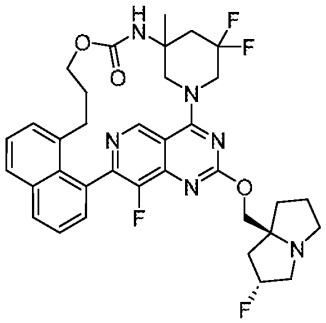
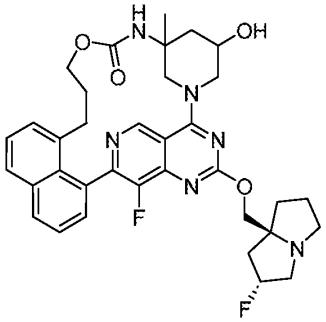
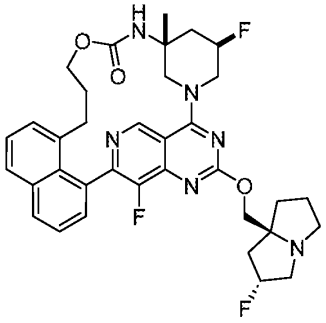
Table 4: A list of compounds prepared in accordance with Example 33.

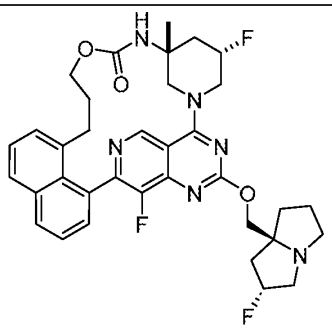
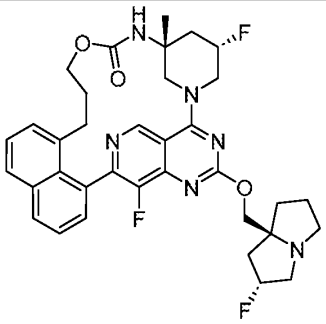
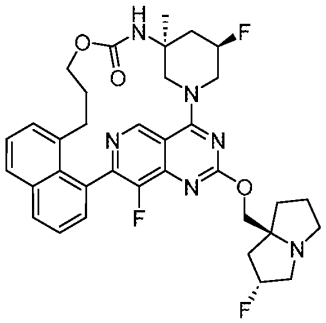
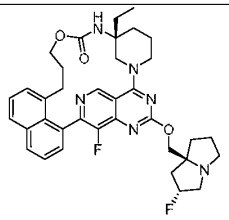
Cmpd ID	Structure	LCMS
18		667.3
7		643.3
15		645.3

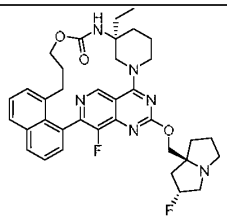
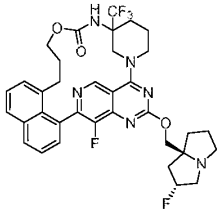
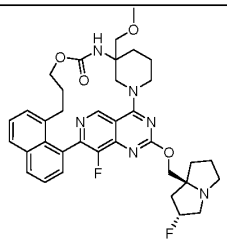
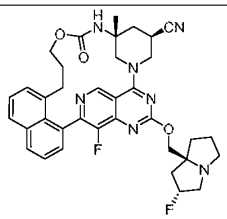
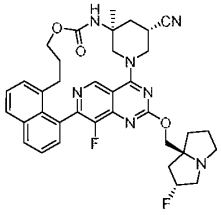
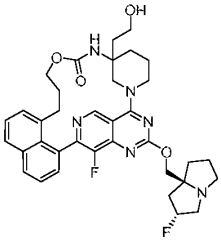
4		645.3
5		645.4
33		631.3
34		631.3

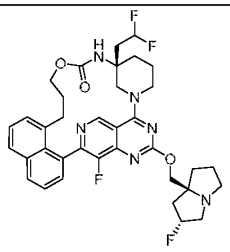
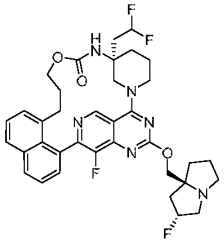
35		613.4
36		613.4
37		629.3
38		633.3

39		631.4
40		631.3
41		654.4
42		645.4

43		645.6
44		665.3
45	 (diasteromeric mixture containing 4 diastereomers)	645.2
46		647.3

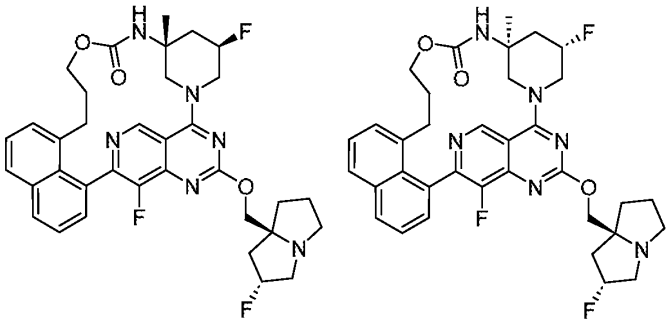
47	 (diasteromeric mixture of Compound 48 and 49)	647.3
48		647.3
49		647.3
93		643.4

94		643.4
96		683.3
99		659.4
106		654.4
107		654.4
108		659.2

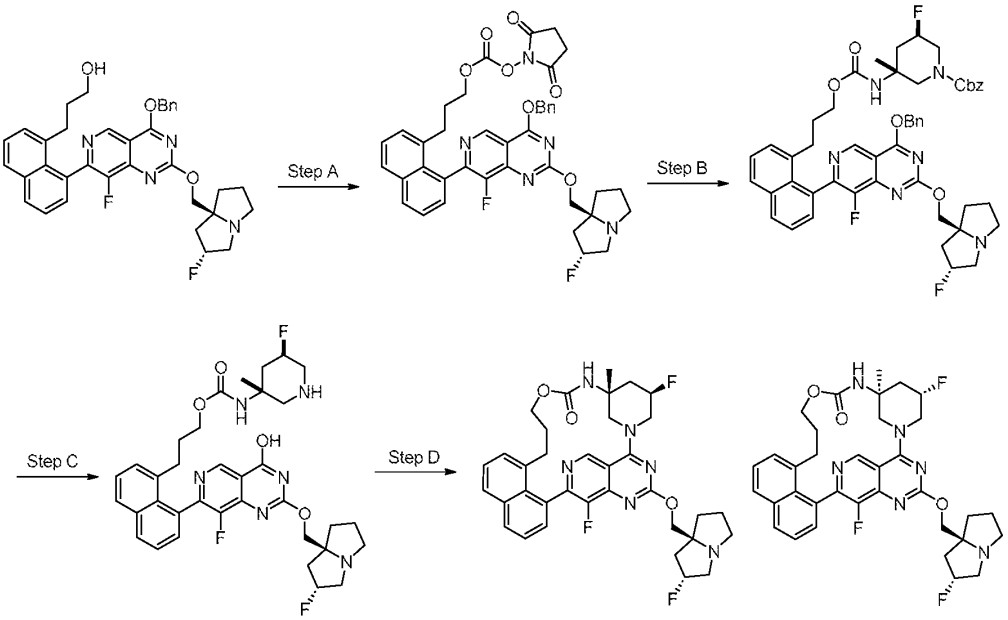
109		679.2
110		679.2

Example 34

Compound 50 and Compound 51



(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S,1^5S)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate. To solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propan-1-ol (0.40 g, 0.64 mmol) in DCM (6 mL) and pyridine (0.10 mL, 1.3 mmol) was added N,N′-disuccinimidyl carbonate (0.49 g, 1.9 mmol). The reaction was stirred at rt for 1 h. The mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.50 g) as a yellow oil, which was used into the next step without further purification.

Step B. benzyl (rel-3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.50 g, 0.68 mmol) and Intermediate I13 (0.20 g, 0.75 mmol) in DCM (6 mL) was added DIPEA (0.24 mL, 1.4 mmol). The reaction was stirred at rt for 12 h. The mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic

layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-50% EtOAc in petroleum ether) to give benzyl (rel-3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.50 g, 78% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 889.3 (M+H).

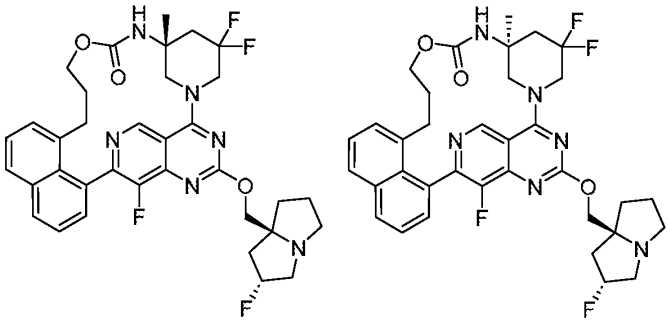
Step C. 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((rel-3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate. A flask containing benzyl (rel-3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.50 g, 0.53 mmol) and Pd/C (10 wt%; 0.50 g, 0.47 mmol) in THF (10 mL) was evacuated and backfilled with H_2 three times. The reaction was stirred at rt under an atmosphere of H2 for 2 h. The suspension was filtered, and the filter cake was washed with THF (30 mL). The filtrate was concentrated under reduced pressure to give 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((rel-3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.35 g, 99% yield) as a yellow solid, which was taken onto the next step without further purification.

Step D. (1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S,1^5S)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((rel-3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.35 g, 0.53 mmol) and DIPEA (0.28 mL, 1.6 mmol) in MeCN (350 mL) was added BrOP (0.61 g, 1.6 mmol). The reaction was stirred at rt for 12 h. The mixture was concentrated under reduced pressure. The residue was diluted with H_2O (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (50% EtOAc in petroleum ether then 10% MeOH in DCM) to afford Compound 46 (as a diastereomeric mixture of Compound 50 and

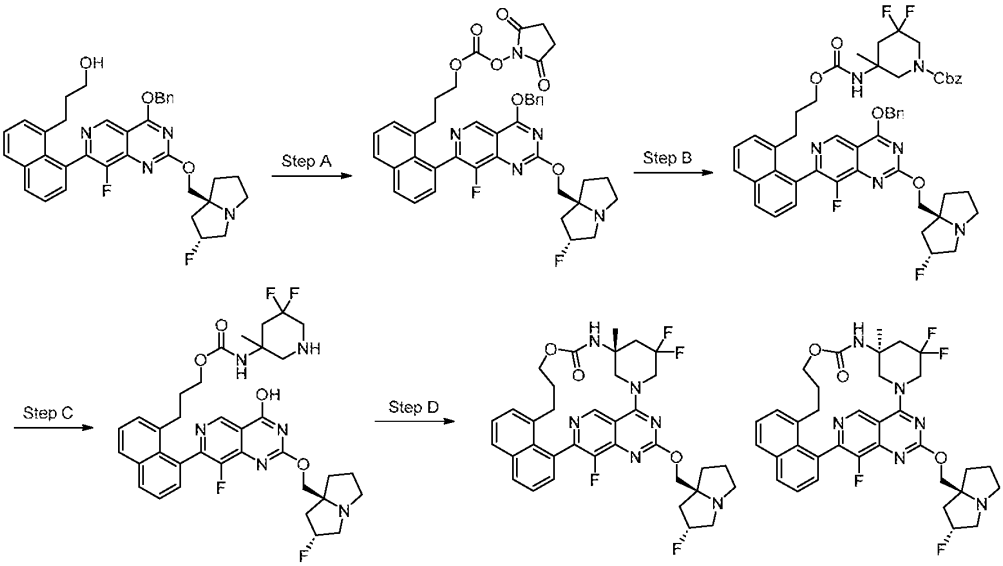
51). The residue was purified by preparative HPLC (47 – 77% MeCN in 0.05% aqueous ammonia hydroxide). The fractions containing the product were lyophilized. The reside was separated by SFC (45% CO_2 - ACN/i-PrOH (0.1% $NH_3 \cdot H_2O$). The fractions containing the product were lyophilized to give (1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.030 g, 9% yield) and (1^3S,1^5S)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.033 g, 10% yield). LCMS (MM-ES+APCI, Pos): m/z 647.4 (M+H). LCMS (MM-ES+APCI, Pos): m/z 647.4 (M+H).

Example 35

Compound 52 and Compound 53



(1^3R)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate. To solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propan-1-ol (0.50 g, 0.80 mmol) in DCM (5 mL) and pyridine (0.32 mL, 4.0 mmol) was added N,N′-disuccinimidyl carbonate (0.61 g, 2.4 mmol). The reaction was stirred at rt for 2 h. The mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.55 g) as a yellow oil, which was used in the next step without further purification.

Step B. benzyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5,5-difluoro-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.55 g, 0.75 mmol) and benzyl 3-amino-5,5-difluoro-3-methylpiperidine-1-carboxylate (0.31 g, 0.89 mmol) in DCM (6 mL) was added DIPEA (0.26 mL, 1.5 mmol). The reaction was stirred at rt for 12 h. The mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with

brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-60% EtOAc in petroleum ether) to give benzyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5,5-difluoro-3-methylpiperidine-1-carboxylate (0.70 g, 97% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 907.5 (M+H).

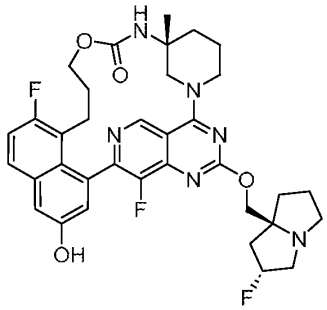
Step C. 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (5,5-difluoro-3-methylpiperidin-3-yl)carbamate. A flask containing benzyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5,5-difluoro-3-methylpiperidine-1-carboxylate (0.70 g, 0.72 mmol) and Pd/C (10 wt%; 0.77 g, 0.72 mmol) in THF (10 mL) was evacuated and backfilled with H_2 three times. The reaction was stirred at rt under an atmosphere of H_2 for 2 h. The suspension was filtered, and the filter cake was washed with THF (5 mL x 3). The filtrate was concentrated under reduced pressure to give 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (5,5-difluoro-3-methylpiperidin-3-yl)carbamate (0.50 g) as a yellow solid, which was taken onto the next step without further purification.

Step D. (1^3R)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (5,5-difluoro-3-methylpiperidin-3-yl)carbamate (0.50 g, 0.73 mmol) and DIPEA (0.64 mL, 3.7 mmol) in MeCN (500 mL) was added BrOP (0.85 g, 2.2 mmol). The reaction was stirred at 40 °C for 16 h. The mixture was concentrated under reduced pressure. The reside was diluted with H_2O (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC (48 – 78% MeCN in 0.05% aqueous ammonia hydroxide). The fractions containing the product were lyophilized. The residue was purified by preparative SFC (55% CO_2-MeCN/EtOH (0.1% NH_3H_2O)). The fractions containing the products were lyophilized to obtain (1^3R)-1^5,1^5,2^8-

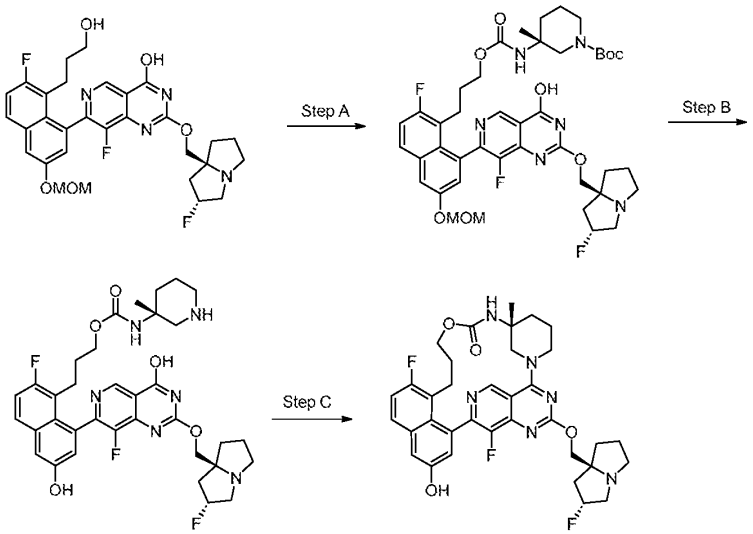
trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.051 g, 46% yield) and (1^3S)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.045 g, 41% yield). LCMS (MM-ES+APCI, Pos): m/z 665.4 (M+H). LCMS (MM-ES+APCI, Pos): m/z 665.3 (M+H).

Example 36

Compound 20 (exemplary synthesis)



(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. tert-butyl (R)-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-

(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of 8-fluoro-7-(7-fluoro-8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-ol (1.49 g, 2.5 mmol) and N.N'-disuccinimidyl carbonate (1.3 g, 5.1 mmol) in DCM (15 mL) was added DIPEA (1.8 mL, 10 mmol). The reaction was heated to 30 °C and stirred at this temperature for 15.5 h. Then a solution of tert-butyl (R)-3-amino-3-methylpiperidine-1-carboxylate (1.6 g, 7.6 mmol) in DCM (3.0 mL) was added. The reaction was stirred for 35 min and then it was concentrated under reduced pressure. The residue was purified via silica gel chromatography (0-10% MeOH in DCM) to obtain tert-butyl (R)-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (2.3 g, 71%). LCMS (MM-ES+APCI, Pos): m/z 825.5 (M+H).

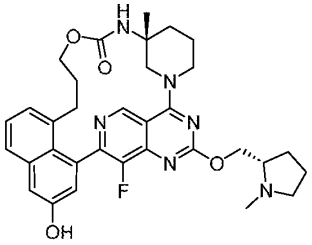
Step B. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate. To a solution of tert-butyl (R)-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (2.1 g, 2.5 mmol) in DCM (10 mL) was added HCl in 1,4-dioxane (4.0 M; 0.45 mL). The reaction was stirred for 30 min at rt and then it was quenched with the slow addition of saturated $NaHCO_3$ solution (10 mL). The mixture was stirred for 10 min and then it was extracted with 25% IPA in $CHCl_3$ (3 X 10 mL). The combined organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure to obtain 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate (1.4 g, 78%), which was taken into the next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 681.3 (M+H).

Step C. (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of bromotri(1-pyrrolidinyl)phosphoniumhexafluorophosphate (1.9 g, 4.0 mmol) and DIPEA (1.7 mL, 10 mmol) in MeCN (70 mL) was added a solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate (1.4 g, 2.0 mmol) in

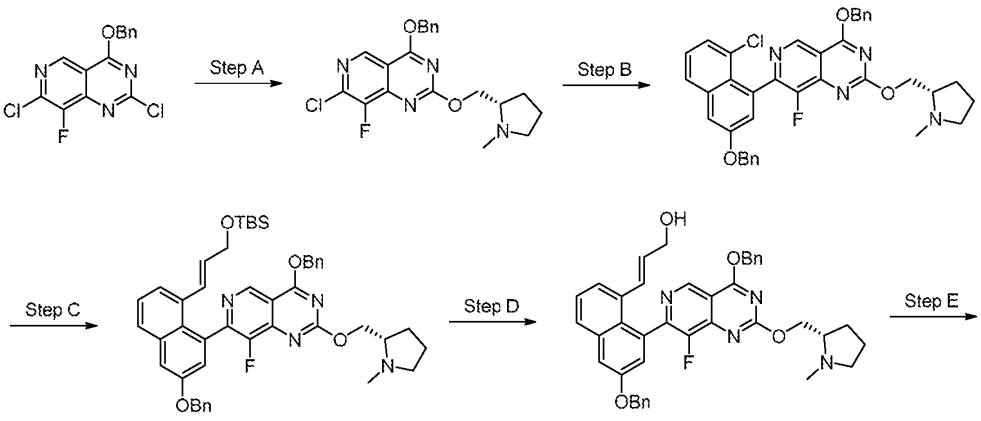
MeCN (5.0 mL) and DMSO (5.0 mL) at 60 °C over 30 min via syringe pump. The reaction was stirred at this temperature for 1 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc (100 mL) and then washed with H_2O (2 X 50 mL) and brine (50 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (0-15% MeOH in DCM) to obtain (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.15 g, 11%). LCMS (MM-ES+APCI, Pos): m/z 663.3 (M+H).

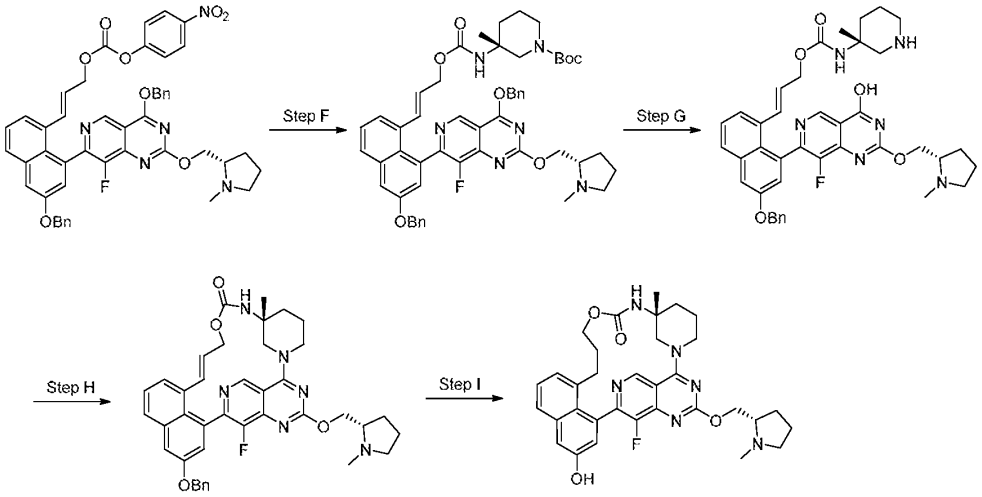
Example 37

Compound 54



(1^3R)-2^8-fluoro-3^3-hydroxy-1^3-methyl-2^2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one





Step A. (S)-4-(benzyloxy)-7-chloro-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidine (3.0 g, 8.8 mmol) and (S)-(1-methylpyrrolidin-2-yl)methanol (1.6 mL, 13 mmol) in MeCN (60 mL) was added DIPEA (3.1 mL, 18 mmol) was added. The reaction was stirred at rt for 1 h and then concentrated under reduced pressure. The residue was suspended in H_2O (20 mL) which was then filtered, and the filter cake was washed with H_2O (30 mL). The solid was further dried under reduced pressure. The product was suspended in MeCN and filtered. The precipitate was washed with MeCN (30 mL x 4). The solid was further dried under reduced pressure to give (S)-4-(benzyloxy)-7-chloro-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidine (2.5 g, 71% yield) as a white solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ = 9.00 (s, 1H), 7.58 (d, J = 6.8 Hz, 2H), 7.47 - 7.38 (m, 3H), 5.67 (s, 2H), 4.48 (dd, J = 4.8, 10.8 Hz, 1H), 4.36 (dd, J = 6.0, 10.8 Hz, 1H), 2.97 (dt, J = 2.8, 6.0 Hz, 1H), 2.69 - 2.61 (m, 1H), 2.38 (s, 3H), 2.26 - 2.16 (m, 1H), 2.02 - 1.91 (m, 1H), 1.76 - 1.61 (m, 3H).

Step B. (S)-4-(benzyloxy)-7-(3-(benzyloxy)-8-chloronaphthalen-1-yl)-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of (S)-4-(benzyloxy)-7-chloro-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidine (2.0 g, 5.0 mmol) and 2-(3-(benzyloxy)-8-chloronaphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.0 g, 5.0 mmol) in 1,4-dioxane (10 mL) and H_2O (1 mL) was added mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.72 g, 0.99 mmol) and K_2CO_3 (2.1 g, 15 mmol). The reaction was sparged with nitrogen for 5 minutes and then it was heated to 70 °C for 6 h. The solution was diluted with H_2O (20 mL)

and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-100% EtOAc in petroleum ether) to give (S)-4-(benzyloxy)-7-(3-(benzyloxy)-8-chloronaphthalen-1-yl)-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidine (1.6 g, 43% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 635.2 (M+H).

Step C. (S,E)-4-(benzyloxy)-7-(3-(benzyloxy)-8-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)naphthalen-1-yl)-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of (S)-4-(benzyloxy)-7-(3-(benzyloxy)-8-chloronaphthalen-1-yl)-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidine (1.4 g, 1.9 mmol), (E)-tert-butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane (0.72 g, 2.4 mmol) in 1,4-dioxane (15 mL) and H_2O (1.5 mL) was added mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.14 g, 0.19 mmol) and K_2CO_3 (0.77 g, 5.6 mmol). The reaction was sparged with nitrogen for 5 minutes and then it was heated to 90 °C for 1 h. The solution was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-100% EtOAc in petroleum ether) to give (S,E)-4-(benzyloxy)-7-(3-(benzyloxy)-8-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)naphthalen-1-yl)-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidine (1.1 g, 68% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 771.3 (M+H).

Step D. (S,E)-3-(6-(benzyloxy)-8-(4-(benzyloxy)-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)prop-2-en-1-ol. To a solution of (S,E)-4-(benzyloxy)-7-(3-(benzyloxy)-8-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)naphthalen-1-yl)-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidine (1.0 g, 1.2 mmol) in THF (10 mL) was added triethylamine-trihydrofluoride (0.56 mL, 3.4 mmol). The reaction was stirred for 1 h at rt and then diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-100% EtOAc in petroleum ether) to give (S,E)-3-(6-(benzyloxy)-8-(4-(benzyloxy)-8-fluoro-2-((1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)prop-2-en-1-ol (0.76 g, 93% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 657.3 (M+H).

Step E. (E)-3-(6-(benzyloxy)-8-(4-(benzyloxy)-8-fluoro-2-(((2S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)allyl (4-nitrophenyl) carbonate. To a solution of (E)-3-(6-(benzyloxy)-8-(4-(benzyloxy)-8-fluoro-2-(((2S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)prop-2-en-1-ol (0.65 g, 0.91 mol) in DCM (6 mL) and pyridine (0.22 mL, 2.7 mmol) at 0 °C was added a solution of 4-nitrophenyl chloroformate (0.55 g, 2.7 mmol) in DCM (2 mL). The mixture was warmed to rt and was stirred for 1 h. The solution was diluted with H_2O (10 mL) and extracted with ethyl acetate (6 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-100% EtOAc in petroleum ether) to give (E)-3-(6-(benzyloxy)-8-(4-(benzyloxy)-8-fluoro-2-(((2S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)allyl (4-nitrophenyl) carbonate (0.63 g, 72% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 822.2 (M+H).

Step F. tert-butyl (R)-3-(((((E)-3-(6-(benzyloxy)-8-(4-(benzyloxy)-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)allyl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of (E)-3-(6-(benzyloxy)-8-(4-(benzyloxy)-8-fluoro-2-(((2S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)allyl (4-nitrophenyl) carbonate (0.60 g, 0.71 mol) and tert-butyl (R)-3-amino-3-methylpiperidine-1-carboxylate (0.23 g, 1.07 mmol) in DMF (10 mL) was added a DIPEA (0.37 mL g, 2.1 mmol). The mixture was stirred at rt for 5 h. The solution was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-25% EtOAc in petroleum ether) to give tert-butyl (R)-3-(((((E)-3-(6-(benzyloxy)-8-(4-(benzyloxy)-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)allyl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.64 g, 98% yield) as a purple oil. LCMS (MM-ES+APCI, Pos): m/z 897.5 (M+H).

Step G. (E)-3-(6-(benzyloxy)-8-(8-fluoro-4-hydroxy-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)allyl ((R)-3-methylpiperidin-3-yl)carbamate. To a solution tert-butyl (R)-3-(((((E)-3-(6-(benzyloxy)-8-(4-(benzyloxy)-8-fluoro-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)allyl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.32 g, 0.35 mmol) in DCM (4 mL) was added TFA (1.0 mL, 13 mmol). The reaction was stirred for 30 min at rt and then it was diluted with H_2O (3 mL) and neutralized with saturated $NaHCO_3$ solution to pH 7. The

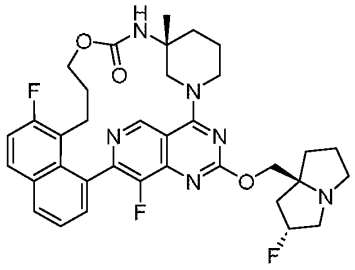
solution was extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (E)-3-(6-(benzyloxy)-8-(8-fluoro-4-hydroxy-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)allyl ((R)-3-methylpiperidin-3-yl)carbamate (0.24 g, 97% yield) as a yellow solid, which was taken into the next step without further purification.

Step H. (1^3R,E)-3^3-(benzyloxy)-2^8-fluoro-1^3-methyl-2^2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-en-8-one. To a solution of (E)-3-(6-(benzyloxy)-8-(8-fluoro-4-hydroxy-2-(((S)-1-methylpyrrolidin-2-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)allyl ((R)-3-methylpiperidin-3-yl)carbamate (0.14 g, 0.20 mmol) and DIPEA (0.17 mL, 0.99 mmol) in DCM (140 mL) was added BOP-Cl (0.15 g, 0.59 mmol) The reaction was stirred at rt for 12 h, after which it was concentrated under reduced pressure. The residue was diluted with saturated $NaHCO_3$ solution (5 mL) and then it was extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-10% MeOH in DCM) to give (1^3R,E)-3^3-(benzyloxy)-2^8-fluoro-1^3-methyl-2^2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-en-8-one (0.070 g, 51% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 689.4 (M+H).

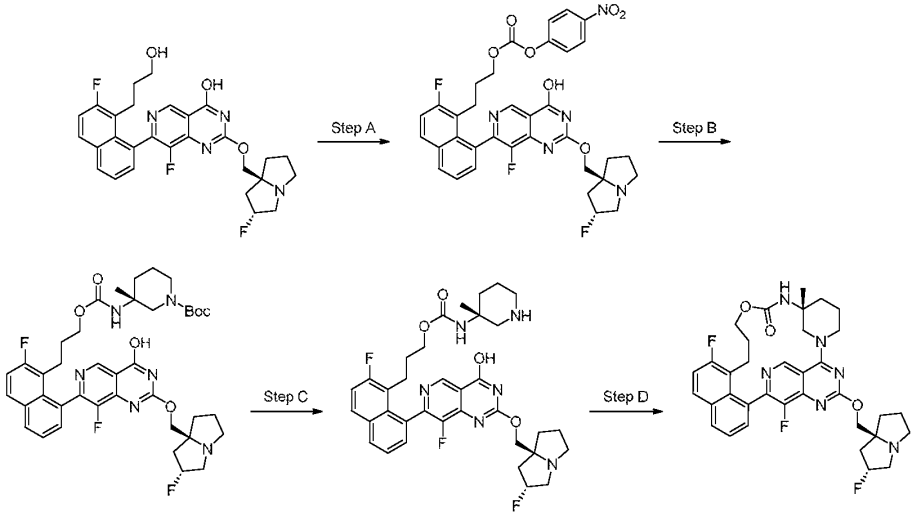
Step I. (1^3R)-2^8-fluoro-3^3-hydroxy-1^3-methyl-2^2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. A slurry of (1^3R,E)-3^3-(benzyloxy)-2^8-fluoro-1^3-methyl-2^2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-en-8-one (0.070 g, 0.10 mmol) and Pd/C (10% wt Pd; 0.02 g, 0.09 mmol) in MeOH (2 mL) and THF (2 mL) was spared with H_2 for 5 min. The reaction was stirred under an atmosphere of H_2 for 2 h. The suspension was filtered, and the filter cake was washed with MeOH (3 mL) The filtrate was concentrated under reduced pressure. The residue was purified via preparative HPLC (32-62% acetonitrile in 0.1% NH_4HCO_3 aqueous solution). The fractions containing the product were lyophilized to obtain (1^3R)-2^8-fluoro-3^3-hydroxy-1^3-methyl-2^2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.0020 g, 3.1% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 601.3 (M+H).

Example 38

Compound 19 (exemplary synthesis)



(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propyl (4-nitrophenyl) carbonate. To a solution of 8-fluoro-7-(7-fluoro-8-(3-hydroxypropyl)naphthalen-1-yl)-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)pyrido[4,3-*d*]pyrimidin-4-ol (Intermediate I21, 0.28 g, 0.53 mmol) and pyridine (0.13 g, 1.6 mmol) in DCM (10 mL) at 0 °C was added 4-nitrophenyl chloroformate (0.32 g, 1.6 mmol). The reaction was warmed to rt and stirred for 2 h. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (50 - 100% EtOAc in petroleum ether) to give 3-(2-fluoro-8-(8-fluoro-2-

(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propyl (4-nitrophenyl) carbonate (0.25 g, 68% yield). LCMS (MM-ES+APCI, Pos): m/z 690.5 (M+H).

Step B. *tert*-butyl (*R*)-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (4-nitrophenyl) carbonate (0.25 g, 0.36 mmol) and *tert*-butyl (3*R*)-3-amino-3-methyl-piperidine-1-carboxylate (0.093 g, 0.44 mmol) in DMF (5 mL) was added DIPEA (0.19 mL, 1.1 mmol) and DMAP (0.044 g, 0.36 mmol). The mixture was stirred at rt for 16 h and was diluted with H_2O (50 mL). The solution was extracted with EtOAc (3 x 50 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (60 - 100% EtOAc in petroleum ether) to give *tert*-butyl (*R*)-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.20 g, 72% yield). LCMS (MM-ES+APCI, Pos): m/z 765.6 (M+H).

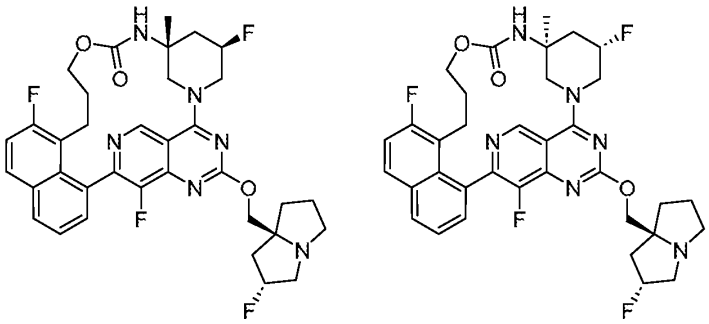
Step C. 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propyl ((*R*)-3-methylpiperidin-3-yl)carbamate. To a solution of *tert*-butyl (*R*)-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylateSSSSSSSSSS (0.20 g, 0.26 mmol) in DCM (5 mL) was added TFA (1.5 g, 13 mmol). The reaction was stirred at rt for 1 h. The mixture was poured into saturated $NaHCO_3$ solution (50 mL) and extracted with DCM (3 x 50 mL). The combined organic phase was washed with brine (50 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propyl ((*R*)-3-methylpiperidin-3-yl)carbamate (0.12 g, 69% yield), which was used directly in the next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 665.6 (M+H).

Step D. (1^3*R*)-2^8,3^7-difluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(2-fluoro-8-(8-fluoro-2-(((2*R*,7a*S*)-2-

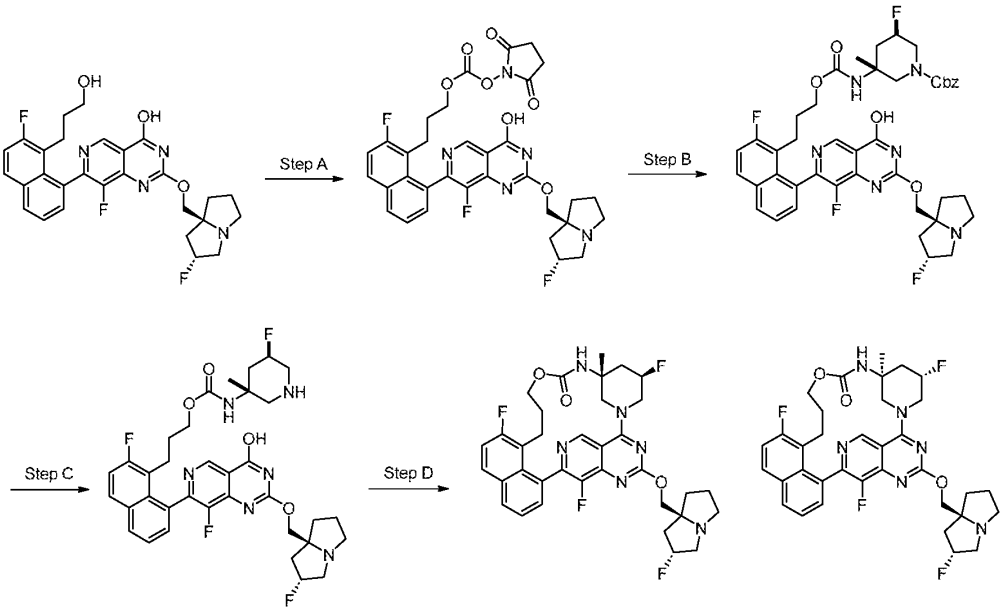
fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-4-hydroxypyrido[4,3-*d*]pyrimidin-7-yl)naphthalen-1-yl)propyl ((*R*)-3-methylpiperidin-3-yl)carbamate (0.12 g, 0.18 mmol) in DCM (10 mL) was added BOP-Cl (0.069 g, 0.27 mmol) and DIPEA (0.070 g, 0.54 mmol). The mixture was stirred at rt for 16 h. The solution was diluted with H_2O (50 mL) and extracted with DCM (3 x 50 mL). The combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (40-70% acetonitrile in 0.05% aqueous TFA). The fractions containing the product were lyophilized to obtain (1^3*R*)-2^8,3^7-difluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.012 g, 10% yield) was obtained as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 647.5 (M+H).

Example 39

Compound 55 and Compound 56



(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S,1^5S)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 2,5-dioxopyrrolidin-1-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl) carbonate. To solution of 8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-ol (0.30 g, 0.58 mmol) in DCM (10 mL) and pyridine (0.14 mL, 1.7 mmol) was added N,N′-disuccinimidyl carbonate (0.44 g, 1.7 mmol). The reaction was stirred at rt for 1 h. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (30 mL x 3). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 2,5-dioxopyrrolidin-1-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl) carbonate (0.36 g) as a yellow oil, which was used in the next step without further purification.

Step B. benzyl (rel-3R,5R)-5-fluoro-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of 2,5-dioxopyrrolidin-1-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl) carbonate (0.36 g, 0.54 mmol) in DCM (10 mL) was added DIPEA (0.19 mL, 1.1 mmol) and Intermediate I13 (0.20, 0.70 mmol). The reaction was stirred at rt for 2 h and then

it was concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-10% EtOH in EtOAc) to give benzyl (rel-3R,5R)-5-fluoro-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.31 g, 62% yield) as a colorless gum. LCMS (MM-ES+APCI, Pos): m/z 817.3 (M+H).

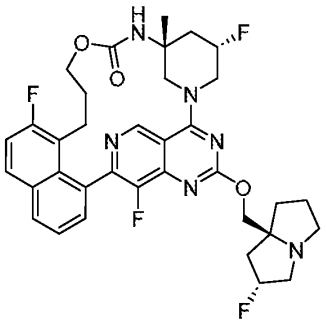
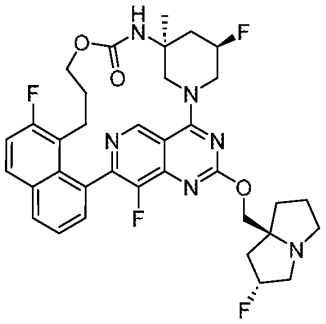
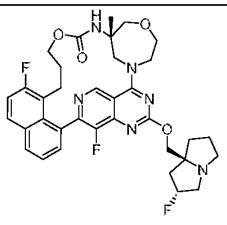
Step C. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((rel-3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate. A flask containing of benzyl (rel-3R,5R)-5-fluoro-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.31 g, 0.34 mmol) and Pd/C (10% wt; 0.30 g) in THF (20 mL) was evacuated and backfilled with H_2 three times. The reaction was stirred at rt under an atmosphere of H_2 for 1 h. The slurry was filtered over Celite, and the pad was washed with MeOH (20 mL x 5). The filtrate was concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((rel-3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.21 g, 79% yield) as a yellow gum. LCMS (MM-ES+APCI, Pos): m/z 683.4 (M+H).

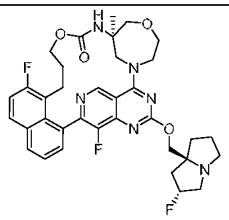
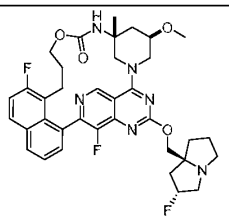
Step D. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S,1^5S)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((rel-3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.19 g, 0.24 mmol) in MeCN (200 mL) was added DIPEA (0.21 mL, 1.2 mmol) and BrOP (0.28 g, 0.72 mmol). The mixture was stirred at rt for 12 h after which it was concentrated under reduced pressure. The residue was diluted with H_2O (20 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (45 – 75% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized. The residue was purified by preparative SFC (45% EtOH with 0.1% $NH_3 \cdot H_2O$ in CO_2) to give

(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.0080 g, 5% yield) and (1^3S,1^5S)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.0080 g, 5% yield). LCMS (MM-ES+APCI, Pos): m/z 665.3 (M+H). LCMS (MM-ES+APCI, Pos): m/z 665.3 (M+H).

Compounds 57-58 were synthesized by following the procedure of Example 39.

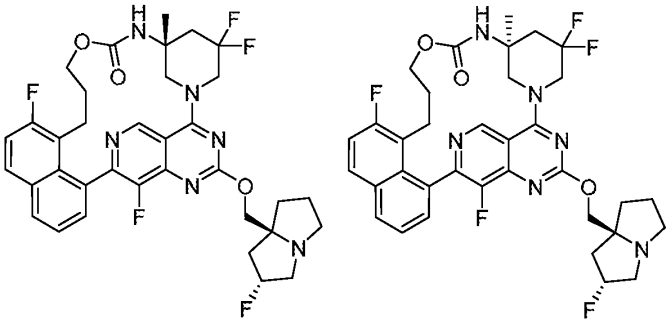
Table 5: A list of compounds synthesized by following the procedure of Example 39.

Cmpd ID	Structure	LCMS
57		665.5
58		665.5
100		663.3

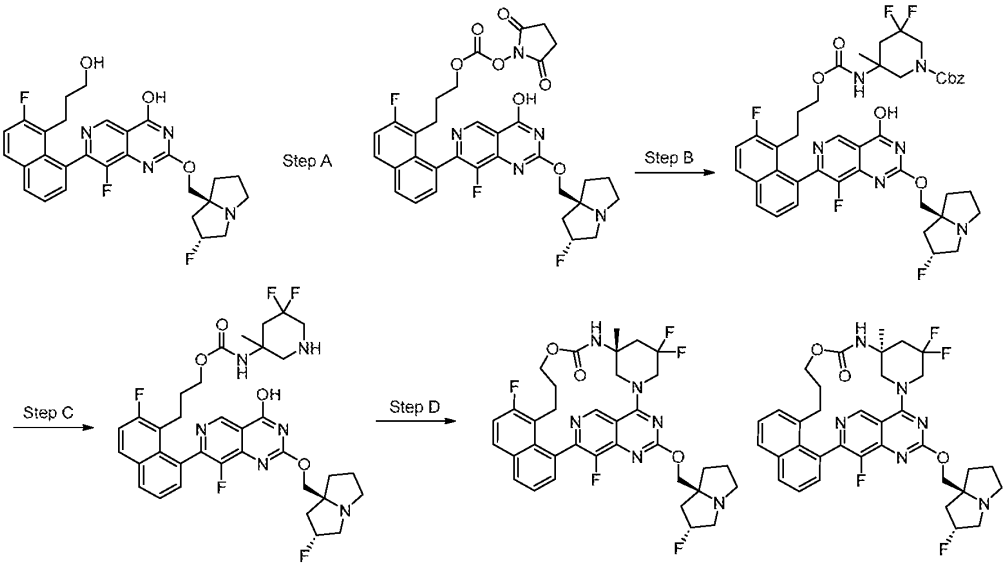
101		663.3
504		677.4

Example 40

Compound 59 and Compound 60



(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)- naphthalenacyclononaphan-8-one



Step A. 2,5-dioxopyrrolidin-1-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl) carbonate. To solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propan-1-ol (0.50 g, 0.95 mmol) in DCM (10 mL) and pyridine (0.31 mL, 3.8 mmol) was added N,N′-disuccinimidyl carbonate (0.70 g, 2.7 mmol). The reaction was stirred at rt for 2 h. The mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 2,5-dioxopyrrolidin-1-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl) carbonate (0.55 g) as a yellow oil, which was used into the next step without further purification.

Step B. benzyl 3,3-difluoro-5-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5-methylpiperidine-1-carboxylate. To a solution of 2,5-dioxopyrrolidin-1-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl) carbonate (0.55 g, 0.83 mmol) and benzyl 3-amino-5,5-difluoro-3-methylpiperidine-1-carboxylate (0.35 g, 1.2 mmol) in DCM (8 mL) was added DIPEA (0.29 mL, 1.7 mmol). The reaction was stirred at rt for 16 h. The mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried

over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-17% EtOH in EtOAc) to give benzyl 3,3-difluoro-5-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5-methylpiperidine-1-carboxylate (0.30 g, 37% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 835.3 (M+H).

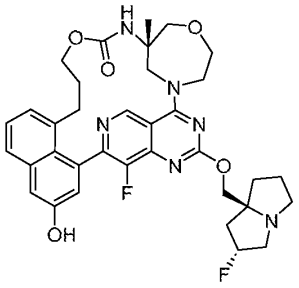
Step C. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (5,5-difluoro-3-methylpiperidin-3-yl)carbamate. A flask containing of benzyl 3,3-difluoro-5-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5-methylpiperidine-1-carboxylate (0.30 g, 0.31 mmol) and Pd/C (10 wt%; 0.20 g, 0.19 mmol) in THF (10 mL) was evacuated and backfilled with H_2 three times. The reaction was stirred at rt under an atmosphere of H_2 for 2 h. The suspension was filtered, and the filter cake was washed with THF (20 mL). The filtrate was concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (5,5-difluoro-3-methylpiperidin-3-yl)carbamate (0.21 g) as a yellow solid, which was taken onto the next step without further purification.

Step D. (1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)- naphthalenacyclononaphan-8-one and (1^3S)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)- naphthalenacyclononaphan-8-one. To a solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (5,5-difluoro-3-methylpiperidin-3-yl)carbamate (0.21 g, 0.30 mmol) and DIPEA (0.26 mL, 1.5 mmol) in MeCN (210 mL) was added BrOP (0.35 g, 0.90 mmol). The reaction was stirred at rt for 16 h. The mixture was concentrated under reduced pressure. The reside was diluted with H_2O (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC (45 – 75% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized. The residue was purified by preparative SFC (50% CO_2 - ACN/*i*-PrOH (0.1% NH_3H_2O)). The

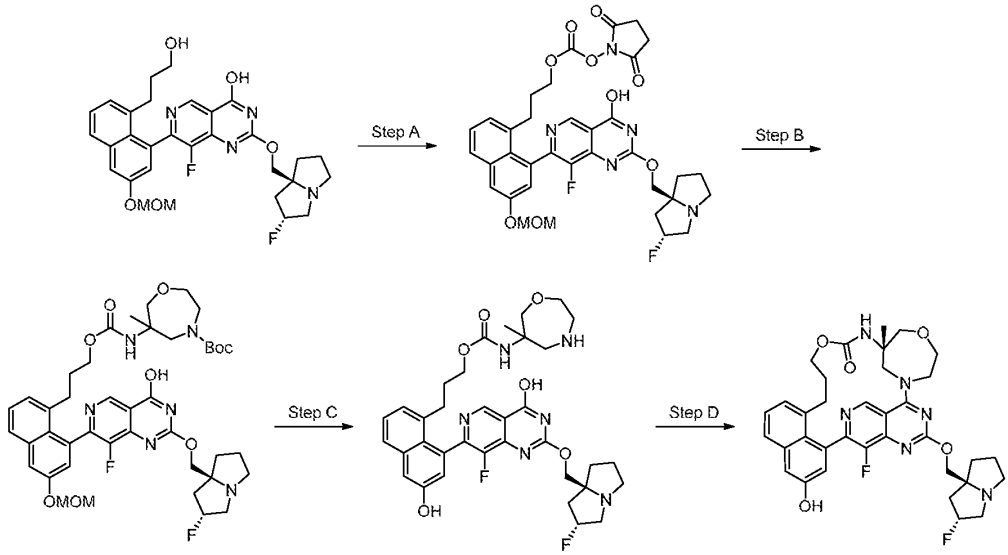
fractions containing the products were lyophilized to obtain (1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)- naphthalenacyclononaphan-8-one (0.021 g, 38%) and (1^3S)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)- naphthalenacyclononaphan-8-one (0.021 g, 38%). LCMS (MM-ES+APCI, Pos): m/z 683.3 (M+H). LCMS (MM-ES+APCI, Pos): m/z 683.3 (M+H).

Example 41

Compound 61



(1^6S)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^6-methyl-7-oxa-9-aza-1(4,6)-oxazepana-2(4,7)-pyrido[4,3-d]pyrimidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 2,5-dioxopyrrolidin-1-yl (3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-

pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl) carbonate. To a solution of 8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-ol (0.100 g, 0.18 mmol) and N,N′-disuccinimidyl carbonate (0.090 g, 0.35 mmol) in DCM (2 mL) was added DIPEA (0.092 mL, 0.53 mmol). The mixture was stirred at rt for 3 h and diluted with H_2O (5 mL). The aqueous layer was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (10% MeOH in DCM) to obtain 2,5-dioxopyrrolidin-1-yl (3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl) carbonate (0.10 g, 80% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 708.3 (M+H).

Step B. tert-butyl 6-(((3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-6-methyl-1,4-oxazepane-4-carboxylate. To solution of2,5-dioxopyrrolidin-1-yl (3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl) carbonate (0.10 g, 0.14 mmol) and tert-butyl 6-amino-6-methyl-1,4-oxazepane-4-carboxylate (0.065 g, 0.28 mmol) in DCM (2 mL) was added DIPEA (0.074 mL, 0.42 mmol). The mixture was stirred at rt for 2 h and then it was diluted with H_2O (5 mL). The aqueous layer was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain tert-butyl 6-(((3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-6-methyl-1,4-oxazepane-4-carboxylate (0.050 g, 43% yield), which was taken onto the next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 823.4 (M+H).

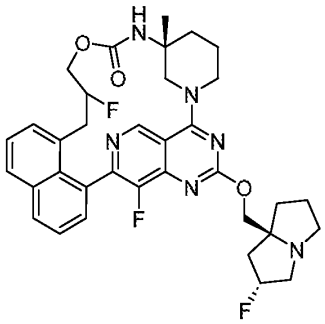
Step C. 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl (6-methyl-1,4-oxazepan-6-yl)carbamate. To a solution of tert-butyl 6-(((3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-6-methyl-1,4-oxazepane-4-carboxylate (0.050 g, 0.061 mmol) in DCM (1.0 mL) was added HCl in

dioxane (2.0 M; 0.20 mL, 0.40 mmol). The reaction was stirred at rt for 2 h and then it was concentrated under reduced pressure to give 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl (6-methyl-1,4-oxazepan-6-yl)carbamate (0.025 g, 58% yield), which was taken onto the next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 679.2 (M+H).

Step D. (1^6S)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^6-methyl-7-oxa-9-aza-1(4,6)-oxazepana-2(4,7)-pyrido[4,3-d]pyrimidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl (6-methyl-1,4-oxazepan-6-yl)carbamate (0.025 g, 0.035 mmol) in MeCN (3 mL) was added DIPEA (0.061 mL, 0.035 mmol) and PyBrOP (0.024 g, 0.052 mmol). The reaction was stirred at rt for 2 h and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC (28 – 58% MeCN in 0.10% NH_4HCO_3). The fractions containing the product were. The residue was purified by preparative HPLC (8 – 38% MeCN in 0.05% mic acid). The fractions containing the product were lyophilized. The residue was purified by preparative HPLC (8 – 38% MeCN in 0.10% TFA). The fractions containing the product were lyophilized to obtain (1^6S)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^6-methyl-7-oxa-9-aza-1(4,6)-oxazepana-2(4,7)-pyrido[4,3-d]pyrimidina-3(1,8)-naphthalenacyclononaphan-8-one (0.0018 g, 6% yield). LCMS (MM-ES+APCI, Pos): m/z 661.2 (M+H).

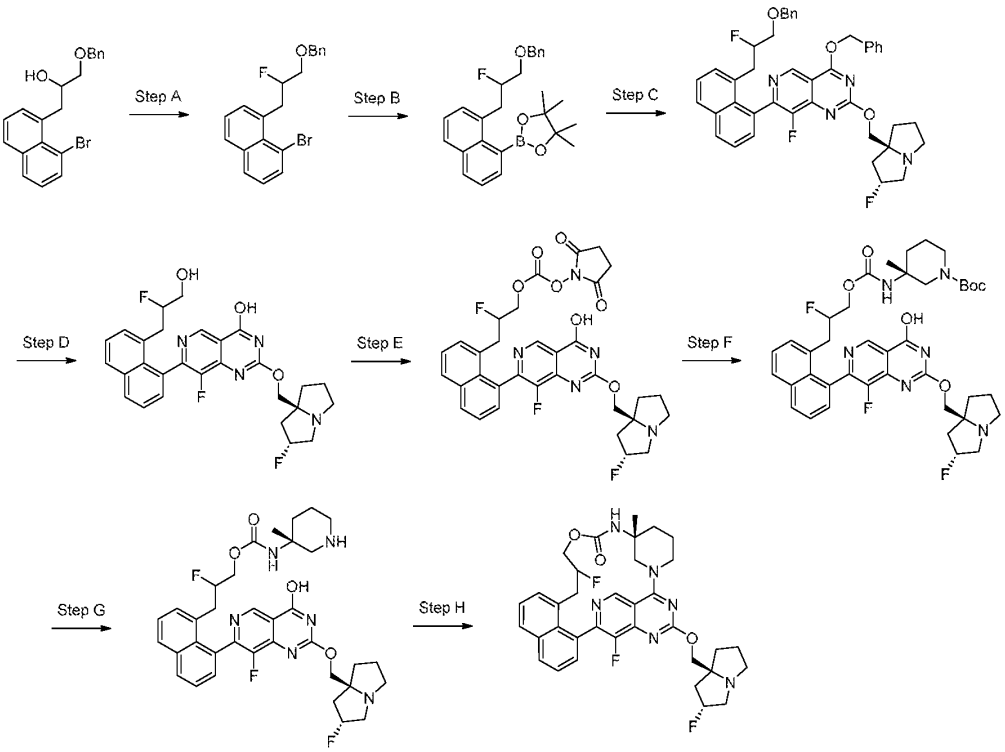
Example 42

Compound 62



(1^3R)-2^8,5-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-

methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 1-(3-(benzyloxy)-2-fluoropropyl)-8-bromonaphthalene. To a solution of Intermediate I19 (3.6 g, 9.6 mmol) in DCM (36 mL) at – 78 °C was added DAST (1.3 mL, 9.6 mmol). The reaction was stirred at this temperature for 1 h after which it was quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-10% EtOAc in petroleum ether). The residue was purified by preparative HPLC (65 – 95% MeCN in 0.1% aqueous formic acid). The fractions containing the product were lyophilized to obtain 1-(3-(benzyloxy)-2-fluoropropyl)-8-bromonaphthalene (0.50 g, 14% yield) as a yellow solid. ^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.06 - 7.88 (m, 3H), 7.54 - 7.45 (m, 2H), 7.40 - 7.26 (m, 6H), 5.14 - 4.91 (m, 1H), 4.62 - 4.49 (m, 2H), 4.16 - 4.00 (m, 1H), 3.79 - 3.61 (m, 3H). ^{19}F NMR: (377 MHz, DMSO-d_6) δ -184.96.

Step B. 2-(8-(3-(benzyloxy)-2-fluoropropyl)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To a solution of 1-(3-(benzyloxy)-2-fluoropropyl)-8-bromonaphthalene

(0.50 g, 1.32 mmol) in THF (5 mL) at 0 °C was added i-PrMgCl-LiCl (1.3 M; 3.0 mL, 3.9 mmol). The reaction was warmed to rt and was stirred for 1 h. Then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.81 mL, 3.95 mmol) was added and the reaction was stirred for an additional 1 h at rt. The mixture was quenched by slow addition of saturated aqueous NH_4Cl (10 mL) and was then extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-10% EtOAc in petroleum ether) to give 2-(8-(3-(benzyloxy)-2-fluoropropyl)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.50 g, 88% yield) as a yellow oil. (400 MHz, DMSO-d_6) δ 7.99 (dd, J = 1.2, 8.0 Hz, 1H), 7.85 (dd, J = 1.6, 7.6 Hz, 1H), 7.65 (dd, J = 1.2, 6.8 Hz, 1H), 7.53 - 7.45 (m, 3H), 7.37 - 7.27 (m, 5H), 5.23 - 4.98 (m, 1H), 4.59 - 4.41 (m, 2H), 4.03 (q, J = 7.2 Hz, 1H), 3.61 - 3.48 (m, 3H), 1.34 (d, J = 6.0 Hz, 12H)

Step C. 4-(benzyloxy)-7-(8-(3-(benzyloxy)-2-fluoropropyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of 2-(8-(3-(benzyloxy)-2-fluoropropyl)naphthalen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.45 g, 1.1 mmol) in 1,4-dioxane (5 mL) and H_2O (1 mL) was added Intermediate I2 (0.40 g, 0.87 mmol), mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2'-amino-1,1'-biphenyl)]palladium(II) (0.063 g, 0.087 mmol), and Cs_2CO_3 (0.85 g, 2.6 mmol). The reaction was sparged with nitrogen for 5 min and then it was heated 90 °C for 1 h. The mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-30% EtOAc in petroleum ether) to give 4-(benzyloxy)-7-(8-(3-(benzyloxy)-2-fluoropropyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.50 g, 78% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 705.3 (M+H).

Step D. 8-fluoro-7-(8-(2-fluoro-3-hydroxypropyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-ol. A solution of give 4-(benzyloxy)-7-(8-(3-(benzyloxy)-2-fluoropropyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.50 g, 0.68 mmol) in TFA (5 mL) was heated to 70 °C for 1 h. The mixture was concentrated under reduced pressure and diluted with H_2O (5 mL). The pH of mixture was adjusted to 7 with saturated aqueous LiOH and was then extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered,

and concentrated under reduced pressure to give 8-fluoro-7-(8-(2-fluoro-3-hydroxypropyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-ol (0.45 g, 74% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 525.2 (M+H).

Step E. 2,5-dioxopyrrolidin-1-yl (2-fluoro-3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl) carbonate. To a solution of give 8-fluoro-7-(8-(2-fluoro-3-hydroxypropyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-ol (0.45 g, 0.50 mmol) and N,N′-disuccinimidyl carbonate (0.255 g, 1.0 mmol) in DCM (5 mL) was added pyridine (0.81 mL, 10 mmol). The mixture was stirred at rt for 1 h and then it was diluted with H_2O (5 mL). The aqueous layer was extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 2,5-dioxopyrrolidin-1-yl (2-fluoro-3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl) carbonate (0.30 g), which was taken onto the next step without further purification. LCMS (MM-ES+APCI, Pos): m/z 666.2 (M+H).

Step F. tert-butyl (3R)-3-(((2-fluoro-3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of 2,5-dioxopyrrolidin-1-yl (2-fluoro-3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl) carbonate (0.30 g, 0.45 mmol) and tert-butyl (3R)-3-amino-3-methyl-piperidine-1-carboxylate (0.193 g, 0.90 mmol) in DCM (3 mL) was added DIPEA (0.24 mL, 1.4 mmol). The mixture was stirred at rt for 1 h and was then diluted with H_2O (5 mL). The solution was extracted with EtOAc (3 x 5 mL) and the combined organic phase was washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (0 - 50% EtOAc in petroleum ether) to give tert-butyl (3R)-3-(((2-fluoro-3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.30 g, 71% yield). LCMS (MM-ES+APCI, Pos): m/z 765.3 (M+H).

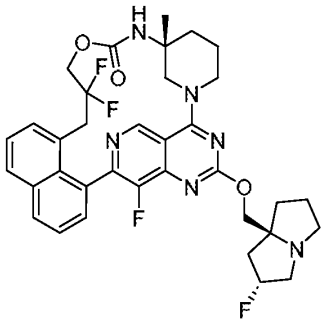
Step G. 2-fluoro-3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-3-

methylpiperidin-3-yl)carbamate. A solution of tert-butyl (3R)-3-(((2-fluoro-3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.30 g, 0.32 mmol) in HCl in 1,4-dioxane (2.0 M; 3.0 mL) was stirred for 5 min at rt. The solution was concentrated under reduced pressure to give 2-fluoro-3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate (0.20 g) which was taken onto the next step without further purification.

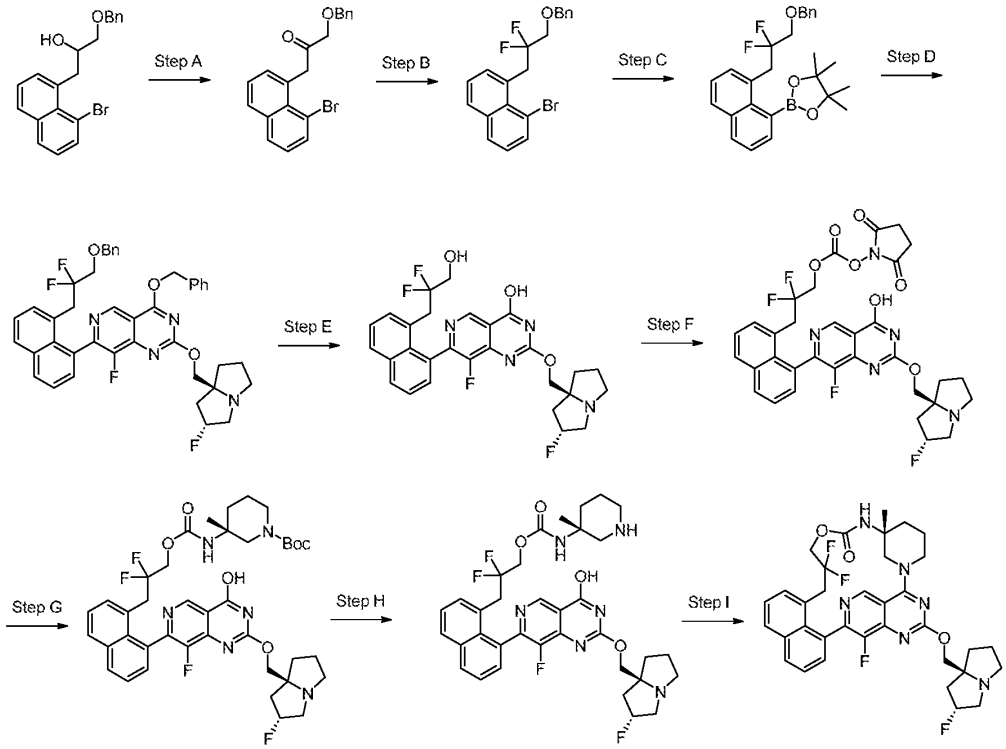
Step H. (1^3R)-2^8,5-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 2-fluoro-3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate (0.20 g, 0.29 mmol) in MeCN (30 mL) was added DIPEA (0.54 mL, 3.1 mmol) followed by PyBrOP (0.40 g, 0.86 mmol). The reaction was heated to 45 °C for 5 h and then it was concentrated under reduced pressure. The residue was diluted with H_2O (5 mL) and then extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (40 – 70% MeCN in 0.04% aqueous ammonia hydroxide + 0.1% NH_4HCO_3). The fractions containing the product were lyophilized to obtain (1^3R)-2^8,5-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.022 g, 11% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 647.3 (M+H).

Example 43

Compound 63



(1^3R)-2^8,5,5-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



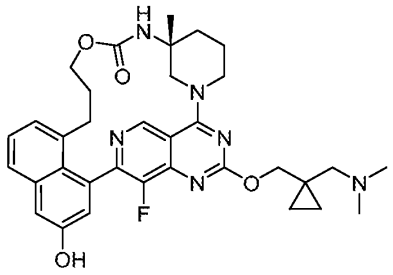
Step A. 1-(benzyloxy)-3-(8-bromonaphthalen-1-yl)propan-2-one. To a solution of 1-(benzyloxy)-3-(8-bromonaphthalen-1-yl)propan-2-ol (9.8 g, 26 mmol) in DCM (120 mL) was added DMP (13 g, 32 mmol). The reaction mixture was stirred at rt for 4 h and then it was quenched by slow addition of saturated aqueous sodium bicarbonate (50 mL). The mixture was extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 - 15% EtOAc in petroleum ether) to give 1-(benzyloxy)-3-(8-bromonaphthalen-1-yl)propan-2-one (9.7 g, 99% yield) as a white solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.87 - 7.77 (m, 3H), 7.46 - 7.33 (m, 6H), 7.30 (d, J = 7.2 Hz, 1H), 7.27 - 7.22 (m, 1H), 4.77 (s, 2H), 4.70 (s, 2H), 4.31 (s, 2H).

Step B. 1-(3-(benzyloxy)-2,2-difluoropropyl)-8-bromonaphthalene. To a flask containing 1-(benzyloxy)-3-(8-bromonaphthalen-1-yl)propan-2-one (5.0 g, 13 mmol) at 0 °C was added BAST (30 mL, 137 mmol). The reaction was heated to 45 °C for 12 h and then it was quenched at 0 °C by slow addition of saturated aqueous sodium bicarbonate (100 mL). The mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 - 2% EtOAc in petroleum ether). The reside was purified by preparative HPLC (70 – 95% MeCN in 0.05% TFA). The fractions containing the product were lyophilized to obtain 1-(3-(benzyloxy)-2,2-difluoropropyl)-8-bromonaphthalene (2.8 g, 52% yield) as a yellow oil. ^{1}H NMR: (400 MHz, DMSO-d6) δ 8.00 (dd, J = 1.6, 6.8 Hz, 2H), 7.90 (dd, J = 1.2, 7.2 Hz, 1H), 7.61 - 7.48 (m, 2H), 7.43 - 7.28 (m, 6H), 4.63 (s, 2H), 4.43 (br t, J = 17.6 Hz, 2H), 3.76 (br t, J = 13.2 Hz, 2H). 19F NMR of 5: (377 MHz, DMSO-d6) δ -103.00.

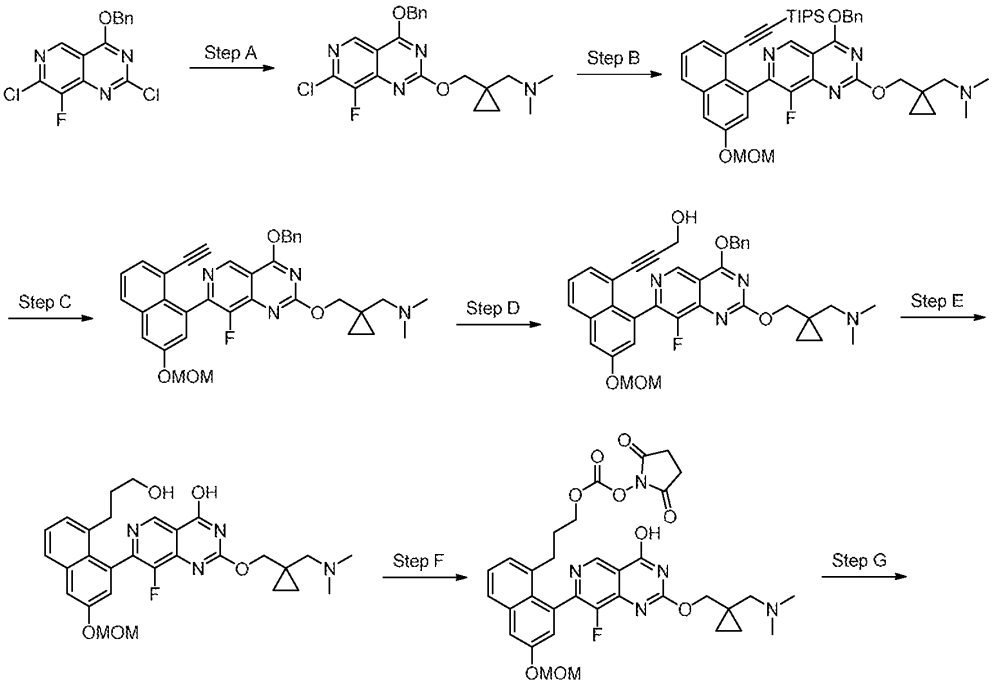
Steps C-I were performed by following Steps B-H in the synthesis of Compound 62.

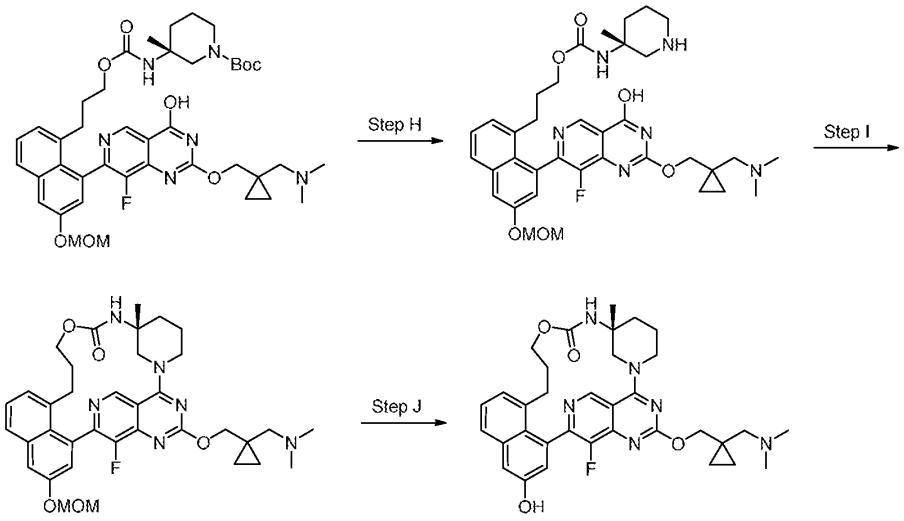
Example 44

Compound 64



(1^3R)-2^2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-2^8-fluoro-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one





Step A. 1-(1-(((4-(benzyloxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine. To a solution of 4-(benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidine (1.5 g, 4.6 mmol) in MeCN (20.0 mL) was added (1-((dimethylamino)methyl)cyclopropyl)methanol (0.74 g, 5.7 mmol) and DIPEA (2.4 mL, 14 mmol). The reaction was stirred at 40 °C for 20 min and then it was diluted with H_2O (50 mL). The mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 -30% EtOAc in petroleum ether) to give 1-(1-(((4-(benzyloxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine (2.2 g, 56% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 417.2 (M+H).

Step B. 1-(1-(((4-(benzyloxy)-8-fluoro-7-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine. To a solution of 1-(1-(((4-(benzyloxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine (1.3 g, 3.0 mmol) and triisopropyl((6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)silane (1.6 g, 3.3 mmol) in 1,4-dioxane (20 mL) and H_2O (4.0 mL) was added mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.33 g, 0.45 mmol) and K_2CO_3 (1.0 g, 7.5 mmol). The flask was evacuated and backfilled with nitrogen three times. The mixture was heated to 95 °C for 30 min and was then diluted with H_2O (50.0 mL). The mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (30.0 mL),

dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20 - 50% ethyl acetate in petroleum ether) to give 1-(1-(((4-(benzyloxy)-8-fluoro-7-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine (3.10 g) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 749.6 (M+H).

Step C. 1-(1-(((4-(benzyloxy)-7-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine. To a solution of 1-(1-(((4-(benzyloxy)-8-fluoro-7-(3-(methoxymethoxy)-8-((triisopropylsilyl)ethynyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine (2.9 g, 3.8 mmol) in THF (30.0 mL) was added TBAF (1.0 M in THF; 4.0 mL, 4.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and was then diluted with H_2O (50.0 mL). The mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (20-100% ethyl acetate in petroleum ether) to give 1-(1-(((4-(benzyloxy)-7-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine (1.9 g, 80% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 593.3 (M+H).

Step D. 3-(8-(4-(benzyloxy)-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol. To a solution of 1,4-bis(dicyclohexylphosphino)-butane (0.055 g, 0.12 mmol) in toluene (1.0 mL) was added (phenylethynyl)copper (0.016 g, 0.098 mmol). The flask was evacuated and backfilled with nitrogen. The mixture was heated to 60 °C for 1 h. The reaction was cooled to rt and then a solution of HCHO (37% in H_2O; 0.36 mL, 4.9 mmol) and 1-(1-(((4-(benzyloxy)-7-(8-ethynyl-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)-N,N-dimethylmethanamine (0.30 g, 0.49 mmol) in toluene (3.0 mL) was added. The mixture was heated to 60 °C for 1 h and was then diluted with H_2O (5 mL) and extracted with ethyl acetate (2 mL x 3). The combined organic layers were washed with brine (3 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (50- 100% ethyl acetate in petroleum ether) to give 3-(8-(4-(benzyloxy)-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol (0.27 g, 83% yield) as a yellow oil. LCMS

(MM-ES+APCI, Pos): m/z 623.2 (M+H).

Step E. 2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-7-(8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-ol. A solution of 3-(8-(4-(benzyloxy)-2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoropyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol 0.27 g, 0.40 g) in THF (40 mL) was passed through a fixed bed (5 mL; 5% Pd/SiO_2) at 0.30 mL/min. The reactor was pressurized with hydrogen 0.3 MPa at a flow rate of 20 mL/min. The solution was collected from the reactor and the bed was washed with THF (40 mL). The collected sample was concentrated under reduced pressure to give 2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-7-(8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-ol (0.23 g) as a yellow solid, which was used into the next step without further purification.

Step F. 3-(8-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate. To solution of 2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-7-(8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-ol (0.21 g, 0.39 mmol) in DCM (3 mL) was added pyridine (0.32 mL, 3.9 mmol) and N,N'-disuccinimidyl carbonate (0.30 g, 1.2 mmol). The reaction was stirred at rt for 1 h and was then diluted with DCM (10 mL). The organic layers were washed with H_2O (10 mL x 3) and brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(8-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.27 g) as a yellow solid, which was used in the next step without further purification.

Step G. tert-butyl (R)-3-(((3-(8-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To solution of 3-(8-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.27 g, 0.39 mmol) in DCM (3.0 mL) was added DIPEA (0.20 mL, 1.2 mmol) and tert-butyl (3R)-3-amino-3-methyl-piperidine-1-carboxylate (0.17 g, 0.78 mmol). The reaction was stirred at rt for 1 h. The solution was diluted with H_2O (10 mL) and extracted with DCM (8 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure.

The residue was purified by silica gel chromatography (0-10% MeOH in DCM) to give tert-butyl (R)-3-(((3-(8-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.22 g, 56% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 777.4 (M+H).

Step H. 3-(8-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (R)-(3-methylpiperidin-3-yl)carbamate. To a solution of tert-butyl (R)-3-(((3-(8-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.21 g, 0.26 mmol) in MeCN (2.0 mL) was added $ZnBr_2$ (0.87 g, 3.9 mmol). The reaction was heated to 70 °C for 5 h. The mixture was diluted with H_2O (6 mL) and extracted with ethyl acetate (2 mL x 3). The combined organic layers were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(8-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (R)-(3-methylpiperidin-3-yl)carbamate (0.174 g) as a yellow solid, which was used into the next step without further purification.

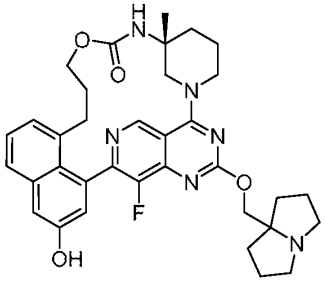
Step I. (1^3R)-2^2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-2^8-fluoro-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(8-(2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-8-fluoro-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (R)-(3-methylpiperidin-3-yl)carbamate (0.17 g, 0.26 mmol) and PyBrOP (0.36 g, 0.77 mmol) in MeCN (200 mL) was added DIPEA (0.22 mL, 1.3 mmol). The reaction was stirred at rt for 16 h and then was diluted with H_2O (30 mL). The mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (1^3R)-2^2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-2^8-fluoro-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.17 g) as a yellow solid, which was used into the next step without further purification.

Step J. (1^3R)-2^2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-2^8-fluoro-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-

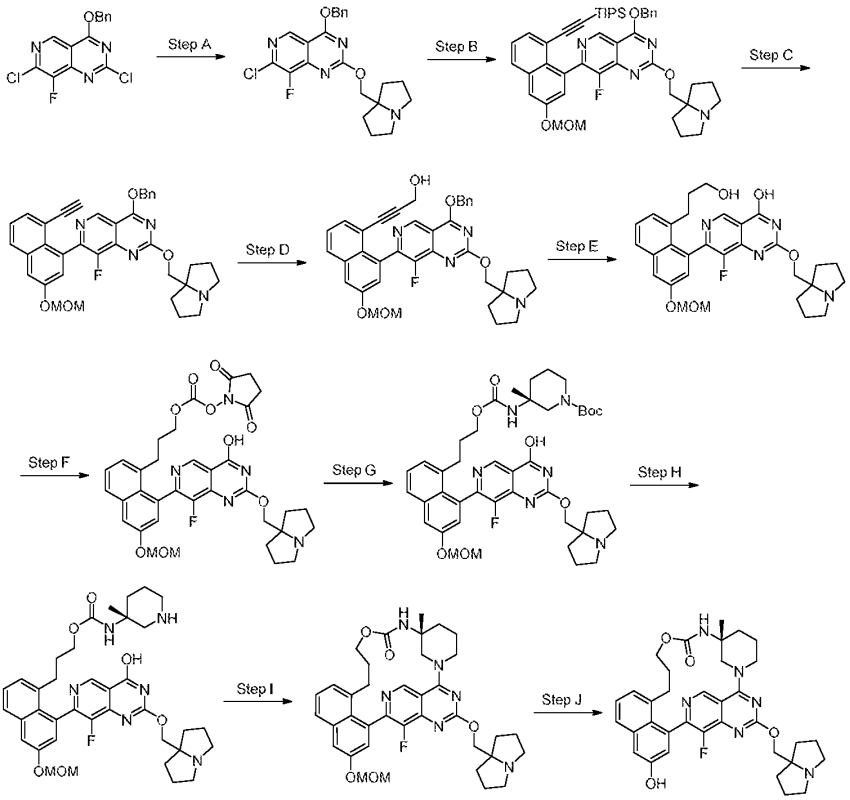
naphthalenacyclononaphan-8-one. A solution of (1^3R)-2^2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-2^8-fluoro-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.170 g, 0.258 mmol) in HCl in dioxane (2.0 M, 2.0 mL, 4.0 mmol) was stirred at rt for 30 min. The mixture was concentrated under reduced pressure. The residue was dissolved in DCM (0.5 mL) and stirred at rt for 30 min. The slurry was filtered and the precipitate was purified by preparative HPLC (10 – 40% MeCN in 0.1% aqueous formic acid). The fractions containing the product were lyophilized. The residue was purified by preparative HPLC (38 – 68% MeCN in 0.04% aqueous ammonia hydroxide + 0.1% NH_4HCO_3). The fractions containing the product were lyophilized. The residue product was purified by normal phase HPLC (10 – 50% EtOH in hexanes). The fractions containing the product were lyophilized to obtain (1^3R)-2^2-((1-((dimethylamino)methyl)cyclopropyl)methoxy)-2^8-fluoro-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.0074 g, 5% yield) as an off-white solid. LCMS (MM-ES+APCI, Pos): m/z 615.3 (M+H).

Example 45

Compound 65



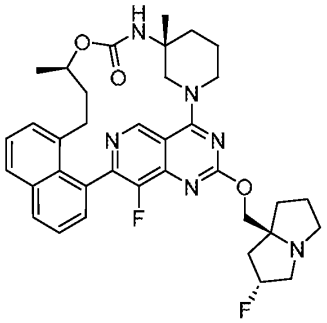
(1^3R)-2^8-fluoro-3^3-hydroxy-1^3-methyl-2^2-((tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Compound 65 was prepared with (tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol, according to the general procedure of Compound 64.

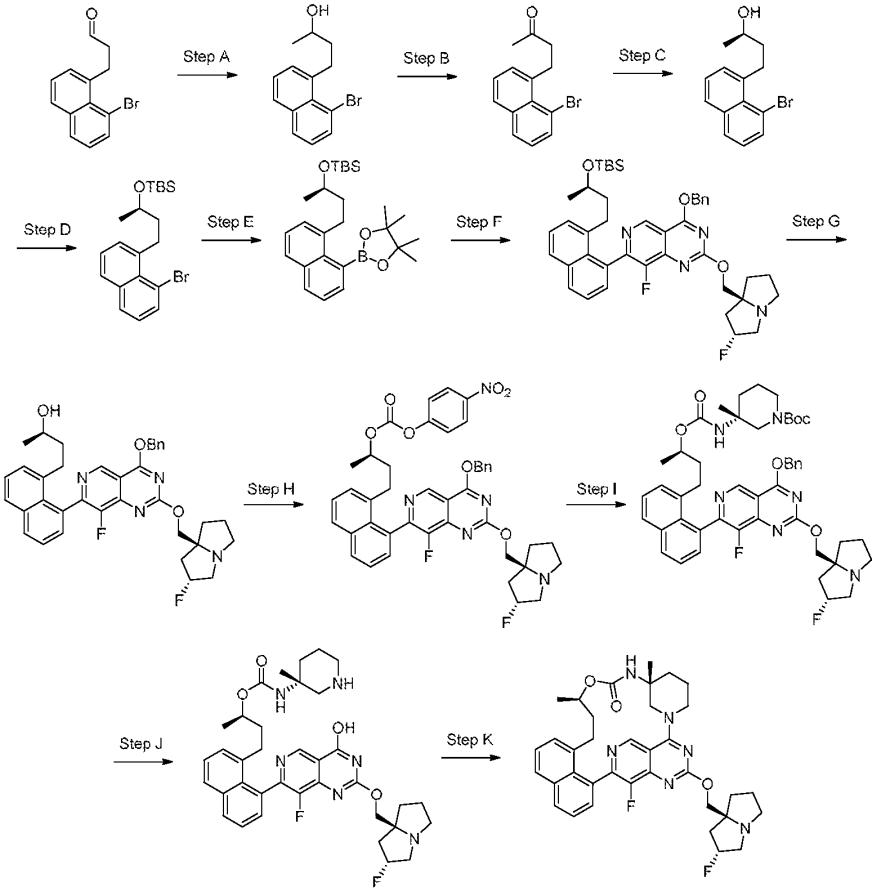
Example 46

Compound 66



(1^3R,6*R*)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3,6-dimethyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8)

naphthalenacyclononaphan-8-one



Step A. 4-(8-bromonaphthalen-1-yl)butan-2-ol. A solution of 3-(8-bromonaphthalen-1-yl)propanal (2.0 g, 7.6 mmol) in THF (20 mL) was then evacuated and back filled with nitrogen three times. The solution was cooled to -78 °C, then methyl magnesium bromide (3.0 M in diethyl ether; 3.8 mL) was added. The mixture was stirred at -78 °C under an atmosphere of nitrogen for 3 h. The mixture was quenched by slow addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 – 10% EtOAc in petroleum ether) to give 4-(8-bromonaphthalen-1-yl)butan-2-ol (1.1 g, 52% yield) as a yellow oil. ^1H NMR: (400 MHz, CDCl3) δ = 7.87 - 7.79 (m, 2H), 7.74 (br dd, J = 1.2, 8.0 Hz, 1H), 7.47 - 7.37 (m, 2H), 7.23 (t, J = 7.6 Hz, 1H), 4.02 - 3.88 (m, 1H), 3.77 - 3.66 (m, 1H), 3.64 - 3.52 (m, 1H), 1.97 - 1.83 (m, 2H), 1.28 (d, J = 6.0 Hz, 3H).

Step B. 4-(8-bromonaphthalen-1-yl)butan-2-one. To a solution of 4-(8-bromonaphthalen-1-yl)butan-2-ol (1.1 g, 3.9 mmol) in DCM (20 mL) at 0 °C was added DMP (1.3 mL, 4.3 mmol) drop wise. The mixture was stirred at 0 °C for 1 h after which it was filtered, and the filter cake was washed with DCM (10 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by preparative TLC (10% EtOAc in petroleum ether) to afford 4-(8-bromonaphthalen-1-yl)butan-2-one (0.80 g 73% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 (ddd, *J* = 1.2, 8.0, 15.2 Hz, 2H), 7.11 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.81 - 6.71 (m, 2H), 6.63 - 6.56 (m, 1H), 3.20 - 3.11 (m, 2H), 2.30 - 2.21 (m, 2H), 1.52 (s, 3H).

Step C. (R)-4-(8-bromonaphthalen-1-yl)butan-2-ol. A solution of (S)-(−)-2-methyl-CBS-oxazaborolidine (0.86 mL, 2.9 mmol) in THF (10 mL) was evacuated and back filled with nitrogen three times. The solution was cooled to 0 °C, then BH_3.THF (1.0 M, 2.9 mL) was added dropwise. The reaction was stirred at 0 °C under an atmosphere of nitrogen for 1 h. Then a solution of 4-(8-bromonaphthalen-1-yl)butan-2-one (0.80 g, 2.9 mmol) in THF (5 mL) was added dropwise and the reaction was stirred at 0 °C for an additional 30 min. The solution was cooled to -30 °C and stirred for 1 h. The mixture was quenched by slow addition of MeOH (10 ml) and was diluted with saturated NH_4Cl (50 mL). The aqueous layer was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0 – 10% EtOAc in petroleum ether) to give (R)-4-(8-bromonaphthalen-1-yl)butan-2-ol (0.79 g, 98% yield) as a yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.83 (dt, *J* = 6.8, 8.0 Hz, 2H), 7.74 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.45 - 7.37 (m, 2H), 7.23 (t, *J* = 7.6 Hz, 1H), 3.95 (qd, *J* = 6.4, 12.4 Hz, 1H), 3.76 - 3.51 (m, 2H), 1.99 - 1.82 (m, 2H), 1.28 (d, *J* = 6.0 Hz, 3H).

Step D. (R)-((4-(8-bromonaphthalen-1-yl)butan-2-yl)oxy)(tert-butyl)dimethylsilane. To a solution of (R)-4-(8-bromonaphthalen-1-yl)butan-2-ol (0.78 g, 2.8 mmol) in DCM (10 mL) at 0 °C was added TBSCl (0.84 g, 5.6 mmol) and imidazole (0.57 g, 8.4 mmol) portion wise. The mixture was warmed to rt and was stirred for 2 h. The mixture was diluted with H_2O (10 mL) and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 – 10% EtOAc in petroleum ether) to afford (R)-((4-(8-bromonaphthalen-1-yl)butan-2-yl)oxy)(tert-butyl)dimethylsilane (0.76 g, 69% yield) as a yellow oil.

Step E. (R)-tert-butyldimethyl((4-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)butan-2-yl)oxy)silane To a solution of (R)-((4-(8-bromonaphthalen-1-

yl)butan-2-yl)oxy)(tert-butyl)dimethylsilane (0.50 g, 1.3 mmol) and bis(pinacolato)diboron (0.48 g, 1.9 mmol) in DMSO (10 mL) was added potassium acetate (0.25 g, 2.5 mmol) and Pd(dppf)Cl_2 (0.093 g, 0.13 mmol). The flask was evacuated and back filled with nitrogen three times. The mixture was heated to 100 °C for 12 h and was then diluted with H_2O (20 mL). The mixture was extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 – 10% EtOAc in petroleum ether) to afford (R)-tert-butyldimethyl((4-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)butan-2-yl)oxy)silane (0.30 g, 54% yield) as a yellow oil. ^1H NMR: (400 MHz, $CDCl_3$) δ = 7.87 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.73 - 7.65 (m, 2H), 7.47 - 7.36 (m, 3H), 3.85 (d, J = 6.0 Hz, 1H), 3.24 (t, *J* = 7.6 Hz, 2H), 1.97 - 1.84 (m, 2H), 1.45 (d, J = 3.6 Hz, 12H), 1.17 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), -0.01 (s, 6H).

Step F. 4-(benzyloxy)-7-(8-((R)-3-((tert-butyldimethylsilyl)oxy)butyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.22 g, 0.45 mmol) and (R)-tert-butyldimethyl((4-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)butan-2-yl)oxy)silane (0.30 g, 0.68 mmol) in 1,4-dioxane (5 mL) and H_2O (0.5 mL) was added mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.033 g, 0.045 mmol) and K_2CO_3 (0.19 g, 1.4 mmol). The flask was evacuated and back filled with nitrogen three times. The mixture was heated to 100 °C and stirred for 2 h. The mixture was diluted with H_2O (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 – 20% EtOAc in petroleum ether) to afford 4-(benzyloxy)-7-(8-((R)-3-((tert-butyldimethylsilyl)oxy)butyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.32 g, 80% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): 725.6 (M+H).

Step G. (R)-4-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)butan-2-ol. To solution of 4-(benzyloxy)-7-(8-((R)-3-((tert-butyldimethylsilyl)oxy)butyl)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.29 g, 0.33 mmol) in THF (5 mL) was added triethylamine-trihydrofluoride (0.16 mL, 0.99 mmol). The mixture was stirred at rt for 12 h and then it was diluted with H_2O

(10 mL). The aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (100% EtOAc) to afford (R)-4-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)butan-2-ol (0.10 g, 46% yield) as a colorless oil. LCMS (MM-ES+APCI, Pos): 611.3 (M+H).

Step H. (R)-4-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)butan-2-yl (4-nitrophenyl) carbonate. To solution of (R)-4-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)butan-2-ol (0.10 g, 0.15 mmol) in DCM (3 ML) was added pyridine (0.061 mL, 0.75 mmol). The mixture was cooled to 0 °C and a solution of 4-nitrophenyl chloroformate (0.091 g, 0.45 mmol) in DCM (1 mL) was added dropwise. The mixture was warmed to rt and was stirred for 12 h. The mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (100% EtOAc) to afford (R)-4-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)butan-2-yl (4-nitrophenyl) carbonate (0.10 g, 74% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): 776.3 (M+H).

Step I. tert-butyl (R)-3-(((((R)-4-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)butan-2-yl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of (R)-4-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)butan-2-yl (4-nitrophenyl) carbonate (0.10 g, 0.11 mmol) and tert-butyl (R)-3-amino-3-methylpiperidine-1-carboxylate (0.036 g, 0.17 mmol) in DMF (5 mL) was added DIPEA (0.043 mg, 0.33 mmol, 0.058 mL). The reaction was stirred at rt for 24 h. The mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (50% EtOAc in petroleum ether) to afford tert-butyl (R)-3-(((((R)-4-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)butan-2-yl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.090 g, 86% yield) was obtained

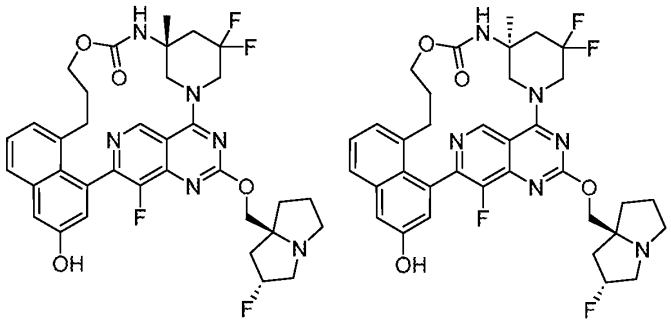
as a colorless oil. LCMS (MM-ES+APCI, Pos): 851.5 (M+H).

Step J. (R)-4-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)butan-2-yl ((R)-3-methylpiperidin-3-yl)carbamate. To a solution of tert-butyl (R)-3-(((((R)-4-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)butan-2-yl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.090 g, 0.096 mmol) in DCM (2 mL) was added TFA (0.77 g, 6.7 mmol, 0.50 mL). The reaction was stirred at rt for 30 min. The solution was neutralized to pH 7 with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (50% EtOAc in petroleum ether) to afford (R)-4-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)butan-2-yl ((R)-3-methylpiperidin-3-yl)carbamate (0.060 g, 85% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): 661.3 (M+H).

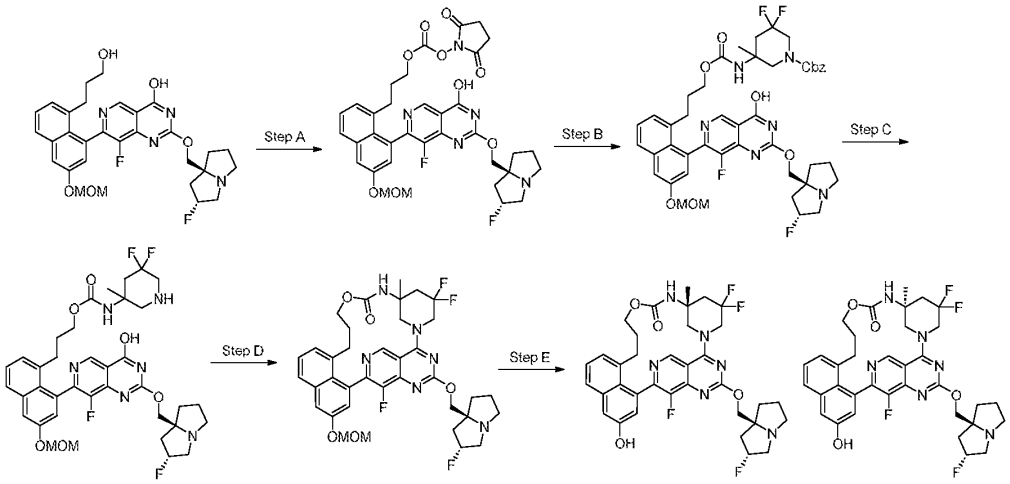
Step K. (1^3R,6*R*)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3,6-dimethyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8) naphthalenacyclononaphan-8-one. To solution of (R)-4-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)butan-2-yl ((R)-3-methylpiperidin-3-yl)carbamate (0.055 g, 0.074 mmol) in DCM (55 mL) was added DIPEA (0.064 mL, 0.37 mmol) and BOP-Cl (0.057 g, 0.22 mmol). The reaction was stirred at rt for 12 h and was then concentrated under reduced pressure. The residue was purified by preparative HPLC (54 – 84% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized. The residue was purified by preparative HPLC (45–75% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized. The residue was purified by preparative HPLC (18–48 % MeCN in 0.225% aqueous formic acid). The fractions containing the product were lyophilized to afford (1^3R,6*R*)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1H-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3,6-dimethyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8) naphthalenacyclononaphan-8-one (0.0065 g 13% yield) as a white solid. LCMS (MM-ES+APCI, Pos): 643.3 (M+H).

Example 47

Compound 67 and Compound 68



(1^3R)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 2,5-dioxopyrrolidin-1-yl (3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl) carbonate. To solution of 8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-ol (0.50 g, 0.80 mmol) in DCM (5 mL) and pyridine (0.32 mL, 4.0 mmol) was added N,N′-disuccinimidyl carbonate (0.62 g, 2.4 mmol). The reaction was stirred at rt for 2 h. The mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The combined organic layer was dried over anhydrous

sodium sulfate, filtered, and concentrated under reduced pressure to give 2,5-dioxopyrrolidin-1-yl (3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl) carbonate (0.55 g, 97% yield) as a yellow oil, which was used into the next step without further purification.

Step B. benzyl 3,3-difluoro-5-(((3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-methylpiperidine-1-carboxylate. To a solution of 2,5-dioxopyrrolidin-1-yl (3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl) carbonate (0.55 g, 0.78 mmol) in DCM (6 mL) was added DIPEA (0.27 mL, 1.6 mmol) and benzyl 3-amino-5,5-difluoro-3-methylpiperidine-1-carboxylate (0.32 g, 0.93 mmol). The reaction was stirred at rt for 1 h. The mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-10% EtOH in EtOAc) to give benzyl 3,3-difluoro-5-(((3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-methylpiperidine-1-carboxylate (0.65 g, 85% yield) as a yellow gum. LCMS (MM-ES+APCI, Pos): 877.4 (M+H).

Step C. 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (5,5-difluoro-3-methylpiperidin-3-yl)carbamate. A flask containing of benzyl 3,3-difluoro-5-(((3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-methylpiperidine-1-carboxylate (0.60 g, 0.61 mmol) and Pd/C (10% wt; 1.0 g, 0.94 mmol) in THF (10 mL) was evacuated and backfilled with H_2 three times. The reaction was stirred at rt under an atmosphere of H_2 for 2 h. The slurry was filtered over Celite, and the pad was washed with THF (5 mL x 3). The filtrate was concentrated under reduced pressure to give 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (5,5-difluoro-3-methylpiperidin-3-yl)carbamate (0.45 g), which was taken onto the next step without further purification.

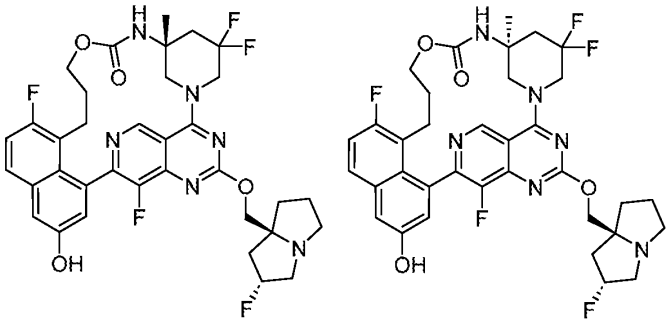
Step D. $1^5,1^5,2^8$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-

yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To solution of 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (5,5-difluoro-3-methylpiperidin-3-yl)carbamate (0.45 g, 0.61 mmol) in DCM (450 mL) was added DIPEA (0.53 mL, 3.0 mmol) and BOP-Cl (0.46 g, 1.8 mmol). The reaction was stirred at rt for 16 h and was then concentrated under reduced pressure. The residue was diluted with saturated aqueous sodium bicarbonate (30 mL) and then extracted with DCM (30 mL x 3). The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (45-75% MeCN in 0.05% aqueous ammonia hydroxide). The fractions containing the product were lyophilized to give 1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.065 g, 14% yield). LCMS (MM-ES+APCI, Pos): 725.3 (M+H).

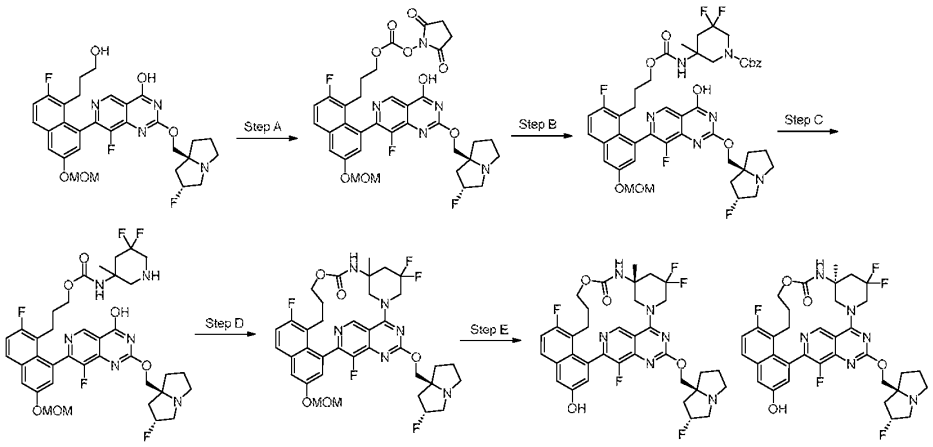
Step E. (1^3R)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.065 g, 0.088 mmol) in DCM (2 mL) was added HCl in 1,4-dioxane (2.0 M; 1.0 mL). The reaction was stirred at rt for 30 min and then it was concentrated under reduced pressure. The residue was purified by chiral SFC (70% CO_2-*i*-PrOH in 0.1% NH_3H_2O) to obtain (1^3R)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.024 g, 39%) and (1^3S)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.021 g, 35%). LCMS (MM-ES+APCI, Pos): 681.3 (M+H). LCMS (MM-ES+APCI, Pos): 681.3 (M+H).

Example 48

Compound 69 and Compound 70



(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 2,5-dioxopyrrolidin-1-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl) carbonate. To solution of 8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-7-(8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-4-ol (0.53 g, 0.78 mmol) in DCM (10 mL) and DIPEA (0.54 mL, 3.1mmol) was added N,N′-disuccinimidyl carbonate (0.60 g, 2.3 mmol). The reaction was stirred at rt for 18 h. The mixture was diluted with H_2O (20 mL)

and extracted with DCM (20 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 2,5-dioxopyrrolidin-1-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl) carbonate (0.56 g) as a yellow solid, which was used into the next step without further purification.

Step B. benzyl 3,3-difluoro-5-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-methylpiperidine-1-carboxylate. To a solution of 2,5-dioxopyrrolidin-1-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl) carbonate (0.50 g, 0.69 mmol) in DCM (10 mL) was added DIPEA (0.36 mL, 2.1 mmol) and benzyl 3-amino-5,5-difluoro-3-methylpiperidine-1-carboxylate (0.29 g, 0.83 mmol). The reaction was stirred at rt for 16 h. The mixture was diluted with H_2O (15 mL) and extracted with DCM (20 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-17% EtOH in EtOAc) to give benzyl 3,3-difluoro-5-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-methylpiperidine-1-carboxylate (0.38 g, 50% yield) as a white solid. LCMS (MM-ES+APCI, Pos): 895.3 (M+H).

Step C. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (5,5-difluoro-3-methylpiperidin-3-yl)carbamate. A flask containing of benzyl 3,3-difluoro-5-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-methylpiperidine-1-carboxylate (0.33 g, 0.33 mmol) and Pd/C (10% wt; 0.30 g, 0.28 mmol) in THF (10 mL) was evacuated and backfilled with H_2 three times. The reaction was stirred at rt under an atmosphere of H_2 for 1.5 h. The slurry was filtered over Celite, and the pad was washed with THF (20 mL). The filtrate was concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (5,5-difluoro-3-methylpiperidin-3-yl)carbamate (0.23 g), which was taken onto the next step without further

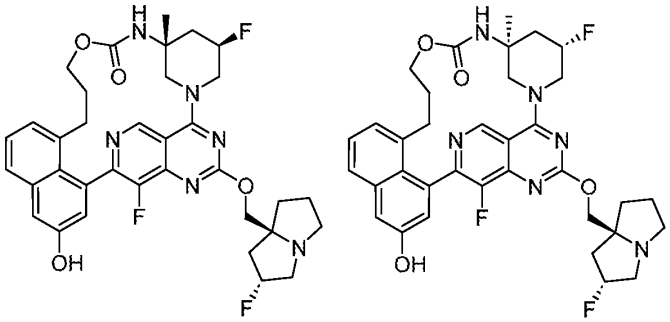
purification.

Step D. $1^5,1^5,2^8,3^7$-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (5,5-difluoro-3-methylpiperidin-3-yl)carbamate (0.23 g, 0.30 mmol) in DCM (230 mL) was added DIPEA (0.26 mL, 1.5 mmol) and BOP-Cl (0.23 g, 0.91 mmol). The reaction was stirred at rt for 16 h and was then concentrated under reduced pressure. The residue was diluted H_2O (20 mL) and then extracted with DCM (20 mL x 3). The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (17% MeOH in EtOAc) to give $1^5,1^5,2^8,3^7$-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.12 g, 43% yield). LCMS (MM-ES+APCI, Pos): 743.3 (M+H).

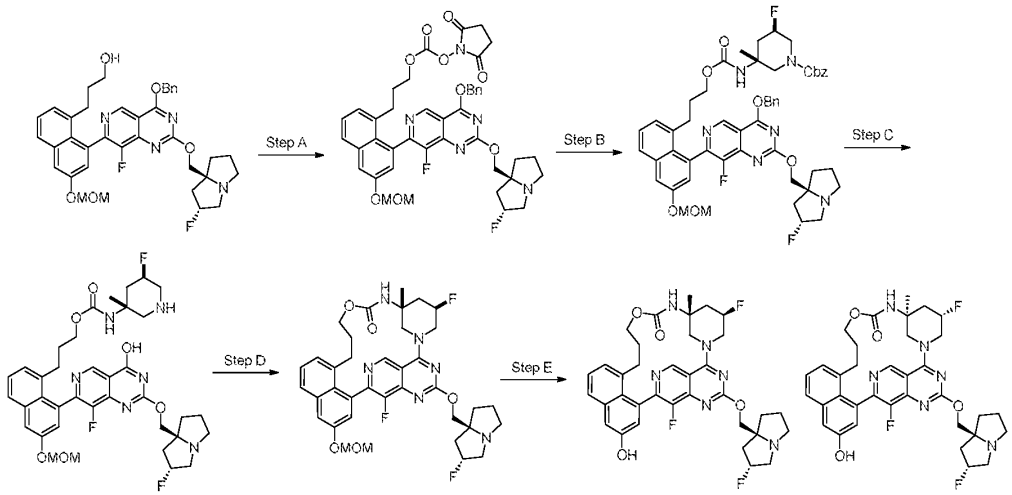
Step E. (1^3R)-$1^5,1^5,2^8,3^7$-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S)-$1^5,1^5,2^8,3^7$-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution $1^5,1^5,2^8,3^7$-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.12 g, 0.13 mmol) in DCM (1 mL) was added HCl in 1,4-dioxane (2.0 M; 1.0 mL). The reaction was stirred at rt for 15 min and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC (35-65% MeCN in 0.1% NH_4HCO_3). The fractions containing the product were lyophilized. The residue was purified by chiral SFC (42% CO_2-EtOH in 0.1% NH_3H_2O) to obtain (1^3R)-$1^5,1^5,2^8,3^7$-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.018, 30%) and (1^3S)-$1^5,1^5,2^8,3^7$-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.019 g, 31%). LCMS (MM-ES+APCI, Pos): 699.3 (M+H). LCMS (MM-ES+APCI, Pos): 699.3 (M+H).

Example 49

Compound 71 and Compound 72



(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S,1^5S)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propan-1-ol (0.50 g, 0.73 mmol, 1 eq) and pyridine

(0.29 mL, 3.6 mmol) in DCM (5 mL) was added N,N′-disuccinimidyl carbonate (0.56 g, 2.2 mmol). The reaction was stirred at rt for 1 h. The mixture was diluted with H2O (10 mL) and then extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure affording 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.55 g, 95% yield) as a yellow oil, which was taken onto the next step without further purification.

Step B. benzyl (rel-3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.55 g, 0.69 mmol) in DCM (6 mL) was added DIPEA (0.24 mL, 1.4 mmol) and benzyl (rel-3R,5R)-3-amino-5-fluoro-3-methylpiperidine-1-carboxylate (0.23 g, 0.83 mmol). The reaction was stirred at rt for 16 h. The mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-60% EtOAc in petroleum ether) to give benzyl (rel-3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.63 g, 92% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): 949.5 (M+H).

Step C. 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((rel-3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate. A flask containing of benzyl (rel-3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.63 g, 0.63 mmol) and Pd/C (10% wt; 0.67 g, 0.63 mmol) in THF (10 mL) was evacuated and backfilled with H_2 three times. The reaction was stirred at rt under an atmosphere of H_2 for 1.5 h. The slurry was filtered over Celite, and the pad was washed with THF (5 mL x 3). The filtrate was concentrated under reduced pressure to give 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-

7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((rel-3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.45 g), which was taken onto the next step without further purification.

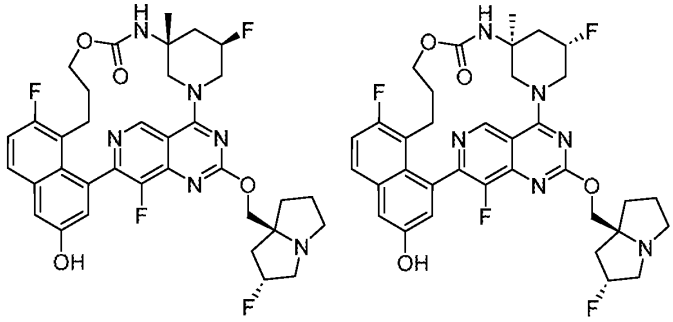
Step D. (rel-1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To solution of 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((rel-3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.45 g, 0.62 mmol) in MeCN (450 mL) was added DIPEA (0.54 mL, 3.1 mmol) and BrOP (0.72 g, 1.9 mmol). The reaction was stirred at rt for 16 h and was then concentrated under reduced pressure. The residue was diluted with H_2O (10 mL) and then extracted with EtOAc (20 mL x 3). The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (48-78% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to give 1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.12 g, 27% yield). LCMS (MM-ES+APCI, Pos): 707.3 (M+H).

Step E. (1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S,1^5S)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.12 g, 0.17 mmol) in DCM (2 mL) was added HCl in 1,4-dioxane (2.0 M, 2.3 mL). The reaction was stirred at rt for 1 h after which it was concentrated under reduced pressure. The residue was purified by SFC (50% CO_2-*i*-PrOH (0.1% NH_3·H_2O)) to give (1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.040 g, 41%) and (1^3S,1^5S)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one

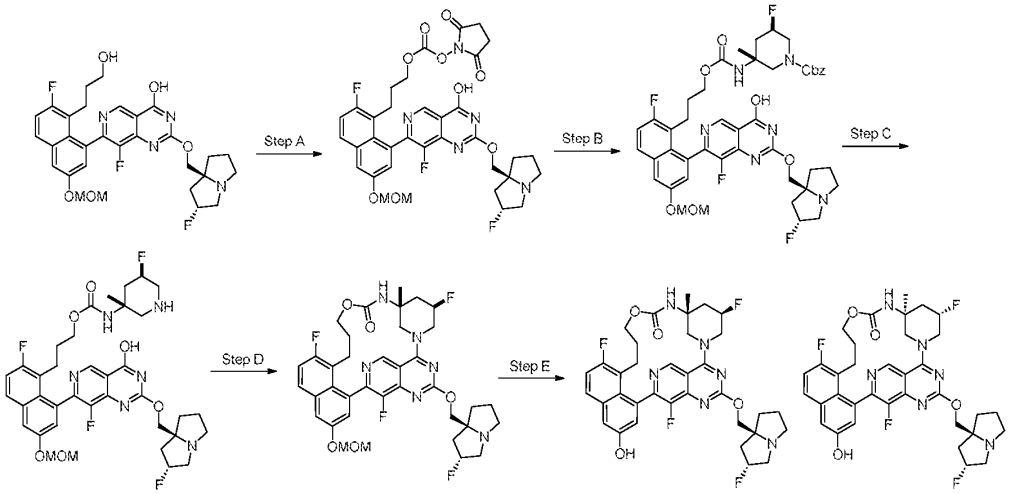
(0.039 g, 40%). LCMS (MM-ES+APCI, Pos): 663.5 (M+H). LCMS (MM-ES+APCI, Pos): 663.5 (M+H).

Example 50

Compound 73 and Compound 74



(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S,1^5S)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 2,5-dioxopyrrolidin-1-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl) carbonate. To a solution of 8-fluoro-7-(7-fluoro-

8-(3-hydroxypropyl)-3-(methoxymethoxy)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-4-ol (0.50 g, 0.68 mmol) and DIPEA (0.60 mL, 3.4 mmol) in DCM (10 mL) was added N,N′-disuccinimidyl carbonate (0.50 g, 2.0 mmol). The reaction was stirred at rt for 18 h. The mixture was diluted with H_2O (10 mL) and then extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure affording 2,5-dioxopyrrolidin-1-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl) carbonate (0.49 g) as a yellow solid, which was taken onto the next step without further purification.

Step B. benzyl (rel-3R,5R)-5-fluoro-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of 2,5-dioxopyrrolidin-1-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl) carbonate (0.49 g, 0.68 mmol) in DCM (10 mL) was added DIPEA (0.35 mL, 2.0 mmol) and benzyl (rel-3R,5R)-3-amino-5-fluoro-3-methylpiperidine-1-carboxylate (0.30 g, 1.1 mmol). The reaction was stirred at rt for 16 h. The mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (10% EtOH in EtOAc) to give benzyl (rel-3R,5R)-5-fluoro-3-(((3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.40 g, 57% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): 877.3 (M+H).

Step C. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((rel-3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate. A flask containing of benzyl (rel-3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.40 g, 0.39 mmol) and Pd/C (10% wt; 0.20 g, 0.19 mmol) in THF (8 mL) was evacuated and backfilled with H_2 three times. The reaction was stirred at rt under an atmosphere of H_2 for 1 h. The slurry was filtered over Celite, and the pad was washed

with THF (15 mL x 3). The filtrate was concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((rel-3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.28 g), which was taken onto the next step without further purification.

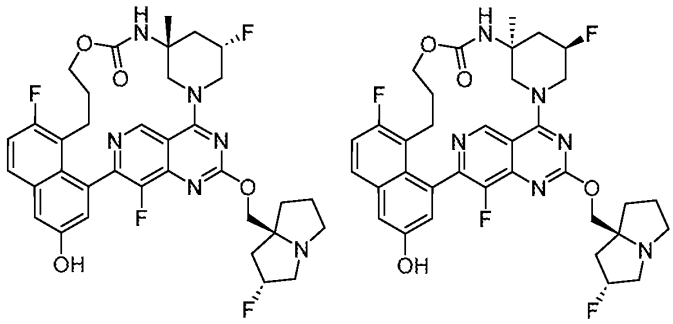
Step D. (rel-1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((rel-3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.28 g, 0.37 mmol) in MeCN (250 mL) was added DIPEA (0.32 mL, 1.9 mmol) and BrOP (0.43 g, 1.1 mmol). The reaction was stirred at rt for 5 h and was then concentrated under reduced pressure. The residue was diluted H_2O (10 mL) and then extracted with EtOAc (20 mL x 3). The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (10% MeOH in EtOAc) to give (rel-1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.28 g, 52% yield). LCMS (MM-ES+APCI, Pos): 725.3 (M+H).

Step E. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S,1^5S)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of (rel-1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.28 g, 0.19 mmol) in DCM (2 mL) was added HCl in 1,4-dioxane (2.0 M, 2.0 mL). The reaction was stirred at rt for 30 min after which it was concentrated under reduced pressure. The residue was purified by preparative HPLC (33-63% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized. The residue was purified by SFC (50% CO_2-*i*-PrOH (0.1% $NH_3{\cdot}H_2O$)) to give (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-

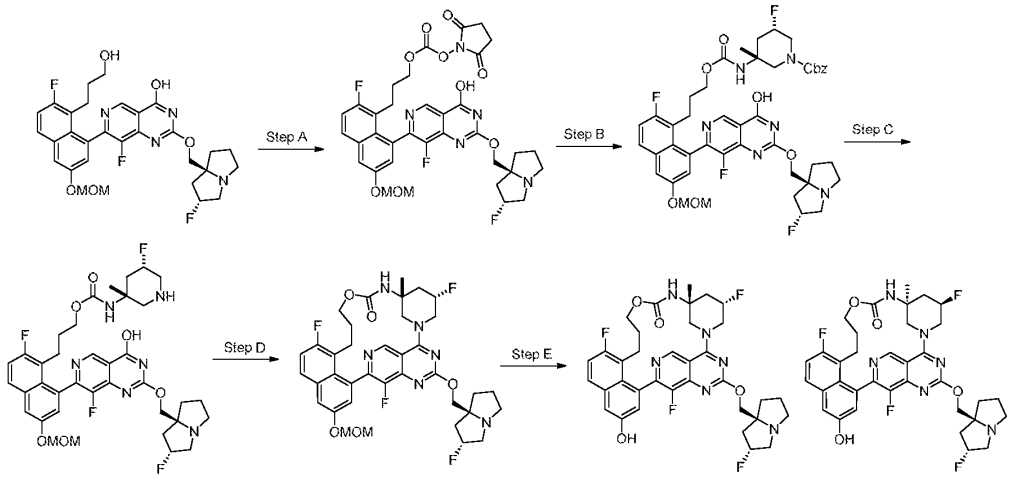
hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.018 g, 38%) and (1^3S,1^5S)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.017 g, 34%). LCMS (MM-ES+APCI, Pos): 681.3 (M+H). LCMS (MM-ES+APCI, Pos): 681.3(M+H).

Example 51

Compound 75 and Compound 76

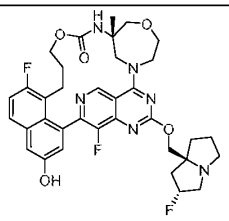
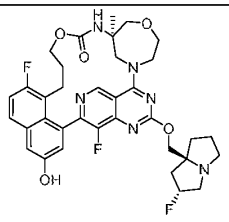
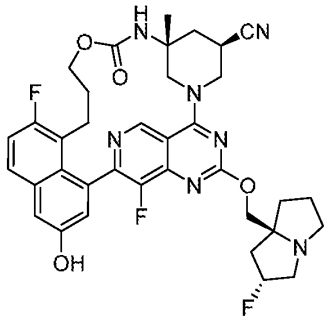
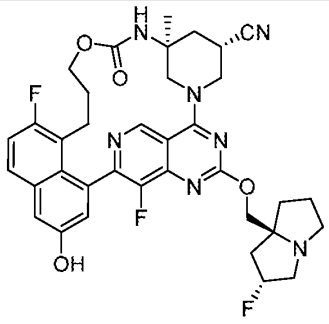


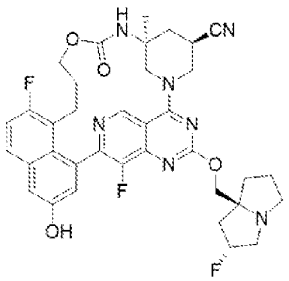
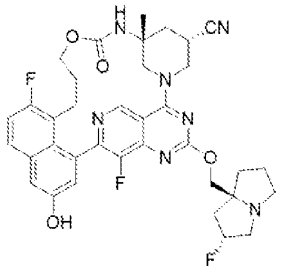
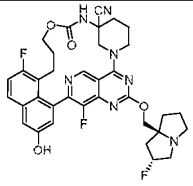
(1^3R,1^5S)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Steps A-E were performed with Intermediate I14 by following the procedure of Compound 73 and Compound 74. Compound 75 and Compound 76 were separated by SFC: (40% CO_2-EtOH (0.1% $NH_3 \cdot H_2O$)). LCMS (MM-ES+APCI, Pos): 681.3 (M+H). LCMS (MM-ES+APCI, Pos): 681.3 (M+H).

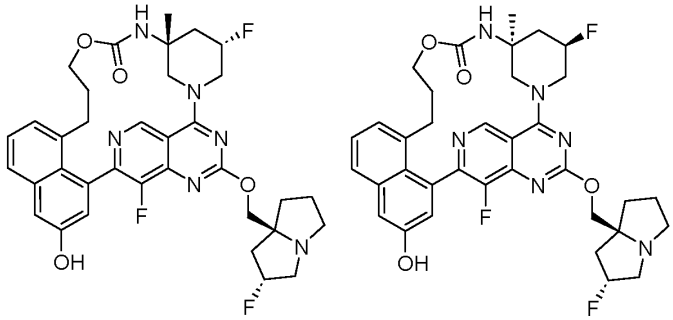
Table 6. Compounds synthesized by following the procedure of Compound 75

Cmpd ID	Structure	LCMS
114		679.3
115		679.3
534		688.4
535		688.4

548		688.3
549		688.3
564		674.2

Example 52

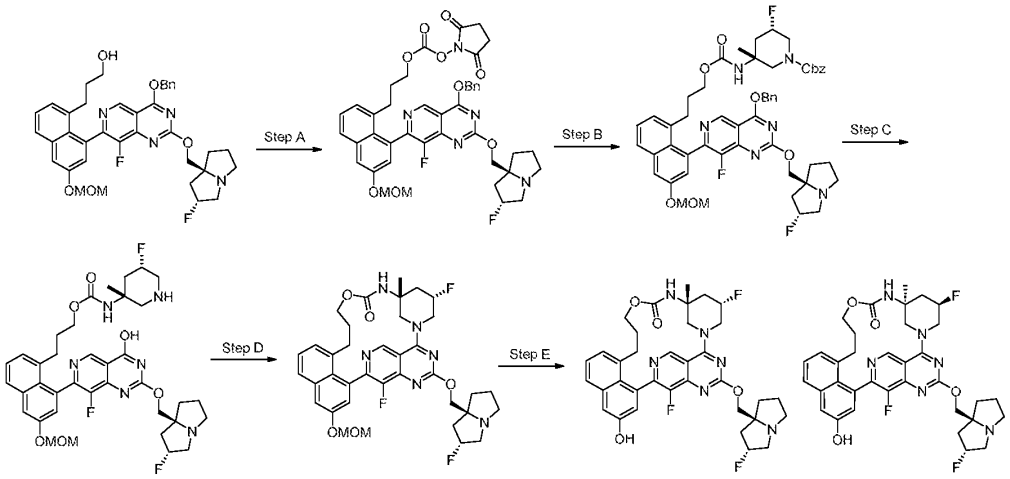
Compound 77 and Compound 78



5

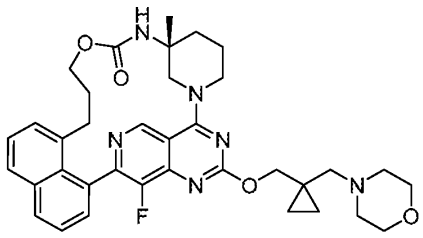
(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-

piperidina-3(1,8)-naphthalenacyclononaphan-8-one

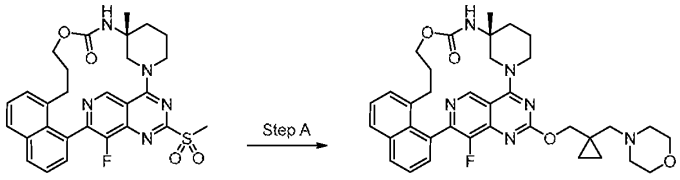


Steps A-E were performed with Intermediate I14, according to the procedure of Compound 71 and Compound 72. Compound 77 and Compound 78 were separated by SFC (50% CO_2-MeCN/*i*-PrOH (0.1% $NH_3{\cdot}H_2O$)). LCMS (MM-ES+APCI, Pos): 663.4 (M+H). LCMS (MM-ES+APCI, Pos): 663.5 (M+H).

Compound 95



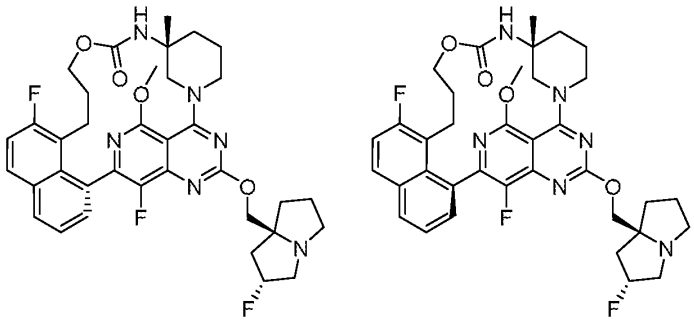
(1^3R)-2^8-fluoro-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



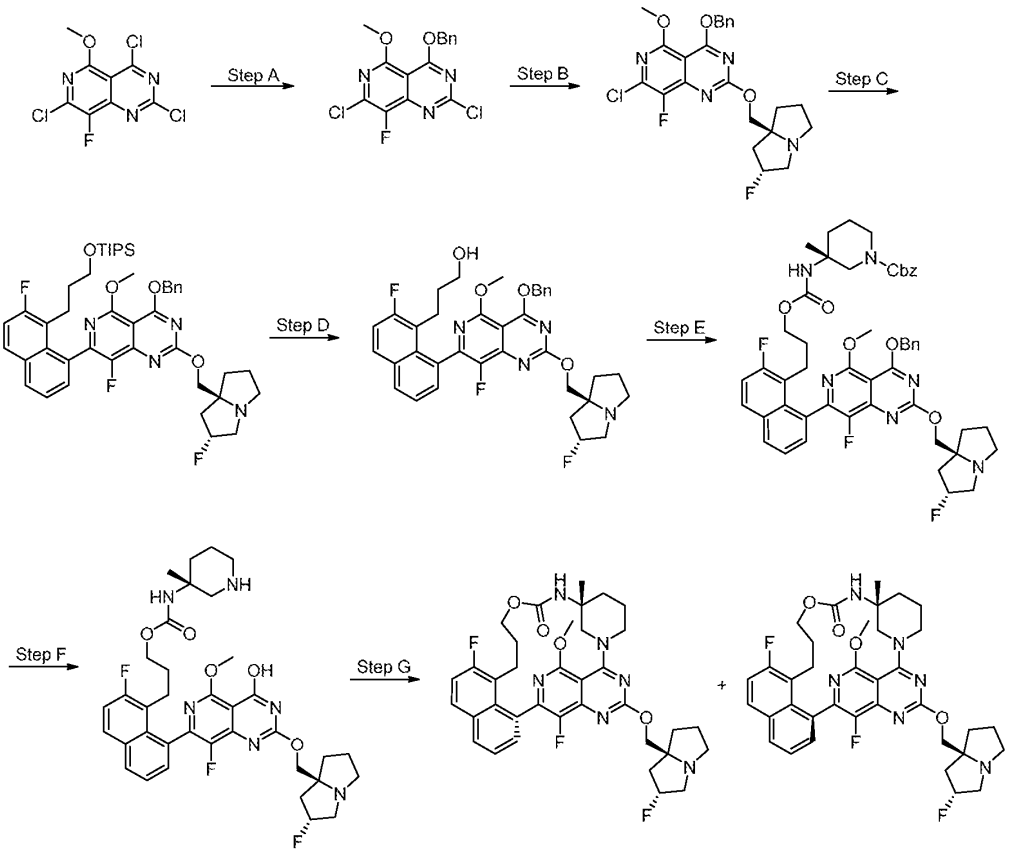
Step A. (1^3R)-2^8-fluoro-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of (1^3R)-2^8-fluoro-1^3-methyl-2^2-(methylsulfonyl)-7-oxa-9-aza-2(4,7)-

pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.017 g, 0.031 mmol) and (1-(morpholinomethyl)cyclopropyl)methanol (0.011 g, 0.063 mmol) in THF (0.16 mL) was added LiHMDS (1M in THF; 0.0034 mL) at 0 °C. The resulting mixture was stirred for 5 h at rt and then quenched with water (2 mL) and extracted with ethyl acetate (3x 5 mL). The combined organic layers were filtered through a phase separator and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 – 20% MeOH in DCM with 0.5% NH_4OH), then purified further by preparative HPLC (5% – 100% MeCN in 0.1% aqueous TFA) to give (1^3R)-2^8-fluoro-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.0073 g, 30% yield). LCMS (MM-ES+APCI, Pos): m/z 641.30 (M+1).

Compound 97 and 98



(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2^5-methoxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2^5-methoxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 4-(benzyloxy)-2,7-dichloro-8-fluoro-5-methoxypyrido[4,3-d]pyrimidine. To a solution of 2,4,7-trichloro-8-fluoro-5-methoxypyrido[4,3-d]pyrimidine (4.0 g, 14 mmol) in DCM (150 mL) at 0 °C was added benzyl alcohol (1.8 mL, 17 mmol) and DIPEA (4.9 mL, 28 mmol). The mixture was stirred at rt for 16 h and then it was diluted with H_2O (50 mL) and extracted with DCM (60 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20-60% EtOAc in petroleum ether) to give 4-(benzyloxy)-2,7-dichloro-8-fluoro-5-methoxypyrido[4,3-d]pyrimidine (4.7 g, 79% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 353.8 (M+H).

Step B. 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxypyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-2,7-dichloro-8-fluoro-5-methoxypyrido[4,3-d]pyrimidine (4.7 g, 11 mmol) and DIPEA (3.9 mL, 22 mmol) in THF (70 mL) was added ((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (2.1 g, 13 mmol). The mixture was heated to 60 °C for 16 h. After cooling to rt,

the solution was diluted with H_2O (150 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (70 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60-100% EtOAc in petroleum ether) to give 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxypyrido[4,3-d]pyrimidine (3.4 g, 64% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 476.9 (M+H).

Step C. 4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxypyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxypyrido[4,3-d]pyrimidine (0.82 g, 1.7 mmol), mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.12 g, 0.17 mmol) and Cs_2CO_3 (1.1 g, 3.4 mmol) in 1,4-dioxane (20 mL) and H_2O (5 mL) was added (3-(2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)triisopropylsilane (1.1 g, 2.1 mmol). The mixture was heated to 90 °C for 2 h. The mixture was diluted with H_2O (70 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (70 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60-100% EtOAc in petroleum ether) to give 4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxypyrido[4,3-d]pyrimidine (1.3 g, 83% yield) as yellow oil. LCMS (MM-ES+APCI, Pos): m/z 801.4 (M+H).

Step D. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxypyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propan-1-ol. To a solution of 4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxypyrido[4,3-d]pyrimidine (1.3 g, 1.4 mmol) in THF (30 mL) was added NEt_3-3HF (1.2 mL, 7.1 mmol). The mixture was stirred at rt for 16 h and then it was diluted with H_2O (20 mL). The pH of mixture was adjusted to 8 with triethylamine and then the solution was extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (60-100% EtOAc in petroleum ether) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxypyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propan-1-ol (0.78 g, 77% yield) as yellow oil. LCMS (MM-ES+APCI, Pos): m/z 645.4 (M+H).

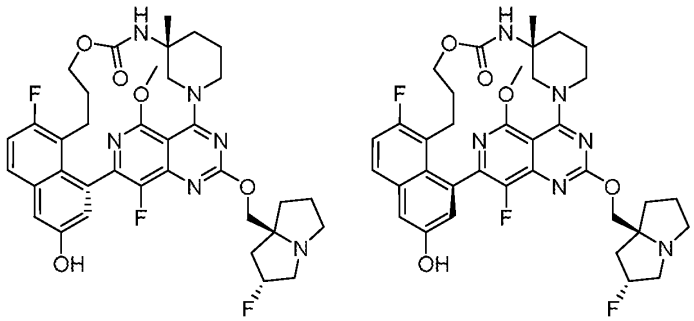
Step E. benzyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxypyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxypyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propan-1-ol (0.78 g, 1.1 mmol) and pyridine (0.26 mL, 3.3 mmol) in DCM (15 mL) was added N,N′-disuccinimidyl carbonate (0.84 g, 3.3 mmol). The mixture was stirred at rt for 1 h and then it was diluted with H_2O (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. To the residue was added DCM (20 mL), DIPEA (0.57 mL, 3.3 mmol), and benzyl (R)-3-amino-3-methylpiperidine-1-carboxylate (0.32 g, 1.3 mmol). The mixture was stirred rt for 1 h and then it was diluted with H_2O (30 mL) and extracted with DCM (30 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60-80% EtOAc in petroleum ether) to give benzyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxypyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.99 g, 89% yield) as colorless oil. LCMS (MM-ES+APCI, Pos): m/z 919.4 (M+H).

Step F. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxy-5-methoxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate. To a solution of benzyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-5-methoxypyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.99 g, 0.96 mmol) in THF (10 mL) was added 10% Pd/C (1.0 g, 0.96 mmol). The flask was then evacuated and backfilled with H_2 three times and then the reaction was stirred under an atmosphere of H_2 for 2 h. The suspension was filtered and the filter cake was washed with THF (100 mL). The filtrate was concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxy-5-methoxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-

yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate (0.66 g) as colorless oil, which was used into the next step without further purification.

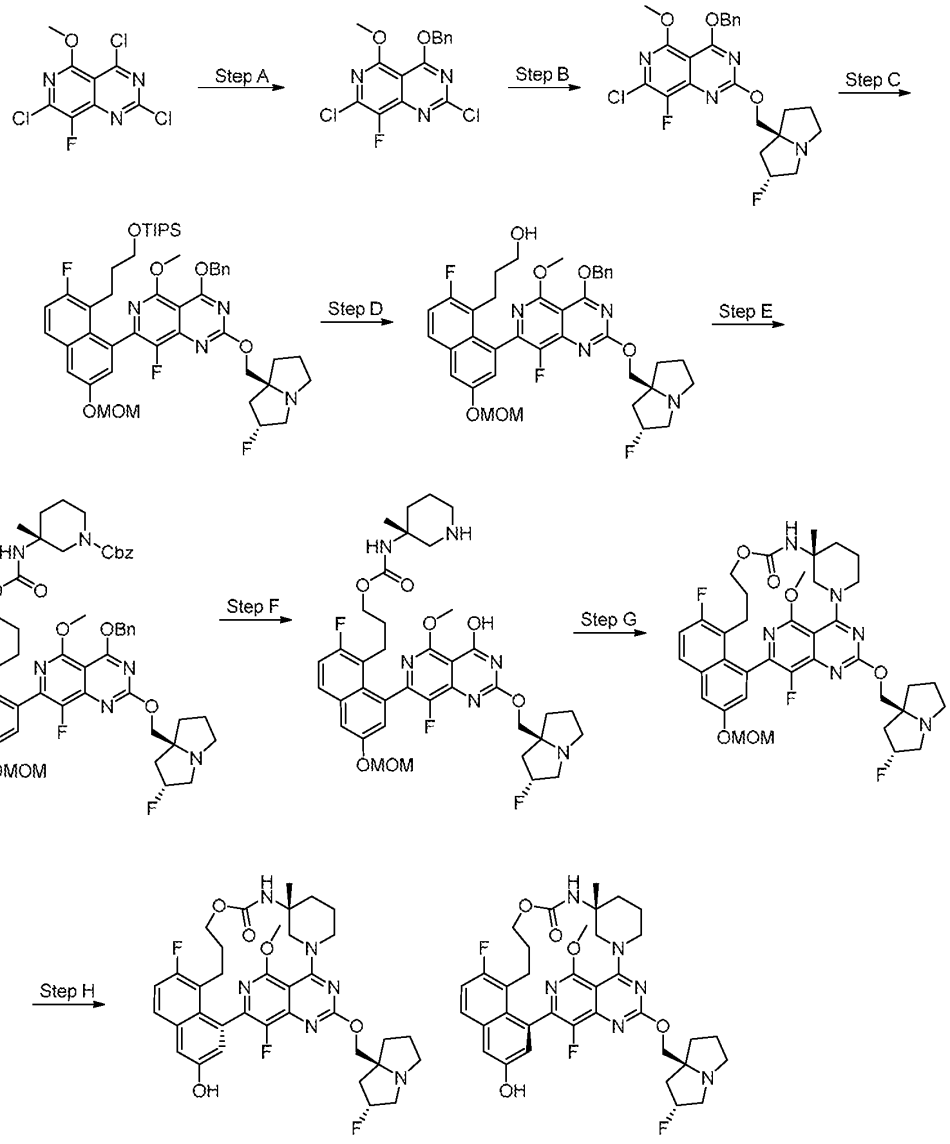
Step G. (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2^5-methoxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2^5-methoxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxy-5-methoxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate (0.66 g, 0.95 mmol) and DIPEA (0.83 mL, 4.8 mmol) in MeCN (600 mL) was added BrOP (1.1 g, 2.9 mmol). The mixture was stirred at rt for 16 h and then it was diluted with H_2O (300 mL) and extracted with ethyl acetate (150 mL x 3). The combined organic layers were washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced. The residue was purified by preparative HPLC (58 – 88% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2^5-methoxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.087 g, 13% yield) as a white solid and (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-2^5-methoxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.092 g, 14% yield). Compound 97: LCMS (MM-ES+APCI, Pos): m/z 677.4 (M+H). Compound 98: LCMS (MM-ES+APCI, Pos): m/z 677.4 (M+H).

Compound 102 and 103



(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-

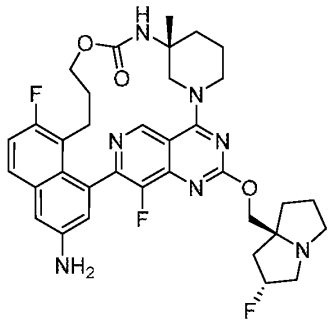
hydroxy-2^5-methoxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-2^5-methoxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Steps A-G were performed with Intermediate I20 (Step C) by following the procedure of Compound 97 and Compound 98. Step H was performed following the procedure of Compound 73 and Compound 74 (Step E). Compound 102 and Compound 103 were purified

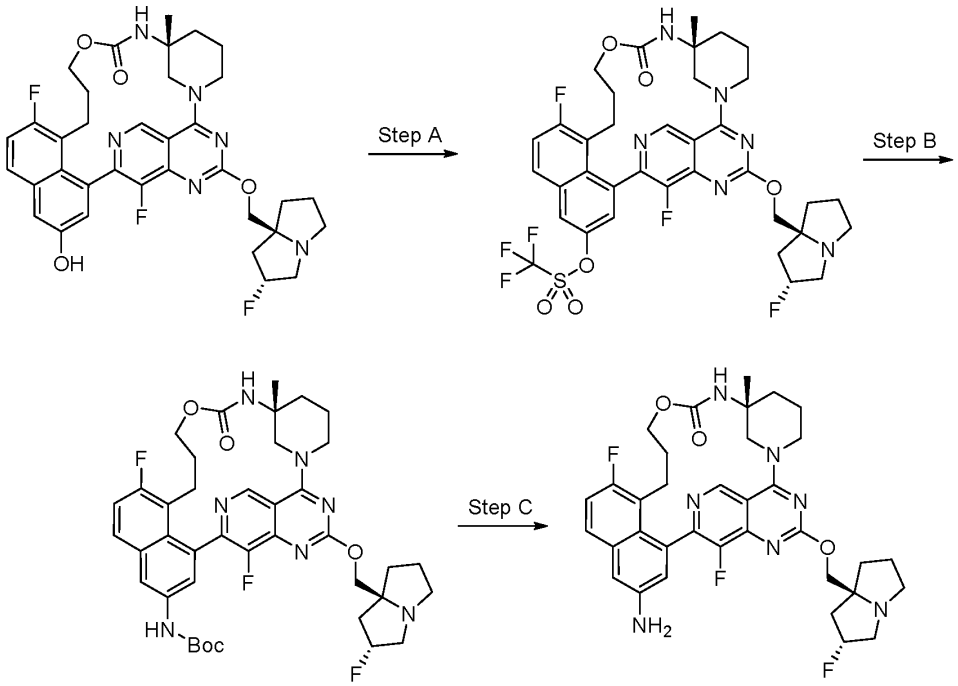
by preparative HPLC (47 – 77% MeCN in 0.1% aqueous NH_4HCO_3). Compound 102: LCMS (MM-ES+APCI, Pos): m/z 693.2 (M+H). Compound 103: LCMS (MM-ES+APCI, Pos): m/z 693.3 (M+H).

Compound 104



5

(1^3R)-3^3-amino-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



10

Step A. (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-

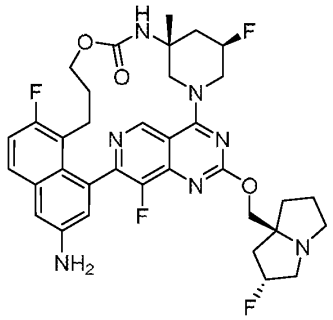
3(1,8)-naphthalenacyclononaphane-3^3-yl trifluoromethanesulfonate. To a solution of (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.20 g, 0.30 mmol) and DIPEA (0.11 mL, 0.60 mmol) in DMF (4 mL) at 0 °C was added 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (0.22 g, 0.62 mmol). The mixture was stirred at 0 °C for 1 h and then it was diluted with H_2O (6 mL) and extracted with EtOAc (2 mL x 3). The combined organic phase was washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (100% EtOAc) to give (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl trifluoromethanesulfonate (0.20 g, 83% yield) as a colorless gum. LCMS (MM-ES+APCI, Pos): m/z 795.3 (M+H).

Step B. tert-butyl ((1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)carbamate. To a solution of (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl trifluoromethanesulfonate (0.20 g, 0.25 mmol), Cs_2CO_3 (0.18 g, 0.54 mmol), and tert-butyl carbamate (0.067 g, 0.57 mmol) in 1,4-dioxane (4 mL) was added $Pd_2(dba)_3$ (0.023 g, 0.025 mmol) and Xantphos (0.044 g, 0.075 mmol). The flask was then evacuated and backfilled with nitrogen three times and then it was heated to 90 °C for 1 h. The suspension was filtered through a pad of Celite and the pad was washed with additional EtOAc (6 mL). The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (100% EtOAc) to give tert-butyl ((1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)carbamate (0.20 g, 82% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 762.3 (M+H).

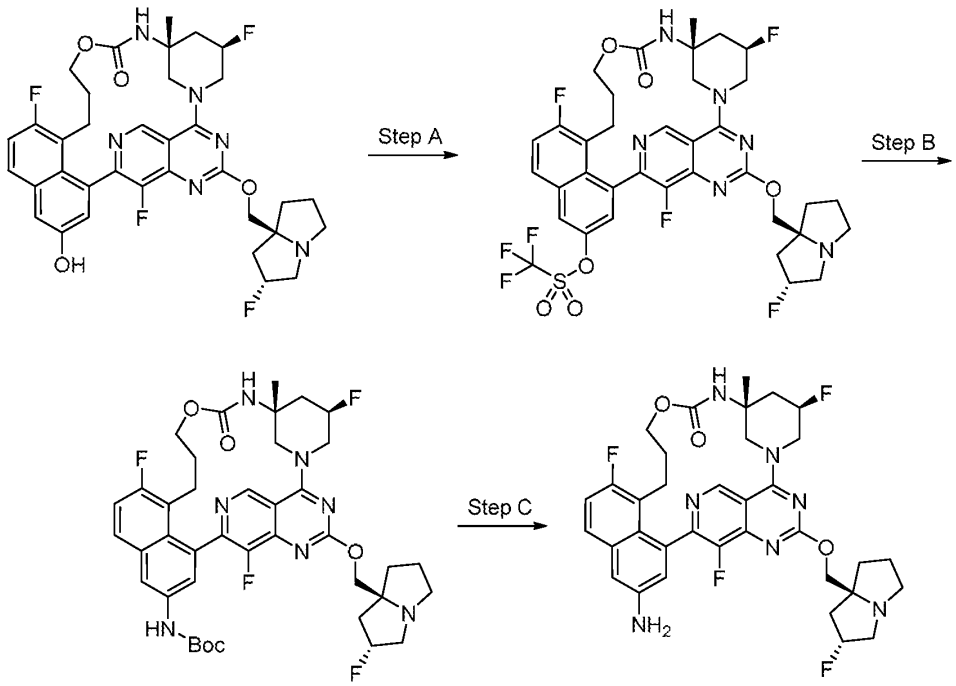
Step C. (1^3R)-3^3-amino-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of tert-butyl ((1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-

oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)carbamate (0.20 g, 0.20 mmol) in DCM (1 mL) was added HCl in 1,4-dioxane (2.0 M; 1.0 mL). The mixture was stirred at rt for 30 min and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC (30 – 60% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain (1^3R)-3^3-amino-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.017 g, 12% yield) as an off-white solid. LCMS (MM-ES+APCI, Pos): m/z 662.2 (M+H).

Compound 119

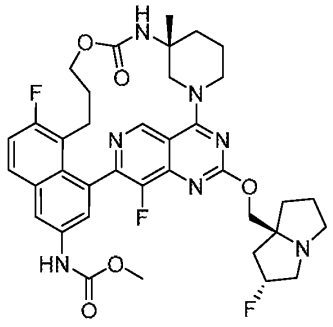


(1^3R,1^5R)-3^3-amino-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one

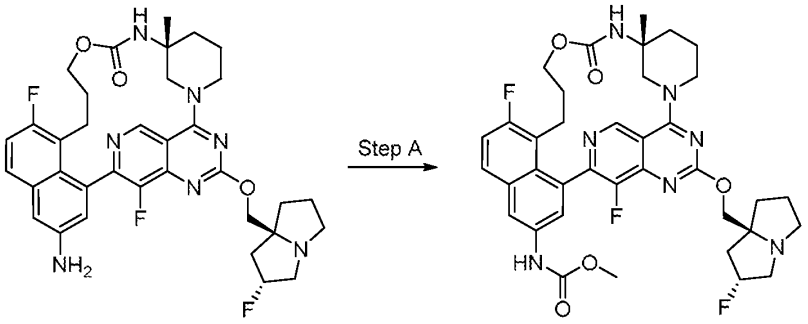


Steps A-C were performed with Compound 74 following the procedure of Compound 104. LCMS (MM-ES+APCI, Pos): m/z 680.2 (M+H).

Compound 120

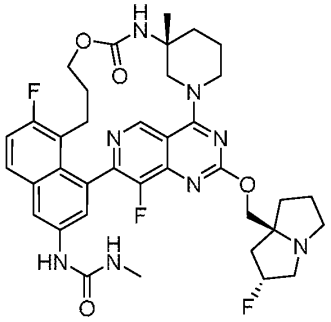


methyl ((1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)carbamate

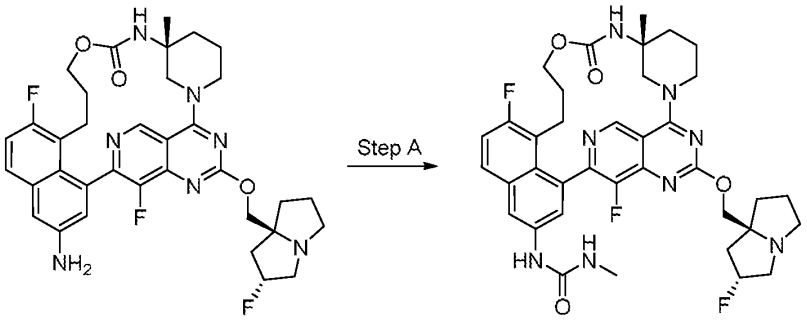


Step A. methyl ((1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)carbamate. To a solution of (1^{3}R)-3^3-amino-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.032 g, 0.048 mmol) and K_2CO_3 (0.013 g, 0.097 mmol) in MeCN (1 mL) was added dimethyl dicarbonate (0.0056 mL, 0.052 mmol). The reaction was stirred at rt for 2 h and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC (40 – 70% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain methyl ((1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)carbamate (0.026 g, 75% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 720.2 (M+H).

Compound 121

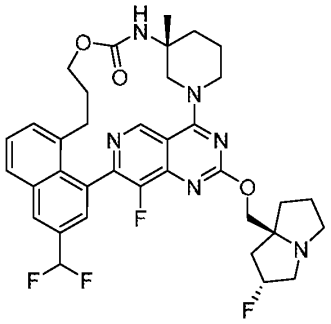


1-((1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)-3-methylurea

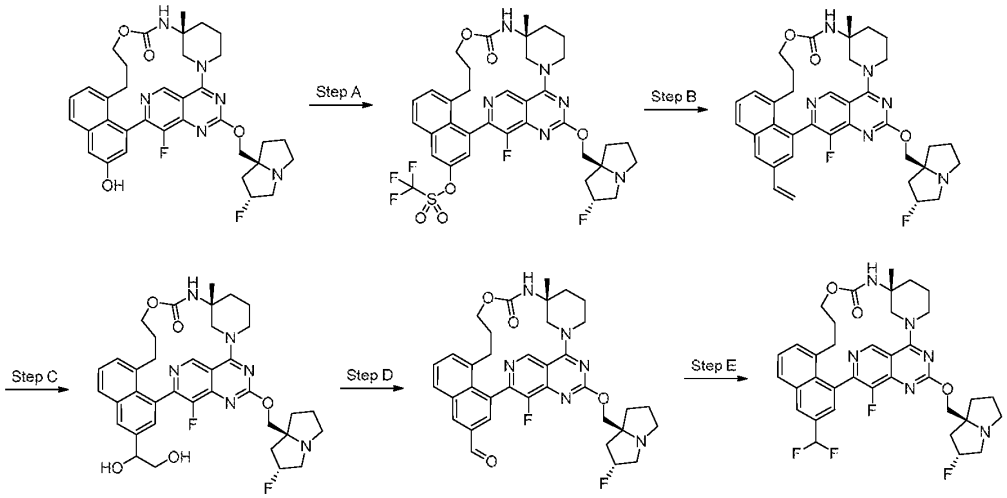


Step A. 1-((1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)-3-methylurea. To a solution of (1^{3}R)-3^3-amino-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.035 g, 0.053 mmol) and NEt_3 (0.022 mL, 0.16 mmol) in DCM (1 mL) was added methylcarbamic chloride (0.010 g, 0.11 mmol) and DMAP (0.0065 g, 0.053 mmol). The reaction was stirred at rt for 3 h and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC (25 – 55% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain 1-((1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)-3-methylurea (0.033 g, 85% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 719.4 (M+H).

Compound 105



(1^{3}R)-3^3-(difluoromethyl)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl trifluoromethanesulfonate. To a solution of (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.20 g, 0.31 mmol) and DIPEA (0.11 mL, 0.60 mmol) in DMF (2 mL) at 0 °C was added 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (0.22 g, 0.62 mmol). The mixture was stirred at 0 °C for 1 h and then it was diluted with H_2O (8 mL) and extracted with EtOAc (10 mL x 5). The combined organic phase was washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl trifluoromethanesulfonate (0.22 g, 76% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 777.2 (M+H).

Step B. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-3^3-vinyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl trifluoromethanesulfonate (0.20 g, 0.21 mmol) in isopropanol (4 mL) was added potassium vinyltrifluoroborate (0.057 g, 0.43 mmol), NEt_3 (0.089 mL, 0.64 mmol) and $Pd(dppf)Cl_2$

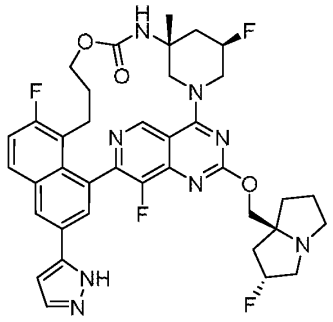
(0.016 g, 0.021 mmol). The mixture was heated to 80 °C for 1 h and then it was concentrated under reduced pressure. The residue was purified by silica gel chromatography (50-100% EtOAc in petroleum ether) to give (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-3^3-vinyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.13 g, 87% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 655.2 (M+H).

Step C. (1^3R)-3^3-(1,2-dihydroxyethyl)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-3^3-vinyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.080 g, 0.11 mmol) in THF (1 mL) and H_2O (0.1 mL) 0 °C was added $K_2OsO_4 \cdot 2H_2O$ (0.0042 g, 0.011 mmol) and NMO (0.013 mL, 0.013 mmol). The mixture was stirred at rt for 1 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-10% MeOH in EtOAc) to give (1^3R)-3^3-(1,2-dihydroxyethyl)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.075 g, 95% yield) as a yellow gum. LCMS (MM-ES+APCI, Pos): m/z 689.3 (M+H).

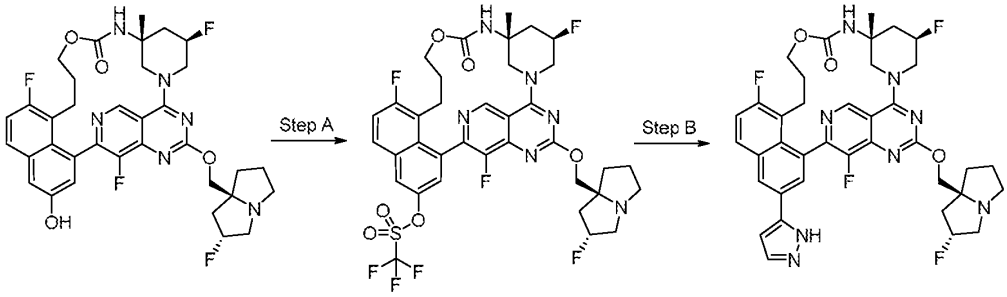
Step D. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-carbaldehyde. To a solution of (1^3R)-3^3-(1,2-dihydroxyethyl)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.055 g, 0.080 mmol) in THF (1 mL) and H_2O (0.1 mL) was added $NaIO_4$ (0.034 g, 0.16 mmol). The mixture was stirred at rt for 1 h and then it was diluted with H_2O (5 mL) and extracted with 10% MeOH in EtOAc (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-5% MeOH in EtOAc) to give (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-carbaldehyde (0.055 g, 99% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 657.3 (M+H).

Step E. (1^3R)-3^3-(difluoromethyl)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To solution of (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-carbaldehyde (0.037 g, 0.053 mmol) in DCM (1 mL) at 0 °C was added BAST (0.12 mL, 0.53 mmol). The mixture was stirred at rt for 12 h and then it was slowly diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (58 – 78% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain (1^3R)-3^3-(difluoromethyl)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.013 g, 35% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 679.2 (M+H).

Compound 122



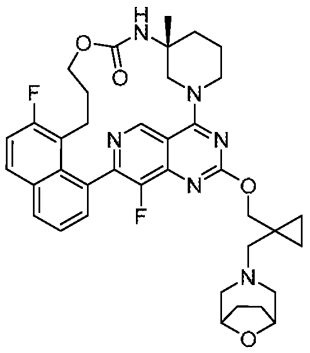
(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-3^3-(1H-pyrazol-5-yl)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



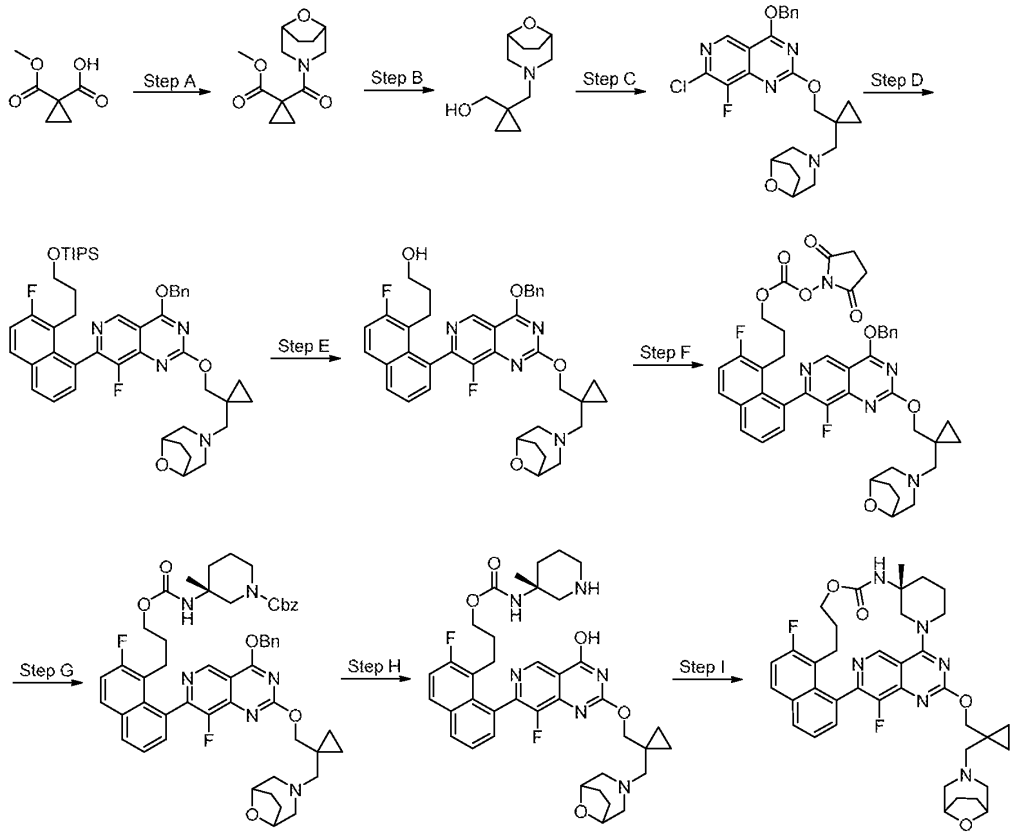
Step A. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl trifluoromethanesulfonate. To a solution of (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.040 g, 0.058 mmol) and DIPEA (0.020 mL, 0.116 mmol) in DMA (1 mL) at 0 °C was added 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (0.042 g, 0.12 mmol). The reaction was stirred at 0 °C for 2 h and then it was quenched by slow addition of H_2O (6 mL). The mixture was extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-50% EtOAc in petroleum ether) to give (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl trifluoromethanesulfonate (0.040 g, 82% yield) as yellow oil. LCMS (MM-ES+APCI, Pos): m/z 813.2 (M+H).

Step B. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-3^3-(1H-pyrazol-5-yl)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl trifluoromethanesulfonate (0.030 g, 0.036 mmol) in 1,4-dioxane (0.5 mL) and H_2O (0.1 mL) was added Pd(dppf)Cl_2 (0.0030 g, 0.0041 mmol), Na_2CO_3 (0.012 g, 0.113 mmol), and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.0090 g, 0.046 mmol). The reaction was heated to 90 °C for 1 h. The suspension was filtered through a pad of Celite. The Celite pad was eluted with EtOAc (20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC (30 – 60% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-3^3-(1H-pyrazol-5-yl)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.0079 g, 29% yield) as white solid. LCMS (MM-ES+APCI, Pos): m/z 731.2 (M+H).

Compound 111



(1^3R)-2^2-((1-(((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-2^8,3^7-difluoro-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. methyl 1-((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)cyclopropane-1-carboxylate. To a solution of 1-(methoxycarbonyl)cyclopropane-1-carboxylic acid (3.0 g, 21 mmol) in DMF (30 mL) was added DIPEA (15 mL, 83 mmol), HATU (12 g, 31 mmol) and

8-oxa-3-azabicyclo[3.2.1]octane·HCl (4.7 g, 31 mmol). The mixture was stirred at rt for 16 h and then it was diluted with H_2O (300 mL). The pH of mixture was adjusted to 4 using 1 M HCl and the mixture extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (5% – 45% MeCN in 0.225% aqueous formic acid). The fractions containing the product were lyophilized to obtain methyl 1-((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)cyclopropane-1-carboxylate (5.5 g, 96% yield) was obtained as yellow oil. LCMS (MM-ES+APCI, Pos): m/z 240.0 (M+H).

Step B. (1-(((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methanol. To a solution of methyl 1-((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octane-3-carbonyl)cyclopropane-1-carboxylate (2.0 g, 8.4 mmol) in THF (20 mL) at 0 °C was added LAH (2.5 M solution in THF; 6.7 mL) dropwise. The mixture was warmed to rt and stirred for 4 h. The reaction was quenched by slow addition of $Na_2SO_4·10H_2O$ (0.97 mL, 4.2 mmol) and was then stirred for another 16 h. The suspension was filtered and the filter cake was washed with THF (20 mL). The filtrate was concentrated under reduced pressure affording (1-(((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methanol (1.6 g, 97% yield). ^{1}H NMR: (400 MHz, MeOH-d_4) δ 4.27 (dd, J = 2.4, 4.4 Hz, 2H), 3.52 - 3.47 (m, 2H), 2.87 - 2.76 (m, 2H), 2.35 (s, 2H), 2.23 (dd, J = 2.0, 11.6 Hz, 2H), 1.99 - 1.93 (m, 2H), 1.90 - 1.84 (m, 2H), 0.49 - 0.43 (m, 2H), 0.37 - 0.27 (m, 2H).

Step C. 3-((1-(((4-(benzyloxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)methyl)-8-oxa-3-azabicyclo[3.2.1]octane. To solution of (1-(((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methanol (1.6 g, 8.1 mmol) in THF (60 mL) at 0 °C was added NaH (60% in mineral oil; 0.34 g, 8.4 mmol) portion wise. The mixture was stirred at 0 °C for 1 h after which 4-(benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidine (2.0 g, 6.0 mmol) was added. The mixture was stirred at 0 °C for 3 h and then it was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (70% – 100% MeCN in0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain 3-((1-(((4-(benzyloxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)methyl)-8-oxa-3-azabicyclo[3.2.1]octane (0.50 g, 17% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 485.1 (M+H).

Step D. 3-((1-(((4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)methyl)-8-oxa-3-azabicyclo[3.2.1]octane. To a solution of 3-((1-(((4-(benzyloxy)-7-chloro-8-fluoropyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)methyl)-8-oxa-3-azabicyclo[3.2.1]octane (0.50 g, 1.0 mmol) in 1,4-dioxane (10 mL) and H_2O (1 mL) was added Cs_2CO_3 (0.67 g, 2.1 mmol), (3-(2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)triisopropylsilane (0.65 g, 1.2 mmol) and mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.075 g, 0.10 mmol). The mixture was heated to 90 °C for 2 h and then it was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-11% EtOAc in hexanes) to give 3-((1-(((4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)methyl)-8-oxa-3-azabicyclo[3.2.1]octane (0.85 g, 97% yield) as yellow oil. LCMS (MM-ES+APCI, Pos): m/z 809.4 (M+H).

Step E. 3-(8-(2-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-4-(benzyloxy)-8-fluoropyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propan-1-ol. To a solution of 3-((1-(((4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)pyrido[4,3-d]pyrimidin-2-yl)oxy)methyl)cyclopropyl)methyl)-8-oxa-3-azabicyclo[3.2.1]octane (0.85 g, 1.0 mmol) in THF (17 mL) was added $3HF{\cdot}NEt_3$ (1.6 mL, 10 mmol). The mixture was heated to 50 °C for 16 h and then it was diluted with H_2O (20 mL). The pH of mixture was adjusted to 9 by using saturated aqueous $NaHCO_3$ and the solution was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-40% EtOAc in hexanes) to give 3-(8-(2-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-4-(benzyloxy)-8-fluoropyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propan-1-ol (0.55 g, 82% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 653.2 (M+H).

Step F. 3-(8-(2-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-4-(benzyloxy)-8-fluoropyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate. To a solution of 3-(8-(2-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-4-(benzyloxy)-8-fluoropyrido[4,3-

d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propan-1-ol (0.55 g, 0.82 mmol) in DCM (10 mL) was added pyridine (0.33 mL, 4.1 mmol) and N,N′-disuccinimidyl carbonate (0.42 g, 1.6 mmol). The mixture was heated to 30 °C for 2 h and then it was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(8-(2-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-4-(benzyloxy)-8-fluoropyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.65 g, 95% yield) as yellow oil. LCMS (MM-ES+APCI, Pos): m/z 794.2 (M+H).

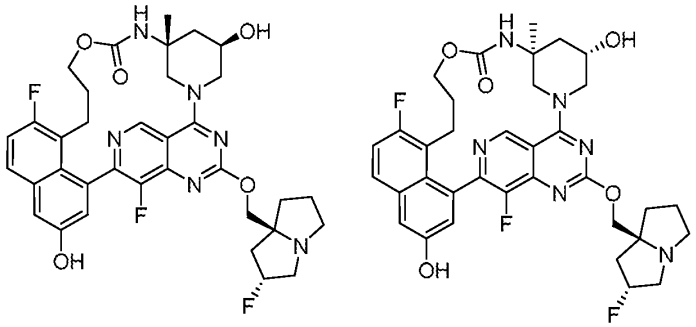
Step G. benzyl (3R)-3-(((3-(8-(2-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-4-(benzyloxy)-8-fluoropyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(2-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-4-(benzyloxy)-8-fluoropyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.65 g, 0.78 mmol) in DCM (10 mL) was added DIPEA (0.41 mL, 2.3 mmol) and benzyl (R)-3-amino-3-methylpiperidine-1-carboxylate (0.29 g, 1.2 mmol). The mixture was heated to 30 °C for 2 h and then it was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-25% EtOAc in petroleum ether) to give benzyl (3R)-3-(((3-(8-(2-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-4-(benzyloxy)-8-fluoropyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.70 g, 93% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 927.3 (M+H).

Step H. 3-(8-(2-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-8-fluoro-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate. To a solution of benzyl (3R)-3-(((3-(8-(2-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-4-(benzyloxy)-8-fluoropyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.70 g, 0.73 mmol) in THF (10 mL) was added 10% Pd/C (0.77 g, 0.73 mmol). The flask was evacuated and backfilled with hydrogen three times and then it was heated to 30 °C for 2 h under an atmosphere of hydrogen. The suspension was filtered, and the filter cake was washed with MeOH (100 mL) and THF (100 mL). The filtrate was concentrated under reduced pressure to give 3-(8-(2-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-

yl)methyl)cyclopropyl)methoxy)-8-fluoro-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate (0.55 g, 96% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 703.4 (M+H).

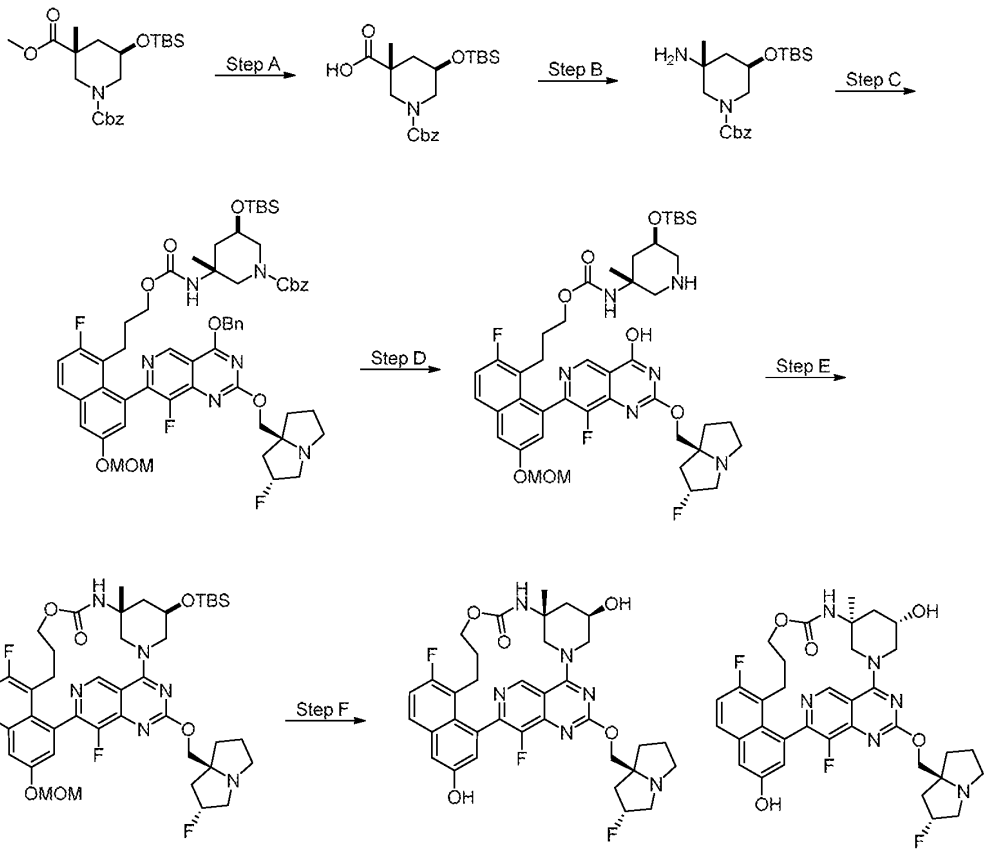
Step I. (1^3R)-2^2-((1-(((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-2^8,3^7-difluoro-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(8-(2-((1-((8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-8-fluoro-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl)carbamate (0.55 g, 0.70 mmol) in MeCN (500 mL) was added DIPEA (3.6 mL, 21 mmol) and BrOP (0.81 g, 2.1 mmol). The mixture was heated to 40 °C for 16 h and then it was concentrated under reduced pressure. The residue was diluted with H_2O (20 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with water (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (30 – 60% MeCN in 0.225% aqueous formic acid). The fractions containing the product were lyophilized and purified by preparative HPLC (62 – 92% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized and purified by preparative HPLC (23 – 53% MeCN in 0.2% aqueous formic acid). The fractions containing the product were lyophilized to give 1^3R)-2^2-((1-(((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)methyl)cyclopropyl)methoxy)-2^8,3^7-difluoro-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.028 g, 6% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 685.3 (M+H).

Compound 117 and 118



(1^3R,1^5R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^5,3^3-dihydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-

piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S,1^5S)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^5,3^3-dihydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. (rel-3R,5R)-1-((benzyloxy)carbonyl)-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-3-carboxylic acid. To a solution of 1-benzyl 3-methyl (3R,5R)-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1,3-dicarboxylate (3.5 g, 8.3 mmol) in MeOH (7 mL), H_2O (7 mL) and THF (28 mL) was added LiOH (0.70 g, 29 mmol). The reaction was stirred at rt for 12 h after which it was diluted with H_2O (50 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (60 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (rel-3R,5R)-1-((benzyloxy)carbonyl)-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-3-carboxylic acid (3.0 g, 89% yield) as a colorless oil, which was used into the next step without further purification.

Step B. benzyl (rel-3R,5R)-3-amino-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1-carboxylate. To a solution of (rel-3R,5R)-1-((benzyloxy)carbonyl)-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-3-carboxylic acid (1.5 g, 3.7 mmol) in THF (120 mL) was added DPPA (3.2 mL, 15 mmol) and DIPEA (9.0 mL, 52 mmol). The mixture was heated to 75 °C for 4 h. After cooling to rt, a solution of KOH (4.1 g, 74 mmol) in H_2O (40 mL) was added dropwise and the mixture was stirred at rt for 12 h. The solution was diluted with H_2O (100 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25-75% EtOAc in petroleum ether) to give benzyl (rel-3R,5R)-3-amino-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1-carboxylate (1.7 g, 61% yield) as colorless oil. ^{1}H NMR: (400 MHz, MeOH-d_4) δ 7.33 - 7.21 (m, 5H), 5.11 - 5.04 (m, 1H), 5.03 - 4.95 (m, 1H), 3.94 - 3.83 (m, 1H), 3.81 - 3.70 (m, 1H), 3.49 - 3.37 (m, 1H), 3.07 (d, J = 13.2 Hz, 1H), 2.99 - 2.71 (m, 1H), 1.74 (dd, J = 4.0, 13.2 Hz, 1H), 1.55 - 1.35 (m, 1H), 1.15 - 1.04 (m, 3H), 0.80 (br s, 9H), 0.00 (br s, 6H).

Step C. benzyl (rel-3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1-carboxylate. To a 40 mL vial equipped with a magnetic stir bar was added benzyl (rel-3R,5R)-3-amino-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1-carboxylate (0.15 g, 0.40 mmol) and 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.22 g, 0.27 mmol) in DCM (4 mL) was added DIPEA (0.094 mL, 0.54 mmol). The mixture was stirred at rt for 12 h after which it was diluted with H_2O (20 mL) and extracted EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25-75% EtOAc in petroleum ether) to give benzyl (rel-3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1-carboxylate (0.25 g, 80% yield) as colorless gum. LCMS (MM-ES+APCI, Pos): m/z 1079.5 (M+H).

Step D. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-

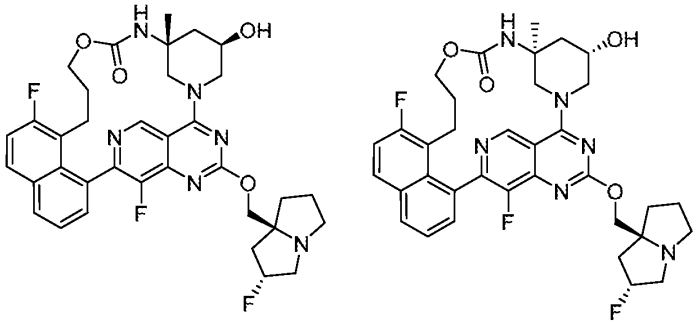
yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((rel-3R,5R)-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidin-3-yl)carbamate. To a solution of benzyl (rel-3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1-carboxylate (0.25 g, 0.22 mmol) in THF (12 mL) was added 10% Pd/C (0.25 g, 0.23 mmol). The flask was then evacuated and backfilled with H_2 three times and it was stirred under an atmosphere of H_2 for 2 h. The suspension was filtered, and the filter cake was washed with THF (5 mL x 5). The filtrate was concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((rel-3R,5R)-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidin-3-yl)carbamate (184 mg) as colorless gum, which was taken onto the next step without further purification.

Step E. (rel-(1^3R,1^5R)-1^5-((tert-butyldimethylsilyl)oxy)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((rel-3R,5R)-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidin-3-yl)carbamate (0.084 g, 0.098 mmol) in MeCN (50 mL) was added DIPEA (0.086 mL, 0.49 mmol) and BrOP (0.11 g, 0.29 mmol). The reaction was stirred at rt for 12 h and then it was concentrated under reduced pressure. The residue was diluted with H_2O (30 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (50-83% EtOAc in petroleum ether) to give (rel-(1^3R,1^5R)-1^5-((tert-butyldimethylsilyl)oxy)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.055 g, 062% yield) as colorless gum. LCMS (MM-ES+APCI, Pos): m/z 837.5 (M+H).

Step F. (1^3R,1^5R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^5,3^3-dihydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S,1^5S)-2^8,3^7-difluoro-2^2-

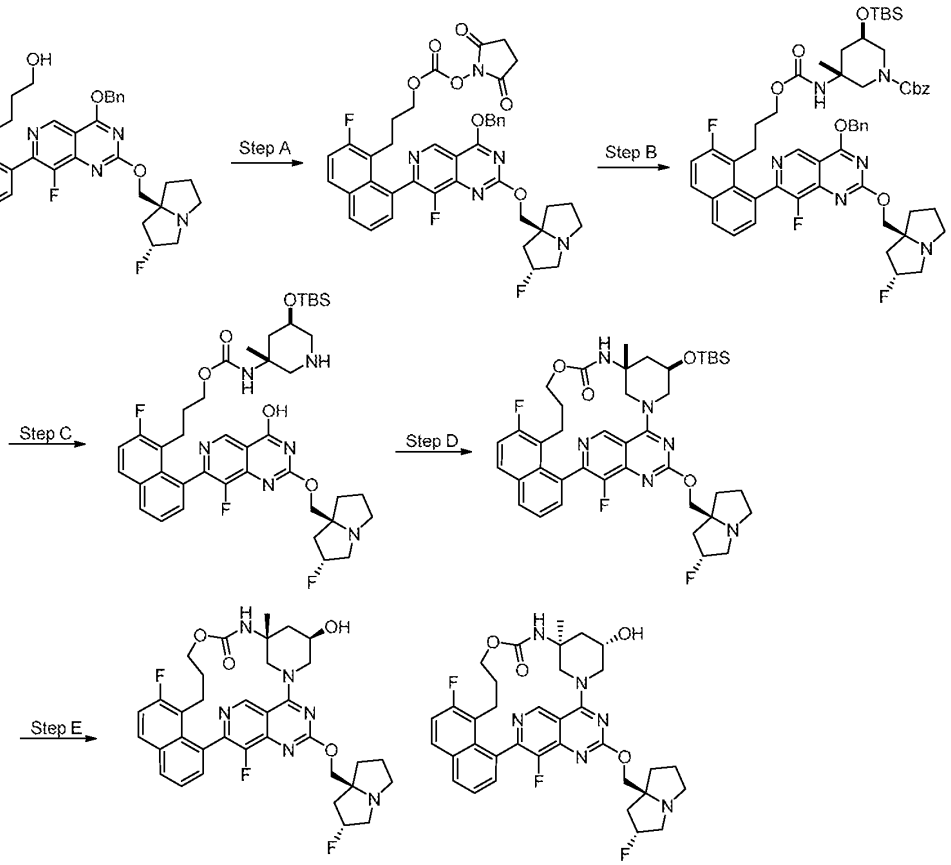
(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^5,3^3-dihydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of (rel-1^3R,1^5R)-1^5-((tert-butyldimethylsilyl)oxy)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.10 g, 0.12 mmol) in DCM (1 mL) was added 2 M HCl in 1,4-dioxane (1 mL). The reaction was stirred for 1 h and then it was concentrated under reduced pressure. The residue was dissolved in MeOH (5 mL) and washed with aq. $NaHCO_3$ solution. The suspension was filtered and the filter cake was washed with DCM (3 mL x 5). The filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC (30 – 60% MeCN in 0.10% aqueous NH_4HCO_3). The fractions containing the product were lyophilized. The residue was purified by SFC (35% CO_2 - ACN/i-PrOH (0.1% $NH_3{\cdot}H_2O$)) to give (1^3R,1^5R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^5,3^3-dihydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.015 g, 18% yield) and (1^3S,1^5S)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^5,3^3-dihydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.017 g, 21% yield). LCMS (MM-ES+APCI, Pos): m/z 679.4 (M+H). LCMS (MM-ES+APCI, Pos): m/z 679.3 (M+H).

Compound 500 and Compound 501



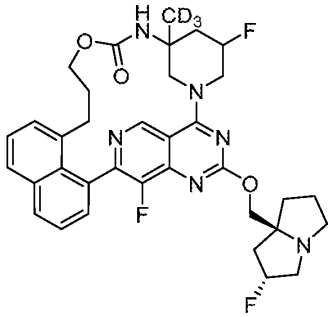
(1^3R,1^5R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^5-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and (1^3S,1^5S)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^5-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-

naphthalenacyclononaphan-8-one

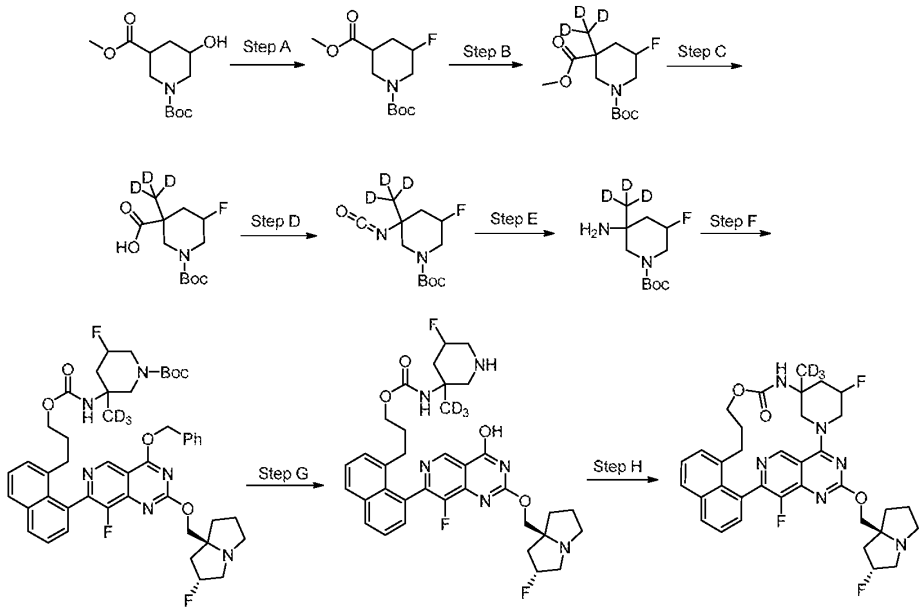


Steps A-E were performed with Intermediate 21 by following the procedure of Compounds 117 and 118. The compounds were separated by SFC (40% CO_2 in EtOH (0.1% $NH_3 \cdot H_2O$)) LCMS (MM-ES+APCI, Pos): m/z 663.3 (M+H). LCMS (MM-ES+APCI, Pos): m/z 663.3 (M+H).

Compound 123:



1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-(methyl-d3)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 1-(tert-butyl) 3-methyl 5-fluoropiperidine-1,3-dicarboxylate. To a solution of 1-(tert-butyl) 3-methyl 5-hydroxypiperidine-1,3-dicarboxylate (10 g, 39 mmol) in DCM (500 mL) at -78 °C was added DAST (7.6 mL, 58 mmol) dropwise. The reaction was stirred at -78 °C for 2 h and then it was warmed to rt and stirred for an additional 3 h. The mixture was quenched by slow addition of aqueous $NaHCO_3$ (150 mL) at 0 °C. The mixture was extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (250 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-20% EtOAc in petroleum ether) to give 1-(tert-butyl) 3-methyl 5-fluoropiperidine-1,3-dicarboxylate (4.5 g, 45% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 262.2 (M+H).

Step B. 1-(tert-butyl) 3-methyl 5-fluoro-3-(methyl-d3)piperidine-1,3-dicarboxylate. To a solution of 1-(tert-butyl) 3-methyl 5-fluoropiperidine-1,3-dicarboxylate (3.0 g, 12 mmol) in THF (30.0 mL) at -70 °C was added LiHMDS (1.0 M in THF; 17 ml) dropwise. The reaction was stirred for 1 h at -70 °C and then CD_3I (2.1 ml, 34 mmol) was dropwise. The

reaction was warmed to rt and stirred for 2 h after which it was diluted with H_2O (30 mL) and extracted with EtOAc (40 mL x 2). The combined organic layers were washed with brine. dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-20% EtOAc in petroleum ether) to give 1-(tert-butyl) 3-methyl 5-fluoro-3-(methyl-d3)piperidine-1,3-dicarboxylate (2.9 g, 90.75%) as a pale yellow liquid. LCMS (MM-ES+APCI, Pos): m/z 223.1 (M+H-tBu).

Step C. 1-(tert-butoxycarbonyl)-5-fluoro-3-(methyl-d3)piperidine-3-carboxylic acid. To a solution of 1-(tert-butyl) 3-methyl 5-fluoro-3-(methyl-d3)piperidine-1,3-dicarboxylate (2.9 g, 11 mmol) in THF (29 mL), MeOH (29 mL), and H_2O (29 mL) was added $LiOH·H_2O$ (1.3 g, 31 mmol). The reaction was stirred at rt for 2 h and then it was concentrated under reduced pressure. The residue was diluted with water (30 mL) and extracted with EtOAc (20mL). The aqueous layer was acidified to pH 2 with 1 M HCl and then extracted with EtOAc (40 mL x 2). The organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 1-(tert-butoxycarbonyl)-5-fluoro-3-(methyl-d3)piperidine-3-carboxylic acid (2.7 g, 98%) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 209.0 (M+H-tBu).

Step D. tert-butyl 5-fluoro-3-isocyanato-3-(methyl-d3)piperidine-1-carboxylate. To a solution of 1-(tert-butoxycarbonyl)-5-fluoro-3-(methyl-d3)piperidine-3-carboxylic acid (2.7 g, 10 mmol) in toluene (27 mL) was added Et_3N (1.5 mL, 10 mmol) and diphenylphosphoryl azide (2.4 mL, 11 mmol). The resulting reaction mixture was heated to 90 °C for 1.5 h and then it was diluted with water (30 mL) and extracted with diethyl ether (40 mL x 2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 5-fluoro-3-isocyanato-3-(methyl-d3)piperidine-1-carboxylate (2.4 g, 91%) as a pale-yellow liquid, which was taken onto the next step without further purification.

Step E. tert-butyl 3-amino-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate. To a solution of tert-butyl 5-fluoro-3-isocyanato-3-(methyl-d3)piperidine-1-carboxylate (2.4 g, 10 mmol) in THF (49 mL) was added 2 N NaOH (49 mL). The reaction was stirred at rt for 2 h and then it was diluted with H_2O (30 mL) and extracted with EtOAc (50 mL x 4). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-10% MeOH in DCM) to give tert-butyl 3-amino-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate (1.0 g, 47%) as a pale yellow liquid. LCMS (MM-ES+APCI, Pos): m/z 236.3 (M+H).

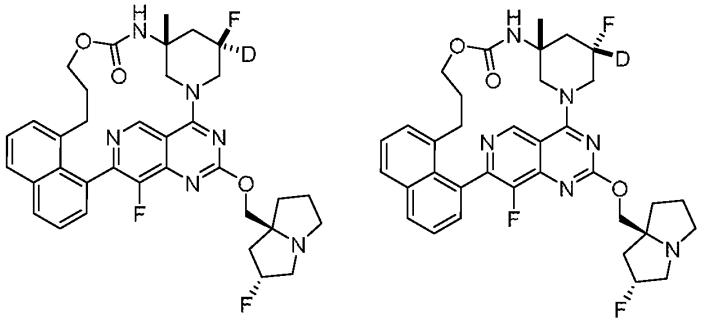
Step F. tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (1.1 g, 1.5 mmol) and DIPEA (0.55 mL, 3.0 mmol) in DCM (11 mL) was added tert-butyl 3-amino-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate (0.50 g, 2.2 mmol). The reaction was stirred for 12 h and then it was diluted with water (30 ml) and extracted with DCM (30ml x 3). Then combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-30% EtOAc in hexanes) to give tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate (1.0 g, 78%) as an off white solid. LCMS (MM-ES+APCI, Pos): m/z 858.4 (M+H).

Step G. 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (5-fluoro-3-(methyl-d3)piperidin-3-yl)carbamate. To a solution of tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate (1.0 g, 1.4 mmol) in DCM (10 mL) at 0 °C was added TFA (3.0 mL). The reaction was stirred for 2 h and then it was diluted with water (30 ml) and extracted with DCM (20 ml). Then aqueous layer was neutralized to pH 7 with saturated aq. $NaHCO_3$ solution and then extracted with DCM (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by C_{18} column chromatography (40% MeCN in H_2O) to give 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (5-fluoro-3-(methyl-d3)piperidin-3-yl)carbamate (0.40 g, 51%) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 668.4 (M+H).

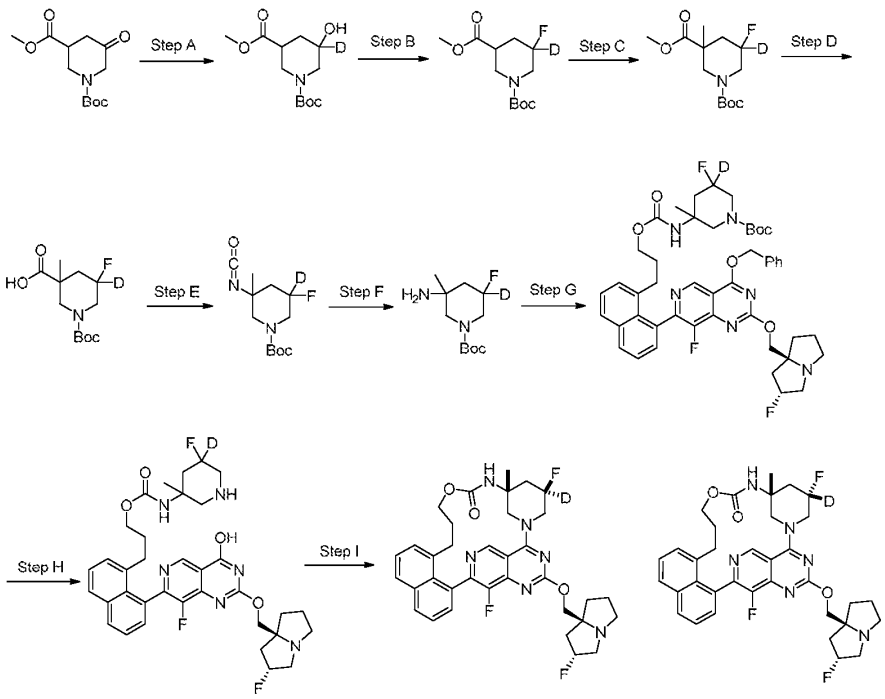
Step H. 1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-(methyl-d_3)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (5-fluoro-3-(methyl-d3)piperidin-3-yl)carbamate (0.40 g, 0.60

mmol) in DMF (4.0 mL) was added bromotris(*N*-methylmethanaminato)-phosphorus hexafluorophosphate (0.23 g, 0.60 mmol) and DIPEA (0.33 mL, 1.8 mmol). The reaction was stirred for 12 h. The mixture was diluted with water (30 ml) and extracted with DCM (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-4% MeOH in DCM) to give 1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-(methyl-d_3)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.011 g, 3%) as an off white solid. LCMS (MM-ES+APCI, Pos): m/z 650.4 (M+H).

Compound 124 and Compound 125



(rel-1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-1^5-d and (rel-1^3R,1^5S)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-1^5-d



Step A. 1-(tert-butyl) 3-methyl 5-hydroxypiperidine-1,3-dicarboxylate-5-d. To a solution of 1-(tert-butyl) 3-methyl 5-oxopiperidine-1,3-dicarboxylate (5.0 g, 19 mmol) in MeOH (50 mL) at 0°C was added $NaBD_4$ (1.2 g, 29 mmol). The reaction was stirred at rt for 2 h. The mixture was diluted with H_2O (150 mL) and then extracted with DCM (150 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 1-(tert-butyl) 3-methyl 5-hydroxypiperidine-1,3-dicarboxylate-5-d (4.5 g, 88.96%) as a pale-yellow liquid, which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 205.0 [M+H-tBu].

Step B. 1-(tert-butyl) 3-methyl 5-fluoropiperidine-1,3-dicarboxylate-5-d. To a solution of 1-(tert-butyl) 3-methyl 5-hydroxypiperidine-1,3-dicarboxylate-5-d (4.5 g, 17 mmol) in DCM (45 mL) at -78°C was added DAST (2.7 ml, 21 mmol). The reaction was stirred at -78°C for 1 h and then it was warmed to rt and stirred for an additional 3 h. The mixture was quenched with saturated $NaHCO_3$ solution (150 mL) then diluted with H_2O (100 mL) and extracted with DCM (200 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15% EtOAc in hexanes) to give 1-(tert-butyl) 3-methyl 5-fluoropiperidine-1,3-dicarboxylate-5-d (1.9 g, 42%) as a yellow liquid. LCMS (MS-ES+APCI, Pos): 206.9 [M+H-tBu].

Step C. 1-(tert-butyl) 3-methyl 5-fluoro-3-methylpiperidine-1,3-dicarboxylate-5-d. To a solution of 1-(tert-butyl) 3-methyl 5-fluoropiperidine-1,3-dicarboxylate-5-d (1.9 g, 7.2 mmol) in THF (18.8 mL) at -78°C was added LiHMDS (1M in THF; 11 ml). The reaction was stirred at -78°C for 1 h then MeI (1.3 ml, 22 mmol). The mixture was warmed to rt and stirred for an additional 3 h. The mixture was quenched with saturated NH_4Cl solution (20 mL) then diluted with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% EtOAc in hexanes) to give 1-(tert-butyl) 3-methyl 5-fluoro-3-methylpiperidine-1,3-dicarboxylate-5-d (1.8 g, 91%) as a yellow liquid. LCMS (MS-ES+APCI, Pos): 221.0 [M+H-tBu].

Step D. 1-(tert-butoxycarbonyl)-5-fluoro-3-methylpiperidine-3-carboxylic-5-d acid. To a solution of 1-(tert-butyl) 3-methyl 5-fluoro-3-methylpiperidine-1,3-dicarboxylate-5-d (1.8 g, 6.5 mmol) in MeOH (9.0 mL) and H_2O (9.0 mL) at 0°C was added $LiOH{\cdot}H_2O$ (0.68 g, 16 mmol). The reaction was stirred at rt for 3 h and then it was quenched with 10% citric acid solution (15 mL). The mixture was diluted with H_2O (20 mL) and extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 1-(tert-butoxycarbonyl)-5-fluoro-3-methylpiperidine-3-carboxylic-5-d acid (1.7 g, 99%) as a yellow solid, which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 207.0 [M+H-tBu].

Step E. tert-butyl 5-fluoro-3-isocyanato-3-methylpiperidine-1-carboxylate-5-d. To a solution of 1-(tert-butoxycarbonyl)-5-fluoro-3-methylpiperidine-3-carboxylic-5-d acid (1.6 g, 6.1 mmol) in toluene (16 mL) was added NEt_3 (0.84 ml, 6.1 mmol) and DPPA (1.4 mL, 6.7 mmol). The reaction was heated to 90 °C for 2 h and then it was diluted with H_2O (60 mL) and extracted with diethyl ether (50 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give tert-butyl 5-fluoro-3-isocyanato-3-methylpiperidine-1-carboxylate-5-d (1.8 g) as a yellow sticky liquid which was taken onto the next step without further purification.

Step F. tert-butyl 3-amino-5-fluoro-3-methylpiperidine-1-carboxylate-5-d. To a solution of tert-butyl 5-fluoro-3-isocyanato-3-methylpiperidine-1-carboxylate-5-d (1.8 g, 6.9 mmol) in THF (36 mL) at 0 °C was added a solution of 2 N NaOH (36 mL). The reaction was stirred at rt for 4 h and then it was diluted with H_2O (90 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (7% MeOH in DCM) to give tert-butyl 3-amino-5-fluoro-3-

methylpiperidine-1-carboxylate-5-d (0.80 g, 56% yield) as a yellow liquid. LCMS (MS-ES+APCI, Pos): 234.1 [M+H].

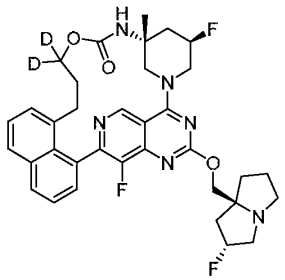
Step G. tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate-5-d. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (1.7 g, 2.3 mmol) in DCM (17 mL) was added tert-butyl 3-amino-5-fluoro-3-methylpiperidine-1-carboxylate-5-d (0.80 g, 3.5 mmol) followed by DIPEA (0.79 mL, 4.6 mmol). The reaction was stirred at rt for 16 h and then it was diluted with H_2O (40 mL) and extracted with DCM (30 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (70% EtOAc in hexanes) to give tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate-5-d (1.1 g, 38%) as a yellow solid. LCMS (MS-ES+APCI, Pos): 856.5 [M+H].

Step H. 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (5-fluoro-3-methylpiperidin-3-yl-5-d)carbamate To a solution of tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate-5-d (1.1 g, 1.3 mmol) in DCM (11 mL) at 0 °C was added TFA (5.5 mL). The reaction was stirred at rt for 4 h. The mixture was quenched by saturated $NaHCO_3$ solution (20 mL) then diluted with H_2O (15 mL) and extracted with DCM (30 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (30-50% MeCN in water) to give 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (5-fluoro-3-methylpiperidin-3-yl-5-d)carbamate (0.5 g, 42%) as a yellow sticky solid. LCMS (MS-ES+APCI, Pos): 666.3 [M+H].

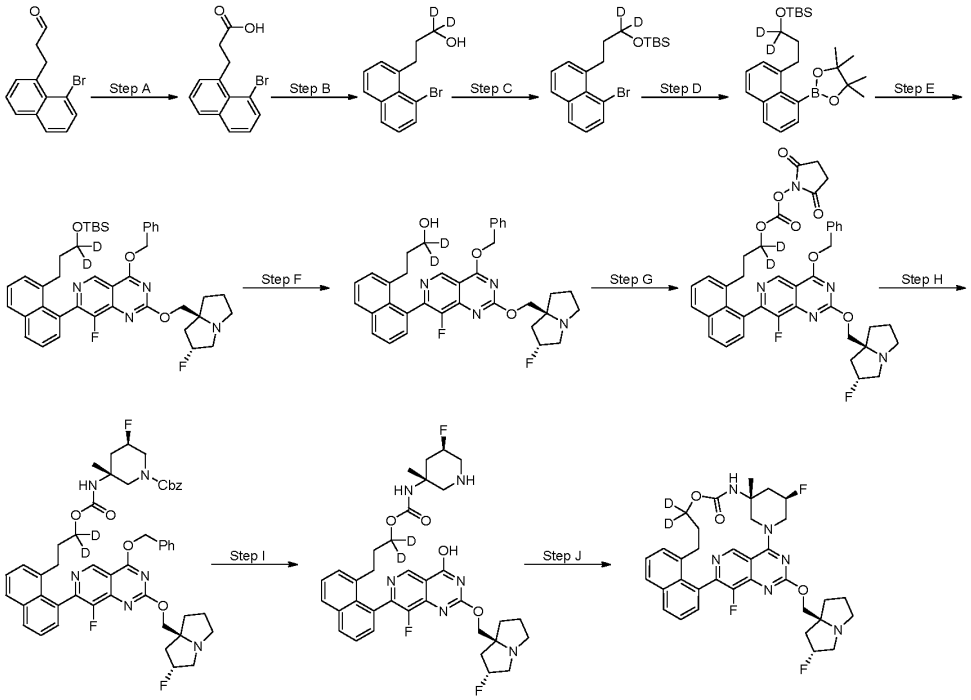
Step I. (rel-1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-1^5-d and (rel-1^3R,1^5S)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-

fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-1^5-d. To solution of 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl (5-fluoro-3-methylpiperidin-3-yl-5-d)carbamate (0.20 g, 0.30 mmol) in DMF (4.0 mL) was added DIPEA (0.15 mL, 0.90 mmol). The solution was stirred at rt for 10 min then BroP (0.11 g, 0.30 mmol) was added portion wise. The reaction was stirred at rt for 16 h and then it was diluted H_2O (15 mL) and then extracted with EtOAc (30 mL x 3). The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (8% MeOH in DCM) to collect two separate product peaks. The fractions containing one product was purified by preparative HPLC (MeCN in 0.05% aqueous TFA) to give (rel-1^{3}R,1^{5}R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-1^5-d (0.040 g, 10%). LCMS (MS-ES+APCI, Pos): 648.1 (M+H). The fractions containing one product was purified by preparative HPLC (MeCN:MeOH:THF [45:45:10] in aqueous 0.05% TFA) to give (rel-1^{3}R,1^{5}S)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-1^5-d (0.014 g, 4%). LCMS (MS-ES+APCI, Pos): 648.4 (M+H).

Compound 126



(1^{3}R,1^{5}R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-6,6-d2



Step A. 3-(8-bromonaphthalen-1-yl)propanoic acid. To a solution of 3-(8-bromonaphthalen-1-yl) propanal (16 g, 61 mmol) in DMF (160 mL) was added Oxone (19 g, 61 mmol). The reaction mixture was stirred at rt for 1 h and then it was diluted with water (500 mL), basified with 1 N NaOH and then extracted with EtOAc (500 mL x 3). The aqueous layer was acidified with 1 M HCl and extracted with EtOAc (500 mL x 2). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 3-(8-bromonaphthalen-1-yl) propanoic acid (13 g, 61% yield) as a light yellow solid.

Step B. 3-(8-bromonaphthalen-1-yl) propan-1,1-d2-1-ol. To a solution of 3-(8-bromonaphthalen-1-yl) propanoic acid (13 g, 47 mmol) in THF (260 mL) at -70 °C was added $LiAlD_4$ (2.4 g, 47 mmol) portion wise. The reaction was stirred at -70 °C for 2 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (22% EtOAc in Hexane) to give 3-(8-bromonaphthalen-1-yl) propan-1,1-d2-1-ol (5.6 g, 42% yield) as a light yellow liquid.

Step C. (3-(8-bromonaphthalen-1-yl) propoxy-1,1-d2)(tert-butyl)dimethylsilane. To a solution of (8-bromonaphthalen-1-yl) propan-1,1-d2-1-ol (5.6 g, 21 mmol) in THF (56 mL) was added imidazole (4.2 g, 63 mmol) and TBSCl (4.7 g, 32 mmol). The reaction was stirred

at rt for 1 h and then it was diluted with H_2O (100 mL) and then extracted with EtOAc (100 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% Hexane) to give (3-(8-bromonaphthalen-1-yl) propoxy-1,1-d2) (tert-butyl) dimethylsilane (5.6 g, 25% yield) as a light yellow liquid.

Step D. tert-butyldimethyl(3-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy-1,1-d2)silane. To a solution of (3-(8-bromonaphthalen-1-yl) propoxy-1,1-d2) (tert-butyl) dimethyl silane (5.6 g, 15 mmol) in 1,4-dioxane (110 mL) was added KOAc (4.2 g, 44 mmol) and B_2Pin_2 (5.4 g, 22 mmol). The solution was sparged with N_2 gas for 10 min, then $PdCl_2$(dppf) (1.1 g, 1.5 mmol) was added. The reaction was heated to 90 °C for 18 h and then it was diluted with H_2O (100 mL) and then extracted with EtOAc (100 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1% EtOAc in hexanes) to give (tert-butyldimethyl(3-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy-1,1-d2)silane (2.8 g, 27% yield) as a colorless liquid. LCMS (MS-ES+APCI, Pos): 429.4 [M+H].

Step E. 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl) oxy)propyl-3,3-d2)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy) pyrido[4,3-d] pyrimidine (2.0 g, 4.4 mmol) in 1,4-dioxane (27 mL) and H_2O (3 mL) was added Cs_2CO_3 (2.5 g, 1.3 mmol) and (tert-butyldimethyl(3-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy-1,1-d2)silane (2.8 g, 6.5 mmol). The reaction was sparged with N_2 for 10 min and then mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.31 g, 0.43 mmol) was added. The reaction was stirred at 90 °C for 1 h and then it was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL × 3) The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (33% EtOAc in hexanes) to give 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl) oxy) propyl-3,3-d2) naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy) pyrido[4,3-d] pyrimidine (1.8 g, 39% yield) as a light-yellow liquid. LCMS (MS-ES+APCI, Pos): 713.4 [M+H].

Step F. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy) pyrido[4,3-d] pyrimidin-7-yl) naphthalen-1-yl) propan-1,1-d2-1-ol. To a

solution of 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl) oxy) propyl-3,3-d2) naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy) pyrido[4,3-d] pyrimidine (1.8 g, 2.5 mmol) in DCM (18 mL) at 0°C was added a solution of TFA (0.64 mL, 6.3 mmol) in DCM (6 mL). The reaction was allowed to warm to rt for 1 h and then it was diluted with H_2O (50 mL) and extracted with DCM (30 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40% EtOAc in hexanes) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy) pyrido[4,3-d] pyrimidin-7-yl) naphthalen-1-yl) propan-1,1-d2-1-ol (1.2 g, 79% yield) as an off white solid. LCMS (MS-ES+APCI, Pos): 599.4 [M+H].

Step G. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl-1,1-d2 (2,5-dioxopyrrolidin-1-yl) carbonate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy) pyrido[4,3-d] pyrimidin-7-yl) naphthalen-1-yl) propan-1,1-d2-1-ol (1.2 g, 2.0 mmol) and pyridine (0.70 mL,10 mmol) in DCM (12 mL) was added bis(2,5-dioxopyrrolidin-1-yl) carbonate (2.6 g, 10 mmol). The reaction was stirred at rt for 1 h and then it was diluted with H_2O (30 mL) and extracted with DCM (30 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl-1,1-d2 (2,5-dioxopyrrolidin-1-yl) carbonate (1.0 g) as an off white solid, which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 740.3 [M+H].

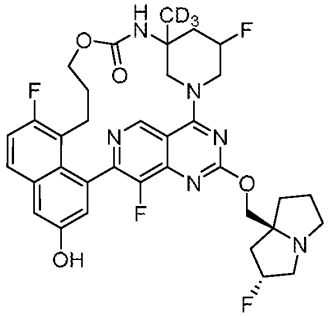
Step H. benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy-1,1-d2)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylat. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl-1,1-d2 (2,5-dioxopyrrolidin-1-yl) carbonate (1.0 g, 1.4 mmol) and pyridine (0.50 mL, 6.8 mmol) in DCM (10 mL) was added benzyl (3R,5R)-3-amino-5-fluoro-3-methylpiperidine-1-carboxylate (0.34 g, 1.4 mmol). The reaction was stirred at rt for 1 h and then it was diluted with water (30 mL) and extracted with DCM (30 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by Al_2O_3 column chromatography (80% EtOAc in hexanes) to give benzyl (3R,5R)-3-(((3-(8-

(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy-1,1-d2)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.72 g, 27% yield) as an off white solid. LCMS (MS-ES+APCI, Pos): 891.5 [M+H].

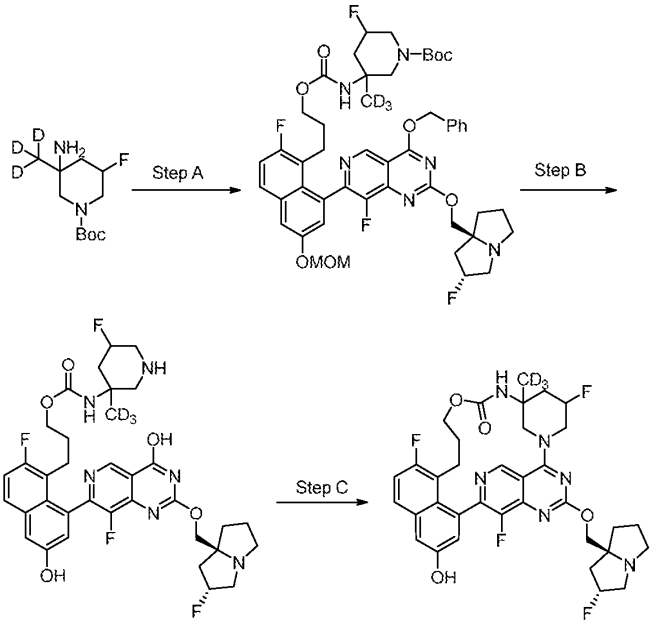
Step I. 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl-1,1-d2 ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate. To a solution of 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl-1,1-d2 ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.72 g, 0.80 mmol) in MeOH (7.2 mL) was added 10% Pd/C (0.72 g).The reaction was stirred at rt under an atmosphere of H_2 for 4 h. The slurry was filtered over Celite, and the pad was washed with MeOH (15 mL x 3). The filtrate was concentrated under reduced pressure to give 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl-1,1-d2 ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.42 g, 78% yield), which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 667.4 [M+H].

Step J. (1^3R,1^5R)-1^5,2^8-difluoro-22-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-6,6-d_2. To solution of 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl-1,1-d2 ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.40 g, 0.59 mmol) in DMF (4 mL) was added BrOP (0.27 g, 0.71 mmol) and DIPEA (0.70 mL, 0.89 mmol). The reaction was stirred at rt for 12 h and then it was diluted water (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by C_{18} column chromatography (58% MeCN in H_2O) to give (1^3R,1^5R)-1^5,2^8-difluoro-22-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-6,6-d_2 (0.048 g, 12% yield) as an off white solid. LCMS (MS-ES+APCI, Pos): 649.4 [M+H].

Compound 127



$1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-(methyl-d3)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one:



Step A. tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (1.2 g, 1.4 mmol) and pyridine (0.33 mL, 4.2 mmol) in DCM (12 mL) was added tert-butyl 3-amino-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate (0.48 g, 2.1 mmol). The reaction was stirred for

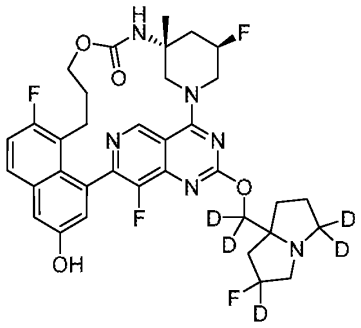
12 h and then it was diluted with water (20 ml) and then extracted with DCM (20 ml x 2). The combined organic layer was dried over anhydrous Na_2SO_4, filter and concentrated under reduced pressure. The residue was purified by neutral alumina column chromatography (0-30% EtOAc in hexanes) to give tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate (0.60 g, 46% yield) as an off white solid. LCMS (MS-ES+APCI, Pos): 936.6 [M+H].

Step B. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl (5-fluoro-3-(methyl-d3)piperidin-3-yl)carbamate. To a solution of tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate (0.60 g, 0.64 mmol) in DCM (6.0 mL) at 0 °C was added TFA (1.8 mL). The reaction was stirred at rt for 2 h and then it was diluted with water (10 mL). The mixture was neutralized with saturated aq. $NaHCO_3$ solution and extracted with EtOAc (15 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by C_{18} column chromatography (50-70% MeCN in H_2O) to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl (5-fluoro-3-(methyl-d3)piperidin-3-yl)carbamate (0.40 g, 89% yield) as an off white solid. LCMS (MS-ES+APCI, Pos): 702.4 [M+H].

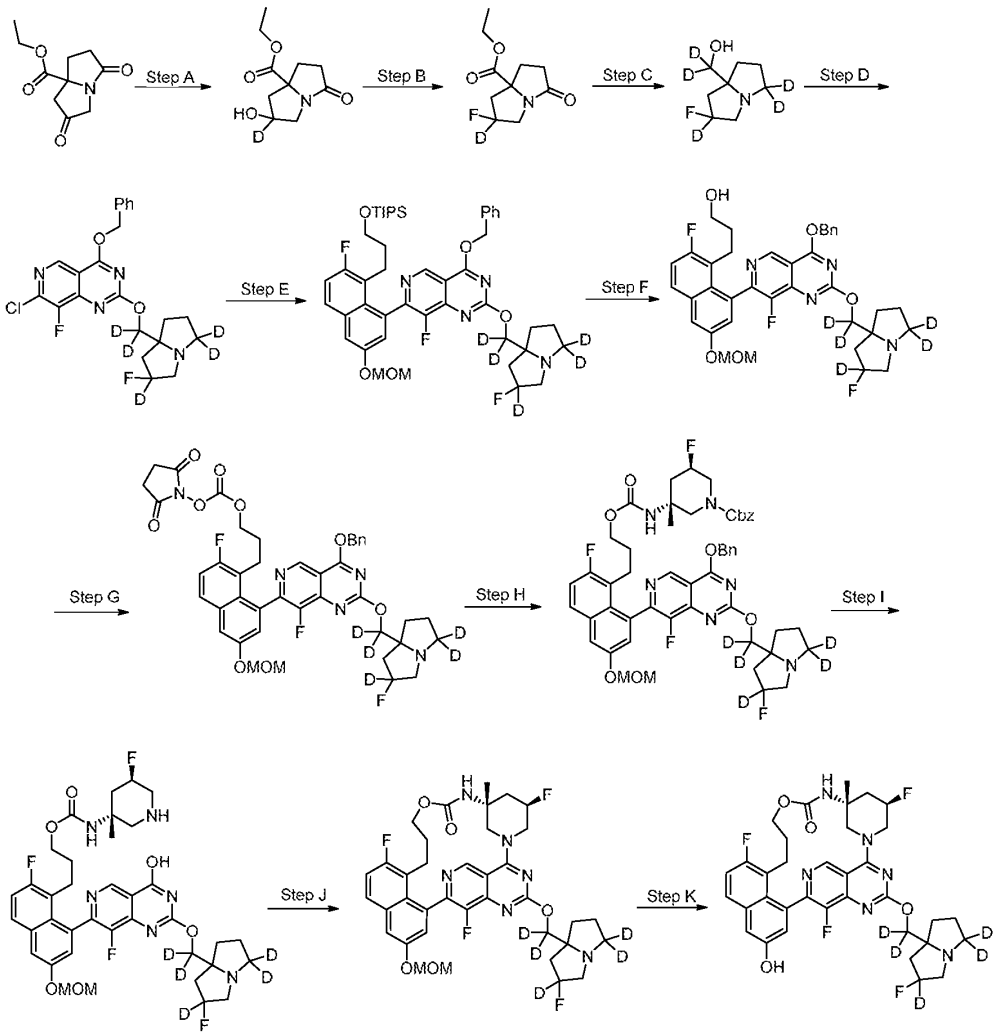
Step C. $1^5,2^8,3^7$-trifluoro-22-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-33-hydroxy-13-(methyl-d3)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl (5-fluoro-3-(methyl-d3)piperidin-3-yl)carbamate (0.40 g, 0.57 mmol) in DMF (4.0 mL) was added BroP (0.26 g, 0.68 mmol) and DIPEA (30 mL, 1.7 mmol). The reaction was stirred at rt for 12 h and then it was diluted with water (20 mL) and extracted with DCM (30 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-3% MeOH in DCM) to give $1^5,2^8,3^7$-trifluoro-22-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-

(methyl-d3)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.017 g, 4% yield) as an off white solid. LCMS (MM-ES+APCI, Pos): 684.3 [M+H].

Compound 128



((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. ethyl 2-hydroxy-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate-2-d.

To a solution of ethyl 2,5-dioxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate (5.0 g, 24 mmol) in EtOH (50 mL) at 0 °C was added $NaBD_4$ (0.39 g, 9.5 mmol). The reaction was stirred at 0 °C for 30 min and then it was quenched with water (5 mL). The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (6% MeOH in DCM) to give ethyl 2-hydroxy-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate-2-d (2.5 g, 49% yield) as a colorless liquid. LCMS (MS-ES+APCI, Pos): 214.9 [M+H].

Step B. ethyl 2-fluoro-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate-2-d. To a solution of ethyl 2-hydroxy-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate-2-d (2.5 g, 12 mmol)

in DCM (25 mL) at -78 °C was added DAST (2.8 g, 18 mmol). The reaction was warmed to rt and stirred for 4 h. The mixture was diluted with water (250 mL) and then extracted with DCM (100 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give ethyl 2-fluoro-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate-2-d as a yellow liquid (2.0 g), which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 217.0 [M+H].

Step C. (2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methan-d2-ol. To a solution of ethyl 2-fluoro-5-oxotetrahydro-1H-pyrrolizine-7a(5H)-carboxylate-2-d (2.0 g, 9.2 mmol) in THF (20 mL) at 0 °C was added $LiAlD_4$ (0.58 g, 14 mmol). The reaction was stirred at 70 °C for 3 h and then it was quenched with water (2.2 mL) followed by 15% NaOH solution (0.80 mL), The mixture was filtered and filtrate was concentrated under reduced pressure to give 2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methan-d2-ol (0.80 g), which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 165.2 [M+H].

Step D. 4-(benzyloxy)-7-chloro-8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidine. To a solution of 2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methan-d2-ol (0.61, 3.7 mmol) and 4-(benzyloxy)-2,7-dichloro-8-fluoropyrido[4,3-d]pyrimidine (1.0 g, 3.1 mmol) in THF (10 mL) was added DIPEA (1.5 mL, 9.3 mmol). The reaction was stirred at 50 °C for 21 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40% EtOAc in hexanes) to give 4-(benzyloxy)-7-chloro-8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidine (0.30 g, 18%) as yellow solid. LCMS (MS-ES+APCI, Pos): 452.2 [M+H].

Step E. 4-(benzyloxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-7-chloro-8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidine (1.1 g, 2.4 mmol) and (3-(2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)triisopropylsilane (1.5 g, 2.9 mmol) in 1,4-dioxane (11.0 mL) and H_2O (1.1 mL) was added Cs_2CO_3 (2.3 g, 7.3 mmol) and mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.17 g, 0.24 mmol). The solution was sparged with N_2 gas for 5 min and then it was heated at 100 °C for 1 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (30 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (35% EtOAc in hexanes) to give 4-(benzyloxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidine (1.0 g, 49 % yield) as a yellow oil. LCMS (MS-ES+APCI, Pos): 836.6 [M+H].

Step F. 3-(8-(4-(benzyloxy)-8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propan-1-ol. To a solution of 4-(benzyloxy)-8-fluoro-7-(7-fluoro-3-(methoxymethoxy)-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidine (0.90 g, 1.1 mmol) in MeCN (9.0 mL) was added pyridine (9.0 mL) and HF·pyridine (4.5 mL). The reaction was stirred at rt for 1 h and then it was concentrated under reduced pressure. The residue was diluted with water (100 mL) and extracted with DCM (50 mL × 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with n-pentane to give 3-(8-(4-(benzyloxy)-8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propan-1-ol (0.55 g, 75% yield) as a white solid. LCMS (MS-ES+APCI, Pos): 680.4 [M+H].

Step G. 3-(8-(4-(benzyloxy)-8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate .

To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propan-1-ol (0.55 g, 0.82 mmol) in DCM (5.5 mL) and pyridine (1.7 mL) was added bis(2,5-dioxopyrrolidin-1-yl) carbonate (0.63 g, 2.2 mmol). The reaction was stirred at rt for 1 h and then it was diluted with water (70 mL) and extracted with DCM (35 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(8-(4-(benzyloxy)-8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.70 g) as a yellow liquid, which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 821.5 [M+H].

Step H. benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-

(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.70 g, 0.85 mmol) and benzyl 3-amino-5-fluoro-3-methylpiperidine-1-carboxylate (0.22 g, 0.85 mmol) in DCM (7 mL) was added pyridine (2.1 mL). The reaction was stirred at rt for 16 h. The mixture was diluted with water (70 mL) and then extracted with DCM (35 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by Al_2O_3 column chromatography (60% EtOAc in hexanes) to give benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.70 g, 84% yield) as a white solid. LCMS (MS-ES+APCI, Pos): 972.6 [M+H].

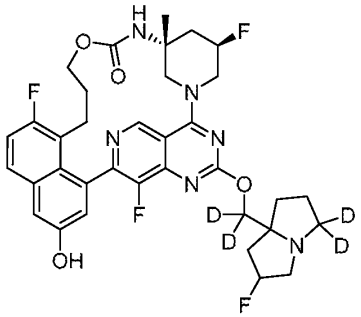
Step I. 3-(2-fluoro-8-(8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate. To a solution of benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.70 g,0.72 mmol) in THF (7.0 mL) was added 10% Pd/C (0.35 g). The reaction was stirred at rt under an atmosphere of H_2(g) for 6 h. The mixture was filtered through Celite and the pad was washed with THF (10 mL x 3). The filtrate was concentrated under reduced pressure. The residue was triturated with n-pentane to give 3-(2-fluoro-8-(8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.45 g, 84% yield). LCMS (MS-ES+APCI, Pos): 748.3 [M+H].

Step J. ((13R,15R)-15,28,37-trifluoro-22-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)-33-(methoxymethoxy)-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(2-fluoro-8-(8-fluoro-2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.40 g, 0.53 mmol) in DMF (4 mL) was added DIPEA (0.27 mL, 1.6 mmol). The mixture was stirred for 30 min and then BroP

(0.24 g, 0.64 mmol) was added. The reaction was stirred at rt for 16 hours then it was diluted water (50 mL) and extracted with EtOAc (20 mL x 2). The organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% MeOH in DCM) to give ((13R,15R)-15,28,37-trifluoro-22-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)-33-(methoxymethoxy)-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.14 g, 36%) as an off white solid. LCMS (MS-ES+APCI, Pos): 730.4 (M+H).

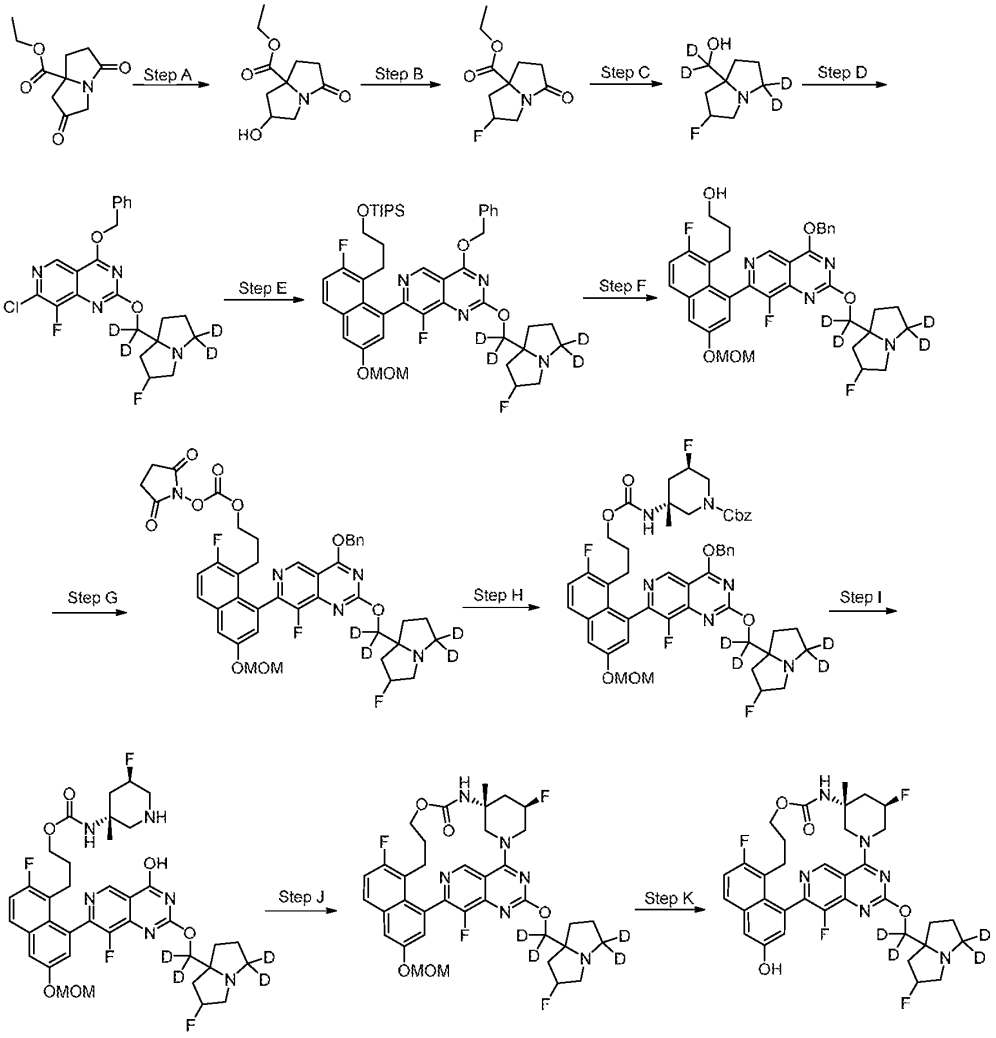
Step K. (((13R,15R)-15,28,37-trifluoro-22-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)-33-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of (((13R,15R)-15,28,37-trifluoro-22-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)-33-(methoxymethoxy)-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.13 g, 0.17 mmol) in DCM (1.3 mL) was added 4 M HCl in 1,4-dioxane (0.65 mL). The reaction was stirred at rt for 30 min and then it was concentrated under reduced pressure. The residue was diluted with saturated solution of $NaHCO_3$ (10 mL) and then extracted with DCM (15 mL x 2). The organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by neutral alumina column chromatography (0-10% MeOH in DCM containing 0.1% NH_3) to give (((13R,15R)-15,28,37-trifluoro-22-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)-33-hydroxy-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.016 g, 13.10% yield) as an off white solid. LCMS (MS-ES+APCI, Pos): 686.4 (M+H).

Compound 129



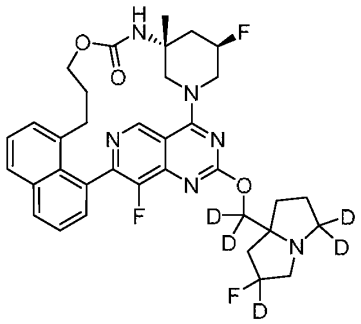
(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-5,5-d_2)methoxy-d2)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-

3(1,8)-naphthalenacyclononaphan-8-one

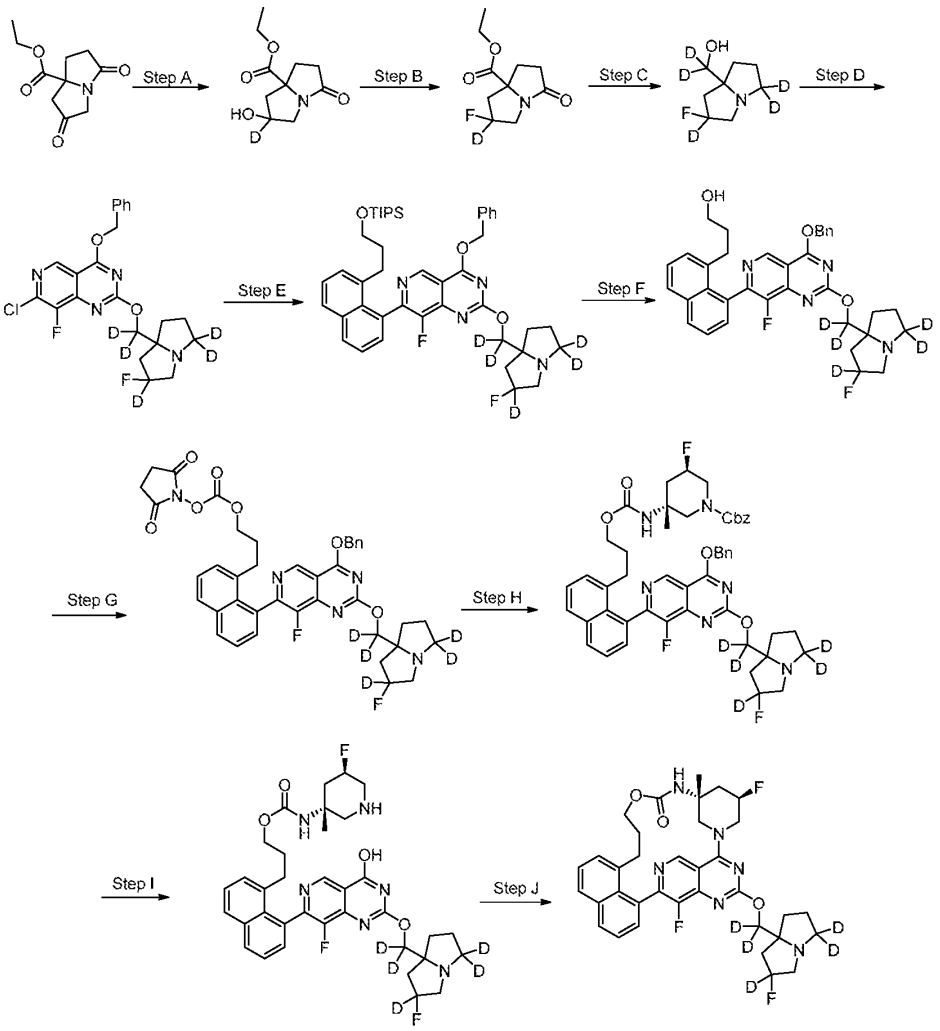


Step A was performed with $NaBH_4$ following the procedure of Compound 128. Steps B-K were performed similarly to Compound 128. LCMS (MM-ES+APCI, Pos): m/z 685.3 (M+H).

Compound 132

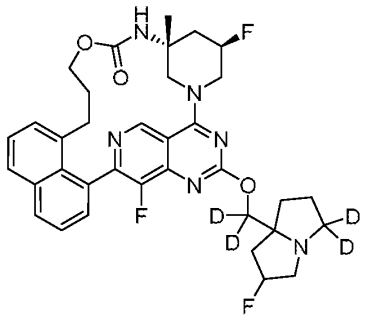


(1^3R,1^5R)-1^5,2^8-difluoro-2^2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-2,5,5-d3)methoxy-d2)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one

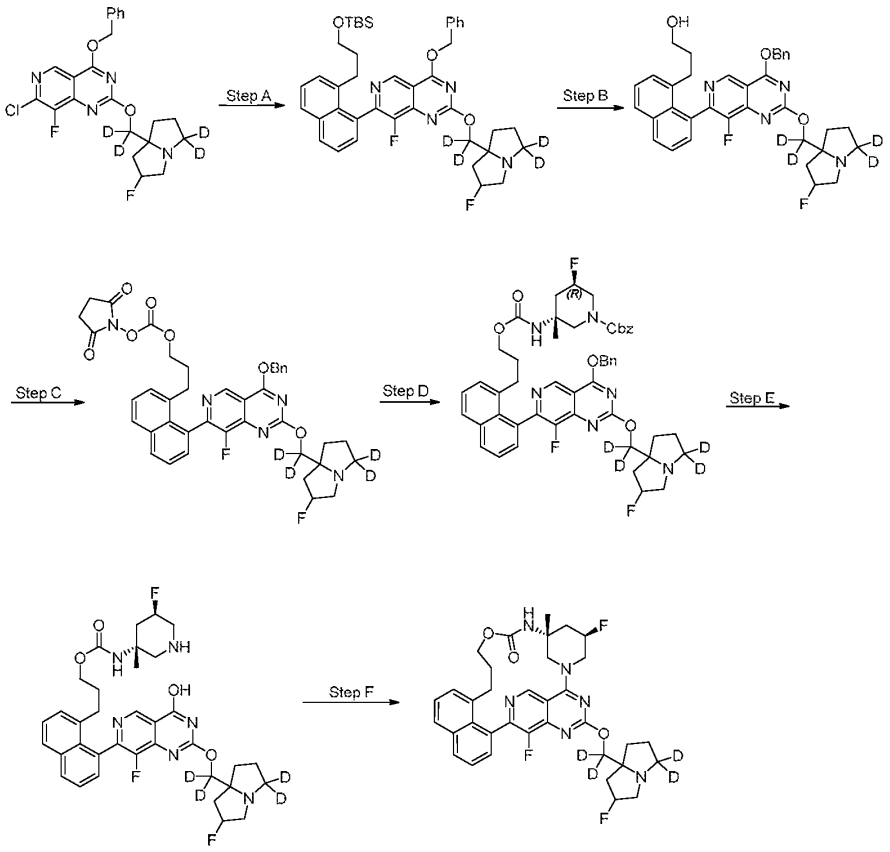


Steps A-J were performed with Intermediate 1 (Step E) by following the procedure of Compound 128. LCMS (MM-ES+APCI, Pos): m/z 652.4 (M+H).

Compound 134

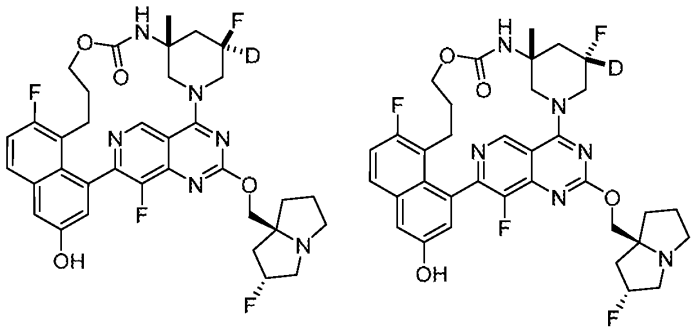


(1^3R,1^5R)-1^5,2^8-difluoro-2^2-((2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl-5,5-d2)methoxy-d2)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one

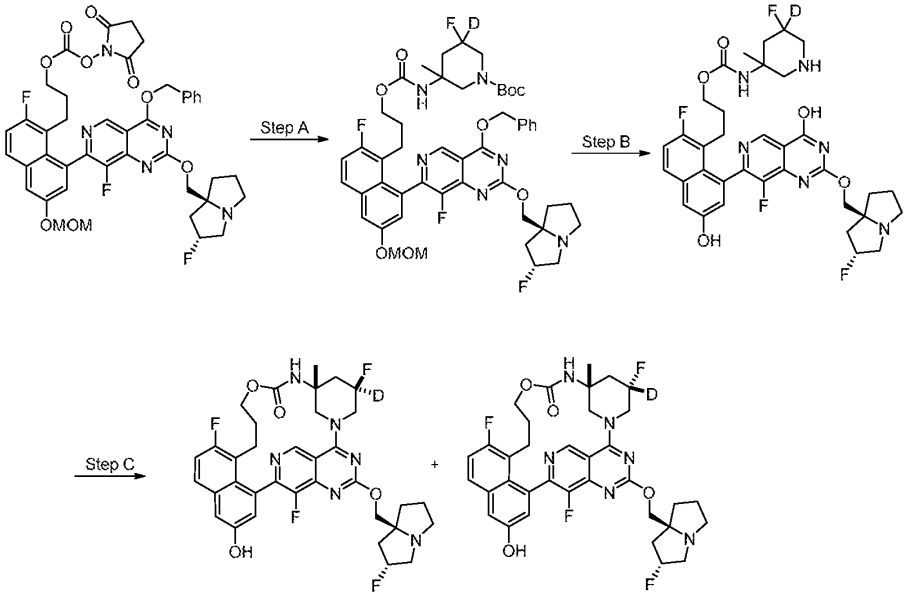


Steps A-F were by following the procedure of Compound 128 (Steps E-J). LCMS (MM-ES+APCI, Pos): m/z 651.4 (M+H).

Compound 130 and Compound 131



(rel-1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-15-d and (rel-1^{3}R,1^{5}S)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-15-d



Step A. tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate-5-d. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-

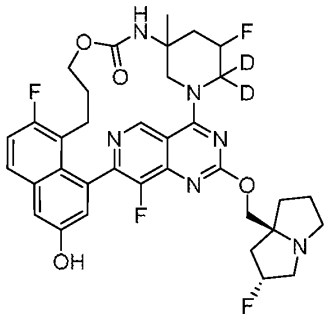
(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (1.4 g, 1.7 mmol) in DCM (14 mL) was added tert-butyl 3-amino-5-fluoro-3-methylpiperidine-1-carboxylate-5-d (0.60 g, 2.6 mmol) and pyridine (0.27 mL, 3.4 mmol). The reaction was stirred at rt for 16 h and then it was diluted with water (30 mL) and extracted with DCM (30 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by neutral alumina column chromatography (65% EtOAc in hexanes) to give tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate-5-d (1.1 g, 46% yield) as a yellow liquid. LCMS (MS-ES+APCI, Pos): 934.5 [M+H].

Step B. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl (5-fluoro-3-methylpiperidin-3-yl-5-d)carbamate. To a solution of tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate-5-d (1.1 g, 1.2 mmol) in DCM (11 mL) at 0 °C was added TFA (5.5 mL). The reaction was stirred at rt for 16 h and then it was quenched with saturated $NaHCO_3$ solution (30 mL). The mixture was diluted with water (20 mL) and extracted with DCM (50 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl (5-fluoro-3-methylpiperidin-3-yl-5-d)carbamate (0.60 g, 73% yield) as a yellow solid, which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 700.3 [M+H].

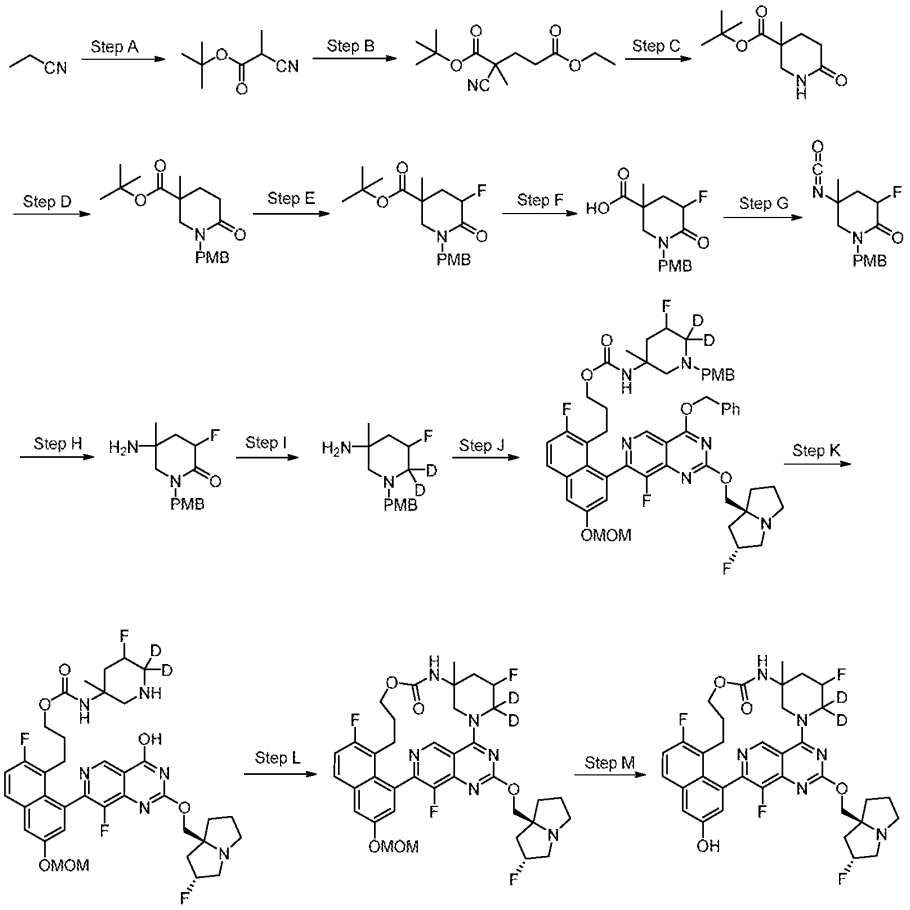
Step C. (rel-1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-15-d and (rel-1^3R,1^5S)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-15-d. To solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl (5-fluoro-3-methylpiperidin-3-yl-5-d)carbamate (0.60

g, 0.86 mmol) in DMF (12 mL) was added DIPEA (0.44 mL, 2.6 mmol). The mixture was stirred at rt for 15 min and then, BrOP (0.39 g, 1.0 mmol) was added portion-wise. The reaction was stirred at rt for 16 h and then it was diluted with water (20 mL) and extracted with EtOAc (30 mL x 3). The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (7% MeOH in DCM). The fractions containing the product were purified by preparative HPLC (MeCN:MeOH [1:1] in 0.05% aqueous formic acid) to give (rel-1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-15-d (0.022 g, 4% yield) as a white solid and rel-1^3R,1^5S)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-15-d (0.008 g, 1% yield) as a white solid. LCMS (MS-ES+APCI, Pos): 682.3 (M+H). LCMS (MS-ES+APCI, Pos): 682.3 (M+H).

Compound 133



1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-1^6,1^6-d_2



Step A. tert-butyl 2-cyanopropanoate. To a solution of diisopropyl amine (77 mL, 550 mmol) in THF (400 mL) at -78 °C was added n-BuLi (1.6 M in THF; 340 mL, 550 mmol). The reaction was stirred at this temperature for 1 h, propionitrile (26 mL, 360 mmol) was added dropwise. The reaction was stirred at -78 °C for 1 h, Boc_2O (88 mL, 380 mmol) was added. The reaction was stirred at this temperature for 1.5 h and then it was warmed to rt and quenched with aq. NH_4Cl solution (500 mL), The mixture was extracted with Et_2O (500 mL x 2). The combined organic layers were washed with 1 M HCl solution (1000 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give tert-butyl 2-cyanopropanoate (56 g) as a pale-yellow liquid, which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 155.1 [M+H].

Step B. 1-(tert-butyl) 5-ethyl 2-cyano-2-methylpentanedioate. To a solution of tert-butyl 2-cyanopropanoate (56 g, 360 mmol) in THF (560 mL) at -78 °C was added LiHMDS (1.0 M

in THF; 540 mL). The reaction was stirred at this temperature for 1 h and then, ethyl 3-bromopropanoate (46 mL, 360 mmol) was added dropwise. The reaction was warmed to rt and then stirred for 4 h. The reaction mixture was quenched with aq. NH_4Cl solution (500 mL) and then extracted with EtOAc (500 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using (0-6% EtOAc in hexanes) to give 1-(tert-butyl) 5-ethyl 2-cyano-2-methylpentanedioate (49 g, 53% yield) as a pale-yellow liquid. LCMS (MS-ES+APCI, Pos): 155.1 [M+H-Boc].

Step C. tert-butyl 3-methyl-6-oxopiperidine-3-carboxylate. To a solution of 1-(tert-butyl) 5-ethyl 2-cyano-2-methylpentanedioate (12 g, 48 mmol) in MeOH (120 mL) was added washed Raney Ni (2.45 g, 20% w/w). The reaction mixture was sparged with H_2 gas for 2 min and then it was heated to 65 °C in a reactor with H_2 gas pressure of 45 bar for 16 h. The mixture was diluted with MeOH (50 mL) and decanted (5 X). The decanted layers were filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was triturated with n-hexane to give tert-butyl 3-methyl-6-oxopiperidine-3-carboxylate (34 g, 83% yield) as an off white solid. LCMS (MS-ES+APCI, Pos): 158.1 [M+H-^{t}Bu].

Step D. tert-butyl 1-(4-methoxybenzyl)-3-methyl-6-oxopiperidine-3-carboxylate. To a solution of tert-butyl 3-methyl-6-oxopiperidine-3-carboxylate (34 g, 160 mmol) in DMF (340 mL) at 0 °C was added NaH (60% in mineral oil; 9.6 g, 240 mmol) portion wise. To this reaction mixture was added PMBCl (32 mL, 240 mmol). The reaction was stirred at rt for 4 h and then it was diluted with H_2O (1000 mL) and extracted with EtOAc (500 mL x 2). The combined organic layers were washed with water (1000 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-30% EtOAc in hexanes) to give tert-butyl 1-(4-methoxybenzyl)-3-methyl-6-oxopiperidine-3-carboxylate (34 g, 63% yield) as a colorless liquid. LCMS (MS-ES+APCI, Pos): 667.4 [2M+H].

Step E. tert-butyl 5-fluoro-1-(4-methoxybenzyl)-3-methyl-6-oxopiperidine-3-carboxylate. To a solution of tert-butyl 1-(4-methoxybenzyl)-3-methyl-6-oxopiperidine-3-carboxylate (34 g, 100 mmol) in THF (335 mL) at -78 °C was added LDA (2.0 M in THF; 100 mL) dropwise. Then, N-fluorobenzenesulfonimide (48 g, 150 mmol) was added dropwise at -78 °C. The reaction was stirred at rt for 3 h and then it was quenched with aq. NH_4Cl solution (200 mL). The mixture was extracted with EtOAc (200 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using (0-50% EtOAc in hexanes) to give

tert-butyl 5-fluoro-1-(4-methoxybenzyl)-3-methyl-6-oxopiperidine-3-carboxylate (20 g, 57% yield) as a brown liquid. LCMS (MS-ES+APCI, Pos): 352.3 [M+H].

Step F. 5-fluoro-1-(4-methoxybenzyl)-3-methyl-6-oxopiperidine-3-carboxylic acid. To a stirred solution of tert-butyl 5-fluoro-1-(4-methoxybenzyl)-3-methyl-6-oxopiperidine-3-carboxylate (5.0 g, 14 mmol) in DCM (100 mL) was added 4 M HCl in 1,4-dioxane (25 mL). The reaction was stirred at rt for 16 h and then it was concentrated under reduced pressure. The residue was triturated using n-hexanes to give 5-fluoro-1-(4-methoxybenzyl)-3-methyl-6-oxopiperidine-3-carboxylic acid (3.0 g) as an off white solid. LCMS (MS-ES+APCI, Pos): 296.2 [M+H].

Step G. 3-fluoro-5-isocyanato-1-(4-methoxybenzyl)-5-methylpiperidin-2-one. To a solution of 5-fluoro-1-(4-methoxybenzyl)-3-methyl-6-oxopiperidine-3-carboxylic acid (3.0 g, 10 mmol) in toluene (30 mL) was added NEt_3 (2.9 mL, 20 mmol) and DPPA (3.1 mL, 11 mmol). The reaction was stirred at 90 °C for 4 h. The mixture was diluted with water (100 mL) and extracted with Et_2O (100 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 3-fluoro-5-isocyanato-1-(4-methoxybenzyl)-5-methylpiperidin-2-one (2.0 g) as a pale yellow liquid, which was taken onto the next step without further purification.

Step H. 5-amino-3-fluoro-1-(4-methoxybenzyl)-5-methylpiperidin-2-one. To a solution of 3-fluoro-5-isocyanato-1-(4-methoxybenzyl)-5-methylpiperidin-2-one (2.0 g, 6.8 mmol) in THF (40 mL) was added 2 N NaOH (40 mL). The reaction was stirred at rt for 2 h. The mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-4% MeOH in DCM) to give 5-amino-3-fluoro-1-(4-methoxybenzyl)-5-methylpiperidin-2-one (1.1 g, 60% yield) as a pale-brown liquid. LCMS (MS-ES+APCI, Pos): 267.1 [M+H].

Step I. 5-fluoro-1-(4-methoxybenzyl)-3-methylpiperidin-6,6-d_2-3-amine. To a solution of 5-amino-3-fluoro-1-(4-methoxybenzyl)-5-methylpiperidin-2-one (1.1 g, 4.1 mmol) in THF (11 mL) and MeOD (3.3 mL) was added $CaCl_2$ (0.92 g, 8.3 mmol) and $NaBD_4$ (0.86 g, 21 mmol). The reaction was stirred at rt for 4 h and then it was poured into ice water (250 mL) and vigorously stirred for a few min. The mixture was extracted with DCM (250 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 5-fluoro-1-(4-methoxybenzyl)-3-methylpiperidin-6,6-d_2-3-amine (0.75 g) as a pale-yellow liquid. which was taken onto the next step without further

purification. LCMS (MS-ES+APCI, Pos): 255.2 [M+H].

Step J. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (5-fluoro-1-(4-methoxybenzyl)-3-methylpiperidin-3-yl-6,6-d_2)carbamate. To a solution of 5-fluoro-1-(4-methoxybenzyl)-3-methylpiperidin-6,6-d_2-3-amine (0.75 g, 2.9 mmol) and 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (2.0 g, 2.5 mmol) in DCM (20 mL) was added pyridine (0.59 mL, 7.4 mmol). The reaction was stirred at rt for 16 h. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using (0-17% EtOAc in hexanes) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (5-fluoro-1-(4-methoxybenzyl)-3-methylpiperidin-3-yl-6,6-d_2)carbamate (1.1 g, 47% yield) as a colorless liquid. LCMS (MS-ES+APCI, Pos): 955.5 [M+H].

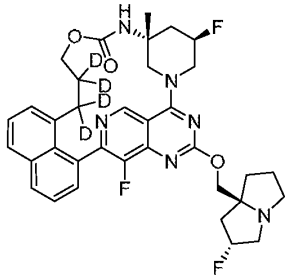
Step K. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (5-fluoro-3-methylpiperidin-3-yl-6,6-d_2)carbamate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (5-fluoro-1-(4-methoxybenzyl)-3-methylpiperidin-3-yl-6,6-d2)carbamate (1.0 g, 1.0 mmol) in MeOH (10 mL) was added 10% Pd/C (1.0 g). The reaction was stirred at rt under an atmosphere of H_2 for 16 h. The mixture was diluted with MeOH (50 mL) and filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was purified by neutral alumina column chromatography using (0-25% MeOH in DCM) to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (5-fluoro-3-methylpiperidin-3-yl-6,6-d_2)carbamate (0.20 g) as a colorless liquid. LCMS (MS-ES+APCI, Pos): 745.3 [M+H].

Step L. 1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-1^6,1^6-d_2. To a solution of 3-(2-

fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl (5-fluoro-3-methylpiperidin-3-yl-6,6-d2)carbamate (0.20 g, 0.26 mmol) in DMF (4.0 mL) was added DIPEA (0.14 mL, 0.80 mmol). The mixture was stirred at rt for 30 min and then BroP (0.13 g, 0.32 mmol) was added. The reaction was stirred at rt for 4 h and then it was diluted with water (100 mL) and extracted with DCM (100 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using (0-10% MeOH in DCM) to give $1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-$1^6,1^6$-d_2 (0.040 g, 21% yield) as an off white solid. LCMS (MS-ES+APCI, Pos): 727.4 [M+H].

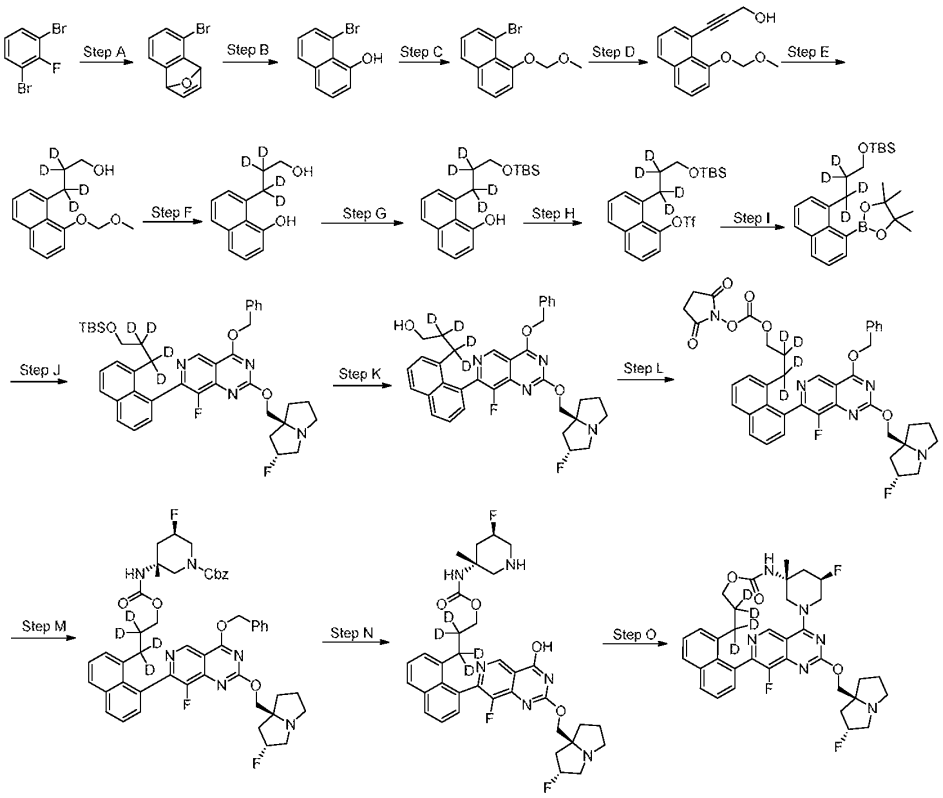
Step M. $1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-$1^6,1^6$-d_2. To a solution of $1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-$1^6,1^6$-d_2 (0.040 g, 0.055 mmol) in DCM (0.80 mL) was added 4 M HCl in 1,4-dioxane (0.080 mL). The reaction was stirred at rt for 30 min and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC (0-40% MeCN in 0.05% aqueous NH_4HCO_3) to give $1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-$1^6,1^6$-d_2 (0.0090 g, 24% yield) as an off white solid. LCMS (MS-ES+APCI, Pos): 683.3 [M+H].

Compound 135



(1^3R,1^5R)-$1^5,2^8$-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)

methoxy)-1[3]-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d] pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-4,4,5,5-d4



Step A. 5-bromo-1.4-di hydro-1,4-epoxynaphthalene. To a solution of 1,3-dibromo-2-fluorobenzene (50 g, 200 mmol) and furan (27 g, 390 mmol) in toluene (750 mL) at – 20 °C was added n-BuLi (1.6 M in hexane; 150 mL)). The mixture was stirred at - 20 °C for 30 min then it was warmed to rt and stirred for 8 h. The mixture was quenched with water (500 mL) and filtered. The aqueous layer was extracted with EtOAc (300 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-10% EtOAc in hexanes) to give 5-bromo-1.4-di hydro-1,4-epoxynaphthalene (18.0 g, 40.98% yield) as a dark yellow liquid. LCMS (MS-ES+APCI, Neg): 221.0 [M-H].

Step B. 8-bromonaphthalen-1-ol. To a solution of 5-bromo-1.4-di hydro-1,4-epoxynaphthalene (19 g, 85 mmol) in MeOH (480 mL) was added HCl (120 mL, 1300 mmol). The reaction was stirred at 60 °C for 6 h and then it was concentrated under reduced

pressure. The residue was purified by silica gel column chromatography (0-1% Et0Ac in hexanes) to give 8-bromonaphthalen-1-ol (13 g, 66% yield).

Step C. 1-bromo-8-(methoxy methoxy) naphthalene. To a solution of 8-bromonaphthalen-1-ol (5.0 g, 22 mmol) and DIPEA (12 mL, 67.24 mmol) in DCM (50 mL) at 0 °C was added chloromethyl methyl ether (4.4g, 29 mmol). The reaction was stirred at 0 °C for 1 h and then it was diluted with water (100 mL) and extracted with EtOAc (3 x50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% EtOAc in hexanes) to give 1-bromo-8-(methoxy methoxy) naphthalene (4.5 g, 75% yield) as a yellow liquid.

Step D. 3-(8-(methoxy methoxy) naphthalen-1-yl) prop-2-yn-1-ol. To a solution of 1-bromo-8-(methoxy methoxy) naphthalene (30 g,110 mmol) in triethylamine (300 mL) was added propargyl alcohol (13 g, 220 mmol), triphenylphosphine (5.8 g, 22 mmol), CuI (2.9 g, 34 mmol) and bis(triphenylphosphine)palladium(II) dichloride (7.9 g, 11 mmol). The reaction was stirred at 80 °C for 5 h. The mixture was diluted with water (500 mL) and EtOAc (500 mL) and filtered. The aqueous layer was extracted with EtOAc (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (35% EtOAc in hexanes) to give 3-(8-(methoxy methoxy) naphthalen-1-yl) prop-2-yn-1-ol (6.0 g, 22% yield) as a brown solid.

Step E. 3-(8-(methoxy methoxy) naphthalen-1-yl) propan-2,2,3,3-d4-1-ol. To a solution of 3-(8-(methoxy methoxy) naphthalen-1-yl) prop-2-yn-1-ol (2.0 g, 8.3 mmol) in methanol-d_4 (20 mL) was added 10% Pd/C (1.6 g). The reaction was stirred in a pressurized reactor under $D_{2(g)}$ atmosphere (50 bar) at rt for 72 h. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-25% EtOAc in hexanes) to give 3-(8-(methoxy methoxy) naphthalen-1-yl) propan-2,2,3,3-d4-1-ol (1.0 g, 49% yield).

Step F. 8-(3-hydroxypropyl-1,1,2,2-d_4) naphthalen-1-ol. To a solution of 3-(8-(methoxy methoxy) naphthalen-1-yl) propan-2,2,3,3-d4-1-ol (0.20 g, 0.79 mmol) in DCM (2.0 mL) at 0 °C was added 4 M HCl in 1,4-dioxane (1.0 mL). The mixture was stirred at rt for 1 h and then it was quenched with sat. aq. $NaHCO_3$ solution (10 mL). The mixture was extracted with DCM (5 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified silica gel chromatography (20% EtOAc in hexanes) to give 8-(3-hydroxypropyl-1,1,2,2-d_4) naphthalen-1-ol (0.025 g, 15% yield) as a light brown liquid. LCMS (MS-ES+APCI, Neg): 204.2 [M-H].

Step G. 8-(3-((tert-butyldimethylsilyl) oxy) propyl-1,1,2,2-d4) naphthalen-1-ol. To a solution of 8-(3-hydroxypropyl-1,1,2,2-d_4) naphthalen-1-ol (0.40 g, 1.9 mmol) and imidazole (0.26 g, 3.9 mmol) in THF (3 mL) at 0 °C was added a solution of TBSCl (0.29 g, 1.9 mmol) in THF (1 mL). The reaction was stirred at rt for 4 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (2% EtOAc in hexanes) to give 8-(3-((tert-butyldimethylsilyl) oxy) propyl-1,1,2,2-d_4) naphthalen-1-ol (0.35 g, 56% yield) as a yellow liquid. LCMS (MS-ES+APCI, Pos): 321.3 [M+H].

Step H. 8-(3-((tert-butyldimethylsilyl) oxy) propyl-1,1,2,2-d4) naphthalen-1-yl trifluoromethanesulfonate. To a solution of 8-(3-((tert-butyldimethylsilyl) oxy) propyl-1,1,2,2-d4) naphthalen-1-ol (0.35 g, 1.1 mmol) and DIPEA (0.28 mL, 1.6 mmol) in DMA (7.0 mL) was added *N*-phenyl-bis(trifluoromethanesulfonimide) (0.58 g, 1.6 mmol). The reaction was stirred at rt for 2 h. The mixture was diluted with water (10 mL) and then extracted with EtOAc (10 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% EtOAc in hexanes) to give 8-(3-((tert-butyldimethylsilyl)oxy)propyl-1,1,2,2-d4)naphthalen-1-yl trifluoromethanesulfonate (0.35 g, 71% yield) as a white solid. LCMS (MS-ES+APCI, Neg): 451.3 [M-H].

Step I. tert-butyldimethyl(3-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy-2,2,3,3-d4)silane. To a solution of 8-(3-((tert-butyldimethylsilyl)oxy)propyl-1,1,2,2-d4)naphthalen-1-yl trifluoromethanesulfonate (0.50 g, 1.1 mmol) and triethylamine (0.67 g, 6.6 mmol) in MeCN (10 mL) was added bis(pinacolato)diboron (0.84 g, 6.6 mmol). To this reaction mixture was added $PdCl_2$(dppf) (0.18 g, 0.22 mmol). The reaction was stirred at 90 °C for 5 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (4% EtOAc in hexanes) to give tert-butyldimethyl(3-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) naphthalen-1-yl) propoxy-2,2,3,3-d_4) silane (0.50 g, 100%) as a red liquid. LCMS (MS-ES+APCI, Pos): 431.3 [M+H].

Step J. 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl) oxy) propyl-1,1,2,2-d4) naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy) pyrido [4,3-d] pyrimidine. To a solution of 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy)pyrido[4,3-d]pyrimidine (0.30 g, 0.67 mmol) in 1,4-dioxane (2.1 mL) and water (0.90 mL) was added Cs_2CO_3 (0.65 g, 2.0 mmol) and tert-butyldimethyl(3-(8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) naphthalen-1-yl)

propoxy-2,2,3,3-d_4) (0.32 g, 0.73 mmol). The reaction was purged with N_2 for 5 min and then mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.048 g, 0.067 mmol) was added. The reaction was stirred at 90 °C for 2 h. The mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (40% EtOAc in hexanes) to give 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl-1,1,2,2-d4)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy) pyrido [4,3-d]pyrimidine (0.15 g, 31.% yield) as a yellow liquid. LCMS (MS-ES+APCI, Pos): 715.3 [M+H].

Step K. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy) pyrido[4,3-d] pyrimidin-7-yl) naphthalen-1-yl) propan-2,2,3,3-d_4-1-ol. To a solution 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl-1,1,2,2-d4)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy) pyrido [4,3-d]pyrimidine (0.35 g, 0.48 mmol) in DCM (3.5 mL) at 0°C was added a solution of TFA (0.094 mL, 1.2 mmol) in DCM (1.0 mL). The reaction was allowed to warmed to rt and stirred for 4 h. The mixture was diluted with sat. aq. $NaHCO_3$ solution (10 mL) and then extracted with DCM (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (60% EtOAc in hexanes) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy) pyrido[4,3-d] pyrimidin-7-yl) naphthalen-1-yl) propan-2,2,3,3-d_4-1-ol (0.25 g, 85% yield) as a yellow solid. LCMS (MS-ES+APCI, Pos): 601.3 [M+H].

Step L.3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl-2,2,3,3-d_4 (2,5-dioxopyrrolidin-1-yl) carbonate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy) pyrido[4,3-d] pyrimidin-7-yl) naphthalen-1-yl) propan-2,2,3,3-d4-1-ol (0.25 g, 0.41 mmol) and pyridine (0.10 mL,1.2 mmol) in DCM (2.5 mL) was added N,N'-disuccinimidyl carbonate (0.32 g, 1.2 mmol). The reaction was stirred at rt for 1 h and then it was diluted with water (10 mL) and extracted with DCM (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl-2,2,3,3-d_4 (2,5-dioxopyrrolidin-1-yl) carbonate (0.29 g) as an off

white solid, which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 742.2 [M+H].

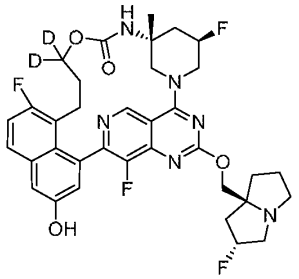
Step M. benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy-2,2,3,3-d_4)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl-2,2,3,3-d4 (2,5-dioxopyrrolidin-1-yl) carbonate (0.29 g, 0.39 mmol) and pyridine (0.094 mL, 1.2 mmol) in DCM (2.9 mL) was added benzyl (3R,5R)-3-amino-5-fluoro-3-methylpiperidine-1-carboxylate (0.11 g, 0.42 mmol). The reaction was stirred at room temperature for 1 h. The mixture was diluted with water (20 mL) and then extracted with DCM (10 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (35% EtOAc in hexanes) to give benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy-2,2,3,3-d4)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.32 g, 92% yield) as yellow solid. LCMS (MS-ES+APCI, Pos): 893.3 [M+H].

Step N. 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl-2,2,3,3-d4 ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate. To a solution of benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propoxy-2,2,3,3-d4)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.27 g,0.30 mmol) in MeOH (2.7 mL) was added 10% Pd/C (0.27 g). The reaction was stirred at room temperature under an atmosphere of H_2 for 5 h. The slurry was filtered over Celite. The filtrate was concentrated under reduced pressure to give 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl-2,2,3,3-d4 ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.20 g), which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 669.3 [M+H].

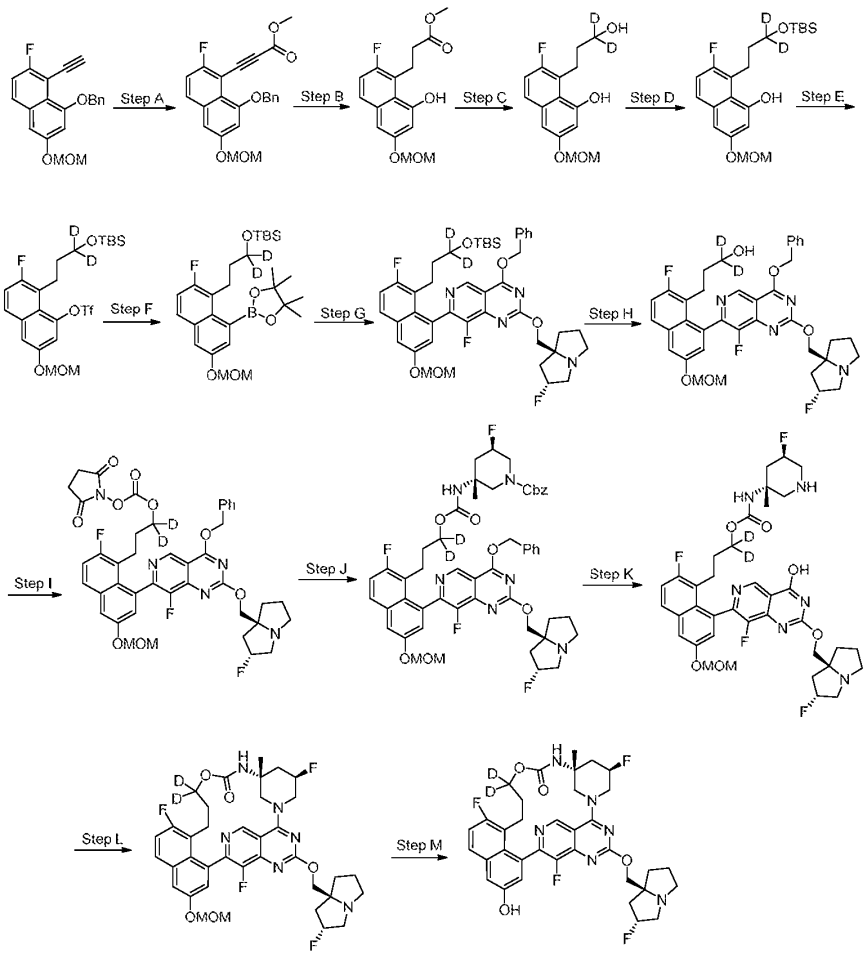
Step O. (1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d] pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-4,4,5,5-d_4. To solution of 3-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl-2,2,3,3-d4 ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate

(0.20 g, 0.29 mmol) in DMF (2 mL) was added BrOP (0.14 g, 0.35 mmol) and DIPEA (0.15 mL, 0.89 mmol). The reaction was stirred at rt for 12 h. The mixture was diluted water (20 mL) and then extracted with DCM (10 mL x 3). The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (35% MeCN in 0.1% aqueous formic acid) to give (13R,15R)-15,28-difluoro-22-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy)-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d] pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-4,4,5,5-d4 (0.015 g, 7% yield) as an off white solid. LCMS (MS-ES+APCI, Pos): 651.3 [M+H].

Compound 136



(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-6,6-d2



Step A. methyl 3-(8-(benzyloxy)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propiolate. To a solution of 8-(benzyloxy)-1-ethynyl-2-fluoro-6-(methoxymethoxy)naphthalene (20 g, 60 mmol) in THF (600 mL) at -78 °C was added LDA (60 mL, 120 mmol). The reaction was stirred at -78 °C for 1 h, then methyl chloroformate (9.2 mL, 120) was added. The reaction was stirred at -78 °C for 5 h. The mixture was quenched with sat. aq. NH_4Cl solution (200 mL) and then extracted with EtOAc (200 mL x 3). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15% EtOAc in hexanes) to give methyl 3-(8-(benzyloxy)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propiolate (12 g, 51% yield) as a yellow liquid. LCMS (MS-ES+APCI, Pos): 395.2 [M+H].

Step B. methyl 3-(2-fluoro-8-hydroxy-6-(methoxymethoxy)naphthalen-1-yl)propanoate. To a solution of methyl 3-(8-(benzyloxy)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propiolate

(10 g, 25 mmol) in IPA (100 mL) and THF (100 mL) was added 10% Pd/C (5.0 g). The reaction was stirred at rt for 16 h. The slurry was filtered through Celite, and the pad was washed with MeOH (100 mL x 3). The filtrate was concentrated under reduced pressure to give methyl 3-(2-fluoro-8-hydroxy-6-(methoxymethoxy)naphthalen-1-yl)propanoate. (7.0 g, 90% yield) as a yellow liquid. LCMS (MS-ES+APCI, Pos): 309.2 [M+H].

Step C. (7-fluoro-8-(3-hydroxypropyl-3,3-d2)-3-(methoxymethoxy)naphthalen-1-ol. To a solution of methyl 3-(2-fluoro-8-hydroxy-6-(methoxymethoxy)naphthalen-1-yl)propanoate (7.0 g, 23 mmol) in THF (140 mL) at 0 °C was added $LiAlD_4$ (2.9 g, 68 mmol). The reaction was stirred at rt for 2 h. The mixture was quenched with sat. aq. NH_4Cl solution (250 mL) and then extracted with EtOAc (250 mL x 3). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give (7-fluoro-8-(3-hydroxypropyl-3,3-d2)-3-(methoxymethoxy)naphthalen-1-ol (5.3 g, 82%) as a brown liquid. LCMS (MS-ES+APCI, Pos): 283.1 [M+H].

Step D. 8-(3-((tert-butyldimethylsilyl)oxy)propyl-3,3-d2)-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol. To a solution of (7-fluoro-8-(3-hydroxypropyl-3,3-d2)-3-(methoxymethoxy)naphthalen-1-ol (5.0 g, 18 mmol) in THF (50 mL) was added imidazole (3.6 g, 53 mmol) and TBSCl (5.3 g, 35 mmol). The reaction was stirred at rt for 1 h. The mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (7% EtOAc in hexanes) to give 8-(3-((tert-butyldimethylsilyl)oxy)propyl-3,3-d2)-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (4.5 g, 64%) as an orange solid. LCMS (MS-ES+APCI, Neg): 395.4 [M-H].

Step E. 8-(3-((tert-butyldimethylsilyl)oxy)propyl-3,3-d2)-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate. To a solution of 8-(3-((tert-butyldimethylsilyl)oxy)propyl-3,3-d2)-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (4.0 g, 10 mmol) in DMA (40 mL) was added DIPEA (2.6 mL, 15 mmol) and N,N-bis(trifluoromethylsulfonyl)aniline (5.4 g, 15 mmol). The reaction was stirred at rt for 1 h. The mixture was diluted with water (150 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% EtOAc in hexanes) to give 8-(3-((tert-butyldimethylsilyl)oxy)propyl-3,3-d2)-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (3.0 g, 56% yield) as a yellow liquid. LCMS (MS-ES+APCI, Neg): 527.3 [M-H].

Step F. tert-butyl(3-(2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy-1,1-d2)dimethylsilane. To a solution of 8-(3-((tert-butyldimethylsilyl)oxy)propyl-3,3-d2)-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (3.0 g, 5.7 mmol) and NEt_3 (4.7 mL, 34 mmol) in MeCN (60 mL) was added bis(pinacolato)diboron (5.0 mL, 34 mmol) and $PdCl_2$(dppf) (1.2 g, 1.4 mmol). The reaction was stirred at 80 °C for 6 h. The mixture was diluted with water (100 mL) and extracted with DCM (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% EtOAc in hexanes) to give tert-butyl(3-(2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy-1,1-d2)dimethylsilane (3.0 g) as a yellow liquid.

Step G. 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl-3,3-d2)-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine(1.75 g, 3.91 mmol), tert-butyl(3-(2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy-1,1-d2)dimethylsilane (3.0 g, 5.9 mmol) and Cs_2CO_3 (3.8 g, 12 mmol) in 1,4-dioxane(15 mL) and water (2.5 mL) was added mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.29 g, 0.39 mmol). The reaction was stirred at 100 °C for 1 h. The mixture was filtered through Celite and the pad was washed with DCM (100 mL). The filtrate was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (35% EtOAc in hexanes) to give 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl-3,3-d2)-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (2.5 g, 82% yield) as a yellow liquid. LCMS: (MS-ES+APCI, Pos): 791.4 [M+H].

Step H. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propan-1,1-d2-1-ol. To a solution of 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl-3,3-d2)-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (2.5 g, 3.2 mmol) in MeCN (25 mL) was added pyridine (13 mL) and HF·pyridine (13 mL). The reaction was stirred at rt for 1 h and then it was diluted with water

(100 mL) and extracted with DCM (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propan-1,1-d2-1-ol (1.2 g) as a yellow liquid, which was taken onto the next step without purification. LCMS (MS-ES+APCI, Pos): 677.3 [M+H].

Step I. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl-1,1-d2 (2,5-dioxopyrrolidin-1-yl) carbonate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propan-1,1-d2-1-ol (1.2 g, 1.8 mmol) and pyridine (0.42 mL, 5.3 mmol) in DCM (12 mL) was added bis(2,5-dioxopyrrolidin-1-yl) carbonate (1.4 g, 5.3 mmol). The reaction was stirred rt for 1 h and then it was diluted with water (30 mL) and extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl-1,1-d2 (2,5-dioxopyrrolidin-1-yl) carbonate (1.5 g) as a yellow liquid. LCMS (MS-ES+APCI, Pos): 818.6 [M+H].

Step J. benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy-1,1-d2)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl-1,1-d2 (2,5-dioxopyrrolidin-1-yl) carbonate (1.5 g, 1.8 mmol) and benzyl (3R,5R)-3-amino-5-fluoro-3-methylpiperidine-1-carboxylate (0.58 g, 2.2 mmol) in DCM (15 mL) was added DIPEA (0.95 mL, 5.5 mmol). The reaction was stirred at rt for 16 h. The mixture was diluted with water (50 mL) and then extracted with DCM (30 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy-1,1-d2)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (1.2 g, 68% yield) as an off white solid, which was taken onto the next step without purification. LCMS (MS-ES+APCI,

Pos): 969.7 [M+H].

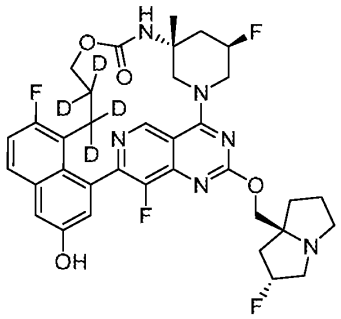
Step K. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl-1,1-d2 ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate. To a solution of benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy-1,1-d2)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (1.1 g, 1.1 mmol) in THF (44 mL) was added 10% Pd/C (1.1 g). The reaction was stirred at rt under an atmosphere of H_2 for 6 h. The slurry was filtered over Celite and the pad was washed with a 1:1 solution of THF: DCM (250 mL). The filtrate was concentrated under reduced pressure. The residue was triturated with n-pentane to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl-1,1-d2 ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.80 g, 95% yield), which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 745.3 [M+H].

Step L. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-6,6-d2. To solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl-1,1-d2 ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.40 g, 0.53 mmol) in DMF (4.0 mL) was added BroP (0.25 g, 0.64 mmol) and DIPEA (0.28 mL, 1.6 mmol). The reaction was stirred at rt for 16 h. The mixture was diluted water (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% MeOH in DCM) to give (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-6,6-d2 (0.050 g, 13% yield) as an off white solid. LCMS: (MS-ES+APCI, Pos): 727.3 [M+H].

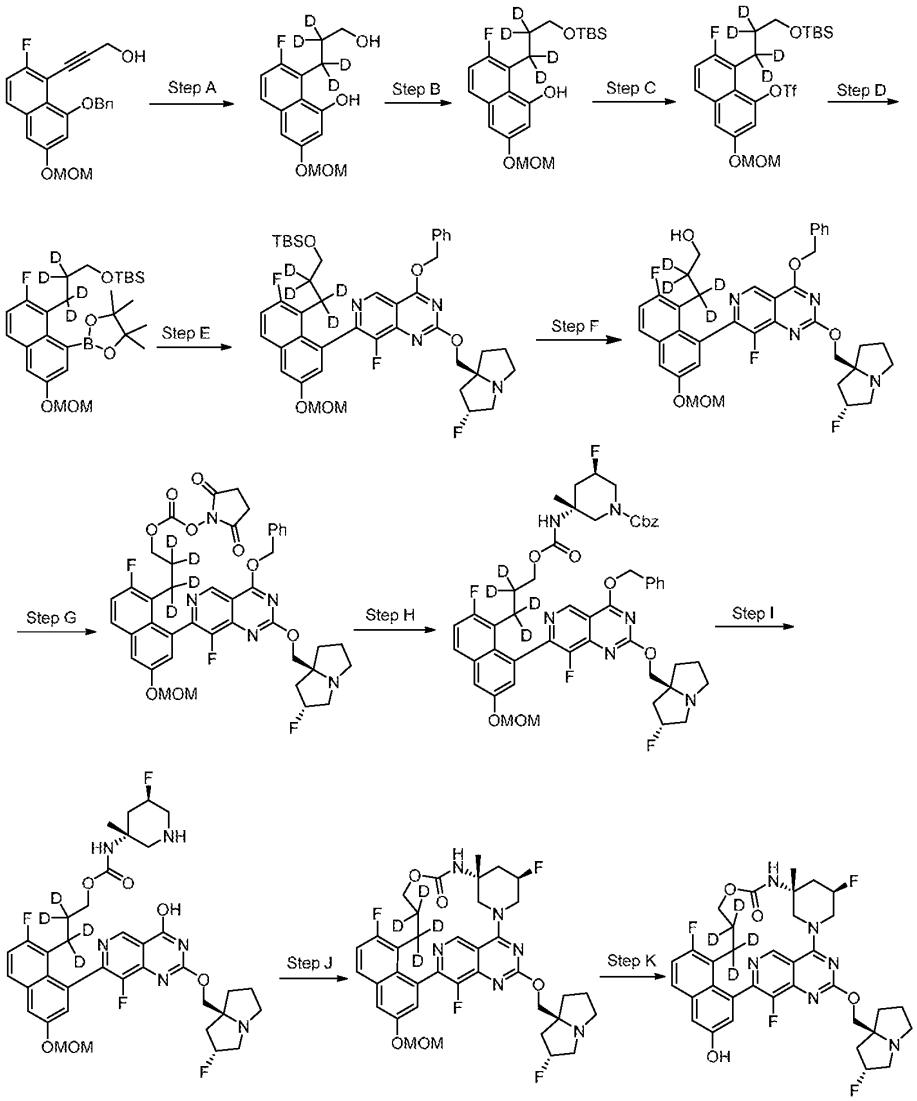
Step M. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-6,6-d2. To solution of (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-

3(1,8)-naphthalenacyclononaphan-8-one-6,6-d2 (0.040 g, 0.055 mmol) in DCM (8 mL) was added 4 M HCl in 1,4-dioxane (0.040 mL). The reaction was stirred at rt for 30 min and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC (50% MeCN and 0.05% aqueous NH_4HCO_3) to give (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-6,6-d2 (0.016 g, 34% yield) as a white solid. LCMS: (MS-ES+APCI, Pos): 683.4 [M+H].

Compound 137



(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-4,4,5,5-d4


Step A
Step B
Step C
Step D
Step E
Step F
Step G
Step H
Step I
Step J
Step K

Step A. 7-fluoro-8-(3-hydroxypropyl-1,1,2,2-d4)-3-(methoxymethoxy)naphthalen-1-ol. To a solution of 3-(8-(benzyloxy)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol (10 g, 27 mmol) in THF (50 mL) and MeOD (50 mL) was added 10% Pd/C (8 g). The reaction was stirred under an atmosphere of D_2 for 72 h. The mixture was filtered over Celite and the pad was washed with THF (15 mL x 3). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15-30% EtOAc in hexanes) to give 7-fluoro-8-(3-hydroxypropyl-1,1,2,2-d4)-3-(methoxymethoxy)naphthalen-1-ol (3.9 g, 50% yield) as a brown liquid. LCMS (MS-ES+APCI, Pos): 285.2 [M+H].

Step B. 8-(3-((tert-butyldimethylsilyl)oxy)propyl-1,1,2,2-d4)-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol. To a solution of 7-fluoro-8-(3-hydroxypropyl-1,1,2,2-d4)-3-(methoxymethoxy)naphthalen-1-ol (3.9 g, 14 mmol) in THF (31 mL) was added imidazole (1.9 g, 27 mmol) and TBDMS-Cl (2.5 g, 17 mmol). Then reaction was stirred for 1 h. The mixture was diluted with cold H_2O (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5-25% EtOAc in hexanes) to give 8-(3-((tert-butyldimethylsilyl)oxy)propyl-1,1,2,2-d4)-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (4.5 g, 83% yield) as a brown liquid. LCMS (MS-ES+APCI, Pos): 399.4 [M+H].

Step C. 8-(3-((tert-butyldimethylsilyl)oxy)propyl-1,1,2,2-d4)-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate. To a solution 8-(3-((tert-butyldimethylsilyl)oxy)propyl-1,1,2,2-d4)-7-fluoro-3-(methoxymethoxy)naphthalen-1-ol (4.5 g, 11 mmol) and DIPEA (3.0 mL, 17 mmol) in DMA (90 mL) was added *N*-phenyl-bis(trifluoromethanesulfonimide) (6.1 g, 17 mmol). The reaction was stirred for 2 h. The mixture was diluted with cold water (250 mL) and extracted with EtOAc (250 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-20% EtOAc in hexanes) to give 8-(3-((tert-butyldimethylsilyl)oxy)propyl-1,1,2,2-d4)-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (4.5 g, 75% yield) as a brown liquid. LCMS (MS-ES+APCI, Neg): 529.3 [M-H].

Step D. tert-butyl(3-(2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy-2,2,3,3-d4)dimethylsilane. To a solution of 8-(3-((tert-butyldimethylsilyl)oxy)propyl-1,1,2,2-d4)-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl trifluoromethanesulfonate (4.5 g, 8.5 mmol) and triethylamine (7.1 mL, 51 mmol) in MeCN (45 mL) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.5 g, 51 mmol) and

$PdCl_2(dppf)\cdot DCM$ (1.7 g, 2.1 mmol). The reaction was stirred at 80 °C for 6 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-10% EtOAc in hexanes) to give tert-butyl(3-(2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy-2,2,3,3-d4)dimethylsilane (2.5 g, 58%) as a light yellow sticky liquid.

Step E. 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl-1,1,2,2-d4)-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. A solution of 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl) methoxy) pyrido[4,3-d] pyrimidine (2.0 g, 4.5 mmol) and tert-butyl(3-(2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy-2,2,3,3-d4)dimethylsilane (2.5 g, 4.9 mmol) in dioxane (18 mL) water (2 mL) was purged with N_2 gas for 5 min. Then to the mixture was added Cs_2CO_3 (4.4 g, 13 mmol) and mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.33 g, 0.45 mmol). The reaction was stirred at 90 °C for 1 h. The mixture was diluted with H_2O (100 mL) and then extracted with EtOAc (50 mL x 2). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25-50% EtOAc in hexanes) to give 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl-1,1,2,2-d4)-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (2.0 g, 56% yield) as a light yellow sticky liquid. LCMS (MS-ES+APCI, Pos): 794.5 [M+H].

Step F. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propan-2,2,3,3-d4-1-ol. To a solution of 4-(benzyloxy)-7-(8-(3-((tert-butyldimethylsilyl)oxy)propyl-1,1,2,2-d4)-7-fluoro-3-(methoxymethoxy)naphthalen-1-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (2.0 g, 2.5 mmol) in MeCN (10 mL) was added pyridine (10 mL) and HF·pyridine (10 mL). The reaction was stirred for 4 h and then it was diluted with cold water (100 mL) and extracted with EtOAc (25 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-15% MeOH in DCM) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-

yl)propan-2,2,3,3-d4-1-ol (0.87 g, 51% yield) as a light yellow sticky liquid. LCMS (MS-ES+APCI, Pos): 679.4 [M+H].

Step G. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl-2,2,3,3-d4 (2,5-dioxopyrrolidin-1-yl) carbonate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propan-2,2,3,3-d4-1-ol (0.85 g, 1.2 mmol) and pyridine (0.30 g, 3.7 mmol) in DCM (8.5 mL) was added bis(2,5-dioxopyrrolidin-1-yl) carbonate (0.96 g, 3.7 mmol). The reaction mixture was stirred for 1 h. Then mixture was diluted with cold water (50 mL) and then extracted with DCM (50 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl-2,2,3,3-d4 (2,5-dioxopyrrolidin-1-yl) carbonate (1.1 g) as a yellow sticky liquid. LCMS (MS-ES+APCI, Pos): 820.3 [M+H].

Step H. benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy-2,2,3,3-d4)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl-2,2,3,3-d4 (2,5-dioxopyrrolidin-1-yl) carbonate (1.1 g, 1.3 mmol) and benzyl (3R,5R)-3-amino-5-fluoro-3-methylpiperidine-1-carboxylate (0.43 g, 1.6 mmol) in DCM (11 mL) was added pyridine (0.32 mL, 4.0 mmol). The reaction was stirred for 12 h. The mixture was diluted with water (100 mL) and then extracted with DCM (50 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15-30% EtOAc in hexanes) to give benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy-2,2,3,3-d4)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.70 g, 54% yield) as a light yellow sticky liquid. LCMS (MS-ES+APCI, Pos): 972.6 [M+H].

Step I. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-

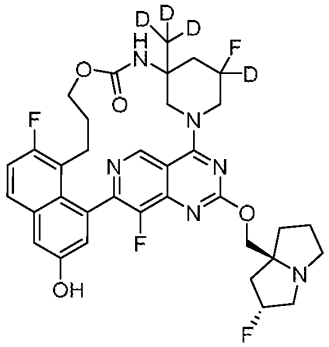
yl)propyl-2,2,3,3-d4 ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate. To a solution of benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy-2,2,3,3-d4)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.55 g, 0.55 mmol) in MeOH (5.5 mL) was added 10% Pd/C (0.55 g). The reaction was stirred under an atmosphere of H_2 for 1 h. The mixture was filtered over Celite and the pad was washed with 1:1 MeOH:DCM (50 mL). The filtrate was concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl-2,2,3,3-d4 ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.40 g, 95% yield) as an off white solid, which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 747.3 [M+H].

Step J. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-4,4,5,5-d4. To solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl-2,2,3,3-d4 ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.40 g, 0.53 mmol) in DMF (4.0 mL) was added BroP (0.25 g, 0.64 mmol) and DIPEA (0.28 mL, 1.6 mmol). The reaction was stirred for 12 h. The mixture was diluted cold water (10 mL) and then extracted with EtOAc (20 mL x 2). The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-7% MeOH in DCM) to give (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-4,4,5,5-d4 (0.090 g, 23% yield) as an off white solid. LCMS: (MS-ES+APCI, Pos): 729.3 (M+H).

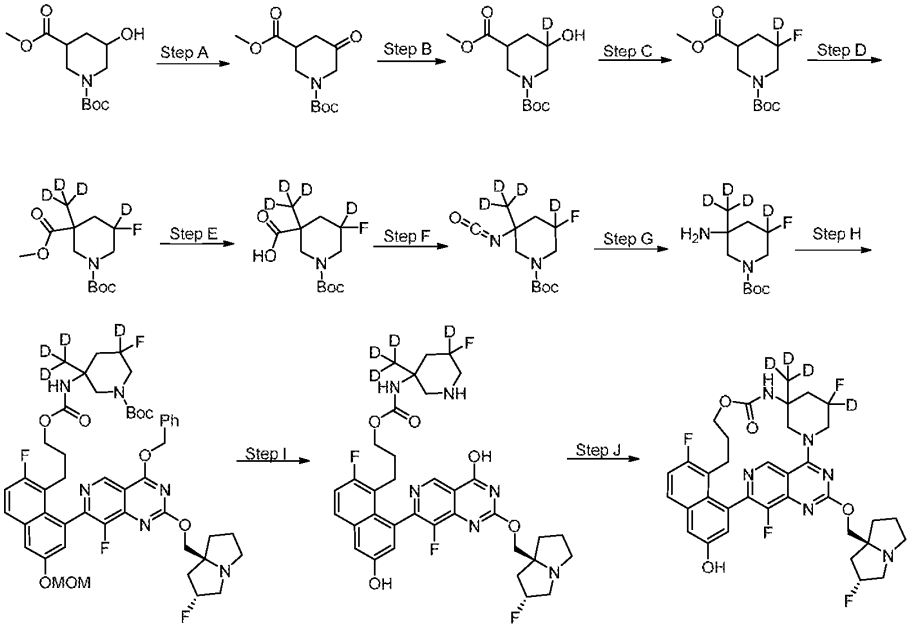
Step K. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-4,4,5,5-d4. To solution of (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-4,4,5,5-d4 (0.080 g, 0.11 mmol) in DCM (0.80 mL) was added 4 M HCl in dioxane (0.16 mL). The reaction was stirred for 1 h and then it was concentrated under reduce pressure. The residue was purified by preparative HPLC (45-55%

MeCN and 0.04% aqueous NH_4HCO_3) to give ($1^3R,1^5R$)-$1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-4,4,5,5-d4 (0.022 g, 29% yield) as a white solid. LCMS: (MS-ES+APCI, Pos): 685.3 (M+H).

Compound 138



$1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-(methyl-d3)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-1^5-d



Step A. 1-(tert-butyl) 3-methyl 5-oxopiperidine-1,3-dicarboxylate. To a solution of 1-(tert-butyl) 3-methyl 5-hydroxypiperidine-1,3-dicarboxylate (10 g, 39 mmol) in DCM (100 mL) was added Celite (10 g) and PCC (25 g, 120 mmol). The reaction was stirred for 16 h. The

mixture was filtered through Celite and the pad was washed with DCM (50 mL). The filtrate was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (30% EtOAc in hexanes) to give 1-(tert-butyl) 3-methyl 5-oxopiperidine-1,3-dicarboxylate (5.0 g, 50.39% yield) as a Pale-yellow liquid. LCMS (MS-ES+APCI, Pos): 202.1 [M-^{t}Bu].

Step B. 1-(tert-butyl) 3-methyl 5-hydroxypiperidine-1,3-dicarboxylate-5-d. To a solution of 1-(tert-butyl) 3-methyl 5-oxopiperidine-1,3-dicarboxylate (5.0 g, 19 mmol) in MeOH (50 mL) at 0 °C was added $NaBD_4$ (1.1 g, 25 mmol) portion wise. The reaction was stirred for 2 h. The mixture was diluted with H_2O (60 mL) and extracted with DCM (60 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 1-(tert-butyl) 3-methyl 5-hydroxypiperidine-1,3-dicarboxylate-5-d (3.0 g, 59 % yield) as a yellow liquid, which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Pos): 205.1 [M+H-^{t}Bu].

Step C. 1-(tert-butyl) 3-methyl 5-fluoropiperidine-1,3-dicarboxylate-5-d. To a solution of 1-(tert-butyl) 3-methyl 5-hydroxypiperidine-1,3-dicarboxylate-5-d (3.0 g, 12 mmol) in DCM (60 mL) at -78 °C was added DAST (2.3 mL, 17 mmol) dropwise. The reaction was stirred for 1 h at this temperature and then it was warm to rt and stirred for 3 h. The mixture was quenched by saturated $NaHCO_3$ solution (30 mL), diluted with H_2O (20 mL) and then extracted with DCM (50 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% EtOAc in hexanes) to give 1-(tert-butyl) 3-methyl 5-fluoropiperidine-1,3-dicarboxylate-5-d (1.2 g, 40% yield) as a yellow liquid. LCMS (MS-ES+APCI, Pos): 207.1 [M+H-^{t}Bu].

Step D. 1-(tert-butyl) 3-methyl 5-fluoro-3-(methyl-d3)piperidine-1,3-dicarboxylate-5-d. To a solution of 1-(tert-butyl) 3-methyl 5-fluoropiperidine-1,3-dicarboxylate-5-d (1.2 g, 4.6 mmol) in THF (12 mL) at -78 °C was added LiHMDS (1.0 M in THF; 6.9 mL) dropwise. The reaction was stirred for 1 h at this temperature and then CD_3I (0.89 mL, 14 mmol) was added dropwise. The reaction was warmed to rt and was stirred for 3 h. The mixture was quenched by saturated NH_4Cl solution (20 mL), diluted with H_2O (10 mL) and then extracted with EtOAc (30 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc in hexanes) to give 1-(tert-butyl) 3-methyl 5-fluoro-3-(methyl-d3)piperidine-1,3-dicarboxylate-5-d (1.1 g, 86% yield) as a yellow liquid. LCMS (MS-ES+APCI, Pos): 224.2 [M-^{t}Bu].

Step E. 1-(tert-butoxycarbonyl)-5-fluoro-3-(methyl-d3)piperidine-3-carboxylic-5-d acid. To a solution of 1-(tert-butyl) 3-methyl 5-fluoro-3-(methyl-d3)piperidine-1,3-dicarboxylate-5-d (1.7 g, 6.1 mmol) in MeOH (8.5 mL) and H_2O (8.5 mL) was added $LiOH{\cdot}H_2O$ (0.51 g, 12 mmol) portion wise. The reaction was stirred for 3 h. The mixture was quenched by 10% citric acid solution (10 mL), diluted with H_2O (10 mL) and then extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 1-(tert-butoxycarbonyl)-5-fluoro-3-(methyl-d3)piperidine-3-carboxylic-5-d acid (1.6 g, 99% yield) as a yellow liquid, which was taken onto the next step without further purification. LCMS (MS-ES+APCI, Neg): 264.3 [M-H].

Step F. tert-butyl 5-fluoro-3-isocyanato-3-(methyl-d3)piperidine-1-carboxylate-5-d. To a solution of 1-(tert-butoxycarbonyl)-5-fluoro-3-(methyl-d3)piperidine-3-carboxylic-5-d acid (1.6 g, 6.0 mmol) in toluene (16 mL) was added triethylamine (0.84 mL, 6.0 mmol) followed by DPPA (1.4 mL, 6.6 mmol). The reaction was stirred at 90 °C for 2 h. The mixture was cooled to rt, diluted with H_2O (25 mL) and then extracted with diethyl ether (30 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give tert-butyl 5-fluoro-3-isocyanato-3-(methyl-d3)piperidine-1-carboxylate-5-d (2.3 g).

Step G. tert-butyl 3-amino-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate-5-d. To a solution of tert-butyl 5-fluoro-3-isocyanato-3-(methyl-d3)piperidine-1-carboxylate-5-d (2.3 g, 8.8 mmol) in THF (46 mL) was added 2 N NaOH (46 mL). The reaction was stirred for 16 h. The mixture was diluted with H_2O (30 mL) and then extracted with EtOAc (40 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% MeOH in DCM) to give tert-butyl 3-amino-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate-5-d (0.85 g, 60% (over two steps yield) as a yellow liquid. LCMS (MS-ES+APCI, Pos): 237.2 [M+H].

Step H. tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate-5-d. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (1.8 g, 2.2 mmol) in DCM (18 mL) was added tert-butyl 3-amino-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate-5-d (0.78 g, 3.3 mmol) followed by pyridine (0.53 mL, 6.6 mmol). The reaction

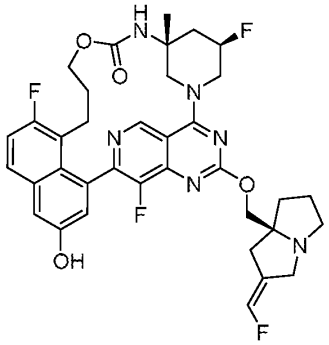
was stirred for 6 h. The mixture was diluted with H_2O (20 mL) and then extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by neutral alumina column chromatography (25% EtOAc in hexanes) to give tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate-5-d (1.2 g, 39% yield) as a white sticky solid. LCMS (MS-ES+APCI, Pos): 937.5 [M+H].

Step I. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl (5-fluoro-3-(methyl-d3)piperidin-3-yl-5-d)carbamate To a solution of tert-butyl 3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-(methyl-d3)piperidine-1-carboxylate-5-d (1.2 g, 1.3 mmol) in DCM (12 mL) was added TFA (3.6 mL). The reaction was stirred for 5 h. The mixture was quenched by saturated $NaHCO_3$ solution (20 mL), diluted with H_2O (10 mL) and then extracted with 10% MeOH in DCM (40 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (20% ACN in 0.1% aqueous formic acid) to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl (5-fluoro-3-(methyl-d3)piperidin-3-yl-5-d)carbamate (0.6 g, 66.67% yield) as an off white solid, LCMS (MS-ES+APCI, Pos): 703.3 [M+H].

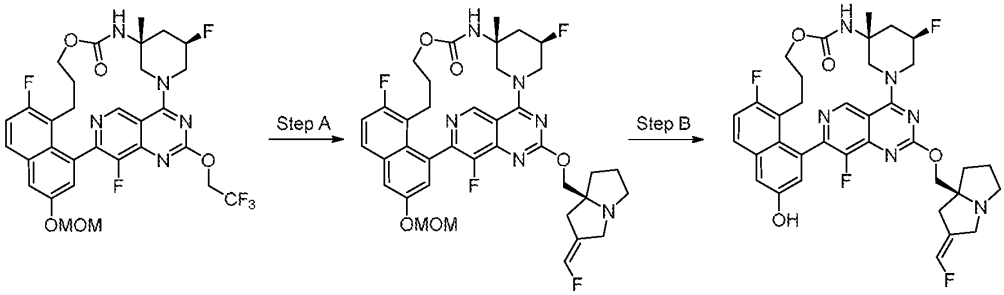
Step J. $1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-(methyl-d3)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-1^5-d. To solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)propyl (5-fluoro-3-(methyl-d3)piperidin-3-yl-5-d)carbamate (0.080 g, 0.11 mmol) in DMF (1.6 mL) was added DIPEA (0.059 mL, 0.34 mmol). The mixture was stirred for 15 min then BrOP (0.053 g, 0.13 mmol) was added portion wise. The reaction was stirred for 16 h. The mixture was diluted with water (15 mL) and then extracted with EtOAc (20 mL x 3). The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (5% MeOH in DCM) to give $1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-

fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-(methyl-d3)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one-1^5-d (Fr-1) (0.008 g, 10.26% yield) as an off white solid. LCMS (MS-ES+APCI, Pos): 685.2 [M+H].

Compound 502



(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one

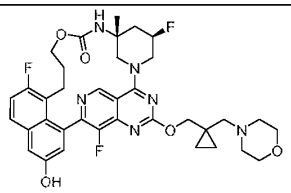
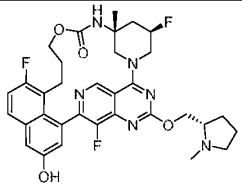


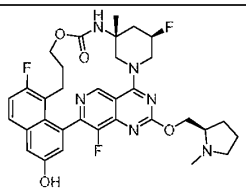
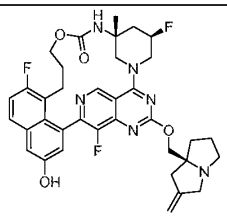
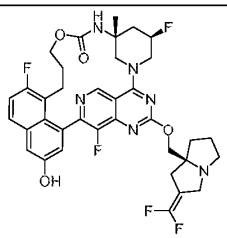
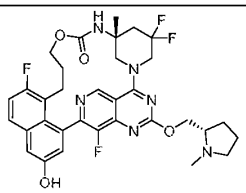
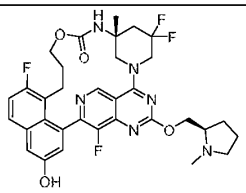
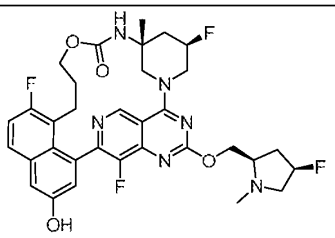
Step A. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-3^3-(methoxymethoxy)-1^3-methyl-2^2-(2,2,2-trifluoroethoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.040 g, 0.056 mmol), (S,Z)-(2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (0.012 g, 0.067 mmol), 4 Å molecular sieves (0.030 g, 0.056 mmol) in THF (1 mL) was added tBuONa (0.011 g, 0.11 mmol). The reaction was stirred at 35 °C for 1 h and then it was diluted with H_2O (5 mL) and extracted with DCM (5 mL x 3). The combined organic layers were washed with brine (5

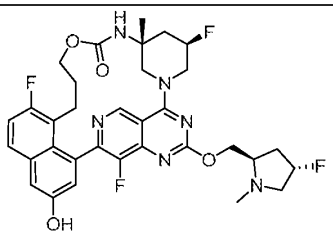
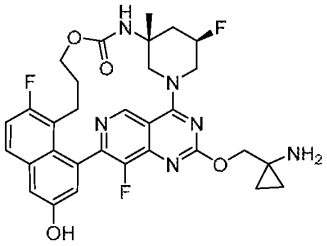
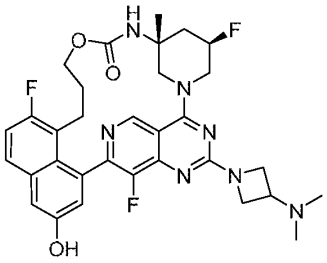
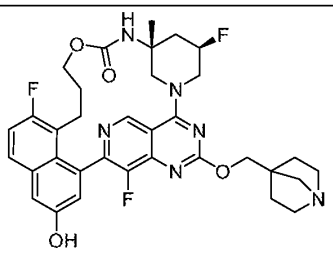
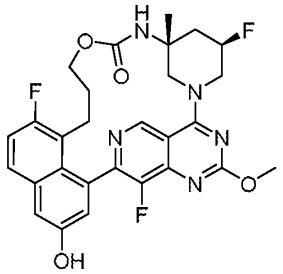
mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.040 g, 97% yield).

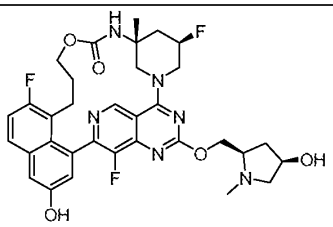
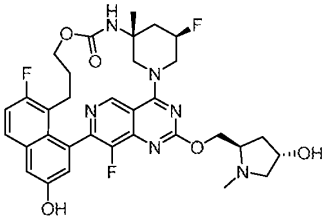
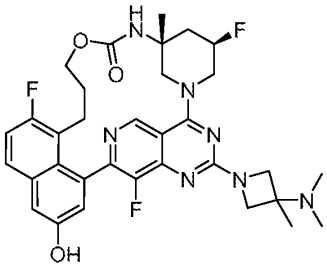
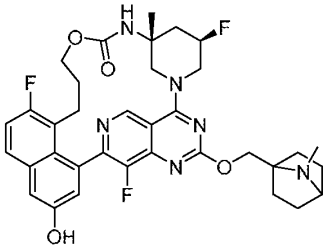
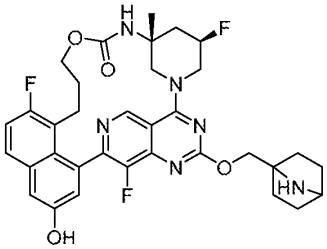
Step B. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-(methoxymethoxy)-13-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.040 g, 0.054 mmol) in DCM (0.50 mL) was added 2 M HCl in dioxane (0.50 mL). The reaction was stirred at rt for 30 min and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC (35-65% MeCN in 0.10% aqueous NH_4HCO_3) to afford (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((S,Z)-2-(fluoromethylene)tetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.0045 g, 12% yield) as a white solid. LCMS: (MS-ES+APCI, Pos): 693.3 [M+H].

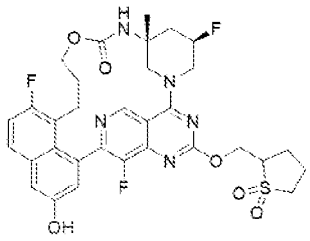
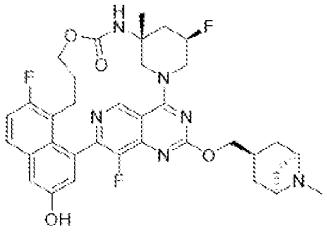
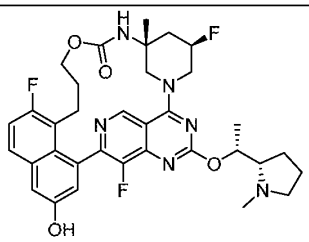
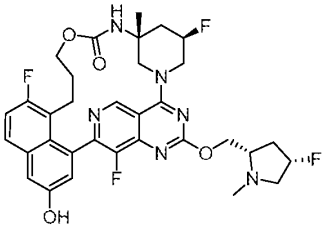
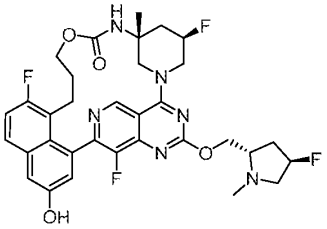
Table 7. Compounds made following procedures for Compound 502

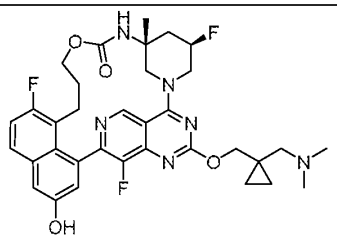
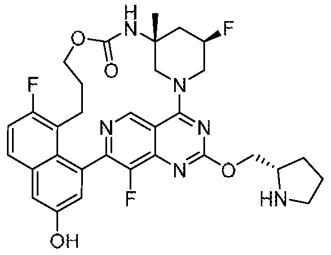
Cmpd ID	Structure	LCMS
505		693.3
506		637.2

507		637.2
508		675.3
509		711.3
510		655.2
511		655.2
512		655.3

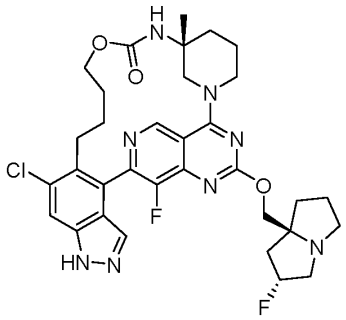
513		655.3
514		609.2
515		622.3
516		649.3
526		554.3

527		653.2
528		653.2
529		636.3
530		663.2
531		649.3

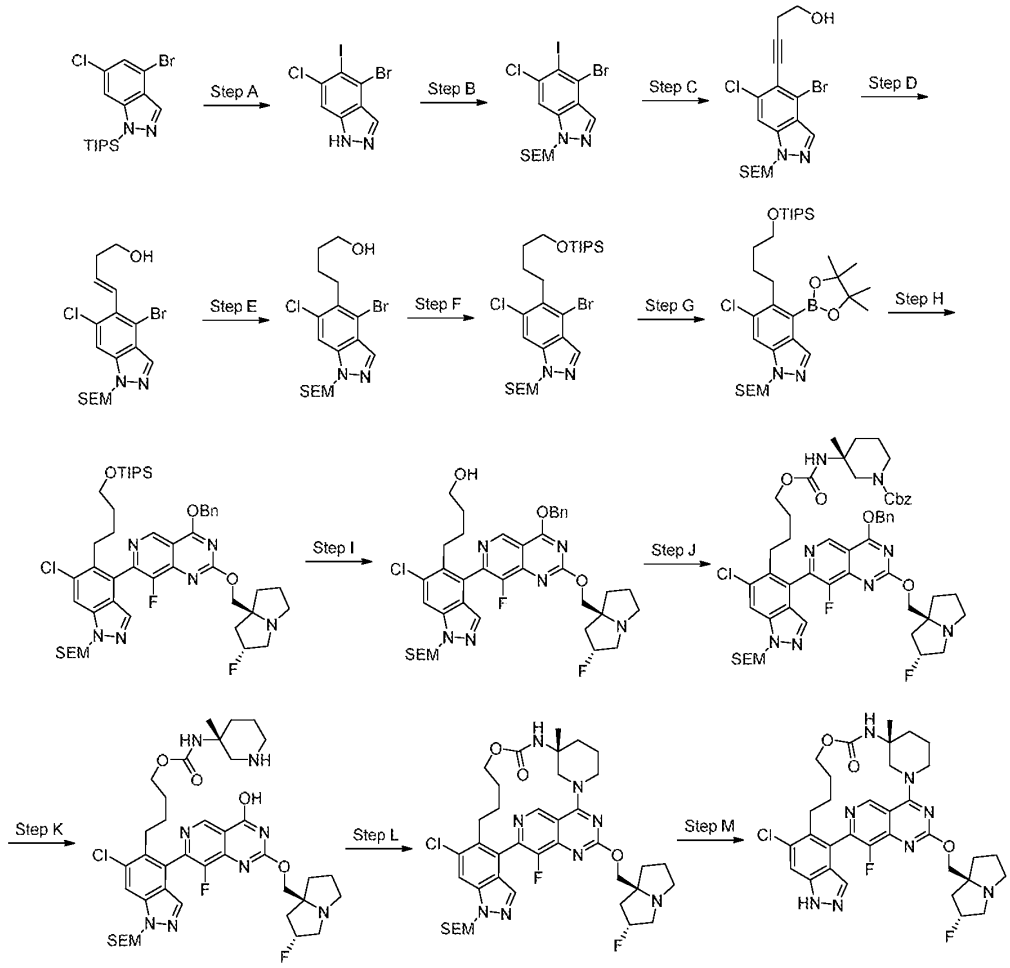
536		672.3
550		663.2
563		651.2
573		655.3
574		655.3

575		651.4
576		623.4

Compound 532



(3^3R)-1^6-chloro-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-methyl-1^1H-6-oxa-4-aza-2(7,4)-pyrido[4,3-d]pyrimidina-1(4,5)-indazola-3(1,3)-piperidinacyclodecaphan-5-one



Step A. 4-bromo-6-chloro-5-iodo-1H-indazole. To a solution of 4-bromo-6-chloro-1-(triisopropylsilyl)-1H-indazole (15 g, 39 mmol) in THF (150 mL) at -78 °C was added LDA (2 M in THF; 25 mL). The mixture was stirred at -78 °C for 1 h, then iodine (13 g, 50 mmol) was added. The reaction was allowed to warm to rt and was stirred for 1 h, after which it was quenched at 0 °C with sat. sodium thiosulfate solution (80 mL). The aqueous layer was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-25% EtOAc in petroleum ether) to give 4-bromo-6-chloro-5-iodo-1H-indazole (13 g, 87% yield) as a yellow oil. LCMS: (MS-ES+APCI, Pos): 358.8 [M+H].

Step B. 4-bromo-6-chloro-5-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole. To a

solution of 4-bromo-6-chloro-5-iodo-1H-indazole (13 g, 34 mmol) in THF (150 mL) at 0 °C was added NaH (60% in mineral oil; 1.8 g, 44 mmol). The mixture was stirred at 0 °C for 30 min then 2-(trimethylsilyl)ethoxymethyl chloride (7.8 mL, 44 mmol) was added. The reaction was stirred at 0 °C for 2 h and then it was quenched with NH_4Cl solution (100 mL). The mixture was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-9% EtOAc in petroleum ether) to give 4-bromo-6-chloro-5-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (8.5 g, 48% yield) as a yellow solid. LCMS: (MS-ES+APCI, Pos): 488.9 [M+H].

Step C. 4-(4-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)but-3-yn-1-ol. To a solution of 4-bromo-6-chloro-5-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (3.2 g, 6.1 mmol) and but-3-yn-1-ol (1.2 mL, 15 mmol) in THF (20 mL) was added CuI (1.2 g, 0.61 mmol), $Pd(PPh_3)_2Cl_2$ (0.85 g, 1.2 mmol) and triethylamine (4.2 mL, 30 mmol). The flask was evacuated and backfilled with nitrogen three times. The mixture was stirred at 50 °C under an atmosphere of nitrogen for 16 h. After cooling to rt, the reaction was diluted with water (50 mL) and extracted with ethyl acetate (100 mL x 3). The organics were washed with brine (200 mL x 2), dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (0-25% EtOAc in petroleum ether) to afford 4-(4-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)but-3-yn-1-ol (2.1 g, 78% yield) as a yellow solid. LCMS: (MS-ES+APCI, Pos): 431.2 [M+H].

Step D. (E)-4-(4-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)but-3-en-1-ol. To a solution of 4-(4-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)but-3-yn-1-ol (2.0 g, 4.5 mmol) in EtOAc (25 mL) was added 5% Rh/Al_2O_3 (4.7 g, 2.3 mmol). The flask was then evacuated and backfilled with H_2 three times. The mixture was stirred at rt under an atmosphere of H_2 for 48 h. The reaction was filtered through a pad of Celite. The Celite pad was eluted with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC (65 – 95% MeCN in 0.225% aqueous FA) to give (E)-4-(4-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)but-3-en-1-ol (1.4 g, 62% yield) as a yellow oil. LCMS: (MS-ES+APCI, Pos): 433.2 [M+H].

Step E. 4-(4-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)butan-1-ol. To a solution of (E)-4-(4-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-

indazol-5-yl)but-3-en-1-ol (1.3 g, 2.6 mmol) in MeOH (15 mL) was added 5% Rh/C (1.0 g, 0.49 mmol). The flask was then evacuated and backfilled with H_2 three times. The mixture was stirred at rt under an atmosphere of H_2 for 48 h. The reaction was filtered through a pad of Celite. The Celite pad was eluted with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC (65 – 95% MeCN in 0.225% aqueous FA) to give 4-(4-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)butan-1-ol (0.48 g, 28% yield) as a yellow oil. LCMS: (MS-ES+APCI, Pos): 435.2 [M+H].

Step F. 4-bromo-6-chloro-5-(4-((triisopropylsilyl)oxy)butyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole. To a solution of 4-(4-bromo-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)butan-1-ol (0.48 g, 0.84 mmol) and imidazole (0.086 g, 1.3 mmol) in DCM (8 mL) was added TIPSCl (0.23 mL, 1.1 mmol). The mixture was stirred at rt for 16 h and then it was diluted with water (20 mL) and extracted with DCM (30 mL x 3). The organics were washed with brine (50 mL x 2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-9% EtOAc in petroleum ether) to give 4-bromo-6-chloro-5-(4-((triisopropylsilyl)oxy)butyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (0.46 g, 93% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 0.8 Hz, 1H), 7.68 (s, 1H), 5.67 (s, 2H), 3.83 - 3.73 (m, 2H), 3.64 - 3.48 (m, 2H), 3.18 - 3.00 (m, 2H), 1.76 - 1.67 (m, 4H), 1.07 - 1.06 (m, 21H), 0.93 - 0.84 (m, 3H), -0.04 (s, 9H).

Step G. 6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(4-((triisopropylsilyl)oxy)butyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole. To a solution of 4-bromo-6-chloro-5-(4-((triisopropylsilyl)oxy)butyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (0.46 g, 0.78 mmol) in THF (6 mL) at -78 °C was added n-BuLi (2.5 M in hexanes; 0.47 mL). The mixture was stirred at -78 °C for 30 min then 2-isopropoxy-4,4,5-trimethyl-1,3,2-dioxaborolane (0.32 mL, 1.6 mmol) was added. The reaction was stirred at -78 °C for 1 h and then it was quenched with NH_4Cl solution (5 ml). The mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-9% EtOAc in petroleum ether) to give 6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(4-((triisopropylsilyl)oxy)butyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (0.32 g, 64% yield) as a yellow solid. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.69 (s, 1H), 5.68 (s, 2H), 3.79 - 3.68 (m, 2H), 3.62 - 3.42 (m, 2H), 3.24 - 3.05 (m, 2H), 1.74 - 1.60 (m, 4H), 1.43 (s, 12H), 1.09 - 1.03 (m, 21H), 0.92 - 0.87 (m, 2H), -0.05 (s, 9H).

Step H. 4-(benzyloxy)-7-(6-chloro-5-(4-((triisopropylsilyl)oxy)butyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.16 g, 0.34 mmol) and 6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(4-((triisopropylsilyl)oxy)butyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazole (0.30 g, 0.47 mmol) in dioxane (4 mL) and H_2O (0.4 mL) was added mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.025 g, 0.034 mmol) and Cs_2CO_3 (0.22 g, 0.67 mmol). The flask was then evacuated and backfilled with nitrogen three times. The mixture was stirred at 90 °C for 1 h. After cooling to rt, the reaction was diluted with water (30 mL) and extracted with ethyl acetate (30 mL x 3). The organics were washed with brine (50 mL x 2), dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-25% EtOAc in petroleum ether) to give 4-(benzyloxy)-7-(6-chloro-5-(4-((triisopropylsilyl)oxy)butyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.20 g, 31% yield) as a yellow solid. LCMS: (MS-ES+APCI, Pos): 921.4 [M+H].

Step I. 4-(4-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)butan-1-ol. To a solutionof 4-(benzyloxy)-7-(6-chloro-5-(4-((triisopropylsilyl)oxy)butyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-4-yl)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.16 g, 0.083 mmol) in THF (2 mL) was added $NEt_3{\cdot}HF$ (0.068 mL, 0.42 mmol). The reaction was stirred at 50 °C for 16 h. The mixture was diluted with H_2O (5 mL) and saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-100% EtOAc in petroleum ether) to give 4-(4-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-

yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)butan-1-ol (0.040 g, 59% yield) as a yellow solid. LCMS: (MS-ES+APCI, Pos): 765.2 [M+H].

Step J. benzyl (3R)-3-(((4-(4-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)butoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of 4-(4-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)butan-1-ol (0.040 g, 0.049 mmol) in DCM (1 mL) at 0 °C was added pyridine (0.016 mL, 0.20 mmol) and N,N′-disuccinimidyl carbonate (0.038 g, 0.15 mmol). The mixture was stirred at 0 °C for 1 h and then triethylamine (0.021 mL, 0.15 mmol) and benzyl (R)-3-amino-3-methylpiperidine-1-carboxylate (0.018 g, 0.074 mmol) was added. The mixture was allowed to warm to rt and stirred for 3 h. The reaction was diluted with water (10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-50% EtOAc in petroleum ether) to give benzyl (3R)-3-(((4-(4-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)butoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.040 g, 75% yield) as a yellow solid. LCMS: (MS-ES+APCI, Pos): 1039.6 [M+H].

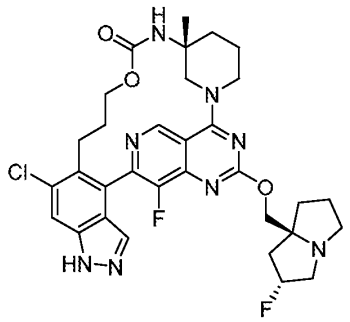
Step K. 4-(6-chloro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)butyl ((R)-3-methylpiperidin-3-yl)carbamate. To a solution of benzyl (3R)-3-(((4-(4-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)butoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.038 g, 0.035 mmol) in THF (4 mL) was added 10% Pd/C (0.037 g, 0.035 mmol). The flask was then evacuated and backfilled with H_2 three times. The mixture was stirred at rt under an atmosphere of H_2 for 1 h. The reaction was filtered through a pad of Celite. The Celite pad was eluted with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure to give 4-(6-chloro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-

1H-indazol-5-yl)butyl ((R)-3-methylpiperidin-3-yl)carbamate (0.025 g, 87% yield) as a yellow solid, which was used directly without further purification. LCMS: (MS-ES+APCI, Pos): 815.4 [M+H].

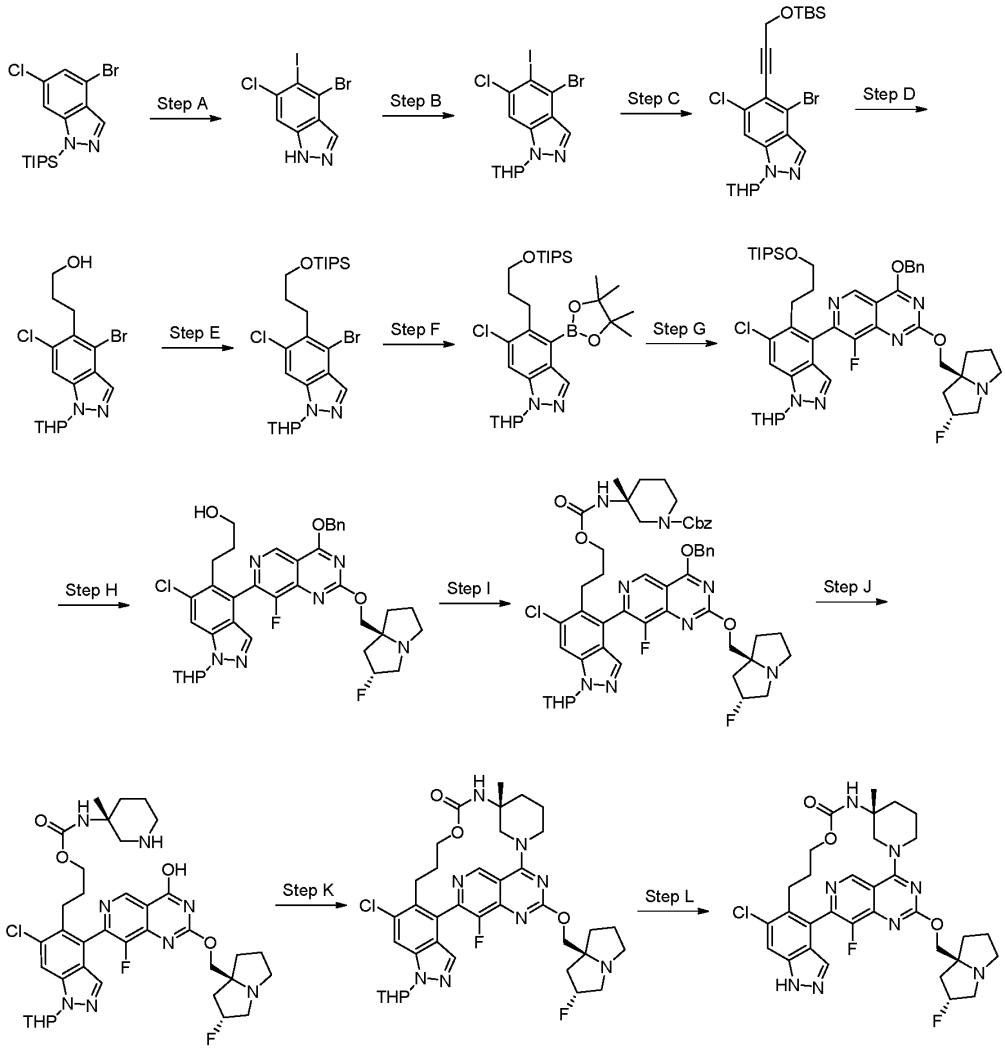
Step L. (3^3R)-1^6-chloro-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-methyl-1^1-((2-(trimethylsilyl)ethoxy)methyl)-1^1H-6-oxa-4-aza-2(7,4)-pyrido[4,3-d]pyrimidina-1(4,5)-indazola-3(1,3)-piperidinacyclodecaphan-5-one. To a solution of 4-(6-chloro-4-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indazol-5-yl)butyl ((R)-3-methylpiperidin-3-yl)carbamate (0.025 g, 0.031 mmol) in CH_3CN (15 mL) was added BroP (0.036 g, 0.092 mmol) and DIPEA (0.027 mL, 0.15 mmol). The mixture was stirred for 16 h and then it was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with DCM (10 mL x 3). The organics were washed with brine (20 mL x 2), dried over sodium sulfate, filtered and concentrated under reduced pressure to give (3^3R)-1^6-chloro-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-methyl-1^1-((2-(trimethylsilyl)ethoxy)methyl)-1^1H-6-oxa-4-aza-2(7,4)-pyrido[4,3-d]pyrimidina-1(4,5)-indazola-3(1,3)-piperidinacyclodecaphan-5-one (0.020 g, 82% yield) as a yellow solid, which was used directly without further purification. LCMS: (MS-ES+APCI, Pos): 797.4 [M+H].

Step M. (3^3R)-1^6-chloro-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-methyl-1^1H-6-oxa-4-aza-2(7,4)-pyrido[4,3-d]pyrimidina-1(4,5)-indazola-3(1,3)-piperidinacyclodecaphan-5-one. To a solution of (3^3R)-1^6-chloro-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-methyl-1^1-((2-(trimethylsilyl)ethoxy)methyl)-1^1H-6-oxa-4-aza-2(7,4)-pyrido[4,3-d]pyrimidina-1(4,5)-indazola-3(1,3)-piperidinacyclodecaphan-5-one (0.020 g, 0.025 mmol) in DCM (1 mL) at 0 °C was added 5% TFA in HFIP (2.0 mL, 0.050 mmol). The mixture was allowed to warm to rt and was stirred for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC (30-60% MeCN in 0.5% aqueous NH_4HCO_3) to give (3^3R)-1^6-chloro-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-methyl-1^1H-6-oxa-4-aza-2(7,4)-pyrido[4,3-d]pyrimidina-1(4,5)-indazola-3(1,3)-piperidinacyclodecaphan-5-one (0.0028 g, 17% yield) as a white solid. LCMS: (MS-ES+APCI, Pos): 667.1 [M+H].

Compound 545

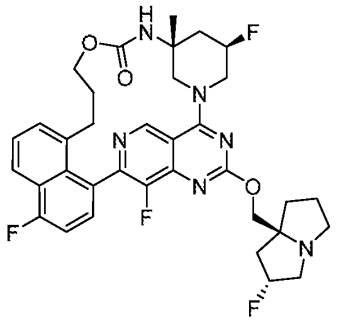


(3^3R)-1^6-chloro-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-methyl-1^1H-6-oxa-4-aza-2(7,4)-pyrido[4,3-d]pyrimidina-1(4,5)-indazola-3(1,3)-piperidinacyclononaphan-5-one

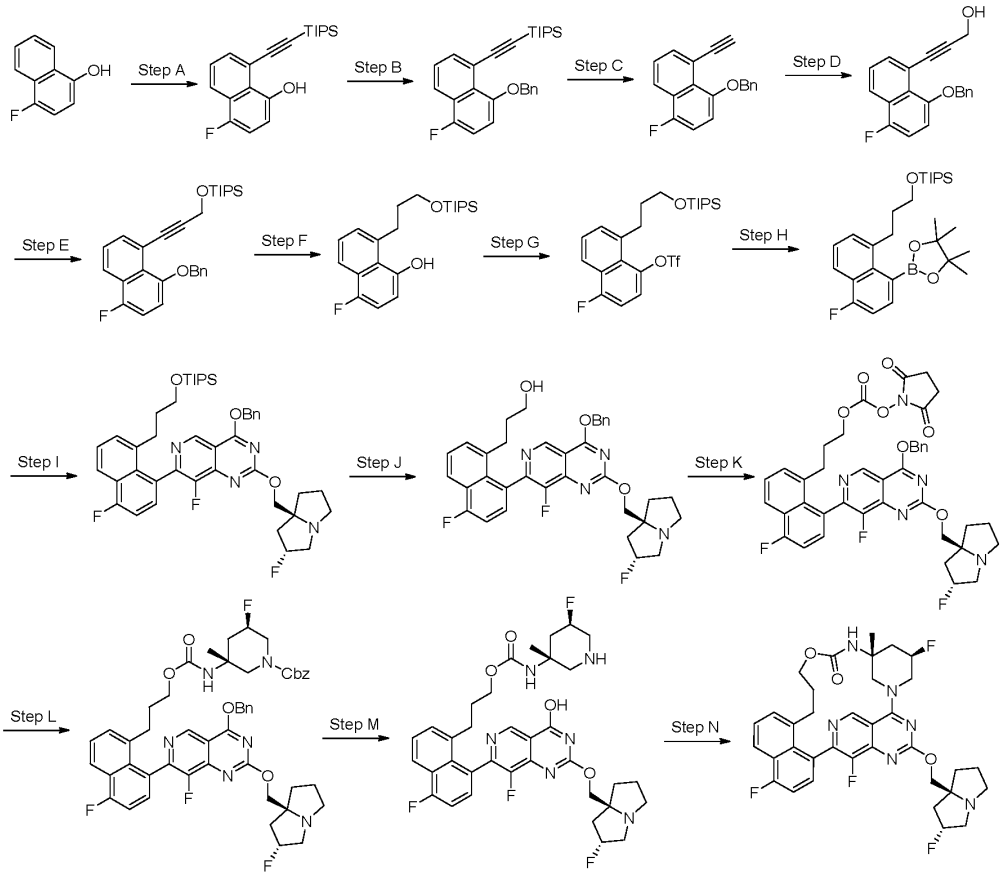


Steps A-L were by following the procedure of Compound 532 (Steps A-M). LCMS (MM-ES+APCI, Pos): m/z 653.2 (M+H).

Compound 533



(1^3R,1^5R)-1^5,2^8,3^4-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. 4-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol. To a solution of 4-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (2.0 g, 12 mmol),

(bromoethynyl)triisopropylsilane (3.9 g, 15 mmol) in DCE (25 mL) was added potassium carbonate (1.7 g, 12 mmol), sodium acetate (0.20 g, 2.5 mmol), and dichloro(p-cymene)ruthenium(II) dimer (0.76 g, 1.2 mmol). The flask was then evacuated and backfilled with nitrogen three times. The mixture was stirred at 40 °C under an atmosphere of nitrogen for 5 h. The reaction mixture was filtered and the filtrate was concentrated under educed pressure. The residue was purified by silica gel column chromatography (100% petroleum ether) to give 4-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (1.3 g, 29% yield) as an orange solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 8.99 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.10 (t, J = 9.2 Hz, 1H), 6.90 (dd, J = 4.8, 8.4 Hz, 1H), 1.26 - 1.13 (m, 21H).

Step B. ((8-(benzyloxy)-5-fluoronaphthalen-1-yl)ethynyl)triisopropylsilane. To a solution of 4-fluoro-8-((triisopropylsilyl)ethynyl)naphthalen-1-ol (1.3 g, 3.6 mmol) in in DMF (30 mL) was added K_2CO_3 (1.5 g, 11 mmol) and BnBr (0.64 mL, 5.4 mmol). The reaction was stirred at rt for 12 h. The mixture was diluted with H_2O (50 mL) and then extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% petroleum ether) to give ((8-(benzyloxy)-5-fluoronaphthalen-1-yl)ethynyl)triisopropylsilane (1.6 g, 98 % yield) as a yellow solid. LCMS: (MS-ES+APCI, Pos): 433.1[M+H].

Step C. 4-(benzyloxy)-5-ethynyl-1-fluoronaphthalene. To a solution of (8-(benzyloxy)-5-fluoronaphthalen-1-yl)ethynyl)triisopropylsilane (1.6 g, 3.6 mmol) in THF (20 mL) was added TBAF (1 M in THF; 7.1 mL). The reaction was stirred at rt for 2 h. The mixture was diluted with H_2O (40 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% petroleum ether) to give 4-(benzyloxy)-5-ethynyl-1-fluoronaphthalene (1.4 g) as a yellow solid. LCMS: (MS-ES+APCI, Pos): 277.1[M+H].

Step D. 3-(8-(benzyloxy)-5-fluoronaphthalen-1-yl)prop-2-yn-1-ol. A flask containing dicyclohexyl(4-(N,N-dimethylamino)phenyl)phosphine (0.51 g, 1.1 mmol) and (phenylethynyl)copper (0.15 g, 0.90 mmol) in toluene (10 mL) was evacuated and backfilled with nitrogen three times. The mixture was stirred at 70 °C for 1 h, then formaldehyde (37% purity; 3.4 mL, 45 mmol) and 4-(benzyloxy)-5-ethynyl-1-fluoronaphthalene (1.3 g, 4.5 mmol) was added. The mixture was stirred at 70 °C for 1 h. The suspension was filtered

through a pad of Celite. The Celite pad was washed with ethyl acetate (80 mL). The mixture was concentrated under reduced pressure. The residue was diluted with H_2O (100 mL) and then extracted with ethyl acetate (150 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-20% EtOAc in petroleum ether) to give 3-(8-(benzyloxy)-5-fluoronaphthalen-1-yl)prop-2-yn-1-ol (1.0 g, 76% yield) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 8.05 (d, *J* = 8.4 Hz, 1H), 7.76 - 7.67 (m, 1H), 7.64 - 7.55 (m, 2H), 7.51 - 7.36 (m, 4H), 7.13 - 7.05 (m, 1H), 6.88 (dd, *J* = 4.4, 8.8 Hz, 1H), 5.23 - 5.12 (m, 2H), 3.99 (br d, *J* = 4.8 Hz, 2H).

Step E. ((3-(8-(benzyloxy)-5-fluoronaphthalen-1-yl)prop-2-yn-1-yl)oxy)triisopropylsilane. To a solution of 3-(8-(benzyloxy)-5-fluoronaphthalen-1-yl)prop-2-yn-1-ol (0.50 g, 1.6 mmol) and imidazole (0.22 g, 3.3 mmol) in DCM (5 mL) at 0 °C was added TIPSCl (0.42 mL, 2.0 mmol). The reaction was warmed to rt and stirred for 1 h. The mixture was diluted with H_2O (250 mL) and extracted with ethyl acetate (100mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-2% EtOAc in petroleum ether) to give ((3-(8-(benzyloxy)-5-fluoronaphthalen-1-yl)prop-2-yn-1-yl)oxy)triisopropylsilane (0.63 g, 83% yield) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$-*d*) δ = 8.02 (d, *J* = 8.4 Hz, 1H), 7.71 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.58 - 7.52 (m, 2H), 7.47 (dd, *J* = 7.2, 8.4 Hz, 1H), 7.43 - 7.38 (m, 2H), 7.37 - 7.32 (m, 1H), 7.05 (dd, *J* = 8.4, 9.6 Hz, 1H), 6.82 (dd, *J* = 4.4, 8.4 Hz, 1H), 5.17 (s, 2H), 4.11 (s, 2H), 1.11 - 1.05 (m, 21H).

Step F. 4-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-ol. To a solution of ((3-(8-(benzyloxy)-5-fluoronaphthalen-1-yl)prop-2-yn-1-yl)oxy)triisopropylsilane (0.63 g, 1.4 mmol) in THF (10 mL) was added 10 % Pd/C (0.72 g, 0.68 mmol). The flask was evacuated and backfilled with H_2 three times. The mixture was stirred at 35 °C for 2 h. The suspension was filtered through a pad of Celite. The Celite pad was washed with THF (60 mL). The filtrate was concentrated under reduced pressure to give 4-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-ol (0.44 g, 86% yield) as yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8.4 Hz, 1H), 7.46 - 7.40 (m, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 6.97 (dd, *J* = 8.4, 9.6 Hz, 1H), 6.79 - 6.73 (m, 1H), 6.36 (s, 1H), 3.72 (t, *J* = 6.0 Hz, 2H), 3.48 (t, *J* = 7.6 Hz, 2H), 2.05 - 1.97 (m, 2H), 1.19 - 1.12 (m, 3H), 1.10 - 1.07 (m, 18H).

Step G. 4-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl trifluoromethanesulfonate. To a solution of 4-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-ol (0.43 g, 1.1 mmol) in DMA (5 mL) was added

DIPEA (0.40 mL, 2.3 mmol) and N-phenyl-bis(trifluoromethanesulfonimide) (0.53 g, 1.5 mmol). The reaction was stirred for 2 h. The mixture was diluted H_2O (10 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% petroleum ether) to give 4-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl trifluoromethanesulfonate (0.46 g, 68% yield) as yellow solid. LCMS: (MS-ES+APCI, Pos): 509.3 [M+H].

Step H. (3-(5-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)triisopropylsilane. To a solution of 4-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl trifluoromethanesulfonate (0.82 g, 1.6 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.4 mL, 9.7 mmol) in MeCN (8 mL) was added triethylamine (1.4 mL, 9.7 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (0.26 g, 0.32 mmol). The solution was sparged with N_2 for 1 min and then it was heated to 80 °C for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-2% EtOAc in petroleum ether) to give (3-(5-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)triisopropylsilane (0.53 g, 63% yield) as yellow oil. LCMS: (MS-ES+APCI, Pos): 487.3 [M+H].

Step I. 4-(benzyloxy)-8-fluoro-7-(4-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of (3-(5-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propoxy)triisopropylsilane (0.30 g, 0.58 mmol) and 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.25 g, 0.53 mmol) in dioxane (4 mL) and H_2O (0.8 mL) was added Cs_2CO_3 (0.34 g, 1.1 mmol) and mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.038 g, 0.052 mmol). The solution was sparged with N_2 for 1 min and then it was heated to 90 °C and stirred for 3 h. The mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (8 mL x 4). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (50% EtOAc in petroleum ether) to give 4-(benzyloxy)-8-fluoro-7-(4-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.22 g, 44% yield) as yellow oil. LCMS: (MS-ES+APCI, Pos): 771.5 [M+H].

Step J. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-

yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-fluoronaphthalen-1-yl)propan-1-ol. To a solution of 4-(benzyloxy)-8-fluoro-7-(4-fluoro-8-(3-((triisopropylsilyl)oxy)propyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.22 g, 0.23 mmol) in THF (2 mL) was added $3HF{\cdot}NEt_3$ (0.75 mL, 4.6 mmol). The reaction was heated to 50 °C for 16 h. The mixture was diluted with saturated aqueous sodium bicarbonate (4 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (50% EtOAc in petroleum ether) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-fluoronaphthalen-1-yl)propan-1-ol (0.11 g, 77% yield) as yellow oil. LCMS: (MS-ES+APCI, Pos): 615.3 [M+H].

Step K. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-fluoronaphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-fluoronaphthalen-1-yl)propan-1-ol (0.11 g, 0.18 mmol) in DCM (1 mL) was added pyridine (0.029 mL, 0.35 mmol) and N,N′-disuccinimidyl carbonate (0.14 g, 0.53 mmol). The reaction was stirred for 1 h. The mixture was diluted with H_2O (2 mL) and extracted with ethyl acetate (4 mL x 6). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-fluoronaphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.12 g, 86% yield) as yellow oil. LCMS: (MS-ES+APCI, Pos): 756.4 [M+H].

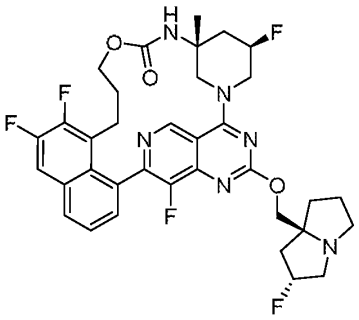
Step L. benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-fluoronaphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-fluoronaphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.13 g, 0.17 mmol) and benzyl (3R,5R)-3-amino-5-fluoro-3-methylpiperidine-1-carboxylate (0.054 g, 0.19 mmol) in DCM (1 mL) was added DIPEA (0.089 mL, 0.51 mmol). The reaction was stirred at 35 °C for 2 h. The mixture was diluted with H_2O (3 mL) and extracted with ethyl acetate (8 mL x 3). The combined organic layers

were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (100% EtOAc) to give benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-fluoronaphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.15 g, 94% yield) as a yellow oil. LCMS: (MS-ES+APCI, Pos): 907.6 [M+H].

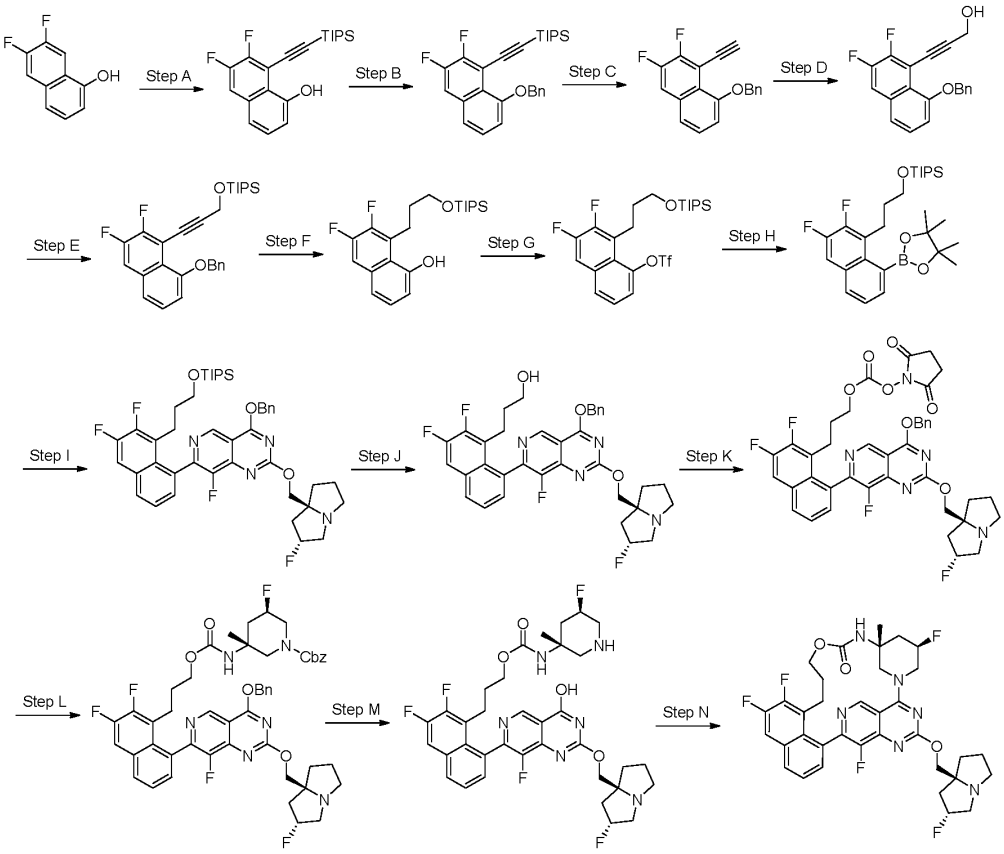
Step M. 3-(5-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate. To a solution of benzyl (3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-5-fluoronaphthalen-1-yl)propoxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.15 g, 0.16 mmol) in THF (4 mL) was added 10% Pd/C (0.10 g, 0.096 mmol). The flask was evacuated and backfilled with H_2 three times. The mixture was stirred for 2 h. The suspension was filtered through a pad of Celite. The Celite pad was washed with THF (30 mL). The mixture was concentrated under reduced pressure to give 3-(5-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.070 g, 64% yield) as yellow oil.

Step N. (1^3R,1^5R)-1^5,2^8,3^4-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(5-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.070 g, 0.10 mmol) in MeCN (36 mL) was added BroP (0.12 g, 0.31 mmol) and DIPEA (0.089 mL, 0.51 mmol). The reaction was stirred at rt for 2 h. The mixture was concentrated under reduced pressure. The residue was diluted with H_2O (10 mL) and extracted with ethyl acetate (12 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (43–73% MeCN in 0.1% aqueous NH_4HCO_3) to give (1^3R,1^5R)-1^5,2^8,3^4-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.018 g, 27% yield) as a white solid. LCMS: (MS-ES+APCI, Pos): 665.4 [M+H].

Compound 546

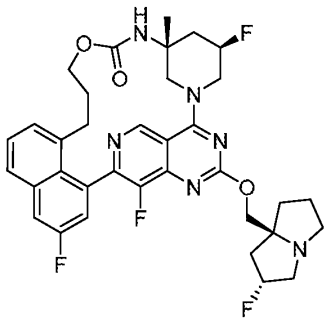


(1^3R,1^5R)-1^5,2^8,3^6,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one

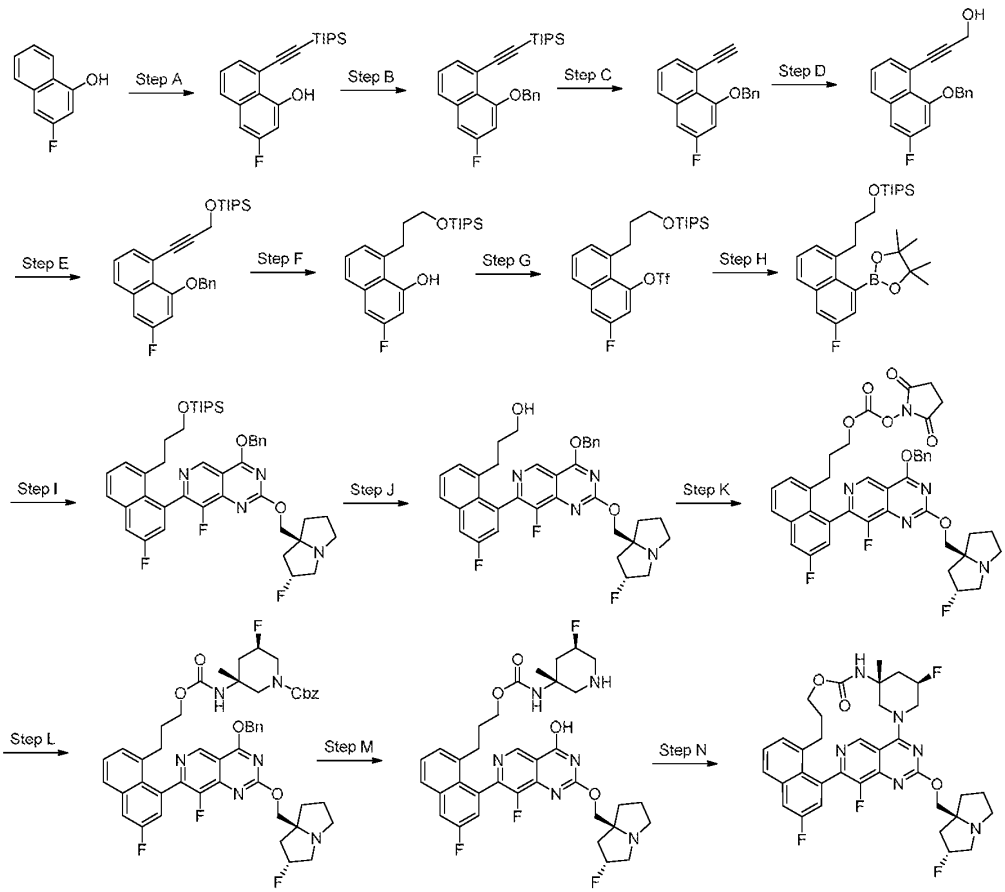


Steps A-N were by following the procedure of Compound 533 (Steps A-N). LCMS (MM-ES+APCI, Pos): m/z 683.3 (M+H).

Compound 547

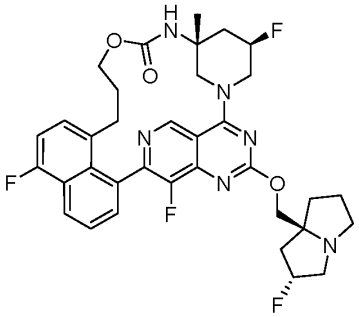


(1^3R,1^5R)-1^5,2^8,3^3-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one

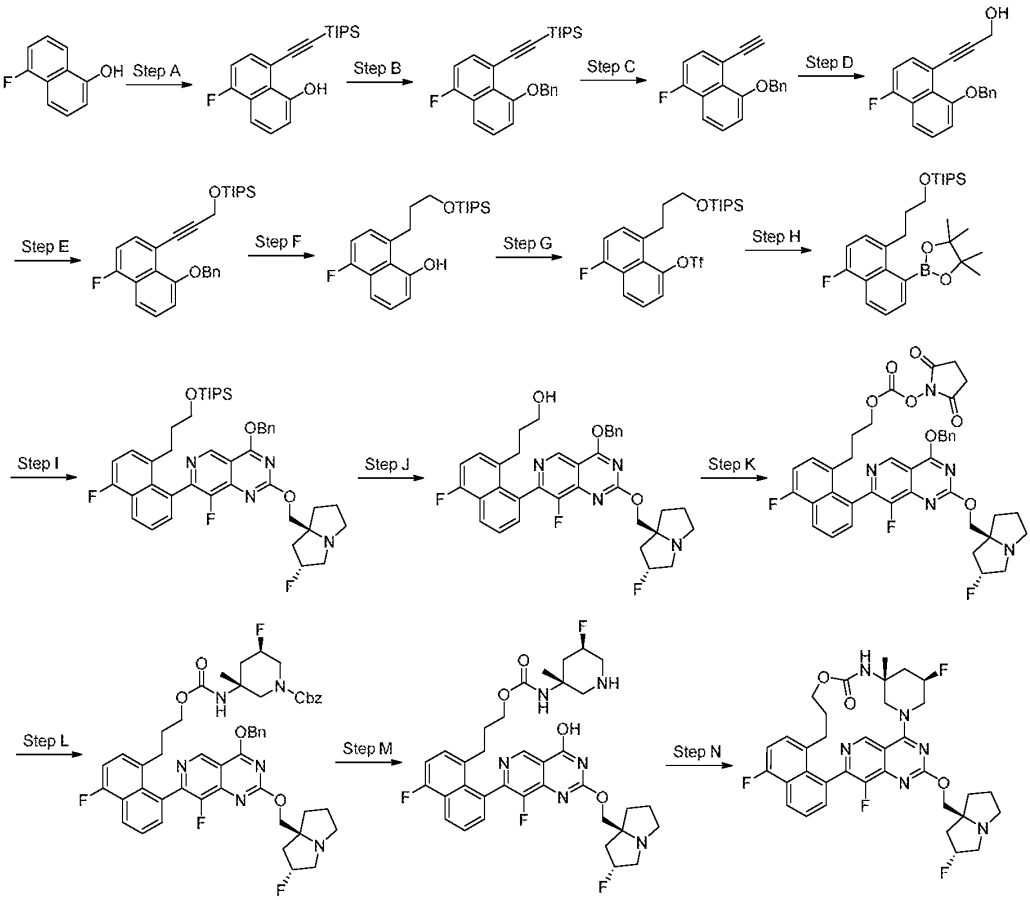


Steps A-N were by following the procedure of Compound 533 (Steps A-N). LCMS (MM-ES+APCI, Pos): m/z 665.5 (M+H).

Compound 560

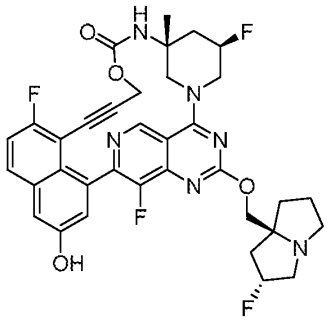


(1^3R,1^5R)-1^5,2^8,3^5-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one

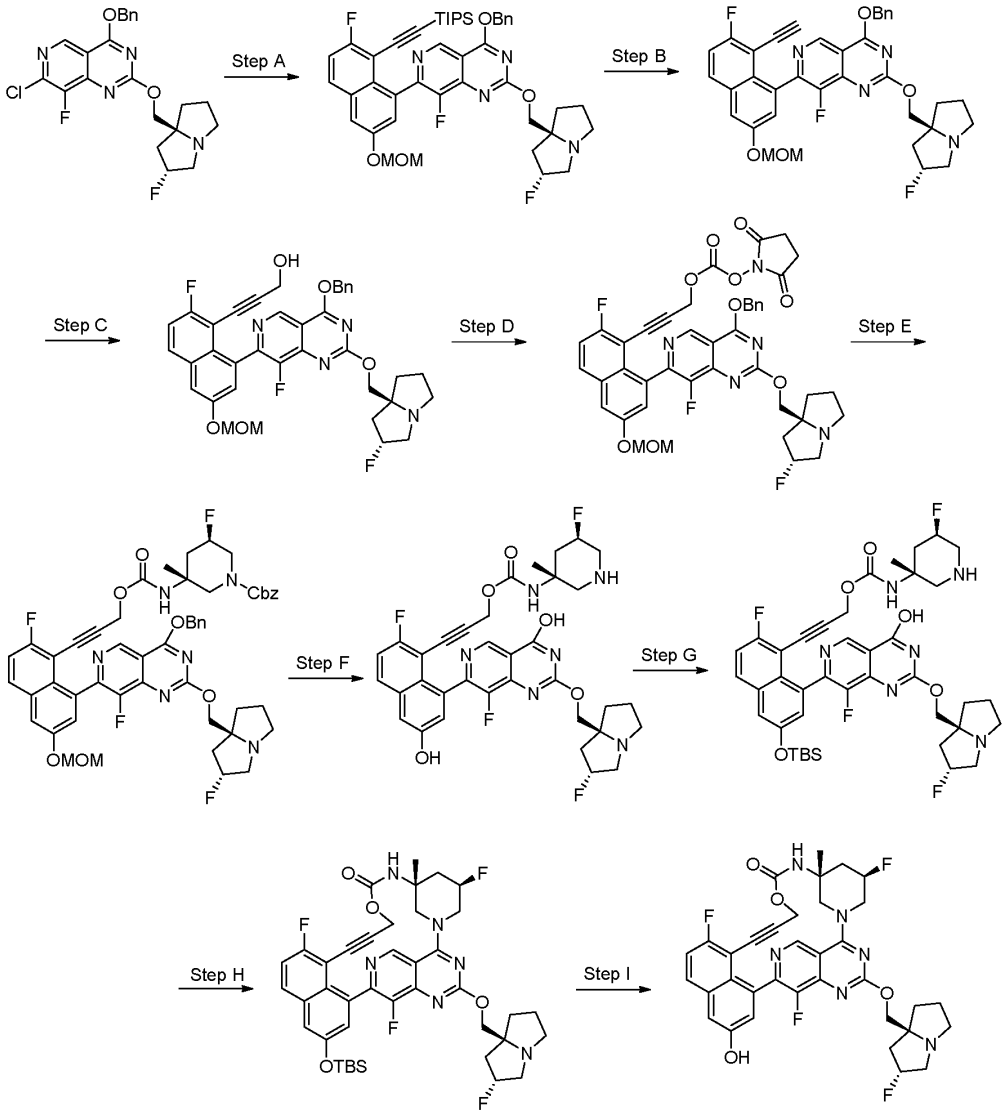


Steps A-N were by following the procedure of Compound 533 (Steps A-N). LCMS (MM-ES+APCI, Pos): m/z 665.3 (M+H).

Compound 551



(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one



Step A. 4-(benzyloxy)-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]pyrimidine. To a solution of 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (1 g, 2.2 mmol) in dioxane (10 mL) and H_2O (1 mL) was added ((2-fluoro-6-(methoxymethoxy)-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethynyl)triisopropylsilane (1.3 g, 2.5 mmol), mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.16 g, 0.22 mmol) and K_2CO_3

(0.77 g, 5.6 mmol). The vial was sparged with nitrogen for 2 min and then it was heated to 90 °C for 2 h. The mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The reside was purified by silica gel column chromatography (0-50% EtOAc in petroleum ether) to give 4-(benzyloxy)-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]pyrimidine (1.0 g, 56% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 797.5 (M+H).

Step B. 4-(benzyloxy)-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]pyrimidine. To a solution of 4-(benzyloxy)-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]pyrimidine (1.0 g, 1.3 mmol) in THF (10 mL) was added $3HF{\cdot}NEt_3$ (0.61 mL, 3.8 mmol). The vial was sparged with nitrogen for 2 min and then it was heated to 50 °C for 12 h. The mixture was diluted with H_2O (5 mL) and then it was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-50% EtOAc in petroleum ether) to give 4-(benzyloxy)-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]pyrimidine (0.70 g, 87% yield) as a yellow solid.

Step C. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol. A flask containing a solution of 2-phenylethynylcopper (0.036 g, 0.22 mmol) and 1,4-bis(dicyclohexylphosphino)-butane (0.12 g, 0.27 mmol) in toluene (7 mL) was sparged with nitrogen for 2 min The mixture was heated to 60 °C for 1 h. To the mixture was added 4-(benzyloxy)-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]pyrimidine (0.70 g, 1.1 mmol) and 37% formaldehyde (0.81 mL, 11 mmol). The flask was sparged with nitrogen for 2 min and then it was heated to 60 °C for 1 h. The mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel

column chromatography (0-100% EtOAc in petroleum ether) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol (0.40 g, 55% yield) as a yellow solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ = 9.25 (s, 1H), 7.80 (br dd, *J* = 5.6, 8.8 Hz, 1H), 7.53 (br s, 3H), 7.47 - 7.35 (m, 4H), 7.30 (br s, 1H), 5.71 (s, 2H), 5.42 - 5.21 (m, 3H), 4.49 (br dd, *J* = 7.2, 10.4 Hz, 1H), 4.28 (br dd, *J* = 10.8, 18.8 Hz, 1H), 3.77 - 3.59 (m, 2H), 3.52 (s, 3H), 3.37 - 3.10 (m, 3H), 3.04 - 2.94 (m, 1H), 2.28 - 2.16 (m, 2H), 2.02 - 1.86 (m, 4H).

Step D. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-yl (2,5-dioxopyrrolidin-1-yl) carbonate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-ol (0.40 g, 0.60 mmol) and pyridine (0.24 mL, 3.0 mmol) in DCM (4 mL) was added N,N -disuccinimidyl carbonate (0.46 g, 1.8 mmol). The reaction was stirred for 1 h and then it was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-yl (2,5-dioxopyrrolidin-1-yl) carbonate (0.48 g, 99% yield), which was taken into the next step without further purification.

Step E. benzyl (3R,5R)-3-((((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-yl)oxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-yl (2,5-dioxopyrrolidin-1-yl) carbonate (0.48 g, 0.59 mmol) in DCM (5 mL) was added DIPEA (0.31 mL, 1.8 mmol) and benzyl (3R,5R)-3-amino-5-fluoro-3-methylpiperidine-1-carboxylate (0.17 g, 0.60 mmol). The mixture was stirred for 1 h and then it was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-50% EtOAc in petroleum ether) to give

benzyl (3R,5R)-3-((((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-yl)oxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.36 g, 63% yield) was obtained as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 963.3 (M+H).

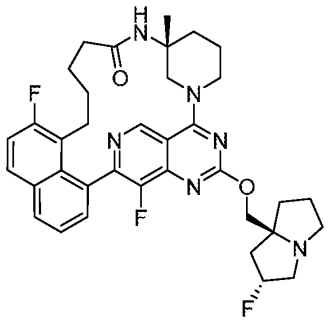
Step F. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)prop-2-yn-1-yl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate. A solution of benzyl (3R,5R)-3-((((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)prop-2-yn-1-yl)oxy)carbonyl)amino)-5-fluoro-3-methylpiperidine-1-carboxylate (0.30 g, 0.31 mmol) in TFA (2.0 mL) was heated to 45 °C for 1 h. The mixture was diluted with H2O (5 mL) and then it was neutralized with sat. aq. NaHCO3 (2 mL). The mixture was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (15 – 45% MeCN in 0.1% aqueous NH_4HCO_3) to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)prop-2-yn-1-yl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.20 g, 92% yield) as a white solid.

Step G. 3-(6-((tert-butyldimethylsilyl)oxy)-2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)prop-2-yn-1-yl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate. To a solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)-6-hydroxynaphthalen-1-yl)prop-2-yn-1-yl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.20 g, 0.29 mmol) and TBSCl (0.052 g g, 0.35 mmol) in DCM (2 mL) was added imidazole (0.039 g, 0.58 mmol) and DMAP (0.0035 g, 0.029 mmol). The reaction was stirred at for 2 h and then it was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 3-(6-((tert-butyldimethylsilyl)oxy)-2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)prop-2-yn-1-yl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.20 g, 86% yield) as a yellow oil, which was taken into the next step without further purification.

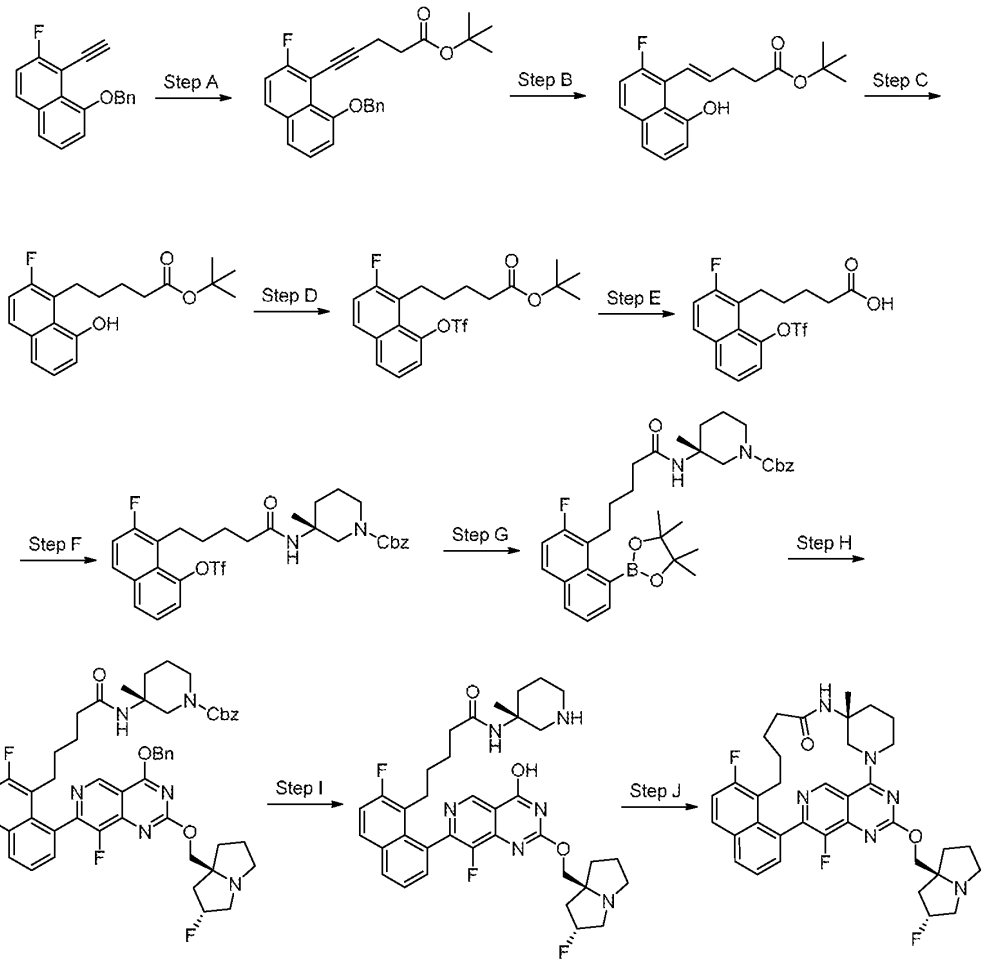
Step H. (1^3R,1^5R)-3^3-((tert-butyldimethylsilyl)oxy)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one. To a solution of 3-(6-((tert-butyldimethylsilyl)oxy)-2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)prop-2-yn-1-yl ((3R,5R)-5-fluoro-3-methylpiperidin-3-yl)carbamate (0.050 g, 0.062 mmol) in MeCN (50 mL) was added BroP (0.072 g, 0.19 mmol) and DIPEA (0.054 mL, 0.31 mmol). The reaction was stirred at for 2 h and then it was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (5% MeOH in DCM) to give (1^3R,1^5R)-3^3-((tert-butyldimethylsilyl)oxy)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one (0.030 g, 61% yield) as a yellow oil.

Step I. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one. To a solution of (1^3R,1^5R)-3^3-((tert-butyldimethylsilyl)oxy)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one (0.030 g, 0.038 mmol) in THF (0.5 mL) was added 3HF·NEt_3 (0.012 mL, 0.076 mmol). The reaction was stirred for 30 min and then it was diluted with H_2O (2 mL) and DIPEA (2 mL). The mixture was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (38 – 68% MeCN in 0.1% aqueous NH_4HCO_3). The residue was repurified by preparative HPLC (10 – 40% MeCN in 0.225% aqueous formic acid) to give (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-4-yn-8-one (0.0023 g, 39% yield) was obtained as a white solid. LCMS (MM-ES+APCI, Pos): m/z 677.3 (M+H).

Compound 552



(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. tert-butyl 5-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)pent-4-ynoate. A solution of triruthenium dodecacarbonyl (0.17 g, 0.27 mmol) and 1-chloro-1,1,1-triphenyl-N-(triphenylphosphoranylidene)phosphoranamine (0.77 g, 1.4 mmol) in NMP (20 mL) was heated to 80 °C for 1 h. To the solution at 80 °C was added 8-(benzyloxy)-1-ethynyl-2-fluoronaphthalene (4 g, 13.46 mmol, 1 eq) and a solution of tert-butyl acrylate (9.8 mL, 67 mmol) in NMP (20 mL). The reaction was stirred at 80 °C for 15 h. The mixture was purified by preparative HPLC (0-100% MeCN in 0.1% aqueous trifluoroacetic acid) to give tert-butyl 5-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)pent-4-ynoate (3.0 g, 54% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 348.9 (M+H-tBu).

Step B. tert-butyl (E)-5-(2-fluoro-8-hydroxynaphthalen-1-yl)pent-4-enoate. To a solution of tert-butyl 5-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)pent-4-ynoate (1.5 g, 3.6 mmol) in THF (10 mL) and *i*-PrOH (10 mL) at 0 °C was added 10% Pd/C (0.39 g, 0.36 mmol) and ammonium formate (2.3 g, 36 mmol). The mixture was stirred for 16 h and then it was diluted with water (50 mL). The suspension was filtered through a pad of Celite. The Celite pad was washed with ethyl acetate (50 mL). The aqueous phase was extracted by ethyl acetate (50 mL x 3). The combined organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give tert-butyl (E)-5-(2-fluoro-8-hydroxynaphthalen-1-yl)pent-4-enoate (1.1 g, 96% yield) as a yellow oil. LCMS (MM-ES+APCI, Neg): m/z 315.2 (M-H).

Step C. tert-butyl 5-(2-fluoro-8-hydroxynaphthalen-1-yl)pentanoate. To a solution of tert-butyl (E)-5-(2-fluoro-8-hydroxynaphthalen-1-yl)pent-4-enoate (1.1 g, 3.3 mmol) in MeOH (5 mL) and THF (5 mL) was added 1-% Pd/C (0.37 g, 0.35 mmol). The flask was evacuated and backfilled with hydrogen three times. The mixture was stirred at 40 °C at 50 Psi of H_2 for 16 h. The suspension was filtered and the filter cake was washed with MeOH (50 mL) and THF (50 mL). The filtrate was concentrated under reduced pressure to give tert-butyl 5-(2-fluoro-8-hydroxynaphthalen-1-yl)pentanoate (1.1 g, 99% yield) as a yellow oil. LCMS (MM-ES+APCI, Neg): m/z 317.2 (M-H).

Step D. tert-butyl 5-(2-fluoro-8-(((trifluoromethyl)sulfonyl)oxy)naphthalen-1-yl)pentanoate. To a solution of tert-butyl 5-(2-fluoro-8-hydroxynaphthalen-1-yl)pentanoate (1.1 g, 3.5 mmol) in DMA (10 mL) was added DIPEA (1.8 mL, 10 mmol) and N-phenyl-bis(trifluoromethanesulfonimide) (1.5 g, 4.2 mmol). The reaction was stirred at 40 °C for 2 h. The mixture was diluted with water (20 mL) and then extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified

by silica gel column chromatography (0-9% EtOAc in petroleum ether) to give tert-butyl 5-(2-fluoro-8-(((trifluoromethyl)sulfonyl)oxy)naphthalen-1-yl)pentanoate (1.6 g, 92% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 394.9 (M+H-tBu).

Step E. 5-(2-fluoro-8-(((trifluoromethyl)sulfonyl)oxy)naphthalen-1-yl)pentanoic acid. To a solution of tert-butyl 5-(2-fluoro-8-(((trifluoromethyl)sulfonyl)oxy)naphthalen-1-yl)pentanoate (1.6 g, 3.2 mmol) in DCM (16 mL) was added TFA (3.8 mL, 51 mmol). The reaction was stirred at 30 °C for 4 h and then it was diluted with water (40 mL). The pH of mixture was adjusted to 7 by using saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 5-(2-fluoro-8-(((trifluoromethyl)sulfonyl)oxy)naphthalen-1-yl)pentanoic acid (1.5 g, 89% yield) as a yellow oil, which was used into the next step directly. LCMS (MM-ES+APCI, Pos): m/z 394.9 (M+H).

Step F. benzyl (R)-3-(5-(2-fluoro-8-(((trifluoromethyl)sulfonyl)oxy)naphthalen-1-yl)pentanamido)-3-methylpiperidine-1-carboxylate. To a solution of 5-(2-fluoro-8-(((trifluoromethyl)sulfonyl)oxy)naphthalen-1-yl)pentanoic acid (1.5 g, 2.8 mmol) in DMF (15 mL) was added HATU (2.2 g, 5.7 mmol) and DIPEA (3.0 mL, 17 mmol). The reaction was stirred for 1 h and then benzyl (R)-3-amino-3-methylpiperidine-1-carboxylate (1.1 g, 4.3 mmol) was added. The mixture was stirred for 1 h and then it was diluted with water (50 mL) and extracted with ethyl acetate (25 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-17% EtOAc in petroleum ether) to give benzyl (R)-3-(5-(2-fluoro-8-(((trifluoromethyl)sulfonyl)oxy)naphthalen-1-yl)pentanamido)-3-methylpiperidine-1-carboxylate (1.7 g, 92% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 625.1 (M+H).

Step G. benzyl (R)-3-(5-(2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)pentanamido)-3-methylpiperidine-1-carboxylate. To a solution f benzyl (R)-3-(5-(2-fluoro-8-(((trifluoromethyl)sulfonyl)oxy)naphthalen-1-yl)pentanamido)-3-methylpiperidine-1-carboxylate (1.7 g, 2.6 mmol) in MeCN (20 mL) was added NEt_3 (2.2 mL, 16 mmol) and $Pd(dppf)Cl_2$ (0.19 g, 0.26 mmol). The vial was evacuated and backfilled with nitrogen three times and then 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.3 mL, 16 mmol) was added. The mixture was stirred at 80 °C for 2 h. The suspension was filtered and the filter cake was washed with MeCN (20 mL). The filtrate was concentrated under reduced pressure. The

residue was purified by silica gel column chromatography (0-17% EtOAc in petroleum ether) to give benzyl (R)-3-(5-(2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)pentanamido)-3-methylpiperidine-1-carboxylate (1.3 g, 43% yield) as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 603.3 (M+H).

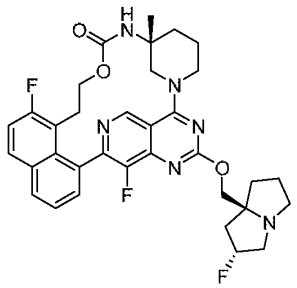
Step H. benzyl (R)-3-(5-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)pentanamido)-3-methylpiperidine-1-carboxylate. To a solution of (R)-3-(5-(2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)pentanamido)-3-methylpiperidine-1-carboxylate (1.3 g, 1.1 mmol) in dioxane (10 mL) and H_2O (2 mL) was added Cs_2CO_3 (0.73 g, 2.2 mmol), 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.50 g, 1.1 mmol) and mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.082 g, 0.11 mmol). The vial was then evacuated and backfilled with nitrogen three times. The mixture was stirred at 90 °C for 2 h. The suspension was filtered and the filter cake was washed with dioxane (20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-25% (25% EtOH in EtOAc) in petroleum ether) to give benzyl (R)-3-(5-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)pentanamido)-3-methylpiperidine-1-carboxylate (0.80 g, 66% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 887.3 (M+H).

Step I. 5-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)-N-((R)-3-methylpiperidin-3-yl)pentanamide. To a solution of benzyl (R)-3-(5-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)pentanamido)-3-methylpiperidine-1-carboxylate (0.40 g, 0.37 mmol) in THF (10 mL) was added 10% Pd/C (0.39 g, 0.37 mmol. The flask was evacuated and backfilled with hydrogen three times. The mixture was stirred under H_2 for 2 h. The suspension was filtered and the filter cake was washed with MeOH (50 mL) and THF (50 mL). The filtrate was concentrated under reduced pressure to give 5-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)-N-((R)-3-methylpiperidin-3-yl)pentanamide (0.29 g, 97% yield) as a colorless oil, which was used in the next step directly. LCMS (MM-ES+APCI, Pos): m/z 663.2 (M+H).

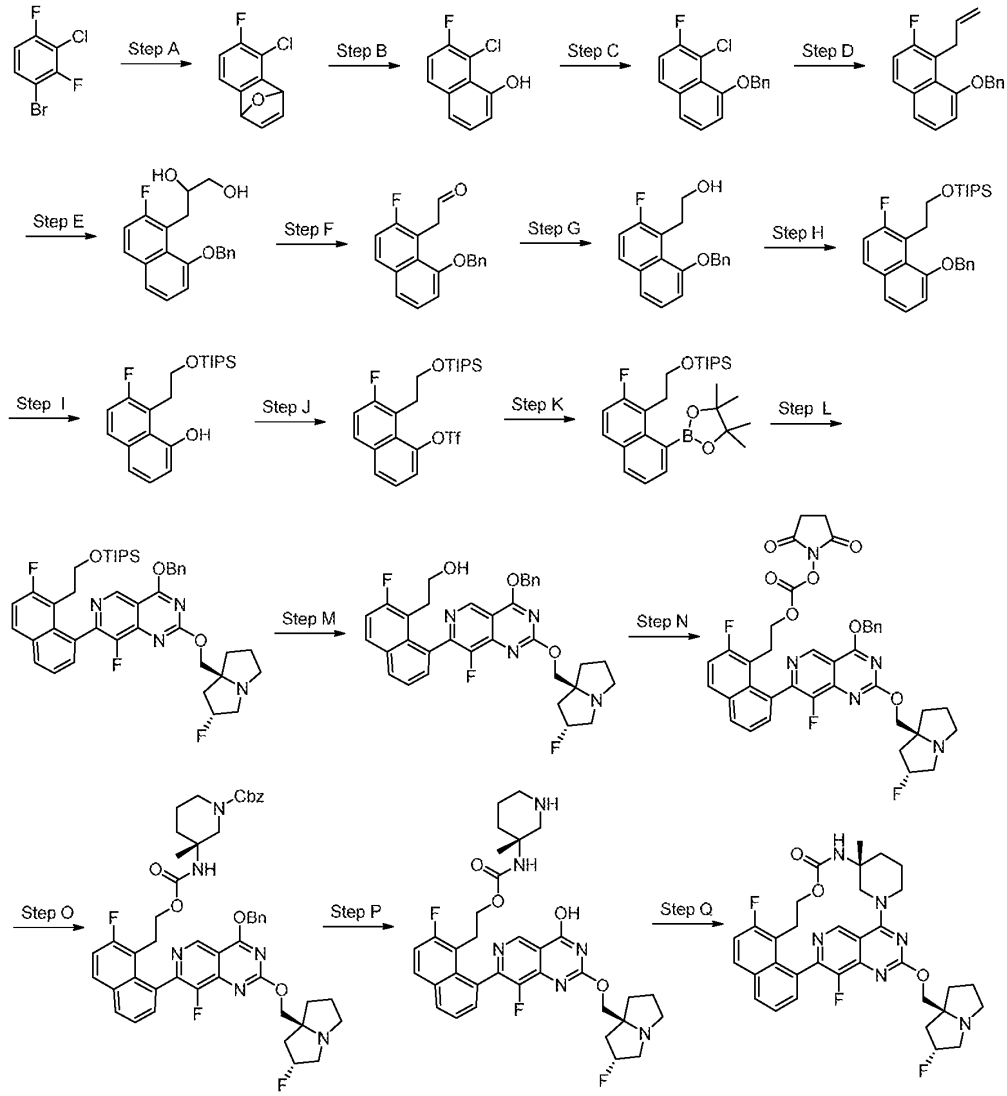
Step J. (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-

yl)methoxy)-1^3-methyl-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 5-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)-N-((R)-3-methylpiperidin-3-yl)pentanamide (0.29 g, 0.36 mmol) in MeCN (300 mL) was added DIPEA (0.63 mL, 3.6 mmol) and BrOP (0.28 g, 0.72 mmol). The mixture was stirred for 16 h and then it was concentrated under reduced pressure. The residue was diluted with DCM (10 mL) and water (10 mL). The mixture was extracted with DCM (10 mL x 3). The combined organic layers were washed with water (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (56 – 76% MeCN in aqueous NH_4HCO_3) to give (1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.029 g, 12% yield) as an off-white solid. LCMS (MM-ES+APCI, Pos): m/z 645.3 (M+H).

Compound 561



(1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-6-oxa-8-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclooctaphan-7-one



Step A. 5-chloro-6-fluoro-1,4-dihydro-1,4-epoxynaphthalene. To a solution of 1-bromo-3-chloro-2,4-difluorobenzene (10 g, 44 msmol) in toluene (100 mL) was added furan (6.0 g, 88 mmol). The flask was evacuated and backfilled with nitrogen three times and then it was cooled to -30 °C. To the cooled solution was added n-BuLi (2.5 M in hexanes; 19 mL). The reaction was stirred at -30 °C for 30 min then it was warmed to rt and stirred for 15.5 h. The mixture was diluted with H_2O (100 mL) and extracted with EtOAC (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (40-60% MeCN in 0.05% aqueous NH_4OH) to give 5-chloro-6-fluoro-1,4-

dihydro-1,4-epoxynaphthalene (4.0 g, 23% yield). LCMS (MM-ES+APCI, Pos): m/z 196.9 (M+H).

Step B. 8-chloro-7-fluoronaphthalen-1-ol. To a solution of 5-chloro-6-fluoro-1,4-dihydro-1,4-epoxynaphthalene (4.5 g, 23 mmol) in EtOH (42 mL) was added 12 M HCl (23 mL). The reaction was heated to 70 °C and stirred for 16 h. The mixture was diluted with H_2O (40 mL) and then it was neutralized with sat. aq. $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 8-chloro-7-fluoronaphthalen-1-ol (4.5 g, 100% yield). ^{1}HNMR: (400 MHz, $CDCl_3$) δ = 7.87 (s, 1H), 7.75 - 7.66 (m, 1H), 7.39 - 7.32 (m, 2H), 7.26 - 7.22 (m, 1H), 7.08 - 6.99 (m, 1H).

Step C. 8-(benzyloxy)-1-chloro-2-fluoronaphthalene. To a solution of 8-chloro-7-fluoronaphthalen-1-ol (4.5 g, 23 mmol) in DMF (45 mL) was added K_2CO_3 (9.5 g, 69 mmol) and benzyl bromide (3.3 mL, 28 mmol). The reaction was stirred at rt for 16 h and then it was diluted with H_2O (500 mL) and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (100% petroleum ether) to give 8-(benzyloxy)-1-chloro-2-fluoronaphthalene (6.0 g, 91% yield). ^{1}HNMR: (400 MHz, $CDCl_3$) δ = 7.74 - 7.65 (m, 1H), 7.58 (d, J = 7.2 Hz, 2H), 7.46 - 7.39 (m, 3H), 7.38 - 7.29 (m, 3H), 7.03 (d, J = 7.6 Hz, 1H), 5.26 (s, 2H).

Step D. 1-allyl-8-(benzyloxy)-2-fluoronaphthalene. To a solution of 8-(benzyloxy)-1-chloro-2-fluoronaphthalene (6.0 g, 21 mmol) and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (14 g, 84 mmol) in 1,4-dioxane (100 mL) and H_2O (10 mL) was added Cs_2CO_3 (14 g, 42 mmol), mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (1.5 g, 2.1 mmol). The reaction was heated to 120 °C and stirred for 16 h. The mixture was extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% petroleum ether) to give 1-allyl-8-(benzyloxy)-2-fluoronaphthalene (6.0 g, 88 mmol). ^{1}HNMR: (400 MHz, $CDCl_3$) δ = 7.71 - 7.65 (m, 1H), 7.53 - 7.47 (m, 2H), 7.44 - 7.36 (m, 4H), 7.31 (s, 1H), 7.27 - 7.21 (m, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.07 - 5.91 (m, 1H), 5.28 - 5.19 (m, 2H), 4.92 - 4.85 (m, 1H), 4.78 (br d, J = 17.2 Hz, 1H), 4.11 - 4.03 (m, 2H).

Step E. 3-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)propane-1,2-diol. To a solution of 1-allyl-

8-(benzyloxy)-2-fluoronaphthalene (5.5 g, 19 mmol) in THF (50 mL) and H_2O (5 mL) at 0 °C was added $K_2OsO_4 \cdot 2H_2O$ (0.69 g, 1.9 mmol) and N-methylmorpholine N-oxide (2.4 g, 21 mmol). The reaction was stirred at rt for 16 h and then it was quenched with Na_2SO_3/H_2O (100 mL). The aqueous phase was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (33 – 50% EtOAc in petroleum ether) to give 3-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)propane-1,2-diol (6.0 g, 98% yield). LCMS (MM-ES+APCI, Pos): m/z 327.3 (M+H).

Step F. 2-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)acetaldehyde. To a solution of 3-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)propane-1,2-diol (6.0 g, 18 mmol) in THF (40 mL) and H_2O (20 mL) was added $NaIO_4$ (7.9 g, 37 mmol). The reaction was stirred at rt for 1 h and then it was quenched with Na_2SO_3/H_2O (20 mL). The aqueous phase was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (17 – 25% EtOAc in petroleum ether) to give 2-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)acetaldehyde (5.0 g, 92% yield). LCMS (MM-ES+APCI, Pos): m/z 295.2 (M+H).

Step G. 2-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)ethan-1-ol. To a solution of 2-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)acetaldehyde (5.0 g, 17 mmol) in EtOH (50 mL) was added $NaBH_4$ (1.3 g, 34 mmol). The reaction was stirred at rt for 1 h and then it was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25 – 33% EtOAc in petroleum ether) to give 2-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)ethan-1-ol (4.2 g, 83% yield). LCMS (MM-ES+APCI, Pos): m/z 297.0 (M+H).

Step H. (2-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)ethoxy)triisopropylsilane. To a solution of 2-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)ethan-1-ol (4.2 g, 14 mmol) in DCM (40 mL) was added imidazole (1.9 g, 28 mmol) and TIPSCl (4.6 mL, 21 mmol). The reaction was stirred at rt for 16 h and then it was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% petroleum ether) to give (2-(8-(benzyloxy)-2-

fluoronaphthalen-1-yl)ethoxy)triisopropylsilane (6.0 g, 94% yield). LCMS (MM-ES+APCI, Pos): m/z 453.3 (M+H).

Step I. 7-fluoro-8-(2-((triisopropylsilyl)oxy)ethyl)naphthalen-1-ol. To a solution of (2-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)ethoxy)triisopropylsilane (3.0 g, 6.6 mmol) in MeOH (30 mL) was added 10% Pd/C (3.5 g, 3.3 mmol). The flask was evacuated and backfilled with H_2 three times. The reaction was stirred at rt under an atmosphere of H_2 for 1 h and then it was filtered through a pad of Celite. The pad was washed with EtOAc (30 mL). The filtrate was concentrated under reduced pressure to give 7-fluoro-8-(2-((triisopropylsilyl)oxy)ethyl)naphthalen-1-ol (2.3 g, 96% yield). LCMS (MM-ES+APCI, Pos): m/z 363.2 (M+H).

Step J. 7-fluoro-8-(2-((triisopropylsilyl)oxy)ethyl)naphthalen-1-yl trifluoromethanesulfonate. To a solution of 7-fluoro-8-(2-((triisopropylsilyl)oxy)ethyl)naphthalen-1-ol (2.3 g, 6.3 mmol) and DIPEA (2.2 mL, 13 mmol) in DMA (23 mL) was added N-phenyl-bis(trifluoromethanesulfonimide) (3.0 g, 8.3 mmol). The reaction was stirred at rt for 16 h and then it was diluted with H_2O (150 mL) and extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (80 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% petroleum ether) to give 7-fluoro-8-(2-((triisopropylsilyl)oxy)ethyl)naphthalen-1-yl trifluoromethanesulfonate (2.7 g, 86% yield). LCMS (MM-ES+APCI, Pos): m/z 495.3 (M+H).

Step K. (2-(2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethoxy)triisopropylsilane. To a solution of 7-fluoro-8-(2-((triisopropylsilyl)oxy)ethyl)naphthalen-1-yl trifluoromethanesulfonate (2.6 g, 5.3 mmol) and $Pd(dppf)Cl_2$ (0.77 g, 1.1 mmol) in MeCN (30 mL) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.6 mL, 32 mmol) and NEt_3 (4.4 mL, 32 mmol). The reaction was heated to 80 °C for 16 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (100% petroleum ether) to give (2-(2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethoxy)triisopropylsilane (2.0 g, 81% yield). LCMS (MM-ES+APCI, Pos): m/z 473.3 (M+H).

Step L. 4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-(2-((triisopropylsilyl)oxy)ethyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine. To a solution of (2-(2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)ethoxy)triisopropylsilane (0.95 g, 2.0 mmol) in 1,4-dioxane (10 mL) and

H_2O (2 mL) was added 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.60 g, 1.3 mmol), Cs_2CO_3 (1.3 g, 4.0 mmol) and mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.29 g, 0.40 mmol). The reaction was heated to 90 °C for 1 h and then it was diluted with H_2O (50 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (9-11% (25% EtOH in EtOAc) in petroleum ether) to give 4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-(2-((triisopropylsilyl)oxy)ethyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.70 g, 69% yield). LCMS (MM-ES+APCI, Pos): m/z 757.4 (M+H).

Step M. 2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)ethan-1-ol. To a solution of 4-(benzyloxy)-8-fluoro-7-(7-fluoro-8-(2-((triisopropylsilyl)oxy)ethyl)naphthalen-1-yl)-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (0.69 g, 0.91 mmol) in THF (7 mL) was added $3HF{\cdot}NEt_3$ (1.5 mL, 9.1 mmol). The reaction was heated to 50 °C for 1 h and then it was diluted with H_2O (10 mL) and DIPEA (2 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (17-25% (25% EtOH in EtOAc) in petroleum ether) to give 2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)ethan-1-ol (0.30 g, 55% yield). LCMS (MM-ES+APCI, Pos): m/z 601.2 (M+H).

Step N. 2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)ethyl (2,5-dioxopyrrolidin-1-yl) carbonate. To a solution of 2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)ethan-1-ol (0.30 g, 0.50 mmol) in DCM (5 mL) was added pyridine (0.20 mL, 2.5 mmol) and N,N'-disuccinimidyl carbonate (0.38 g, 1.5 mmol). The reaction was stirred at rt for 1 h and then it was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 2-(8-(4-

(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)ethyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.37 g, 100% yield). LCMS (MM-ES+APCI, Pos): m/z 742.2 (M+H).

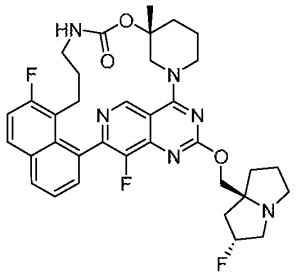
Step O. benzyl (R)-3-(((2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)ethoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of 2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)ethyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.37 g, 0.50 mmol) and benzyl (R)-3-amino-3-methylpiperidine-1-carboxylate (0.15 g, 0.60 mmol) in DCM (5 mL) was added DIPEA (0.26 mL, 1.5 mmol). The reaction was stirred at rt for 16 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25-33% (25% EtOH in EtOAc) in petroleum ether) to give benzyl (R)-3-(((2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)ethoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.40 g, 92% yield). LCMS (MM-ES+APCI, Pos): m/z 875.3 (M+H).

Step P. 2-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethyl ((R)-3-methylpiperidin-3-yl)carbamate. To a solution of benzyl (R)-3-(((2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)ethoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.30 g, 0.34 mmol) in THF (3 mL) was added 10% Pd/C (0.73 g, 0.69 mmol). The flask was evacuated and backfilled with H_2 three times. The reaction was stirred at rt under an atmosphere of H_2 for 1 h and then it was filtered through a pad of Celite. The pad was washed with EtOAc (10 mL). The filtrate was concentrated under reduced pressure to give 2-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethyl ((R)-3-methylpiperidin-3-yl)carbamate (0.20 g, 90% yield). LCMS (MM-ES+APCI, Pos): m/z 875.3 (M+H).

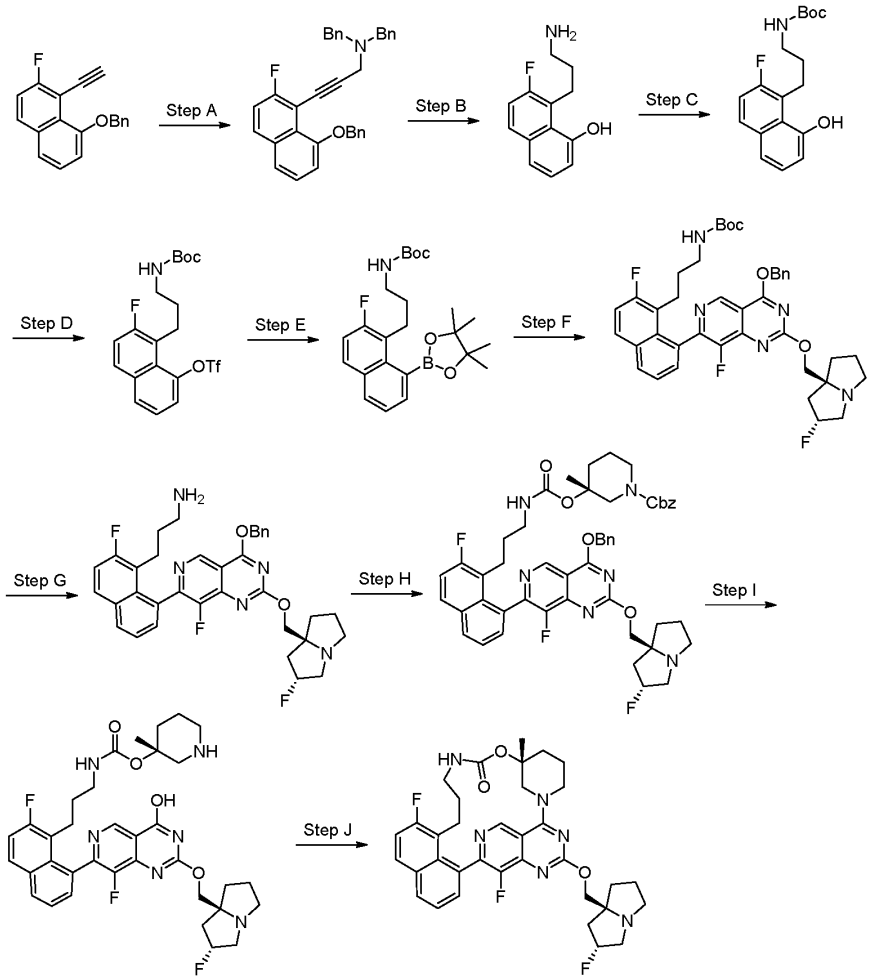
Step Q. (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-6-oxa-8-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclooctaphan-7-one. To a solution of 2-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-

yl)naphthalen-1-yl)ethyl ((R)-3-methylpiperidin-3-yl)carbamate (0.20 g, 0.31 mmol) in MeCN (80 mL) was added BrOP (0.36 g, 0.92 mmol) and DIPEA (0.27 mL, 1.5 mmol). The reaction was stirred at rt for 1 h and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC (42-72% MeCN in 0.1% aqueous NH_4HCO_3) to give (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-6-oxa-8-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclooctaphan-7-one (0.016 g, 8% yield). LCMS (MM-ES+APCI, Pos): m/z 633.3 (M+H).

Compound 562



(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-9-oxa-7-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



Step A. N,N-dibenzyl-3-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)prop-2-yn-1-amine. To a solution of 8-(benzyloxy)-1-ethynyl-2-fluoronaphthalene (8.0 g, 25 mmol) in 1,4 dioxane (80 mL) was added dibenzylamine (7.2 mL, 37 mmol), paraformaldehyde (4.5 g, 50 mmol), and $CuCl_2$ (0.33 g, 2.5 mmol). The reaction was heated to 40 °C for 40 h and then it was filtered. The filter cake was washed with 1,4-dioxane (40 mL) and then the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-9% EtOAc in hexanes) to give N,N-dibenzyl-3-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)prop-2-yn-1-amine (8.0 g, 65% yield). LCMS (MM-ES+APCI, Pos): m/z 486.2 (M+H).

Step B. 8-(3-aminopropyl)-7-fluoronaphthalen-1-ol. To a solution of N,N-dibenzyl-3-(8-(benzyloxy)-2-fluoronaphthalen-1-yl)prop-2-yn-1-amine (8.0 g, 16 mmol) in MeOH (40 mL) and THF (40 mL) was added 10% Pd/C (1.7 g, 1.6 mmol). The flask was evacuated and

backfilled with H_2 three times. The reaction was stirred at 40 °C under 50Psi H_2 for 6 h and then it was filtered through a pad of Celite. The pad was washed with MeOH (50 mL) and THF (50 mL). The filtrate was concentrated under reduced pressure to give 8-(3-aminopropyl)-7-fluoronaphthalen-1-ol (3.5 g, 99% yield). LCMS (MM-ES+APCI, Pos): m/z 220.1 (M+H).

Step C. tert-butyl (3-(2-fluoro-8-hydroxynaphthalen-1-yl)propyl)carbamate. To a solution of 8-(3-aminopropyl)-7-fluoronaphthalen-1-ol (3.5 g, 16 mmol) in 1,4-dioxane (40 mL) was added DIEPA (5.6 mL, 32 mmol) and Boc_2O (3.5 gm 16 mmol). The reaction was stirred at rt for 16 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-9% EtOAc in hexanes) to give tert-butyl (3-(2-fluoro-8-hydroxynaphthalen-1-yl)propyl)carbamate (3.3 g, 47% yield). LCMS (MM-ES+APCI, Pos): m/z 219.9 (M+H-Boc).

Step D. 8-(3-((tert-butoxycarbonyl)amino)propyl)-7-fluoronaphthalen-1-yl trifluoromethanesulfonate. To a solution of tert-butyl (3-(2-fluoro-8-hydroxynaphthalen-1-yl)propyl)carbamate (3.2 g, 7.2 mmol) in DMA (40 mL) was added DIPEA (2.5 mL, 14 mmol) and N-phenyl-bis(trifluoromethanesulfonimide) (3.1 g, 8.6 mmol). The reaction was heated to 40 °C for 4 h and then it was diluted with H_2O (100 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-9% EtOAc in hexanes) to give 8-(3-((tert-butoxycarbonyl)amino)propyl)-7-fluoronaphthalen-1-yl trifluoromethanesulfonate (3.6 g, 92% yield). LCMS (MM-ES+APCI, Pos): m/z 395.9 (M+H-tBu).

Step E. tert-butyl (3-(2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propyl)carbamate. To a solution of 8-(3-((tert-butoxycarbonyl)amino)propyl)-7-fluoronaphthalen-1-yl trifluoromethanesulfonate (3.5 g, 6.4 mmol) and $Pd(dppf)Cl_2$ (1.1 g, 1.3mmol) in MeCN (40 mL) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.6 mL, 39 mmol) and NEt_3 (5.4 mL, 39 mmol). The reaction was heated to 80 °C for 2 h and then it was filtered. The filter cake was washed with MeCN (20 mL and then the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-9% EtOAc in hexanes) to give tert-butyl (3-(2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propyl)carbamate (3.3 g, 55% yield). LCMS (MM-ES+APCI, Pos): m/z 374.0 (M+H-tBu).

Step F. tert-butyl (3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-

pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl)carbamate. To a solution of tert-butyl (3-(2-fluoro-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)propyl)carbamate (1.1 g, 1.1 mmol) in 1,4-dioxane (20 mL) and H_2O (2 mL) was added 4-(benzyloxy)-7-chloro-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidine (1.0 g, 2.2 mmol), Cs_2CO_3 (1.5 g, 4.5 mmol) and mesylate[(di(1-adamantyl)-n-butylphosphine)-2-(2′-amino-1,1′-biphenyl)]palladium(II) (0.16 g, 0.22 mmol). The reaction was heated to 90 °C for 1 h and then it was filtered. The filter cake was washed with 1,4-dioxane (20 mL) and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-33% (25% EtOH in EtOAc) in petroleum ether) to give tert-butyl (3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl)carbamate (1.0 g, 45% yield). LCMS (MM-ES+APCI, Pos): m/z 714.2 (M+H).

Step G. 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propan-1-amine. To a solution of tert-butyl (3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl)carbamate (1.0 g, 1.0 mmol) in HFIP (9.5 mL) at 0 °C was added TFA (0.5 mL). The reaction was stirred at 0 °C for 16 h and then it was neutralized with sat. aq. NaHCO3 solution. The mixture was extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (15 – 35% MeCN in 0.225% aqueous formic acid) to give 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propan-1-amine (0.15 g, 24% yield). LCMS (MM-ES+APCI, Pos): m/z 614.2 (M+H).

Step H. benzyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl)carbamoyl)oxy)-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propan-1-amine (0.080 g, 0.13 mmol) in DCM (2 mL) was added DIPEA (0.11 mL, 0.63 mmol) and benzyl (R)-3-methyl-3-(((4-nitrophenoxy)carbonyl)oxy)piperidine-1-carboxylate (0.093 g, 0.20 mmol).

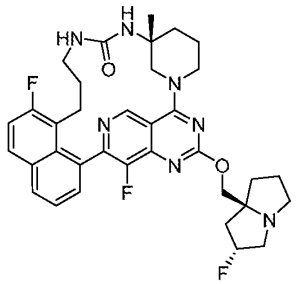
The reaction was stirred at 40 °C for 16 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-33% (25% EtOH in EtOAc) in petroleum ether) to give benzyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl)carbamoyl)oxy)-3-methylpiperidine-1-carboxylate (0.060 g, 54% yield). LCMS (MM-ES+APCI, Pos): m/z 889.3 (M+H).

Step I. (R)-3-methylpiperidin-3-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl)carbamate. To a solution of benzyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl)carbamoyl)oxy)-3-methylpiperidine-1-carboxylate (0.060 g, 0.067 mmol) in THF (10 mL) was added 10% Pd/C (0.071 g, 0.067 mmol). The flask was evacuated and backfilled with H_2 three times. The reaction was stirred at 40 °C under an atmosphere of H_2 for 8 h and then it was filtered through a pad of Celite. The pad was washed with MeOH (50 mL) and THF (50 mL). The filtrate was concentrated under reduced pressure to give (R)-3-methylpiperidin-3-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl)carbamate (0.050 g, 94% yield). LCMS (MM-ES+APCI, Pos): m/z 665.2 (M+H).

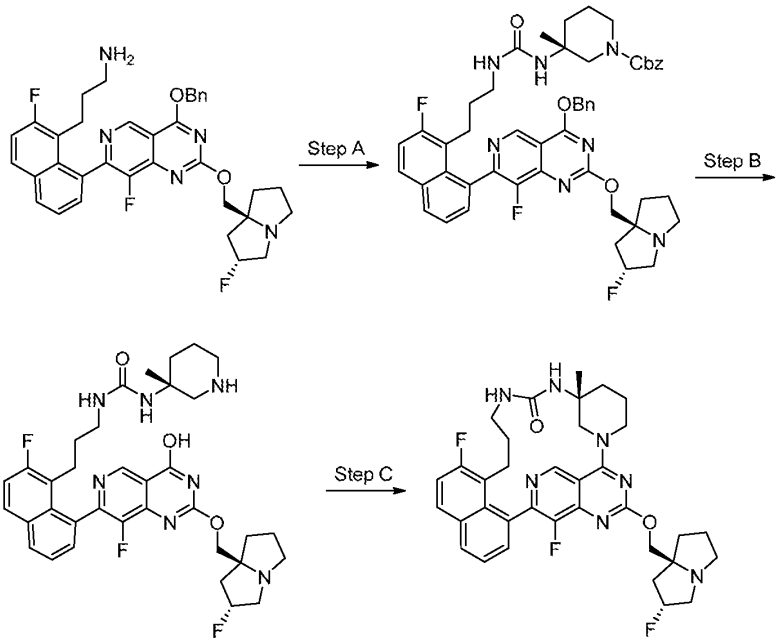
Step J. (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-9-oxa-7-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of (R)-3-methylpiperidin-3-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl)carbamate (0.050 g, 0.064 mmol) in MeCN (50 mL) was added BrOP (0.074 g, 0.19 mmol) and DIPEA (0.11 mL, 0.64 mmol). The reaction was stirred at rt for 16 h and then it was concentrated under reduced pressure. The residue was diluted with H_2O (20 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with water (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (46-76% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized. The residue was purified again by preparative HPLC (46-76% MeCN in 0.225% aqueous formic acid) to give (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-9-oxa-7-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.0024

g, 6% yield). LCMS (MM-ES+APCI, Pos): m/z 647.2 (M+H).

Compound 565



(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7,9-diaza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



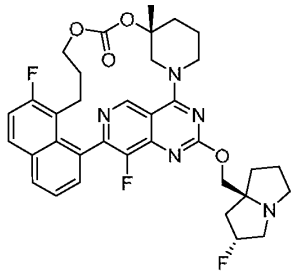
Step A. benzyl (R)-3-(3-(3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl)ureido)-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propan-1-amine (0.10 g, 0.084 mmol) in DCM (2 mL) was added DIPEA (0.073 mL, 0.42 mmol) and benzyl (R)-3-((((2,5-dioxopyrrolidin-1-yl)oxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.066 g, 0.17 mmol). The

reaction was stirred at rt for 2 h and then it was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-33% (25% EtOH in EtOAc) in petroleum ether) to give benzyl (R)-3-(3-(3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl)ureido)-3-methylpiperidine-1-carboxylate (0.060 g, 70% yield). LCMS (MM-ES+APCI, Pos): m/z 888.4 (M+H).

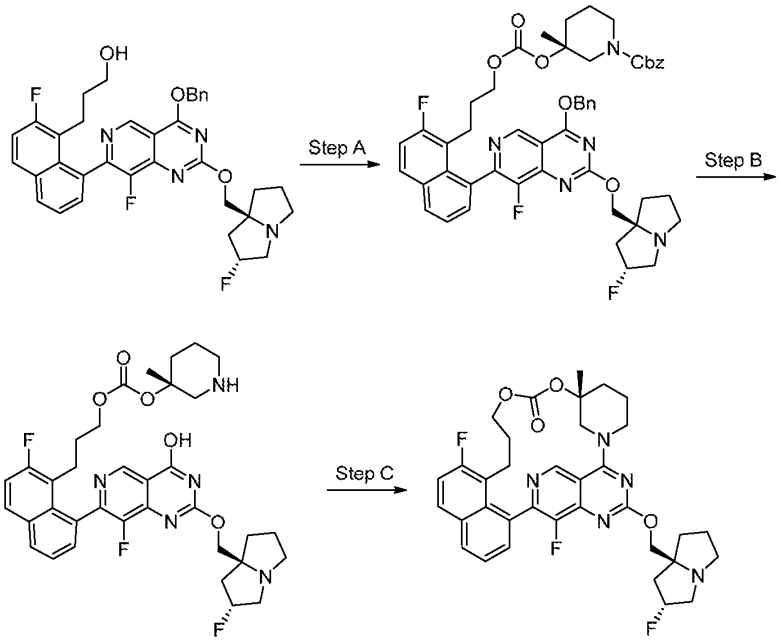
Step B. 1-(3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl)-3-((R)-3-methylpiperidin-3-yl)urea. To a solution of benzyl (R)-3-(3-(3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propyl)ureido)-3-methylpiperidine-1-carboxylate (0.060 g, 0.059 mmol) in THF (10 mL) was added 10% Pd/C (0.063 g, 0.059 mmol). The flask was evacuated and backfilled with H_2 three times. The reaction was stirred at 40 °C under an atmosphere of H_2 for 8 h and then it was filtered through a pad of Celite. The pad was washed with MeOH (50 mL) and THF (50 mL). The filtrate was concentrated under reduced pressure to give (R)-3-methylpiperidin-3-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl)carbamate (0.060 g, 97% yield). LCMS (MM-ES+APCI, Pos): m/z 664.2 (M+H).

Step C. (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7,9-diaza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of (R)-3-methylpiperidin-3-yl (3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl)carbamate (0.060 g, 0.057 mmol) in MeCN (60 mL) was added BrOP (0.067 g, 0.17 mmol) and DIPEA (0.10 mL, 0.57 mmol). The reaction was stirred at rt for 16 h and then it was concentrated under reduced pressure. The residue was diluted with H_2O (20 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with water (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (39-69% MeCN in 0.1% aqueous NH_4HCO_3) to give (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7,9-diaza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.0047 g, 13% yield). LCMS (MM-ES+APCI, Pos): m/z 646.3 (M+H).

Compound 566



(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7,9-dioxa-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



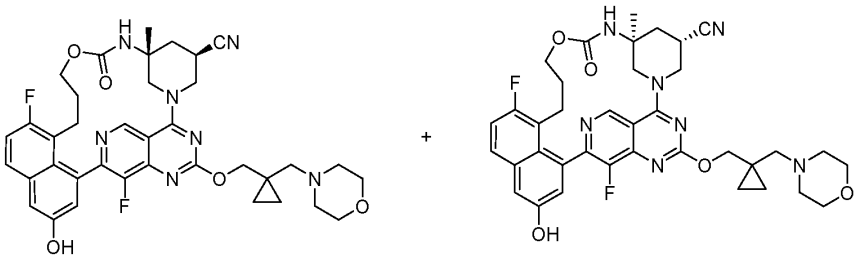
Step A. benzyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propoxy)carbonyl)oxy)-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propan-1-ol (0.15 g, 0.24 mmol) in toluene (2 mL) was added benzyl (R)-3-methyl-3-(((4-nitrophenoxy)carbonyl)oxy)piperidine-1-carboxylate (0.12 g, 0.29 mmol) and DMAP (0.12 g, 0.96 mmol). The reaction was stirred at 55 °C for 12 h and then it was diluted with H_2O (5

mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-100% EtOAc in petroleum ether) to give benzyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propoxy)carbonyl)oxy)-3-methylpiperidine-1-carboxylate (0.18 g, 79% yield). LCMS (MM-ES+APCI, Pos): m/z 890.5 (M+H).

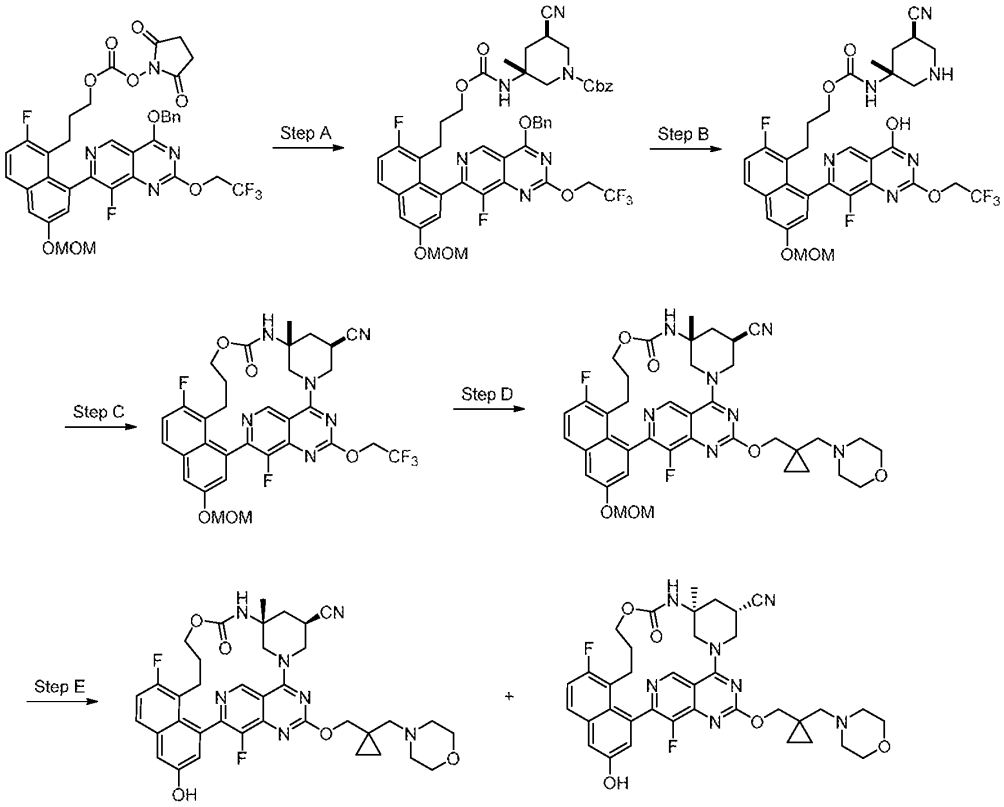
Step B. 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl) carbonate. To a solution of benzyl (R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoronaphthalen-1-yl)propoxy)carbonyl)oxy)-3-methylpiperidine-1-carboxylate (0.18 g, 0.19 mmol) in THF (3 mL) was added 10% Pd/C (0.40 g, 0.38 mmol). The flask was evacuated and backfilled with H_2 three times. The reaction was stirred at rt under an atmosphere of H_2 for 1 h and then it was filtered through a pad of Celite. The pad was washed with THF (10 mL). The filtrate was concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl) carbonate (0.090 g, 72% yield).

Step C. (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7,9-dioxa-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of 3-(2-fluoro-8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)propyl ((R)-3-methylpiperidin-3-yl) carbonate (0.090 g, 0.14 mmol) in MeCN (100 mL) was added BrOP (0.16 g, 0.41 mmol) and DIPEA (0.12 mL, 0.68 mmol). The reaction was stirred at rt for 12 h and then it was concentrated under reduced pressure. The residue was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (48-78% MeCN in 0.1% aqueous NH_4HCO_3) to give (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7,9-dioxa-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.021 g, 23% yield). LCMS (MM-ES+APCI, Pos): m/z 648.3 (M+H).

Compounds 567 and 568



(1^3R,1^5R)-2^8,3^7-difluoro-3^3-hydroxy-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-1^5-carbonitrile and (1^3S,1^5S)-2^8,3^7-difluoro-3^3-hydroxy-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-1^5-carbonitrile



Step A. benzyl (rel-3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-

yl)propoxy)carbonyl)amino)-5-cyano-3-methylpiperidine-1-carboxylate. To a solution of 3-(8-(4-(benzyloxy)-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propyl (2,5-dioxopyrrolidin-1-yl) carbonate (0.54 g, 0.71 mmol) and benzyl (rel-3R,5R)-3-amino-5-cyano-3-methylpiperidine-1-carboxylate (0.25 g, 0.93 mmol) in DCM (5 mL) was added DIPEA (0.25 mL, 1.4 mmol). The reaction was stirred at 35 °C for 16 h. The mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-20% EtOAc in petroleum ether) to give benzyl (rel-3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-cyano-3-methylpiperidine-1-carboxylate (0.59 g, 83% yield). LCMS (MM-ES+APCI, Pos): m/z 915.2 (M+H).

Step B. 3-(2-fluoro-8-(8-fluoro-4-hydroxy-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((rel-3R,5R)-5-cyano-3-methylpiperidin-3-yl)carbamate. To a solution of benzyl (rel-3R,5R)-3-(((3-(8-(4-(benzyloxy)-8-fluoro-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-2-fluoro-6-(methoxymethoxy)naphthalen-1-yl)propoxy)carbonyl)amino)-5-cyano-3-methylpiperidine-1-carboxylate (0.59 g, 0.59 mmol) in THF (10 mL) was added 10% Pd/C (0.38 g, 0.35 mmol). The flask was evacuated and backfilled with H_2 three times. The reaction was stirred at rt under an atmosphere of H_2 for 1 h and then it was filtered through a pad of Celite. The pad was washed with THF (40 mL). The filtrate was concentrated under reduced pressure to give 3-(2-fluoro-8-(8-fluoro-4-hydroxy-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((rel-3R,5R)-5-cyano-3-methylpiperidin-3-yl)carbamate (0.40 g, 85% yield). LCMS (MM-ES+APCI, Pos): m/z 691.1 (M+H).

Step C. (rel-1^3R,1^5R)-2^8,3^7-difluoro-3^3-(methoxymethoxy)-1^3-methyl-8-oxo-2^2-(2,2,2-trifluoroethoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-1^5-carbonitrile. To a solution of 3-(2-fluoro-8-(8-fluoro-4-hydroxy-2-(2,2,2-trifluoroethoxy)pyrido[4,3-d]pyrimidin-7-yl)-6-(methoxymethoxy)naphthalen-1-yl)propyl ((rel-3R,5R)-5-cyano-3-methylpiperidin-3-yl)carbamate (0.40 g, 0.50 mmol) in MeCN (200 mL) was added BrOP (0.59 g, 1.5 mmol) and DIPEA (0.44 mL, 2.5 mmol). The reaction was stirred at rt for 16 h and then it was concentrated under reduced pressure. The residue was diluted with H_2O (10 mL) and

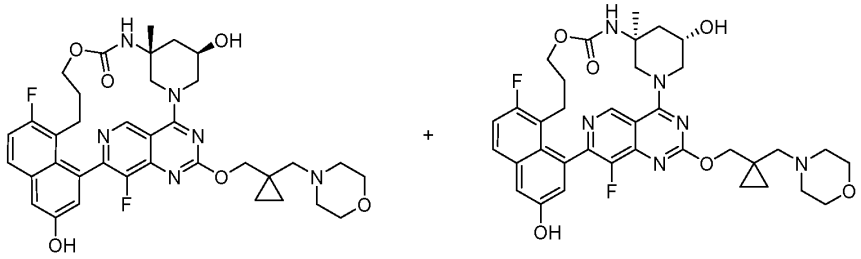
extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatograpyhy (0-50% EtOAc in petroleum ether) to give (rel-1^3R,1^5R)-2^8,3^7-difluoro-3^3-(methoxymethoxy)-1^3-methyl-8-oxo-2^2-(2,2,2-trifluoroethoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-1^5-carbonitrile (0.080 g, 23% yield). LCMS (MM-ES+APCI, Pos): m/z 673.2 (M+H).

Step D. (rel-1^3R,1^5R)-2^8,3^7-difluoro-3^3-(methoxymethoxy)-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-1^5-carbonitrile. To a solution of (rel-1^3R,1^5R)-2^8,3^7-difluoro-3^3-(methoxymethoxy)-1^3-methyl-8-oxo-2^2-(2,2,2-trifluoroethoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-1^5-carbonitrile (0.037 g, 0.053 mmol) in THF (0.5 mL) at 0 °C was added (1-(morpholinomethyl)cyclopropyl)methanol (0.018 g, 0.11 mmol) followed by sodium tert-butoxide (2.0 M in THF; 0.052 mL) and 4Å MS (0.010 g, 0.053 mmol). The reaction was stirred at rt for 17 h. The suspension was filtered and the filter cake was washed with THF (10 mL). The filtrate was concentrated under reduced pressure to give (rel-1^3R,1^5R)-2^8,3^7-difluoro-3^3-(methoxymethoxy)-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-1^5-carbonitrile (0.039 g, 100% yield).

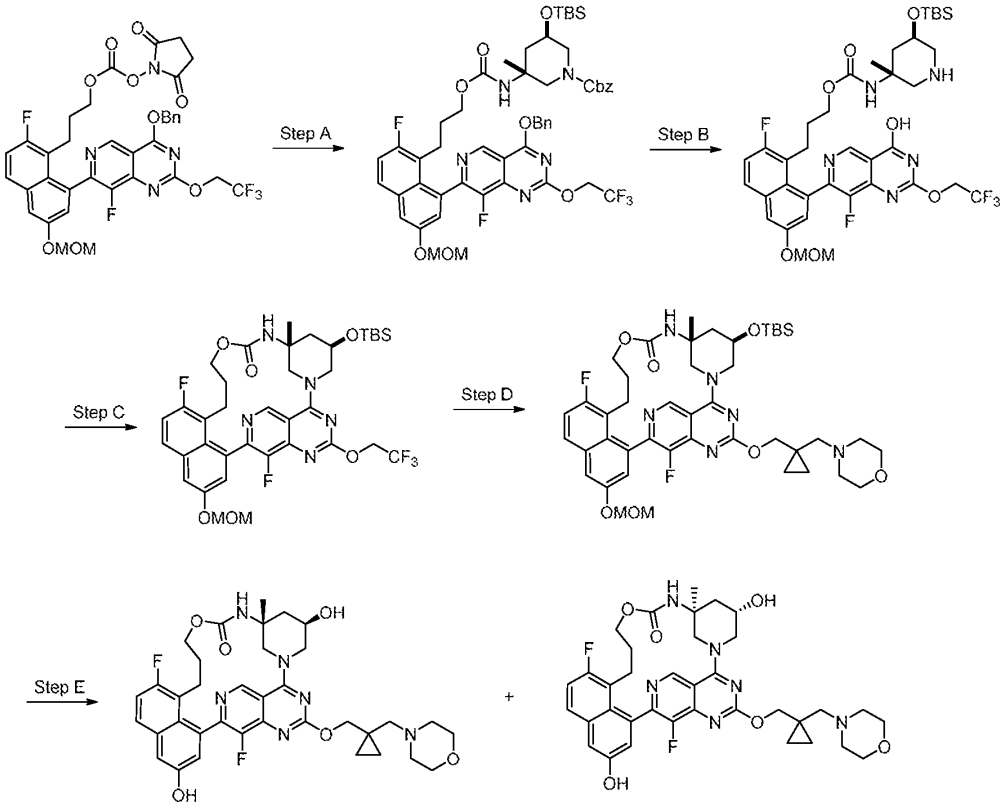
Step E. (1^3R,1^5R)-2^8,3^7-difluoro-3^3-hydroxy-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-1^5-carbonitrile and (1^3S,1^5S)-2^8,3^7-difluoro-3^3-hydroxy-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-1^5-carbonitrile. To a solution of (rel-1^3R,1^5R)-2^8,3^7-difluoro-3^3-(methoxymethoxy)-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-1^5-carbonitrile (0.039, 0.052 mmol) in DCM (0.60 mL) was added 2 M HCl in dioxane (0.2 mL). The reaction was stirred at rt for 1 h and then it was diluted with triethylamine and concentrated under reduced pressure. The residue was purified by preparative HPLC (35-65% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized. The residue was purified

by SFC (60% EtOH (0.1% NH_3H_2O) in CO_2) to give ($1^3R,1^5R$)-$2^8,3^7$-difluoro-3^3-hydroxy-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-1^5-carbonitrile (0.0054 g, 36%) and ($1^3S,1^5S$)-$2^8,3^7$-difluoro-3^3-hydroxy-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-1^5-carbonitrile (0.0048 g, 32% yield). LCMS (MM-ES+APCI, Pos): m/z 700.5 (M+H). LCMS (MM-ES+APCI, Pos): m/z 700.4 (M+H).

Compound 569 and Compound 570

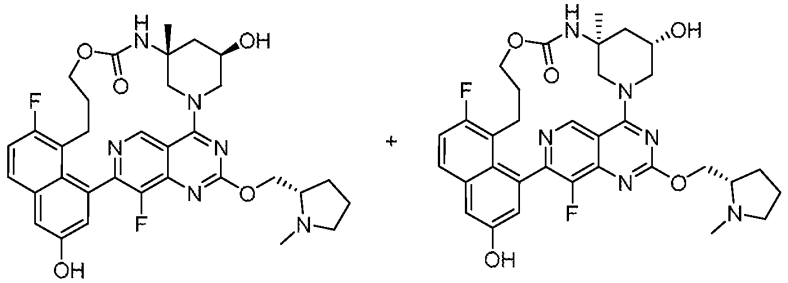


($1^3R,1^5R$)-$2^8,3^7$-difluoro-$1^5,3^3$-dihydroxy-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one and ($1^3S,1^5S$)-$2^8,3^7$-difluoro-$1^5,3^3$-dihydroxy-1^3-methyl-2^2-((1-(morpholinomethyl)cyclopropyl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one



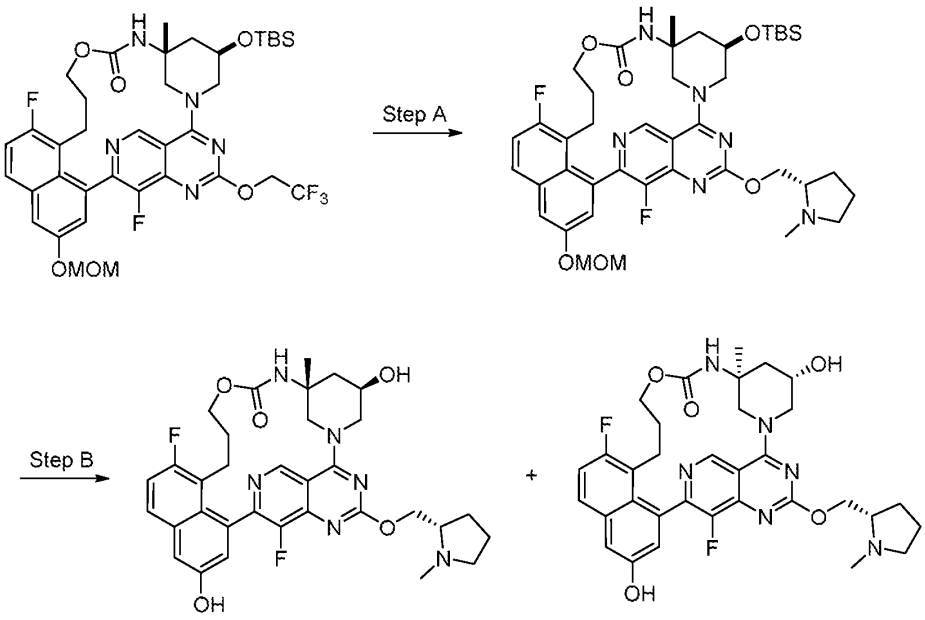
Steps A-E were performed by following the procedure of Compounds 567 and 568 using benzyl (rel-3R,5R)-3-amino-5-((tert-butyldimethylsilyl)oxy)-3-methylpiperidine-1-carboxylate in step A. The products were separated by SFC (40% MeOH (0.1% NH_3H_2O) in CO_2). Compound 569: LCMS (MM-ES+APCI, Pos): m/z 691.4 (M+H). Compound 570: LCMS (MM-ES+APCI, Pos): m/z 691.4 (M+H).

Compound 571 and Compound 572



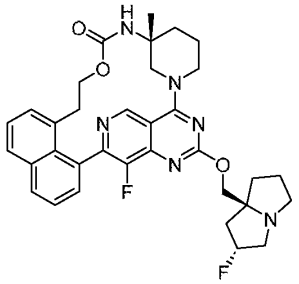
(1^3R,1^5R)-2^8,3^7-difluoro-1^5,3^3-dihydroxy-1^3-methyl-2^2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-

naphthalenacyclononaphan-8-one and (1^3S,1^5S)-2^8,3^7-difluoro-1^5,3^3-dihydroxy-1^3-methyl-2^2-(((S)-1-methylpyrrolidin-2-yl)methoxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one

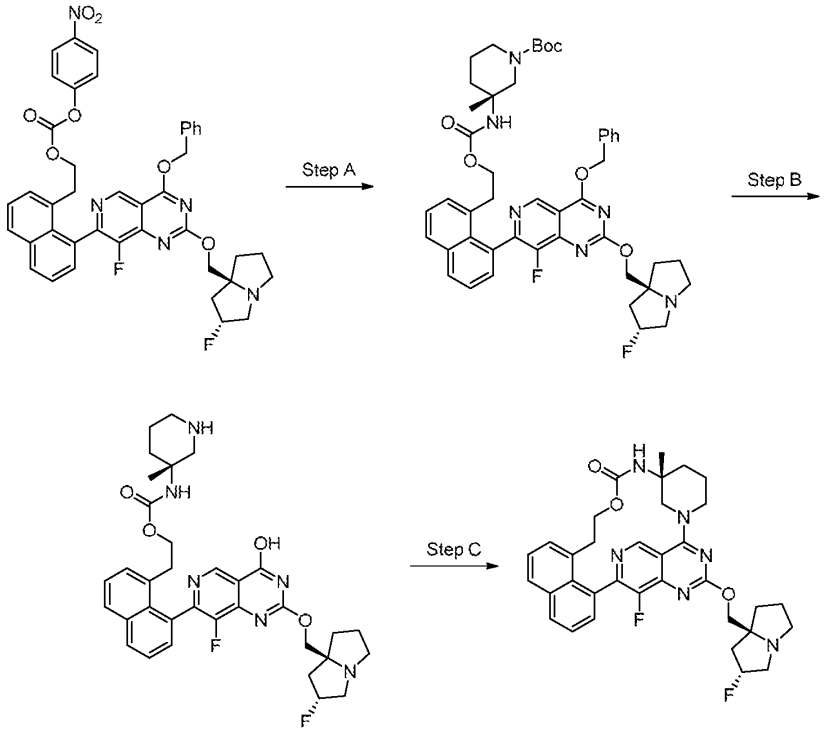


Steps A-B were performed by following the procedure of Compounds 567 and 568 (Steps D-E) using (S)-(1-methylpyrrolidin-2-yl)methanol in step A. The products were separated by SFC (40% EtOH (0.1% NH_3H_2O) in CO_2). Compound 571: LCMS (MM-ES+APCI, Pos): m/z 635.4 (M+H). Compound 572: LCMS (MM-ES+APCI, Pos): m/z 635.4 (M+H).

Compound 3



(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-6-oxa-8-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclooctaphan-7-one



Step A. tert-butyl (R)-3-(((2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate. To a solution of tert-butyl (R)-3-amino-3-methylpiperidine-1-carboxylate (0.13 g, 0.61 mmol) and 2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethyl (4-nitrophenyl) carbonate (0.20 g, 0.26 mmol) in DMF (4 mL) was added DIPEA (0.11 mL, 0.64 mmol) and DMAP (0.031 g, 0.26 mmol). The reaction was stirred for 1.5 h and then it was diluted with H_2O (15 mL) and extracted with ethyl acetate (8 mL × 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25-38% EtOAc in petroleum ether) to give tert-butyl (R)-3-(((2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.14 g, 63% yield) was obtained as a light yellow solid. LCMS (MM-ES+APCI, Pos): m/z 823.4 (M+H).

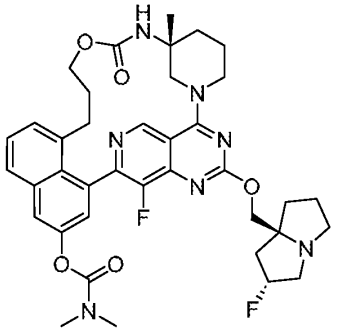
Step B. 2-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethyl ((R)-3-

methylpiperidin-3-yl)carbamate. To a solution of tert-butyl (R)-3-(((2-(8-(4-(benzyloxy)-8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)pyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethoxy)carbonyl)amino)-3-methylpiperidine-1-carboxylate (0.14 g, 0.16 mmol) in DCM (3 mL) was added TFA (1.0 mL, 14 mmol), The reaction was stirred at for 1 h and then it was slowly quenched with saturated $NaHCO_3$. The mixture was diluted with H_2O (10 mL) and extracted with DCM (3 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 2-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethyl ((R)-3-methylpiperidin-3-yl)carbamate (0.12 g), which was used into the next step without further purification.

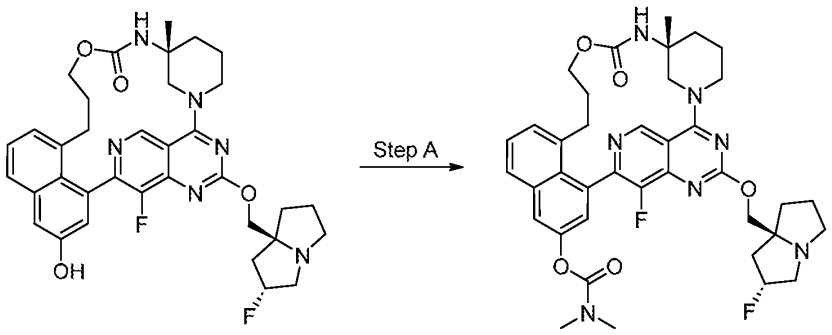
Step C. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-6-oxa-8-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclooctaphan-7-one. To a solution of 2-(8-(8-fluoro-2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-4-hydroxypyrido[4,3-d]pyrimidin-7-yl)naphthalen-1-yl)ethyl ((R)-3-methylpiperidin-3-yl)carbamate (0.11 g, 0.17 mmol) in THF (2 mL) was added BOP-Cl (0.089 g, 0.35 mmol) and DIPEA (0.031 mL, 0.18 mmol). The reaction was stirred at for 1 h. The mixture was diluted with H_2O (4 mL) and extracted with ethyl acetate (2 mL × 3). The combined organic layers were concentrated under reduced pressure. The residue was purified by preparative HPLC (40-70% MeCN in 0.08% aqueous NH_4HCO_3) to obtain (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-6-oxa-8-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclooctaphan-7-one (0.0060 g, 6% yield) as white solid. LCMS (MM-ES+APCI, Pos): m/z 615.2 (M+H).

Example procedure A. acid chloride coupling

Compound 79

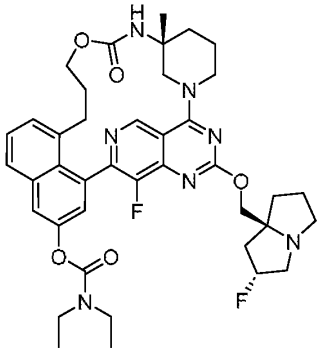
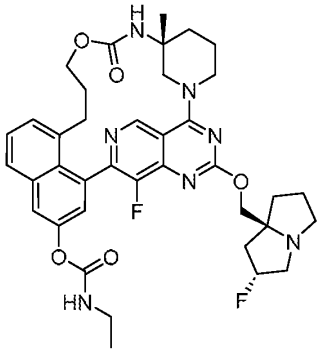
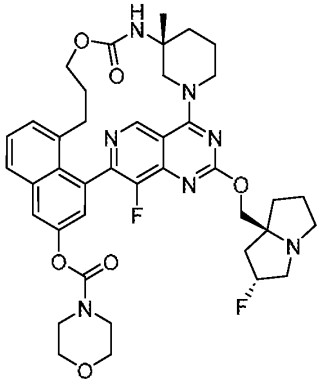


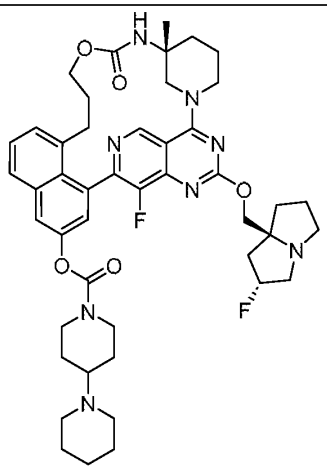
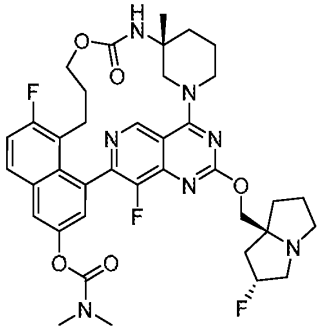
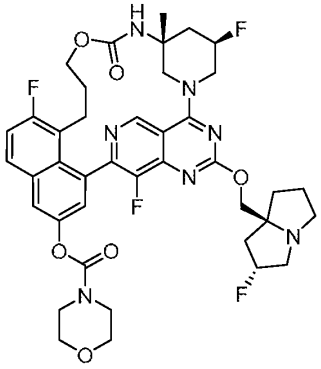
(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl dimethylcarbamate

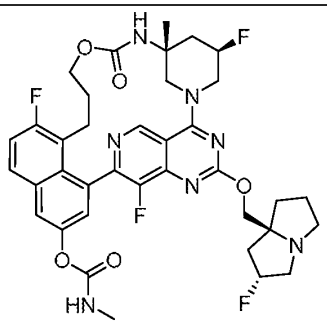
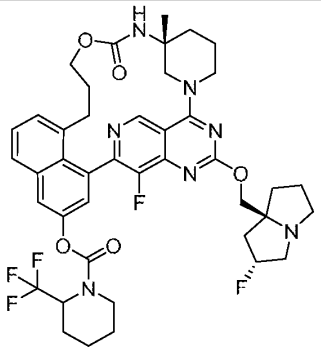
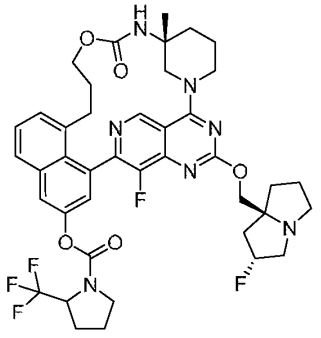


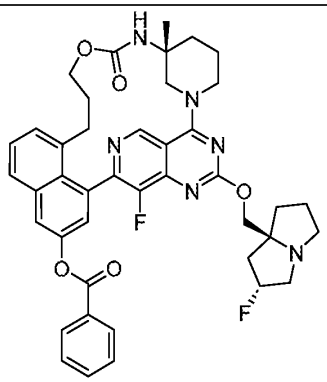
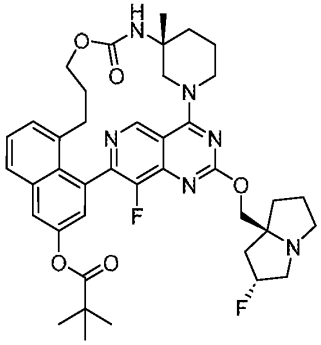
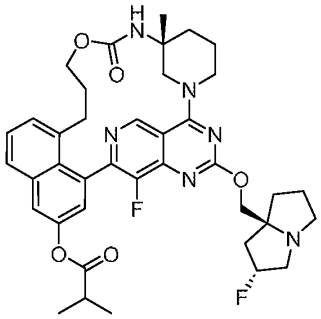
Step A. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-33-yl dimethylcarbamate. To solution of Compound 2 (0.020 g, 0.031 mmol) and triethylamine (0.00086 mL, 0.0062 mmol) in DCM (1 mL) was added dimethylcarbamic chloride (0.0043 mL, 0.047 mmol). The reaction was stirred for 1 h at rt. The mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (3 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparative HPLC (43 – 73% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl dimethylcarbamate (0.014 g, 63% yield) as a white solid. LCMS (MM-ES+APCI, Pos): 716.4 (M+H).

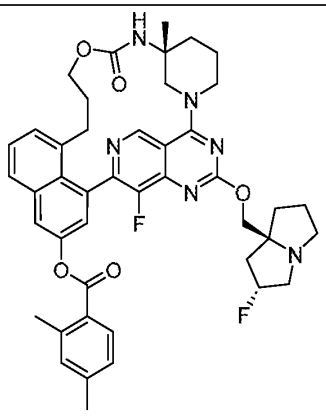
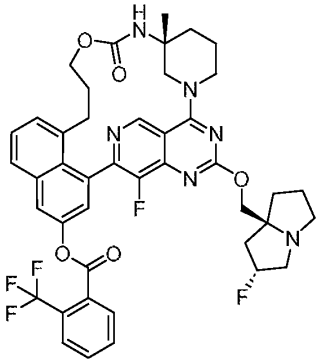
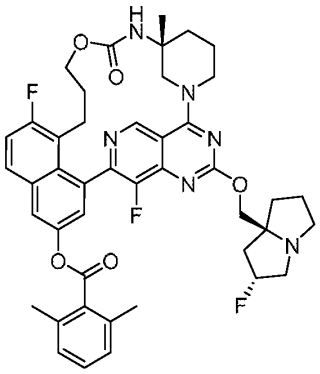
Table 8. Compounds synthesized by following the example procedure A

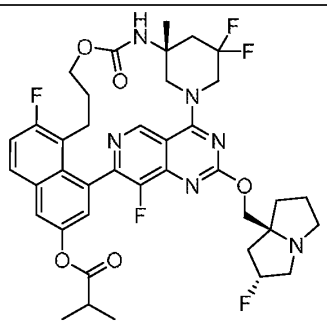
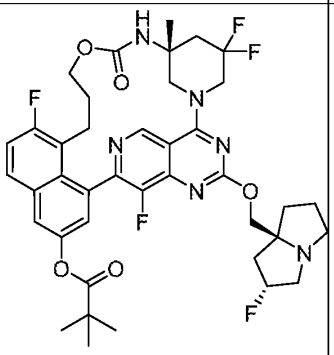
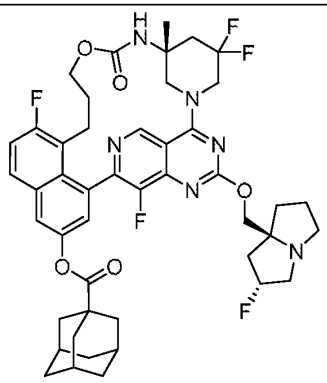
Cmpd ID	Structure	Name	LCMS	Procedure
80		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl diethylcarbamate	744.4	A
81		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl ethylcarbamate	716.4	A
82		(1^3R)-28-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl morpholine-4-carboxylate	758.3	A

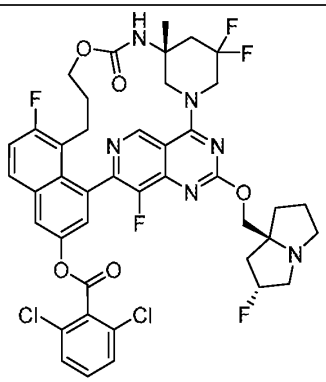
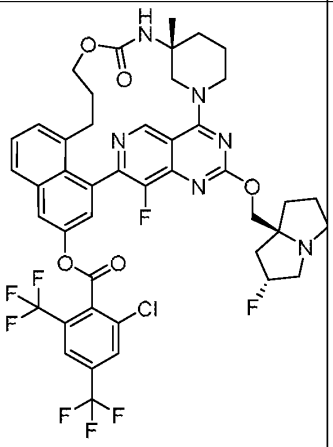
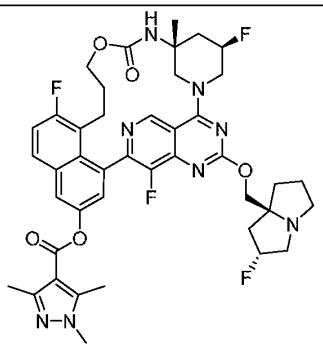
83		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl [1,4'-bipiperidine]-1'-carboxylate	839.4	A
273		(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl dimethylcarbamate	734.4	A
326		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl morpholine-4-carboxylate	794.4	A

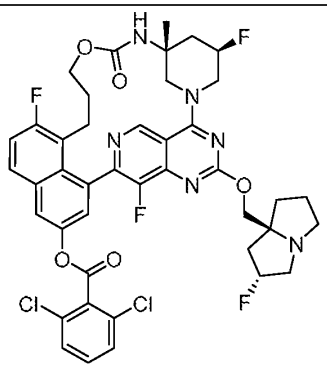
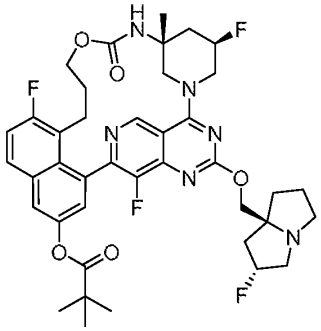
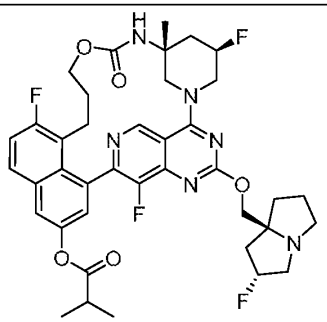
355		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl methylcarbamate	738.3	A
154		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(trifluoromethyl)piperidine-1-carboxylate	824.3	A
158		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(trifluoromethyl)pyrrolidine-1-carboxylate	810.3	A

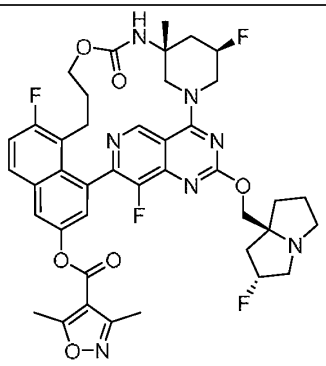
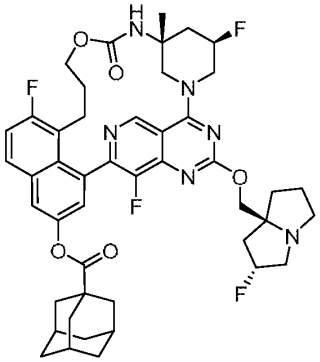
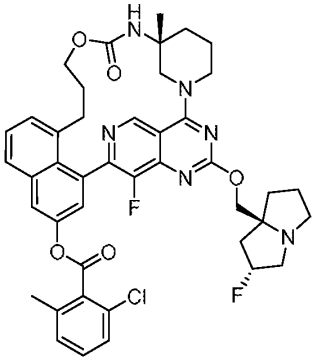
84		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl benzoate	749.3	A
85		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl pivalate	729.3	A
86		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl isobutyrate	715.3	A

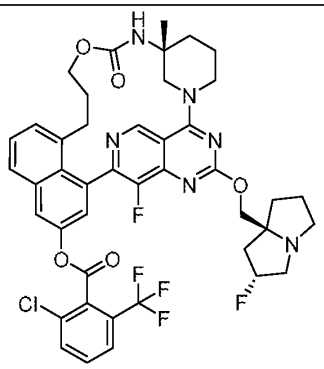
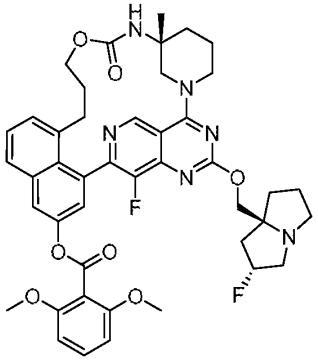
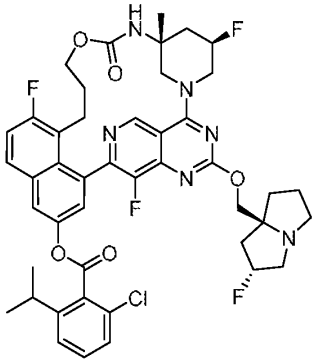
90		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,4-dimethylbenzoate	777.5	A
91		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(trifluoromethyl)benzoate	817.4	A
274		(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,6-dimethylbenzoate	795.4	A

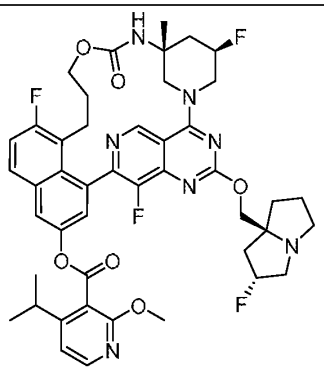
288		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl isobutyrate	769.4	A
289		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl pivalate	783.3	A
290		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3r,5r,7r)-adamantane-1-carboxylate	861.6	A

292		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,6-dichlorobenzoate	871.4	A
271		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-chloro-4,6-bis(trifluoromethyl)benzoate	919.3	A
309		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 1,3,5-trimethyl-1H-pyrazole-4-carboxylate	817.3	A

331		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,6-dichlorobenzoate	853.2	A
345		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl pivalate	765.5	A
357		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl isobutyrate	751.4	A

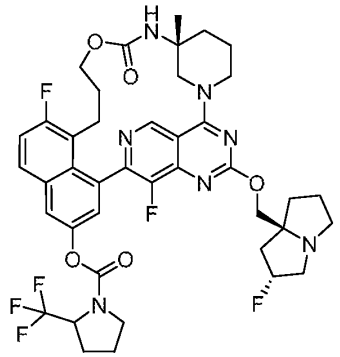
368		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,5-dimethylisoxazole-4-carboxylate	804.2	A
375		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3r,5r,7r)-adamantane-1-carboxylate	843.4	A
156		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-chloro-6-methylbenzoate	797.4	A

163		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-chloro-6-(trifluoromethyl)benzoate	851.3	A
182		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,6-dimethoxybenzoate	809.6	A
492		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-chloro-6-isopropylbenzoate	861.1	A

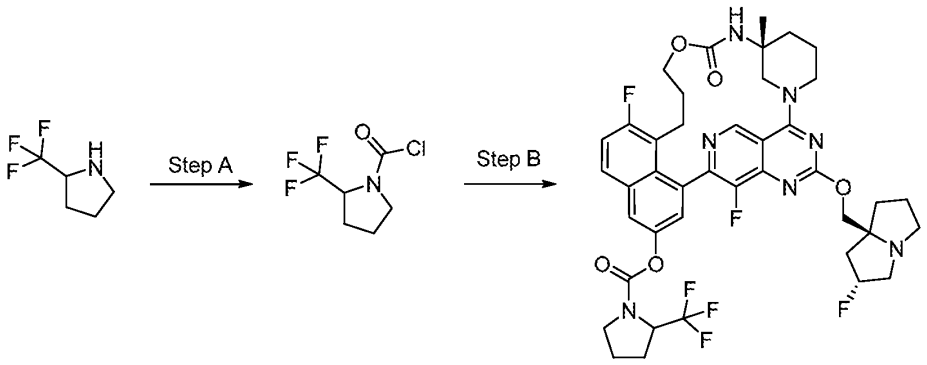
494		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-isopropyl-2-methoxynicotinate	858.4	A

Example procedure B. acid chloride coupling

Compound 278



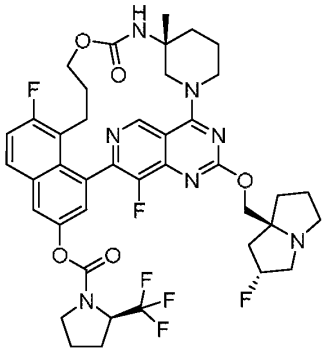
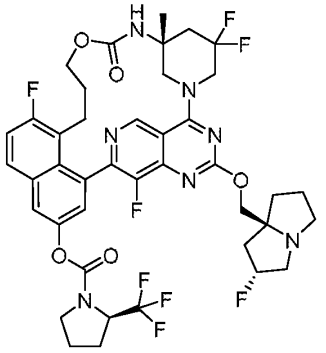
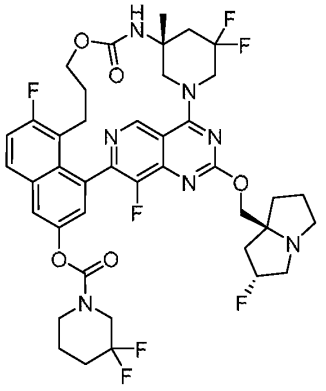
(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(trifluoromethyl)pyrrolidine-1-carboxylate

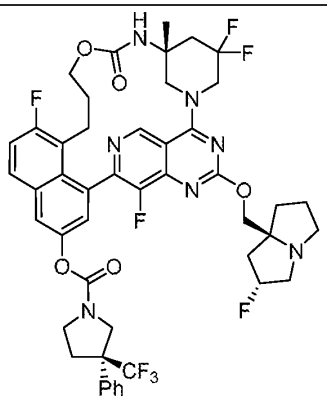
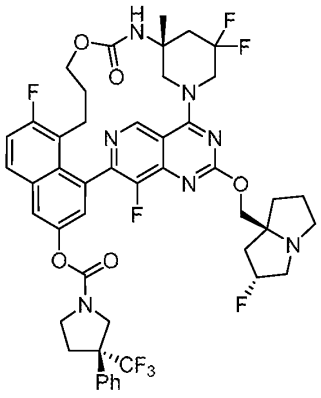
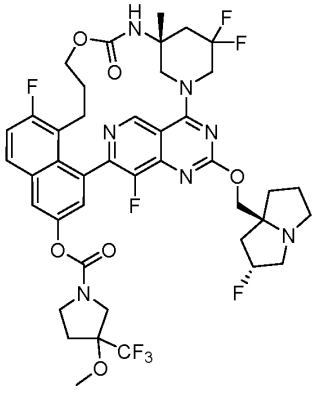


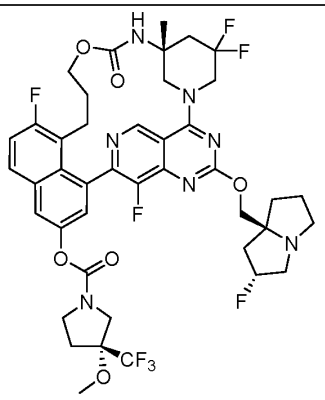
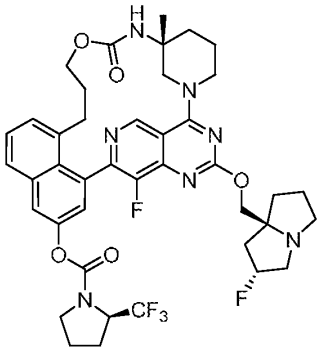
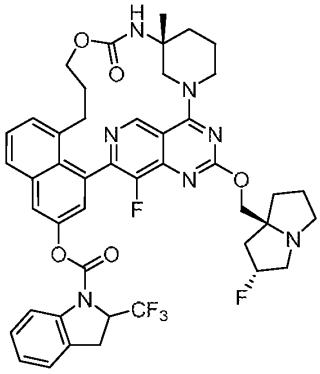
Step A. 2-(trifluoromethyl)pyrrolidine-1-carbonyl chloride. To a solution of pyridine (0.012 mL mg, 1.5 mmol) in DCM (2 mL) at 0 °C was added bis(trichloromethyl) carbonate (0.11 g, 0.36 mmol). The mixture was stirred at 0 °C for 30 min then 2-(trifluoromethyl)pyrrolidine (0.10 g, 0.72 mmol) was added in one portion. The mixture was stirred at rt for 1 hand then it was concentrated under reduced pressure to give 2-(trifluoromethyl)pyrrolidine-1-carbonyl chloride (140 mg) as yellow oil, which was used into the next step without further purification.

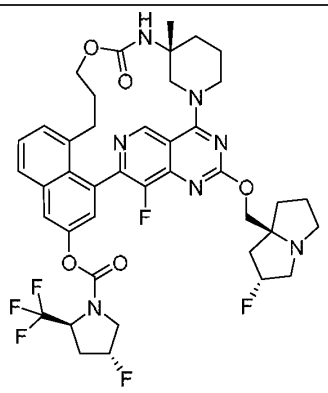
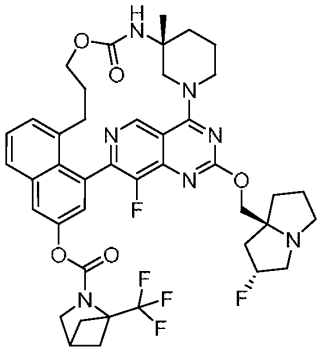
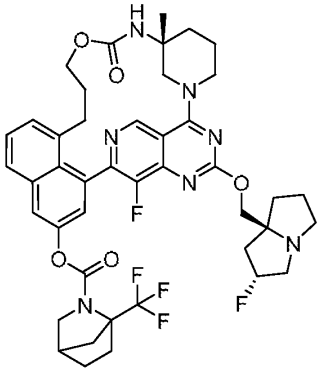
Step B. (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(trifluoromethyl)pyrrolidine-1-carboxylate. To a solution of (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.030 g, 0.045 mmol), pyridine (0.011 mL, 0.14 mmol) and DMAP (0.00055 g, 0.0045 mmol) in DCM (2 mL) was added 2-(trifluoromethyl)pyrrolidine-1-carbonyl chloride (0.060 g, 0.30 mmol). The reaction was heated to 40 °C for 16 h and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC (28 – 58% MeCN in 0.225% aqueous formic acid). The fractions containing the product were lyophilized to obtain (1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(trifluoromethyl)pyrrolidine-1-carboxylate (0.0063 g, 17% yield) as an off-white solid. LCMS (MM-ES+APCI, Pos): 828.3 (M+H).

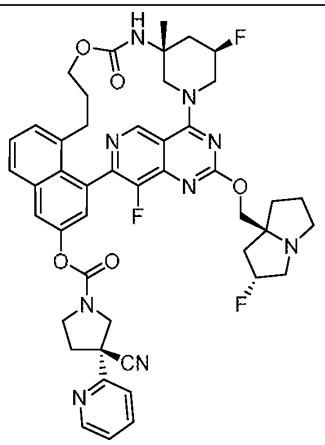
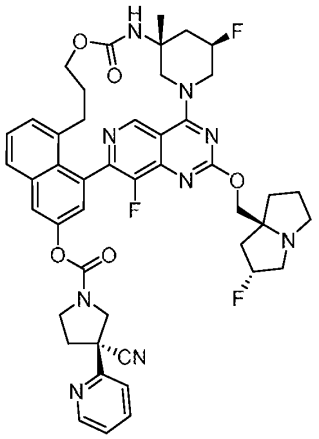
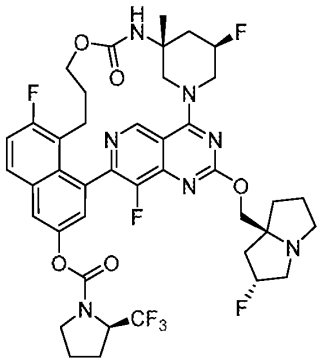
Table 9. Compounds synthesized by following the example procedure B

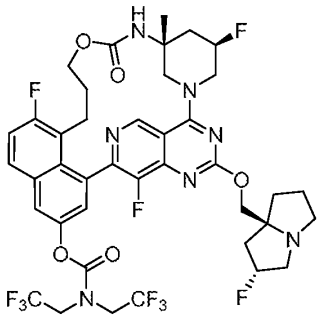
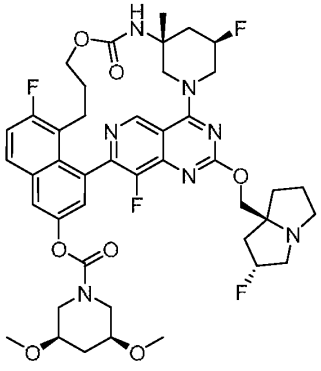
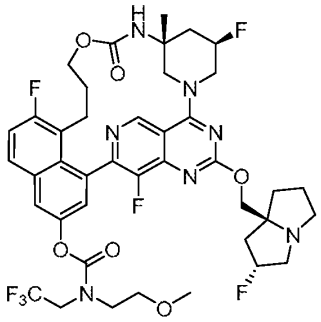
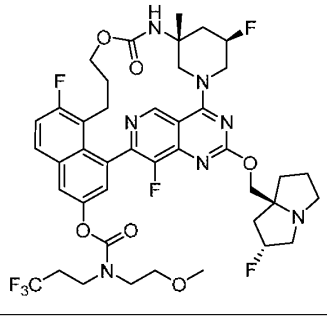
Cmpd ID	Structure	Name	LCMS	Procedure
281		(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-(trifluoromethyl)pyrrolidine-1-carboxylate	828.4	B
286		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-(trifluoromethyl)pyrrolidine-1-carboxylate	864.4	B
293		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-difluoropiperidine-1-carboxylate	846.4	B

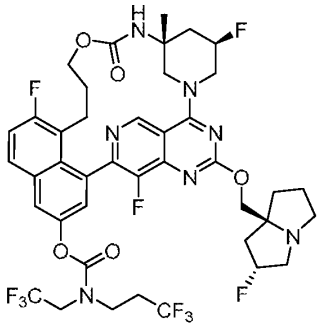
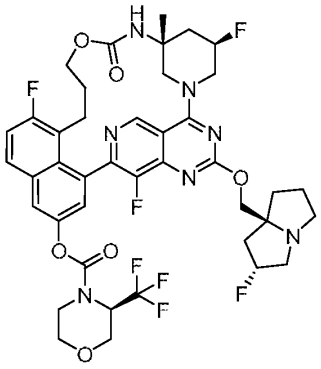
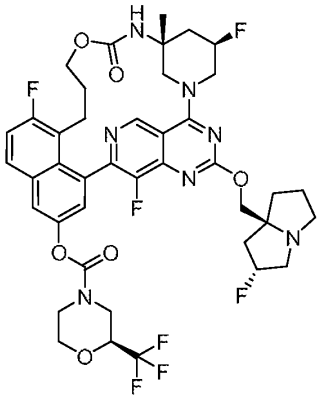
294		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-phenyl-3-(trifluoromethyl)pyrrolidine-1-carboxylate	940.3	B
295		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-phenyl-3-(trifluoromethyl)pyrrolidine-1-carboxylate	940.3	B
296		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-methoxy-3-(trifluoromethyl)pyrrolidine-1-carboxylate	894.4	B

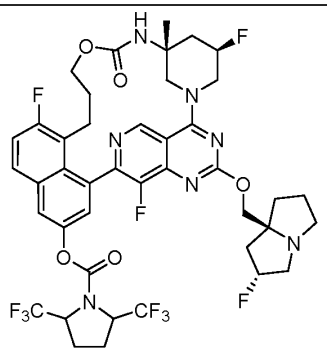
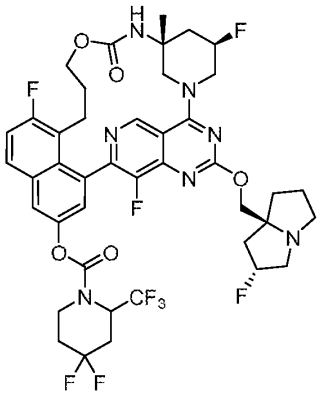
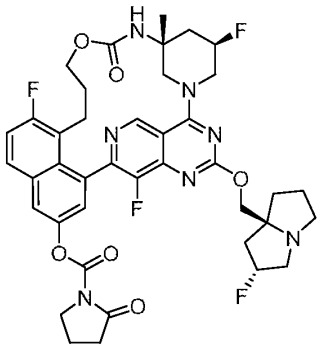
297		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-methoxy-3-(trifluoromethyl)pyrrolidine-1-carboxylate	894.3	B
236		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-(trifluoromethyl)pyrrolidine-1-carboxylate	810.4	B
243		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(trifluoromethyl)indoline-1-carboxylate	858.4	B

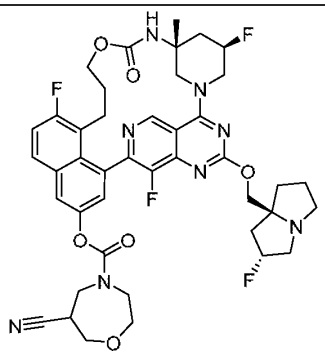
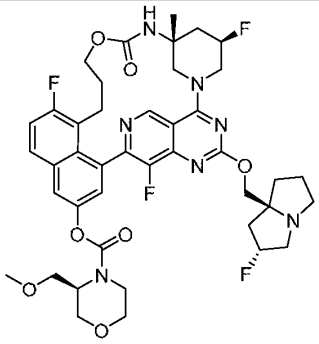
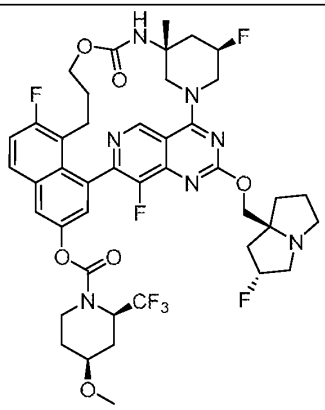
259		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S,4R)-4-fluoro-2-(trifluoromethyl)pyrrolidine-1-carboxylate	828.3	B
241		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 1-(trifluoromethyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate	822.3	B
247		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 1-(trifluoromethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylate	836.3	B

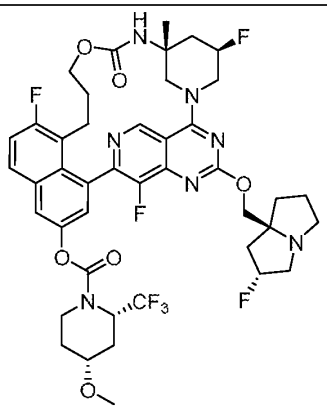
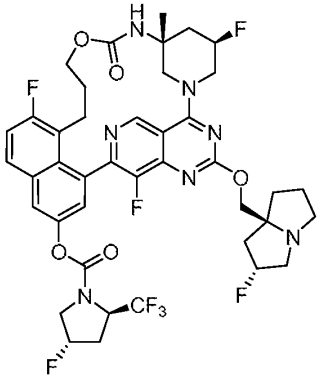
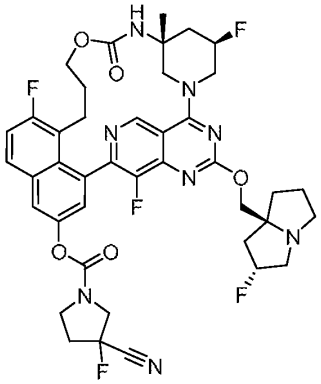
304		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-cyano-3-(pyridin-2-yl)pyrrolidine-1-carboxylate	862.4	B
305		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-cyano-3-(pyridin-2-yl)pyrrolidine-1-carboxylate	862.4	B
306		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-(trifluoromethyl)pyrrolidine-1-carboxylate	846.2	B

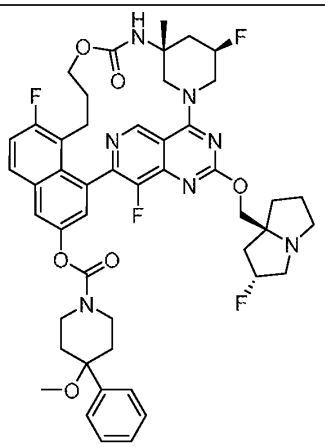
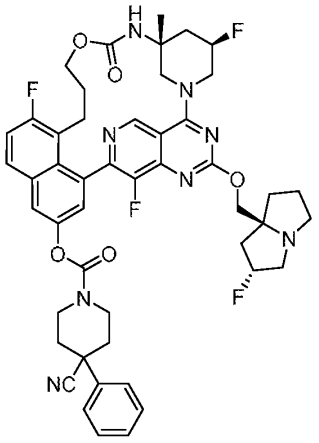
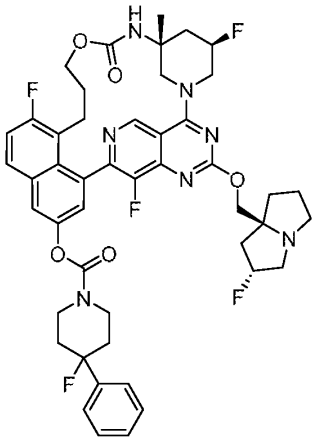
354		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl bis(2,2,2-trifluoroethyl)carbamate	888.5	B
358		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R,5S)-3,5-dimethoxypiperidine-1-carboxylate	852.5	B
361		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2-methoxyethyl)(2,2,2-trifluoroethyl)carbamate	864.3	B
362		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl	878.5	B

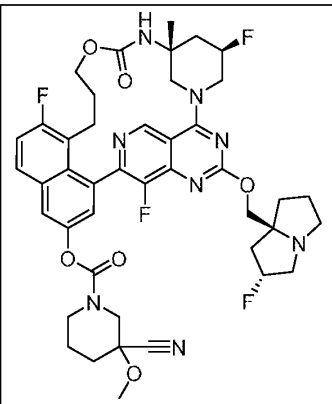
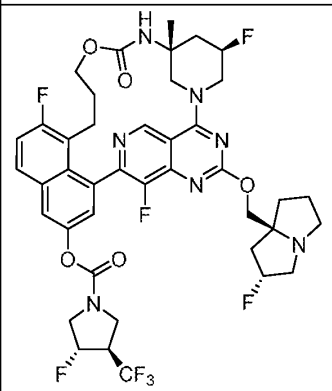
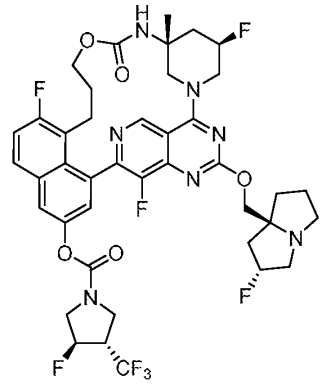
		(2-methoxyethyl)(3,3,3-trifluoropropyl)carbamate		
363		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2,2,2-trifluoroethyl)(3,3,3-trifluoropropyl)carbamate	902.3	B
365		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-(trifluoromethyl)morpholine-4-carboxylate	862.2	B
366		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S)-2-(trifluoromethyl)morpholine-4-carboxylate	862.2	B

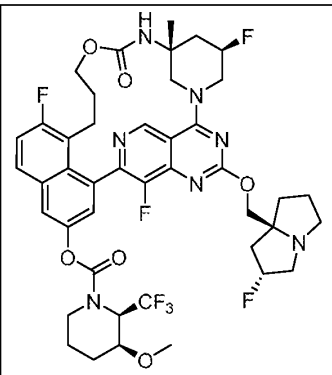
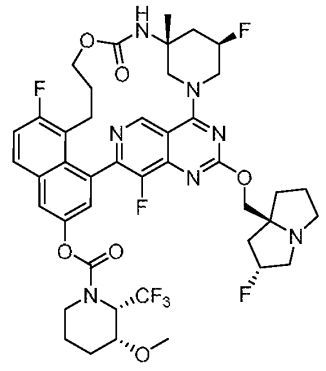
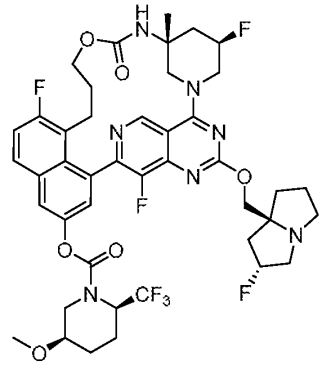
380		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,5-bis(trifluoromethyl)pyrrolidine-1-carboxylate	914.3	B
382		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,4-difluoro-2-(trifluoromethyl)piperidine-1-carboxylate	896.5	B
383		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-oxopyrrolidine-1-carboxylate	792.4	B

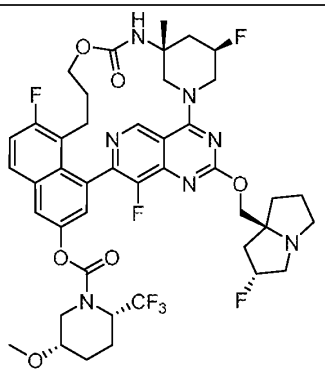
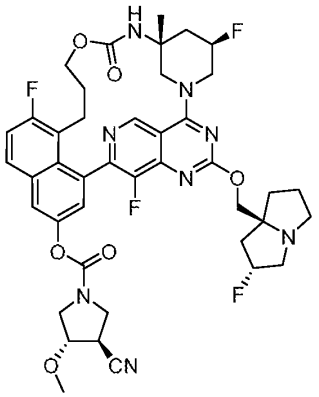
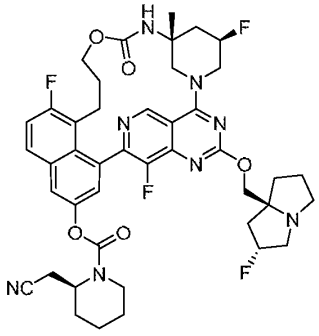
386		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 6-cyano-1,4-oxazepane-4-carboxylate	833.4	B
389		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-(methoxymethyl)morpholine-4-carboxylate	838.4	B
394		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R,4S)-4-methoxy-2-(trifluoromethyl)piperidine-1-carboxylate	890.4	B

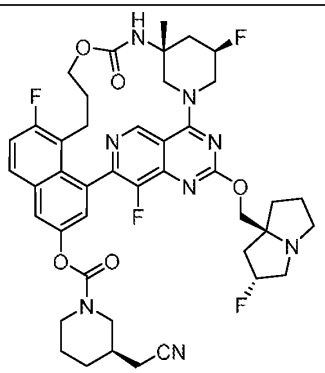
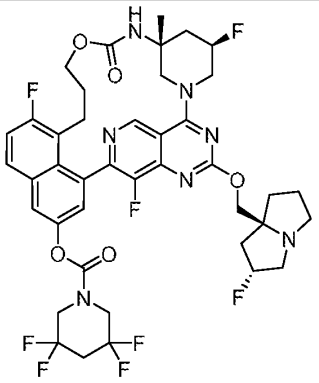
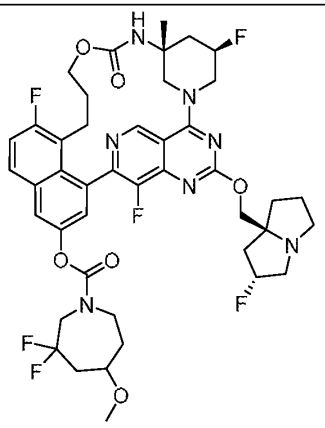
395		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S,4R)-4-methoxy-2-(trifluoromethyl)piperidine-1-carboxylate	890.3	B
396		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R,4S)-4-fluoro-2-(trifluoromethyl)pyrrolidine-1-carboxylate	864.6	B
397		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-cyano-3-fluoropyrrolidine-1-carboxylate	821.2	B

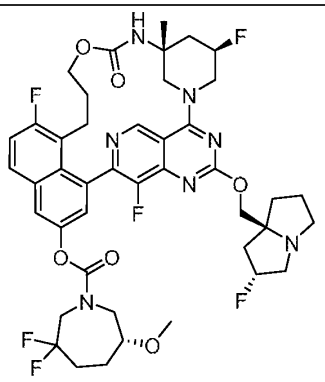
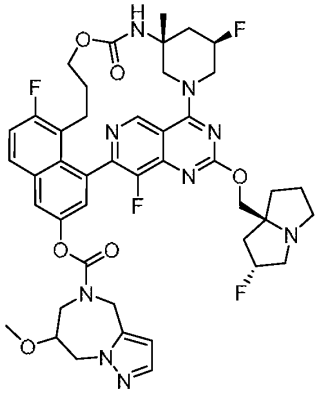
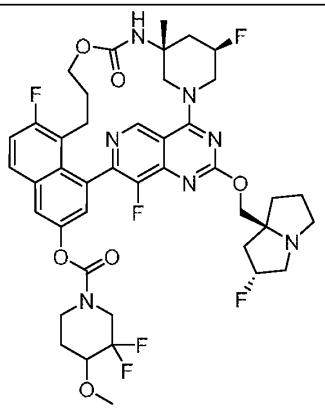
400		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxy-4-phenylpiperidine-1-carboxylate	898.6	B
401		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-cyano-4-phenylpiperidine-1-carboxylate	893.5	B
402		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-fluoro-4-phenylpiperidine-1-carboxylate	886.3	B

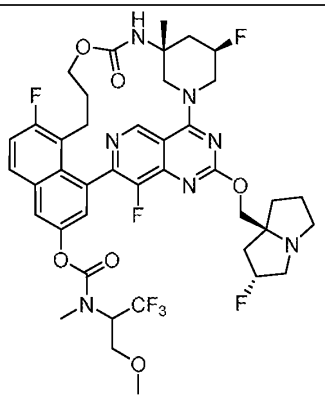
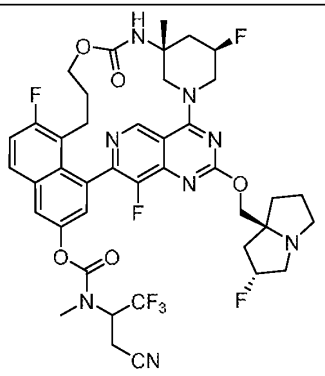
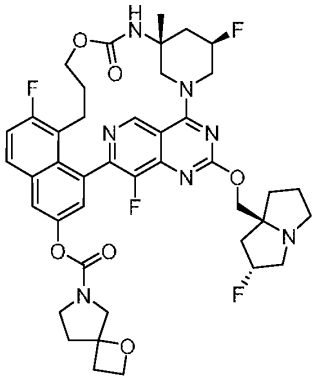
404		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-cyano-3-methoxypiperidine-1-carboxylate	847.3	B
407		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S,4R)-3-fluoro-4-(trifluoromethyl)pyrrolidine-1-carboxylate	864.4	B
408		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R,4S)-3-fluoro-4-(trifluoromethyl)pyrrolidine-1-carboxylate	864.4	B

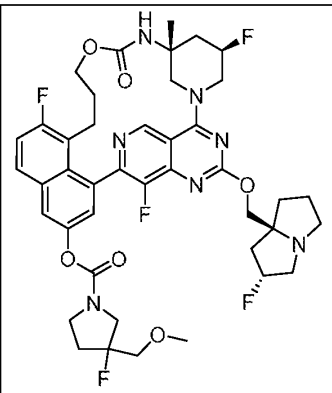
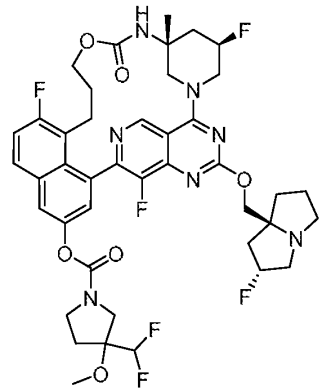
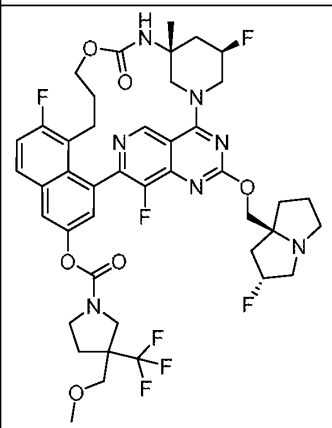
409		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R,3S)-3-methoxy-2-(trifluoromethyl)piperidine-1-carboxylate	890.6	B
410		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S,3R)-3-methoxy-2-(trifluoromethyl)piperidine-1-carboxylate	890.5	B
411		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R,5R)-5-methoxy-2-(trifluoromethyl)piperidine-1-carboxylate	890.3	B

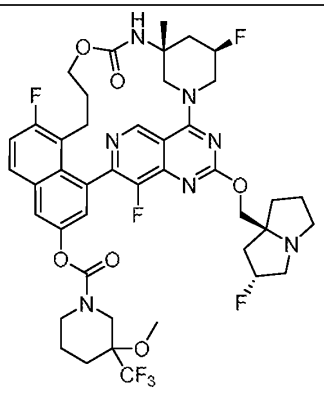
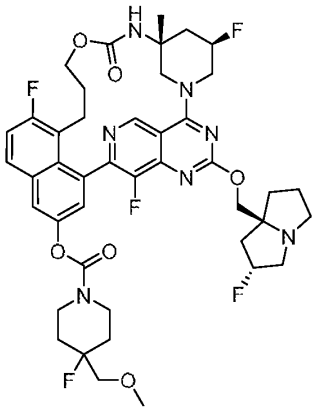
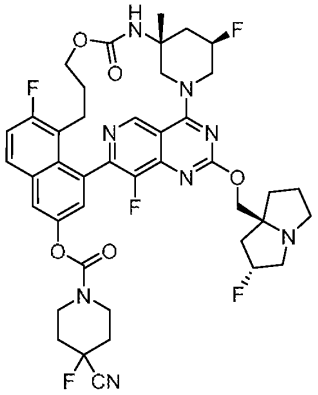
412		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S,5S)-5-methoxy-2-(trifluoromethyl)piperidine-1-carboxylate	890.3	B
413		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S,4S)-3-cyano-4-methoxypyrrolidine-1-carboxylate	833.5	B
415		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S)-2-(cyanomethyl)piperidine-1-carboxylate	831.3	B

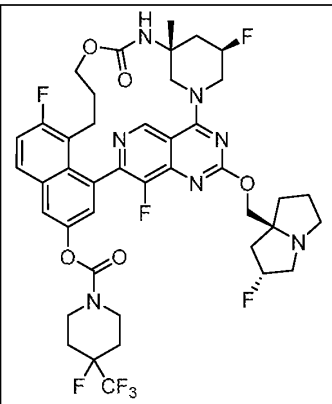
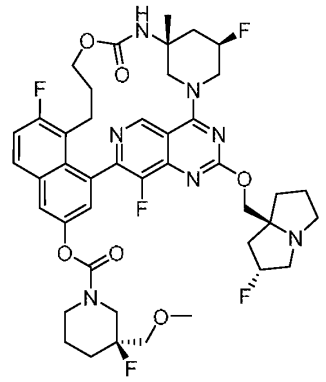
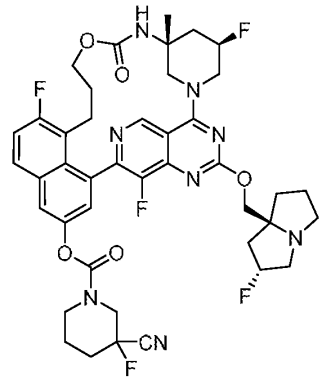
417		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-(cyanomethyl)piperidine-1-carboxylate	831.4	B
418		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3,5,5-tetrafluoropiperidine-1-carboxylate	864.5	B
419		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-difluoro-5-methoxyazepane-1-carboxylate	872.5	B

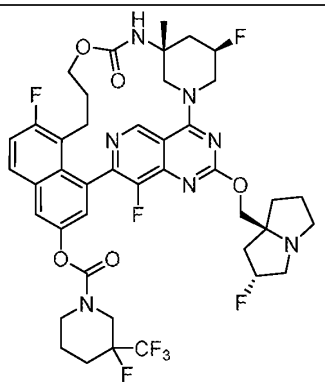
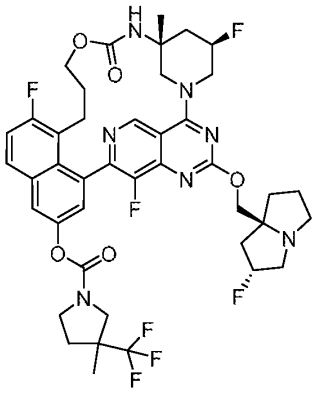
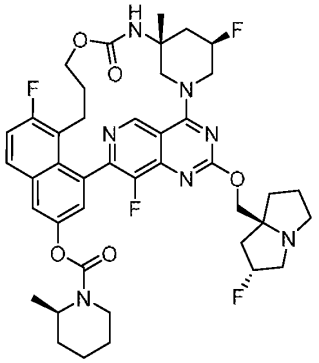
420		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (6R)-3,3-difluoro-6-methoxyazepane-1-carboxylate	872.4	B
421		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 7-methoxy-7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate	874.3	B
422		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-difluoro-4-methoxypiperidine-1-carboxylate	858.4	B

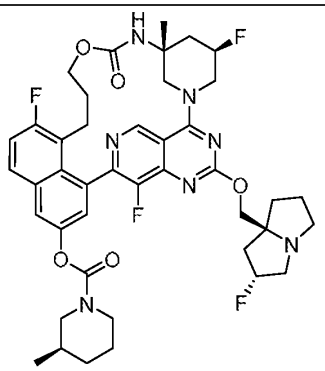
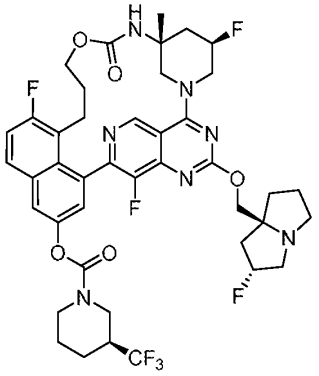
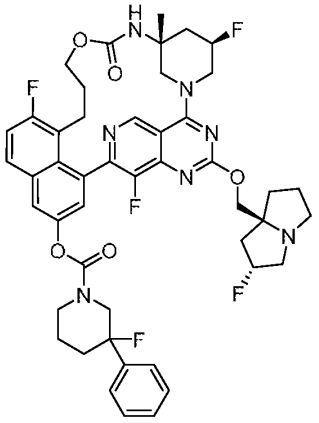
424		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl methyl(1,1,1-trifluoro-3-methoxypropan-2-yl)carbamate	864.3	B
425		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3-cyano-1,1,1-trifluoropropan-2-yl)(methyl)carbamate	859.3	B
427		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 1-oxa-6-azaspiro[3.4]octane-6-carboxylate	820.6	B

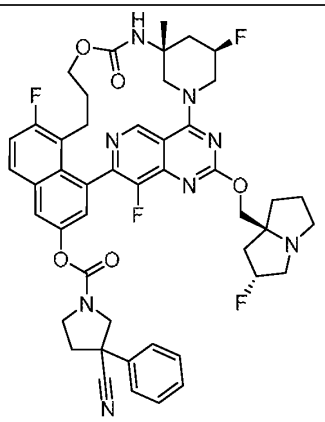
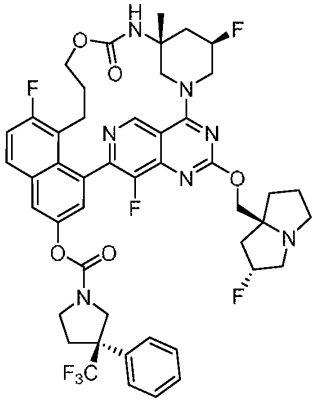
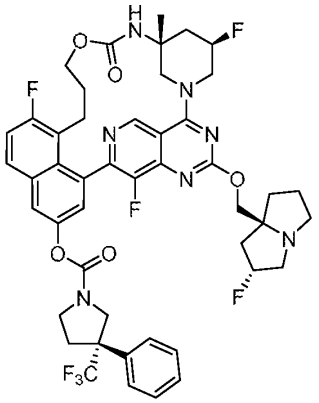
428		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-fluoro-3-(methoxymethyl)pyrrolidine-1-carboxylate	840.4	B
429		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(difluoromethyl)-3-methoxypyrrolidine-1-carboxylate	858.4	B
430		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(methoxymethyl)-3-(trifluoromethyl)pyrrolidine-1-carboxylate	890.4	B

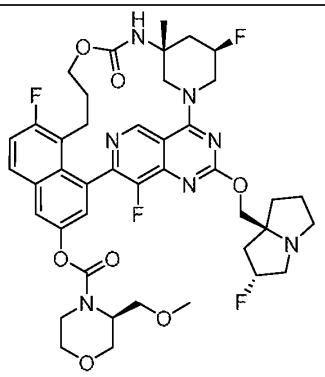
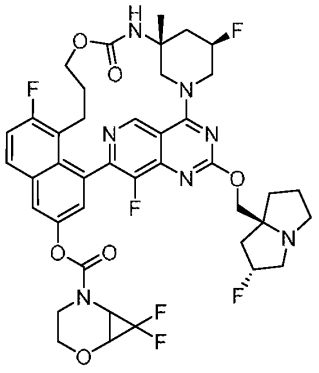
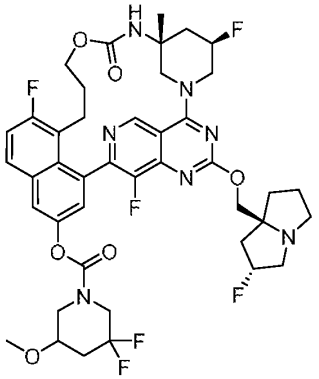
431		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-methoxy-3-(trifluoromethyl)piperidine-1-carboxylate	890.4	B
433		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-fluoro-4-(methoxymethyl)piperidine-1-carboxylate	854.3	B
435		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-cyano-4-fluoropiperidine-1-carboxylate	835.3	B

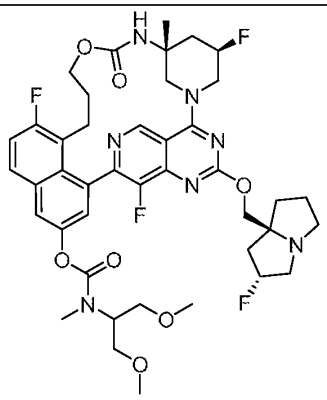
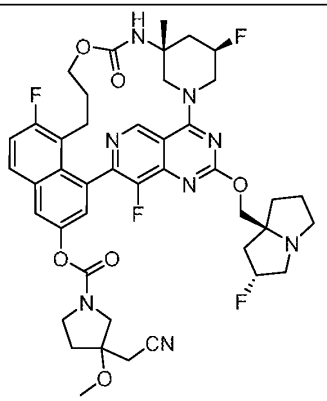
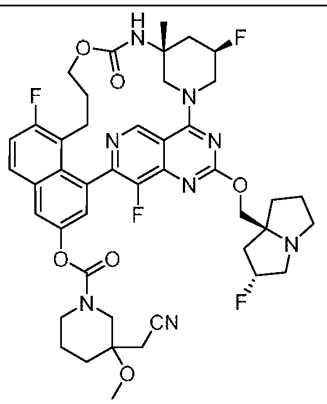
438		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-fluoro-4-(trifluoromethyl)piperidine-1-carboxylate	878.4	B
439		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-fluoro-3-(methoxymethyl)piperidine-1-carboxylate	854.5	B
440		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-cyano-3-fluoropiperidine-1-carboxylate	835.3	B

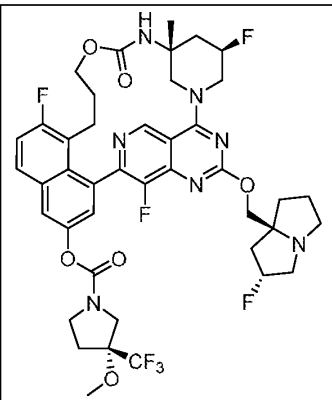
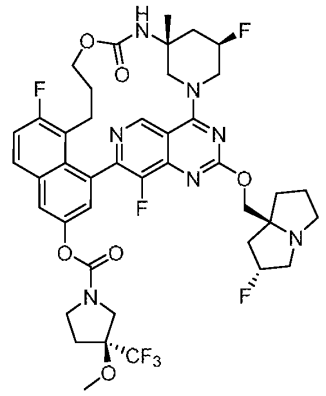
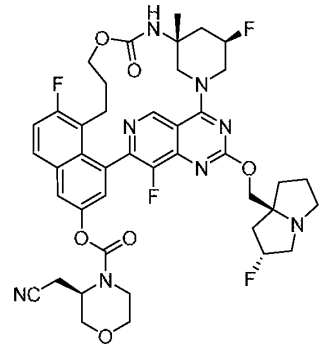
441		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-fluoro-3-(trifluoromethyl)piperidine-1-carboxylate	878.3	B
442		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-methyl-3-(trifluoromethyl)pyrrolidine-1-carboxylate	860.4	B
450		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-methylpiperidine-1-carboxylate	806.3	B

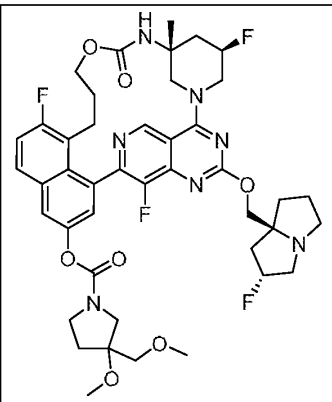
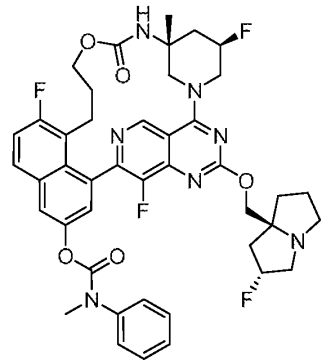
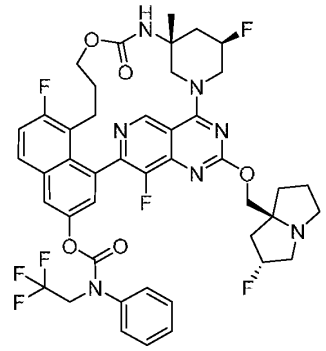
451		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-methylpiperidine-1-carboxylate	806.5	B
452		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-(trifluoromethyl)piperidine-1-carboxylate	860.4	B
453		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-fluoro-3-phenylpiperidine-1-carboxylate	886.3	B

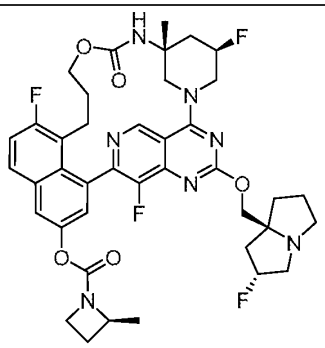
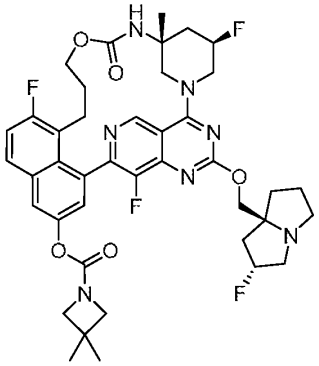
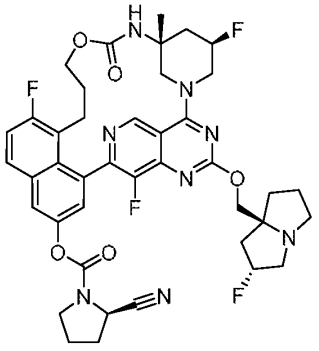
454		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-cyano-3-phenylpyrrolidine-1-carboxylate	879.3	B
455		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-phenyl-3-(trifluoromethyl)pyrrolidine-1-carboxylate	922.4	B
456		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-phenyl-3-(trifluoromethyl)pyrrolidine-1-carboxylate	922.5	B

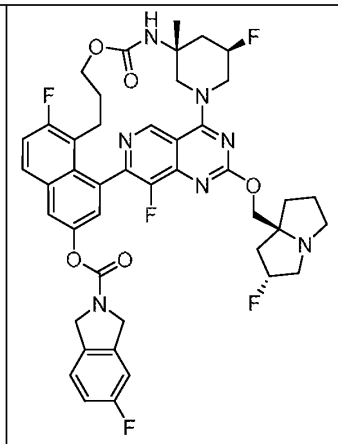
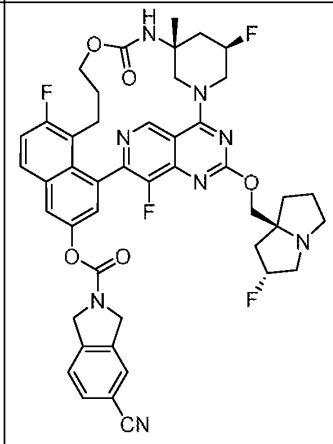
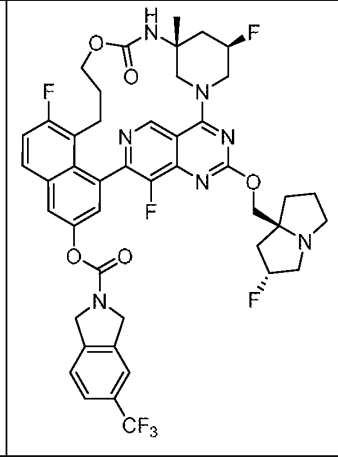
457		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-(methoxymethyl)morpholine-4-carboxylate	838.3	B
459		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 7,7-difluoro-2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate	842.4	B
460		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 7,7-difluoro-2-oxa-5-azabicyclo[4.1.0]heptane-5-carboxylate	858.3	B

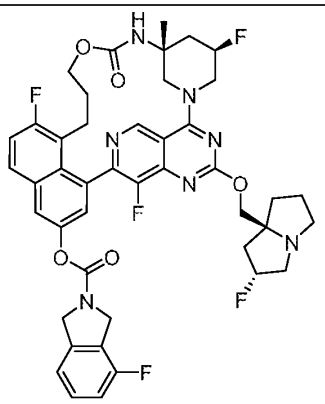
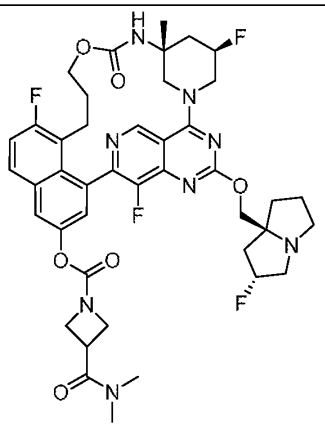
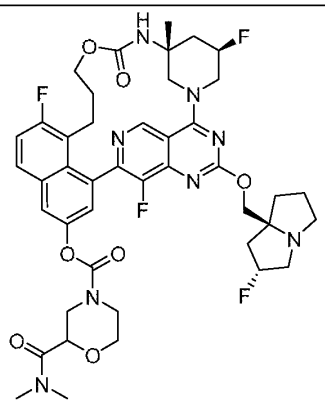
461		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (1,3-dimethoxypropan-2-yl)(methyl)carbamate	840.4	B
462		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(cyanomethyl)-3-methoxypyrrolidine-1-carboxylate	847.5	B
463		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(cyanomethyl)-3-methoxypiperidine-1-carboxylate	861.4	B

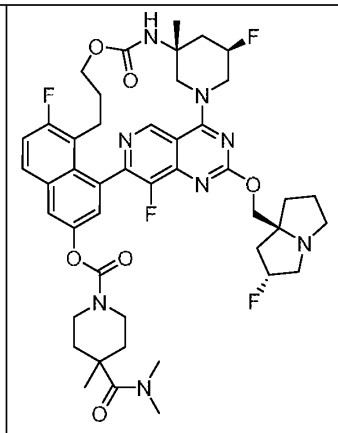
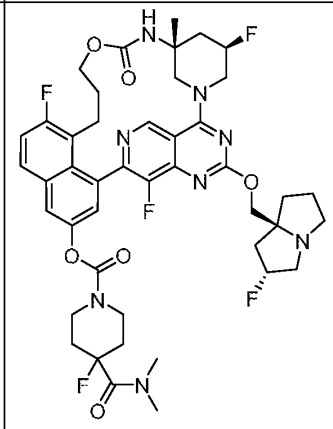
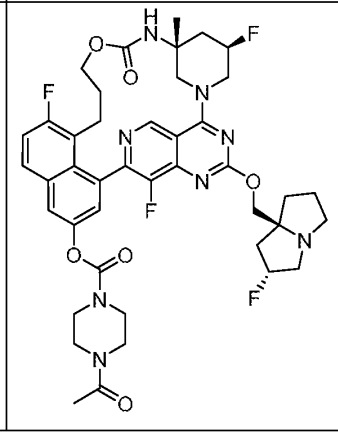
464		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-methoxy-3-(trifluoromethyl)pyrrolidine-1-carboxylate	876.3	B
465		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-methoxy-3-(trifluoromethyl)pyrrolidine-1-carboxylate	876.3	B
466		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-(cyanomethyl)morpholine-4-carboxylate	833.5	B

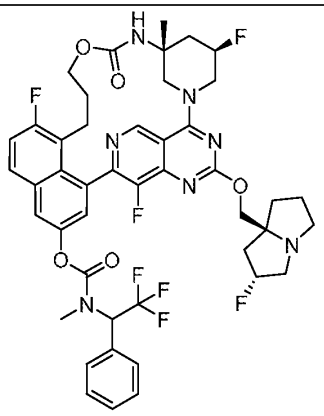
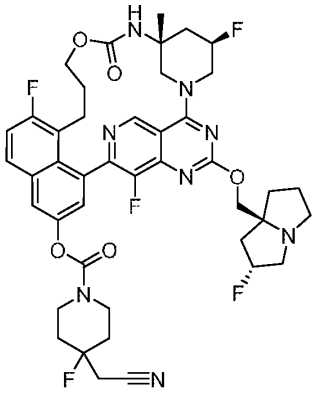
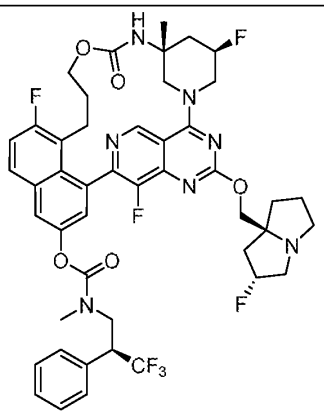
467		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-methoxy-3-(methoxymethyl)pyrrolidine-1-carboxylate	852.3	B
470		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl methyl(phenyl)carbamate	814.3	B
471		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl phenyl(2,2,2-trifluoroethyl)carbamate	882.4	B

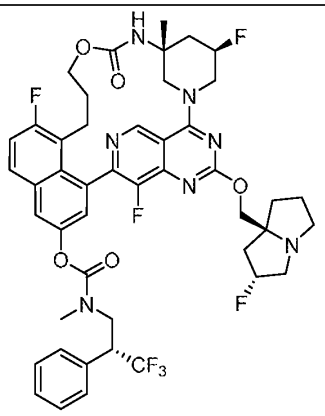
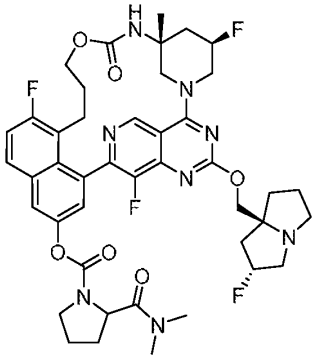
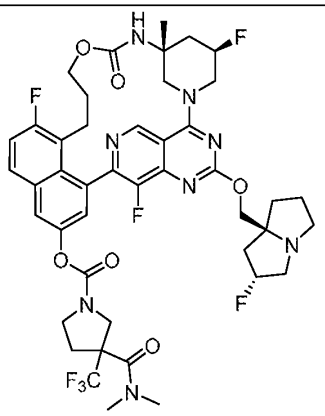
473		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S)-2-methylazetidine-1-carboxylate	778.3	B
475		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-dimethylazetidine-1-carboxylate	792.5	B
476		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-cyanopyrrolidine-1-carboxylate	803.3	B

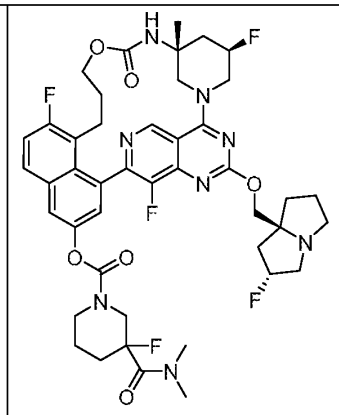
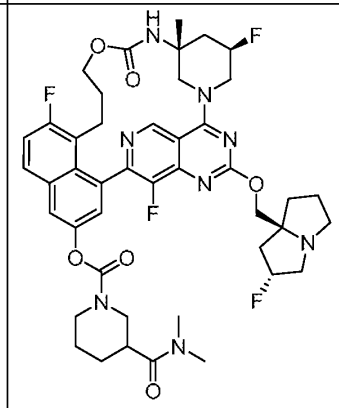
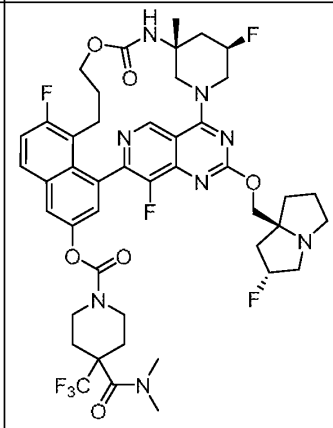
477		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 5-fluoroisoindoline-2-carboxylate	844.5	B
478		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 5-cyanoisoindoline-2-carboxylate	851.4	B
479		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 5-(trifluoromethyl)isoindoline-2-carboxylate	894.3	B

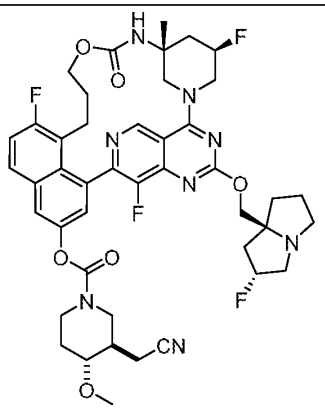
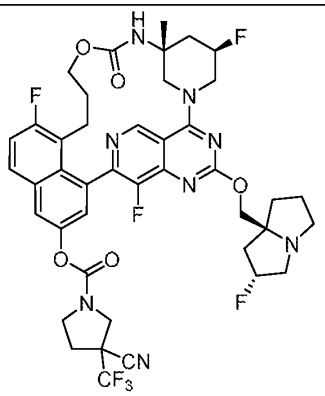
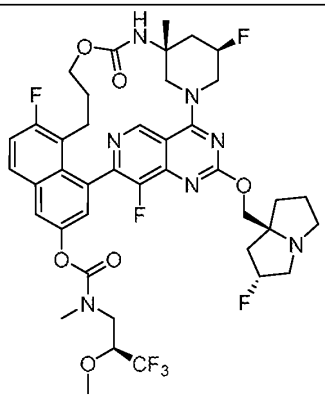
480		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-fluoroisoindoline-2-carboxylate	844.3	B
482		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(dimethylcarbamoyl)azetidine-1-carboxylate	835.3	B
483		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(dimethylcarbamoyl)morpholine-4-carboxylate	865.3	B

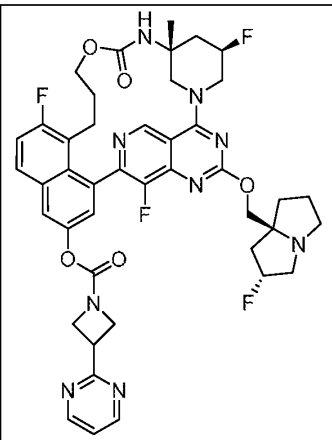
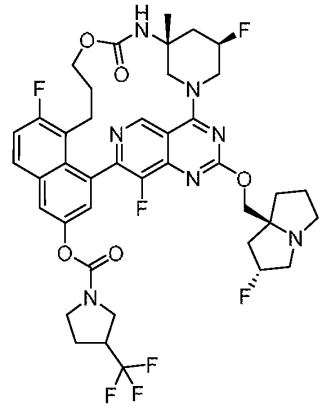
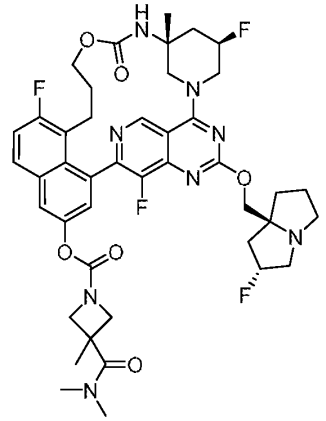
484		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-(dimethylcarbamoyl)-4-methylpiperidine-1-carboxylate	877.6	B
485		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-(dimethylcarbamoyl)-4-fluoropiperidine-1-carboxylate	881.5	B
487		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-acetylpiperazine-1-carboxylate	835.3	B

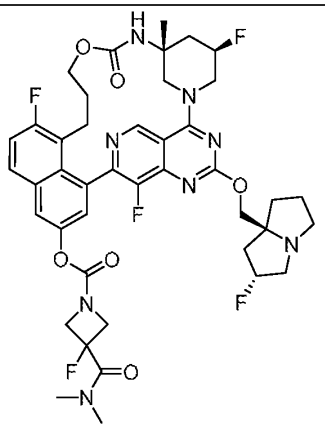
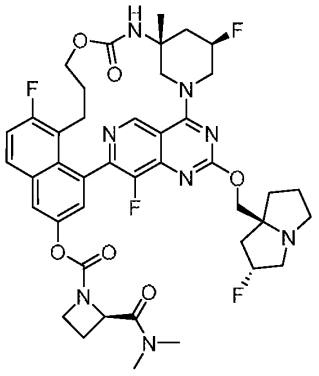
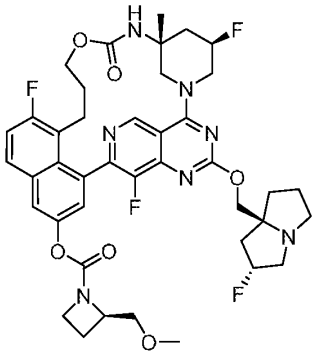
488		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl methyl(2,2,2-trifluoro-1-phenylethyl)carbamate	896.5	B
489		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-(cyanomethyl)-4-fluoropiperidine-1-carboxylate	849.5	B
490		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl methyl((S)-3,3,3-trifluoro-2-phenylpropyl)carbamate	910.5	B

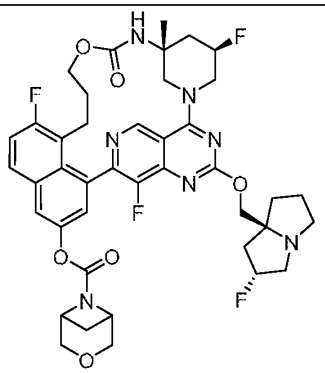
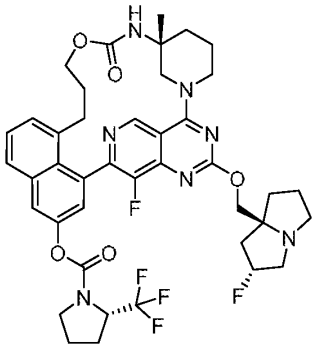
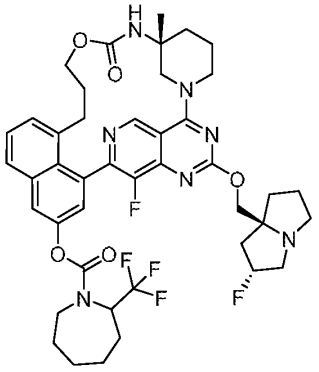
491		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl methyl((R)-3,3,3-trifluoro-2-phenylpropyl)carbamate	910.4	B
495		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(dimethylcarbamoyl)pyrrolidine-1-carboxylate	849.3	B
496		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(dimethylcarbamoyl)-3-(trifluoromethyl)pyrrolidine-1-carboxylate	917.3	B

497		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(dimethylcarbamoyl)-3-fluoropiperidine-1-carboxylate	881.3	B
498		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(dimethylcarbamoyl)piperidine-1-carboxylate	864.4	B
499		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-(dimethylcarbamoyl)-4-(trifluoromethyl)piperidine-1-carboxylate	931.4	B

518		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (rel-3R,4R)-3-(cyanomethyl)-4-methoxypiperidine-1-carboxylate	861.3	B
519		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-cyano-3-(trifluoromethyl)pyrrolidine-1-carboxylate	871.5	B
520		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl methyl((S)-3,3,3-trifluoro-2-methoxypropyl)carbamate	864.4	B

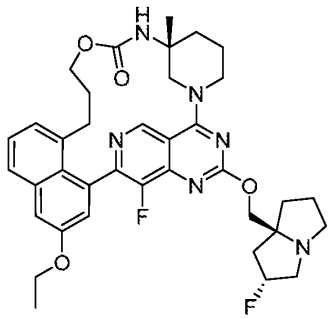
544		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(pyrimidin-2-yl)azetidine-1-carboxylate	842.5	B
553		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(trifluoromethyl)pyrrolidine-1-carboxylate	846.6	B
555		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(dimethylcarbamoyl)-3-methylazetidine-1-carboxylate	849.4	B

556		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(dimethylcarbamoyl)- 3-fluoroazetidine-1-carboxylate	853.5	B
557		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-(dimethylcarbamoyl)azetidine-1-carboxylate	835.4	B
558		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-(methoxymethyl)azetidine-1-carboxylate	808.4	B

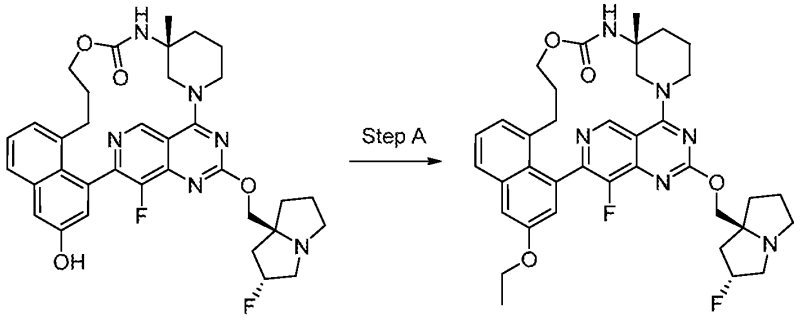
559		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (1R,5S)-3-oxa-6-azabicyclo[3.1.1]heptane-6-carboxylate	806.4	B
219		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S)-2-(trifluoromethyl)pyrrolidine-1-carboxylate	810.6	B
223		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(trifluoromethyl)azepane-1-carboxylate	838.5	B

Example procedure C. Alkylation

Compound 89



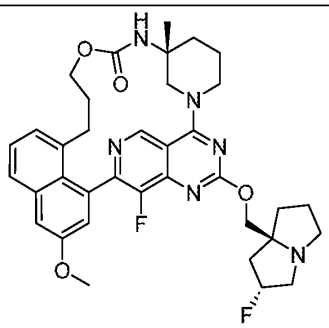
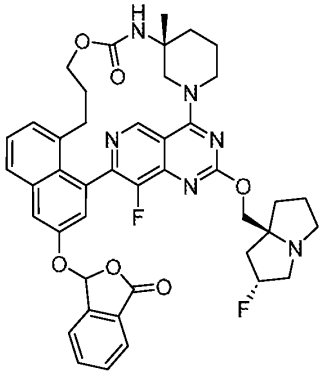
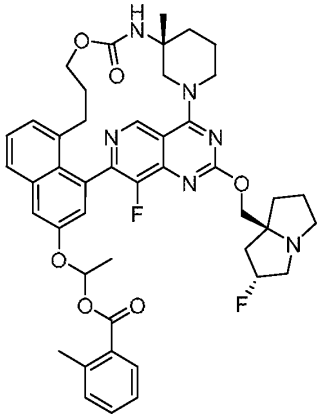
(1^3R)-3^3-ethoxy-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one

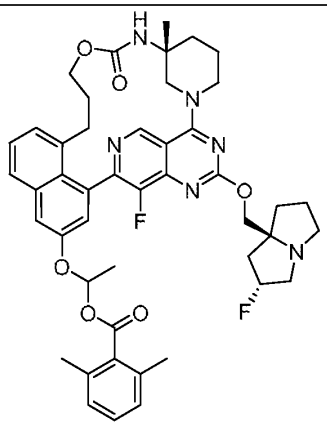
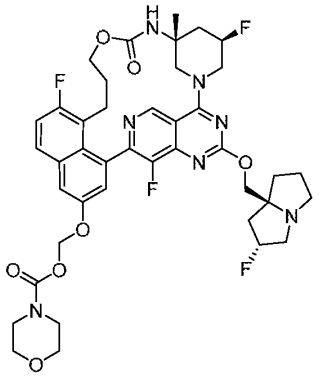
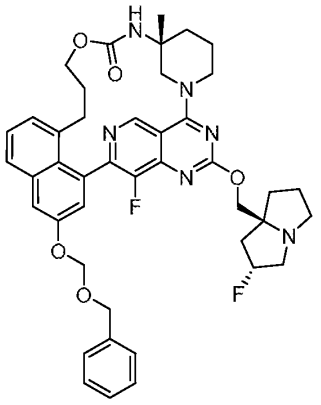


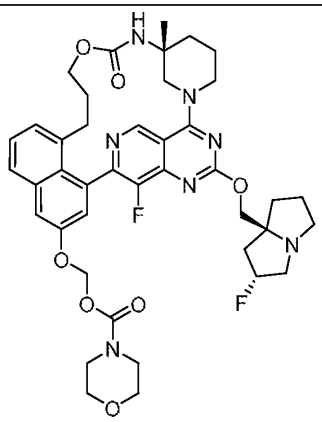
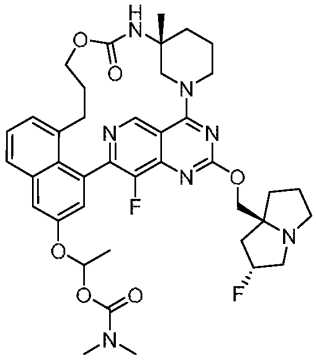
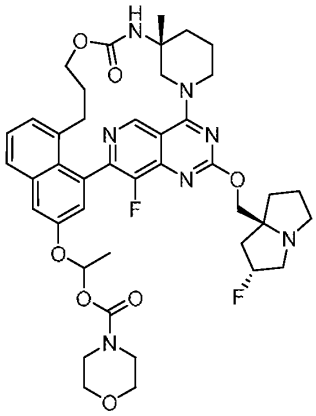
Step A. (1^3R)-3^3-ethoxy-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one. To a solution of (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.030 g, 0.043 mmol) in MeCN (0.5 mL) was added K_2CO_3 (0.0012 g, 0.087 mmol) and ethyl bromide (0.0039 mL, 0.052 mmol). The reaction was stirred at rt for 16 h and then it was filtered. The filtrate was purified by preparative HPLC (60 – 90% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized. The residue was purified by normal phase preparative HPLC: (5 – 45% EtOH in hexanes). The fractions containing the product were lyophilized to obtain (1^3R)-3^3-ethoxy-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.0071

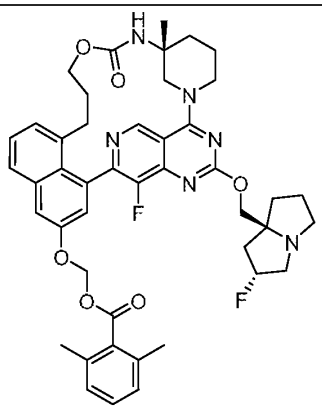
g, 24% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): 673.4 (M+H).

Table 10. Compounds synthesized by following the example procedure C

Cmpd ID	Structure	Name	LCMS	Procedure
87		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-methoxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one	659.4	C
88		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-3^3-((3-oxo-1,3-dihydroisobenzofuran-1-yl)oxy)-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one	777.3	C
235		1-((((1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)ethyl 2-methylbenzoate	807.3	C

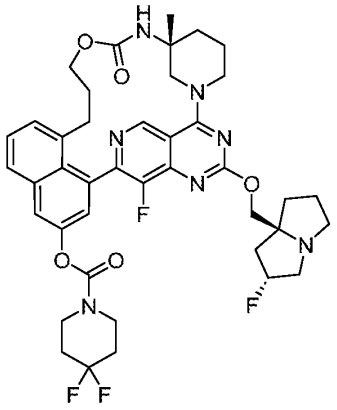
242		1-(((1[3]R)-2[8]-fluoro-2[2]-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1[3]-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3[3]-yl)oxy)ethyl 2,6-dimethylbenzoate	821.4	C
313		(((1[3]R,1[5]R)-1[5],2[8],3[7]-trifluoro-2[2]-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1[3]-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3[3]-yl)oxy)methyl morpholine-4-carboxylate	824.3	C
165		(1[3]R)-3[3]-((benzyloxy)methoxy)-2[8]-fluoro-2[2]-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1[3]-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one	765.3	C

153		(((1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl morpholine-4-carboxylate	788.3	C
190		1-(((1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)ethyl dimethylcarbamate	760.4	C
179		1-(((1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)ethyl morpholine-4-carboxylate	802.4	C

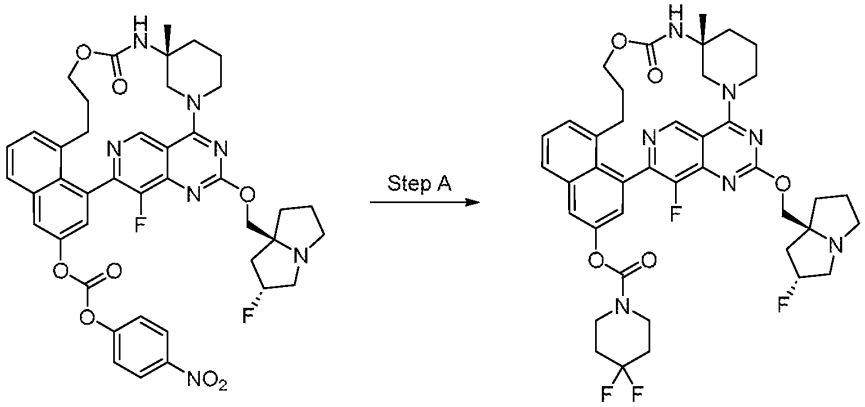
218		(((1[3]R)-2[8]-fluoro-2[2]-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1[3]-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3[3]-yl)oxy)methyl 2,6-dimethylbenzoate	807.3	C

Example procedure D. Carbonate displacement - Using N-hydroxy succinimide carbonate (Intermediate I40) in place of 4-nitrophenyl carbonate

Compound 140



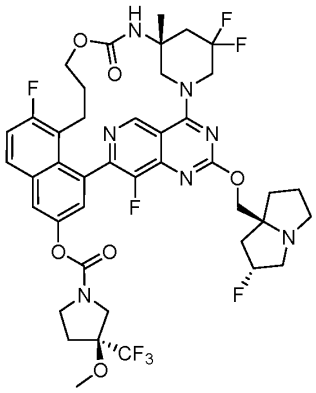
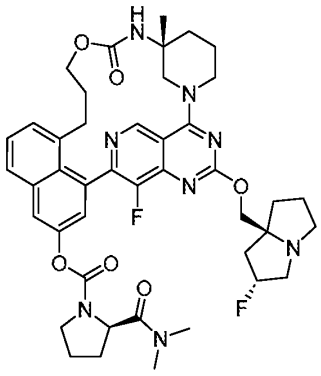
(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,4-difluoropiperidine-1-carboxylate

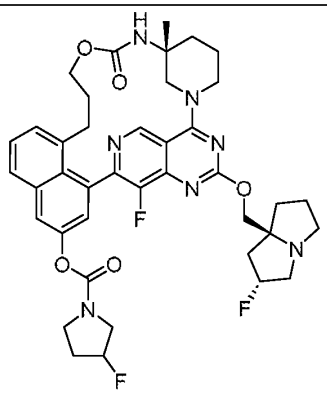
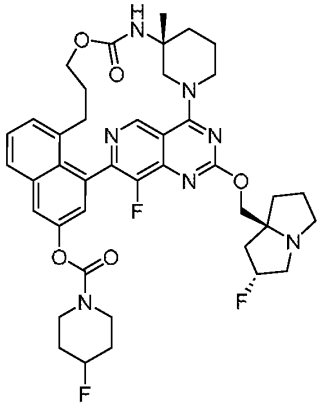
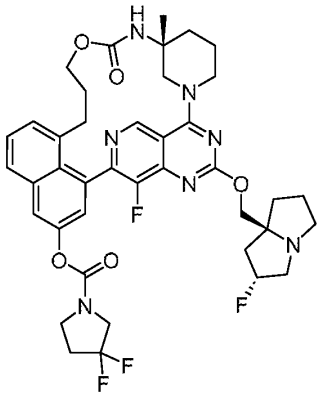


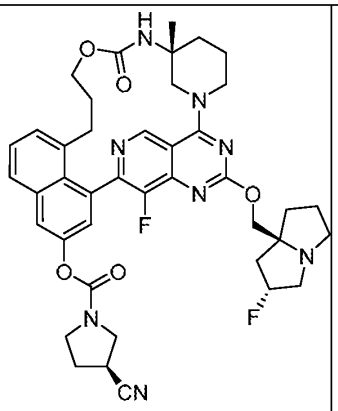
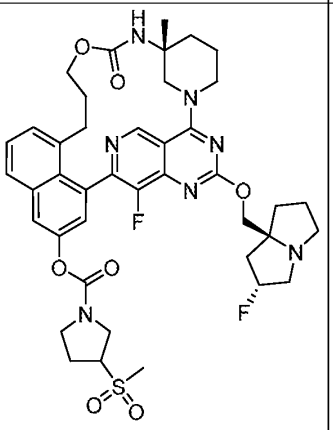
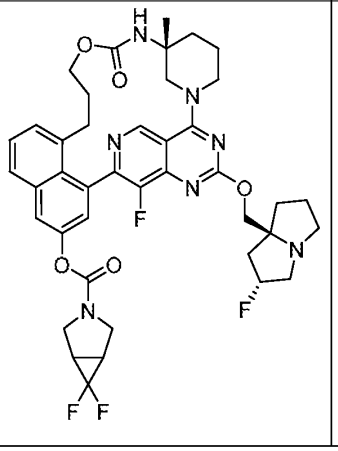
Step A. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,4-difluoropiperidine-1-carboxylate. To a solution of intermediate I23 (0.060 g, 0.07 mmol) and DIPEA (0.026 mL, 0.148 mmol) in DCM (0.5 mL) was added 4,4-difluoropiperidine (0.012 g, 0.096 mmol). The reaction was stirred at rt for 1 h after which it was concentrated under reduced pressure. The crude product was purified by preparative HPLC (15 – 45% MeCN in 0.225% aqueous formic acid). The

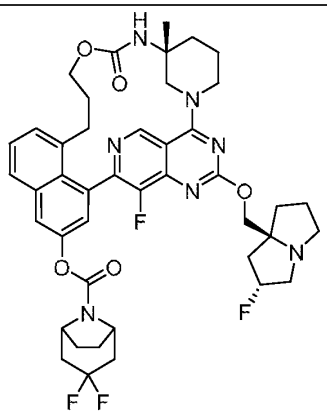
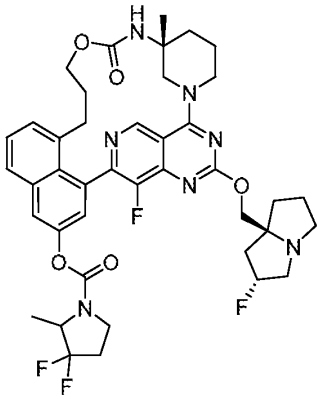
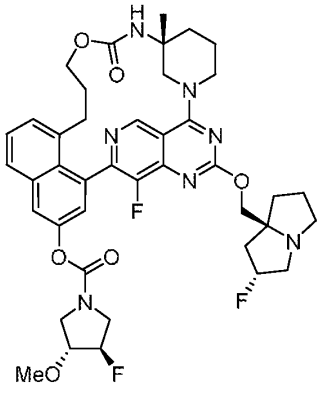
fractions containing the product were lyophilized to obtain (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,4-difluoropiperidine-1-carboxylate (0.029 g, 48% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 792.4 (M+H).

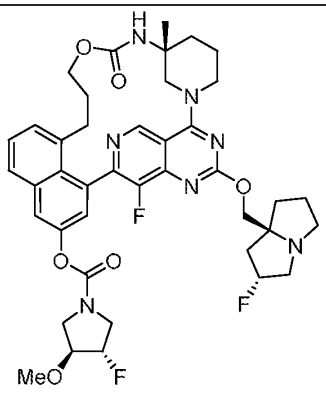
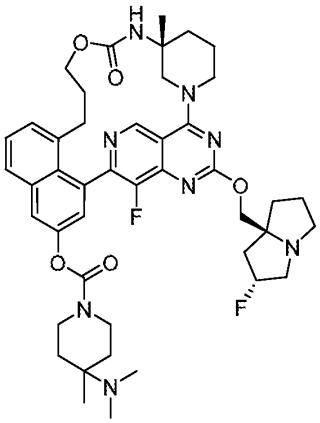
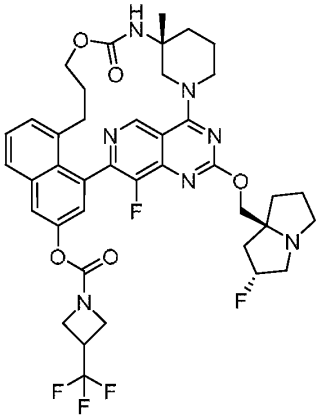
Table 11. Compounds synthesized by following the example procedure D

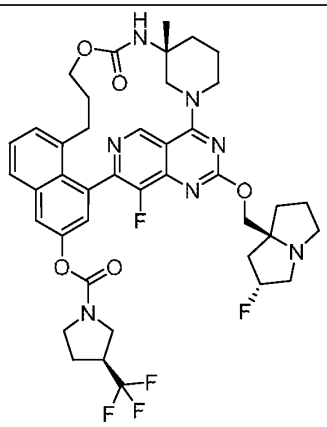
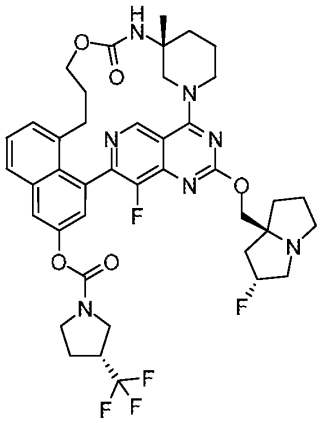
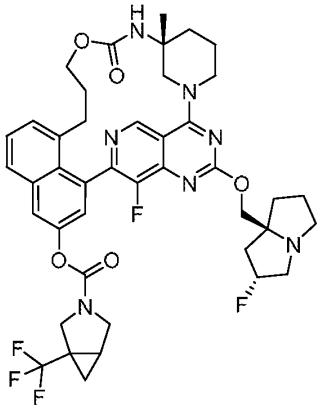
Cmpd ID	Structure	Name	LCMS	Procedure
298		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-methoxy-3-(trifluoromethyl)pyrrolidine-1-carboxylate	894.4	D
141		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-(dimethylcarbamoyl)pyrrolidine-1-carboxylate	813.4	D

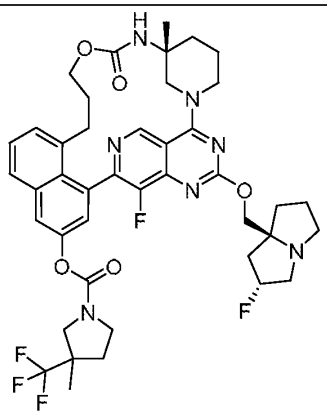
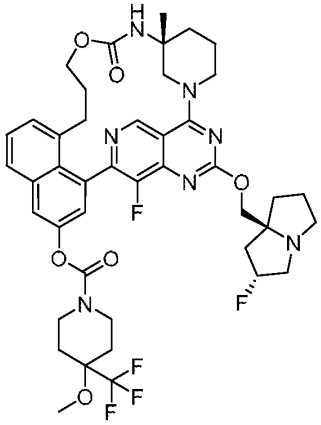
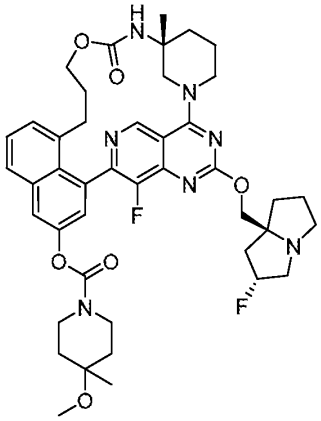
142		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-fluoropyrrolidine-1-carboxylate	760.4	D
143		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-fluoropiperidine-1-carboxylate	774.3	D
144		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-difluoropyrrolidine-1-carboxylate	778.2	D

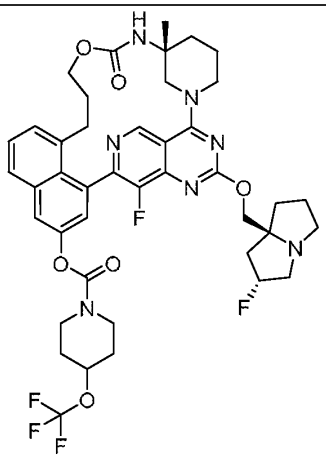
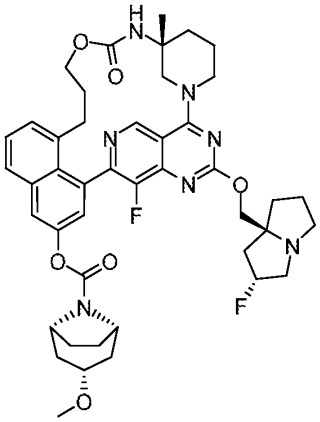
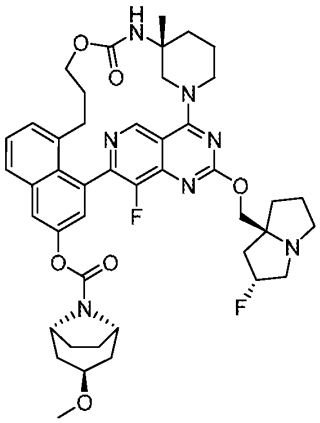
230		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-cyanopyrrolidine-1-carboxylate	767.4	D
231		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(methylsulfonyl)pyrrolidine-1-carboxylate	820.5	D
232		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 6,6-difluoro-3-azabicyclo[3.1.0]hexane-3-carboxylate	790.2	D

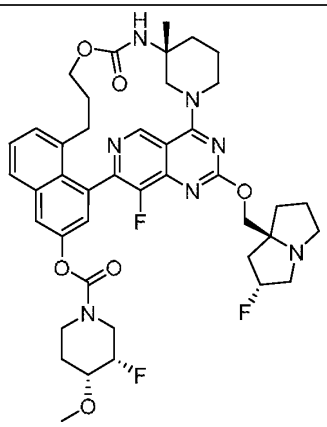
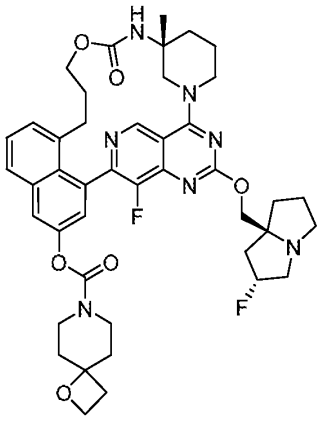
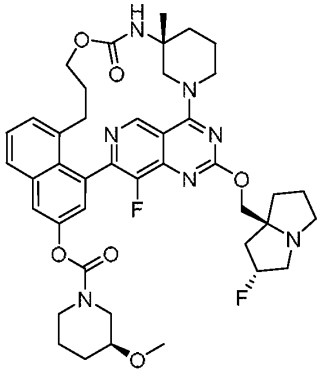
233		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (1R,5S)-3,3-difluoro-8-azabicyclo[3.2.1]octane-8-carboxylate	818.5	D
234		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-difluoro-2-methylpyrrolidine-1-carboxylate	792.6	D
237		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R,4R)-3-fluoro-4-methoxypyrrolidine-1-carboxylate	790.4	D

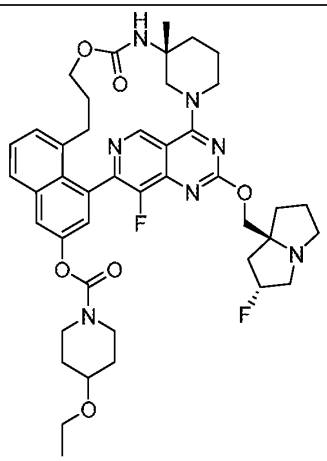
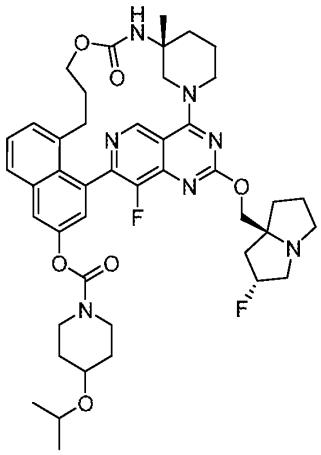
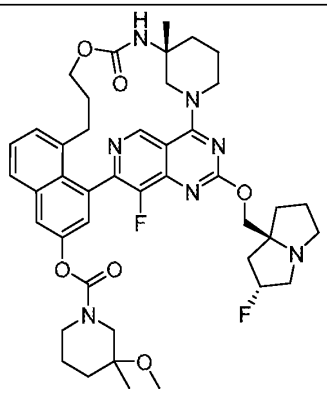
238		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S,4S)-3-fluoro-4-methoxypyrrolidine-1-carboxylate	790.4	D
239		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-(dimethylamino)-4-methylpiperidine-1-carboxylate	813.4	D
240		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(trifluoromethyl)azetidine-1-carboxylate	796.4	D

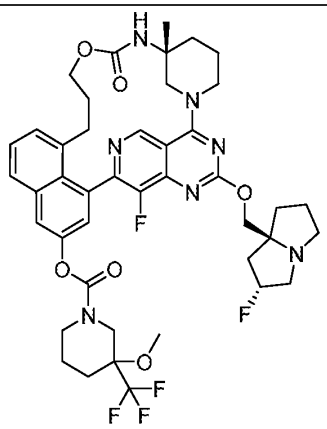
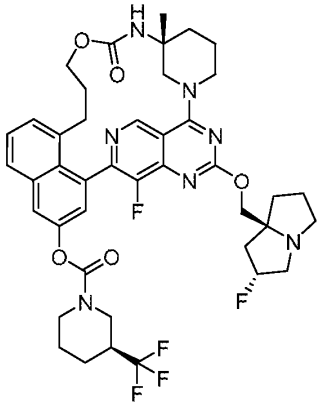
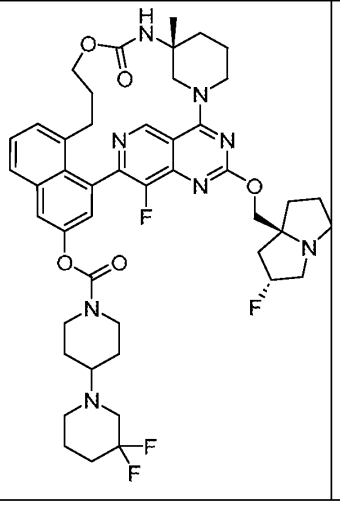
245		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-(trifluoromethyl)pyrrolidine-1-carboxylate	810.4	D
246		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-(trifluoromethyl)pyrrolidine-1-carboxylate	810.3	D
248		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 1-(trifluoromethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate	822.2	D

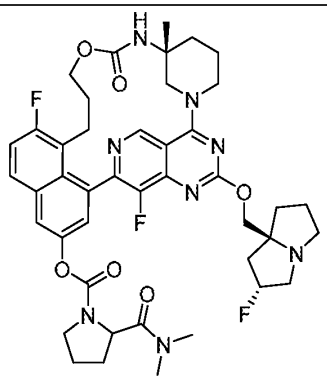
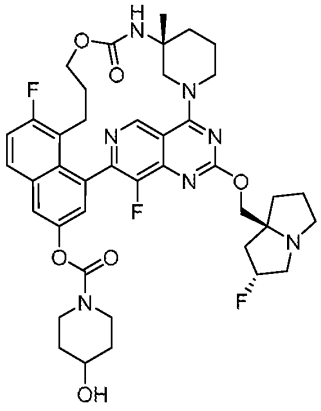
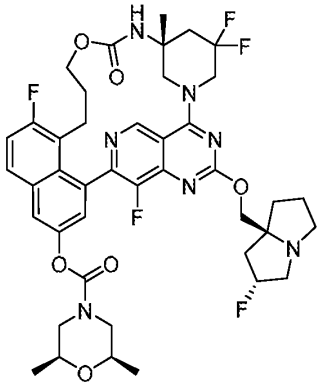
249		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-methyl-3-(trifluoromethyl)pyrrolidine-1-carboxylate	824.3	D
251		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxy-4-(trifluoromethyl)piperidine-1-carboxylate	854.4	D
252		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxy-4-methylpiperidine-1-carboxylate	800.3	D

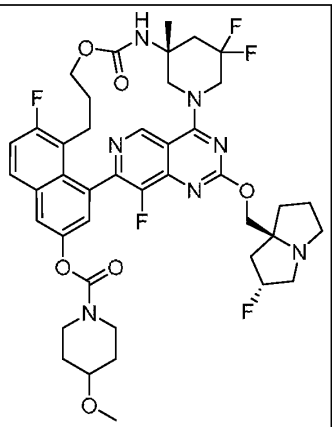
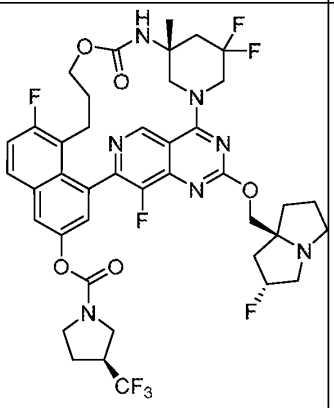
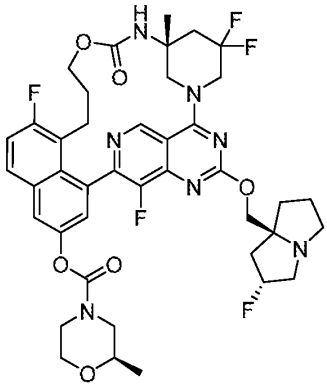
253		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-(trifluoromethoxy)piperidine-1-carboxylate	840.4	D
254		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (1R,3s,5S)-3-methoxy-8-azabicyclo[3.2.1]octane-8-carboxylate	812.4	D
265		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (1R,3r,5S)-3-methoxy-8-azabicyclo[3.2.1]octane-8-carboxylate	812.5	D

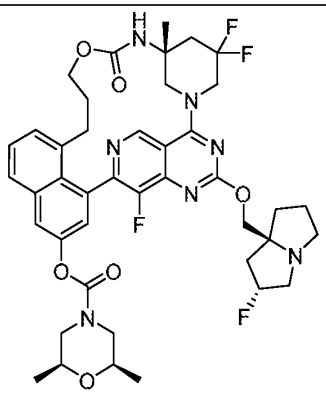
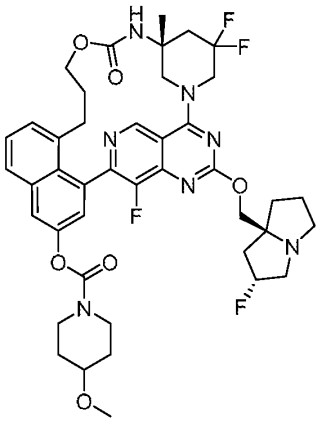
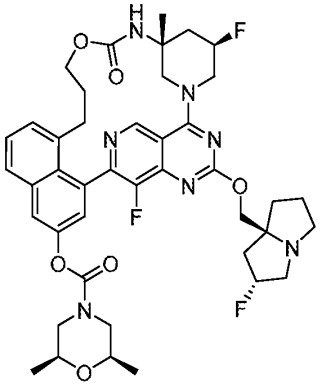
255		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S,4R)-3-fluoro-4-methoxypiperidine-1-carboxylate	804.4	D
256		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 1-oxa-7-azaspiro[3.5]nonane-7-carboxylate	798.5	D
257		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-methoxypiperidine-1-carboxylate	786.4	D

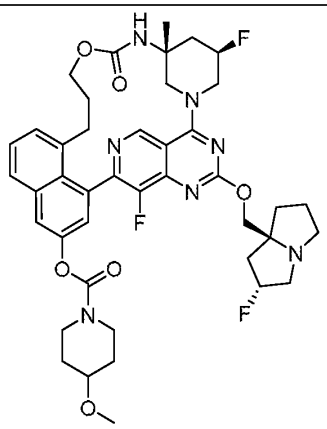
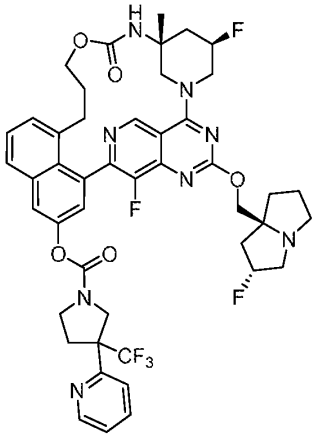
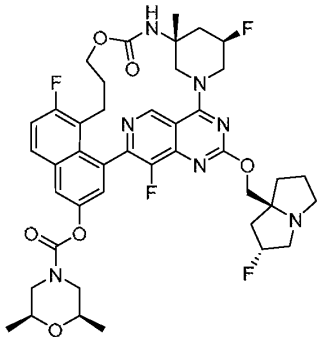
263		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-ethoxypiperidine-1-carboxylate	800.4	D
264		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-isopropoxypiperidine-1-carboxylate	814.4	D
266		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-methoxy-3-methylpiperidine-1-carboxylate	800.5	D

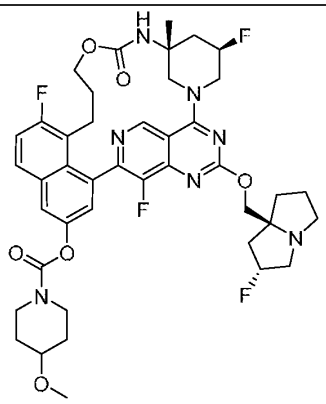
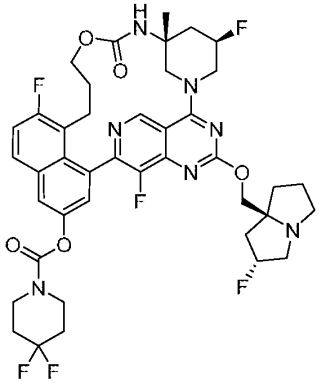
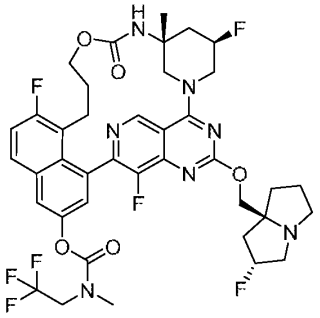
267		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-methoxy-3-(trifluoromethyl)piperidine-1-carboxylate	854.4	D
270		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-(trifluoromethyl)piperidine-1-carboxylate	824.4	D
139		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-difluoro-[1,4'-bipiperidine]-1'-carboxylate	875.4	D

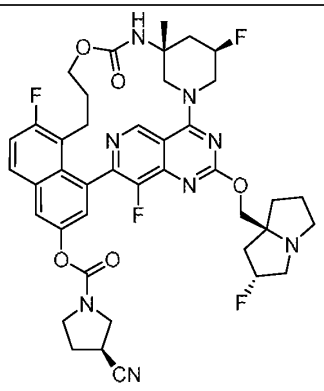
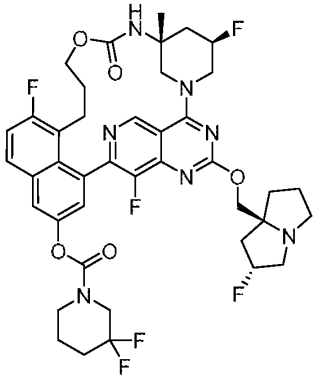
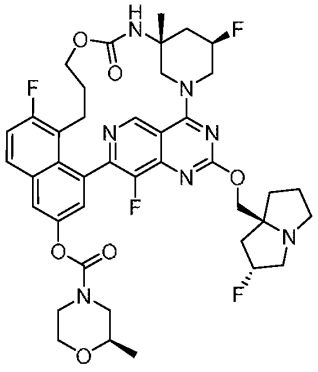
276		(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(dimethylcarbamoyl)pyrrolidine-1-carboxylate	831.3	D
279		(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-hydroxypiperidine-1-carboxylate	790.2	D
283		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S,6R)-2,6-dimethylmorpholine-4-carboxylate	840.5	D

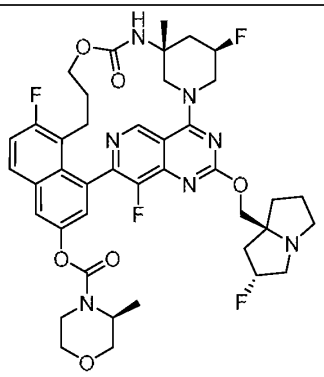
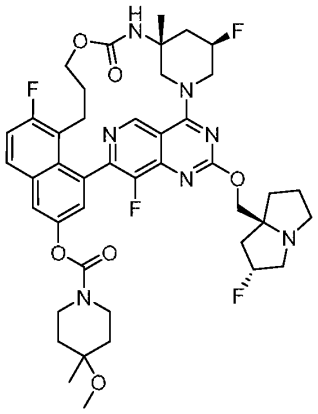
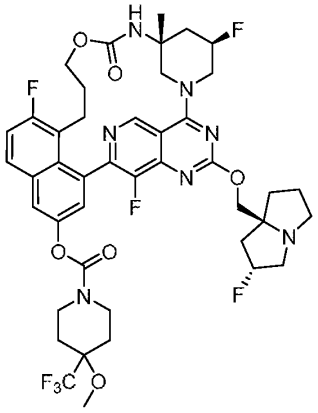
284		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxypiperidine-1-carboxylate	840.3	D
285		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-(trifluoromethyl)pyrrolidine-1-carboxylate	864.4	D
291		(1^3R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-methylmorpholine-4-carboxylate	826.5	D

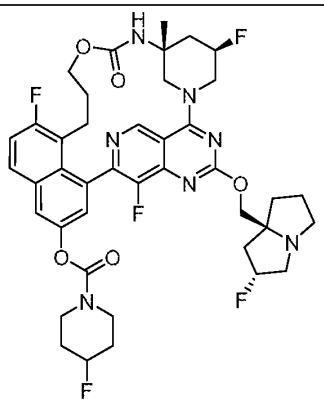
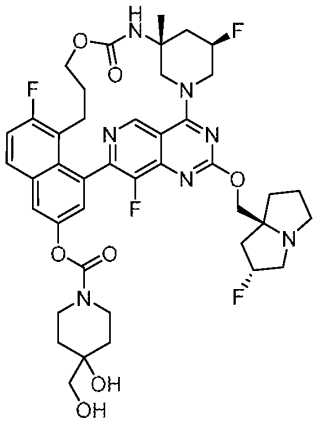
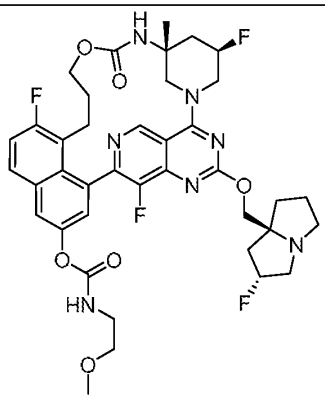
299		(1^3R)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S,6R)-2,6-dimethylmorpholine-4-carboxylate	822.3	D
300		(1^3R)-1^5,1^5,2^8-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxypiperidine-1-carboxylate	822.2	D
301		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S,6R)-2,6-dimethylmorpholine-4-carboxylate	804.3	D

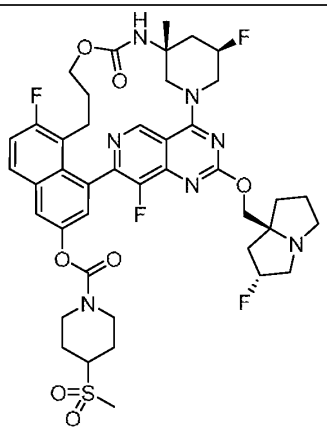
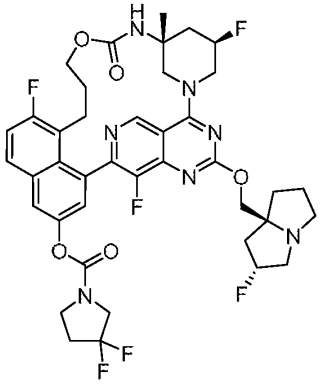
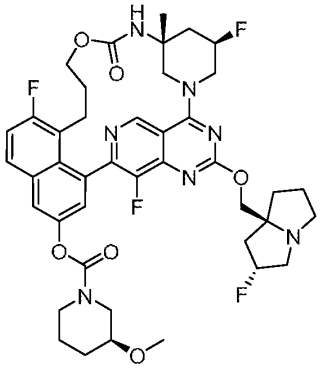
302		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxypiperidine-1-carboxylate	804.4	D
303		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(pyridin-2-yl)-3-(trifluoromethyl)pyrrolidine-1-carboxylate	905.5	D
307		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S,6R)-2,6-dimethylmorpholine-4-carboxylate	822.4	D

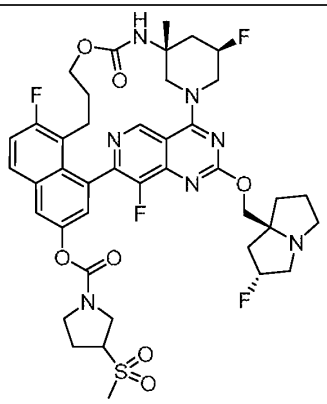
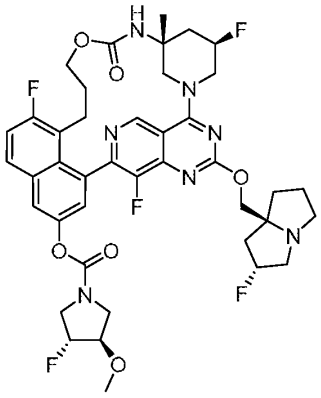
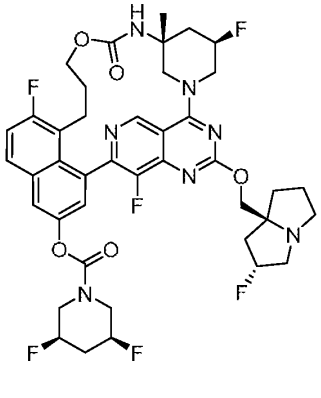
308		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxypiperidine-1-carboxylate	822.3	D
311		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,4-difluoropiperidine-1-carboxylate	828.1	D
315		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl methyl(2,2,2-trifluoroethyl)carbamate	820.3	D

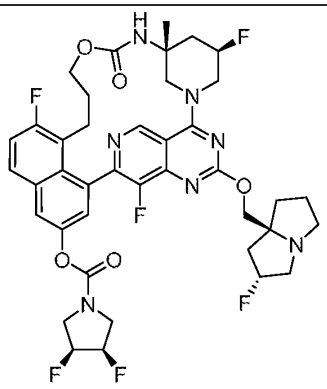
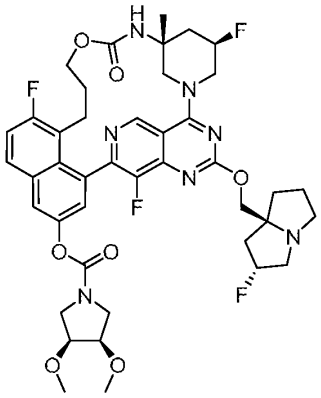
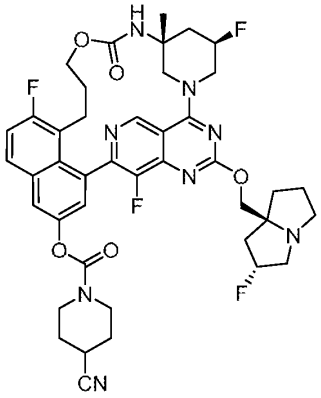
316		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-cyanopyrrolidine-1-carboxylate	803.2	D
317		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-difluoropiperidine-1-carboxylate	828.4	D
318		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-methylmorpholine-4-carboxylate	808.4	D

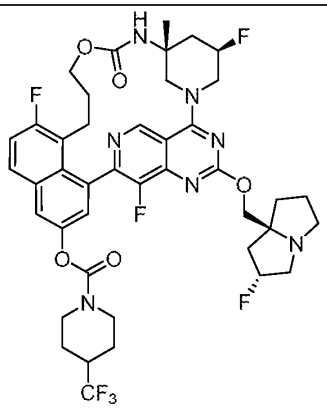
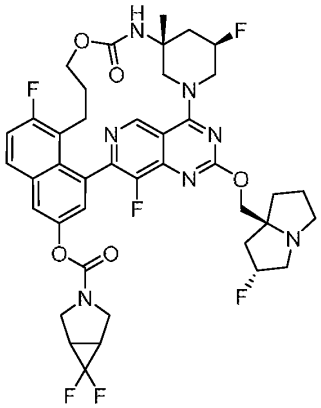
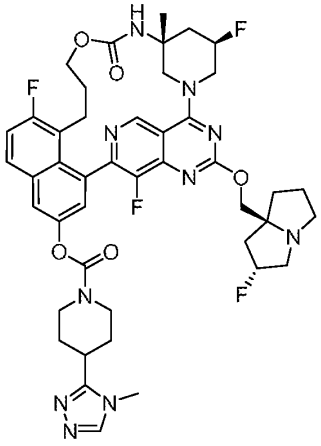
319		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-methylmorpholine-4-carboxylate	808.3	D
320		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxy-4-methylpiperidine-1-carboxylate	836.4	D
321		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxy-4-(trifluoromethyl)piperidine-1-carboxylate	890.4	D

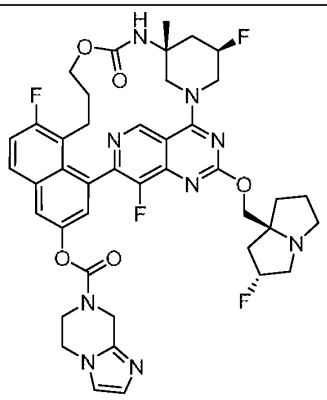
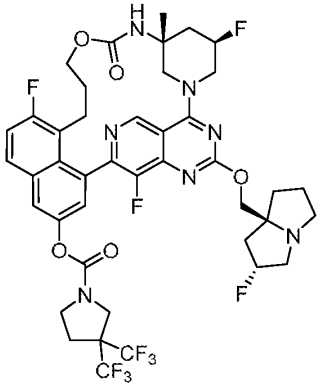
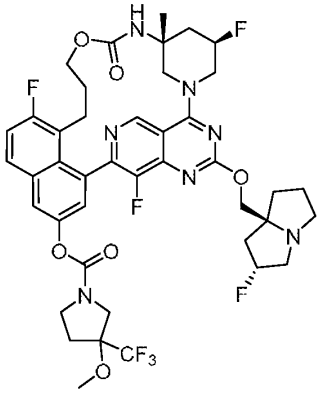
322		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-fluoropiperidine-1-carboxylate	810.3	D
323		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-hydroxy-4-(hydroxymethyl)piperidine-1-carboxylate	838.4	D
324		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2-methoxyethyl)carbamate	782.4	D

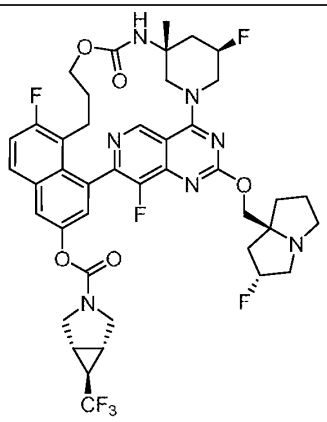
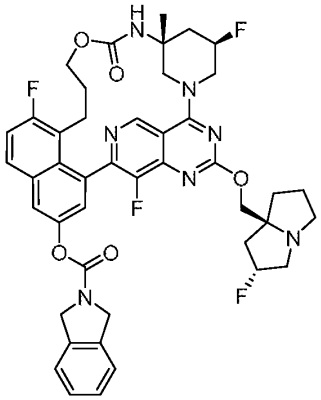
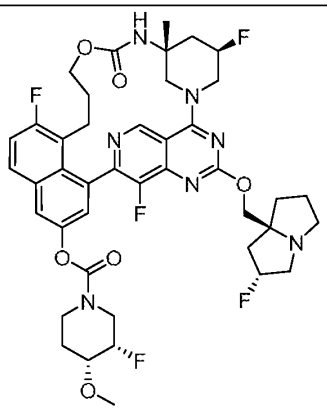
325		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-(methylsulfonyl)piperidine-1-carboxylate	870.2	D
327		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-difluoropyrrolidine-1-carboxylate	814.3	D
330		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-methoxypiperidine-1-carboxylate	822.1	D

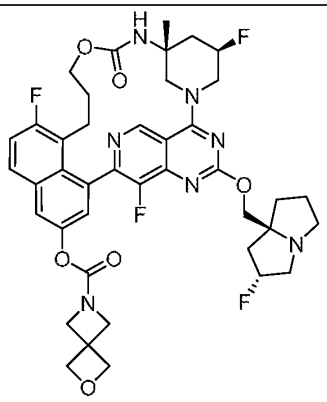
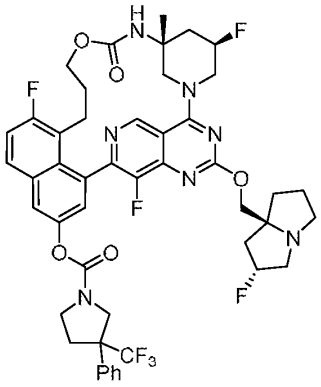
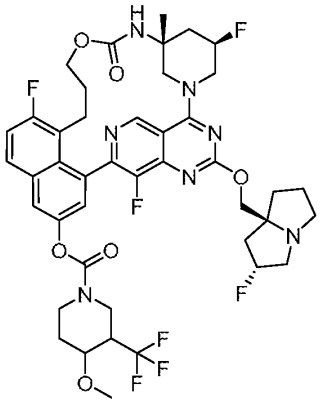
334		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(methylsulfonyl)pyrrolidine-1-carboxylate	856.4	D
335		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R,4R)-3-fluoro-4-methoxypyrrolidine-1-carboxylate	826.4	D
337		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R,5S)-3,5-difluoropiperidine-1-carboxylate	828.3	D

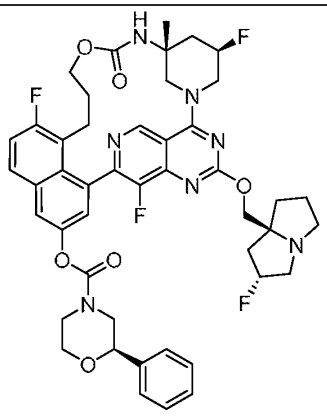
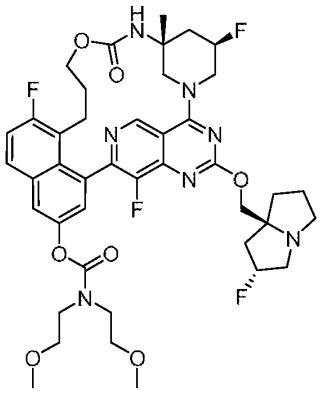
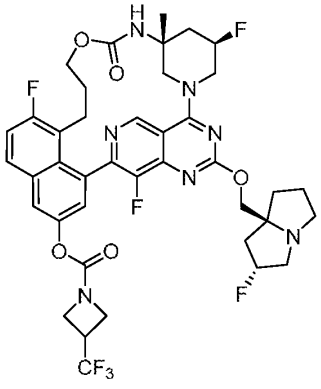
338		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S,4R)-3,4-difluoropyrrolidine-1-carboxylate	814.2	D
339		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S,4R)-3,4-dimethoxypyrrolidine-1-carboxylate	838.2	D
340		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-cyanopiperidine-1-carboxylate	817.3	D

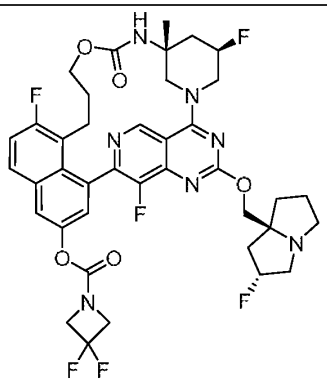
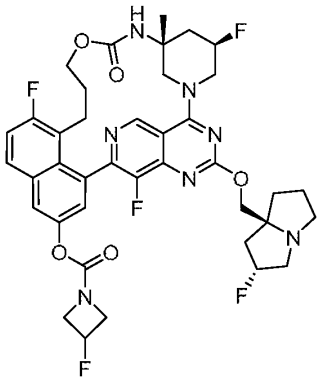
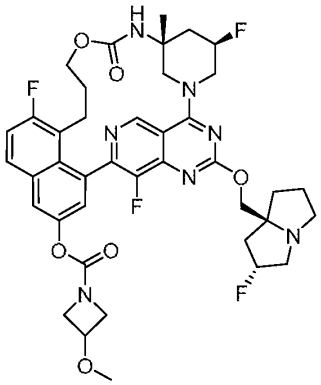
341		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-(trifluoromethyl)piperidine-1-carboxylate	860.3	D
342		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 6,6-difluoro-3-azabicyclo[3.1.0]hexane-3-carboxylate	826.3	D
343		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-(4-methyl-4H-1,2,4-triazol-3-yl)piperidine-1-carboxylate	873.4	D

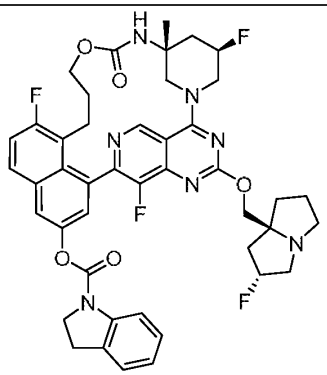
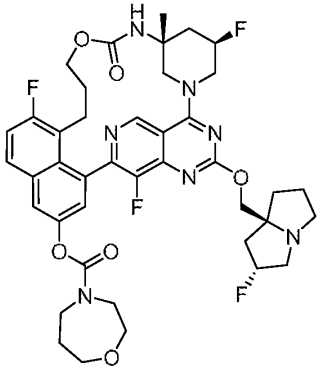
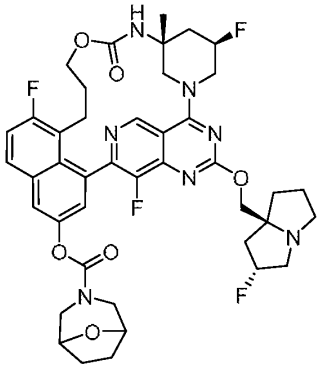
347		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate	830.4	D
349		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-bis(trifluoromethyl)pyrrolidine-1-carboxylate	914.4	D
350		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-methoxy-3-(trifluoromethyl)pyrrolidine-1-carboxylate	876.2	D

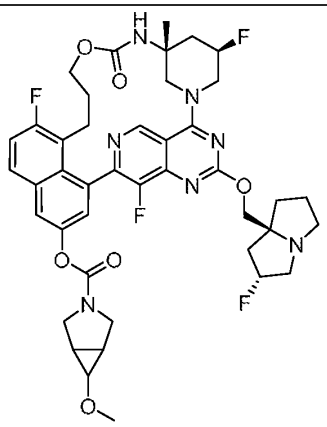
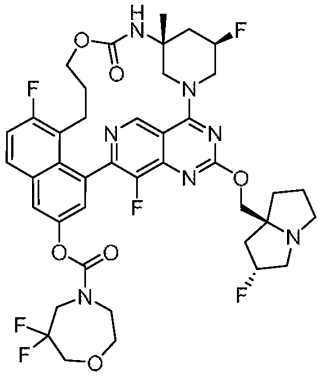
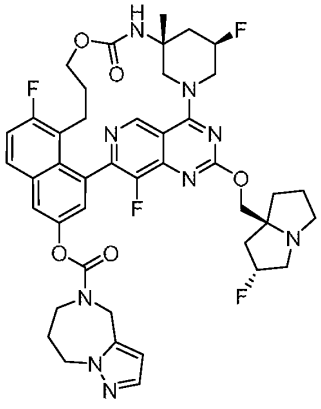
351		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (1R,5S,6r)-6-(trifluoromethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate	858.2	D
352		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl isoindoline-2-carboxylate	826.4	D
353		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S,4R)-3-fluoro-4-methoxypiperidine-1-carboxylate	840.4	D

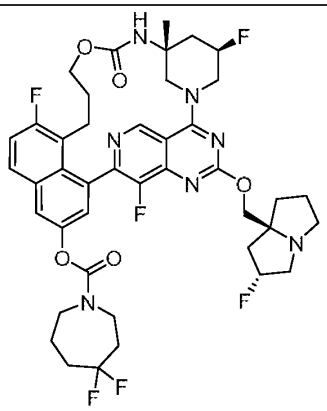
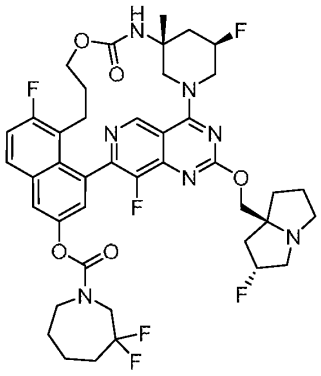
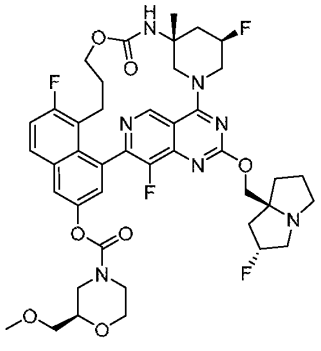
356		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-oxa-6-azaspiro[3.3]heptane-6-carboxylate	806.2	D
360		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-phenyl-3-(trifluoromethyl)pyrrolidine-1-carboxylate	922.3	D
364		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxy-3-(trifluoromethyl)piperidine-1-carboxylate	890.3	D

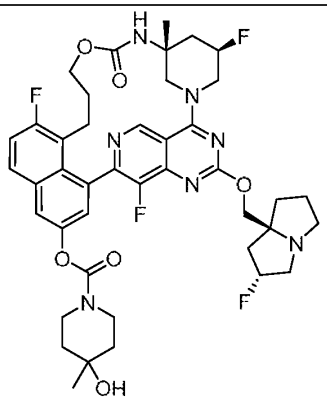
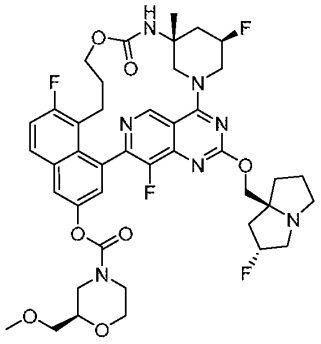
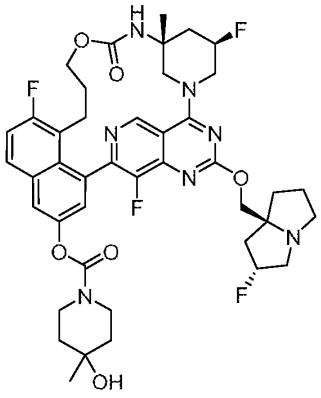
367		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-phenylmorpholine-4-carboxylate	870.4	D
369		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl bis(2-methoxyethyl)carbamate	840.5	D
370		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(trifluoromethyl)azetidine-1-carboxylate	832.4	D

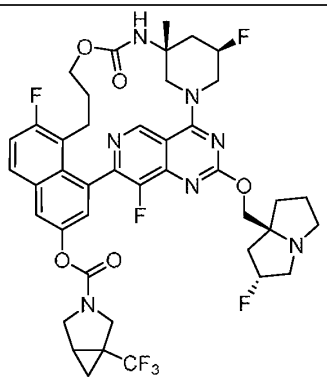
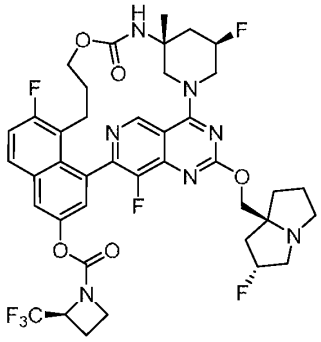
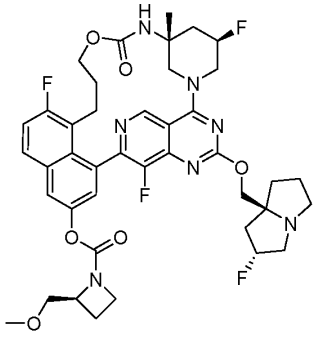
371		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-difluoroazetidine-1-carboxylate	800.3	D
372		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-fluoroazetidine-1-carboxylate	782.4	D
373		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-methoxyazetidine-1-carboxylate	794.5	D

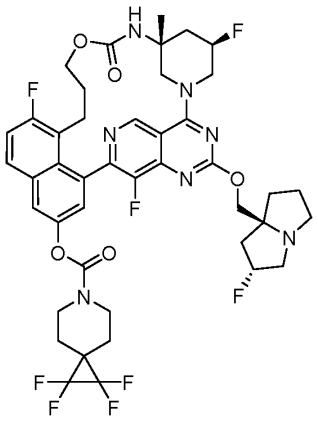
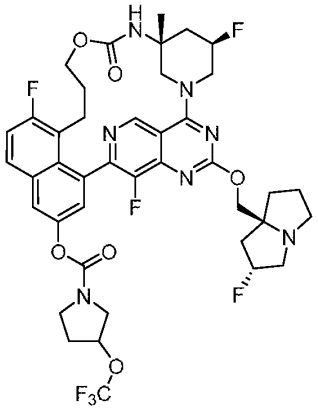
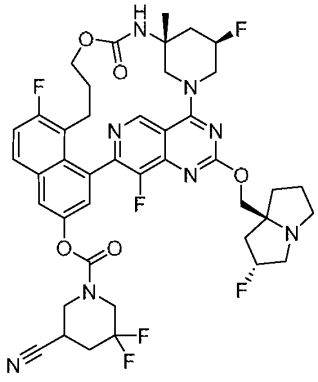
376		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl indoline-1-carboxylate	826.3	D
377		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 1,4-oxazepane-4-carboxylate	808.4	D
378		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate	820.3	D

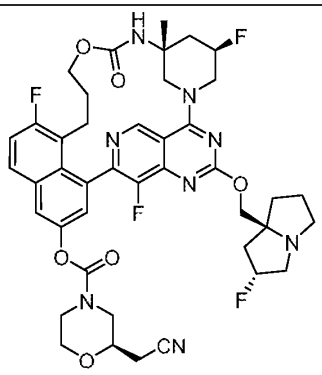
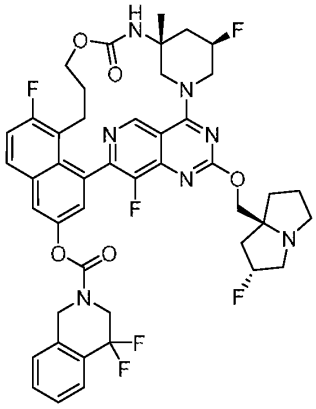
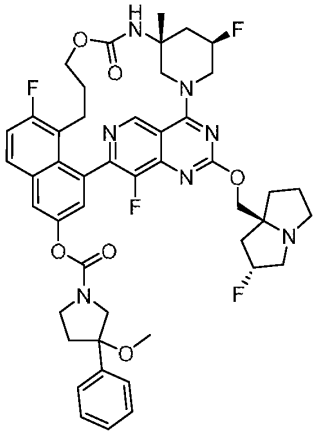
379		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 6-methoxy-3-azabicyclo[3.1.0]hexane-3-carboxylate	820.6	D
384		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 6,6-difluoro-1,4-oxazepane-4-carboxylate	844.3	D
385		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 7,8-dihydro-4H-pyrazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate	844.3	D

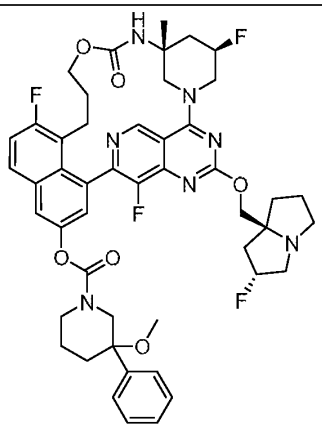
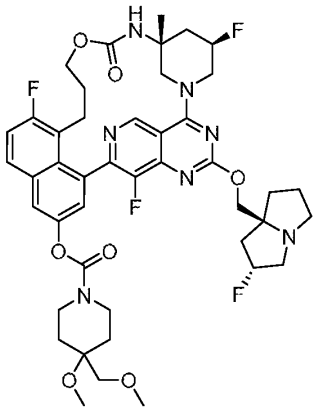
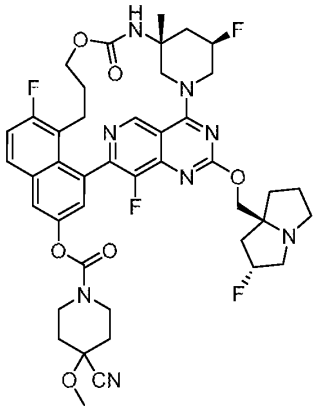
387		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,4-difluoroazepane-1-carboxylate	842.5	D
388		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-difluoroazepane-1-carboxylate	842.5	D
390		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-(methoxymethyl)morpholine-4-carboxylate	838.3	D

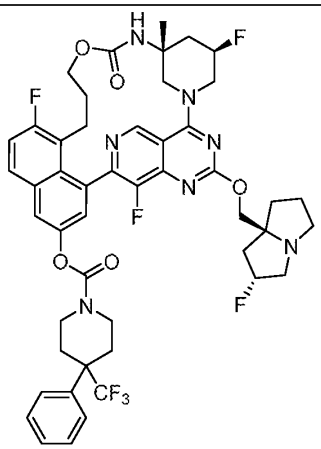
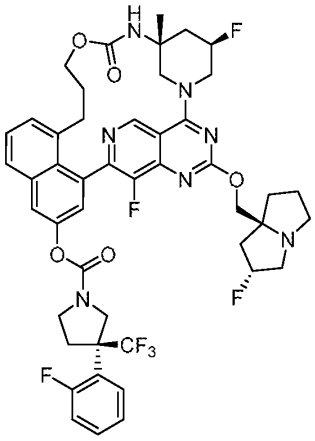
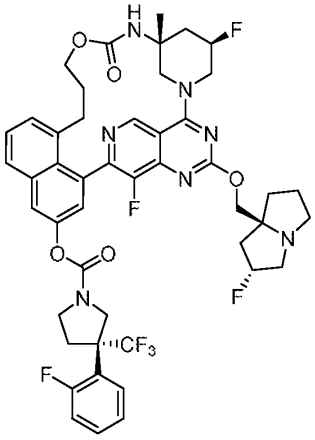
391		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-hydroxy-4-methylpiperidine-1-carboxylate	822.5	D
390		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-(methoxymethyl)morpholine-4-carboxylate	838.3	D
391		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-hydroxy-4-methylpiperidine-1-carboxylate	822.5	D

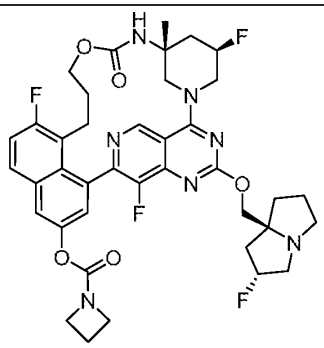
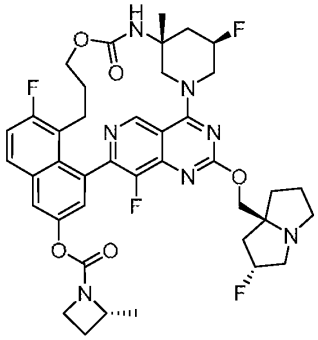
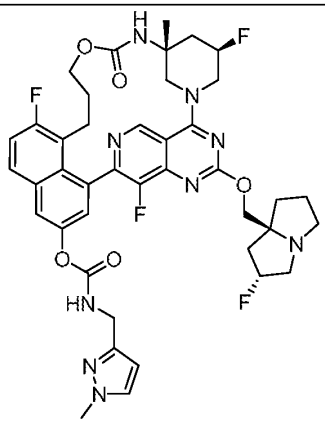
393		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 1-(trifluoromethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate	858.5	D
398		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S)-2-(trifluoromethyl)azetidine-1-carboxylate	832.5	D
399		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S)-2-(methoxymethyl)azetidine-1-carboxylate	808.5	D

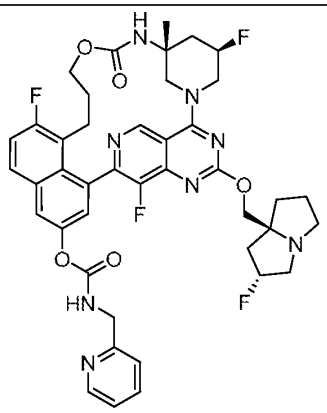
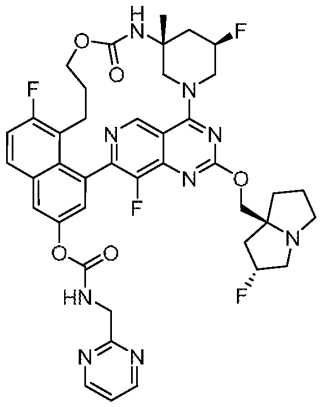
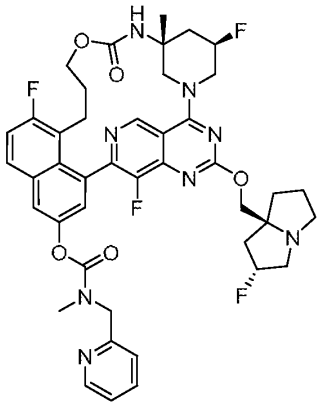
403		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 1,1,2,2-tetrafluoro-6-azaspiro[2.5]octane-6-carboxylate	890.5	D
406		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(trifluoromethoxy)pyrrolidine-1-carboxylate	862.5	D
414		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 5-cyano-3,3-difluoropiperidine-1-carboxylate	853.4	D

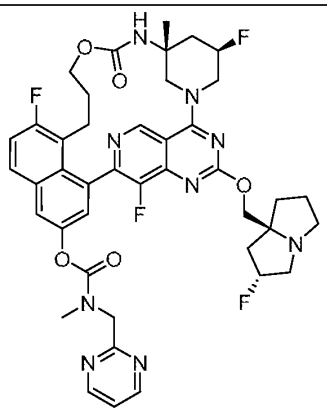
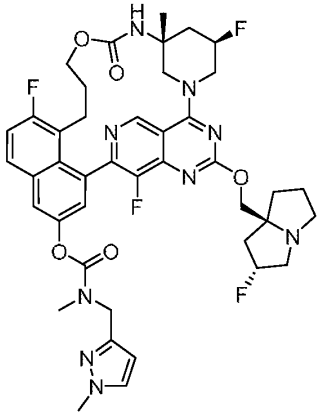
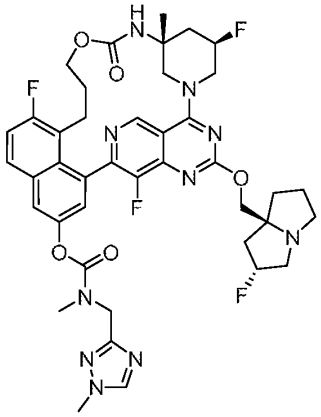
416		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-(cyanomethyl)morpholine-4-carboxylate	833.4	D
423		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,4-difluoro-3,4-dihydroisoquinoline-2(1H)-carboxylate	876.3	D
426		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-methoxy-3-phenylpyrrolidine-1-carboxylate	884.5	D

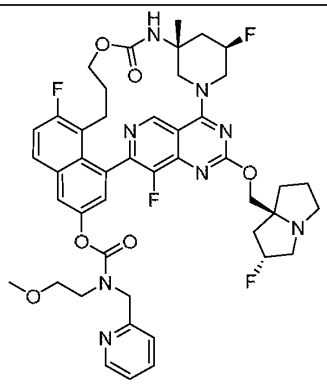
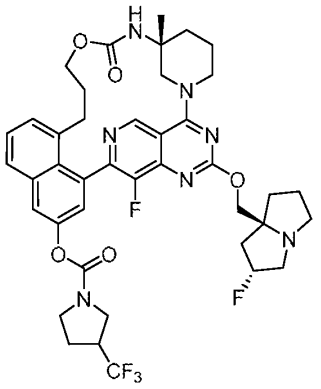
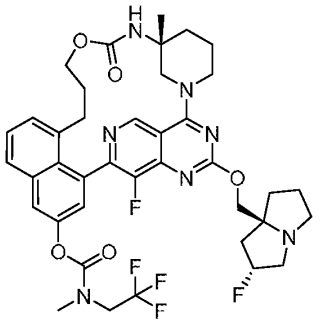
432		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-methoxy-3-phenylpiperidine-1-carboxylate	898.5	D
434		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxy-4-(methoxymethyl)piperidine-1-carboxylate	866.3	D
436		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-cyano-4-methoxypiperidine-1-carboxylate	847.4	D

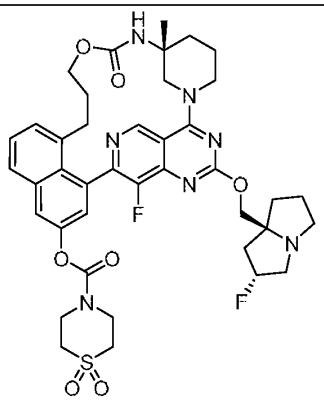
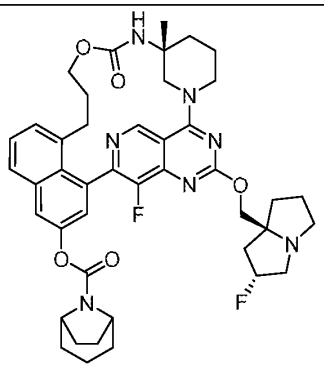
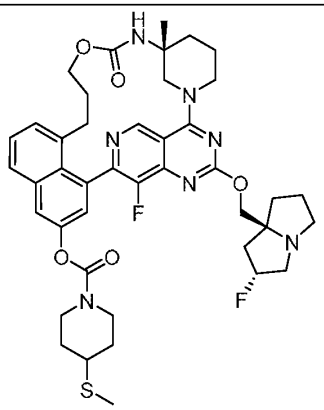
437		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-phenyl-4-(trifluoromethyl)piperidine-1-carboxylate	936.4	D
468		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-(2-fluorophenyl)-3-(trifluoromethyl)pyrrolidine-1-carboxylate	922.5	D
469		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-(2-fluorophenyl)-3-(trifluoromethyl)pyrrolidine-1-carboxylate	922.6	D

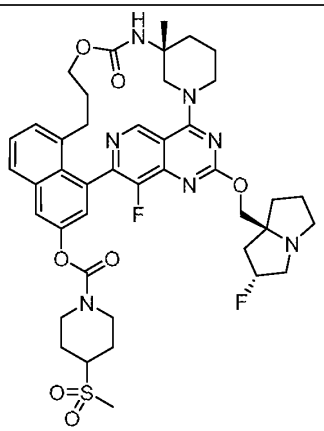
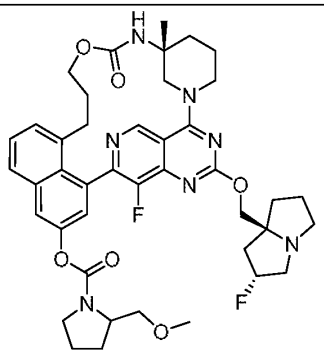
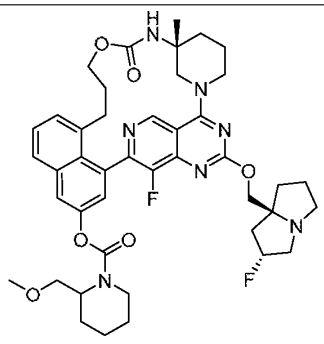
472		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl azetidine-1-carboxylate	764.4	D
474		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-methylazetidine-1-carboxylate	778.3	D
523		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl ((1-methyl-1H-pyrazol-3-yl)methyl)carbamate	818.5	D

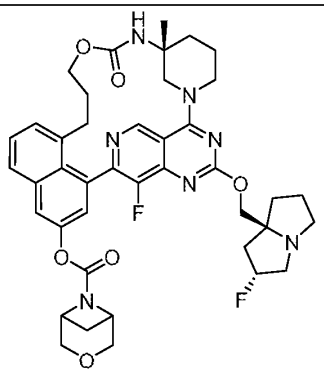
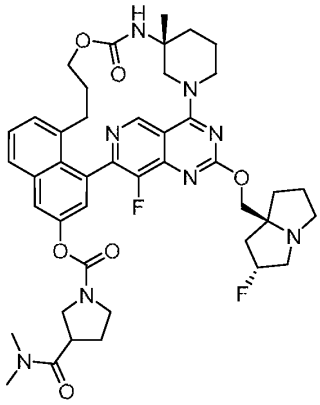
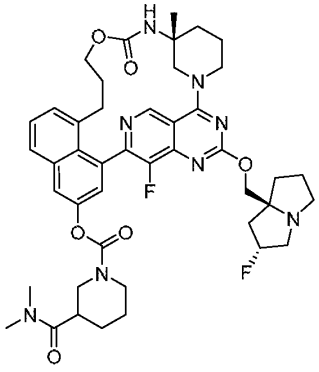
538		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (pyridin-2-ylmethyl)carbamate	815.3	D
539		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (pyrimidin-2-ylmethyl)carbamate	816.4	D
540		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl methyl(pyridin-2-ylmethyl)carbamate	829.4	D

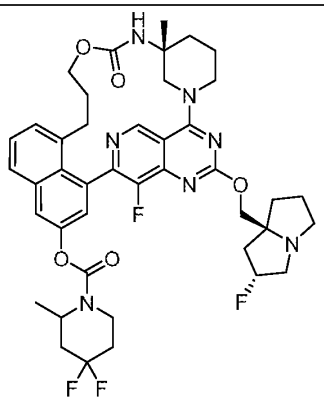
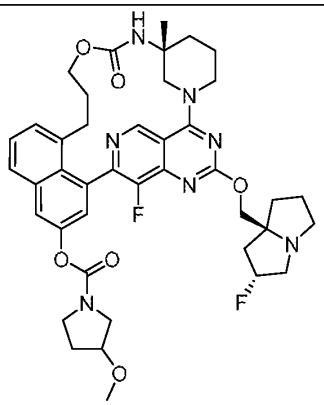
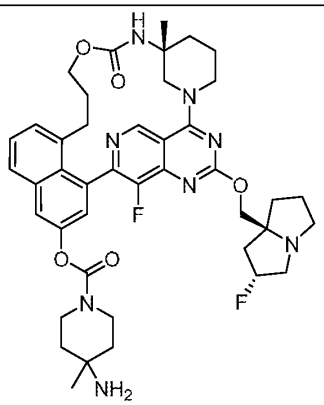
541		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl methyl(pyrimidin-2-ylmethyl)carbamate	830.5	D
542		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl methyl((1-methyl-1H-pyrazol-3-yl)methyl)carbamate	832.3	D
543		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl methyl((1-methyl-1H-pyrazol-3-yl)methyl)carbamate	833.3	D

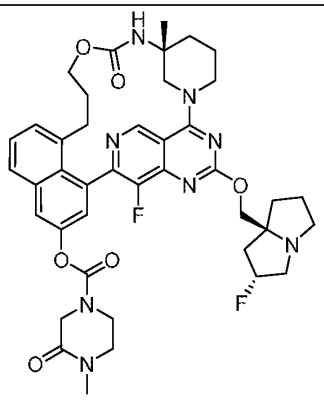
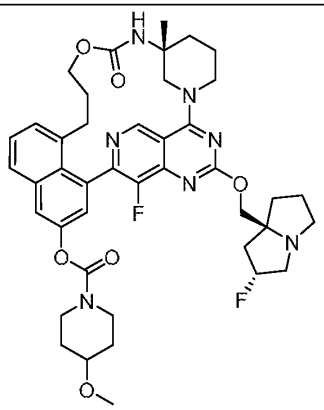
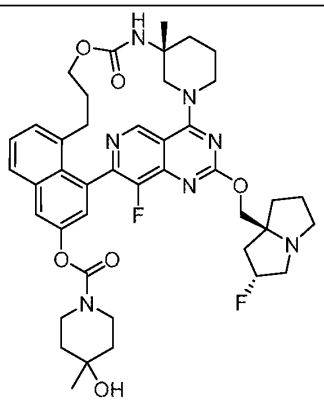
554		(1^3R,1^5R)-1^5,2^8-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2-methoxyethyl)(pyridin-2-ylmethyl)carbamate	873.4	D
145		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(trifluoromethyl)pyrrolidine-1-carboxylate	810.4	D
146		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl methyl(2,2,2-trifluoroethyl)carbamate	784.5	D

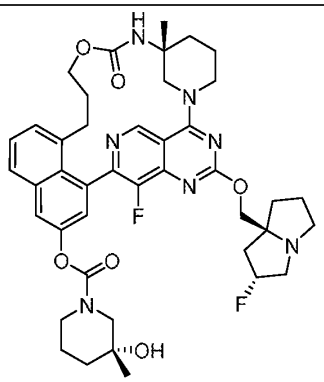
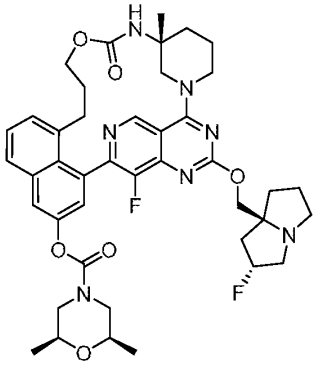
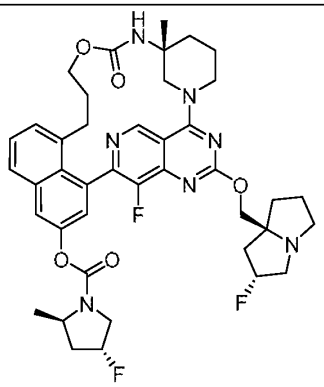
147		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl thiomorpholine-4-carboxylate 1,1-dioxide	806.3	D
148		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (1R,5S)-8-azabicyclo[3.2.1]octane-8-carboxylate	782.5	D
149		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-(methylthio)piperidine-1-carboxylate	802.2	D

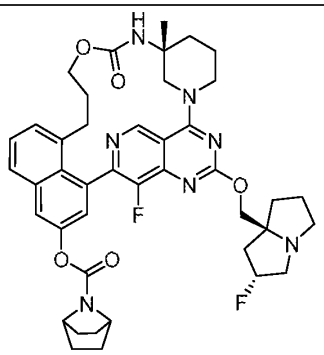
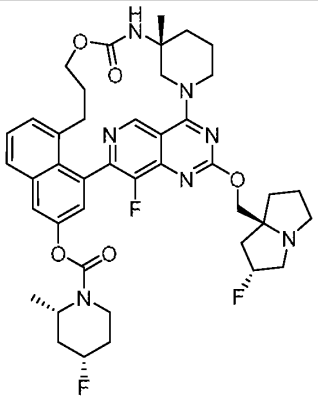
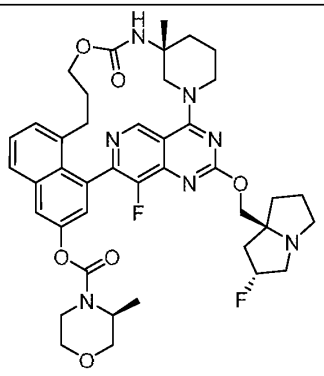
150		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-(methylsulfonyl)piperidine-1-carboxylate	834.5	D
151		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(methoxymethyl)pyrrolidine-1-carboxylate	786.4	D
155		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(methoxymethyl)piperidine-1-carboxylate	800.5	D

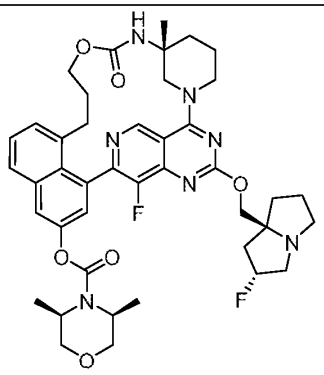
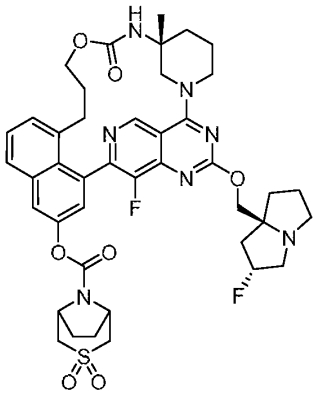
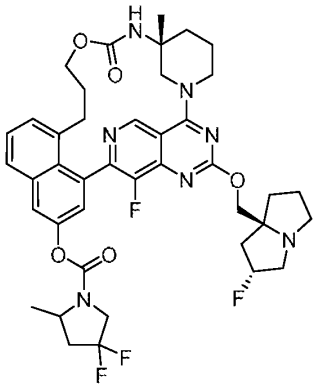
159		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (1R,5S)-3-oxa-6-azabicyclo[3.1.1]heptane-6-carboxylate	770.5	D
160		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(dimethylcarbamoyl)pyrrolidine-1-carboxylate	813.5	D
161		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(dimethylcarbamoyl)piperidine-1-carboxylate	827.4	D

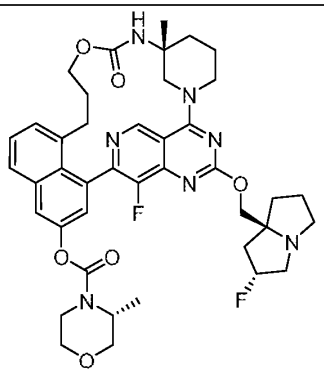
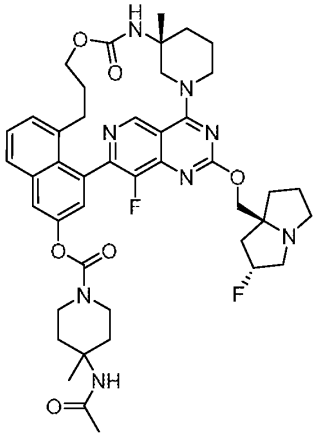
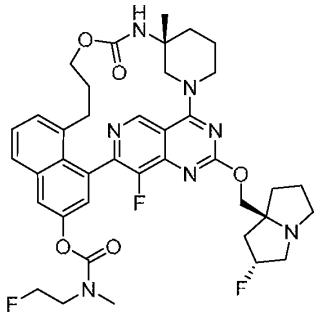
162		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,4-difluoro-2-methylpiperidine-1-carboxylate	806.3	D
164		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-methoxypyrrolidine-1-carboxylate	772.5	D
167		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-amino-4-methylpiperidine-1-carboxylate	785.4	D

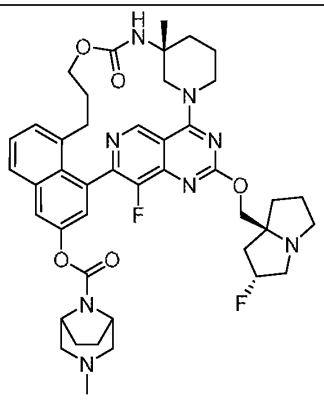
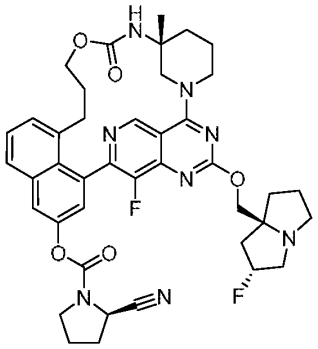
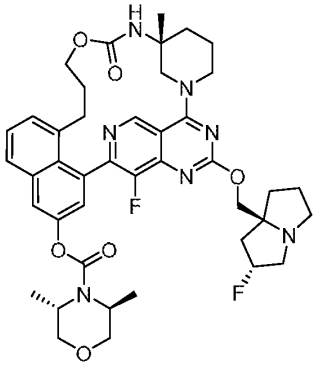
168		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methyl-3-oxopiperazine-1-carboxylate	785.4	D
170		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxypiperidine-1-carboxylate	786.3	D
171		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-hydroxy-4-methylpiperidine-1-carboxylate	786.3	D

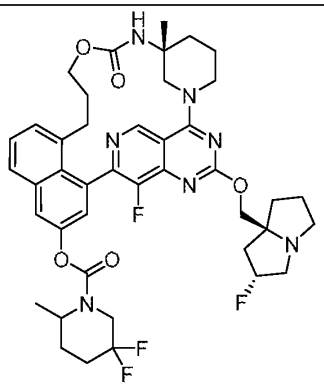
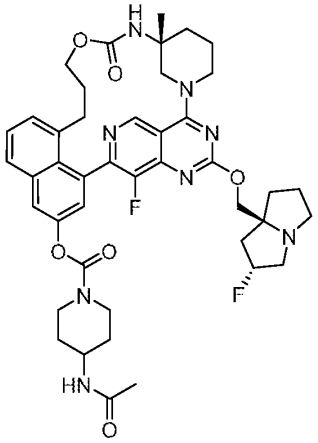
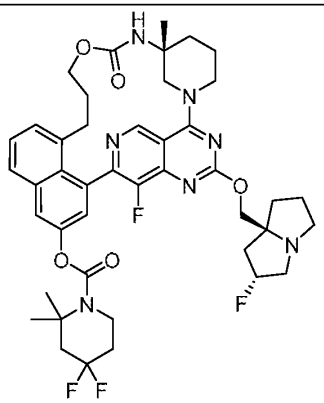
172		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-hydroxy-3-methylpiperidine-1-carboxylate	786.4	D
173		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S,6R)-2,6-dimethylmorpholine-4-carboxylate	786.3	D
176		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R,4R)-4-fluoro-2-methylpyrrolidine-1-carboxylate	774.4	D

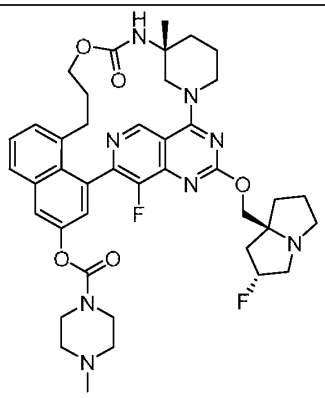
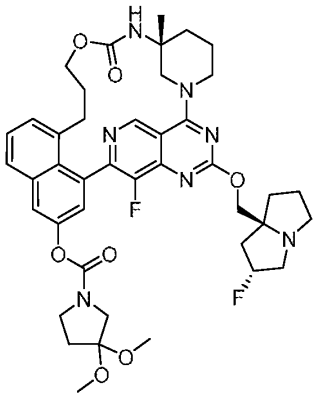
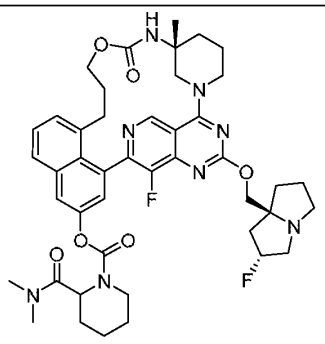
174		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 7-azabicyclo[2.2.1]heptane-7-carboxylate	768.5	D
180		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S,4S)-4-fluoro-2-methylpiperidine-1-carboxylate	788.4	D
212		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S)-3-methylmorpholine-4-carboxylate	772.6	D

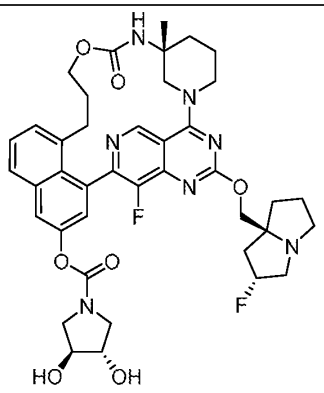
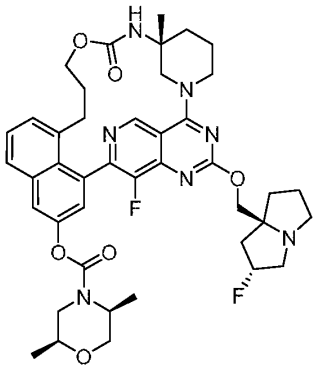
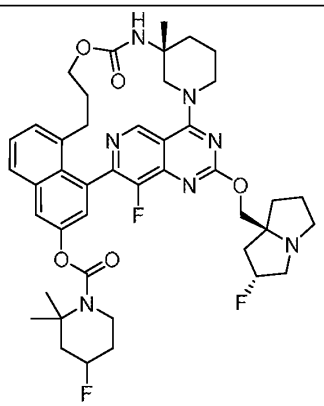
227		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R,5S)-3,5-dimethylmorpholine-4-carboxylate	786.5	D
221		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (1R,5S)-3-thia-8-azabicyclo[3.2.1]octane-8-carboxylate 3,3-dioxide	832.3	D
193		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,4-difluoro-2-methylpyrrolidine-1-carboxylate	792.4	D

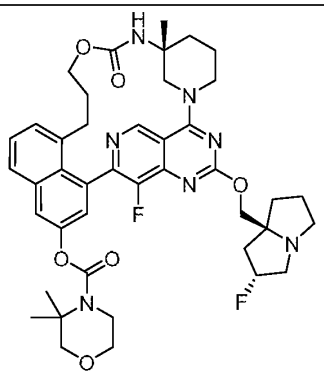
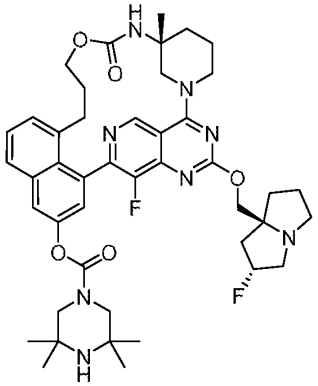
226		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-methylmorpholine-4-carboxylate	772.5	D
187		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-acetamido-4-methylpiperidine-1-carboxylate	827.6	D
213		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2-fluoroethyl)(methyl)carbamate	748.6	D

210		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (1R,5S)-3-methyl-3,8-diazabicyclo[3.2.1]octane-8-carboxylate	797.3	D
229		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-cyanopyrrolidine-1-carboxylate	767.3	D
211		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S,5S)-3,5-dimethylmorpholine-4-carboxylate	786.2	D

197		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 5,5-difluoro-2-methylpiperidine-1-carboxylate	806.4	D
188		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-acetamidopiperidine-1-carboxylate	813.3	D
194		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,4-difluoro-2,2-dimethylpiperidine-1-carboxylate	820.3	D

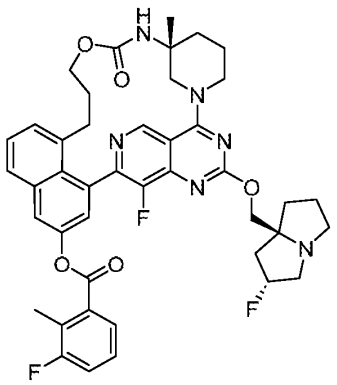
209		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methylpiperazine-1-carboxylate	771.4	D
225		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-dimethoxypyrrolidine-1-carboxylate	802.2	D
195		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(dimethylcarbamoyl)piperidine-1-carboxylate	827.4	D

224		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3S,4S)-3,4-dihydroxypyrrolidine-1-carboxylate	774.4	D
222		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S,5S)-2,5-dimethylmorpholine-4-carboxylate	786.3	D
196		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-fluoro-2,2-dimethylpiperidine-1-carboxylate	802.3	D

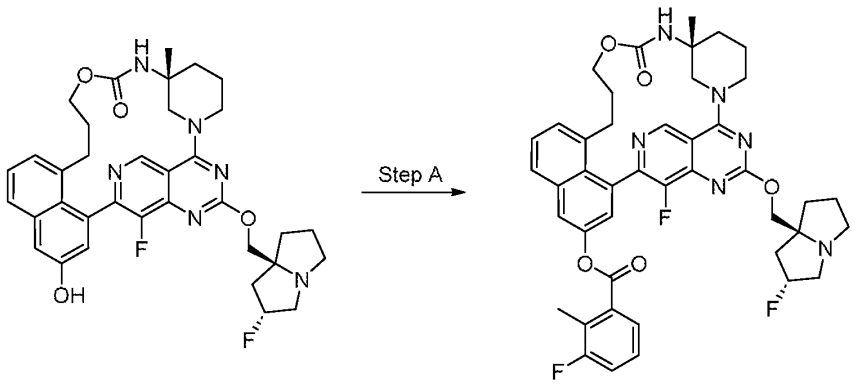
175		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-dimethylmorpholine-4-carboxylate	786.3	D
207		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3,5,5-tetramethylpiperazine-1-carboxylate	813.8	D

Example procedure E. EDCI coupling

Compound 92

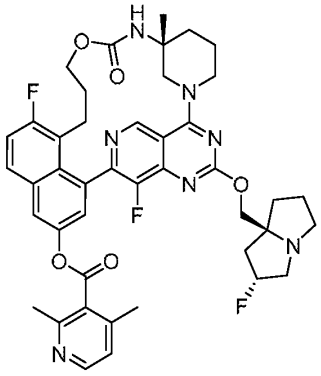


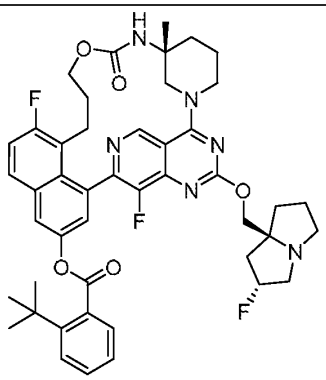
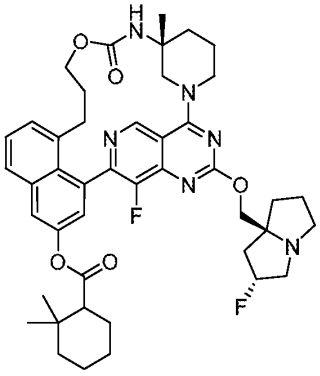
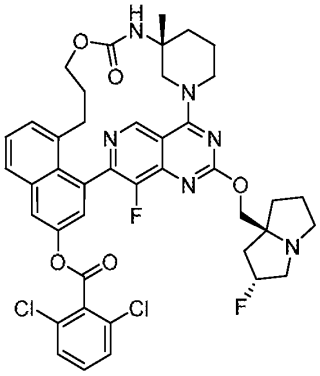
(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-fluoro-2-methylbenzoate

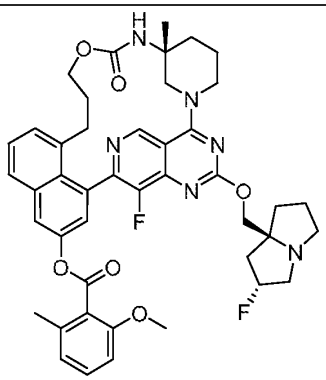
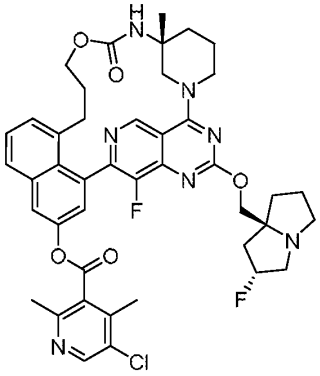
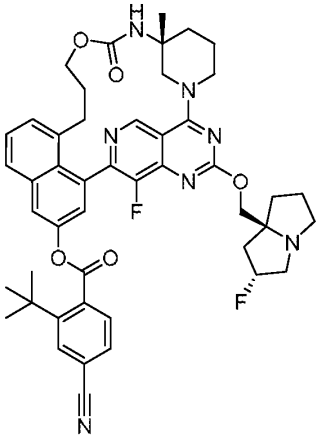


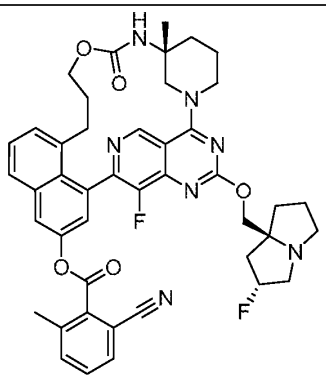
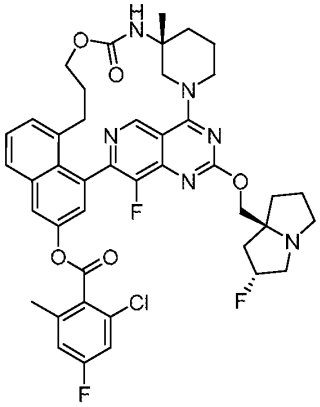
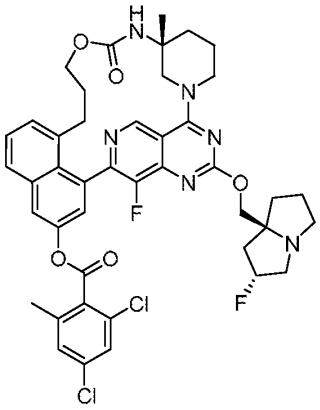
Step A. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-fluoro-2-methylbenzoate. To a solution of Compound 2 (0.050 g, 0.076 mmol) and 3-fluoro-2-methylbenzoic acid (0.018 g, 0.115 mmol) in DCM (1 mL) was added EDCI (0.022 g, 0.115 mmol) and DMAP (0.0093 g, 0.076 mmol). The reaction was stirred at rt for 1 h and then it was concentrated under reduced pressure. The crude product was purified by preparative HPLC (60 – 90% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-fluoro-2-methylbenzoate (0.032 g, 52% yield) as a yellow solid. LCMS (MM-ES+APCI, Pos): m/z 781.4 (M+H).

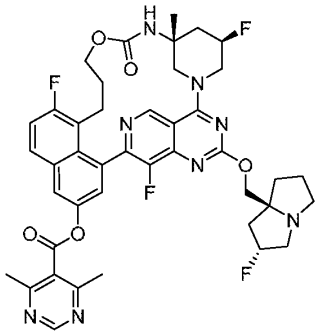
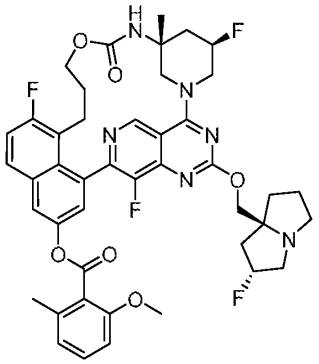
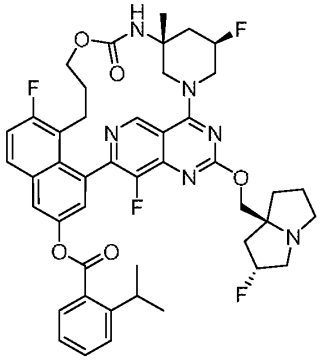
Table 12. Compounds synthesized by following the example procedure E

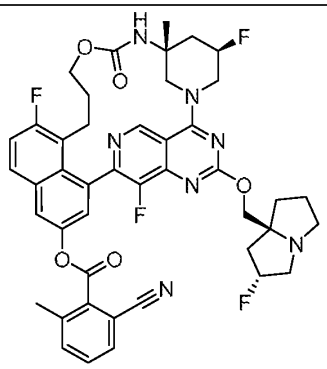
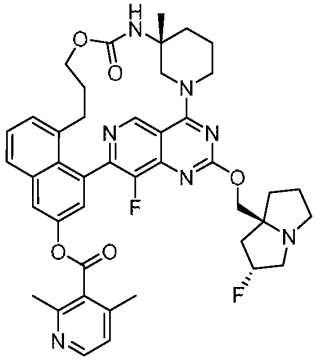
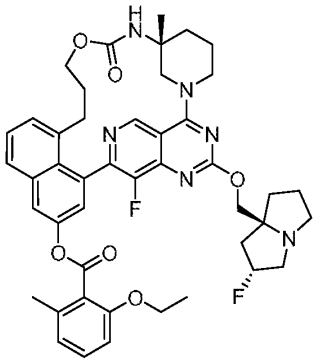
Cmpd ID	Structure	Name	LCMS	Procedure
275		(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,4-dimethylnicotinate	796.3	E

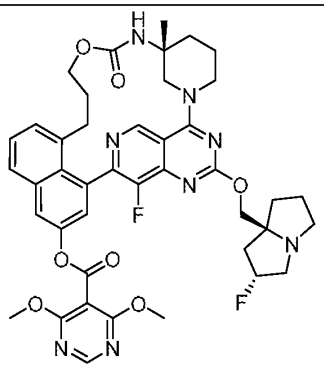
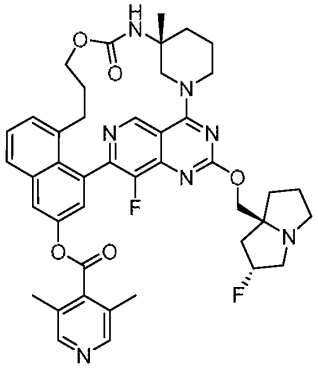
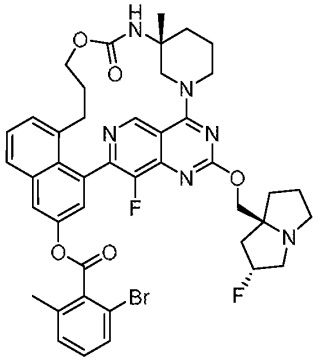
277		(1^3R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(tert-butyl)benzoate	823.3	E
244		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,2-dimethylcyclohexane-1-carboxylate	783.5	E
250		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,6-dichlorobenzoate	817.5	E

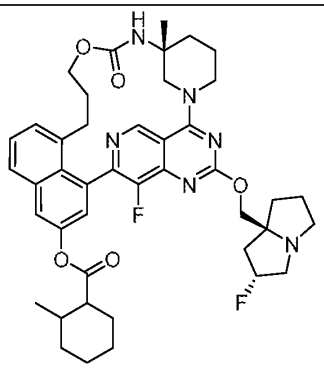
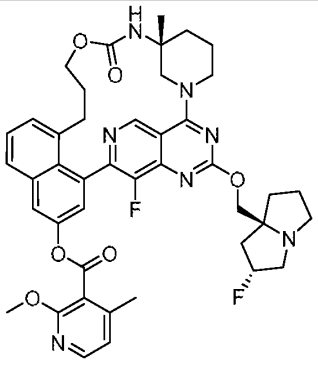
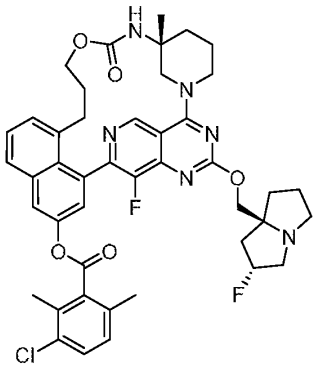
258		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-methoxy-6-methylbenzoate	793.5	E
260		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 5-chloro-2,4-dimethylnicotinate	812.3	E
262		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(tert-butyl)-4-cyanobenzoate	830.3	E

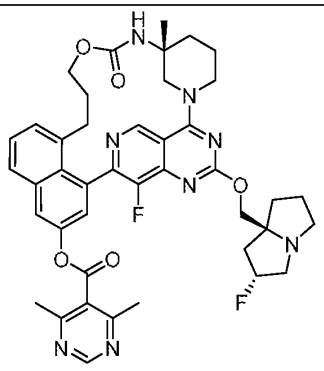
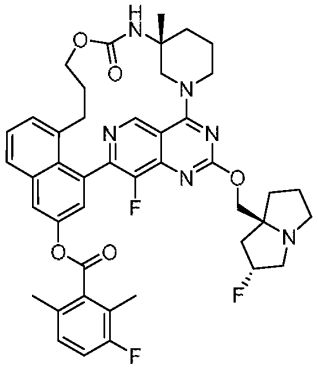
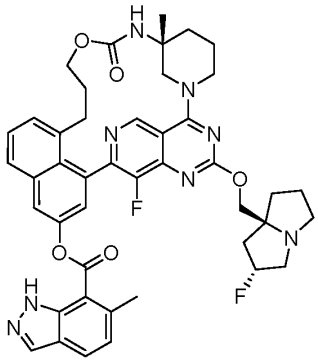
268		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-cyano-6-methylbenzoate	788.4	E
269		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-chloro-4-fluoro-6-methylbenzoate	815.2	E
272		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,4-dichloro-6-methylbenzoate	831.3	E

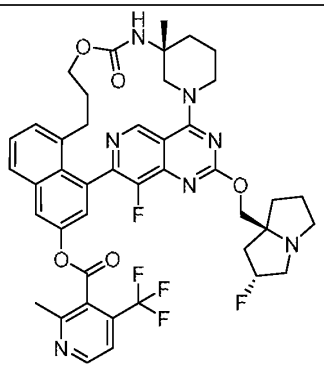
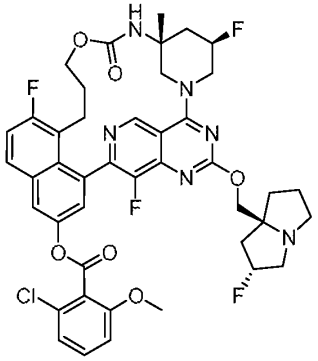
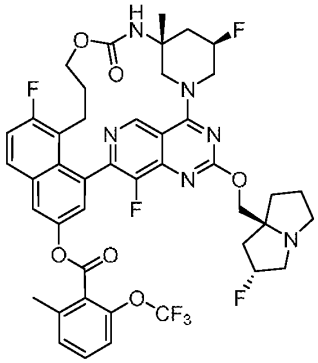
310		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,6-dimethylpyrimidine-5-carboxylate	815.2	E
314		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-methoxy-6-methylbenzoate	829.4	E
344		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-isopropylbenzoate	827.3	E

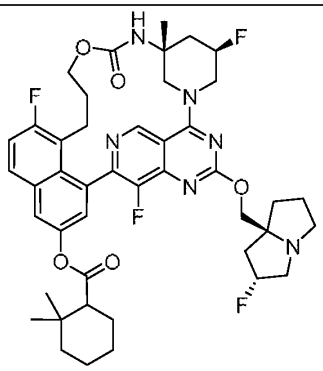
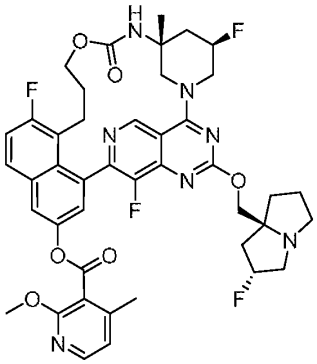
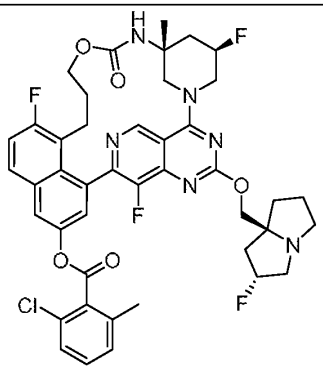
346		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-cyano-6-methylbenzoate	824.3	E
152		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,4-dimethylnicotinate	778.5	E
157		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-ethoxy-6-methylbenzoate	807.4	E

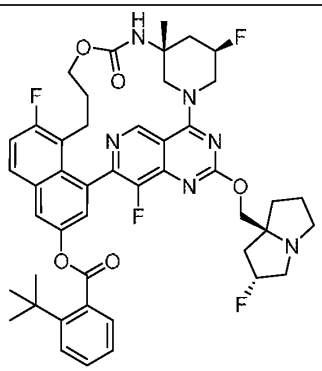
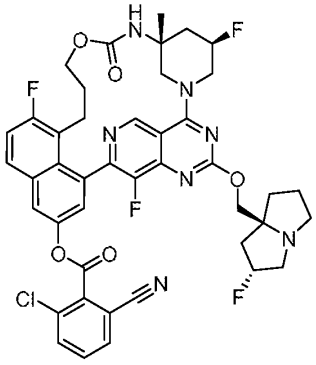
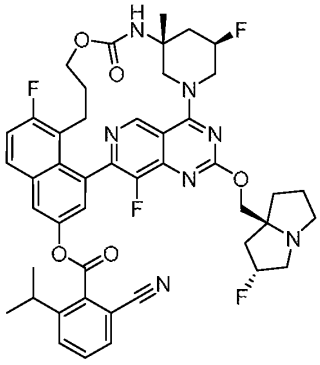
166		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,6-dimethoxypyrimidine-5-carboxylate	811.4	E
169		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,5-dimethylisonicotinate	778.4	E
198		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-bromo-6-methylbenzoate	841.1 / 843.1	E

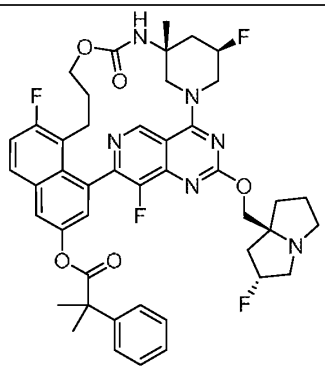
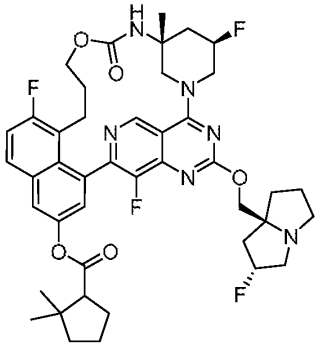
228		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-methylcyclohexane-1-carboxylate	769.1	E
177		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-methoxy-4-methylnicotinate	794.3	E
191		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-chloro-2,6-dimethylbenzoate	811.5	E

181		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,6-dimethylpyrimidine-5-carboxylate	779.5	E
208		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-fluoro-2,6-dimethylbenzoate	795.3	E
185		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 6-methyl-1H-indazole-7-carboxylate	803.5	E

178		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-methyl-4-(trifluoromethyl)nicotinate	832.5	E
405		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-chloro-6-methoxybenzoate	849.4	E
443		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-methyl-6-(trifluoromethoxy)benzoate	883.5	E

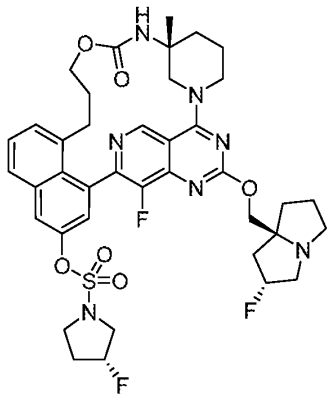
449		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,2-dimethylcyclohexane-1-carboxylate	819.4	E
458		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-methoxy-4-methylnicotinate	830.5	E
481		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-chloro-6-methylbenzoate	833.4	E

486		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(tert-butyl)benzoate	841.5	E
493		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-chloro-6-cyanobenzoate	844.2	E
521		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-cyano-6-isopropylbenzoate	852.3	E

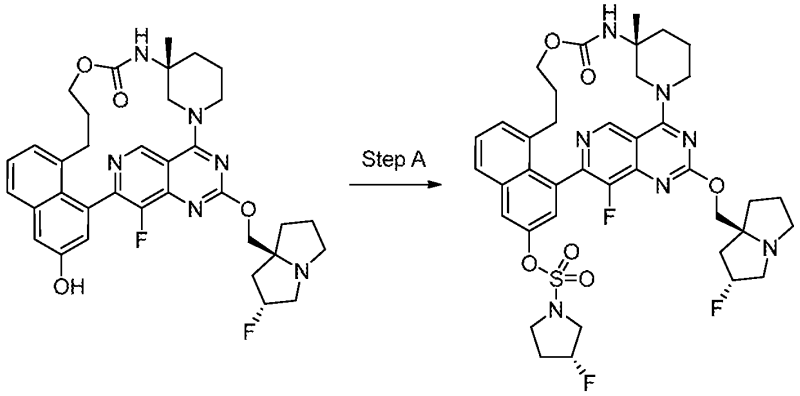
522		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-methyl-2-phenylpropanoate	827.3	E
537		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,2-dimethylcyclopentane-1-carboxylate	805.5	E

Example Procedure F. sulfonyl chloride

Compound 183



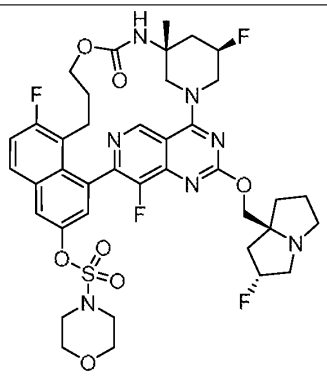
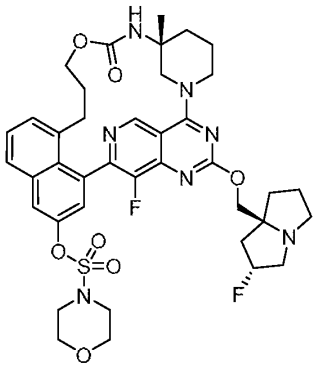
(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-fluoropyrrolidine-1-sulfonate

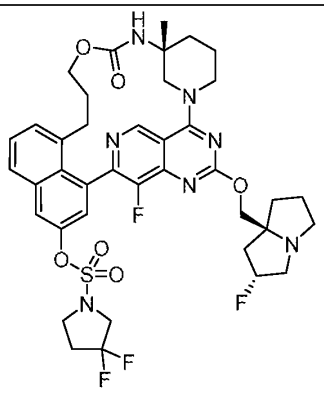
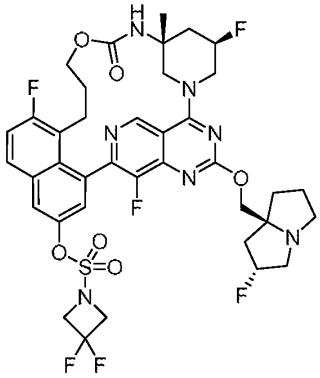


Step A. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-fluoropyrrolidine-1-sulfonate. To a solution of (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.070 g, 0.11 mmol) in THF (0.5 mL) at 0 °C was added NaH (60% in mineral oil; 0.0087 g, 0.22 mmol). The mixture was stirred for 5 min then (R)-3-fluoropyrrolidine-1-sulfonyl chloride (0.025 g, 0.13 mmol). The mixture was allowed to warm to rt and was stirred for 1 h. The mixture was diluted with H_2O (5 mL) and extracted

with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (23 – 53% MeCN in 0.225% aqueous formic acid). The fractions containing the product were lyophilized and the residue was further purified by preparative HPLC (52 – 82% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (3R)-3-fluoropyrrolidine-1-sulfonate (0.023 g, 27% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 796.2 (M+H).

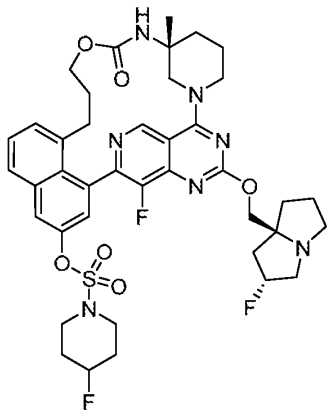
Table 13. Compounds synthesized by following the example procedure F

Cmpd ID	Structure	Name	LCMS	Procedure
348		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl morpholine-4-sulfonate	830.3	F
199		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl morpholine-4-sulfonate	794.2	F

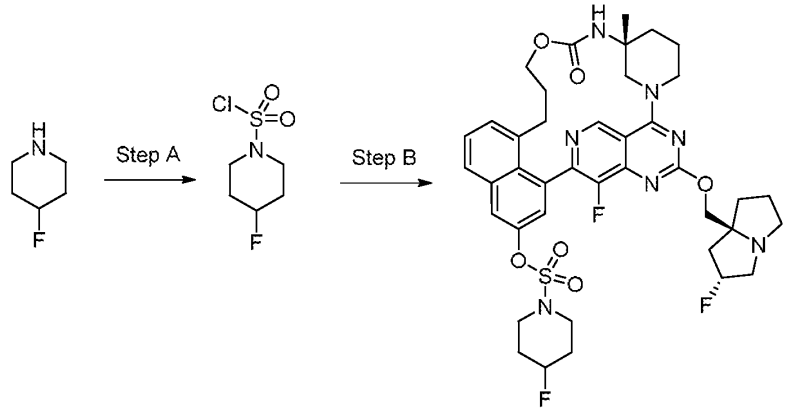
184		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-difluoropyrrolidine-1-sulfonate	814.5	F
525		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-difluoroazetidine-1-sulfonate	836.2	F

Example Procedure G. makes sulfonyl chloride then add in

Compound 200



(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-fluoropiperidine-1-sulfonate

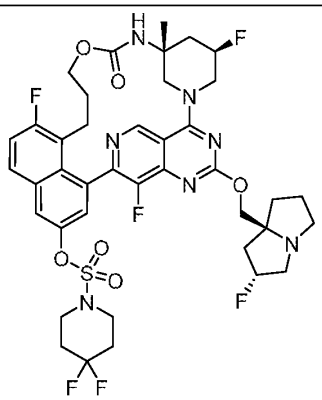


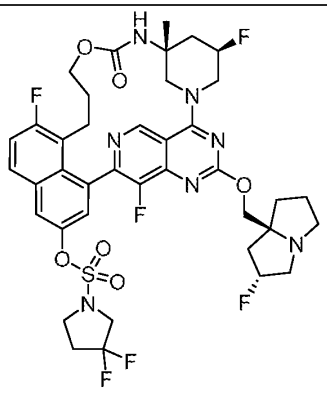
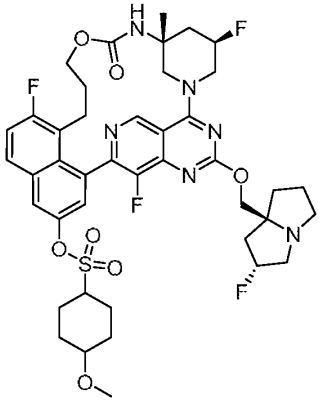
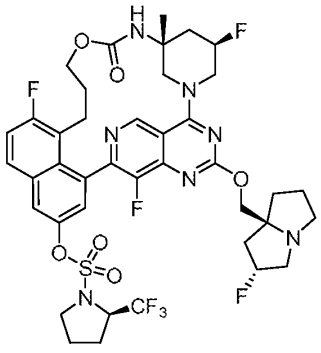
Step A. 4-fluoropiperidine-1-sulfonyl chloride. To a solution of 4-fluoropiperidine (0.10 g, 0.97 mmol) and NEt_3 (0.27 mL, 1.9 mmol) in DCM (1 mL) at 0 °C was added sulfuryl chloride (0.12 mL, 1.2 mmol). The reaction was allowed to warm to rt and was stirred for 1 h. The reaction was diluted with H_2O (5 mL) and then extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 4-fluoropiperidine-1-sulfonyl chloride (0.10 g, 51% yield) as a colorless oil.

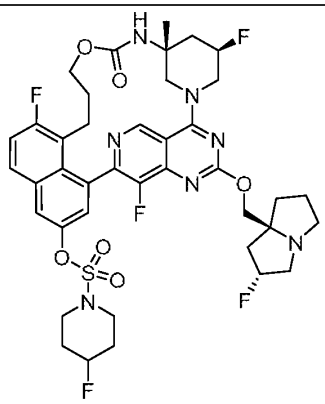
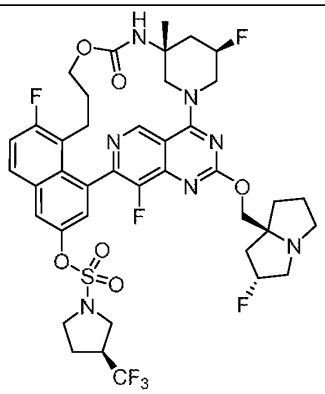
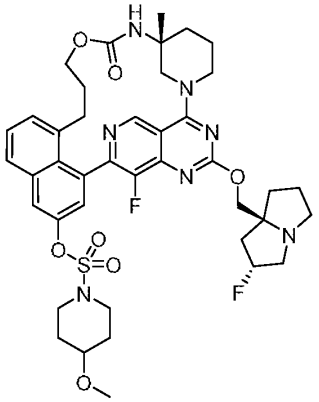
Step B. (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-

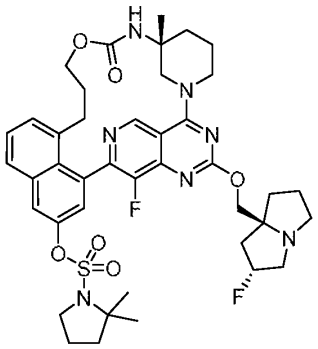
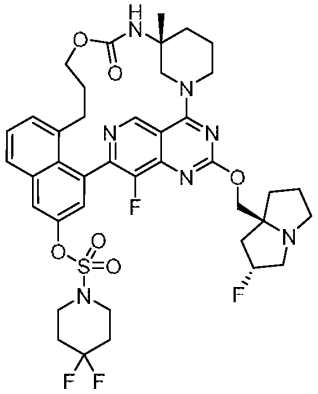
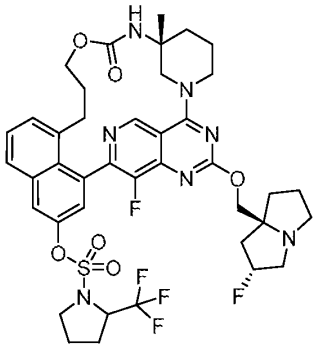
1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-fluoropiperidine-1-sulfonate. To a solution of (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.050 g, 0.077 mmol) in THF (0.50 mL) at 0 °C was added NaH (60% in mineral oil; 0.0061 g, 0.15 mmol). The mixture was stirred for 5 min then 4-fluoropiperidine-1-sulfonyl chloride (0.019 g, 0.092 mmol). The mixture was allowed to warm to rt and was stirred for 1 h. The mixture was diluted with H_2O (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (8 – 48% MeCN in 0.225% aqueous formic acid). The fractions containing the product were lyophilized to obtain (1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-fluoropiperidine-1-sulfonate (0.036 g, 57% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 810.3 (M+H).

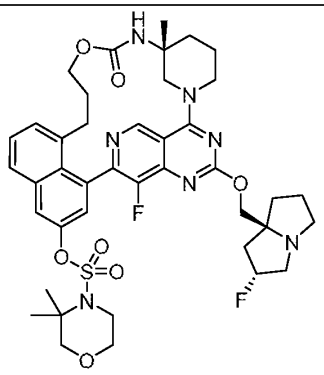
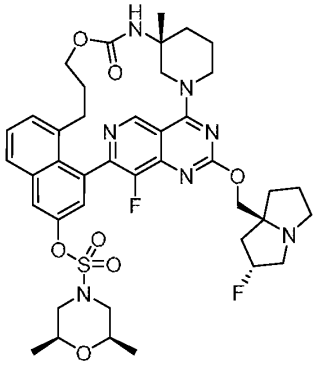
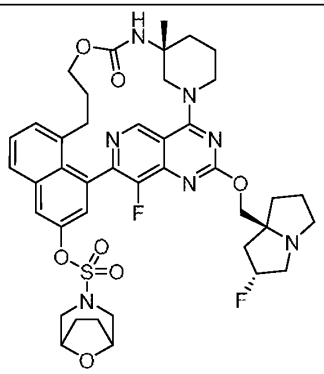
Table 13. Compounds synthesized by following the example procedure F

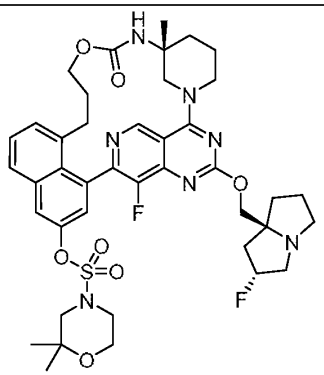
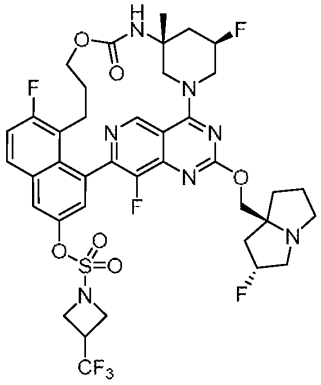
Cmpd ID	Structure	Name	LCMS	Procedure
312		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,4-difluoropiperidine-1-sulfonate	864.2	G

328		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-difluoropyrrolidine-1-sulfonate	850.2	G
332		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxycyclohexane-1-sulfonate	858.2	G
333		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-2-(trifluoromethyl)pyrrolidine-1-sulfonate	882.3	G

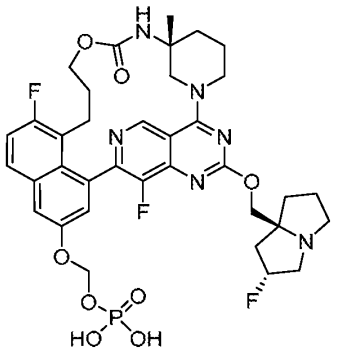
336		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-fluoropiperidine-1-sulfonate	846.2	G
374		(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2R)-3-(trifluoromethyl)pyrrolidine-1-sulfonate	882.3	G
220		(1^3R)-28-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4-methoxypiperidine-1-sulfonate	822.5	G

206		(1^3R)-28-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,2-dimethylpyrrolidine-1-sulfonate	806.3	G
202		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 4,4-difluoropiperidine-1-sulfonate	828.7	G
201		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2-(trifluoromethyl)pyrrolidine-1-sulfonate	846.4	G

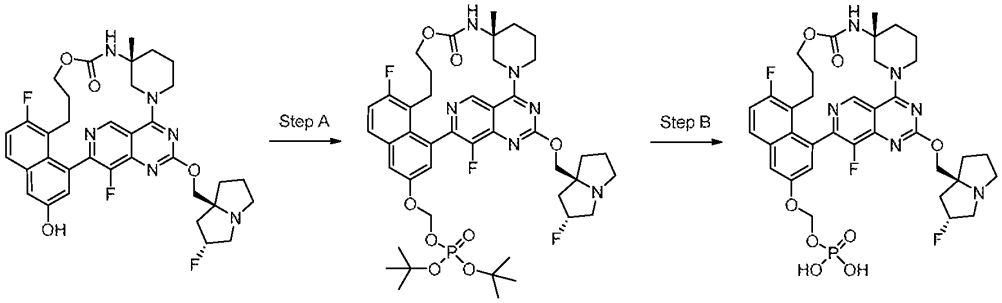
214		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,3-dimethylmorpholine-4-sulfonate	822.4	G
205		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (2S,6R)-2,6-dimethylmorpholine-4-sulfonate	822.2	G
203		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (1R,5S)-8-oxa-3-azabicyclo[3.2.1]octane-3-sulfonate	820.7	G

204		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 2,2-dimethylmorpholine-4-sulfonate	822.2	G
524		(1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3-(trifluoromethyl)azetidine-1-sulfonate	868.4	G

Compound 282



(((1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl dihydrogen phosphate

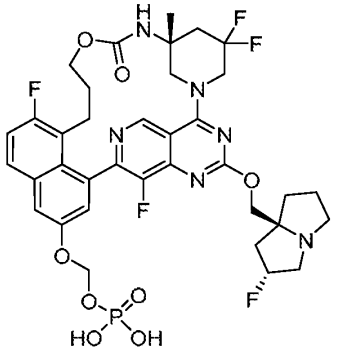


Step A. di-tert-butyl ((((1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl) phosphate. To a solution of (1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.030 g, 0.045 mmol) and di-tert-butyl (chloromethyl) phosphate (0.018 g, 0.068 mmol) in DCM (1 mL) was added DIPEA (0.016 mL, 0.091 mmol). The reaction was stirred at rt for 2 h and then it was concentrated under reduced pressure to give di-tert-butyl ((((1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl) phosphate (0.030 g, 75% yield) as yellow oil.

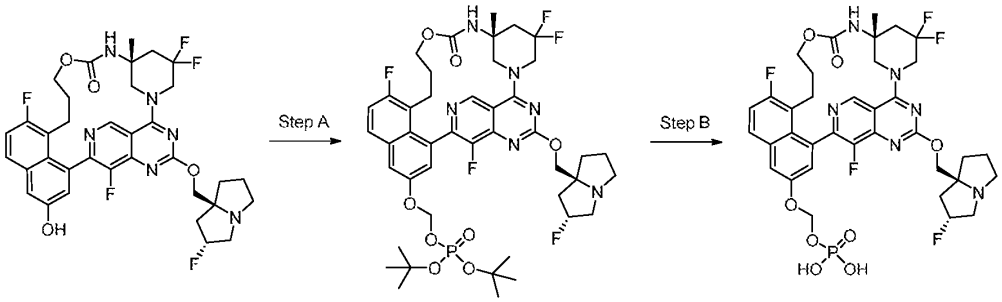
Step B. (((1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-

3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl dihydrogen phosphate. To a solution of di-tert-butyl ((((1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl) phosphate (0.030 mg, 0.034 mmol) in DCM (1.2 mL) was added TFA (0.20 mL, 2.7 mmol). The mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC (8 – 38% MeCN in 0.1% aqueous NH_4HCO_3). The fractions containing the product were lyophilized to obtain (((1^{3}R)-2^8,3^7-difluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl dihydrogen phosphate (0.0098 g, 37% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 773.3 (M+H).

Compound 287

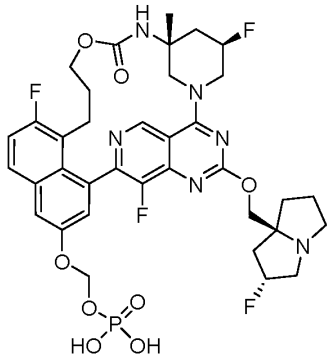


(((1^{3}R)-1^5,1^5,2^8,3^7-tetrafluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-13-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl dihydrogen phosphate

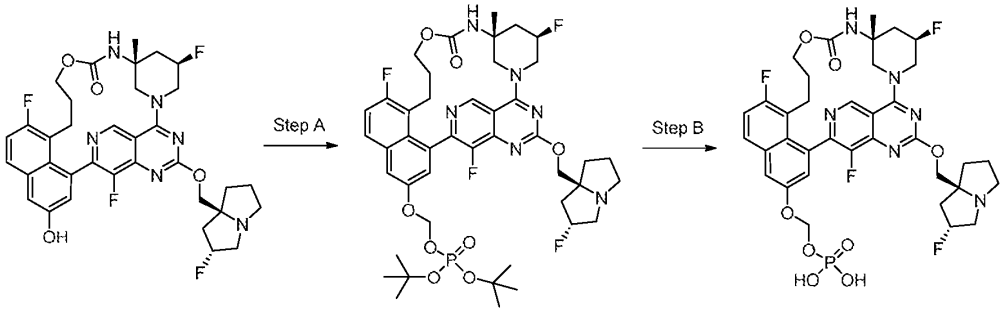


Compound 287 was synthesized according to procedures for Compound 282. LCMS (MM-ES+APCI, Pos): m/z 809.2 (M+H).

Compound 329

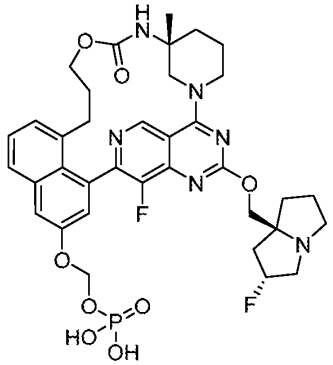


(((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl dihydrogen phosphate



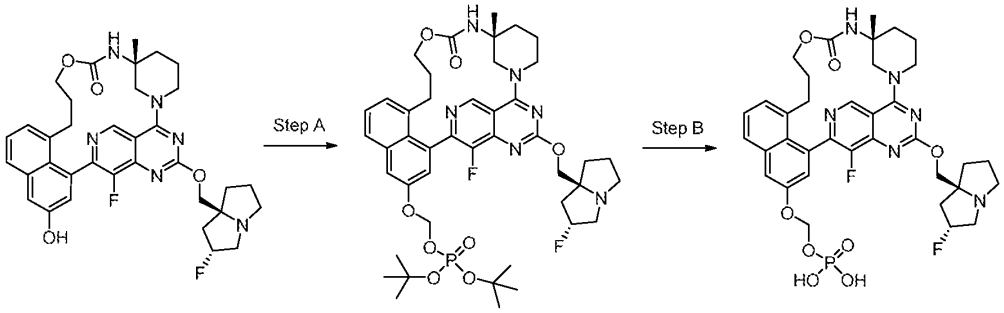
Compound 329 was synthesized according to procedures for Compound 282. LCMS (MM-ES+APCI, Pos): m/z 791.2 (M+H).

Compound189



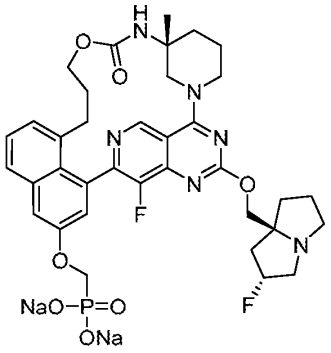
(((1^3*R*)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-

naphthalenacyclononaphane-3[3]-yl)oxy)methyl dihydrogen phosphate

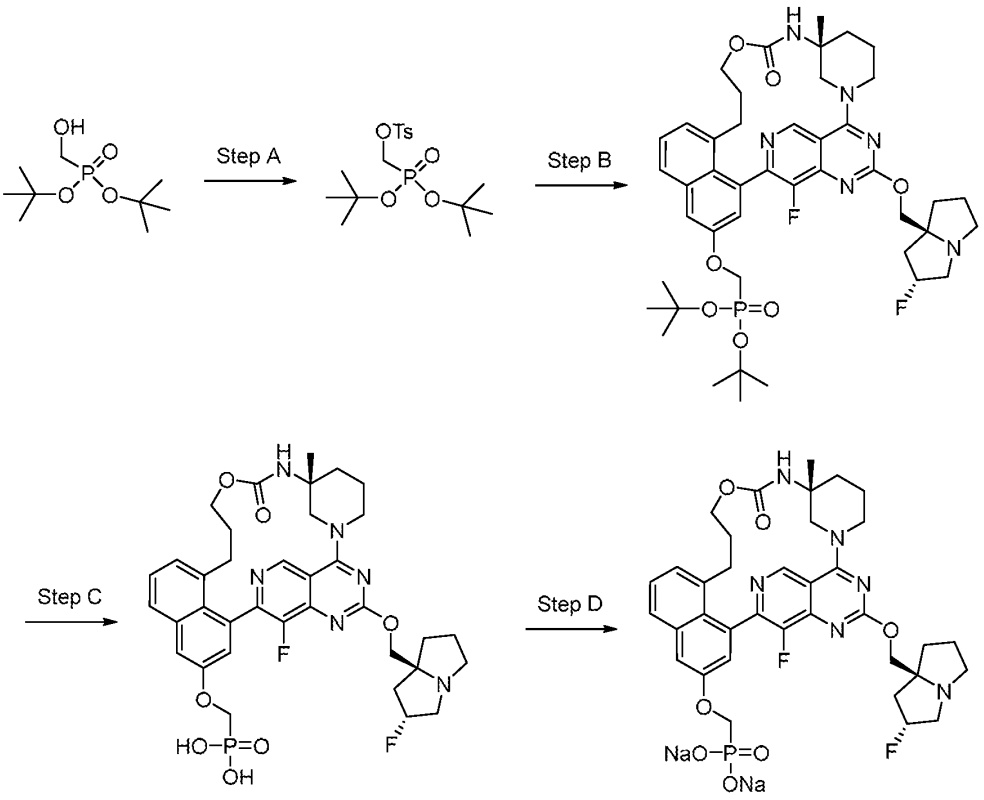


Compound 189 was synthesized according to procedures for Compound 282. LCMS (MM-ES+APCI, Pos): m/z 755.2 (M+H).

Compound 261



sodium ((((1[3]R)-2[8]-fluoro-2[2]-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1[3]-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3[3]-yl)oxy)methyl)phosphonate



Step A. (di-tert-butoxyphosphoryl)methyl 4-methylbenzenesulfonate. To a solution of di-tert-butyl (hydroxymethyl)phosphonate (0.10 g, 0.45 mmol), NEt_3 (0.068 mL, 0.49 mmol), DMAP (0.0055 g, 0.045 mmol) in DCM (2 mL) was added 4-toluenesulfonyl chloride (0.094 g, 0.49 mmol). The mixture was stirred at rt for 12 h and then it was concentrated under reduced pressure. The residue was purified by silica gel chromatography (9-50% EtOAc in petroleum ether) to give di-tert-butoxyphosphoryl)methyl 4-methylbenzenesulfonate (0.11 g, 61% yield) as a white solid. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 4.03 (d, J = 10.0 Hz, 2H), 2.46 (s, 3H), 1.48 (s, 18H).

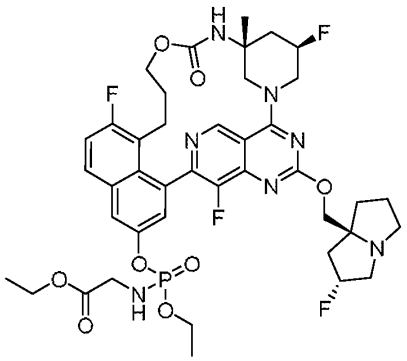
Step B. di-tert-butyl ((((1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl)phosphonate. To a solution of (1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.050 g, 0.078 mmol), Cs_2CO_3 (0.076 g, 0.23 mmol) in DMF (1.5 mL) was added di-tert-butoxyphosphoryl)methyl 4-methylbenzenesulfonate (0.060 g, 0.16 mmol). The reaction was stirred at 60 °C for 8 h. The mixture was diluted with

saturated aqueous NH_4Cl (3 mL) and then extracted with ethyl acetate (2 mL x 3). The combined organic layers were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give di-tert-butyl ((((1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl)phosphonate as a yellow oil. LCMS (MM-ES+APCI, Pos): m/z 851.3 (M+H).

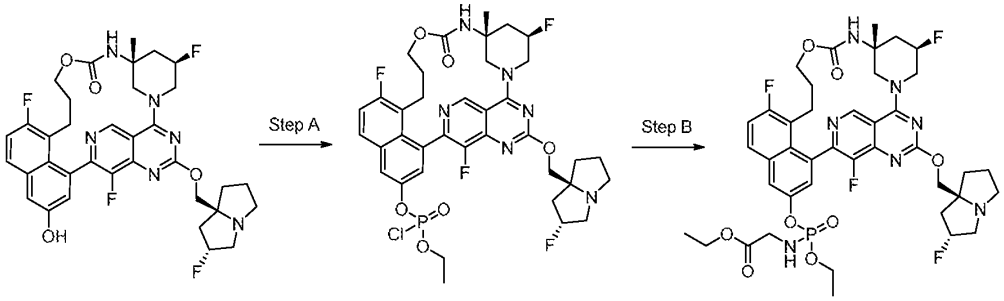
Step C. ((((1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl)phosphonic acid. To a solution of di-tert-butyl ((((1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl)phosphonate (0.070 g, 0.47 mmol) in DCM (1.2 mL) was added TFA (0.2 mL). The reaction was stirred for 30 min and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC (8-38% MeCN in 0.1% aqueous NH_4HCO_3) to obtain ((((1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl)phosphonic acid (0.025 g, 70% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 739.3 (M+H).

Step D. sodium ((((1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl)phosphonate. To a solution of ((((1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl)phosphonic acid (0.010 g, 0.013 mmol) in MeCN (5 mL) and H_2O (10 mL) was added 0.1 M aqueous NaOH (0.24 mL). The solution was lyophilized to obtain sodium ((((1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)methyl)phosphonate (0.0084 g, 75% yield) as a light yellow solid. LCMS (MM-ES+APCI, Pos): m/z 739.4 (M+H-2Na).

Compound 359



ethyl (ethoxy(((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)phosphoryl)glycinate

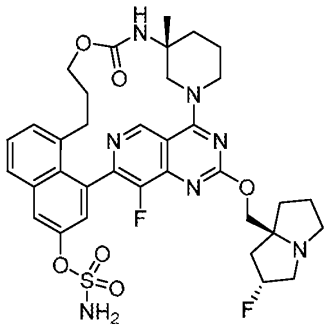


Step A. ethyl ((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) phosphorochloridate. To a solution of (1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.040 g, 0.058 mmol) and triethylamine (0.016 mL, 0.12 mmol) in THF (0.5 mL) at 0 °C was added ethyl phosphorodichloridate (0.014 mL, 0.12 mmol). The mixture was stirred at 0 °C for 2 h and then it was concentrated under reduced pressure to give ethyl ((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) phosphorochloridate (0.040 g, 85% yield) as a yellow solid.

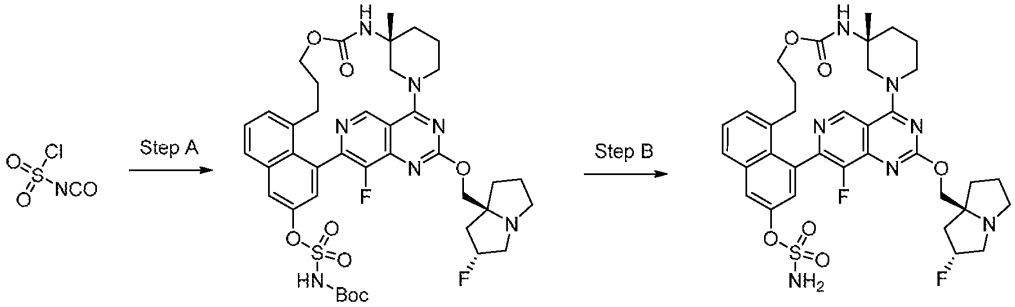
Step B. ethyl (ethoxy(((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)phosphoryl)glycinate. To a

solution of ethyl ((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) phosphorochloridate (0.040 g, 0.050 mmol) and triethylamine (0.014 mL, 0.099 mmol) in THF (0.5 mL) at 0 °C was added ethyl glycinate HCl (0.0083 g, 0.060 mmol). The reaction was stirred at rt for 1 h. The suspension was filtered and the filter cake was washed with acetonitrile (3 mL). The filtrate was concentrated under reduced pressure. The residue was purified by preparative HPLC (15 – 45% MeCN in 0.225% aqueous formic acid) to give ethyl (ethoxy(((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)phosphoryl)glycinate (0.0056 g, 13% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 874.5 (M+H).

Compound 215



(1^3*R*)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl sulfamate

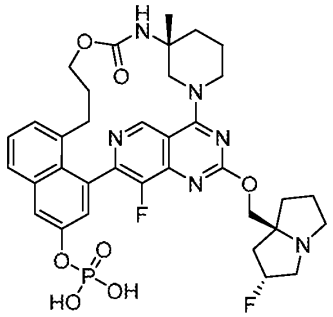


Step A. (1^3*R*)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (tert-butoxycarbonyl)sulfamate. To solution of

sulfurisocyanatidic chloride (0.022 g, 0.16 mmol) and DCM (1.0 mL) at 0 °C was added *t*-BuOH (0.0063 g, 0.085 mmol) followed by a solution of ((1^{3}R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.050 g, 0.078 mmol) and triethylamine (0.012 mL, 0.085 mmol) in DCM (1 mL). The mixture was stirred at 0 °C for 1 h and then at rt for 12 h. The mixture was diluted with water (5 mL) and extracted with DCM (4 mL x 3). The combined organic layers were washed with brine (4 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford (1^3*R*)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (tert-butoxycarbonyl)sulfamate (0.030 g, 47% yield) as a clear oil.

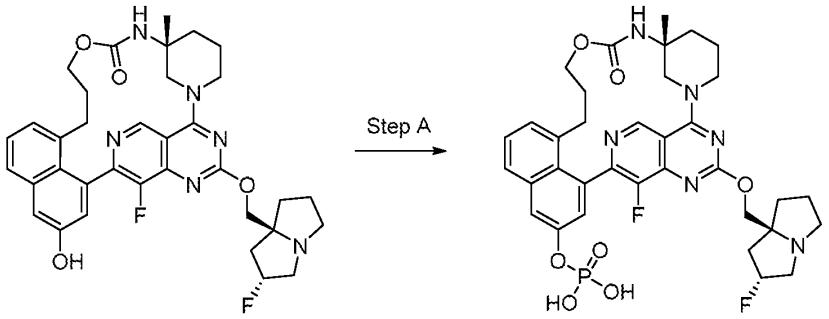
Step B. (1^3*R*)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl sulfamate. To a solution of (1^3*R*)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (tert-butoxycarbonyl)sulfamate (0.030 g, 0.036 mmol) in DCM (1 mL) was added TFA (0.30 mL, 4.0 mmol). The mixture was stirred at rt for 1 h and then concentrated under reduced pressure. The residue was purified by preparative HPLC (30 – 60% MeCN in aqueous NH_4HCO_3) to give (1^3*R*)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-*d*]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl sulfamate (0.0056 g, 20% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 724.4 (M+H).

Compound 192



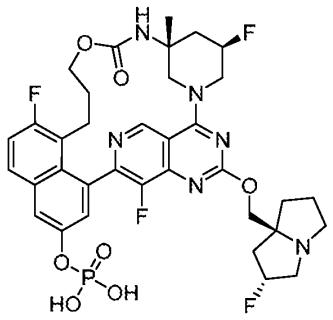
(1^3*R*)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-

methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl dihydrogen phosphate

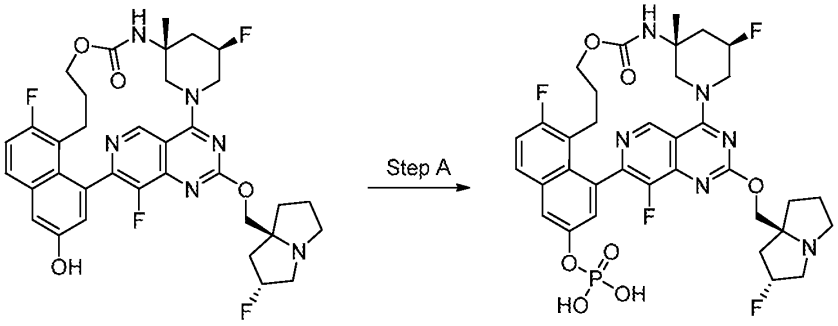


Step A. (1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl dihydrogen phosphate. To a solution of (1^3*R*)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.070 g, 0.11 mmol) and DIPEA (0.056 mL, 0.32 mmol) in MeCN (1 mL) at 0 °C was added $POCl_3$ (0.025 g, 0.16 mmol). The mixture was stirred at 0 °C for 30 min and then it was diluted with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (1 – 30% MeCN in 0.1% aqueous NH_4HCO_3). The residue was purified again by preparative HPLC (15 – 45% MeCN in 0.225% aqueous formic acid). The residue was purified again by preparative HPLC (1 – 30% MeCN in 0.1% aqueous NH_4HCO_3) to obtain (1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl dihydrogen phosphate (0.023 g, 30% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 725.4 (M+H).

Compound 392

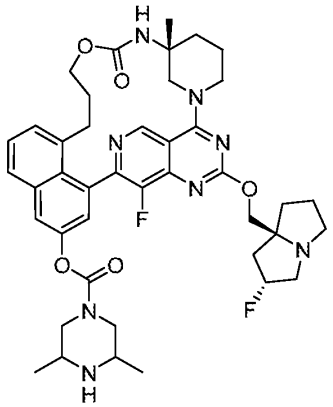


(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl dihydrogen phosphate

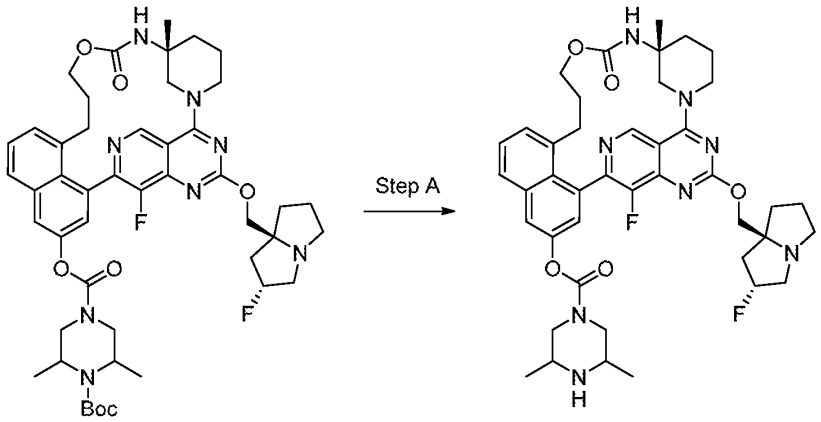


Step A was performed with (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one following the procedure for Compound 192. LCMS (MM-ES+APCI, Pos): m/z 761.3 (M+H).

Compound 186

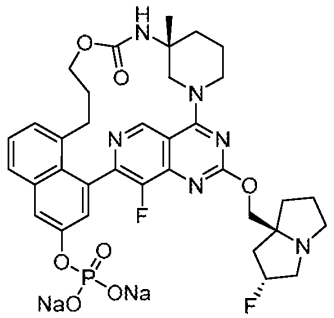


(1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,5-dimethylpiperazine-1-carboxylate

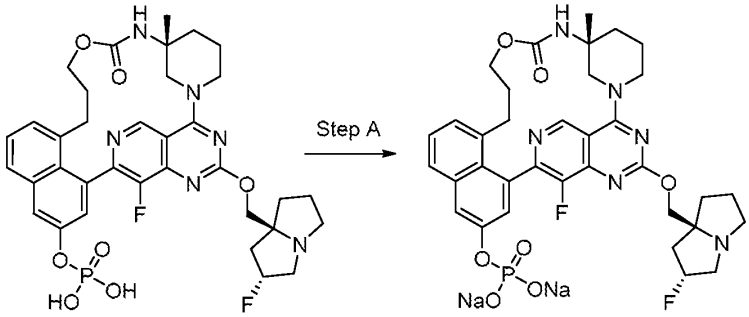


Step A. (1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,5-dimethylpiperazine-1-carboxylate. To a solution of 1-(tert-butyl) 4-((1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) 2,6-dimethylpiperazine-1,4-dicarboxylate (0.060 g, 0.068 mmol, prepared according to example procedure D) in DCM (1 mL) was added 2 M HCl in dioxane (1 mL). The mixture was stirred for 1 h, after which it was concentrated under reduced pressure. The residue was purified by preparative HPLC (35 – 65% MeCN in 0.1% aqueous NH_4HCO_3) to obtain (1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl 3,5-dimethylpiperazine-1-carboxylate (0.018 g, 34% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 785.6 (M+H).

Compound 217

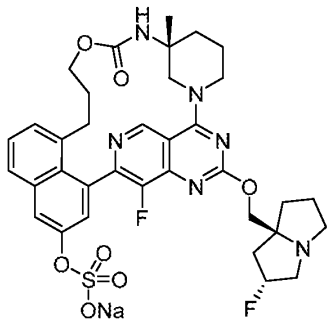


Sodium (1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl phosphate

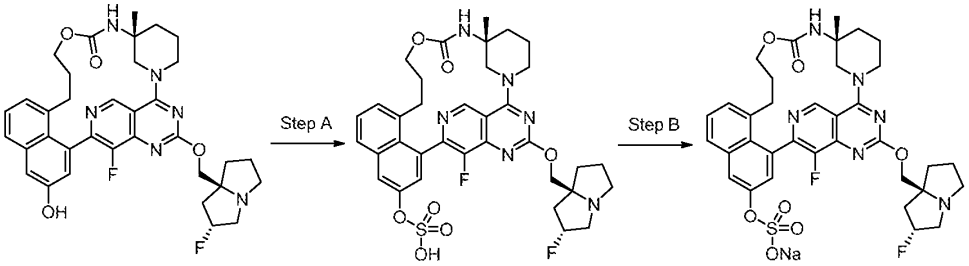


Step A. Sodium (1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl phosphate. To a solution of (1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl dihydrogen phosphate (0.023 g, 0.033 mmol) in MeCN (5 mL) and H_2O (20 mL) was added 0.5 M NaOH (0.11 mL). The mixture was stirred at rt for 5 min, after which it was lyophilized to afford sodium (1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl phosphate (0.022 g, 0.027 mmol, 87% yield) as an off-white solid. LCMS (MM-ES+APCI, Pos): m/z 725.2 (M+H-2Na).

Compound 216



sodium (1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl sulfate

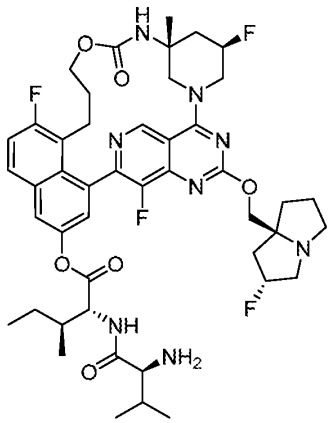


Step A. (1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl hydrogen sulfate. To solution of sulfurisocyanatidic chloride (0.022 g, 0.16 mmol) and DCM (1.0 mL) at 0 °C was added *t*-BuOH (0.006.3 g, 0.085 mmol) followed by a solution of ((1^3R)-2^8-fluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.050 g, 0.078 mmol) and triethylamine (0.012 mL, 0.085 mmol) in DCM (1 mL). The mixture was stirred at 0 °C for 1 h and then at rt for 12 h. The reaction mixture was diluted with water (5 mL) and extracted with DCM (4 mL x 3). The combined organic layers were washed with brine (4 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (32 – 62% MeCN in 0.1% aqueous NH_4HCO_3) to give (1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl hydrogen sulfate (0.0085 g, 14% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 725.3 (M+H).

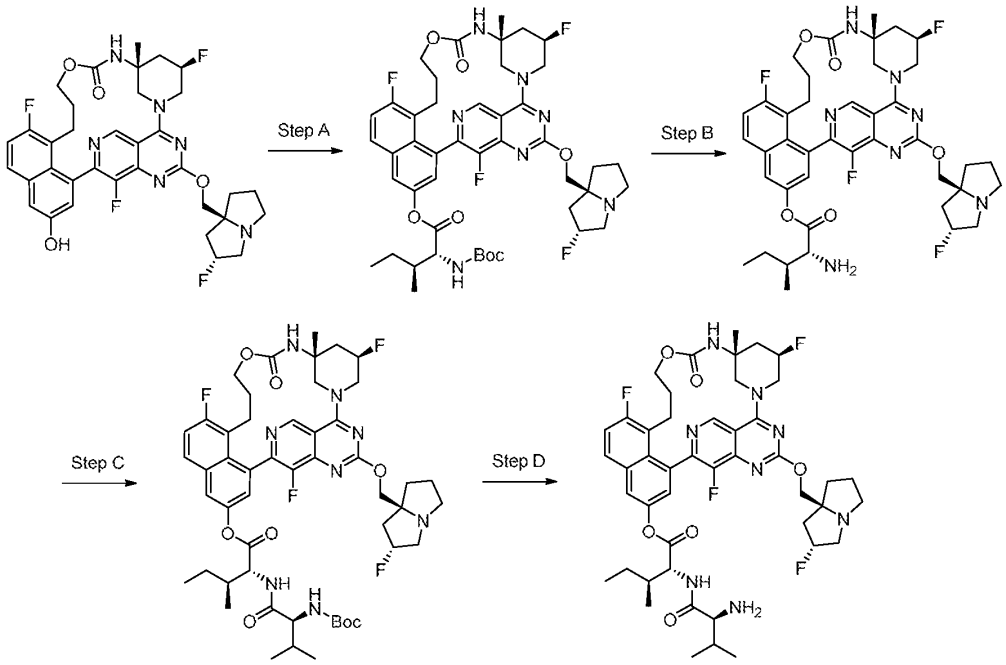
Step B. sodium (1^3R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-

3(1,8)-naphthalenacyclononaphane-3^3-yl sulfate. To a solution of (1^{3}R)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl hydrogen sulfate (0.0085 g, 0.011 mmol) in MeCN (1 mL) and H_2O (2 mL) was added NaOH (0.5 M, 0.020 mL). The mixture was stirred at rt for 5 min. The mixture was diluted with H_2O (15 mL) and MeCN (2 mL). The mixture was lyophilized to obtain, sodium (1^3*R*)-2^8-fluoro-2^2-(((2*R*,7a*S*)-2-fluorotetrahydro-1*H*-pyrrolizin-7a(5*H*)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl sulfate (0.0063 g, 0.0084 mmol, 72% yield) was obtained as a white solid. LCMS (MM-ES+APCI, Pos): m/z 725.1 (M+H-Na).

Compound 381



(1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl L-valyl-D-alloisoleucinate



Step A. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (tert-butoxycarbonyl)-D-alloisoleucinate. To a solution of (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.040 g, 0.059 mmol) and (tert-butoxycarbonyl)-D-alloisoleucine (0.020 g, 0.088 mmol) in DCM (1 mL) was added EDCI (0.017 g, 0.088 mmol) and DMAP (0.0072 g, 0.059 mmol). The reaction was stirred for 1 h and then it was diluted with H_2O (5 mL) and extracted with DCM (5 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-75% EtOAc in hexanes) to give (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (tert-butoxycarbonyl)-D-alloisoleucinate (0.042 g, 80% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 894.4 (M+H).

Step B. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl D-alloisoleucinate. To a solution of (1^3R,1^5R)-

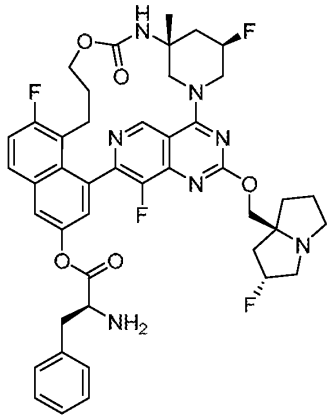
$1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (tert-butoxycarbonyl)-D-alloisoleucinate (0.040 g, 0.045 mmol) in DCM (1.0 mL) was added 2 M HCl in dioxane (1.0 mL). The reaction was stirred for 30 min and then it was concentrated under reduced pressure to give (1^3R,1^5R)-$1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl D-alloisoleucinate (0.035 g), which was taken onto the next step without further purification.

Step C. (1^3R,1^5R)-$1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (tert-butoxycarbonyl)-L-valyl-D-alloisoleucinate. To a solution of (1^3R,1^5R)-$1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl D-alloisoleucinate (0.035 g, 0.042 mmol) and DIPEA (0.022 mL, 0.13 mmol) in DCM (1 mL) was added (tert-butoxycarbonyl)-D-valine (0.014 g, 0.063 mmol) and HATU (0.024 g, 0.063 mmol). The mixture was stirred for 1 h. and then it was diluted with H_2O (5 mL) and extracted with DCM (5 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0-75% EtOAc in hexanes) to give (1^3R,1^5R)-$1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (tert-butoxycarbonyl)-L-valyl-D-alloisoleucinate (0.040 g, 83% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 993.6 (M+H).

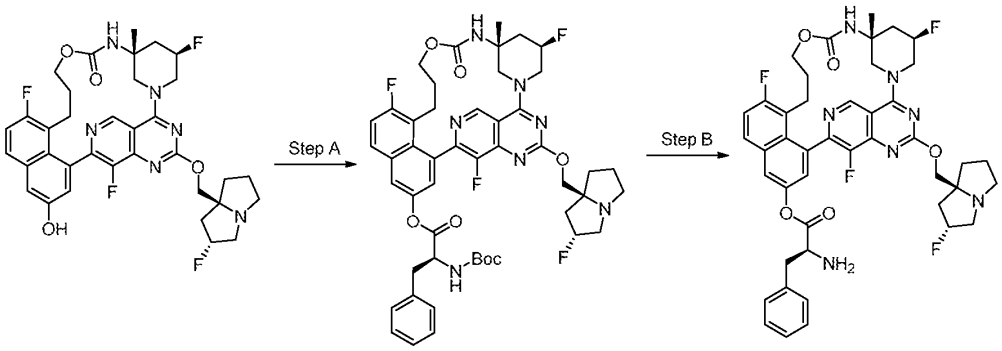
Step D. (1^3R,1^5R)-$1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl L-valyl-D-alloisoleucinate. To a solution of (1^3R,1^5R)-$1^5,2^8,3^7$-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (tert-butoxycarbonyl)-L-valyl-D-alloisoleucinate (0.040 g, 0.035 mmol) in DCM (1 mL) was added 2 M HCl in dioxane (1 mL). The reaction was stirred for 1 h and then it was concentrated under reduced pressure. The residue was

purified by preparative HPLC (15 – 45% MeCN in 0.05% aqueous HCl) to give (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl L-valyl-D-alloisoleucinate (0.0064 g, 19% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 893.6 (M+H).

Compound 444



(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl L-phenylalaninate

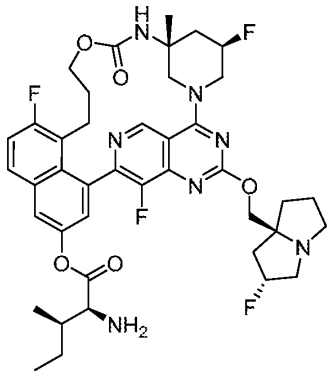


Step A. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (tert-butoxycarbonyl)-L-phenylalaninate. To a solution of (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-

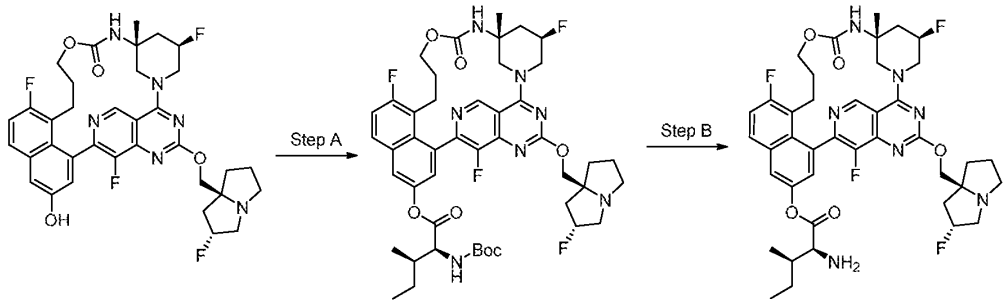
1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.030 g, 0.044 mmol) and (tert-butoxycarbonyl)-L-phenylalanine (0.015 g, 0.057 mmol) in DCM (1 mL) was added EDCI (0.017 g, 0.088 mmol) and DMAP (0.016 g, 0.13 mmol). The reaction was stirred for 1 h and then it was diluted with H_2O (2 mL) and extracted with DCM (4 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (tert-butoxycarbonyl)-L-phenylalaninate (0.040 g, 98% yield), which was taken onto the next step without further purification.

Step B. (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl L-phenylalaninate. To a solution of (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl (tert-butoxycarbonyl)-L-phenylalaninate (0.040 g, 0.043 mmol) in DCM (0.5 mL) was added 2 M HCl in dioxane (0.5 mL). The reaction was stirred for 30 min and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC: (13 – 43% MeCN in 0.05% aqueous HCl). The residue was purified again by preparative HPLC (16 – 38% MeCN in 0.05% aqueous HCl) to give (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl L-phenylalaninate (0.010 g, 22% yield) as white solid. LCMS (MM-ES+APCI, Pos): m/z 828.3 (M+H).

Compound 445

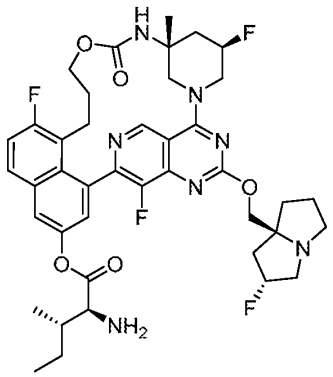


(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl L-alloisoleucinate

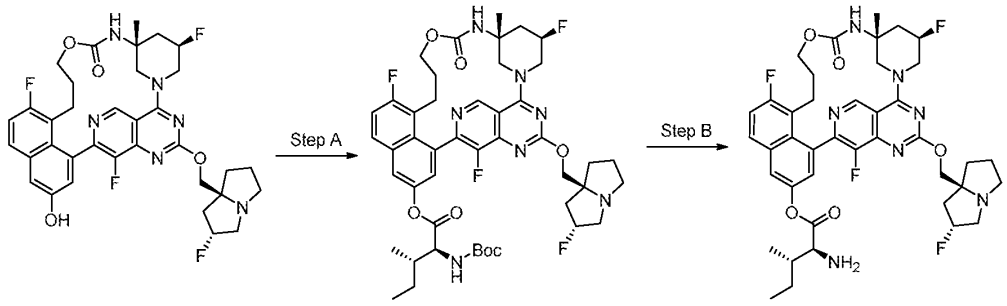


Steps A-B were performed with (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.030 g, 0.044 mmol) following the procedures for Compound 444. LCMS (MM-ES+APCI, Pos): m/z 794.3 (M+H).

Compound 446

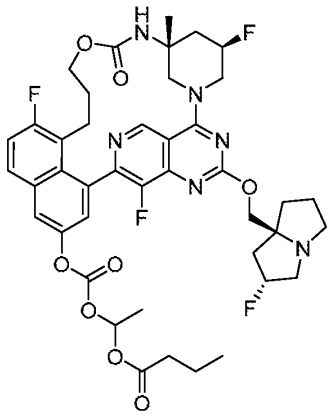


(1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl L-isoleucinate

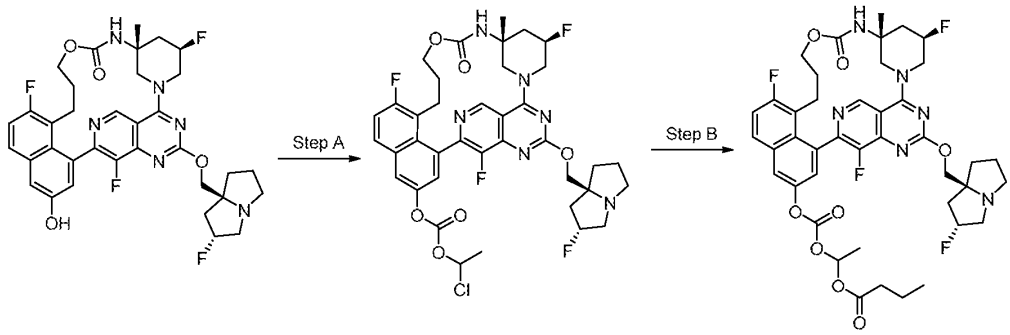


Steps A-B were performed with (1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one following the procedures for Compound 444. LCMS (MM-ES+APCI, Pos): m/z 794.3 (M+H).

Compound 447



1-(((((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)carbonyl)oxy)ethyl butyrate

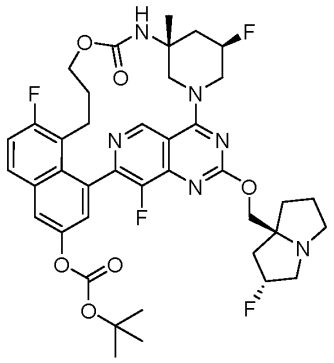


Step A. 1-chloroethyl ((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) carbonate. To a solution of (1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.040 g, 0.058 mmol, 1 eq) and pyridine (0.0094 mL, 0.12 mmol) in DCM (1 mL) at 0 °C was added 1-chloroethyl carbonochloridate (0.013 g, 0.088 mmol). The reaction was stirred for 1 h and then it was diluted with H_2O (5 mL) and extracted with DCM (5 mL x 3). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 1-chloroethyl ((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) carbonate (0.045 g, 98% yield), which was used into the next step without further purification.

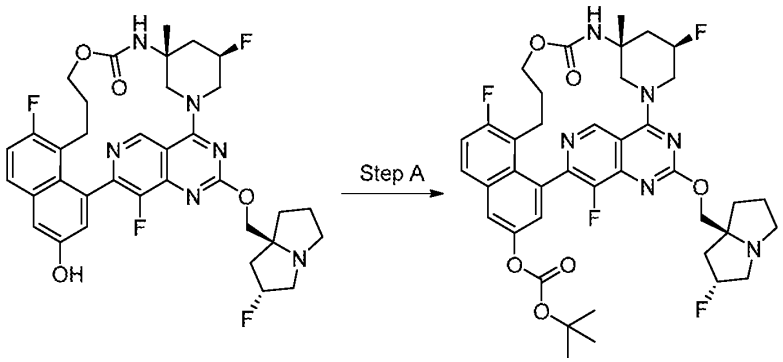
Step B. 1-(((((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)carbonyl)oxy)ethyl butyrate. To a solution of 1-chloroethyl ((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) carbonate (0.040 g, 0.051 mmol) in butyric acid (1.0 mL) was added Ag_2O (0.012 g, 0.051 mmol). The reaction was heated to 95 °C for 1 h. The solution was diluted with sat. aq. $NaHCO_3$ solution (3 mL) and then it was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (26 – 56% MeCN in 0.1% aqueous

NH_4HCO_3) to give 1-(((((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl)oxy)carbonyl)oxy)ethyl butyrate (0.021 g, 50% yield) as an off-white solid. LCMS (MM-ES+APCI, Pos): m/z 839.2 (M+H).

Compound 448



tert-butyl ((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) carbonate



Step A. tert-butyl ((1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) carbonate. To a solution of (1^{3}R,1^{5}R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-3^3-hydroxy-1^3-methyl-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphan-8-one (0.030 g, 0.044 mmol, 1 eq) and triethylamine (0.012 mL, 0.088 mmol) in THF (0.5 mL) was added Boc_2O (0.019 g, 0.088

mmol) and DMAP (0.00054 g, 0.0044 mmol). The reaction was stirred for 1 h and then it was concentrated under reduced pressure. The residue was purified by preparative HPLC (55 – 85% MeCN in 0.1% aqueous NH_4HCO_3) to give tert-butyl ((1^3R,1^5R)-1^5,2^8,3^7-trifluoro-2^2-(((2R,7aS)-2-fluorotetrahydro-1H-pyrrolizin-7a(5H)-yl)methoxy)-1^3-methyl-8-oxo-7-oxa-9-aza-2(4,7)-pyrido[4,3-d]pyrimidina-1(1,3)-piperidina-3(1,8)-naphthalenacyclononaphane-3^3-yl) carbonate (0.013 g, 38% yield) as a white solid. LCMS (MM-ES+APCI, Pos): m/z 781.5 (M+H).

Biological Assays

KRAS wild type and mutant enzyme assays

Activity against KRAS wild type and mutant enzymes were determined in biochemical assays using purified full-length isoforms using a custom HTRF competition binding assay. Compounds were tested in 11 point 1:3 serial dilutions, typical final concentration range from 10,000nM to 0.17nM. Test compounds were dissolved in DMSO and added to assay plates using a Tecan D300e dispenser.

Enzyme, a custom fluorescent probe, and streptavidin-Europium were added using a SPT Labtech Dragonfly. After a 60 min incubation at room temperature, the plate was read using a multimode reader and the emission ratio of 665 nm to 615 nm was determined. This ratio was converted to percent of control (POC). [1-(high control-sample signal)/(high control-low control)]*100. Wells without compound were used to determine high control values and wells without enzyme were used to determine low control values. The POC values were fit using a four-parameter logistic model and the value where the fit curve was equal to 50 POC was reported as the IC50 using the Signals VitroVivo software package (PerkinElmer). Final assay conditions were: 50 mM HEPES pH 7.5, 10 mM MgCl2, 1 mM EDTA, 0.01% Brij-35, and 1 mM DTT. The enzyme source, final enzyme concentration, and final tracer concentration can be found in Table 14.

Table 14: Enzyme assay data summary

Enzyme	KRAS WT	KRAS G12D	KRAS G12V	KRAS G12C	KRAS G12R
Tracer conc.	32 nM	13 nM	20 nM	28 nM	51 nM

Phosphorylated ERK (pERK) Cell Assay for KRAS (G12D, G12V):

AsPC-1 (KRAS G12D) and SW480 (KRAS G12D) were cultured in RPMI1640 with

10% fetal bovine serum. Cells were plated into a 384-well cell culture plate at cell densities of 6,000 cells/well for AsPC-1 and SW480. The following day, cells were treated with compound using three-fold serial dilutions ranging from 10 μM to .5 nM for 4 hours at 37°C, 5% CO_2.

Post-treatment, cell lysates were prepared and phospho-ERK was measured using the HTRF Advanced Phospho-ERK (Thr202/Tyr204) detection kit (Revvity#64AERPEH). Lysis buffer containing 1x phosphor and total protein blocking reagent (Revvity#64KB1AAC) was added, and cells were incubated for 40 min. at 4°C under shaking conditions. Plates were centrifuged at 1500 rpm for 3 min. and cell lysates were transferred to a detection plate (Revvity#6008289) with premixed antibody solutions (Revvity#64AERPEH). Plates were centrifuged at 1000 rpm for 1 min, incubated at 25°C for 120 min, followed by an overnight incubation at 4°C. The plates were read on the EnVision or the PHERAstar multimode plate reader via HTRF dual wavelength detection.

For data analysis, the 100 percent of control (POC) was determined using DMSO treated samples, and 0 POC was determined using the top concentration of a control compound. A 4-paramter logistic curve was fitted to the POC values as a function of compound concentration to determine the IC_{50} value. A summary of the IC_{50} value is provided in Tables 15-16.

Table 15: Enzyme assay data for selected compounds

The symbol "A" indicates an IC_{50} less than 50 nM. The symbol "B" indicates an IC_{50} in the range of greater than or equal to 50 nM to 500 nM. The symbol "C" indicates an IC_{50} in the range of greater than or equal to 500 nM to 5,000 nM. The symbol "D" indicates an IC_{50} greater than or equal to 5,000 nM.

Compound Number	G12D HTRF (nM)	G12C HTRF (nM)	G12V HTRF (nM)	G12R HTRF (nM	G12WT HTRF (nM)
1	A	A	A	A	A
2	A	A	A	A	A
3	A	A	A	A	A
4	A	A	A	A	A
5	C	C	C	C	C

6	A	A	A	A	A
7	A	A	A	B	A
8	C	C	D	D	C
9	D	C	C	D	C
10	A	A	A	A	A
11	B	B	B	B	B
12	D	D	D	D	D
13	D	D	D	D	D
14	A	A	B	B	A
15	A	A	A	A	A
16	A	A	A	A	A
18	D	D	D	D	D
19	A	A	A	A	A
20	A	A	A	A	A
21	A	A	A	A	A
22	A	A	A	A	A
23	A	B	B	B	B
24	A	B	B	B	B
25	A	A	A	A	A
26	A	A	A	A	A
27	A	A	A	A	A
28	A	A	A	B	A
29	D	D	D	D	D
30	A	A	A	A	A
31	B	C	C	C	C
32	A	A	A	A	A
33	B	B	B	B	B
34	D	D	D	D	D
35	C	C	C	C	C
36	C	D	D	C	
37	A	A	A	A	A
38	A	B	B	B	B

39	B	B	B	B	B
40	A	A	A	A	A
41	A	B	B	B	B
42	A	A	A	A	A
43	B	B	B	B	B
44	A	A	A	A	A
45	A	A	A	A	A
46	A	A	A	A	A
47	A	A	A	A	A
54	A	A	A	A	A
61	A	A	A	A	A
62	A	A	A	A	A
63	A	A	A	A	A
64	A	A	A	A	A
65	A	A	A	A	A
66	A	A	A	B	A
67	A	A	A	A	A
68	A	A	A	A	A
69	A	A	A	A	A
70	A	A	A	A	A
93	B	B	B	C	B
94	D	D	D	D	D
95	A	A	A	A	A
96	A	A	A	B	A
97	C	C	D	D	C
98	A	A	A	A	A
99	C	D	C	D	C
100	A	A	A	A	A
101	B	B	B	C	C
102	B	B	B	B	B
103	A	A	A	A	A
104	A	A	A	A	A

105	A	A	A	B	A
106	A	A	A	A	A
107	B	C	B	C	B
108	C	B	B	C	B
109	D	D	D	D	D
110	D	D	D	D	D
111	D	D	D	D	D
114	A	A	A	A	A
115	A	A	A	A	A
117	B	B	B	B	B
118	A	A	A	A	A
119	A	A	A	A	A
120	B	B	B	B	B
121	A	A	A	A	A
122	A	A	A	A	A
123	A	A	A	A	A
124	A	A	A	A	A
125	A	A	A	A	A
126	A	A	A	A	A
127	A	A	A	A	A
128	A	A	A	A	A
129	A	A	A	A	A
130	A	A	A	A	A
131	A	A	A	A	A
132	A	A	A	A	A
133	A	A	A	A	A
134	A	A	A	A	A
135	A	A	A	A	A
136	A	A	A	A	A
137	A	A	A	A	A
138	A	A	A	A	A
500	B	B	B	B	B

501	A	A	A	A	A
502	A	A	A	A	A
503	A	A	A	A	A
504	A	A	A	B	B
505	A	A	A	A	A
506	A	A	A	A	A
507	A	A	A	A	A
508	A	A	A	A	A
509	A	A	A	A	A
510	A	A	A	A	A
511	A	A	A	A	A
512	A	A	A	A	A
513	A	A	A	A	A
514	A	A	A	A	A
515	A	A	A	A	A
516	A	A	A	A	A
526	A	A	A	A	A
527	A	A	A	A	A
528	A	A	A	A	A
529	A	A	A	A	A
530	A	A	A	A	A
531	A	A	A	A	A
532	-	-	-	-	-
533	A	A	A	A	A
534	A	A	A	A	A
535	A	A	B	A	A
536	A	A	A	A	A
545	A	A	A	A	A
546	A	A	A	A	A
547	A	A	A	A	A
548	B	B	B	B	B
549	A	A	A	A	A

550	A	A	A	A	A
551	A	A	A	A	A
552	B	C	C	C	C
560	A	A	A	A	A
561	A	A	A	B	A
562	D	D	D	D	D
563	A	A	A	A	A
564	A	A	A	A	A
565	B	B	B	B	B
567	A	A	A	A	A
568	B	B	B	B	B
569	A	A	A	A	A
570	A	A	A	A	A
571	A	A	A	A	A
572	B	B	B	B	B
573	A	A	A	A	A
574	A	A	A	A	A
575	A	A	A	A	A
576	A	A	A	A	A

Table 16: KRAS cellular assay results for selected compounds

The symbol "A" indicates an IC_{50} less than 50 nM. The symbol "B" indicates an IC_{50} in the range of greater than or equal to 50 nM to 1,000 nM. The symbol "C" indicates an IC_{50} in the range of greater than or equal to 1,000 nM to 10,000 nM. The symbol "D" indicates an IC_{50} greater than or equal to 10,000 nM.

Compound Number	G12D pERK (nM)	G12V pERK (nM)
1	B	B
2	A	A
3	A	A
4	B	B
5	D	D
6	C	C
7	C	B
8	D	D
9	D	D
10	C	C
11	C	C
12	D	D
13	C	D
14	C	C
15	B	C
16	A	A
18	D	D
19	B	B
20	A	A
21	C	C
22	B	B
23	C	C
24	C	C
25	B	B
26	B	B

27	B	B
28	B	C
29	D	D
30	B	B
31	D	D
32	C	C
33	C	C
34	D	D
35	D	D
36	D	D
37	C	C
38	C	C
39	D	D
40	D	C
41	C	C
42	B	B
43	C	C
44	B	B
45	A	A
46	A	B
47	C	C
48	B	B
49	D	D
50	A	B
51	C	C
52	B	B
53	D	D
54	A	A
55	A	A
56	D	D
57	B	B
58	C	C

59	A	A
60	C	C
61	A	A
62	B	B
63	B	B
64	A	A
65	A	A
66	C	C
67	B	B
68	A	A
69	B	A
70	A	A
71	A	A
72	A	A
73	A	A
74	A	A
75	A	B
76	A	A
77	B	B
78	A	A
93	C	D
94	D	D
95	B	B
96	C	C
97	D	D
98	B	B
99	D	D
100	B	B
101	D	D
102	B	B
103	A	A
104	A	A

105	C	C
106	B	B
107	C	C
108	D	C
109	C	C
110	C	C
111	D	D
114	B	B
115	A	A
117	C	B
118	A	A
119	A	A
120	B	B
121	B	C
122	A	B
123	B	B
124	A	A
125	B	B
126	A	A
127	A	A
128	A	A
129	A	A
130	A	A
131	A	A
132	A	A
133	A	A
134	A	B
135	A	B
136	A	A
137	A	A
138	A	A
500	B	B

501	A	A
502	A	A
503	B	C
504	D	C
505	A	A
506	A	A
507	A	A
508	A	A
509	A	A
510	A	A
511	A	A
512	A	A
513	A	A
514	A	A
515	A	A
516	A	A
526	B	B
527	A	A
528	A	A
529	A	A
530	A	A
531	B	B
532	A	D
533	B	B
534	A	A
535	B	B
536	B	B
545	A	A
546	A	A
547	A	B
548	B	C
549	A	B

550	B	B
551	A	A
552	C	D
560	A	B
561	B	B
562	D	D
563	A	A
564	A	A
565	C	C
567	A	A
568	A	A
569	A	A
570	A	A
571	A	A
572	D	D
573	A	A
574	A	A
575	A	A
576	B	B

Phosphorylated ERK (pERK) HTRF Cell Assay for KRAS cell panel

NCI-H2009 (KRAS G12A), H358 (KRAS G12C), AsPC-1 (KRAS G12D), PSN1 (KRAS G12R), A549 (KRAS G12S), SW480 (KRAS G12V), HCT116 (KRAS G13D), NCI-H460 (KRAS Q61H), and PC-9 (KRAS WT) cells were plated at appropriate densities for 70% - 80% confluence. The following day, cells were treated with compound using three-fold serial dilutions ranging from 10 μM to .5 nM for 4 hours at 37°C, 5% CO_2.

Post-treatment, cell lysates were prepared and phospho-ERK was measured using the HTRF Advanced Phospho-ERK (Thr202/Tyr204) detection kit. Lysis buffer containing 1x phosphor and total protein blocking reagent was added, and cells were incubated for 40 min. at 4°C under shaking conditions. Plates were centrifuged at 1500 rpm for 3 min. and cell lysates were transferred to a detection plate with premixed antibody solutions. Plates were centrifuged at 1000 rpm for 1 min, incubated at 25°C for 120 min, followed by an overnight incubation at 4°C. The plates were read on the EnVision or the PHERAstar multimode plate reader via HTRF

dual wavelength detection.

For data analysis, the 100 percent of control (POC) was determined using DMSO treated samples, and 0 POC was determined using the top concentration of a control compound. A 4-parameter logistic curve was fitted to the POC values as a function of compound concentration to determine the IC_{50} value.

Table 17. Phosphorylated ERK (pERK) HTRF cell assay data.

Cell Type	Tumor Type	Mutation	Cmpd 2	Cmpd 73	Cmpd 71	Cmpd 55	Cmpd 69	Cmpd 19	Cmpd 74
PC9	Lung Adenocarcinoma	KRAS WT	14	0.51	0.51	58	0.51	1130	0.50
NCI-H2009	Lung Adenocarcinoma	KRAS G12A	0.12	0.51	0.51	4	0.51	13	0.18
H358	Lung Adenocarcinoma	KRAS G12C	0.25	0.51	0.51	17	0.51	64	0.23
AsPC-1	Pancreatic Cancer	KRAS G12D	0.64	0.28	0.34	13	0.79	102	0.26
A549	Lung Adenocarcinoma	KRAS G12S	0.13	0.51	0.51	14	0.51	37	0.17
SW480	Colorectal Cancer	KRAS G12V	0.57	0.32	0.25	18	0.84	89	0.31
HCT116	Colorectal Cancer	KRAS G13D	0.66	0.51	0.51	53	0.51	115	0.29
NCI-H460	Lung Adenocarcinoma	KRAS Q61H	0.15	0.51	0.51	9	0.51	26	0.17

Phosphorylated ERK (pERK) HTRF Cell Assay for EGF Challenge KRAS (ON) assay

AsPC-1 (KRAS G12D), and SW480 (KRAS G12V) were cultured in RPMI1640 with 10% fetal bovine serum. Cells were plated into a 384-well cell culture plate at cell densities of 6,000 cells/well. The following day, cells were stimulated with EGF (50ng/mL) for 30 minutes at 37°C, 5% CO_2. Cells were then treated with compound using three-fold serial dilutions ranging from 10 μM to .5 nM for 2 hours at 37°C, 5% CO_2.

Post-treatment, cell lysates were prepared and phospho-ERK was measured using a HTRF phospho-ERK (Thr202/Tyr204) detection kit. Lysis buffer containing 1x phosphor and total protein blocking reagent was added, and cells were incubated for 40 min. at 4°C under shaking conditions. Plates were centrifuged at 1500 rpm for 3 min. and cell lysates were transferred to a detection plate with premixed antibody solutions. Plates were centrifuged at 1000 rpm for 1 min, incubated at 25°C for 120 min, followed by an overnight incubation at 4°C. The plates were read on the EnVision or the PHERAstar multimode plate reader via HTRF dual wavelength detection.

For data analysis, the 100 percent of control (POC) was determined using DMSO treated samples, and 0 POC was determined using the top concentration of a control compound. A 4-parameter logistic curve was fitted to the POC values as a function of compound concentration to determine the IC_{50} value.

Table 18. Representative compounds of the inventions are nM inhibitors of mutant KRAS cell lines forced into the active GTP KRAS(ON) state.

Cellular (+/-) EGF Challenge				
Compound	Cell Line	(-) EGF IC_{50}	(+) EGF IC_{50}	Fold Change
Representative Compound A	AsPC-1 (G12D)	1.3 nM	5.2 nM	4.1x
	SW480 (G12V)	2.6 nM	7.9 nM	3.0x
Representative Compound B	AsPC-1 (G12D)	1.1 nM	3.4 nM	2.5X
	SW480 (G12V)	2.4 nM	6.0 nM	3.2X

Mechanistic cellular assay in the presence of EGF forces KRAS into the active GTP KRAS(ON) state and provides a direct measurement of GTP KRAS(ON) inhibition (*see* Beltran, P. J. et. al., (2024, April 5-10) *BBO-8520, a first-in-class, direct inhibitor of* $KRAS^{G12C}$ *(ON), locks GTP-bound* $KRAS^{G12C}$ *in the state 1 conformation resulting in rapid and complete blockade of effector binding* [Conference abstract]. American Association for Cancer Research Annual Meeting 2024, San Diego, CA, United States). Minimal shift in IC_{50}s of a representative compound of the inventions (+/-) EGF challenge for both Aspc1(G12D) and SW480(G12V) lines indicates a KRAS(ON) mechanism. These data for a representative

compound of the inventions mirror the data of the tricomplex RAS(ON) inhibitor RMC-6236 both in IC_{50} potency and fold change (+/-) EGF.

Surface Plasmon Resonance (SPR) Binding Assays

Protein Immobilization

Custom made biotinylated Avi-tagged KRAS, HRAS and NRAS proteins were immobilized onto a streptavidin sensor chip mounted in a Biacore 1K+ according to the standard immobilization protocol, including three conditioning steps with 1 M NaCl in 50 mM NaOH. The proteins were diluted to 5 μg mL^{-1} in running buffer (10mM HEPES pH 7.5, 150mM NaCl, 0.05% v/v Tween-20; 5 mM $MgCl_2$, 1% v/v DMSO) and approximately 1200 RU of protein was immobilized in a single flow cell using the "Aim for" function. A "blank" channel was also prepared using the "Blank Immobilization" option; the channel was conditioned three times as for the active channel, but no protein sample was applied.

Off-state SPR Binding Assay

GDP was included in the running buffer at a final concentration of 500 nM. The assay was run at 25° C with a data collection rate of 10 Hz and the flow rate set to 30 μL min^{-1}. Compound samples were prepared as six concentrations in 3-fold serial dilutions in 96 well plates using a D300e dispenser and DragonFly dispenser. All samples were injected over both a reference surface and the active protein surface. Samples were injected using the single cycle kinetic command with each association lasting 300 s, followed by a single dissociation phase lasting 7200 s, followed by a regeneration step with glycine pH 3 for 30 s. Solvent correction samples were injected once at the beginning of the assay, and once at the end. Data was analyzed using the Biacore Evaluation Software, and all data was fit using a 1:1 kinetic binding model.

On-chip Nucleotide Exchange and On-state SPR binding Assay

GMppCp was included in the running buffer at a final concentration of 10 μM instead of GDP. Proteins were immobilized as described above. To exchange the GDP-bound proteins to GMppCp-bound, 1000nM SOS1 protein was injected for 800 s at 30 μL min^{-1}. Exchange was confirmed by injecting 100nM cRAF protein for 60 s with a 120 s dissociation at 30 μL min^{-1} to verify cRAF association with each RAS protein. Compound binding was assessed as described above for the Off-state binding assay.

Table 19. Representative Compounds of A and B of the inventions show nM binding to KRAS(ON) with selectivity over H/NRAS

RAS(ON) SPR Binding Assay K_D								
	KRAS						HRAS	NRAS
	WT	G12V	G12D	G12C	G13D	Q61H	WT	WT
Representative Compound A	1.3 nM	1.6 nM	0.6 nM	0.3 nM	1.1 nM	1.9 nM	>5000 nM	>5000nM
Representative Compound B	1.1 nM	3.3 nM	0.7 nM	0.9 nM	0.7 nM	1.2 nM	>5000 nM	>5000 nM

RAS(OFF) SPR Binding Assay K_D								
	KRAS						HRAS	NRAS
	WT	G12V	G12D	G12C	G13D	Q61H	WT	WT
Representative Compound A	0.006 nM	0.010 nM	0.005 nM	0.023 nM	0.008 nM	0.007 nM	29 nM	131 nM
Representative Compound B	0.002 nM	0.001 nM	0.0003 nM	0.03 nM	0.001 nM	0.005 nM	7.7 nM	35 nM

Kinetic SPR binding assay of representative compounds of the inventions to WT and mutant KRAS(ON) are loaded with the GTP stable analog GMPPCP. The data in Table 8 confirms a representative compound of the inventions binds to active forms of KRAS(ON), consistent with crystallographic data. Similar SPR experiment with HRAS and NRAS shows >1000x selectivity for KRAS(ON) over H/NRAS isoforms. Selectivity for KRAS over other RAS isoforms may provide tolerability advantages vs. Pan-RAS inhibition. Barbicid et. al. reported that the genetic deletion of H-, N-, and K-RAS in mice stopped proliferation, and induced senescence in keratinocytes, leading to severe hypoproliferation in vivo.

Mouse PK AUC and S9 Comparison between prodrug and parent

Table 20. Mouse PK AUC and S9 comparison between prodrug and parent, compound 2

Parent	**Compound #**	**Parent AUC_{last} (ng*hr/mL)[a]**	**Prodrug AUC_{last} (ng*hr/mL)**	**Relative Parent AUC From Prodrug[b]**	**Prodrug / Parent Ratio**	**Mouse Intestinal/Liver S9 % remaining (T=60 min)[c, d]**
2	84	303	ND	0.7X	ND	0 / 0
(AUC_{last}=432	159	91	4477	0.2X	10X	89 / 91

ng*hr/mL)	156	77	7435	0.2X	17X	92 / 89
	145	379	5069	0.9X	12X	82 / 64
	140	623	482	1.4X	1.1X	02/ 02
	177	175	1533	0.4X	3.5X	14 / 11
	144	476	1651	1.1X	3.8X	01 / 37
	184	ND	3714	ND	8.6X	99 / 100

a- Dosing 30 mg/kg PO of parent in mouse b- (Parent AUC from prodrug)/(Parent AUC from direct)

c- No cofactor only (Hydrolysis)

d-% compound remaining after preincubation with S9 fraction for 60 minutes

Table 21. Mouse PK AUC and S9 comparison between prodrug and parent, compound 74

Parent	cmpd #	Parent AUC_{last} (ng*hr/mL)[a]	Prodrug AUC_{last} (ng*hr/mL)	Relative Parent AUC From Prodrug[b]	Prodrug / Parent Ratio	Mouse Intestinal/Liver S9 % remaining (T=60 min)[c, d]
74 (AUC_{last}=1718 ng*hr/mL)	306	295	13276	0.2X	8X	78 / 87
	350	1790	1997	1X	1.2X	75 / 46
	365	104	4690	0.1X	2.7X	71 / 63

a- Dosing 30 mg/kg PO of parent in mouse b- (Parent AUC from prodrug)/(Parent AUC from direct)

c- No cofactor only (Hydrolysis)

d-% compound remaining after preincubation with S9 fraction for 60 minutes

S9 Assay materials and methods (liver and intestine)

Test Compounds:

No.	Compound ID	Batch No	Stock Conc.(mM)	Final Conc.(μM)
1	11	11	10	1
2	12	12	10	1
3	13	13	10	1
Control	7-hydroxycoumarin	NA	10	1
Control	mycophenolate mofetil	NA	10	1

Experimental Procedure:

Buffer Preparation: 73.21 g $K_2HPO_4•3H_2O$ (AR grade) and 10.78 g KH_2PO_4 (AR grade) were dissolved in ultra-pure water. The final volume was 4000 mL and concentration was 100 mM. The pH value of the final solution was adjusted to pH 7.40±0.10 with H_3PO_4/KOH. Test Compound and Control Working Solution Preparation: 5 μL of compound stock solution (10 mM in dimethyl sulfoxide (DMSO)) were diluted with 495 μL of ACN (intermediate solution concentration: 100 μM)

Intestinal S9 Preparation:

Intestinal S9 Information			
S9	**Product information**	**Source**	Abbreviation
CD-1 Mouse intestinal S9	Cat. No. M1000.IS9(NP) Lot No. 2210131	Xenotech	MIS9

Liver S9 Information			
S9	**Product information**	**Source**	Abbreviation
CD-1 Mouse liver S9	Cat. No. M1000.S9 Lot No. 2210244	Xenotech	MLS9

Preparation Procedure:

Content of intestinal S9 mixture	Volume(μL)	Working Conc.	Final Conc.
MIS9 (4 mg-protein/mL)	1250	1.0 mg/ml	0.5 mg/ml
100 mM PB Buffer	3750	-	-
Total volume	5000	-	-

Content of liver S9 mixture	Volume(μL)	Working Conc.	Final Conc.
MLS9 (20 mg-protein/mL)	710	2.0 mg/ml	1.0 mg/ml
100 mM PB Buffer	6390	-	-
Total volume	7100	-	-

Stop Solution Preparation: Cold (4°C) acetonitrile (ACN) containing 250 nM tolbutamide and 250 nM labetalol as internal standards (IS) was used as the stop solution.

Assay Procedure: An Apricot automation workstation was used to add 100 µL/well of IS9 solution to all reaction plates (Blank, T0, T5, T15, T30, T45 and T60). An Apricot automation workstation was used to add 600 µL/well of stop solution to T0 reaction plate. Using an Apricot automation workstation,98 µL/well of 100 mM PB were added to all 96-well reaction plates (Blank, T0, T5, T15, T30, T45, T60). All reaction plates containing mixtures of buffer and IS9 were pre-incubated at 37°C for 10 minutes. After pre-incubation, an Apricot automation workstation was used to add 2 µL/well of compound working solution to every reaction plate except Blank (T0, T5, T15, T30, T45 and T60) to start the reaction. The reaction plates were incubated at 37°C, and timer was started. An Apricot automation workstation was used to add 600 µL/well of stop solution to each reaction plate at its appropriate end time point to terminate the reaction. Each plate was sealed and shaken for 10 minutes. After shaking, each plate was centrifuged at 4000 rpm and 4°C for 20 minutes. During centrifugation, an Apricot automation workstation was used to add 300 µL/well of HPLC water to eight new 96-well plates. After centrifugation, an Apricot automation workstation was used to transfer 100 µL of supernatant from each reaction plate to its corresponding bioanaylsis plate. Each bioanalysis plate was sealed and shaken for 10 minutes prior to LC-MS/MS analysis

Final Concentration of Each Component in Incubation Medium	
Component	**Concentration**
IS9	0.5 mg protein/mL
Test Compound	1 µM
Control Compound	1 µM
ACN	0.99%
DMSO	0.01%

Reaction Plates Incubation		
Time Point	**Start Time**	**End Time**
Blank	1:00:00	0:00:00
T60	1:00:00	0:00:00
T45	0:45:00	0:00:00
T30	0:30:00	0:00:00
T15	0:15:00	0:00:00
T5	0:05:00	0:00:00
T0	Stop solution was added prior to compounds and cofactor solutions	

Data Analysis:

The equation of first order kinetics was used to calculate T1/2 and $CL_{int(S9)}$ (μL/min/mg):

Equation of first order kinetics:

$$C_t = C_0 \bullet e^{-k_e \bullet t}$$

$$when\ C_t = \frac{1}{2} C_0\ ,$$

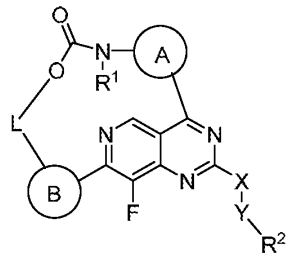
$$T_{1/2} = \frac{Ln2}{k_e} = \frac{0.693}{k_e}$$

$CL_{int(S9)}$ = 0.693 / $T_{1/2}$ / mg S9 protein per mL

CLint(liver) = CLint(S9) × mg S9/g liver weight × g liver weight/kg body weight

Listing of Claims:

1. A compound having the following structure of Formula (I):



(I)

or a stereoisomer of the compound, salt of the compound or tautomer of the compound thereof;

wherein:

A is 4-11 membered heterocyclylene, wherein the 4-11 membered heterocyclylene is optionally substituted;

B is an arylene or 5-14 membered heteroarylene, wherein the arylene or 5-14 membered heteroarylene is optionally substituted, wherein the 5-14 membered heteroarylene is not indazolylene;

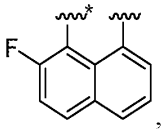
R^1 is a hydrogen or C_1-C_3 alkyl;

R^2 is a hydrogen, 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, -(C_1-C_3 alkylene)-heteroaryl, aryl fused to 4-8 membered heterocyclyl, or amine, wherein the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, 4-8 membered heterocyclyl, or amine is optionally substituted;

L is C_1-C_8 alkylene, C_2-C_8 alkenylene, C_2-C_8 alkynylene, or C_1-C_8 heteroalkylene. wherein the C_1-C_8 alkylene, C_2-C_8 alkenylene, C_2-C_8 alkynylene, or C_1-C_8 heteroalkylene is optionally substituted;

X is -O-, -NR^3-, or a direct bond, wherein R^3 is a hydrogen or C_1-C_3 alkyl; and

Y is C_1-C_5 alkylene, C_1-C_5 deuteroalkylene, or a direct bond, wherein the C_1-C_5 alkylene or C_1-C_5 deuteroalkylene is optionally substituted, wherein:

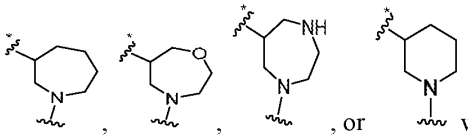
when B is , L is not C_2 alkylene, wherein ~~* indicates the location

of a bond to L and ~~ indicates the location of a bond to the pyridine group.

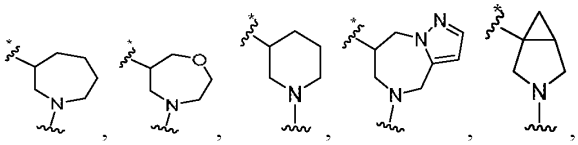
2. The compound of claim 1, wherein the 4-11 membered heterocyclylene of A is pyrrolidinylene, piperidinylene, morpholinylene, azepanylene, oxazepanylene, or diazepanylene.

3. The compound of claim 1, wherein the 4-11 membered heterocycloalkylene of A is azepanylene, piperidinylene, or oxazepanylene.

4. The compound of claim 1, wherein the 4-11 membered heterocycloalkylene of A has one of the following structures:

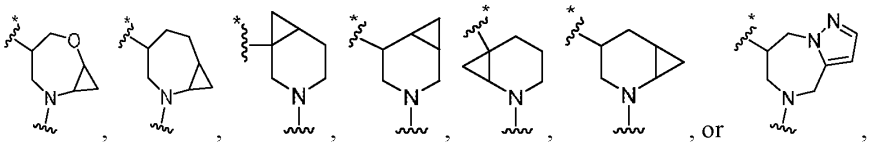

, wherein ~~* indicates the location of a bond to the carbamate group and ~~ indicates the location of a bond to the pyrimidine group.

5. The compound of claim 1, wherein the 4-11 membered heterocycloalkylene of A has one of the following structures:


, wherein ~~* indicates the location of a bond to the carbamate group and ~~ indicates the location of a bond to the pyrimidine group, wherein the 4-11 membered heterocycloalkylene is optionally substituted.

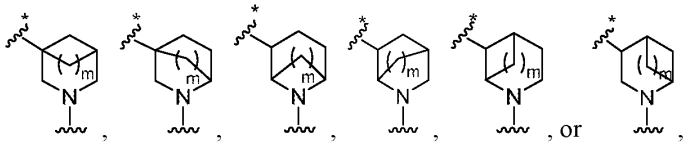
6. The compound of claim 1, wherein the 4-11 membered heterocyclylene of A is a fused bicyclic heterocyclylene or a bridged bicyclic heterocyclylene.

7. The compound of claim 6, wherein the fused bicyclic heterocyclylene has one of the following structures:


, wherein

~~* indicates the location of a bond to the carbamate group, and ~~ indicates the location of a bond to the pyrimidine group.

8. The compound of claim 6, wherein the bridged bicyclic heterocyclylene has one of the following structures:


, wherein m is 1 or 2 and ~~* indicates the location of a bond to a carbamate group, and ~~ indicates the location of a bond to the pyrimidine group.

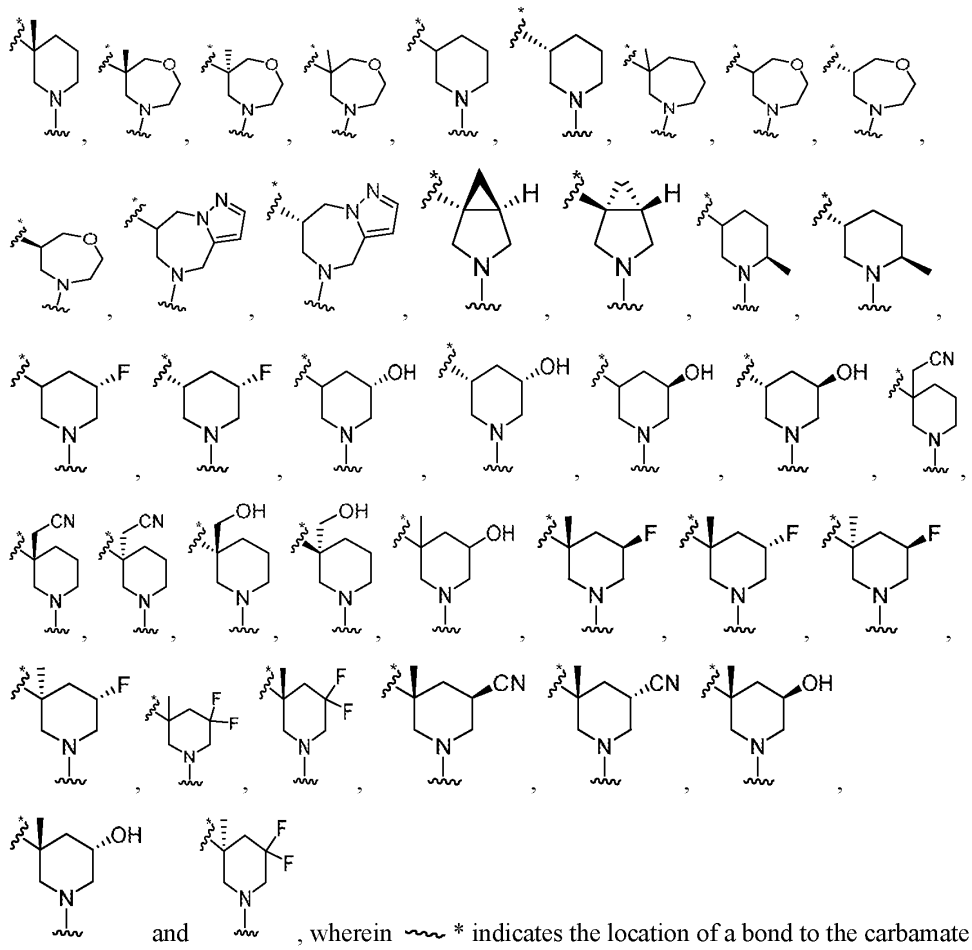
9. The compound of any one of claims 1-8, wherein the 4-11 membered heterocyclylene of A is substituted with one or more substituents each independently selected from C_1-C_4 alkyl, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, C_1-C_4 alkylene-CN, halo, amine, hydroxyl, -and $C(=O)CH_3$.

10. The compound of any one of claims 1-8, wherein the 4-11 membered heterocyclylene of A is substituted with one or more substituents each independently selected from $-CH_3$, $-CD_3$, -D, -F, -CN, $-CH_3CN$, $-NH_2$, $-CH_2OCH_3$, $-OCH_3$, $-CF_2H$, $-CF_3$, -OH, $-C_1$-C_3 alkylalcohol, and C_1-C_3 alkoxyl.

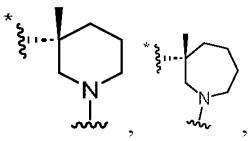
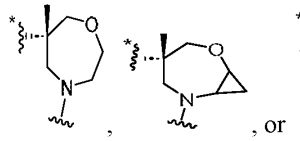
11. The compound of any one of claims 1-8, wherein the 4-11 membered heterocyclylene of A is substituted with one or more substituents each independently selected from $-CH_3$, -F, -OH, $-CH_2CN$, and $-CH_2OH$.

12. The compound of any one of claims 1-8, wherein the 4-11 membered heterocyclylene of A is substituted with one or more substituents each independently selected from $-C_1$-C_4 alkyl, -OH, -halo and -CN.

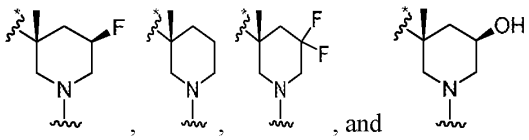
13. The compound of claim 1, wherein A is selected from the group consisting of:



and , wherein * indicates the location of a bond to the carbamate group and indicates the location of a bond to the pyrimidine group.

14. The compound of any one of claims 1-13, wherein A is  ,  , or , wherein * indicates the location of a bond to a carbamate group and indicates the location of a bond to the pyrimidine group.

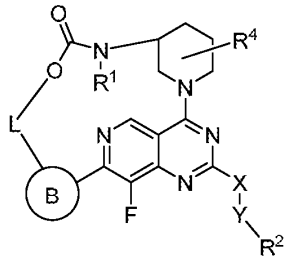
15. The compound of claim 1, wherein A is selected from the group consisting of:



, and , wherein * indicates the location of a bond to the carbamate group and indicates the location of a bond to the pyrimidine group.

16. The compound of any one of claims 1-14, wherein B is an arylene or 5-10 membered heteroarylene, wherein the arylene or 5-10 membered heteroarylene is optionally substituted, wherein the 5-10 membered heteroarylene is not indazolylene.

17. The compound of claim 1, wherein the compound has the following structure of Formula (IA):



(IA)

wherein:

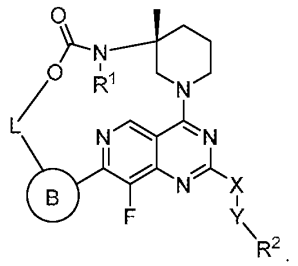
R^4 is a hydrogen, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, or -C(=O)CH_3;

and wherein the remaining variables are as defined in claim 1.

18. The compound of claim 14, wherein R^4 is -H, -CH_3, -F, -Cl, -CN, -NH_2, -CH_2OCH_3, -OCH_3, -CF_2H, -CF_3, -OH, -C_1-C_3 alkylalcohol, C_1-C_3 alkoxyl, or -C(=O)CH_3.

19. The compound of claim 17 or 18, wherein R^4 is -CH_3.

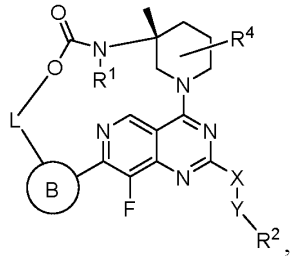
20. The compound of claim 16, wherein the compound has the following structure of Formula (IA-2):



(IA-2)

wherein the variables are as defined in claim 1.

21. A compound having the following structure of Formula (IA-3):



(IA-3)

or a stereoisomer of the compound, tautomer of the compound, or a pharmaceutically acceptable salt thereof, wherein:

R^4 is -H;

B is an arylene or heteroarylene, wherein the arylene or heteroarylene is optionally substituted;

R^1 is a hydrogen or C_1-C_3 alkyl;

R^2 is a hydrogen, 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, -(C_1-C_3 alkylene)-heteroaryl, aryl fused to 4-8 membered heterocyclyl, or amine, wherein the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, 4-8 membered heterocyclyl, or amine is optionally substituted;

L is C_1-C_8 alkylene, C_1-C_8 alkenylene, C_1-C_8 alkynylene, or C_1-C_8 heteroalkylene. wherein the C_1-C_8 alkylene, C_1-C_8 alkenylene, C_1-C_8 alkynylene, or C_1-C_8 heteroalkylene is optionally substituted;

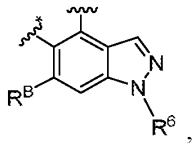
X is -O-, -NR^3-, or a direct bond, wherein R^3 is a hydrogen or C_1-C_3 alkyl; and

Y is C_1-C_5 alkylene, C_1-C_5 deuteroalkylene, or a direct bond, wherein the C_1-C_5 alkylene or C_1-C_5 deuteroalkylene is optionally substituted,

or a stereoisomer of the compound, salt of the compound or tautomer of the compound thereof.

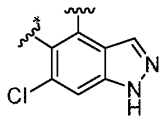
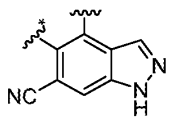
22. The compound of claim 21, wherein B is arylene or 5-18 membered heteroarylene.

23. The compound of claim 21, wherein B is arylene or 5-14 membered heteroarylene.

24. The compound of claim 21, wherein B is , wherein ~* indicates the location of a bond to L and ~ indicates the location of a bond to the pyridine group, wherein

R^B is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O- C_1-C_4 alkylene, halo, hydroxyl, $-C(=O)CH_3$, NH_2, $-NH(CH_3)$, $N(CH_3)_2$;

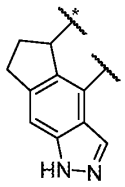
R^6 is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$ wherein R^{X1}, R^{X2}: are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, and wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy can be substituted with: C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, -$C(O)NR^{X3}R^{X4}$ wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, or prodrug moiety R^5.

25. The compound of claim 21, wherein B is  or , wherein ~* indicates the location of a bond to L and ~ indicates the location of a bond to the pyridine group.

26. The compound of any one of claims 1-25, wherein the arylene of B is a phenylene or naphthylene.

27. The compound of any one of claims 1-25, wherein the heteroarylene of B is a pyridinylene.

28. The compound of any one of claims 1-25, wherein the heteroarylene of B is



, wherein ~~* indicates the location of a bond to the carbamate group and ~~ indicates the location of a bond to the pyrimidine group.

29. The compound of any one of claims 1-28, wherein the arylene or heteroarylene of B is optionally substituted with one or more substituents each independently selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, alkylene-cyclyl, heterocyclyl, aryl, heteroaryl, and a prodrug functional moiety R^5, wherein the alkylene-cyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy, wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy is optionally substituted with C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, or -C(O)$NR^{X3}R^{X4}$, wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy.

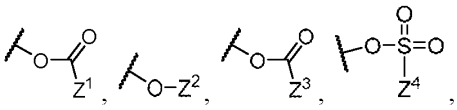
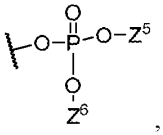
30. The compound of any one of claims 1-29, wherein the arylene or heteroarylene of B is optionally substituted with one or more substituents each independently selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, C_1-C_4 alkylene-C_6-C_{10} aryl, C_1-C_4 alkylene-(5-10 membered heteroaryl), C_1-C_4 alkylene-C_3-C_{10} cycloalkyl, C_1-C_4 alkylene-(3-10 membered heterocyclyl), 3-10 membered heterocyclyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, and a prodrug functional moiety R^5, wherein the C_1-C_4 alkylene-C_6-C_{10} aryl, C_1-C_4 alkylene-(5-10 membered heteroaryl), C_1-C_4 alkylene-C_3-C_{10} cycloalkyl, C_1-C_4 alkylene-(3-10 membered heterocyclyl), 3-10 membered heterocyclyl, C_6-C_{10} aryl, or 5-10 membered heteroaryl is optionally substituted, wherein R^{X1}, R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy and wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-}

$_{4}$alkoxy is optionally substituted with C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl , heterocyclyl, or -C(O)$NR^{X3}R^{X4}$, wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy.

31. The compound of any one of claims 1-30, wherein the arylene or heteroarylene of B is optionally substituted with one or more substituents each independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, CN and a prodrug functional moiety R^5.

32. The compound of any one of claims 1-31, wherein the arylene or heteroarylene of B is substituted with one or more substituents each independently selected from C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, and a prodrug functional moiety R^5.

33. The compound of any one of claims 1-30, wherein the arylene or heteroarylene of B is substituted with one or more substituents each independently selected from -CH_3, -F, -Cl, -CN, -NH_2, -CH_2OCH_3, -OCH_3, -CF_2H, -CF_3, -OH, -C_1-C_3 alkylalcohol, C_1-C_3 alkoxyl, and a prodrug functional moiety R^5.

34. The compound of any one of claims 1-33, wherein the prodrug functional moiety R^5 is selected from the group consisting of , and , wherein:

Z^1 and Z^4 are each independently

(i) -$NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, C_{1-4} heteroalkyl, or aryl wherein the alkyl, haloalkyl, alkoxy, heteroalkyl, aryl is optionally substituted with C_{1-4} alkyl, C_{1-4} haloalkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, or -C(O)$NR^{X3}R^{X4}$, wherein the heteroaryl is optionally substituted with C_{1-4} alkyl, R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy;

(ii) optionally substituted monocyclic, fused or bridged bicyclic 4-11 membered N-containing heterocyclyl or 4-11 membered N-containing heteroaryl, wherein the point of

attachment is on N;

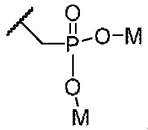
(iii) optionally substituted C_{1-8} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, or C_{1-6} heteroalkylene;

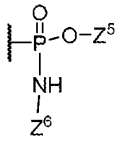
(iv) optionally substituted 4-8 membered cycloalkyl, 4-10 membered aryl; or

(v) -OM, wherein M is a metal;

Z^2 is

(i) R″, (R)—O—(R), (R)—S—(R), (R)—O—(R)-X, (R)—S—(R)-X, wherein the X is optionally substituted cycloalkyl, heterocyclyl, aryl, heteroaryl, (R)—O—C(O)—R′, or (R)—O—C(O)—O—R′, wherein R″ is optionally substituted C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} heteroalkyl, wherein R is optionally substituted C_{1-8} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, or C_{1-6} heteroalkylene; wherein R′ is optionally substituted -$NR^{X1}R^{X2}$, C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-8} haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, wherein R^{X1} and R^{X2} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy;

(ii)  , where M is a metal;

(iii) 

(iv) optionally substituted 4-10 membered aryl, 4-11 membered heteroaryl, 4-8 membered cycloalkyl, 4-10 membered heterocyclyl;

Z^3 is

(i) R″, which is optionally substituted C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-6} heteroalkyl; or

(ii) amino acid residue; or

(iii) optionally substituted 4-10 membered aryl, 4-11 membered heteroaryl, 4-8 membered cycloalkyl or 4-10 membered heterocyclyl;

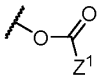
Z^5 and Z^6 are each independently

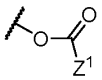
(i) hydrogen; or

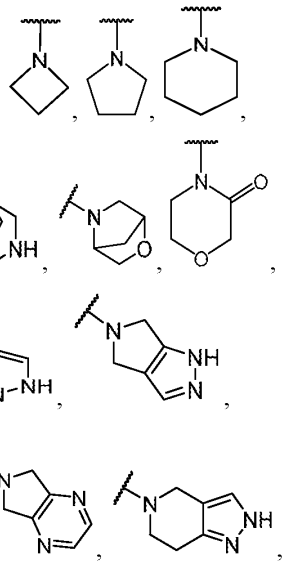
(ii) R″, (R)—O—(R), (R)—S—(R), (R)—O—(R)-X, (R)—S—(R)-X, wherein the X is optionally substituted cycloalkyl, heterocyclyl, aryl, heteroaryl, (R)—O—C(O)—R′, or (R)—O—C(O)—O—R′, wherein R″ is optionally substituted C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6}

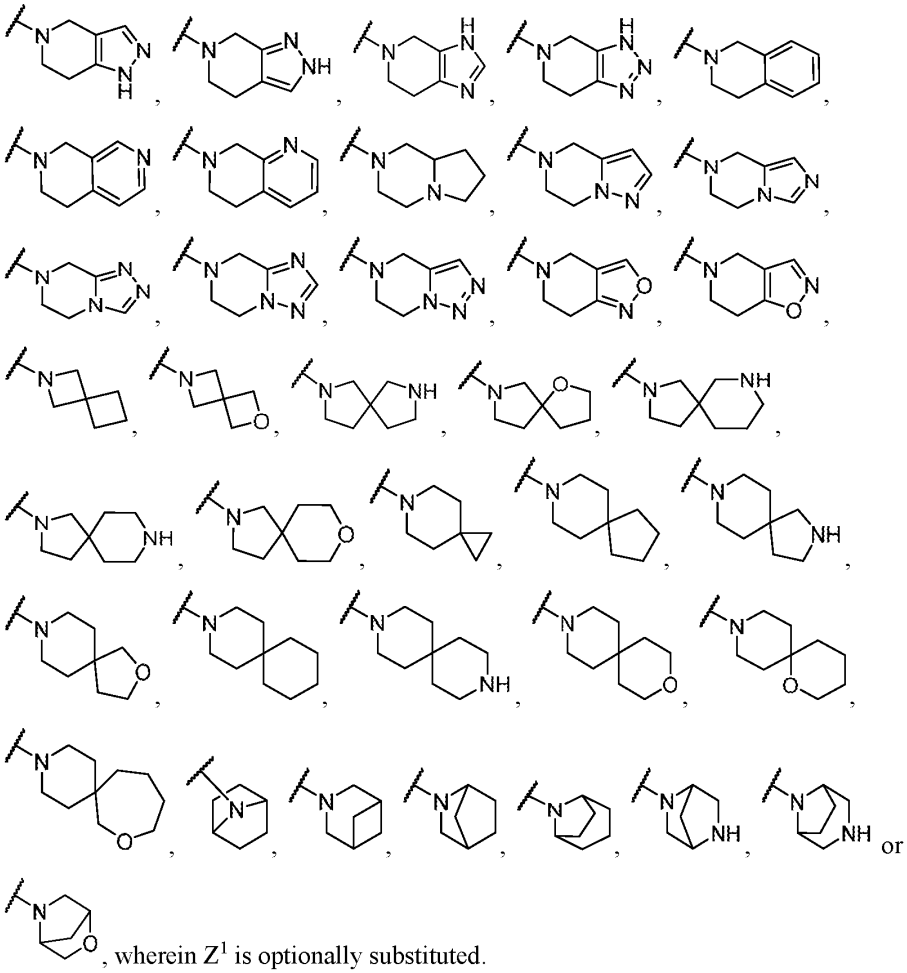
alkynyl, or C_{1-6} heteroalkyl, wherein R is optionally substituted C_{1-8} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, or C_{1-6} heteroalkylene; wherein R′ is optionally substituted -$NR^{X1}R^{X2}$, C_{1-8} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-8} haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, wherein R^{X1} and R^{X2} are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy; or

(iii) optionally substituted 4-10 membered aryl, 4-11 membered heteroaryl, 4-8 membered cycloalkyl or 4-10 membered heterocyclyl.

35. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 is , wherein Z^1 is monocyclic, fused or bridged bicyclic 4-11 membered N-containing heterocyclyl or 4-11 membered N-containing heteroaryl optionally substituted with 0 to 4 substituents, wherein the point of attachment is on N.

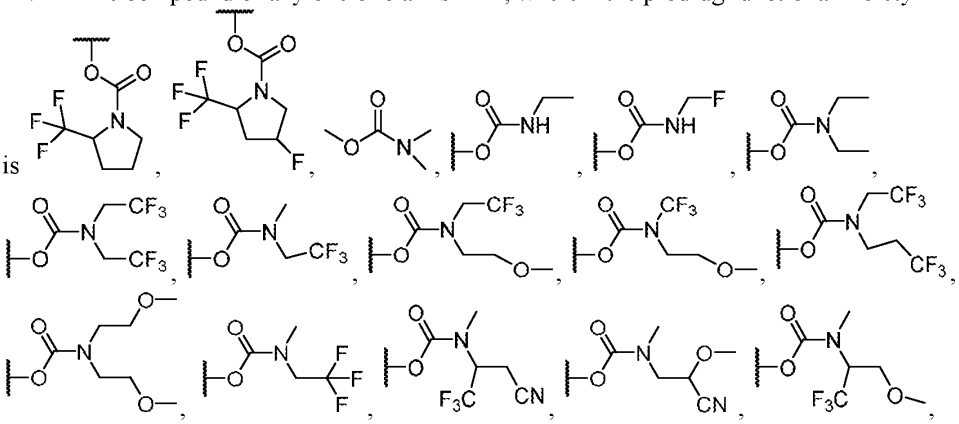
36. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 is , wherein Z^1 is monocyclic, fused or bridged bicyclic 4-11 membered N-containing heterocyclyl or 4-11 membered N-containing heteroaryl optionally substituted with 2 to 3 substituents, wherein the point of attachment is on N.

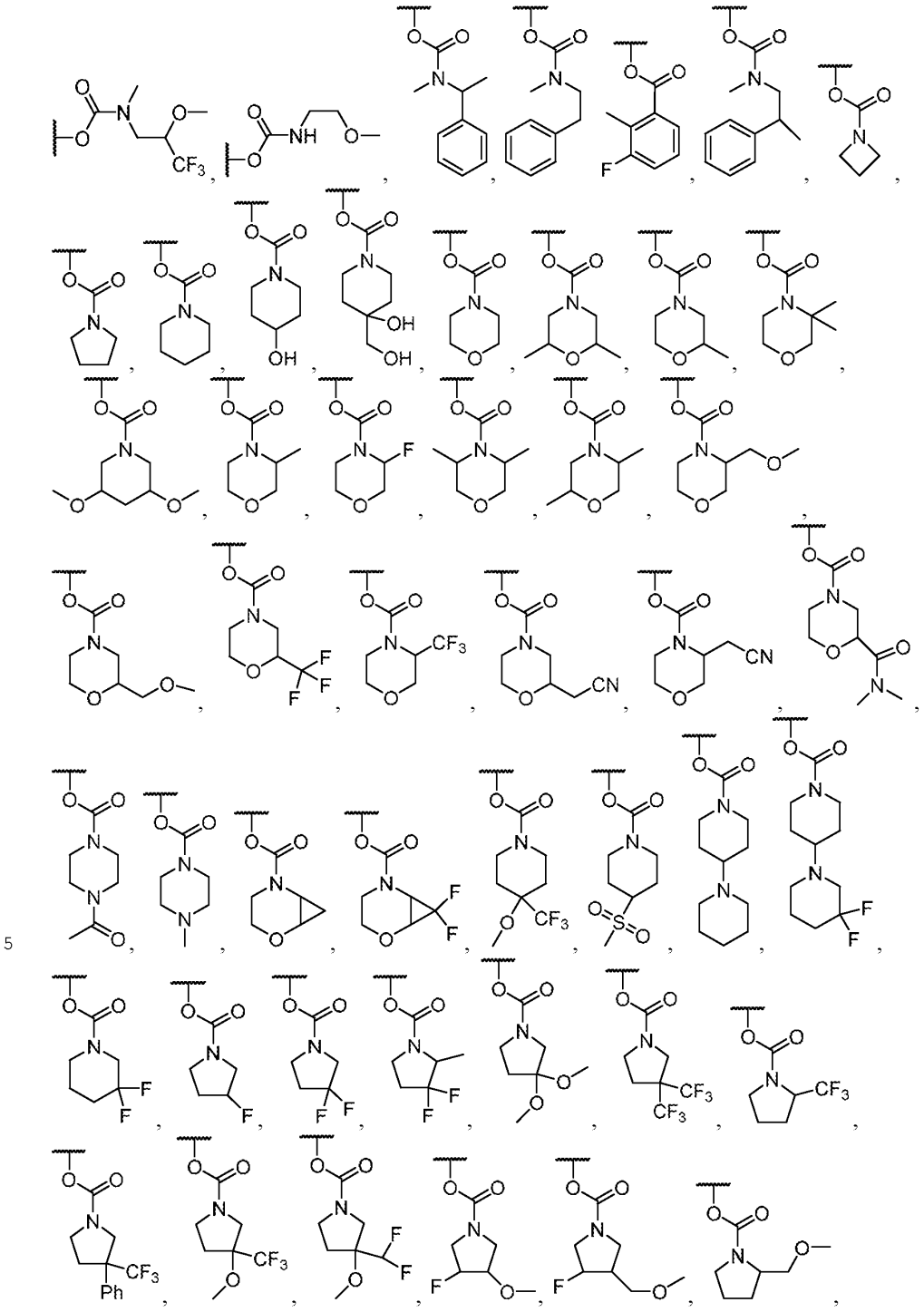
37. The compound of any one of claims 1-34, wherein Z^1 is 

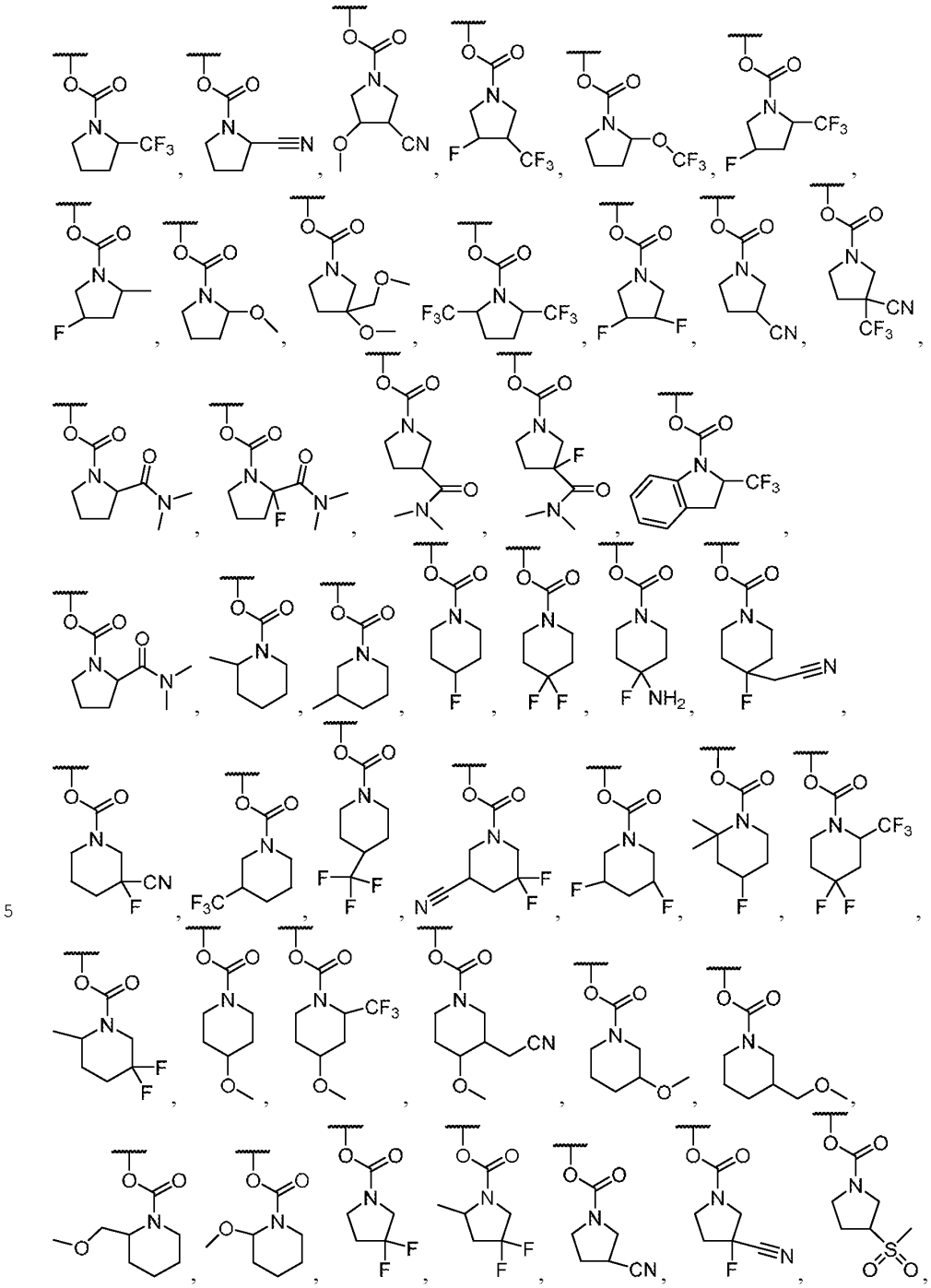


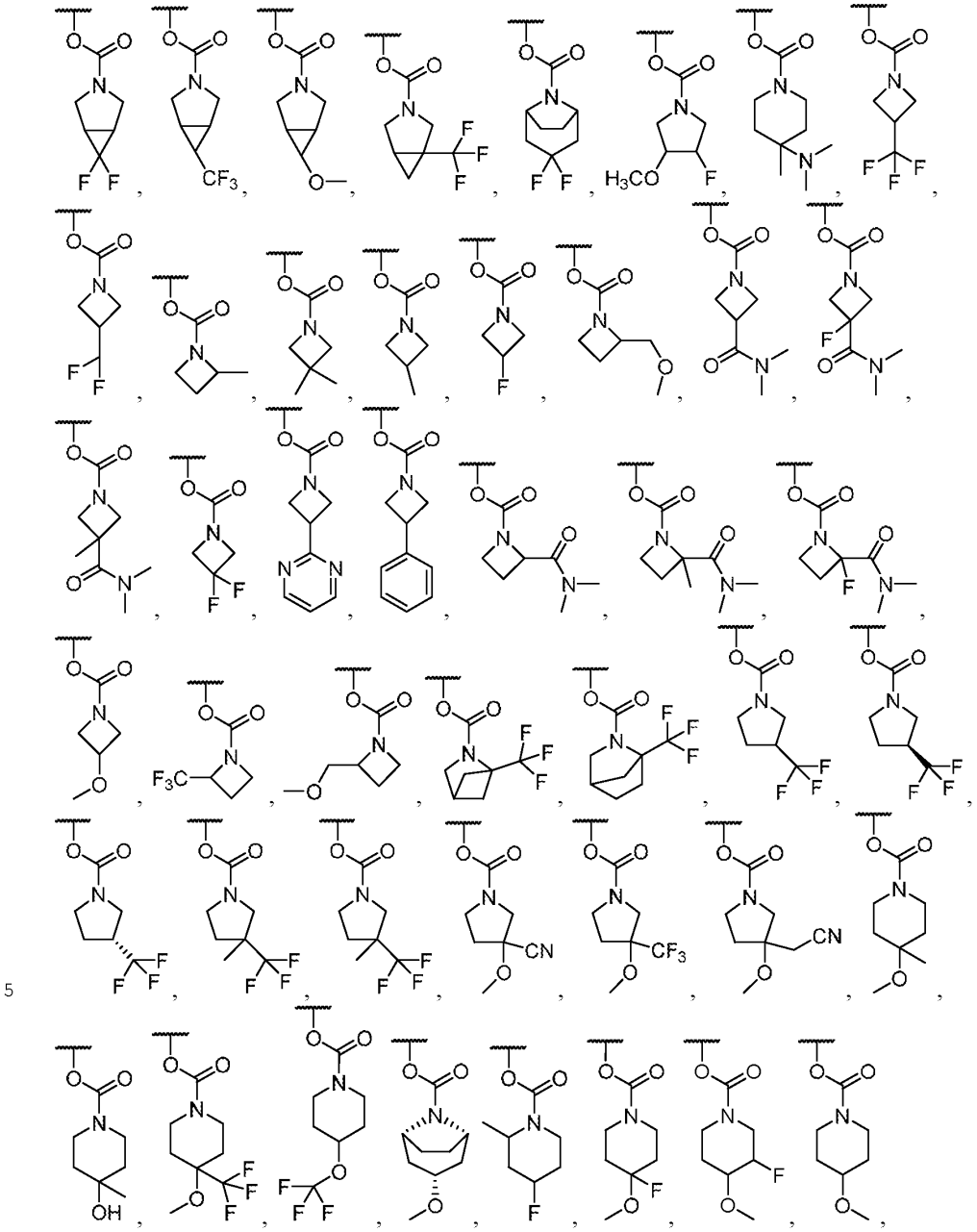
, wherein Z^1 is optionally substituted.

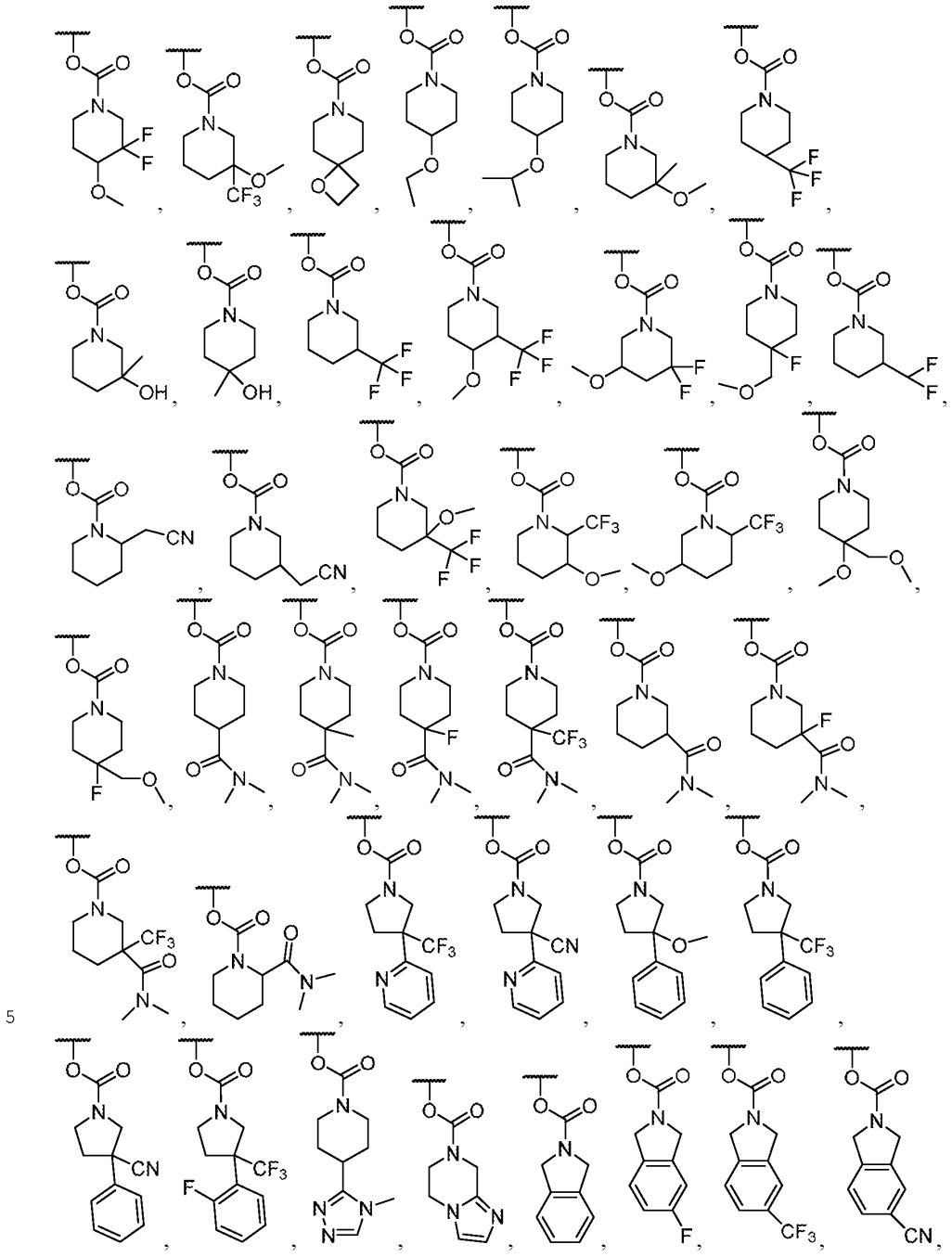
38. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 is

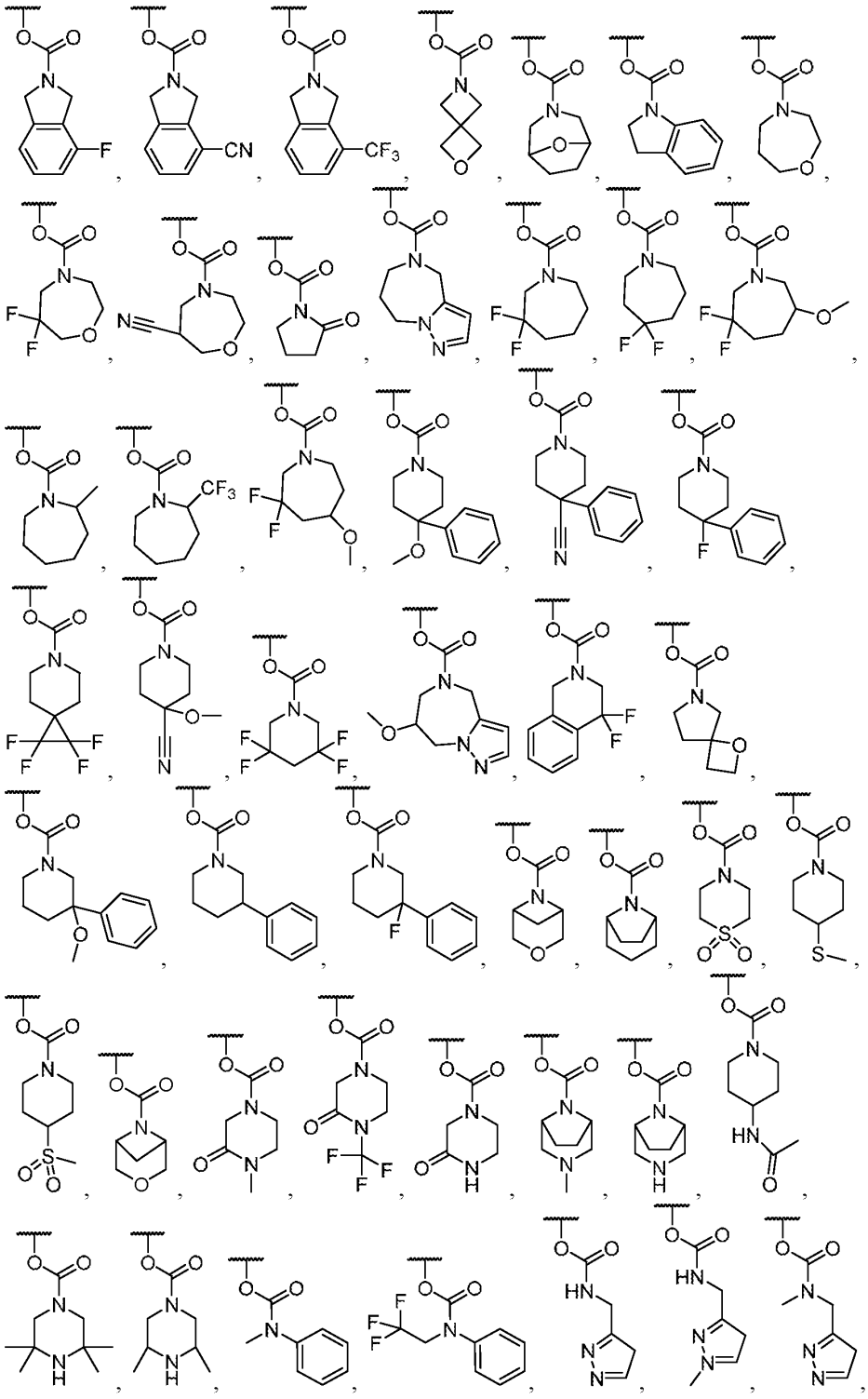


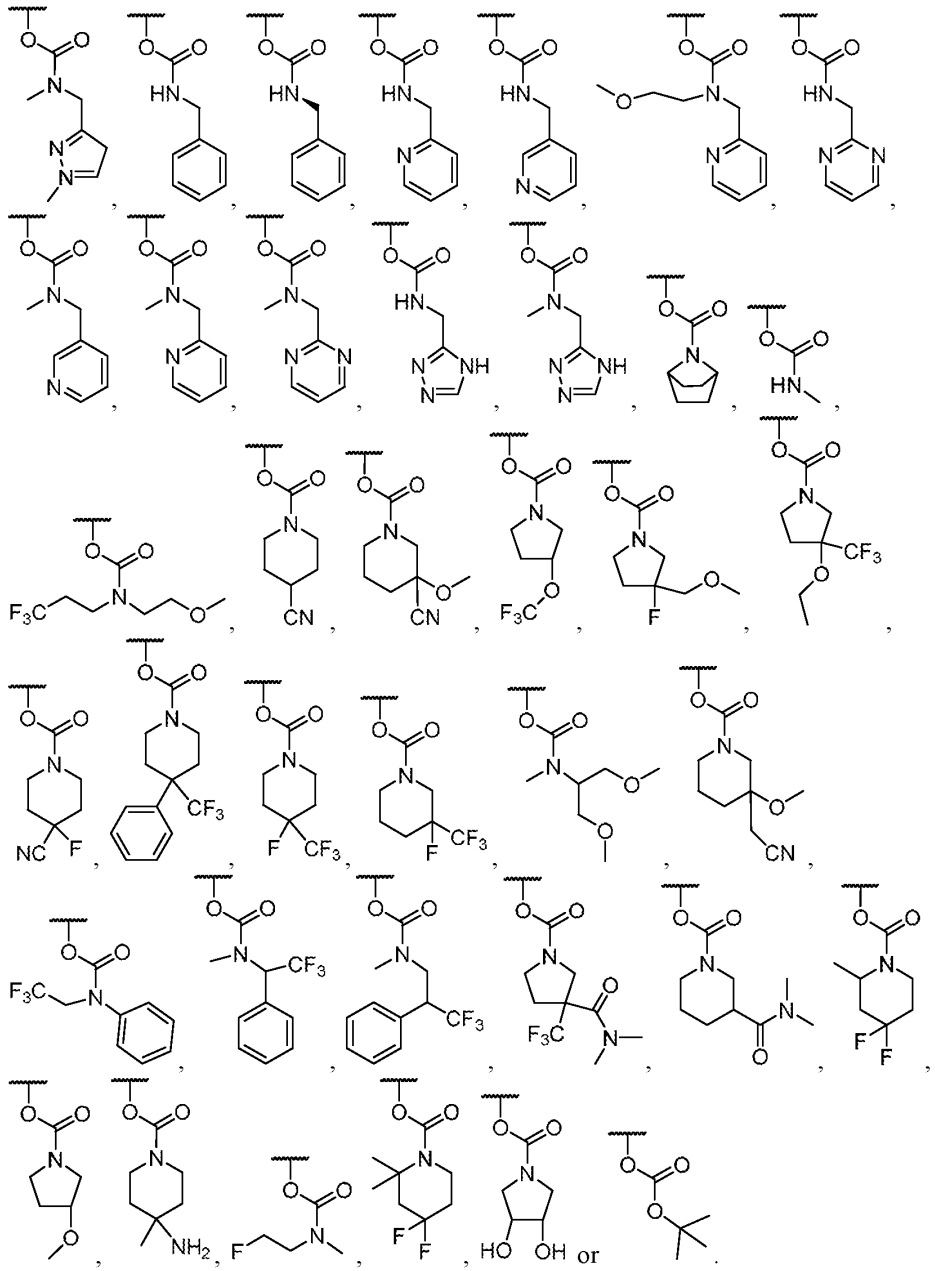






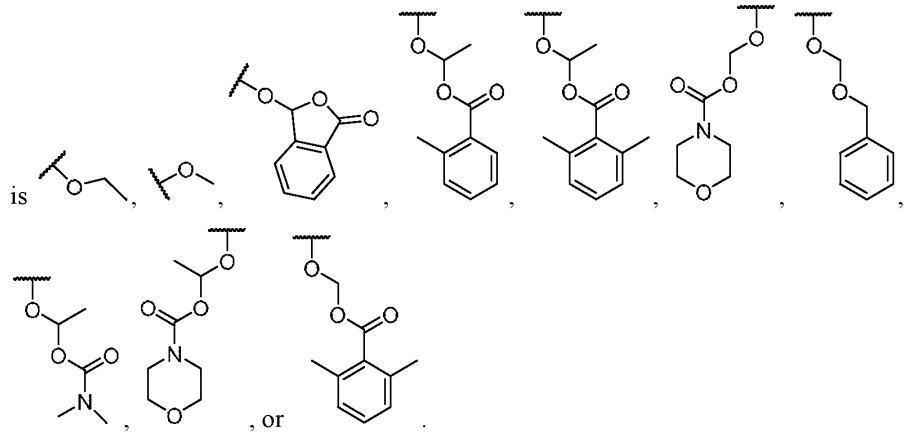


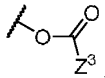


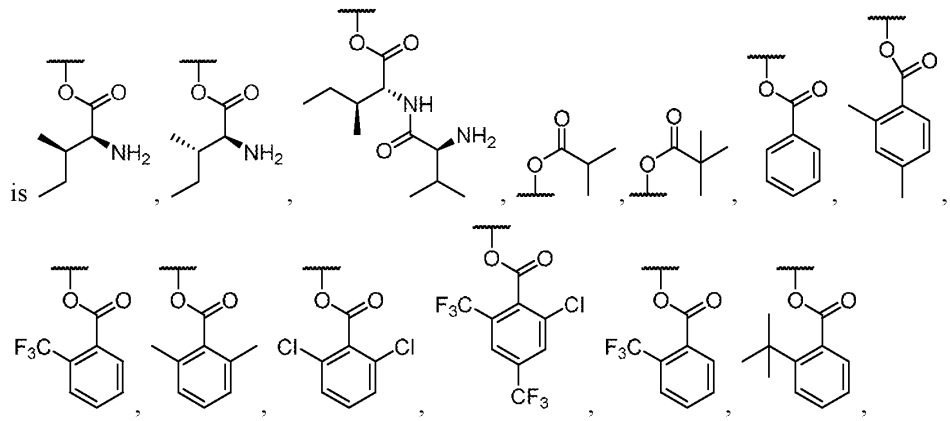


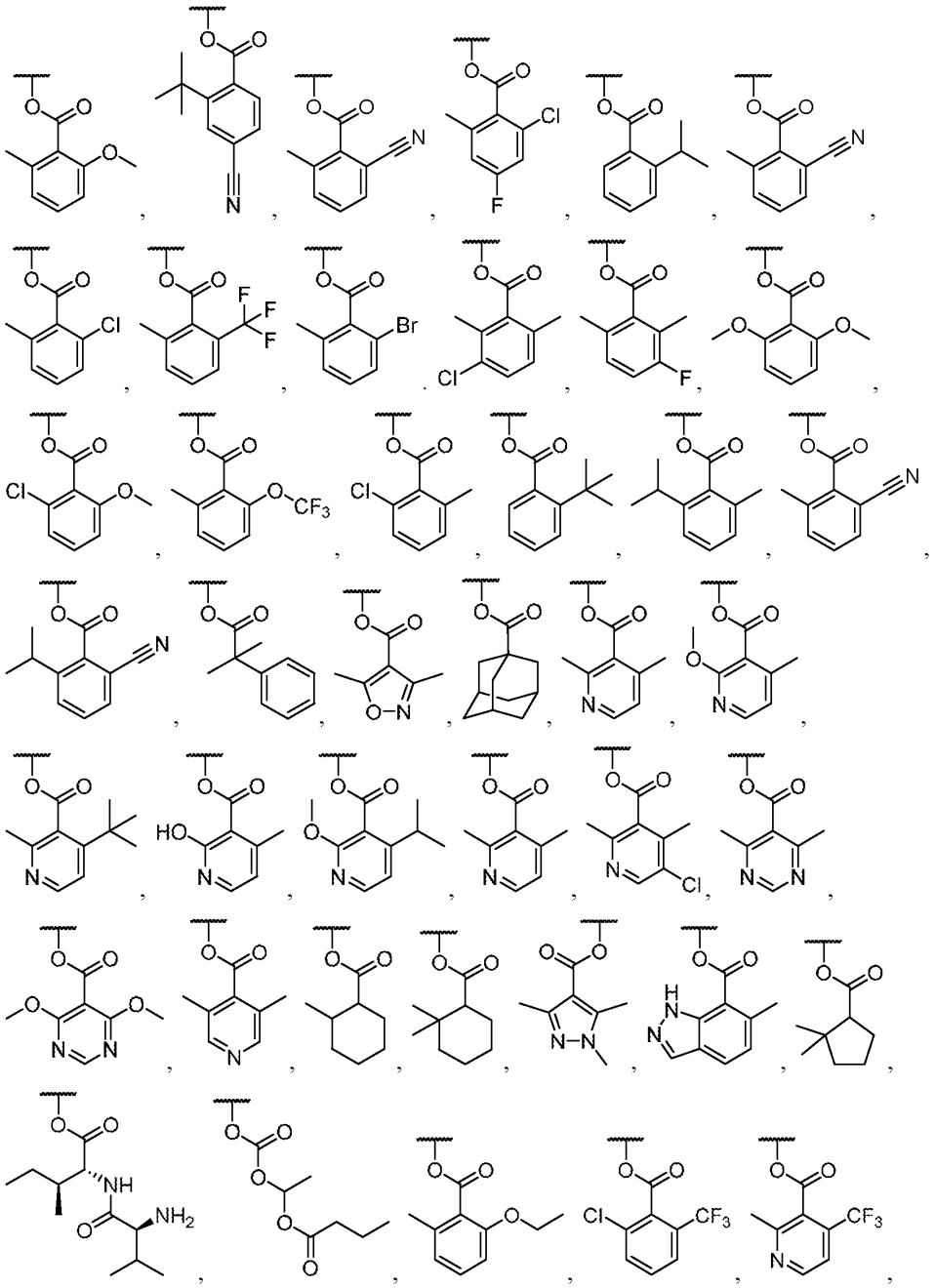
39. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 is , wherein Z^2 is C_{1-3} alkyl, (C_{1-3} alkylene)—O—(C_{1-3} alkyl), (C_{1-3} alkylene)—O—

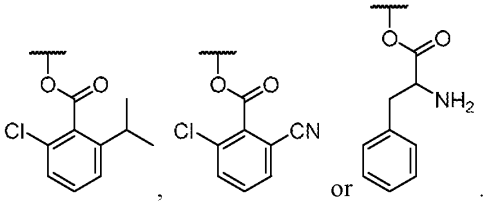
C(O)—X, wherein the alkyl and X are optionally substituted.

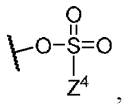
40. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 is , or .

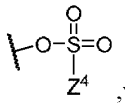
41. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 is ,wherein Z^3 is optionally substituted 4-10 membered aryl, 4-11 membered heteroaryl, 4-8 membered cycloalkyl, 4-10 membered heterocyclyl.

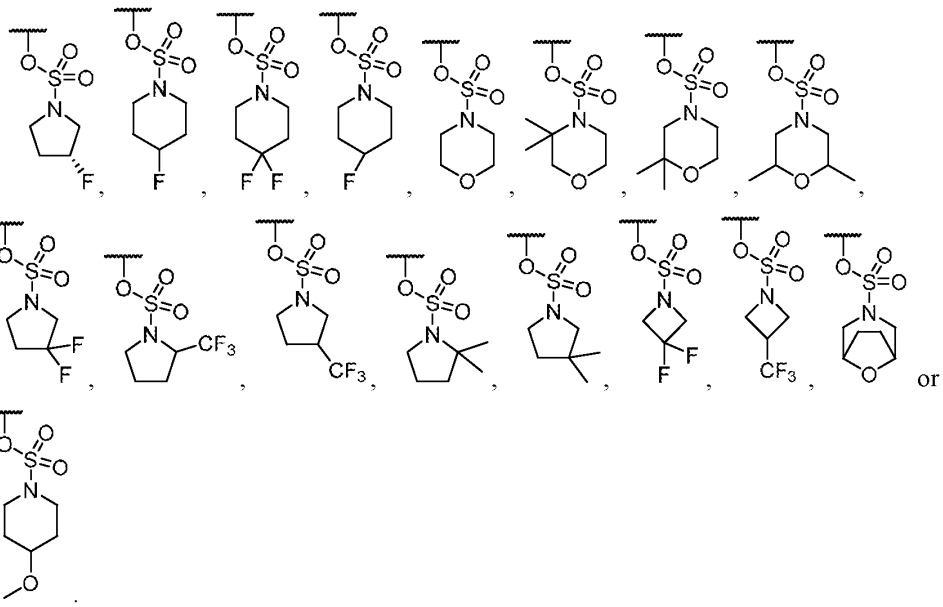
42. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 is 

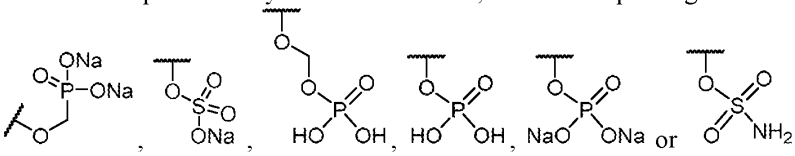


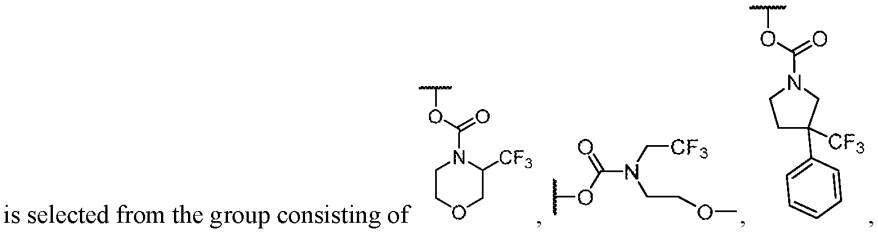
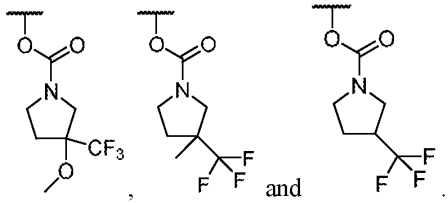


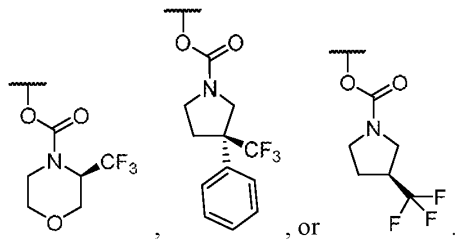
43. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 is , wherein Z^4 is monocyclic, fused or bridged bicyclic 4-11 membered N-containing heterocyclyl or 4-11 membered N-containing heteroaryl optionally substituted with 0 to 4 substituents, wherein the point of attachment is on N.

44. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 is ,wherein Z^4 is monocyclic, fused or bridged bicyclic 4-11 membered N-containing heterocyclyl or 4-11 membered N-containing heteroaryl optionally substituted with 2 to 3 substituents, wherein the point of attachment is on N.

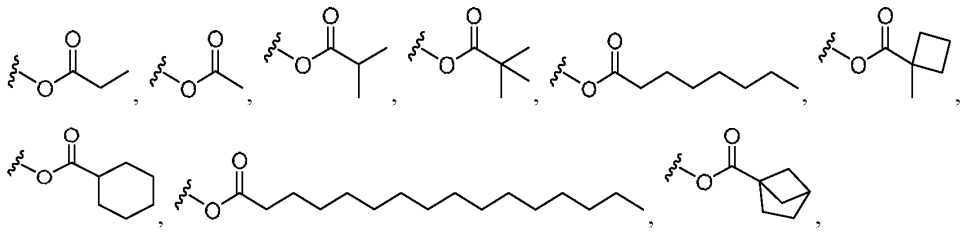
45. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 is .

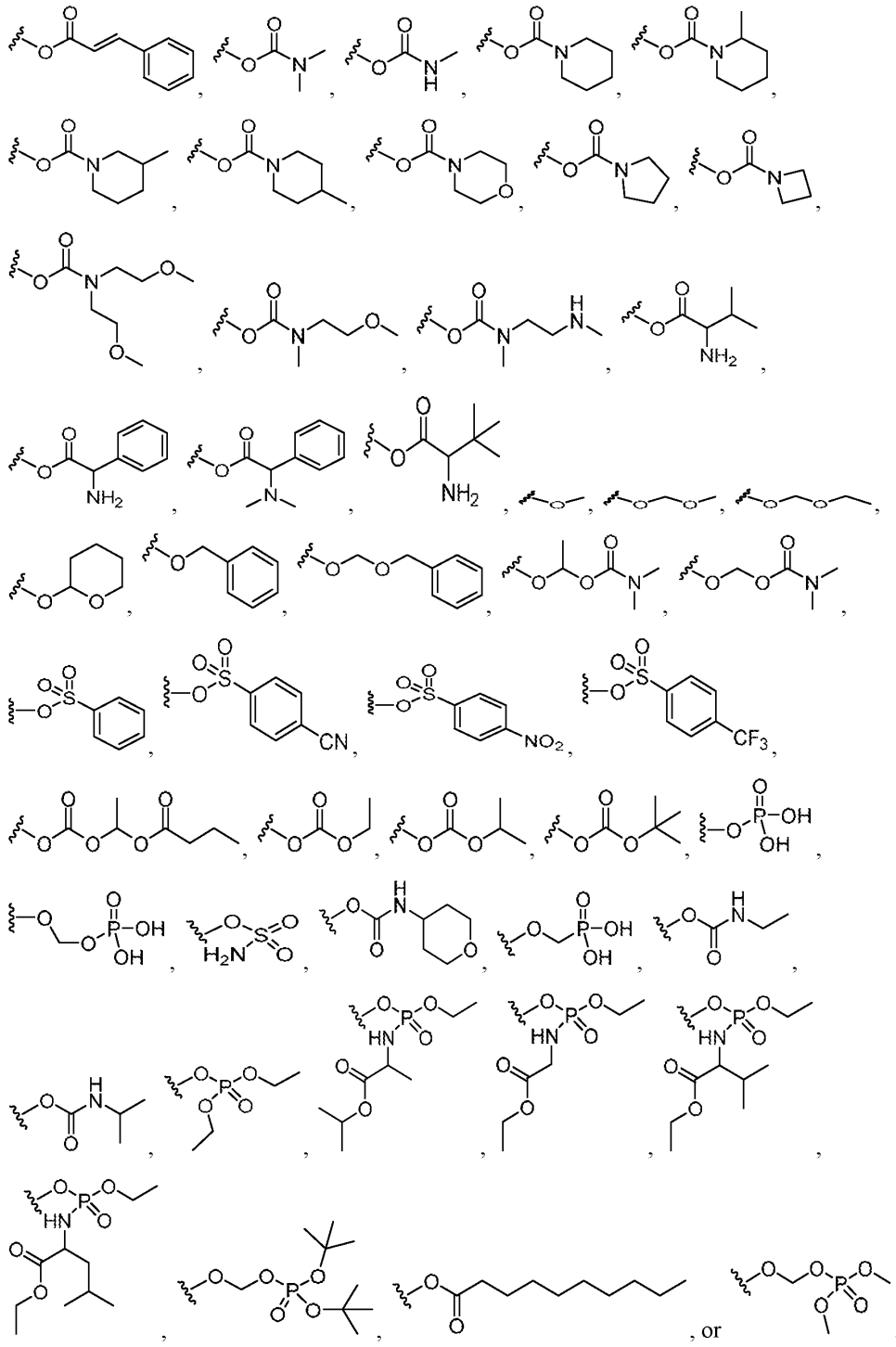
46. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 is .

47. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 is selected from the group consisting of , , and .

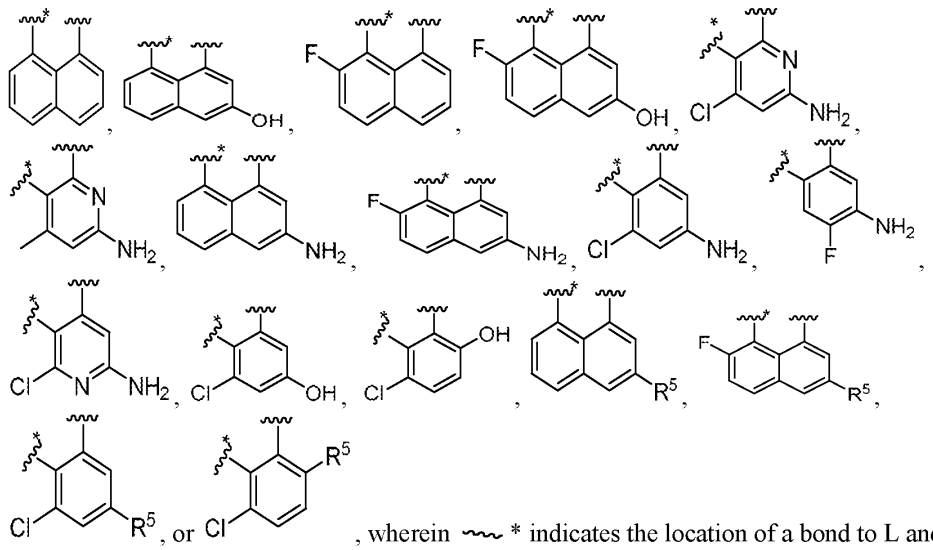
48. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 is .

49. The compound of any one of claims 1-34, wherein the prodrug functional moiety R^5 has one of the following structures:

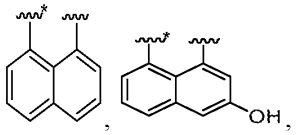


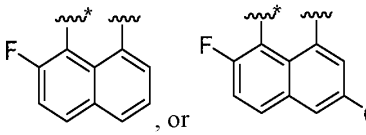


50. The compound of any one of claims 1-49, wherein B has one of the following structures:

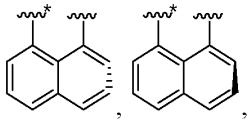


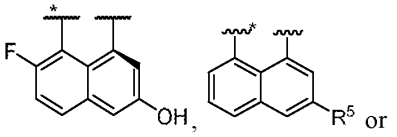
, wherein ~~* indicates the location of a bond to L and ~~ indicates the location of a bond to the pyridine group.

51. The compound of any one of claims 1-50, wherein B is 

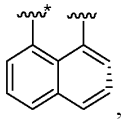
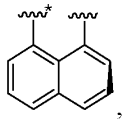
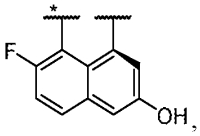
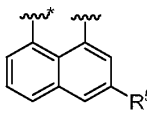
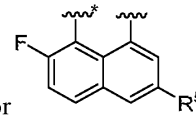


, wherein ~~* indicates the location of a bond to L and ~~ indicates the location of a bond to the pyridine group.

52. The compound of any one of claims 1-51, wherein B is 



, wherein B is further optionally substituted, wherein ~~* indicates the location of a bond to L and ~~ indicates the location of a bond to the pyridine group.

53. The compound of any one of claims 1-52, wherein B is , , ,  or , wherein ~~* indicates the location of a bond to L and ~~ indicates the location of a bond to the pyridine group.

54. The compound of any one of claims 1-53, wherein the C_1-C_8 alkylene, C_2-C_8 alkenylene, C_2-C_8 alkynylene, or C_1-C_8 heteroalkylene of L is substituted with one or more substituents each independently selected from halo, -D, C_1-C_4 alkyl, and C_3-C_5 cycloalkyl.

55. The compound of any one of claims 1-54, wherein the C_1-C_8 alkylene, C_2-C_8 alkenylene, C_2-C_8 alkynylene, or C_1-C_8 heteroalkylene of L is substituted with one or more substituents each independently selected from -F, -D, $-CH_3$, $-CH_2CH_3$, $-CF_3$, and $-CF_2H$; or one or more carbon atoms of the C_1-C_8 alkylene, C_2-C_8 alkenylene, C_2-C_8 alkynylene, or C_1-C_8 heteroalkylene are substituted with a substituent each independently selected from  and .

56. The compound of any one of claims 1-53, wherein L is selected from the group consisting of: C_1-C_8 alkylene, C_2-C_8 alkenylene, and C_2-C_8 alkynylene, wherein the C_1-C_8 alkylene, C_2-C_8 alkenylene, and C_2-C_8 alkynylene are optionally substituted with one or more substituents each independently selected from halo and -D.

57. The compound of any one of claims 1-53, wherein L is selected from the group consisting of: C_1-C_6 alkylene, C_2-C_6 alkenylene, and C_2-C_6 alkynylene, wherein the C_1-C_6 alkylene, C_2-C_6 alkenylene, and C_2-C_6 alkynylene are optionally substituted with one or more substituents each independently selected from halo and -D.

58. The compound of any one of claims 1-53, wherein L is selected from the group consisting of: C_2-C_4 alkylene, C_2-C_4 alkenylene, and C_2-C_4 alkynylene, wherein the C_2-C_4

alkylene, C_2-C_4 alkenylene, and C_2-C_4 alkynylene are optionally substituted with one or more substituents each independently selected from halo and -D.

59. The compound of any one of claims 1-55, wherein L is selected from the group consisting of: $–(CH_2)_4$-, $–(CH_2)_3$-, $–(CH_2)_2$-, *–CH_2CH=CH–**, *–$(CH_2)_2CH$=CH–**, *–$(CH_2)_2C$≡C–**, *–CH_2C≡C–**, $–CH_2CHFCH_2–$, $–CH_2CF_2CH_2–$, *–$CH(CH_3)CH_2CH_2$–**, *–$(CH_2)CH(CH_2)$- **, *–$(CH_2)_2CH(CH_2)$- **, *–$(CH_2)C(CH)_2$-**, and *–$(CH_2)_2C(CH_2)$-**, wherein * indicates the location of the bond to the carbamate group and ** indicates the location of the bond to B group.

60. The compound of any one of claims 1-55, wherein L is selected from the group consisting of: $–(CH_2)_4$-, $–(CH_2)_3$-, $–(CH_2)_2$-, *–CH_2CH=CH–**, *–$(CH_2)_2CH$=CH–**, *–$(CH_2)_2C$≡C–**, *–CH_2C≡C–**, $–CH_2CHFCH_2–$, $–CH_2CF_2CH_2–$, and *–$CH(CH_3)CH_2CH_2$–**, wherein * indicates the location of the bond to the carbamate group and ** indicates the location of the bond to B group.

61. The compound of any one of claims 1-60, wherein L is $–(CH_2)_3$-, $–(CH_2)_2$-, *–$(CH_2)CH(CH_2)$-**, *–$(CH_2)_2CH(CH_2)$-**, *–$(CH_2)C(CH)_2$-**, or *–$(CH_2)_2C(CH_2)$-**, wherein * indicates the location of the bond to the carbamate group and ** indicates the location of the bond to B group.

62. The compound of any one of claims 1-61, wherein L is $–(CH_2)_3$- or $–(CH_2)_2$-.

63. The compound of any one of claims 1-62, wherein L is $–(CH_2)_3$-.

64. The compound of any one of claims 1-63, wherein the 4-8 membered cycloalkyl of R^2 is a cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl.

65. The compound of any one of claims 1-64, wherein the 4-10 membered heterocyclyl of R^2 is azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, oxanyl, piperazinyl, morpholinyl, dioxanyl, azepanyl, oxepanyl, homopiperazinyl, or oxazepanyl.

66. The compound of any one of claims 1-65, wherein the 4-10 membered heterocyclyl of R^2 is azetidinyl, pyrrolidinyl, morpholinyl, or piperidinyl.

67. The compound of any one of claims 1-66, wherein the heteroaryl of R^2 is imidazolyl, pyrazolyl, or pyridinyl.

68. The compound of any one of claims 1-67, wherein the 4-10 membered heterocyclyl of R^2 is a fused bicyclic heterocyclyl, a spiro bicyclic heterocyclyl, or a bridged bicyclic heterocyclyl.

69. The compound of any one of claims 1-68, wherein the fused bicyclic heterocyclyl of R^2 is hexahydro-1H-pyrrolizinyl, octahydro-6λ^2-pyrrolo[3,4-b]pyridinyl, octahydro-1H-cyclopenta[b]pyridinyl, hexahydro-1H-pyrrolo[2,1-c][1,4]oxazinyl, 2-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.1.0]hexanyl, or 1,2,3,4-tetrahydroisoquinolinyl.

70. The compound of any one of claims 1-69, wherein the spiro bicyclic heterocyclyl of R^2 is tetrahydro-1'H,3'H-spiro[cyclopropane-1,2'-pyrrolizinyl] or 5-azaspiro[2.4]heptanyl.

71. The compound of any one of claims 1-70, wherein the bridged bicyclic heterocyclyl of R^2 is 2-oxa-5-azabicyclo[2.2.1]heptanyl.

72. The compound of any one of claims 1-71, wherein the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, or amine of R^2 is substituted with one or more substituents each independently selected from H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, C_1-C_4 alkylene-C_6-C_{10} aryl, C_1-C_4 alkylene-(5-10 membered heteroaryl), C_1-C_4 alkylene-C_3-C_{10} cycloalkyl, C_1-C_4 alkylene-(3-10 membered heterocyclyl), 3-10 membered heterocyclyl, C_6-C_{10} aryl, 5-10 membered heteroaryl, C_1-C_4 alkylene- $NR^{X1}R^{X2}$, $=CH_2$, $=CF_2$ or =CFH, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy.

73. The compound of any one of claims 1-72, wherein the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, or amine of R^2 is substituted with one or more substituents each independently selected from halo, deuterium, C_1-C_4 alkyl, C_1-C_4 alkylene-$N(R^X)_2$, C_1-C_4 alkylene-(4-10 membered heterocyclyl), C_1-C_4 heteroalkyl, hydroxyl, $=CH_2$,

$=CF_2$, $=CFH$, and heteroaryl, each R^X is independently hydrogen or C_1-C_4 alkyl.

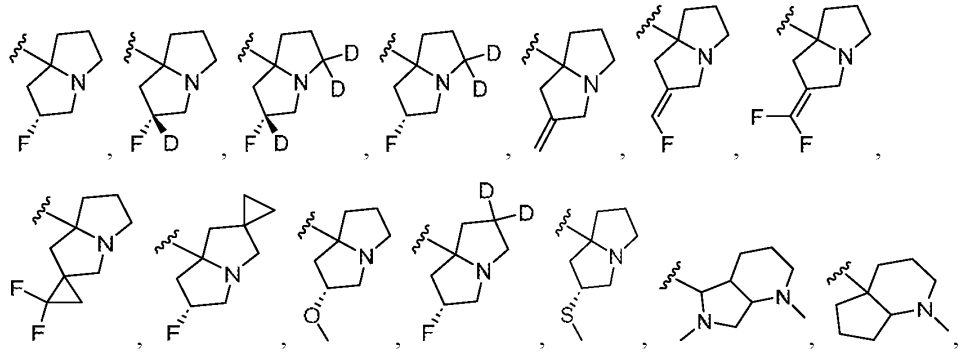
74. The compound of claim 73, wherein the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, or amine of R^2 is substituted with one or more substituents each independently selected from $-CH_3$, -F, -CN, $-NH_2$, $-CH_2OCH_3$, $-OCH_3$, $-CF_2H$, $-CF_3$, -OH, $=CH_2$, $=CF_2$, $=CFH$, heteroaryl, $-C_1$-C_3 alkylalcohol, C_1-C_3 alkoxyl, and deuterium, $-CH_2N(CH_3)_2$, and $-CH_2$-(6-membered heterocyclyl).

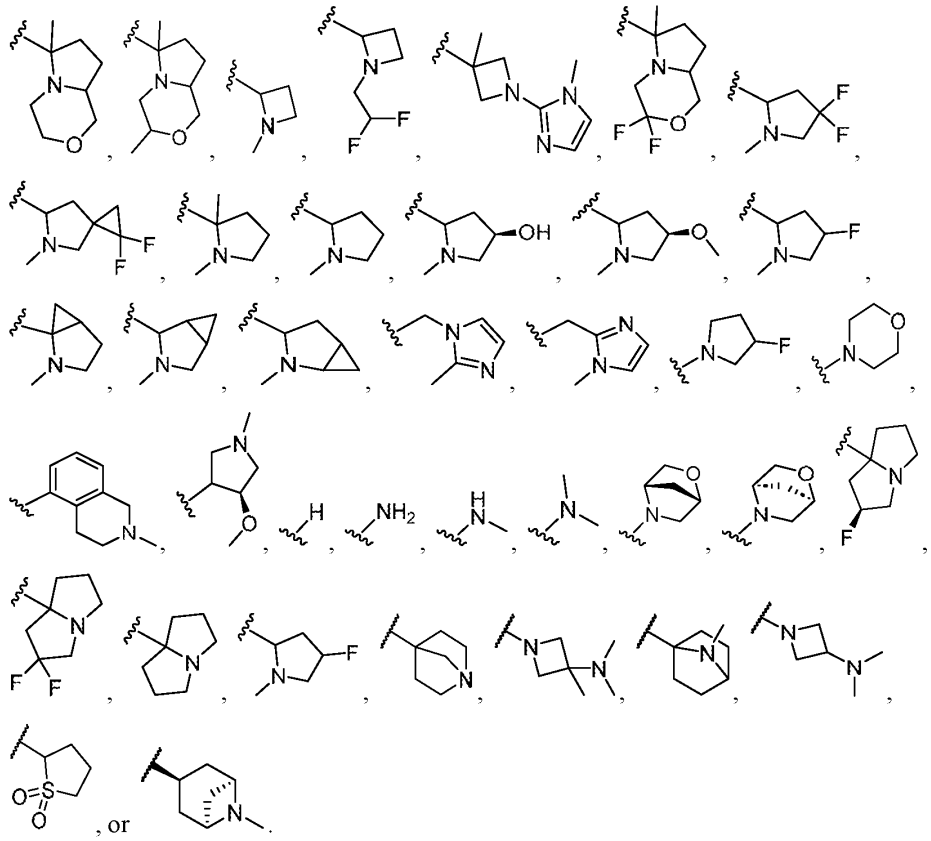
75. The compound of claim 73, wherein the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, or amine of R^2 is substituted with one or more substituents each independently selected from the group consisting of $-CH_3$, -F, $=CF_2$, $=CFH$, $=CH_2$, and -OH.

76. The compound of any one of claims 1-75, wherein the amine of R^2 is $-NH_2$, $-NH(CH_3)$, or $-N(CH_3)_2$.

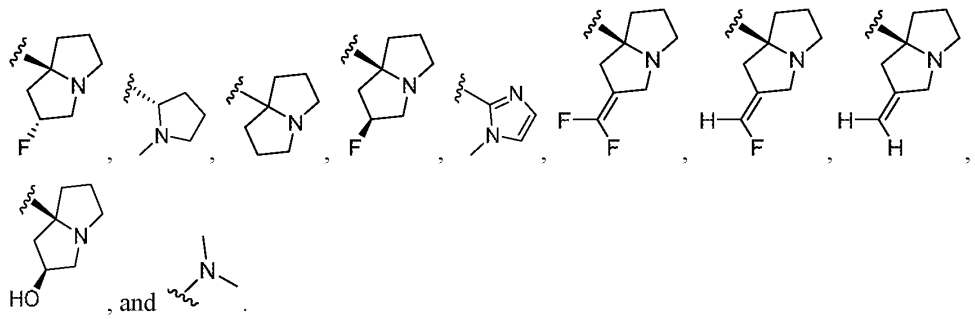
77. The compound of claim 73, wherein R^2 is selected from the group consisting of 4-10 membered heterocyclyl, 5-6 membered heteroaryl, and amine, wherein the 4-10 membered heterocyclyl, 5-6 membered heteroaryl, and amine are optionally substituted with one or more substituents each independently selected from the group consisting of $-CH_3$, -F, $=CF_2$, $=CFH$, $=CH_2$, and -OH.

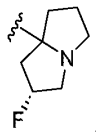
78. The compound of any one of claims 1-77, wherein R^2 has one of the following structures:

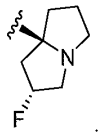




79. The compound of any one of claims 1-77, wherein R^2 is selected from the group consisting of:



80. The compound of any one of claims 1-79, wherein R^2 is .

81. The compound of any one of claims 1-79, wherein R^2 is .

82. The compound of any one of claims 1-81, wherein R^1 is a hydrogen, $-CH_2CH_3$, or $-CH_3$.

83. The compound of any one of claims 1-82, wherein R^1 is a hydrogen.

84. The compound of any one of claims 1-83, wherein R^3 is a hydrogen or $-CH_3$.

85. The compound of any one of claims 1-84, wherein Y is $-CH_2-$, $-CD_2-$, $-CH(CH_3)-$, $-CD(CH_3)-$, $-CD(CD_3)-$, or a direct bond.

86. The compound of any one of claims 1-84, wherein Y is $-CH_2-$, $-CD_2-$, $-CH_2-CH_2-$, or a direct bond.

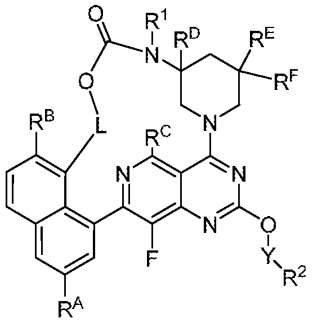
87. The compound of any one of claims 1-86, wherein Y is $-CH_2-$.

88. The compound of any one of claims 1-87, wherein the C_1-C_5 alkyl or C_1-C_5 deuteroalkyl of Y is substituted with methyl, dimethyl, or cyclopropyl.

89. The compound of any one of claims 1-86, wherein X is -O- or a direct bond.

90. The compound of any one of claims 1-86, wherein X is -O-.

91. A compound having the following structure of Formula (III):



(III)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein

L is selected from the group consisting of linear C_3-C_5 alkylene and linear C_3-C_5 deuteroalkylene, wherein the linear C_3-C_5 alkylene or linear C_3-C_5 deuteroalkylene is optionally substituted with C_1-C_2 alkyl, C_1-C_2 haloalkyl, CN, halo, OH, NH_2, -$NH(CH_3)$ or $N(CH_3)_2$;

R^A is selected from the group consisting of alkylenecyclyl, heterocyclyl, aryl, or heteroaryl, H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy, wherein the alkylene-cyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted, wherein the C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy is optionally substituted with C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl , heterocyclyl, -C(O)$NR^{X3}R^{X4}$ wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, or prodrug moiety R^5;

R^B is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, and wherein the alkyl, haloalkyl, alkoxy can be substituted with C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl , heterocyclyl, or -C(O)$NR^{X3}R^{X4}$, wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy;

R^C is selected from the group consisting of H, D, C_1-C_2 alkyl, C_1-C_2 alkoxy, halo, CN, NH_2, -$NH(CH_3)$, and $N(CH_3)_2$;

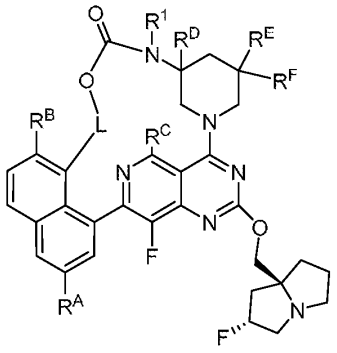
R^D is selected from the group consisting of H, D, C_1-C_3 alkyl, C_1-C_2 deuteroalkyl, C_1-C_3 haloalkyl, C_1-C_3 alkylalcohol, (C_1-C_3 alkylene)-O-(C_1-C_3 alkyl), and CN;

R^E and R^F are each independently selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, and $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, and wherein the alkyl, haloalkyl, alkoxy can be substituted with: C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, -C(O)$NR^{X3}R^{X4}$, wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy;

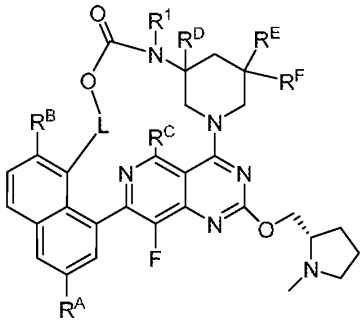
R^1 is selected from the group consisting of H, D, C_1-C_2 alkyl, C_1-C_2 alkoxy, halo, CN, NH_2, -$NH(CH_3)$, and $N(CH_3)_2$;

Y is selected from the group consisting of C_1-C_5 alkylene, C_1-C_5 deuteroalkylene, or a direct bond, wherein the C_1-C_5 alkylene or C_1-C_5 deuteroalkylene is optionally substituted;R^2 is selected from the group consisting of hydrogen, 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, -(C_1-C_3 alkylene)-heteroaryl, aryl fused to 4-8 membered heterocyclyl, and amine, wherein the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, 4-8 membered heterocyclyl, or amine is optionally substituted.

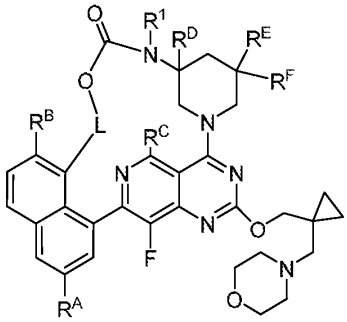
92. The compound of claim 91, wherein the compound has one of the following structures of Formula (IIIA), (IIIB) or (IIIC):



(IIIA)



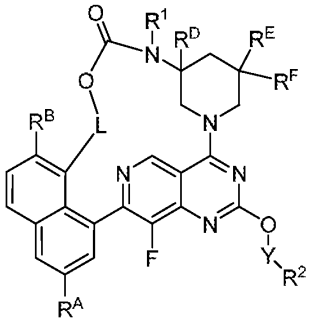
(IIIB)



(IIIC)

wherein the variables are as defined in claim 91.

93. The compound of claim 1 or 86, wherein the compound has the following structure of Formula (III-1):



(III-1)

wherein

L is selected from the group consisting of linear C_3-C_5 alkylene and linear C_3-C_5 deuteroalkylene, wherein the linear C_3-C_5 alkylene or linear C_3-C_5 deuteroalkylene is optionally substituted with C_1-C_2 alkyl, C_1-C_2 haloalkyl, CN, halo, OH, NH_2, -$NH(CH_3)$ or $N(CH_3)_2$;

R^A is selected from the group consisting of alkylenecyclyl, heterocyclyl, aryl, or heteroaryl, H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4}alkylene-C_{1-4}alkoxy, wherein the alkylene-cyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted, wherein the C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy is optionally substituted with C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl , heterocyclyl, -C(O)$NR^{X3}R^{X4}$ wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, or prodrug moiety R^5;

R^B is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, and wherein the alkyl, haloalkyl, alkoxy can be substituted with C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, or -C(O)$NR^{X3}R^{X4}$, wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy;

R^D is selected from the group consisting of H, D, C_1-C_3 alkyl, C_1-C_2 deuteroalkyl, C_1-C_3 haloalkyl, C_1-C_3 alkylalcohol, (C_1-C_3 alkylene)-O-(C_1-C_3 alkyl), and CN;

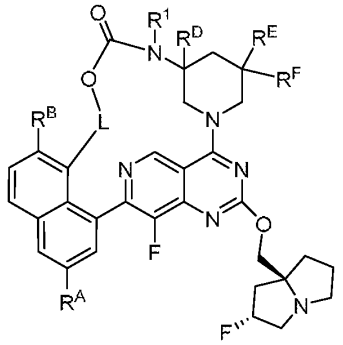
R^E and R^F are each independently selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, and $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, and wherein the alkyl, haloalkyl, alkoxy can be substituted with: C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, -C(O)$NR^{X3}R^{X4}$, wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy;

R^1 is selected from the group consisting of H, D, C_1-C_2 alkyl, C_1-C_2 alkoxy, halo, CN, NH_2, -$NH(CH_3)$, and $N(CH_3)_2$;

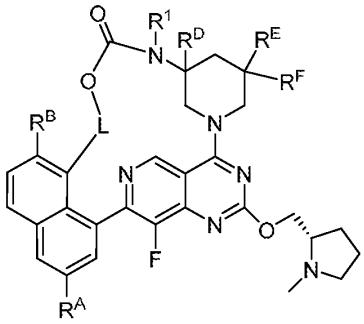
Y is selected from the group consisting of C_1-C_5 alkylene, C_1-C_5 deuteroalkylene, or a direct bond, wherein the C_1-C_5 alkylene or C_1-C_5 deuteroalkylene is optionally substituted;R^2 is selected from the group consisting of hydrogen, 4-8 membered cycloalkyl, 4-10 membered heterocyclyl, heteroaryl, -(C_1-C_3 alkylene)-heteroaryl, aryl fused to 4-8 membered heterocyclyl, and amine, wherein the 4-8 membered cycloalkyl, 4-10 membered heterocyclyl,

heteroaryl, 4-8 membered heterocyclyl, or amine is optionally substituted.

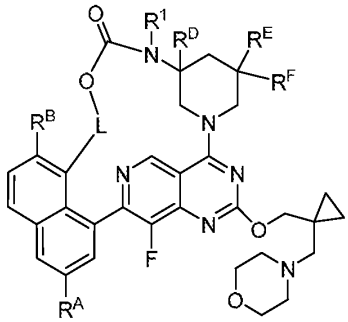
94. The compound of any one of claim 1, 91, 92, or 93, wherein the compound has one of the following structures of Formula (IIIA), (IIIB) or (IIIC):



(III-1A)



(III-1B)

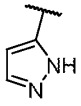
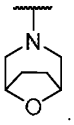


(III-1C)

wherein the variables are as defined in claim 91.

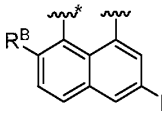
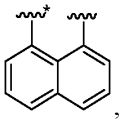
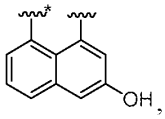
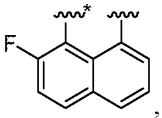
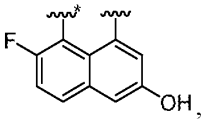
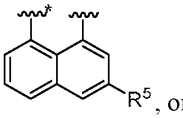
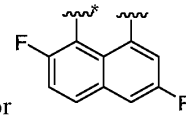
95. The compound of any one of claim 91-94, wherein L is selected from the group

consisting of unsubstituted linear C_3-alkylene, unsubstituted linear C_4-alkylene, linear C_3-alkylene substituted with -CH_3, CN, F, or Cl, or linear C_4-alkylene substituted with -CH_3, CN, F, or Cl.

96. The compound of any one of claim 91-95, wherein R^A is selected from the group consisting of H, OH, C_1-C_4 alkylalcohol, F, Cl, C_1-C_2 alkyl, C_1-C_2 haloalkyl, CN, NH_2, -$NH(CH_3)$, $N(CH_3)_2$, -$NHC(O)NHCH_3$, -CHF_2, R^5 prodrug moiety,  and .

97. The compound of any one of claims 91-96, wherein R^B is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 heteroalkyl, halo, NH_2, -$NH(CH_3)$, $N(CH_3)_2$, and OH.

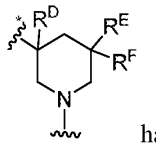
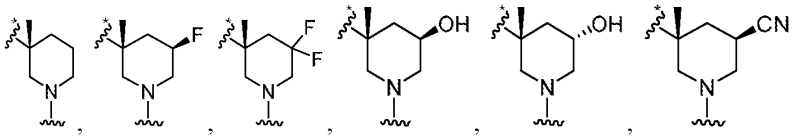
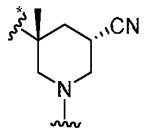
98. The compound of any one of claims 91-97, wherein R^B is selected from the group of H, CH_3, F, and Cl.

99. The compound of any one of claims 91-98, wherein  has the structure of the following: , , , , , or , wherein ~~* indicates the location of a bond to L and ~~ indicates the location of a bond to the pyrimidine group.

100. The compound of any one of claims 91-99, wherein R^C is selected from the group consisting of H, -CH_3, and -OCH_3.

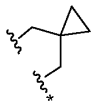
101. The compound of any one of claims 91-100, wherein R^D is selected from the group consisting of -CH_3, C_1-haloalkyl, -CF_3, -CH_2CH_2OH, -CH_2OH, -CH_2CHF_2, and -CH_2-O-CH_3.

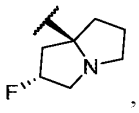
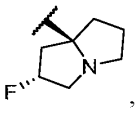
102. The compound of any one of claims 91-101, wherein R^E and R^F are each independently selected from the group consisting of H, D, F, Cl, CH_3, C_1 haloalkyl, and -OCH_3.

103. The compound of any one of claims 91-102, wherein  has the structure of the following: ,  or , wherein ~~* indicates the location of a bond to the carbamate group and ~~ indicates the location of a bond to the pyrimidine group.

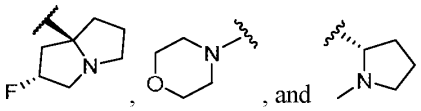
104. The compound of any one of claims 91-103, wherein R^1 is selected from the group consisting of H, CH_3, and C_1 haloalkyl.

105.The compound of any one of claims 91-104, wherein Y is C_1-C_3 alkylene optionally substituted with C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, cyclopropyl, and $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, C_{1-4} alkyl, or C_{1-4} haloalkyl.

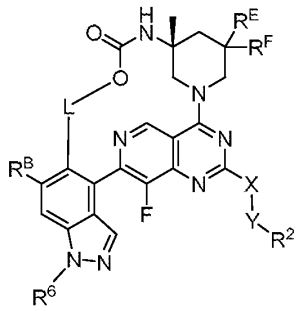
106. The compound of any one of claims 91-105, wherein Y is substituted C_3 alkylene, wherein the substituted C_3 alkylene is , wherein ~~ represents the point of attachment to X and ~~* represents the point of attachment to R^2.

107. The compound of any one of claims 91-106, wherein R^2 is selected from the group consisting of , morpholinyl, or pyrrolidinyl, wherein , morpholinyl, or pyrrolidinyl is optionally substituted with C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, cyclopropyl, or $NR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} are each independently H, $C_{1\text{-}4}$ alkyl, or $C_{1\text{-}4}$ haloalkyl.

108. The compound of any one of claims 91-107, where in R^2 is selected from the group consisting of:



109. A compound having the following structure of Formula (IV):



(IV)

or a stereoisomer of the compound, tautomer of the compound, or salt thereof, wherein

L is selected from the group consisting of : C_1-C_8 alkylene, C_2-C_8 alkenylene, C_2-C_8 alkynylene, C_1-C_8 heteroalkylene, wherein the C_1-C_8 alkylene, C_1-C_8 alkenylene, C_1-C_8 alkynylene, or C_1-C_8 heteroalkylene is optionally substituted, —O-(C_1-C_8 alkylene)—, —O-(C_2-C_8 alkenylene)—, —O-(C_2-C_8 alkynylene)—, —O-(C_1-C_8 heteroalkylene)—, —S-(C_1-C_8 alkylene)—, —S-(C_2-C_8 alkenylene)—, —S-(C_2-C_8 alkynylene)—, —S-(C_1-C_8 heteroalkylene)—, —NR-(C_1-C_8 alkylene)—, —NR-(C_2-C_8 alkenylene)—, —NR-(C_2-C_8 alkynylene)—, and —NR-(C_1-C_8 heteroalkylene)—;

R^B is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4

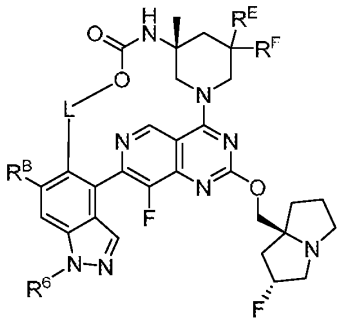
deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O- C_1-C_4 alkylene, halo, hydroxyl, -C(=O)CH_3, NH_2, -NH(CH_3), N(CH_3)$_2$;

R^6 is selected from the group consisting of H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 deuteroalkyl, -D, C_1-C_4 heteroalkyl, CN, C_1-C_4 alkylene-CN, C_1-C_3 alkylalcohol, C_1-C_4 alkylene-O-C_1-C_4 alkyl, halo, hydroxyl, -C(=O)-C_1-C_3 alkyl, $NR^{X1}R^{X2}$ wherein R^{X1}, R^{X2}: are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, and wherein the C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy can be substituted with: C_{1-4} alkyl, halo, OH, CN, aryl, heteroaryl, cycloalkyl, heterocyclyl, -C(O)$NR^{X3}R^{X4}$ wherein R^{X3} and R^{X4} are each independently H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4}alkylene-C_{1-4}alkoxy, or prodrug moiety R^5;

X, Y, and R^2 are as defined in claim 17;

R^E and R^F are each independently H, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 heteroalkyl, halo, $NR^{X1}R^{X2}$, hydroxyl, or CN, wherein R^{X1} and R^{X2} are each independently H or C_{1-4} alkyl.

110. The compound of claim 109, wherein the compound has the following structure of Formula (IVA):



(IVA)

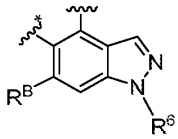
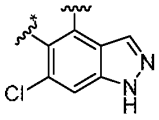
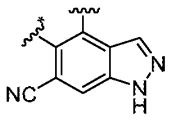
wherein the variables are as defined in claim 109.

111. The compound of claim 109 or 110, wherein L is linear C_2-C_5 alkylene optionally substituted with C_1-C_4 alkyl, C_1-C_4 heteroalkyl, halo, amine, hydroxyl, or CN.

112. The compound of any one of claims 109-111, wherein R^B is H, F, Cl, -CH_3, -CD_3, -CF_3, -CH_2CH_3, OH, CN, or NH_2.

113. The compound of any one of claims 109-112, wherein R^6 is H, F, Cl, $-CH_3$, $-CD_3$, $-CF_3$, $-CH_2CH_3$, OH, CN, or NH_2.

114. The compound of any one of claims 109-113, wherein R^B is CN or Cl.

115. The compound of any one of claims 109-114, wherein  has the structure of following:  or  wherein ~* indicates the location of a bond to L and ~ indicates the location of a bond to the pyridine group.

116. The compound of any one of claims 109-115, wherein R^E and R^F are each independently H, F, Cl, $-CH_3$, $-CD_3$, $-CF_3$, $-CH_2CH_3$, OH, CN, or NH_2.

117. The compound of claim 1, wherein the compound is selected from Table 1.

118. A pharmaceutical composition comprising a compound of any one of claims 1-117 and a pharmaceutically acceptable carrier.

119. The pharmaceutical composition of claim 118, further comprising an additional therapeutic agent.

120. The compound of any one of claims 1-117 or the pharmaceutical composition of claim 113 or 114 for use in treating a disease associated with a mutation in KRAS.

121. A method of treating a disease associated with G12D, G12V, G12C, G12S, G12A, G12R, Q61H, G13D mutation in KRAS or a wild-type KRAS mutation in a subject in need thereof, comprising: administering the compound of any one of claims 1-118 or the pharmaceutical composition of claim 118 or 119 to the subject.

122. The method of claim 121, wherein the subject is an animal.

123. The method of claim 121 or claim 122, wherein the subject is a human.

124. The compound for use or the method of any one of claims 120-123, wherein the disease associated with a mutation in KRAS is a cancer.

125. The compound for use or the method of claim 124 , wherein the cancer is pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC), colorectal cancer, endometrial endometrioid adenocarcinoma, rectal adenocarcinoma, gastric cancer, or lung cancer.